

**Psoriasis Update:
Current Management
Landscape and
Access to Therapy**

**Diabetes Update:
Treatment Guidelines
and Managed
Care Implications**

**Strategies for Staying
Ahead of Specialty Drug
Trends: Focus on the
Medical Pharmacy Benefit**

**Leveraging Technology
to Improve
Adherence and
Optimize Outcomes**

Magellan Rx Report

MEDICAL AND PHARMACY BENEFIT MANAGEMENT

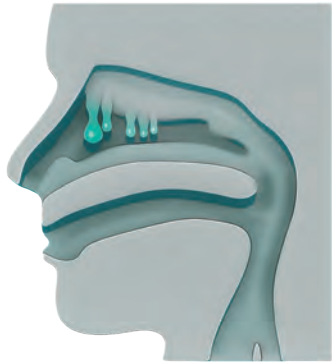
Summer 2019



**Medical Oncology
Biosimilars:
Barriers and Cost
Implications**

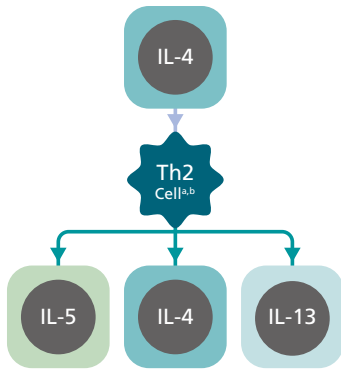
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Nasal Polypsis—A Recurring Disease



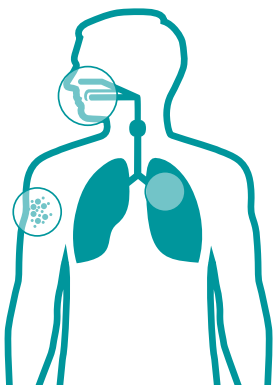
Nasal polyposis

A systemic chronic disease characterized by sinus growths and persistent debilitating symptoms that account for high health care utilization and costs^{1,2}



Type 2 inflammation^a (IL-5, IL-4, IL-13)

Plays an important role in the pathogenesis of nasal polyposis and other Type 2 conditions, such as asthma³



Common comorbidities

~**66%** Allergic rhinitis⁴

~**55%** Asthma⁴

~**16.5%** Atopic dermatitis⁵

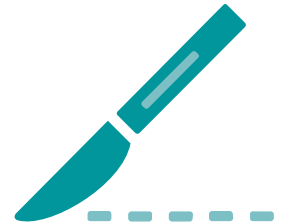
IL=interleukin.

^aType 2 inflammation describes the inflammatory pathway in which Type 2 T-helper cells, basophils, mast cells, ILC2 cells, and other immune cells contribute to the production of the inflammatory cytokines IL-4, IL-5, and IL-13;³ ^bA total of 869 patients from the Global Allergy and Asthma European Network (GA²LEN) study;⁷ ^cProspective, multicenter cohort of adult patients undergoing ESS for medically recalcitrant chronic rhinosinusitis with nasal polyps performed between August 2004 and February 2015; N=197 and N=129 at 6 and 18 months, respectively;⁶ ^dAmong 137 patients who had prior surgery for CRS with nasal polyps in the GA²LEN cohort.⁸

Despite current treatment approaches, unresolved inflammation often leads to recurring disease⁶

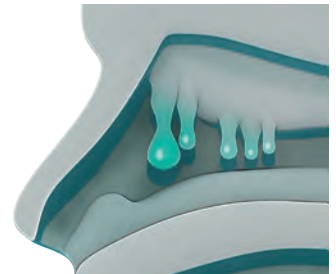
Surgery

46% of patients undergo endoscopic sinus surgery (ESS)^{7,b}



Polyp recurrence

40% of patients have recurring polyps within 18 months of ESS^{6,c}



Revision surgery

59% of patients undergo revision ESS^{8,d}



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REGENERON

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Magellan Rx Report

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A NOTE FROM OUR CMO



Dear Managed Care Colleagues,

Welcome to our summer 2019 issue of the Magellan Rx™ Report! The Food and Drug Administration (FDA) started 2019 off strong with eight novel drug approvals in the first four months. The rest of this year is likely to be busy

as well, with 50 novel drugs pending review for the remainder of 2019. Magellan Rx Management™ takes pride in preparing payers for these approvals with our MRx Pipeline. As in each Magellan Rx™ Report, we provide our readers with an up-to-date look into emerging therapies and treatment updates, as well as managed care trends and insights.

In this issue of the Magellan Rx™ Report, our cover story features an in-depth discussion of medical oncology biosimilars and associated implications in managed care. This article highlights the ways biosimilars may impact oncology management while outlining the factors influencing whether the potential cost savings associated with biosimilars will be realized.

A second feature article gives readers an update on hemophilia treatment, focusing on the economic burden of the disease and the overall impact on managed care. The article also gives an overview of the current state of hemophilia management and highlights emerging hemophilia therapies.

Showcasing a recent presentation at an Academy of Managed Care Pharmacy meeting, this issue also looks into the impact technology may have on patient engagement. With the increasing popularity of mobile devices and reliance on technology, new opportunities continue to arise to improve patient engagement and adherence through the utilization of several mobile applications and messaging.

Other timely topics featured in this issue include the Managed Care Newsstand highlighting current hot topics; an update on psoriasis treatment and management; a discussion of new noninsulin diabetes products; an exploration of strategies for managing the medical pharmacy benefit; and a spotlight on the 2018 Magellan Rx Management Medical Pharmacy Trend Report.

To learn more about Magellan Rx Management and our support of payer initiatives of the future, please feel free to contact us at MagellanRxReport@magellanhealth.com. As always, I value any feedback that you may have, and thanks for reading!

Sincerely,

A handwritten signature in black ink, appearing to read 'ccarney'.

Caroline Carney
Chief Medical Officer,
Magellan Rx Management



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MANAGED CARE NEWSSTAND

AMA Report Shows Decreases in Opioid, Increases in Naloxone Prescribing

The American Medical Association (AMA) Opioid Task Force released a report on June 5 detailing trends in addressing the opioid epidemic. The report stated opioid prescriptions were down, naloxone prescriptions were up, and the use of state prescription drug monitoring program databases have increased by 650% since 2014. The report noted very positive trends, though the epidemic remains a tremendous challenge. The task force's chair stated that "physicians must continue to demonstrate leadership." More than 70,000 people died of drug overdose last year, with two-thirds of overdoses attributed to prescription or illicit opioids, including synthetic opioids such as fentanyl.

Senate Leaders Introduce Mental Health Parity Bill

Senate Bill (S.B.) 1737 would require comparative analysis on the design and application of nonquantitative treatment limits (NQTs) between medical and surgical benefits and mental health and substance-use disorder benefits if requested by the secretary of Labor, Treasury, or Health and Human Services. In addition, the legislation directs the secretaries to select 50 random health insurance providers annually for a comparative NQTL analysis. The bill's cosponsors, U.S. Senators Bill Cassidy (R-LA) and Chris Murphy (D-CT), were cosponsors of the Mental Health Reform Act of 2016.

The legislation has the support of more than 50 organizations, including the American Psychiatric Association, the National



Dr. Sharpless stated that this guidance, along with the agency's Biosimilars Action Plan, "is building a solid regulatory foundation for the review and approval of biosimilar and interchangeable biologics designed to improve patient access to lower-cost options."

Council for Behavioral Health, the National Alliance on Mental Illness, and the Legal Action Center. S.B. 1737 comes on the heels of other mental health parity bills that were introduced in the House the week of May 20 and designed to strengthen the mental health parity law that has been in place since 1998. It is not clear if action will be taken on these bills this summer.

FDA Announces Final Guidance on Pathway for Interchangeable Biologics

On May 10, the FDA released its long-awaited final technical guidance on demonstrating interchangeability of a

biosimilar with its reference product. The final guidance overviews the core scientific considerations in demonstrating interchangeability and explains the scientific recommendations for an application or a supplement for a proposed interchangeable product. The FDA also said it plans to issue separate guidance with more detailed recommendations to support the design and evaluation of comparative analytical studies and related scientific considerations needed to support an application.

A statement issued by Acting FDA Commissioner Ned Sharpless, MD, explains the guidance is intended to help promote competition in the biologic market. Dr. Sharpless stated that this guidance, along with the agency's Biosimilars Action Plan, "is building a solid regulatory foundation for the review and approval of biosimilar and interchangeable biologics designed to improve patient access to lower-cost options." Magellan Rx Management strongly supports efforts to promote the availability of interchangeable biosimilars.

CMS Releases 2020–21 MA, Part D Drug Pricing Final Rule

On May 23, the Centers for Medicare & Medicaid Services (CMS) released the 2020–21 Medicare Advantage (MA) and Medicare Part D Drug Pricing Final Rule. Importantly, this final rule is unrelated to the pending Removal of Safe Harbor Protection for Rebates and Creation of New Safe Harbor Protection for Point-of-Sale Reductions in Price Proposed Rule, comments on which, as of June, have yet to be finalized.

In relation to the priorities raised by Magellan in our public comments (Jan. 25), CMS finalized policies relating to electronic prescribing and the real-time benefit tool (RTBT), mindful of our concerns. Notably, the agency has finalized a delayed

effective date of Jan. 1, 2021, and is providing flexibility on the choice of RTBTs. The agency did not finalize the proposals for plan flexibility to manage the protected classes of the pharmacy price concessions in the negotiated price; it did, however, codify existing policy allowing prior authorization and step therapy to be used for beneficiaries initiating new therapy for all protected-class drugs, except antiretrovirals. CMS also finalized its proposal to prohibit prescription drug plans from restricting a network pharmacy from informing enrollees about a prescription drug cash price that is below the cost sharing or negotiated price amount for the same drug under the plan.

CMS Guidance: Medicaid, CHIP-Managed Care MLR Requirements for Third-Party Vendors

On May 15, CMS issued an Informational Bulletin for states clarifying requirements for the calculation of Medicaid and Children's Health Insurance Program (CHIP) managed care organizations' (MCOs') medical loss ratios (MLRs) under the Medicaid and CHIP Managed Care Final Rule (April 25, 2016). Specifically, the guidance clarifies how the adjusted premium revenue should be calculated under the MLR requirements, including clarifying that certain amounts paid to third-party vendors be excluded from incurred claims. It also clarifies such vendors are required to provide all underlying data associated with MLR reporting to the MCO to ensure accuracy.

The guidance clarifies MLR requirements for rating periods beginning on or after July 1, 2017, for Medicaid and state fiscal years beginning on or after July 2, 2018, for CHIP. CMS will "begin working with states to conduct financial audits" to make sure MCOs are complying. The guidance is not applicable to fee-for-service contracts, such as contracts Magellan holds directly

with a country or state for administrative services.

Veterans Legislation on Suicide Prevention, Benefits Passes House

On May 22, the U.S. House of Representatives passed a package of nine veterans bills concerning VA benefits and suicide prevention. All nine bills were passed without objection. The legislation expands readjustment counseling services for returning military personnel and requires more in-depth reports of suicides on the grounds of federal facilities. The legislation also provides a yearly cost-of-living increase for veterans. It also recommends a new division to be established with the Veterans Administration involving employment and education. Currently, those efforts are within the Veterans Benefits Administration. This proposal is designed to give these issues greater focus within the department. The legislation now moves to the Senate.

ICER: Revised Protocol Assessing Prescription Drug Price Increases, Alternative Models for Rebates

The Institute for Clinical and Economic Review (ICER) published its revised protocol for conducting a new annual analysis to determine whether or not significant prescription drug price increases have been accompanied by new clinical evidence that could support those increases. The guidance was developed from a meeting with a multi-stakeholder group comprised of representatives from patient-advocacy groups, pharmaceutical companies, Medicaid, and private payers.

The draft protocol will be used to conduct Unsupported Price Increase Assessments, with the first report scheduled to be

released Oct. 8, 2019. This upcoming report will focus on at least 10 prescription drugs that have experienced the most significant price increases over the past 24 months.

ICER also published "Value, Access, and Incentives for Innovation: Policy Perspectives on Alternative Models for Pharmaceutical Rebates," in collaboration with the Office of Health Economics. The new white paper explores how reforming or eliminating prescription drug rebates may affect drug pricing, patient access, and incentives for future innovation, and is intended to help guide policymakers as they consider multiple options, including those recently proposed by the Trump administration.

The paper outlines the potential advantages and disadvantages of three alternatives to the rebate model that currently drives pharmaceutical price negotiation:

- (1) 100% pass-through (i.e., all rebates flow to plan sponsors);
- (2) point-of-sale rebates for patients (i.e., as proposed by the Trump administration); and
- (3) elimination of rebates and a move to upfront discounts.

The paper was developed following a December 2018 meeting of ICER's membership program, during which leaders from the pharmaceutical and insurance industries convened to share perspectives on rebates and possible paths forward.



Strategies for Staying Ahead of Specialty Drug Trends

Focus on the Medical Pharmacy Benefit

In an era of accelerated medical improvements and rapid drug development, it is important to develop strategies to manage trends and monitor the specialty drug pipeline. 2018 was a record-breaking year for FDA drug approvals, with the most in more than a decade.¹



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Director, Specialty Clinical
Solutions
Magellan Rx Management

Of the drugs approved, 49 were specialty products.¹ More than 50% of the newly approved specialty drugs are categorized as covered under the medical benefit. Advances in specialty drugs will, as in previous years, continue to drive up medical pharmacy spend. Unlike the real-time settlement for specialty drugs processed through pharmacy benefits, claims processed under medical benefits are delayed. Delays in claims and in Healthcare Common Procedure Coding System (HCPCS) codes for new-to-market drugs limit a health plan's ability to understand in real time the cost associated with medical benefit medications. Retrospective analysis over the past five years highlights the importance of addressing the increasing cost to the medical benefit and the managed care enterprise posed by specialty drugs.



Carly Rodriguez, PharmD
Pharmacy Director, Clinical
Innovation
Moda Health

Commercial data from 2017 reveals that 94% of total commercial drug spend is comprised of specialty drug spending on just 15% of patients.² Overall, commercial medical pharmacy spend increased 18% from \$25.49 PMPM in 2016 to \$29.97 in 2017.² Figure 1 displays the 68% overall increase in spend from 2013 to 2017. Costs for the top 10 drugs on the commercial market average \$45,000 per patient per year, with the top five spend medications being: Remicade® (infliximab), Neulasta® (pegfilgrastim), Rituxan® (rituximab), Herceptin® (trastuzumab), and Avastin® (bevacizumab). These therapies have remained the top five spend for the past nine years. Biosimilars for these products have been approved by the FDA and will likely launch in 2019. Therefore, these numbers are likely to change in upcoming years. Medicare statistics show 21% of patients drove 95% of medical pharmacy spend, and PMPM costs increased 12% from \$46.56 in 2016 to \$52.19 in 2017; see figure 2 for a 22% increase from 2013 to 2017.² This is the largest PMPM increase for Medicare within the past five years. The top 10 drugs in the Medicare population account for an average annual spend of \$11,000.² When comparing the annual trend, commercial costs were driven by larger amounts of drugs being used per patient. However, in the Medicare market, the primary driver of spend was the increased prevalence of patients using specialty drugs.

Figure 1: Commercial Medical Pharmacy PMPM Trends 2013–2017²

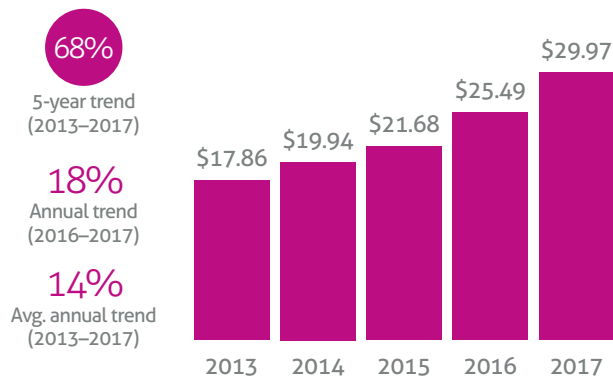
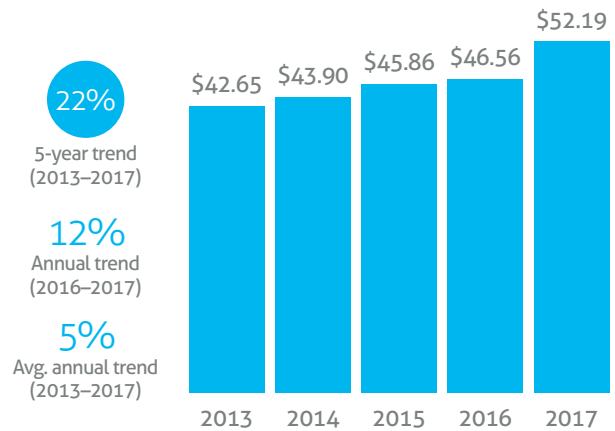


Figure 2: Medicare Medical Pharmacy PMPM Trends 2013–2017²



Addressing Medical Pharmacy Spend

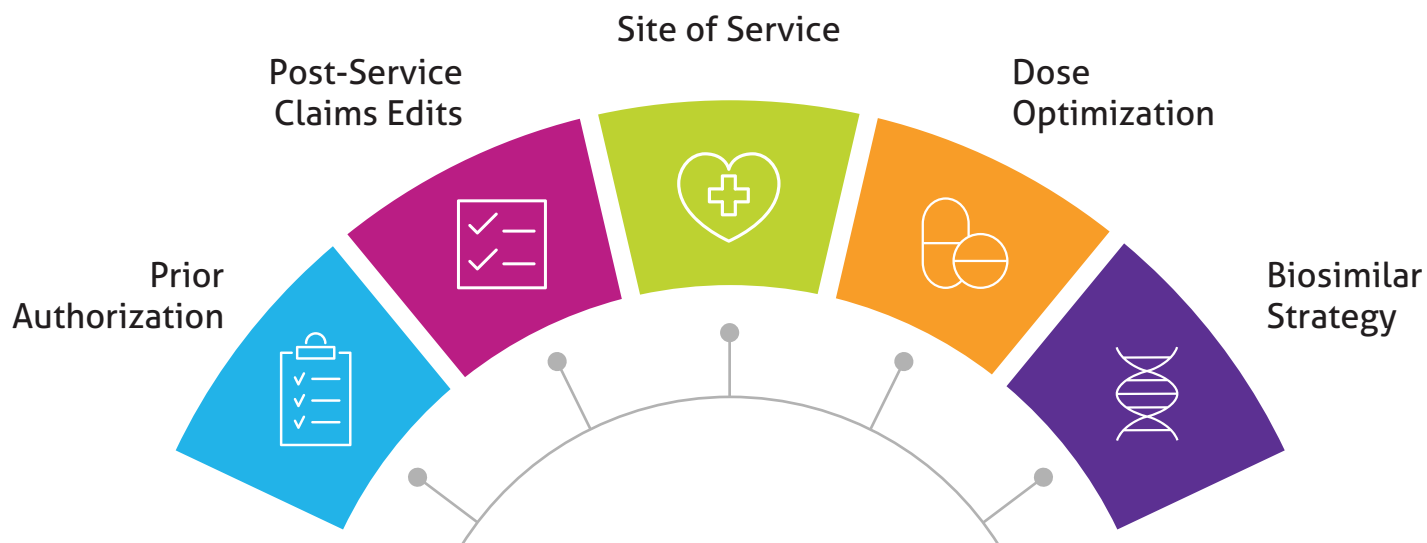
Better management of the rapid rise in medical pharmacy spend requires a multifaceted approach. Possible techniques include prior authorizations, post-service claims edits, dose optimization, encouraging biosimilar adoption, and site-of-service management. Analysis of the medical benefit cost over the past few years indicates a large variance in specialty drug expenditure based on location at which treatment was administered. For example, administering Remicade® (infliximab) costs on average \$4,645 at a physician's office, \$6,692 at home, and \$11,081 at outpatient hospital administration sites.² Similarly, administering Stelara® (ustekinumab) costs \$12,092 on average at a physician's office, \$15,564 at home, and \$31,385 at outpatient hospital administration sites.² Therefore, coordinating administration to specific sites of service can help reduce drug spend while still providing clinically appropriate access to care.

Moda, a Portland, Oregon-based health plan, uses a multifaceted approach to address increasing medical pharmacy spend. Approximately five years ago, the health plan noticed an increasing portion of outpatient expenses shifting from the pharmacy to the medical benefit. Within calendar year 2013, the company had a nearly 18% trend in medical pharmacy spend. The first step the company took to reduce cost was to implement a prior-authorization program in partnership with Magellan Rx. The pilot program started with 18 infusion medications — primarily oncology and oncology-support therapies. Since initiation, this program has expanded exponentially, growing to include more than 150 drugs. Simultaneously, a post-service claims edit program was launched. Medical drug claims were cross-referenced against authorization for diagnosis, billing units, and other factors to identify claims that did not match. After identification, these claims underwent further review and adjustment.

Following the successful implementation of these two programs, Moda started a site-of-service program in 2017. Although the development and implementation of this program proved to be labor-intensive, the effort proved to be worthwhile given the savings achieved. Claims data reviews of Moda's medical spending over 2015 and 2016 showed that when administered at a hospital outpatient infusion center, drug costs were double the cost of the same therapies administered in provider offices or by home infusion. Despite the dramatic savings associated with physician offices and home-infusion services, the overwhelming portion of utilization occurred in a hospital outpatient setting. Moda's approach to implementing a site-of-service program targeted five areas: collaborating with Magellan Rx, tracking benefit and policy updates, developing an in-scope drug list, establishing a preferred home-infusion provider while working proactively with key hospital providers, and successfully shifting members to preferred sites in order to realize savings.

Collaboration With Magellan Rx

The partnership between Moda and Magellan Rx began in the early stages of the program development. Moda had previously contracted with Magellan Rx for prior authorizations, and Magellan Rx had an established voluntary program with a team of clinicians experienced in researching and coordinating care at alternative treatment sites. With previous experience in this space and their existing framework, Magellan Rx was able to help Moda develop, implement, and administer a customized, mandatory site-of-service program.



Benefit and Policy Changes

Given the size of the health plan, Moda opted to implement a mandatory site-of-service model. Compared to voluntary programs, mandatory programs typically have upward of 75% success rates. This method allowed the company to achieve meaningful savings and a return on investment. Phase I of the program required specialty drugs to undergo a prior authorization, allowing Moda to transition patients to less costly sites of service. A 60-day waiver period helped to ensure the ease of transition and allow for the appropriate time required to identify an alternate site of service. To incentivize and mitigate potential negative member experience, the program was designed to ensure a financial benefit to members for utilizing the most cost-effective site of service, which was home infusion. In the implementation, for example, one large medical group chose a benefit design with no cost-sharing and a waived deductible in exchange for utilizing a preferred home-infusion provider. Moda also adopted a “no worse than” ideology, meaning members were exempt from the site-of-service change if it would result in a higher out-of-pocket cost for the member. Although this situation was relatively rare, it helped to alleviate negative member experience. Moda has continued to track exemptions to the site-of-service policy for future improvements in the second phase of the program.



When modeling the program’s potential savings, Moda estimated a 70% rate of shift in the site of service. Every potential member eligible for the site-of-service program was evaluated for a potential site shift, and, to date, the program has achieved an 86% overall shift rate.

Targeted Medications

Claims data identified high-spend infusion drugs with cost variation based on site of service. Once a drug was identified, all similar drugs within the category were included to remove unintended incentives for prescriber product selection. For instance, all biologics for autoimmune conditions, such as rheumatoid arthritis, Crohn's disease, and psoriasis, were included. A market scan ensured all medications included within the scope of the program could be delivered by home-infusion providers. The initial list included 25 medications for treatment of autoimmune diseases, enzyme replacement, amyotrophic lateral sclerosis, immunodeficiencies, and human immunodeficiency virus. All oncology medications were intentionally excluded in the initial program. As the programs develop and gain experience, oncology medications may be added as appropriate. Currently, this program includes 30 medications and is expected to continue to grow.

Preferred Provider Relationship

Prior to 2017, Moda did not have a preferred home-infusion provider, and the company had more than 20 home-infusion providers billing for services. After identifying a preferred home-infusion provider, members were guided through the Magellan Rx infusion-referral center. Moda also focused on key hospital-provider partnerships with risk-sharing arrangements and value-based payment models to provide proactive communication. Working alongside these partners, Moda aimed to mitigate the impact to stakeholders through the program design when possible. Moda was able to negotiate favorable reimbursement rates with hospital partners who have their own home infusion and ambulatory infusion services in exchange for allowing referrals to remain within the hospital system instead of shifting them to an independent infusion provider.

Results

Moda's site-of-service program launched in October 2017. When modeling the program's potential savings, Moda estimated a 70% rate of shift in the site of service. Every potential member eligible for the site-of-service program was evaluated for a potential site shift, and, to date, the program has achieved an 86% overall shift rate. Additionally, the program is maintaining a shift rate greater than 80% each quarter. To date, the company has been able to outperform initial projections. Prior to implementing the plan, Moda had \$17.4 million in combined hospital outpatient and non hospital specialty-drug-administration spend.

One year post-implementation, the program was able to reduce the total cost associated with purchasing and administering these medications to \$14.9 million by shifting the site of service. The total annual cost was reduced by just under \$3 million even while increasing the number of members treated by 30%.

Keys to Success and Moving Forward

In developing a plan for the site-of-service program, Moda's success was dependent on several key factors. The first was proper development of benefit design. The second was the plan's ability to align member incentives to reward the utilization of the most cost-effective yet clinically appropriate location. The third was provider education regarding the program and the reasons for implementation. This involvement allowed providers to identify and address concerns they had with the program and ultimately lead to creative solutions while achieving lower costs and allowing them to retain members within their system. Finally, the identification of a preferred home-infusion provider for the program was a crucial factor. These strategies have helped Moda, in partnership with Magellan Rx, to begin to address the rising cost of specialty spend. Clearly, this trend has created a need for proper, effective medical pharmacy management. In the face of an ever-growing number of emerging specialty therapies, payers may have to reevaluate and explore new avenues to approaching management of these costs.

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Medical Oncology Biosimilars

Barriers and Cost Implications

As reported in the summer 2018 issue of the Magellan Rx Report, biologic agents are the fastest growing class of therapeutics and a major driver behind the rising costs associated with prescription drugs.¹ While some biologics are self-administered injections, a large percentage are administered in the outpatient setting by a healthcare professional.



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Development
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As such, most biologics are commonly billed under the medical benefit for commercially insured patients and under Medicare Part B for Medicare members. The Centers for Medicare & Medicaid Services (CMS) recently updated its drug-spending dashboard. According to these figures, drugs billed under the Medicare Part B medical benefit totaled \$30.4 billion in spend in 2017.²

Since the creation of the Biologics Price Competition and Innovation (BCPI) Act in 2009, the healthcare industry has eagerly anticipated the price relief expected from the introduction of biosimilar competition.³ To date, that price relief has been very slow to materialize. While the Food and Drug Administration (FDA) has approved 18 biosimilars as of April 2019, less than half of those products have been commercially launched, and those that have launched are encountering a variety of barriers to uptake.

Many of the current biologic agents, as well as those in the pipeline, are utilized for the treatment of cancer. A review of the cancer literature reveals two simultaneous realities. First, the overall cancer death rate in the U.S. has dropped by 27% over the time period of 1991 to 2016.⁴ While this decline in cancer mortality is primarily the result of advances in cancer prevention, such as drastically reduced tobacco usage and improvements in cancer screening, advances due to innovative drug therapies have also contributed to the reduction in cancer fatalities. The second reality is the introduction of the term “financial toxicity” into the lexicon of medical literature. Out-of-pocket costs associated with cancer care have been associated with personal bankruptcy, reduced access to care, and financial distress for many patients.⁵



According to national sales data, the highest expenditure of antineoplastic agents administered in hospital outpatient departments and clinics from 2011 to 2016 were rituximab, bevacizumab, and trastuzumab.

Cost Impact of Oncology Biosimilars

According to national sales data, the highest expenditure of antineoplastic agents administered in hospital outpatient departments and clinics from 2011 to 2016 were rituximab, bevacizumab, and trastuzumab.⁶ Although more recent data reveal that the checkpoint inhibitors (e.g. nivolumab and pembrolizumab) have taken over some of the top expenditure spots, rituximab, bevacizumab, and trastuzumab are still in the top 10 drugs by expenditure for Medicare Part B. These three drugs accounted for \$3.6 billion in Medicare spend in 2017.² Excitement about the potential savings opportunities with these drugs are growing, as all three of these agents currently have at least one FDA-approved biosimilar waiting to be launched.

The launch dates for these three biosimilars (rituximab, bevacizumab, and trastuzumab) are currently unknown due to sealed legal agreements dictating these terms; however, launch is widely speculated to occur for all three of these products sometime in 2019. Rituximab and bevacizumab currently each have one FDA-approved biosimilar and trastuzumab currently has five, with the most recent having been approved in June 2019. Based on historical data regarding previous biosimilar launches in the U.S., it is anticipated these biosimilars will come to market with a minimum 15% discount off current prices for their respective reference biologics.⁷ With a Medicare Part B spend in 2017 of \$3.6 billion, this represents the theoretical potential for more than \$500 million in Medicare savings annually — but will this potential be realized? Several factors may contribute to answering this question. Along with the overarching issue of provider comfort level and willingness to utilize biosimilars, other circumstances that may impact the realization of savings potential include practical implications associated with biologic naming conventions,

indication extrapolation issues, individual institutional policies, and reimbursement structures. Each of these factors will be considered below.

Biologic Naming Conventions

The FDA recently retracted its original proposed strategy with regard to biologic naming conventions. In January 2017, the FDA published a guidance document regarding nonproprietary naming of biological products. This document stated that all biologics, including originator biologics, related biological products, and biosimilar products would be required to add a four-letter distinguishing suffix to their core nonproprietary name. At that time, the FDA stated that the purpose of the distinguishing suffixes was to advance the goal of patient safety by allowing more accurate tracking of individual products for the purposes of pharmacovigilance and to “avoid inaccurate perceptions of the safety and effectiveness of biological products based on their licensure pathway.”⁸

In March 2019, the FDA released an update to this guidance stating that the FDA no longer intends to require modification of the nonproprietary name for biologics that have already been licensed and approved. Among the reasons cited by the FDA for this decision were the “substantial costs” that would be associated with changing the name of existing, approved biologics. This decision was met with some dissatisfaction from biosimilar proponents who believe it will hinder biosimilar uptake. However, the FDA asserted that they “aim to mitigate the risk of false perceptions from healthcare providers and patients that there [is] a difference in the relative safety and effectiveness of these biological products based on their name.”⁹ Another consideration with regard to naming of biologic products is its impact on how medications will be listed in electronic medical record order sets and how that may potentially drive provider selection of product.

Indication Extrapolation

Another factor impacting the cost-savings potential of the therapeutic oncology biosimilars is the issue of indication extrapolation. According to the biosimilar approval pathway, at least one comparative clinical trial in a representative patient population is recommended. The concept of extrapolation supports the approval of the biosimilar for additional indications already in place for the reference biologic. Extrapolation to additional indications is not automatic and is considered by the FDA on a case-by-case basis subject to the availability of sufficient scientific justification for each indication. In some situations, however, the originator biologic may have patent-exclusivity rights to a particular indication, such as orphan drug designation exclusivity. In these situations, a biosimilar may not receive approval for that particular indication regardless of the scientific evidence. This caveat prevented Mvasi (bevacizumab-awwb) from being granted the indication for treatment of ovarian cancer due to exclusivity rights of Avastin® (bevacizumab) for this indication.

The lack of complete duplication of indications between the originator biologic and the biosimilar is sometimes referred to as a “skinny label.” A skinny label may also be driven by a biosimilar manufacturer’s decision to seek a limited number of indications with the hope of being able to launch their product sooner. Biosimilar Truxima (rituximab-abbs) is an example of a skinny label where the manufacturer (Celltrion/Teva) elected to seek approval for only three of Rituxan®’s (rituximab) approved indications.¹⁰ For trastuzumab, the indication extrapolation is different based on the four different approved biosimilars. For example, three of the four products are labeled with all of the same indications as the originator product, Herceptin®, while one product, Herzuma (trastuzumab-pkrb) does not carry identical indications and lacks the indication for use in gastric cancer.^{11, 12, 13, 14}

Individual Institutional Policies

On May 10, the FDA issued the final guidance document regarding establishment of interchangeability. To date, no biosimilar manufacturers have attempted to achieve an interchangeability designation. While interchangeability will be determined by the FDA at the federal level and substitution policies will be determined by the states, individual institutional pharmacy and therapeutics (P&T) committees will also have a role in determining how biosimilar substitution is handled within organizations. It is possible that institutional P&T committees may elect to implement an overall strategic policy for adding biosimilars to the formulary and address global therapeutic interchange policies for the institution that would have a direct impact on biosimilar utilization within the institution.

Reimbursement Structures

Based on the 2009 BPCI Act, the FDA is charged with establishing the regulatory framework to ensure rigorous evaluation regarding issues of both safety and efficacy of biosimilars.³ While sustained post marketing evidence will likely be necessary to increase both provider and patient confidence over time, the FDA approval of biosimilars is ultimately an indicator of equal safety and efficacy between the originator biologic and the biosimilar. Based on a long-standing principle of formulary management, if equal efficacy and safety have been established, then comparisons between the costs of the products becomes a valid consideration for drug utilization.

Establishing reimbursement structures for biosimilars has been a moving target to date. The CMS originally proposed that all biosimilars for a given product would share the same reimburse-

ment code — the Healthcare Common Procedure Coding System (HCPCS). This proposal was widely seen as a disincentive for the continued investment in developing biosimilars, since this could lead to a “race to the bottom” in price, potentially making it difficult for manufacturers to recoup their investment for developing and bringing a biosimilar to market. In response, the CMS issued a guidance in January 2018 stating that all approved biosimilars will receive a unique HCPCS code.¹⁵ In addition to this policy reversal, the CMS has taken other concrete steps to support a favorable Medicare reimbursement structure for biosimilars to incentivize uptake.

One such step is that all biosimilars, not just the first approved biosimilar for a reference product, will be eligible for pass-through status for 340B institutions. With the 2018 change in 340B reimbursement rules, originator biologics will be reimbursed at ASP minus 22.5%, while all newly approved biosimilars with pass-through status will be reimbursed at ASP plus 6% of the reference biologic for a maximum of three years.¹⁶

In addition, beginning in 2019, Medicare Advantage Plans are now allowed to implement step-therapy programs for drugs reimbursed under Medicare Part B. This means health plans administering the Medicare Advantage benefit have the option to institute step-therapy requirements mandating the use of a biosimilar prior to use of the originator biologic.¹⁷

On the other hand, commercial payers will also need to determine how they will handle biosimilar reimbursement. One strategy that has been discussed includes a “fixed” reimbursement for all products, including both the originator biologic and all approved biosimilar versions of the product. Another way to think of this pric-



ing structure is to establish a maximum allowable cost (MAC) for the entire group of products, and providers would be able to choose whichever product they prefer. With a set reimbursement rate, the provider would be financially incentivized to utilize the product that can be purchased at the lowest cost in a buy-and-bill system.

Other ideas include differential reimbursement, wherein a higher markup margin is paid for the biosimilar products compared to the reference biologic.¹⁸ There are potential pitfalls with either of these systems, and incorporation of differential reimbursement percentages may erode cost savings for payers. Additionally, an ideal reimbursement policy would also ensure out-of-pocket savings for patients when utilizing biosimilars.

Impact on Managed Care

The savings anticipated with biosimilars have not yet been fully realized. In 2019, the first oncology-therapeutic biosimilars will likely be launched. These three biologics, rituximab, bevacizumab, and trastuzumab, currently account for billions of dollars of annual spend and are among the top drug expenditures in the U.S. health system. The availability of FDA-approved biosimilars for these three products represents an unprecedented opportunity for cost savings. These cost savings would not only benefit the U.S. healthcare system overall but could also provide financial incentives for private payers, providers, and patients. Numerous factors will determine if all stakeholders are able to realize the cost savings offered by the introduction of these therapeutic-oncology biosimilars.

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Psoriasis Update

Current Management Landscape and Access to Therapy

Psoriasis vulgaris is a common chronic, inflammatory skin disease characterized by red plaques with silvery scale. It most commonly affects the scalp, knees, elbows, and presacral region; however, any area of the skin may be affected.¹



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The severity of disease is partially defined by the total body surface area (BSA) impacted; mild disease impacts <3% BSA, moderate disease impacts 3% to 10% BSA, and severe disease impacts >10% BSA.¹ Disease severity may also be defined by other factors, such as the emotional consequences of disease or the location in which it occurs. For example, psoriasis may be considered severe if it involves the hands, feet, scalp, face, or genital area, or when it causes persistent pruritis. The Psoriasis Area Severity Index (PASI) is a scale used to quantify the extent and severity of disease, taking into consideration the total BSA affected as well as the intensity of symptoms of redness, scaling, and plaque thickness. A PASI score of 0 indicates no disease, while a score of 72 indicates the greatest severity of disease. While the PASI scale is commonly used in clinical trials to monitor response to therapy or assess disease severity, it is not generally used in clinical practice.¹

Psoriasis presents in both children and adults, affecting approximately 3.2% of the overall population.² While there are approximately 5 million adults diagnosed in the U.S., recent estimates suggest that somewhere between 0.4% and 2.28% of affected adults with psoriasis are undiagnosed.² The incidence of psoriasis appears to be rising gradually; one retrospective study reported that the incidence of psoriasis almost doubled from 50.8 cases per 100,000 between 1970 and 1974 to 100.5 cases per 100,000 between 1995 and 1999.³ The increase may be attributed to genetic and environmental triggers, as well as lifestyle changes. There is also speculation that increasing prevalence could be related to lower response rates or development of resistance to currently available treatment options.^{3, 4}

While psoriasis is most commonly associated with the hallmark skin lesions, it is a chronic, multisystem inflammatory disorder that follows a relapsing pattern of disease that can significantly impact quality of life.¹ Approximately 25% to 30% of patients with psoriasis develop psoriatic arthritis, an inflammatory arthritis characterized by joint pain, stiffness, and swelling. Psoriatic arthritis can affect any part of the body and, like psoriasis, follows a relapsing pattern of disease.⁵

Table 1: Biologic Agents for the Treatment of Psoriasis^{1, 8-19}

Brand (Generic)	Mechanism of Action	Maintenance Dose & Route of Administration	FDA Approval for Psoriasis	Maintenance Therapy Cost Per Month*
Humira® (adalimumab)	Anti-TNF	40 mg subcutaneous injection every 2 weeks	January 2008	40 mg/0.8 mL: WAC: \$5,174 AWP: \$6,209 ASP: (J1035 x 2): \$3,637
Enbrel® (etanercept)	Anti-TNF	50 mg subcutaneous injection once per week	April 2004	50 mg/1 mL: WAC: \$5,174 AWP: \$6,209 ASP: (J1438 x 2): \$3,294
Remicade® (infliximab)	Anti-TNF	5 mg/kg IV infusion administered every 8 weeks**	September 2006	350 mg*** (4 x 100 mg): WAC: \$2,336 AWP: \$2,803 ASP: (J1745 x 40): \$1,299
Cimzia® (certolizumab pegol)	Anti-TNF	200–400 mg every other week (weight-based dosing)	May 2018	400 mg (2 x 200 mg/1 mL): WAC: \$8,655 AWP: \$10,386 ASP: (J0717 x 400): \$6,506
Stelara® (ustekinumab)	Anti-IL-12/IL-23 (binds p40 subunit)	45–90 mg administered subcutaneously every 12 weeks (weight-based dosing)	September 2009	90 mg/1 mL: WAC: \$7,335 AWP: \$8,802 ASP: (J3357 x 90): \$5,721
Cosentyx® (secukinumab)	Anti-IL-17A	300 mg subcutaneous injection every 4 weeks	January 2015	300 mg (2 x 150 mg/1 mL): WAC: \$10,358 AWP: \$12,429 ASP: N/A
Taltz® (ixekizumab)	Anti-IL-17A	80 mg subcutaneous injection every 4 weeks	March 2016	80 mg/1 mL: WAC: \$5,368 AWP: \$6,442 ASP: N/A
Siliq (brodalumab)	Anti-IL-17 receptor	210 mg subcutaneous injection every 2 weeks	February 2017	210 mg/1.5 mL: WAC: \$3,500 AWP: \$4,200 ASP: N/A
Tremfya® (guselkumab)	Anti-IL-23 (binds p19 subunit)	100 mg subcutaneous injection every 8 weeks	July 2017	100 mg/1 mL: WAC: \$5,430 AWP: \$6,516 ASP: N/A
Ilumya™ (tildrakizumab)	Anti-IL-23 (binds p19 subunit)	100 mg administered subcutaneously every 12 weeks	March 2018	100 mg/1 mL: WAC: \$4,418 AWP: \$5,302 ASP: (J3245 x 100): \$4,229

Abbreviations: ASP = average sales price; AWP = average wholesale price; IL = interleukin; IV = intravenous; TNF = tumor necrosis factor; WAC = wholesale acquisition cost

*Prices updated as of June 17, 2019. Source: Medi-Span Price Rx Pro. ASP not available for drugs that do not yet have a J-Code assigned.

**Time interval can be modified and dose per kg can be increased according to the patient's response.

***70 kg patient weight utilized to calculate dose; Remicade® pricing accounted for 4 x 100 mg vials and included 50 mg wastage (70 kg x 5 mg/kg = 350 mg dose + 50 mg wasted = 400 mg = 4 vials)

Current Treatment Guidelines

The majority of patients with mild to moderate psoriasis are able to manage their disease with topical medications, such as corticosteroids, emollients, vitamin D analogs, tar, and topical retinoids.^{1, 6} For the face or other sensitive areas, steroid-sparing options, including tacrolimus or pimecrolimus, may be preferred. UVB phototherapy may also be used for refractory disease, alone or in combination with topical therapy.⁶

Topical therapy, with or without phototherapy, may be inadequate for the management of patients with moderate to severe psoriasis,^{6, 7} who will likely require systemic therapy, such as retinoids, methotrexate, cyclosporine, apremilast, or biologic agents if they fail to respond to systemic therapies alone. Biologic therapies commonly used in the management of psoriasis fall into two categories, including the anti-tumor necrosis factor (TNF) agents and the anti-interleukin (IL) agents.^{6, 7} Biologic agents for the treatment of psoriasis can be found in Table 1.

The American Academy of Dermatology updated its psoriasis treatment guidelines in February 2019 (Table 2).¹ While these updated guidelines outline the clinical evidence and treatment considerations for use of biologics in psoriasis, an important addition to this iteration is a comprehensive discussion of the comorbidities associated with psoriasis. As previously mentioned, while psoriasis is primarily known for its hallmark inflammatory skin manifestations, the disease is also associated with comorbidities such as psoriatic arthritis, cardiovascular disease, and Crohn's disease.¹ Of note, patients with psoriasis are also at a greater risk of metabolic syndrome, diabetes, and cancer.¹ Additionally, psoriasis can have a profound impact on quality of life, putting patients at an increased risk of anxiety and depression.²⁰ The updated guidelines provide recommendations on how providers can better educate patients about their condition and other diseases to which they may be more vulnerable.^{1, 20}

Table 2: Key Guideline Recommendations from the American Academy of Dermatology¹

Brand (Generic)	Recommendation (Strength)*	Clinical Evidence
TNF Inhibitors		
Humira® (adalimumab)	<ul style="list-style-type: none"> • Monotherapy in moderate to severe disease (A) • Monotherapy in moderate to severe disease affecting palms and soles (A) • Monotherapy in moderate to severe disease affecting nails (A) • Monotherapy in moderate to severe disease affecting scalp (B) • Monotherapy in other subtypes (pustular or erythrodermic) of moderate to severe plaque psoriasis (B) • Monotherapy in psoriasis of any severity when significant psoriatic arthritis is present (A) 	<ul style="list-style-type: none"> • Multiple studies comparing adalimumab to placebo, methotrexate, and other biologics have established efficacy in moderate to severe disease. • PASI75 achieved in 71% of patients receiving adalimumab at week 16 (versus 7% with placebo). • PASI90 achieved in 45% of patients receiving adalimumab at week 16 (versus 2% with placebo). • Head-to-head comparison with guselkumab in VOYAGE1 and VOYAGE2 studies: More patients achieved both PASI75 and PASI90 with guselkumab than with adalimumab. In VOYAGE2, at week 16, rates of PASI90 were 70% and 46.8% for guselkumab and adalimumab, respectively. • Efficacy-limiting immunogenicity may occur; coadministration with methotrexate may reduce immunogenicity. • Definitive response to treatment best assessed after 12 to 16 weeks.
Enbrel® (etanercept)	<ul style="list-style-type: none"> • Monotherapy in moderate to severe disease (A) • Monotherapy in moderate to severe disease affecting scalp and nails (A) • Monotherapy in other subtypes (pustular or erythrodermic) of moderate to severe plaque psoriasis (B) • Monotherapy in psoriasis of any severity when significant psoriatic arthritis is present (A) 	<ul style="list-style-type: none"> • Multiple studies comparing etanercept to placebo, methotrexate, and other biologics have established efficacy in moderate to severe disease. • PASI75 achieved in 49% of patients receiving etanercept 50 mg twice weekly at week 12 (versus 3% with placebo; p<0.05). • Definitive response to treatment best assessed after 12 to 16 weeks.
Remicade® (infliximab)	<ul style="list-style-type: none"> • Monotherapy in moderate to severe disease (A) • Monotherapy in moderate to severe disease affecting palms and soles (B) • Monotherapy in moderate to severe disease affecting scalp and nails (B) • Monotherapy in other subtypes (pustular or erythrodermic) of moderate to severe plaque psoriasis (C) • Monotherapy in psoriasis of any severity when significant psoriatic arthritis is present; infliximab also inhibits radiographically detected damage of joints (A) 	<ul style="list-style-type: none"> • Multiple studies comparing infliximab to placebo, methotrexate, and other biologics have established efficacy in moderate to severe disease. • PASI75 achieved in 75.5% of patients receiving infliximab 5 mg/kg at week 10 (versus 1.9% with placebo; p<0.001). • PASI90 achieved in 45.2% of patients receiving infliximab 5 mg/kg at week 10 (versus 0.5% with placebo; p<0.001). • Substantial risk of development of antibodies to infliximab, resulting in loss of clinical response. Addition of methotrexate to infliximab should be strongly considered for all patients to reduce immunogenicity of infliximab. • Infusion reactions may occur; administration of acetaminophen, hydroxyzine, ranitidine, and methylprednisolone immediately prior to administration may reduce risk and prolong drug survival. • Definitive response to treatment best assessed after 8 to 10 weeks.

Table 2: Key Guideline Recommendations from the American Academy of Dermatology¹ (cont.)

Cimzia® (certolizumab pegol)	<ul style="list-style-type: none"> • Treatment option in adults with severe plaque psoriasis who have failed to respond to, or are unsuitable for, other systemic treatments • Additional treatment option for women before or during pregnancy and while breastfeeding²³ 	<ul style="list-style-type: none"> • Several clinical studies demonstrated efficacy in plaque psoriasis. • PASI75 achieved in 83% of patients receiving certolizumab 400 mg every other week at week 12 (versus 7% with placebo; p<0.001). • Likely to have similar class characteristics as other TNF inhibitors regarding treatment combination, efficacy in difficult-to-treat areas, and possibly immunogenicity (no data on these topics currently available). • Definitive response to treatment best assessed after 12 to 16 weeks.
IL Inhibitors		
Stelara® (ustekinumab)	<ul style="list-style-type: none"> • Monotherapy in moderate to severe disease (A) • Monotherapy in moderate to severe disease affecting palms and soles (B) • Monotherapy in moderate to severe disease affecting nails (B) • Monotherapy in moderate to severe disease affecting scalp (C) • Monotherapy in other subtypes (palmoplantar, pustular, or erythrodermic) of moderate to severe plaque psoriasis (C) • Monotherapy in psoriasis of any severity when significant psoriatic arthritis is present (A) 	<ul style="list-style-type: none"> • Multiple studies comparing ustekinumab to placebo and other biologics have established efficacy in moderate to severe disease. • PASI75 achieved in 66.7 to 67.1% of patients receiving ustekinumab 45 mg at week 12 (versus 3.7% with placebo). • Head-to-head comparison with secukinumab 300 mg in CLEAR study: More patients achieved PASI90 with secukinumab than with ustekinumab. At week 16, rates of PASI90 were 79% and 57.6% for secukinumab and ustekinumab, respectively. • Head-to-head comparison with ixekizumab in IXORA-S study: More patients achieved PASI90 with ixekizumab than with ustekinumab. At week 12, rates of PASI90 were 72.8% and 42.2% for ixekizumab and ustekinumab, respectively. • Efficacy-limiting immunogenicity may occur. • Definitive response to treatment best assessed after 12 weeks.
Cosentyx® (secukinumab)	<ul style="list-style-type: none"> • Monotherapy in moderate to severe disease (A) • Monotherapy in moderate to severe disease affecting the head and neck, including scalp (B) • Monotherapy in moderate to severe disease affecting nails (A) • Monotherapy in moderate to severe palmoplantar plaque psoriasis (A) • Monotherapy in moderate to severe palmoplantar pustulosis (B) • Monotherapy in erythrodermic psoriasis (C) • Monotherapy in plaque psoriasis when associated with psoriatic arthritis (A) 	<ul style="list-style-type: none"> • Several clinical studies demonstrated efficacy in plaque psoriasis. • PASI75 achieved in 77.1 to 81.6% of patients receiving secukinumab 300 mg at week 12 (versus 4.5 to 4.9% with placebo; p<0.001). • Head-to-head comparison with etanercept in FIXTURE study: More patients achieved PASI75 with secukinumab than with etanercept. At week 12, rates of PASI75 were 77.1% and 44% for secukinumab 300 mg and etanercept, respectively. • Neutralizing anti-drug antibodies are rare and not associated with loss of efficacy. • Definitive response to treatment best assessed after 12 weeks.

Table 2: Key Guideline Recommendations from the American Academy of Dermatology¹ (cont.)

Taltz® (ixekizumab)	<ul style="list-style-type: none"> • Monotherapy in moderate to severe disease (A) • Monotherapy in moderate to severe disease affecting scalp (B) • Monotherapy in erythrodermic psoriasis (B) • Monotherapy in moderate to severe disease affecting nails (B) • Monotherapy in generalized pustular psoriasis (B) • Monotherapy in plaque psoriasis when associated with psoriatic arthritis (A) 	<ul style="list-style-type: none"> • Several clinical studies demonstrated efficacy in plaque psoriasis. • PASI75 achieved in 84.2% of patients receiving ixekizumab at week 12 (versus 53.4% with etanercept and 7.3% with placebo). • PASI90 achieved in 65.3% of patients receiving ixekizumab (versus 25.7% with etanercept and 3.1% with placebo). • Definitive response to treatment best assessed after 12 weeks.
Siliq™ (brodalumab)	<ul style="list-style-type: none"> • Monotherapy in moderate to severe disease (A) • Monotherapy in generalized pustular psoriasis (B) 	<ul style="list-style-type: none"> • Several clinical studies demonstrated efficacy in plaque psoriasis. • PASI75 achieved by 67% to 86% of patients receiving brodalumab 210 mg at week 12 (versus 6% to 8% with placebo; p<0.001). • Head-to-head comparison with ustekinumab in AMAGINE-2 and AMAGINE-3 studies: More patients achieved PASI90 with brodalumab than with ustekinumab. <ul style="list-style-type: none"> ◦ AMAGINE-2: At week 12, rates of PASI90 were 70% and 47% for brodalumab 210 mg and ustekinumab, respectively. ◦ AMAGINE-3: At week 12, rates of PASI90 were 69% and 48% for brodalumab 210 mg and ustekinumab, respectively. • Presence of antidrug antibodies has been demonstrated; no neutralizing antibodies detected. • Black box warning for suicidal ideation/completed suicides. Brodalumab can be prescribed only through restricted REMS program.
Tremfya® (guselkumab)	<ul style="list-style-type: none"> • Monotherapy in moderate to severe disease (A) • Monotherapy in scalp, nail, and plaque-type palmoplantar psoriasis (A) 	<ul style="list-style-type: none"> • Several clinical studies demonstrated efficacy in plaque psoriasis compared to placebo and active comparator up to 52 weeks. • PASI90 achieved by 70% of patients receiving guselkumab at week 16 (versus 46.8% with adalimumab and 2.4% with placebo). • Nonresponders to adalimumab who switched to guselkumab: PASI90 achieved by 66.1% of patients receiving guselkumab at week 48. • Presence of antidrug antibodies has been demonstrated; neutralizing antibodies have been found. Antibodies not generally associated with changes in clinical response. • Definitive response to treatment best assessed after 12 weeks.
Ilumya™ (tildrakizumab)	<ul style="list-style-type: none"> • Monotherapy in moderate to severe disease (A) 	<ul style="list-style-type: none"> • Several clinical studies demonstrated efficacy in plaque psoriasis. • PASI75 achieved in 66% of patients receiving tildrakizumab 200 mg at week 12 (versus 48% with etanercept and 6% with placebo). • PASI90 achieved in 37% of patients receiving tildrakizumab 200 mg (versus 21% with etanercept and 1% with placebo). • Neutralizing antidrug antibodies associated with reduced efficacy have been reported. • Definitive response to treatment best assessed after 12 weeks.

*Key guideline recommendations, not all-inclusive

Abbreviations: REMS = Risk Evaluation and Mitigation Strategy

Definitions: PASI75 = 75% improvement in PASI score; PASI90 = 90% improvement in PASI score; PASI100 = 100% improvement in PASI score

Agents in Development

The updated guidelines also highlight an investigational monoclonal antibody, risankizumab, that is currently being reviewed by the FDA for the treatment of moderate to severe plaque psoriasis.^{1, 21} Risankizumab subsequently received FDA approval for this indication on April 23, 2019. Of note, risankizumab has the same mechanism of action as Tremfya® (guselkumab) and Ilumya™ (tildrakizumab), which exert their effect by selectively inhibiting the p19 subunit of IL-23. Risankizumab has demonstrated efficacy across several Phase II and Phase III trials.²¹ In a Phase II controlled trial (n=166), patients were randomized to treatment with subcutaneous risankizumab, administered according to one of three possible regimens (a single 18-mg dose at week 0; 90-mg doses at weeks 0, 4, and 16; or 180-mg doses at weeks 0, 4, and 16), or ustekinumab (45-mg doses for body weight ≤100 kg or 90-mg doses for body weight >100 kg at weeks 0, 4, and 16).²¹ At week 12, 77% of patients receiving any regimen of risankizumab achieved PASI90 compared to 40% of patients treated with ustekinumab (p<0.001). Furthermore, 45% of patients receiving either the 90-mg or 180-mg regimen of risankizumab achieved PASI100, compared to 18% of patients treated with ustekinumab.²¹ Market analysts predict that risankizumab may become the best in class for psoriasis due to impressive PASI90 data, as well as a regimen that allows for dosing every 12 weeks.²²

Trends in Clinical Practice

As the treatment guidelines clearly illustrate, the treatment landscape for psoriasis is extremely crowded when it comes to biologic options.¹ Given the numerous therapeutic options, treatment selection is increasingly based on patient-specific factors, such as patient preference, convenience, and out-of-pocket costs, as well as the safety profile of the biologic. To differentiate a new product in a crowded field, manufacturers are raising the therapeutic bar and evaluating their product's efficacy in terms of PASI90 as a gold standard instead of PASI75, the measurement that has historically been used in clinical trials. This trend highlights the significant advancements that have been made in the treatment of psoriasis since the first biologic was approved for this indication in 2004.^{1, 8-17} In addition, there have been head-to-head comparisons among the biologic products in clinical trials, which help providers and payers make well-supported, evidence-based decisions in terms of selecting a treatment option for a specific patient or creating drug-management strategies for a health plan.^{1, 8-17} Furthermore, increased competition in this therapeutic area may ultimately lead to cost savings for payers, as they may opt to implement formulary strategies that include selection of preferred products.

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Spotlight

2018 Magellan Rx Management Medical Pharmacy Trend Report

The Magellan Rx Management Medical Pharmacy Trend Report is an annually published resource highlighting medical drug trend and analytics. The Trend Report includes primary and secondary analyses of provider-administered drugs, which are infused or injected and paid under the medical benefit.



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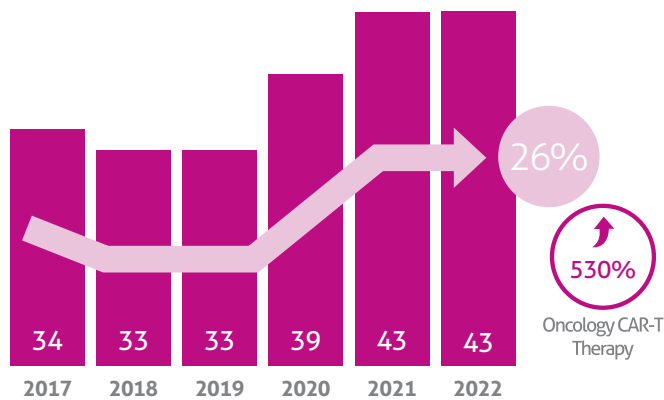
The data comprise the results from Magellan Rx's 2018 survey, including responses from 45 commercial and Medicare Advantage payers representing more than 105 million lives across the country. Results also include health plan paid-claims data analyses across commercial and Medicare Advantage payers, as well as the Medicaid line of business, which is new to the 2018 Report.

The Trend Report includes medical benefit utilization and trend data for 1,065 Healthcare Common Procedure Coding System (HCPCS) codes across outpatient sites of service, including the physician office, home, and hospital outpatient facility. This represented an increase of 140 HCPCS codes from the previous Report, demonstrating the rapid growth in classified drugs managed on the medical benefit. Of note, 2017 is the most recent calendar year analyzed due to the lag associated with medical benefit claims data in terms of allowing adequate time for claims run-out, and thus ensure that finalized claims are included in the analysis and publication. New to the Trend Report in 2018 are forecasting results for seven high-impact disease categories that were determined to show potential growth within the category over the next five years.

2018 Key Trends: Medical Benefit Billion-Dollar Drugs, 2017–2022

The number of drugs with projected annual sales of more than a billion dollars, or billion-dollar drugs, is projected to grow 26% from 34 in 2017 to 43 by 2022 (Figure 1). All 43 of these projected billion-dollar drugs are currently available on the market today, and increased utilization and growth in expenditures on these products is anticipated. This projection highlights the need for proper utilization management, targeted dosing optimization, and other management tactics for these high-cost medical specialty drugs, which will help promote quality of care and prudent savings of healthcare dollars.

Figure 1: 2018 Key Trends
Medical Benefit Billion-Dollar Drugs, 2017–2022



Source: 2018 Magellan Rx Management Medical Pharmacy Trend Report, 9th Edition

The differences in PMPM spend and trends between the lines of business is largely attributed to differences in unit costs and site-of-service combinations based on differences in reimbursement methodologies, such as hospital outpatient reimbursement based on percent of billed charges versus other standard percent markup strategies in physician office and home infusion.

Percentage of Drug Spend

Medical pharmacy continues to be driven by low-volume, high-cost specialty medications, with almost all of medical pharmacy spend attributed to specialty drug costs across lines of business. The Trend Report highlights that 15% of patients drove 94% of the PMPM spend in commercial; 21% drove 95% in Medicare; and 14% drove 91% in Medicaid. All lines of business played out a similar story of a small percentage of patients driving the majority of spend for drugs on the medical benefit. Spend in medical pharmacy is also very concentrated in a few products, with the top 50 medical pharmacy drugs making up 75% of spend in the commercial segment; up to 80% in Medicaid; and 84% in Medicare.

2018 Key Trends: Oncology CAR-T Therapy

Trend Report forecasting projected growth of chimeric antigen receptor T-cell (CAR-T) therapies of 530% from 2017 to 2022 (Figure 1). This represents an increase from \$0.10 per member per month (PMPM) in 2017 to \$0.63 PMPM by 2022. Just more than 75% of that growth is due to agents available on the market today. We project these currently available CAR-T therapies to gain spend and utilization, making it especially important to manage them appropriately given these are typically administered within the hospital inpatient setting.

Medical Benefit Drug Trend Highlights

PMPM by Line of Business

The Trend Report explores medical pharmacy PMPM spend and trend for the past five years for commercial, Medicare, and Medicaid lines of business. The total PMPM spend for the commercial line of business in 2017 was \$29.97, with the annual trend at 18% and the average annual trend for the past five years at 14%. The overall five-year trend for commercial business is 68%, representing tremendous growth. Medicare PMPM spend is higher than commercial, at \$52.19, likely due to the older population it serves, with a slightly lower annual trend, at 12%, and a significantly lower five-year trend, at 22%. The Medicaid line of business displayed a similar five-year trend to Medicare, at 17%, but a much lower PMPM spend, at \$8.29, likely due to the Medicaid population skewing younger and greater utilization of lower-cost products such as infused antibiotics, injectable steroids, and contraceptives.

Category Profile Highlights: Oncology

The Trend Report details seven categories with forecasting models to show their potential growth, taking into consideration the drugs in the current pipeline. Full profiles for all categories can be found in the full Trend Report.



The Trend Report details seven categories with forecasting models to show their potential growth, taking into consideration the drugs in the current pipeline. Full profiles for all categories can be found in the full Trend Report.

Figure 2: Oncology Category Profile

2017 CATEGORY PMPM



\$10.12

COMMERCIAL

\$24.25

MEDICARE

\$2.87

MEDICAID

UPCOMING BIOSIMILARS
Rituxan, Herceptin,
Avastin

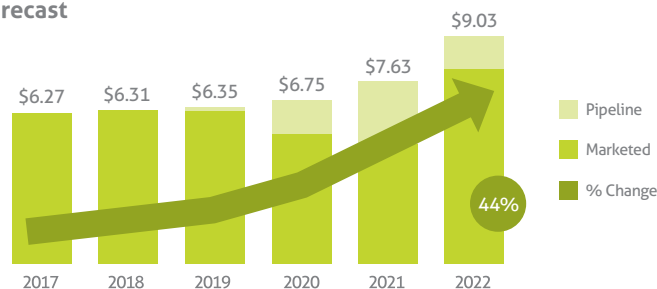
TOP 5 FOR COMMERCIAL
TOP 10 FOR MEDICARE
TOP 15 FOR MEDICAID

Avastin Cost
Per Claim

\$2,034
PHYSICIAN

\$7,794
HOSPITAL OP

Forecast



Source: 2018 Magellan Rx Management Medical Pharmacy Trend Report, 9th Edition

The Trend Report presents oncology as the category with the highest spend. Oncology agents make up 34% of the total medical pharmacy spend for commercial, 46% for Medicare, and 35% for Medicaid (Figure 2). The Trend Report outlines the variation in members utilizing oncology agents: 1.7 per 1,000 in commercial, 8 per 1,000 in Medicare, and 0.6 per 1,000 in Medicaid. The disparities illustrate the variation in utilization among the lines of business and the resulting differences in PMPM. Oncology PMPM spend was \$10.12 in commercial, \$24.25 in Medicare, and \$2.87 in Medicaid. Forecasting for the oncology category shows a projected growth rate of 44% by 2022, with increased utilization and expanded indications for new products along with the pipeline of new agents. Figure 2 shows highlights of the oncology category, illustrating a small sample of the type of profile that can be found in the full Trend Report.



[The Trend Report] features insights from 45 U.S. payers representing more than 105 million medical pharmacy lives; 33 of these payers managed Medicare Advantage as well as commercial populations.

Medical Benefit Drug Management Survey Highlights

The Trend Report highlights results from a payer survey conducted annually during summer. It features insights from 45 U.S. payers representing more than 105 million medical pharmacy lives; 33 of these payers managed Medicare Advantage as well as commercial populations. The respondent sample was split with 53% representing smaller plans (covering fewer than 1 mil-

lion lives) and 47% representing larger plans (covering more than 1 million lives). Survey participants represented all major lines of business: commercial, Medicare Advantage, managed Medicaid, and health insurance exchanges.

Survey Responses: Site-of-Service Programs

Site-of-service (SOS) programs are intended to direct members to the lowest-cost site of drug administration. In most circumstances, this is the physician's office, since hospital outpatient centers may be two to four times the cost in comparison, depending on the drug and regimen. Commercial payers find high levels of success with SOS programs; more than 67% of commercial payers with these programs report an average savings of 61%. Payers have been slower to adopt SOS programs for Medicare members; little more than a third have an SOS strategy, and 25% of those have experienced average savings of only 5%. Medicare may be a difficult population in which to implement this type of program due to the unique rules the program has around offering patient choices, as well as the strict turnaround times for coverage determinations and the Centers for Medicare & Medicaid Services' well-known discouragement of edits in Medicare Advantage.

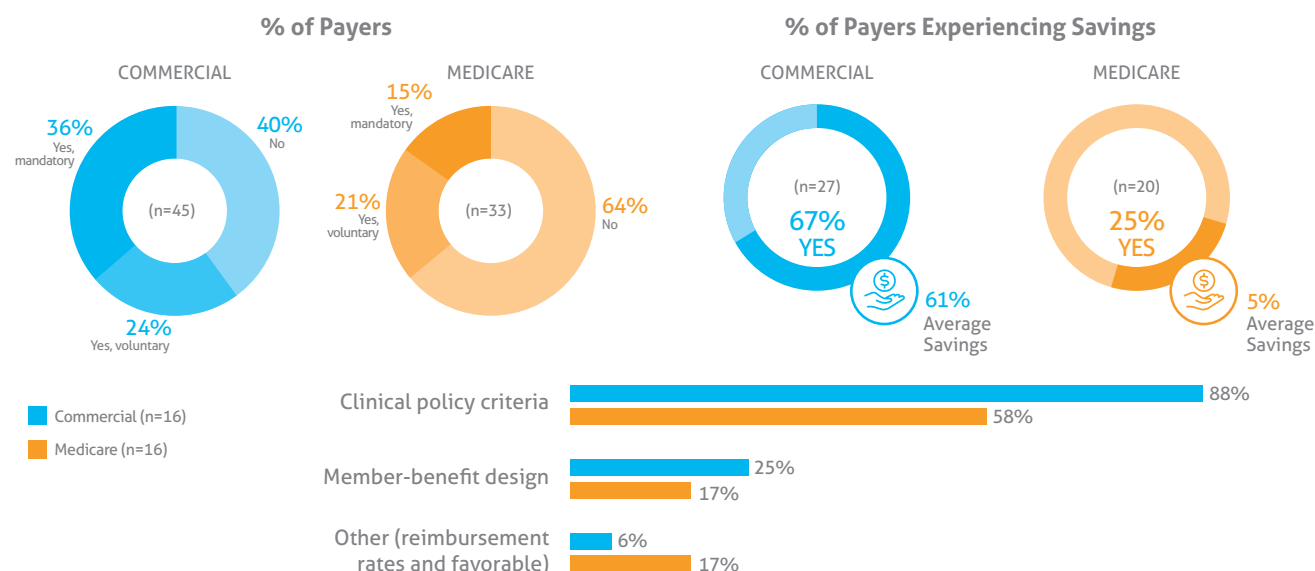
Payers most often executed their SOS program through criteria embedded in their clinical policy. A quarter of commercial payers and 17% of Medicare payers include the SOS program in their member-benefit design. A small group of commercial payers encourage use of their SOS program through favorable reimbursement rates, available when medical-benefit drugs are administered through the lowest cost of SOS.

Figure 3 illustrates some of the detailed breakdown of medical-benefit drug-management survey responses relating to SOS programs. Much more detail and additional approaches to medical benefit drug management can be found in the full Trend Report.

Where to Find the Trend Report

The information discussed here can be found along with a wealth of other valuable insights, data, and resources in the full Magellan Rx Management Medical Pharmacy Trend Report, 9th Edition. Access the annual Trend Reports at: <https://www1.magellanrx.com/magellan-rx/publications/medical-pharmacy-trend-report.aspx>.

Figure 3: Payer Survey — Site-of-Service Programs



Source: 2018 Magellan Rx Management Medical Pharmacy Trend Report, 9th Edition



Treatment Update: Hemophilia

Hemophilia is a rare, monogenic, X-linked, recessive bleeding disorder that affects approximately 20,000 individuals in the U.S.¹ The two most common subtypes, hemophilia A and B, are associated with deficiencies in coagulation factors VIII and IX, respectively, that occur due to mutations in the clotting factor genes.



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Disorders Institute

As a result of this disruption in the clotting cascade, individuals with hemophilia experience uncontrolled bleeding episodes. Hemophilia A is the most common subtype, accounting for approximately 80% to 85% of those impacted by hemophilia.²

The severity of disease correlates to the degree of clotting-factor deficiency. Individuals with >5% to <40% of normal clotting factor typically have mild symptoms, and severe bleeding episodes may only occur with major trauma or surgery.² Individuals with ≥1% to 5% of normal clotting factor may have moderate symptoms, with periodic spontaneous episodes and prolonged bleeding after minor trauma or surgery. Individuals who experience the most severe symptoms are those with <1% of normal clotting factor. At this level of disease severity, spontaneous bleeding into the joints and muscles may occur without trauma or provocation at a frequency of approximately four to five bleeds per month. Such bleeding episodes typically affect weight-bearing joints, including the knees and ankles, and may ultimately lead to the development of painful and debilitating hemophilic arthropathy.²⁻⁴ In addition, individuals with the most severe form of hemophilia are at increased risk for life-threatening bleeds, including intracranial hemorrhage. To reduce the risk of morbidity and mortality, patients with hemophilia are generally managed with clotting-factor concentrates to replace their missing clotting factor, both in the acute treatment setting as well as prophylactically.^{3,4}

In the current era, the most severe treatment-related complication in hemophilia is the development of inhibitors in the form of IgG antibodies that neutralize clotting factors.² When a patient develops inhibitors, the anticipated recovery and half-life of the clotting-factor concentrate are severely diminished. As a result, treatment with clotting-factor concentrate becomes very challenging, and patients may require significantly higher doses or alternative agents.²

Inhibitors occur more commonly in hemophilia A, with a cumulative incidence of 20% to 30% in severe hemophilia and 5% to 10% in mild or moderate hemophilia.² The incidence of inhibitors is much lower in hemophilia B, occurring in less than 5% of patients. The risk of developing inhibitors in persons with severe hemophilia is greatest during the first 20 exposure days to the factor.⁵ In severe hemophilia A, the median age of inhibitor development is three years, while in mild to moderate disease, the median age is approximately 30 years and commonly coincides with the intensive factor-concentrate exposure that occurs with surgery. In severe disease, inhibitors do not alter the site, frequency, or severity of bleeding; however, inhibitors may neutralize endogenous factor in patients with mild to moderate disease, effectively changing the hemophilia of these individuals to severe disease.²

Economic Burden

Unfortunately, hemophilia is a chronic condition for which there is currently no cure, so patients will require prophylactic treatment with exogenous clotting-factor concentrates indefinitely.² The cost of factor replacement is substantial and varies from patient to patient based on considerations such as disease severity, the patient's weight, whether or not they have inhibitors, and frequency of bleeding events. The total healthcare resource utilization associated with the management of hemophilia is significant; in addition to the supplementation of clotting factor, patients also generally require more office visits, hospitalizations, medical procedures, and laboratory testing compared to individuals without hemophilia.²⁻⁴ Some studies have estimated that the average annual cost of managing a patient with hemophilia in the U.S. is approximately \$140,000 to \$155,000.^{3, 4, 6} Furthermore, the management of patients who develop inhibitors is estimated to be up to five times greater than those who have not developed inhibitors. Patients with inhibitors are at a twofold greater risk of hospitalization due to bleeding complications, and their exogenous factor concentrate consumption may also be significantly higher. In addition to requiring higher doses of factor concentrate, these patients usually also require bypassing agents or immune-tolerance-induction therapy. It is estimated that the annual cost of managing a patient with inhibitors ranges from \$697,000 to more than \$1 million.^{3, 4, 6}

In addition to the staggering direct costs associated with this chronic disease, patients with hemophilia and their caregivers experience significant lost productivity due to complications of their disease, including bleeding events and hospitalizations, which result in absences from school or work.³ The Hemophilia Experiences, Results, and Opportunities (HERO) initiative was



The total healthcare resource utilization associated with the management of hemophilia is significant; in addition to the supplementation of clotting factor, patients also generally require more office visits, hospitalizations, medical procedures, and laboratory testing compared to individuals without hemophilia.

created to enhance understanding and awareness surrounding the psychosocial issues faced by individuals with hemophilia. This study indicated that among the patients with hemophilia who were surveyed, 80% (n=537) reported some negative impact (ranging from very large to small) of their disease on their employment. Furthermore, 40% (n=243) indicated that they selected their job based on their healthcare needs. For parents of children with hemophilia, the majority of respondents (63%; n=351) reported that having a child with hemophilia negatively impacted their employment.³

Treatment of Hemophilia: Past, Present, and Future

The World Federation of Hemophilia treatment guidelines state that the primary goal of treatment is to prevent and treat bleeding episodes with the deficient clotting factor using the appropriate exogenous factor concentrate whenever possible.² Patients with

moderate disease who maintain clotting factor levels >1 IU/dL experience infrequent spontaneous bleeds and better preservation of joint function. Even if clotting factor levels cannot be consistently maintained at >1 IU/dL, prophylaxis has still been demonstrated to be beneficial.²

The treatment of choice for hemophilia is replacement of clotting factor with factor VIII concentrate in hemophilia A and factor IX concentrate in hemophilia B.² There are currently many factor-replacement products on the market (37 in the U.S.), and they are all generally effective. As such, the selection of a factor-replacement product is based on the safety and purity of the product, the risk of developing inhibitors, the pharmacokinetic properties, and cost. Factor concentrate products with a longer half-life are generally preferred, as they allow for less frequent administration, reducing the risk of catheter-associated complications.²

Substitutive Therapy

In November 2017, the Food and Drug Administration (FDA) approved Roche's Hemlibra (emicizumab-kxwh), a bispecific monoclonal antibody indicated for routine prophylaxis to prevent or reduce the occurrence of bleeding episodes in adult and pediatric patients (newborn and older) with hemophilia A with inhibitors.⁷ Subsequently, in October 2018, the FDA granted the additional indication of treatment of hemophilia A, regardless of inhibitor status.⁸ Emicizumab-kxwh exerts its pharmacologic effect by bridging activated factor IX and factor X, allowing the coagulation cascade to continue and restoring hemostasis. It is administered subcutaneously and has multiple dosing options, including once weekly, every two weeks, or every four weeks, depending on the dose. Emicizumab-kxwh is designed to be used in place of exogenous factor concentrate and to bypass agents for bleeding prevention; however, factor VIII or factor VIII bypassing agents may be needed during the first week of emicizumab-kxwh prophylaxis thereafter.^{7,8}

The initial FDA approval of emicizumab-kxwh was based on two clinical trials, including one trial in adults and adolescents with severe hemophilia A and inhibitors (HAVEN 1) and another trial in pediatric patients with severe hemophilia A and inhibitors (HAVEN 2).⁹ In HAVEN 1, patients receiving prophylaxis with emicizumab-kxwh experienced an annualized bleeding rate (ABR) requiring treatment with coagulation factor of 2.9 compared to 23.3 in patients not receiving prophylaxis, yielding an ABR reduction of 87%.^{7,9} In the pediatric population enrolled in HAVEN 2, 94.7% of patients (n=54) had no bleeds warranting treatment at the data cutoff. Investigators were able to monitor bleeds in patients treated with emicizumab-kxwh. Of 23 patients who were



The World Federation of Hemophilia treatment guidelines state that the primary goal of treatment is to prevent and treat bleeding episodes with the deficient clotting factor using the appropriate exogenous factor concentrate whenever possible.

treated for at least 12 weeks (median 38.1 weeks), 87% had no bleeding events (ABR 0.2 events).¹⁰ Within the total study population of 57 patients, three bleeds occurred and were treated; one in a joint, one in a muscle, and one in a hip.¹⁰

The expanded indication for emicizumab-kxwh was based on the results of HAVEN 3 and HAVEN 4.⁸ HAVEN 3 enrolled adults and adolescents 12 years of age and older with hemophilia A without inhibitors. Patients who received emicizumab-kxwh once weekly or every two weeks experienced 96% and 97% reductions in treated bleeds, respectively, compared to patients who received no prophylaxis (95% confidence interval [CI], 92.5 to 98.0; $P<0.0001$ and 95% CI, 93.4 to 98.3; $P<0.0001$, respectively).⁸ In an intra-patient comparison of patients who previously received factor VIII-prophylaxis in a noninterventional study and switched to emicizumab-kxwh (n=48), prophylaxis with emicizumab-kxwh resulted in a statistically significant reduction of 68% in treated bleeds (95% CI, 48.6 to 80.5; $P<0.0001$); of note, not all patients were on the same factor VIII-prophylaxis schedule, thus making the factor VIII-prophylaxis portion of the study not entirely prospective. The HAVEN 3 trial results suggested that emicizumab was at least as effective as factor VIII prophylaxis in the prevention of bleeding events in persons with severe hemophilia A.⁸

Though emicizumab-kxwh may offer a novel treatment option that eliminates the need for venous access for prophylactic care, there are some safety concerns associated with it. As of March 2019, there have been a total of 10 deaths reported in emicizumab-kxwh clinical trials, expanded access, compassionate use, and the post-marketing setting.¹² The causes of death included rectal hemorrhage, sepsis, intracranial hemorrhage, pre-existing pseudotumor associated with severe hemophilia A, cecal perforation, sudden cardiac death, and traumatic head injury. It should be noted that in each case, the cause of death was determined to be unrelated to emicizumab-kxwh.¹¹ As of March 2019, 2,500 patients have received emicizumab-kxwh worldwide in the clinical trial, expanded access, compassionate use, and post-marketing settings.^{11, 12} Of these patients, more than 20 have had thrombotic complications, including a few with thrombotic microangiopathies, and at least three have developed drug-neutralizing antibodies (ADAs) to emicizumab.^{11, 12}

Hemostatic Rebalancing Therapies

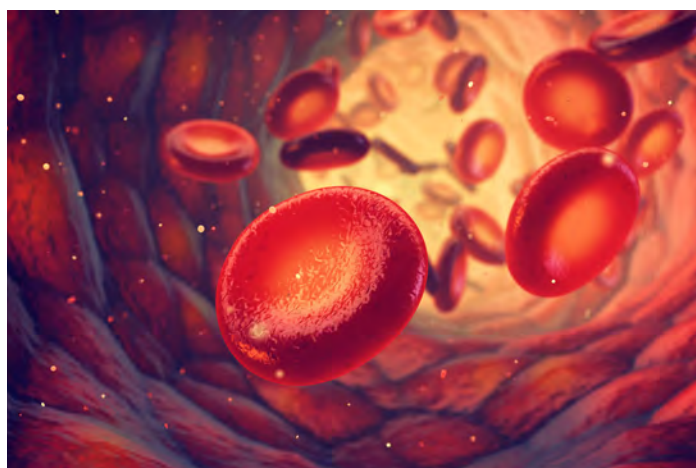
Fitusiran (Alnylam) is a ribonucleic acid (RNA) interference (RNAi) therapeutic that targets antithrombin in the liver.¹³ Fitusiran interferes with antithrombin translation by binding to and degrading antithrombin messenger-RNA, effectively silencing antithrombin gene expression and preventing antithrombin synthesis. Given its unique mechanism of action, fitusiran has the potential to promote hemostasis and prevent bleeding events in patients with hemophilia A or B.¹³ In early clinical trials, a monthly subcutaneous administration of fitusiran 80 mg was associated with mean maximum antithrombin lowering of 87%.¹³ In September 2017, the FDA placed a clinical hold on the clinical-development program of fitusiran after a patient with hemophilia A died of swelling in the brain due to a thrombotic event in the phase II trial. The hold was subsequently lifted by the FDA in December 2017 after better risk-mitigation strategies were incorporated into the trial's protocol.¹⁴ Currently, the ATLAS phase III clinical trial is ongoing, and it includes three separate trials that will enroll patients with hemophilia A and B, with or without inhibitors, as well as patients receiving prophylactic therapy.¹⁴

Concizumab (Novo Nordisk) is an investigational monoclonal antibody that inhibits tissue-factor pathway inhibitor (TFPI).¹⁵ TFPI is critical in controlling the tissue-factor-associated procoagulant response. Antibodies to TFPI have been shown to shorten clotting times and have enhanced the generation of both factor Xa and thrombin. Concizumab exerts its pharmacologic effect by binding TFPI via the Kunitz 2 domain, which prevents the interaction of TFPI with the factor Xa-active site. It can be administered intravenously or subcutaneously and has demonstrated a favorable

safety profile, as well as concentration-dependent procoagulant effects in phase I trials.¹⁵ Concizumab, given subcutaneously once daily, is currently being evaluated in the ongoing EXPLORER clinical program, which includes patients with hemophilia A and B with or without inhibitors.^{15, 16}

Gene Therapy

There are currently several gene therapies in Phase I/II and Phase III development for the treatment of hemophilia. Valoctocogene roxaparvovec (BioMarin) is an investigational gene therapy that uses an adeno-associated virus (AAV)-factor VIII vector to deliver the missing gene needed to produce factor VIII.¹⁷ As such, valoctocogene roxaparvovec has the potential to cure the clinical manifestations of hemophilia A and eliminate the need for ongoing treatment with factor-replacement products.¹⁷ In May 2018, BioMarin announced updated results from a phase I/II trial of valoctocogene roxaparvovec, which included 104 weeks of data for patients that received the higher dose of the gene therapy.¹⁸ According to the press release, patients on the higher dose experienced a 97% reduction in mean ABR, and most patients no longer required their preventative-factor replacement. Furthermore, in the first year of treatment with valoctocogene roxaparvovec, 71% of patients experienced no bleeds at all, compared to just 14% at enrollment.¹⁸ At year two, 86% of patients had experienced no bleeds. Of note, median factor VIII levels appear to plateau in year two; however, the data indicates that factor VIII levels did remain in normal range.^{18, 19} BioMarin announced that they plan to file for FDA approval in the second half of 2019 based on the data from the ongoing Phase I/II trial.²⁰



SPK-8011 (Spark Therapeutics) is an investigational gene therapy that utilizes a recombinant AAV (rAAV) vector to deliver the missing gene needed to produce factor VIII.²¹ Similar to valoctocogene roxaparvovec, one-time administration of SPK-8011 has the



There are currently several gene therapies in Phase I/II and Phase III development for the treatment of hemophilia.

potential to cure hemophilia A. The safety and efficacy of SPK-8011 are currently being evaluated in an ongoing Phase I/II study. As of February 2019, the first 12 study participants had each received one of three doses.²¹ The investigators reported that no factor VIII-neutralizing antibodies developed, and the gene therapy appeared to be safe and well tolerated. In terms of efficacy, a 94% reduction in bleeds and a 95% reduction in exogenous factor replacement were observed across all three doses four weeks post-administration.²¹ Of the seven patients who received the highest dose, five patients achieved stable factor VIII levels four weeks post-administration. These five patients did not experience any bleeding events during 46 weeks of follow-up and experienced a 99% reduction in exogenous factor replacement. Additional data from the ongoing trial is anticipated in mid-2019.²¹

Additional gene therapies currently in development include, among others, SPK-8016 (Spark Therapeutics), which is currently being studied in an ongoing Phase I/II trial that will enroll patients with hemophilia A with inhibitors, SPK-9001 (Pfizer/Spark Therapeutics), which is currently being studied in an ongoing phase II trial of patients with hemophilia B,²¹ and AMT-061, uniQure's (QURE) gene therapy candidate, in an open-label Phase 2b clinical trial evaluating patients with severe and moderately severe hemophilia B.^{21, 22} Early clinical data for SPK-9001 demonstrated a 98% reduction in ABR in patients with hemophilia B.²¹

Implications for Managed Care

While exogenous factor replacement has been the mainstay of therapy since it revolutionized the treatment of hemophilia in the 1970s, the treatment landscape is currently undergoing dramatic


changes due to advances in RNAi and gene therapy.²³ While these innovative new treatment approaches may significantly improve or even cure hemophilia, several unanswered questions remain. Arguably, the most significant concern for payers will be the high cost of these novel therapies. While we will likely have to wait until the FDA approval of fitusiran to know how much it will cost, we may be able to learn from the recent FDA approval of another RNAi therapeutic from the same company. Alnylam's Onpattro (patisiran) was approved in August 2018 for the treatment of polyneuropathy caused by hereditary transthyretin-mediated (hATTR) amyloidosis. It is important to note that patisiran's indication is an ultra-rare orphan disease that is unrelated to hemophilia.²⁴ Of note, the American Journal of Managed Care and Specialty Pharmacy blog reports that Alnylam has been working with commercial insurance plans to offer value-based contracts for patisiran, in which the level of reimbursement will be tied to patient outcomes. Given the high potential cost as well as the size of the potential treatment pool of fitusiran, payers will likely be very interested in similar value-based agreements.

Gene therapy that offers a cure for hemophilia has the potential to change the paradigm of hemophilia management; however, questions regarding the durability of effect remain. When establishing a list price for a curative gene therapy, manufacturers will likely take into consideration the cost of managing an individual patient over their lifetime. Given the precedent set by the first FDA-approved gene therapy that came to market with a \$850,000 price tag, some analysts predict that a gene therapy for hemophilia could cost upward of \$1.5 million.²⁵ Given the uncertainty surrounding the durability of effect with valoctocogene roxaparvovec, value-based contracts that would make payment contingent on long-term efficacy may be an attractive option for payers. In addition, gene therapy poses a unique challenge in that it has an extremely high, one-time cost, rather than a high cost spread out over months or years. Payers and manufacturers may consider alternative payment models, to ensure that these groundbreaking therapies are available to the patients who need them.²⁶

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Leveraging Technology to Improve Medication Adherence and Optimize Health Outcomes



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Benefits and Deficiencies of Traditional Patient Management Strategies

Medication adherence has been, and continues to be, one of the most important barriers to address in healthcare. Nonadherence is estimated to account for half of all treatment failures nationwide, 125,000 deaths annually, and nearly \$300 billion a year in costs to the U.S. healthcare system in additional doctor visits, emergency department visits, and hospitalizations.¹ A growing body of evidence shows that improved medication adherence can lead to better clinical outcomes and reduce overall cost of care in many disease categories.² As effective but costly new therapies get introduced, ensuring the success of treatment outcomes and justifying the associated costs require addressing the issue of low adherence to therapy.

Managed care organizations (MCOs) often implement patient-management programs to promote better adherence in targeted populations. These programs frequently focus on patient and/or provider outreach via traditional means of communication — telephone, fax, and mailings (Table 1). While these strategies can be effective, using only these communication modalities can present challenges. Limitations include availability of human resources, time constraints, and changes in the ways people communicate with one another. Collectively, these factors can impact a program's ability to engage members.³

New approaches to improving patient engagement that harness advances in technology are being explored. For example, given that there are now more mobile devices on the planet than human beings, smart devices offer a widely-accessible means of delivering patient education.^{4,5} Tools such as text messaging, live videoconferencing, video on demand, personalized learning modules, and artificial intelligence can also be utilized to reach patients through the convenience of their personal mobile

Table 1: Reach and Engagement Rates Per Modality

Modality	Reach Rates	Engagement Rates
Telephonic	45–65%	23–38%
Lettering Campaigns	97–99%	1–3%
Faxing Campaigns	25–35%	5–8%
Interactive Voice Response	85–99%	2–15%

Source: 2018 Magellan Rx Management Medical Pharmacy Trend Report, 9th Edition

device. These technological advancements have the potential to improve patient engagement and communication. However, questions around cost, patient and payer acceptance, privacy protection, usability, and the ability to positively impact health outcomes and reduce healthcare costs require careful assessment of these modes of communication. MCOs can benefit from familiarization with the opportunities and challenges offered by alternative methods of patient education and, when appropriate, consider integrating these solutions into their larger patient-management strategies. When evaluating such programs, it is imperative for plans to develop a method for measuring the impact of any new approaches to engagement on clinical outcomes, as well as to assess the feasibility of integrating these programs into the existing health system infrastructure.

Various Technological Advances and Their Place in Improving Health Outcomes

As availability of wearable technology increases and tech manufacturers begin to pair up with data and healthcare firms, there is an increasing focus on utilizing such wearable devices to communicate with patients. Estimates suggest that roughly two-thirds of the world's population are unique subscribers to mobile technology. The growth in utilization and availability of wearable technologies and mobile devices in the U.S. (Figure 1) suggests the U.S. healthcare system may represent a prime environment for utilizing these technologies to enhance healthcare.⁶

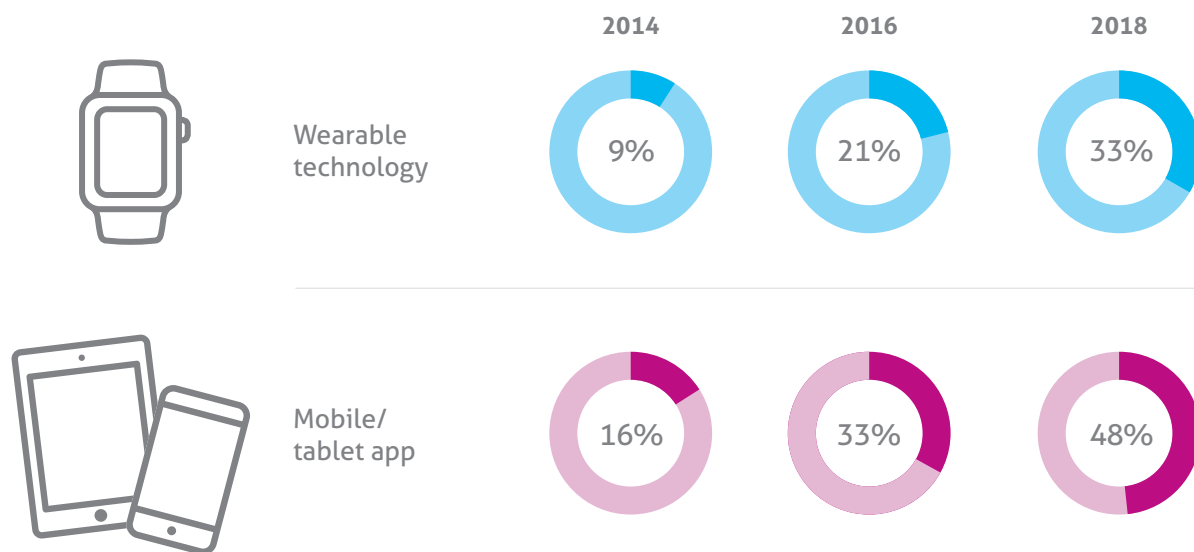
With a population of 83.1 million, millennials now represent the largest segment of the U.S. population.⁷ Many healthcare providers believe that millennials as patients cannot be handled in the same manner as previous generations.⁸ Comparing millennials to their older counterparts, survey results show that

59% of 65- to 69-year-olds own smartphones and only 49% do among 70- to 74-year-olds.⁹ However, there is a sense among healthcare innovators that new approaches will be needed to reach and retain these highly-coveted millennial consumers. One strategy that is drawing attention is the use of digital communication, which may include a variety of technologies.



As availability of wearable technology increases and tech manufacturers begin to pair up with data and healthcare firms, there is an increasing focus on utilizing these devices to communicate with patients.

Figure 1: Utilization and Availability of Wearable Technologies and Mobile Devices⁸



Text Messages

More than 300,000 text messages are sent every second in the U.S.¹⁰ Statistics have shown that 95% of all text messages are read within three minutes of being sent, and the average response time to a text message lands somewhere around 90 seconds.¹⁰ Consumer surveys have shown that text messaging is not only the most frequent activity performed on smartphones but is generally preferred over face-to-face communication.¹¹

A review of studies that focused on the use of short messaging service (SMS) to deliver appointment reminders and compliance-related messages showed that, from the perspective of both providers and patients, these approaches were widely accepted as effective.¹² Just as provider offices frequently ask patients for preferred methods of contact, health plans and patient programs may do the same. Consideration of resources required to develop, implement, and maintain such programs would, of course, be necessary.

If implemented with appropriate privacy protections, text messaging can also provide a gateway for interactive question-and-answer exchanges that could be used to collect patient informa-

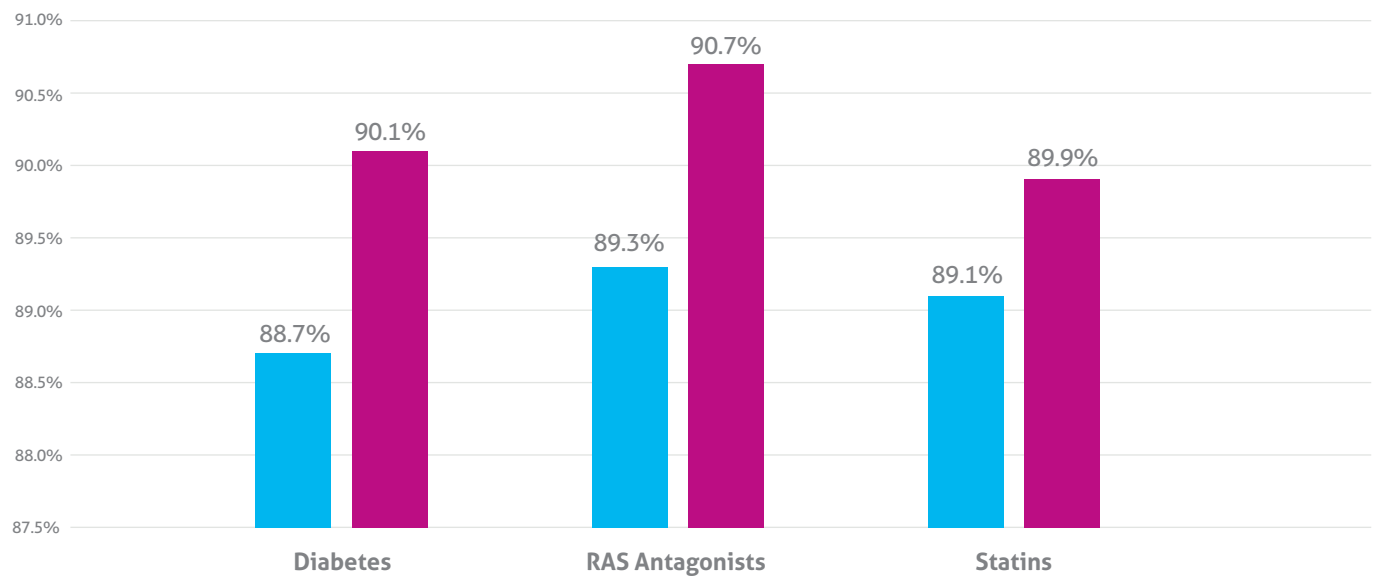
tion quickly and relay it to providers. Setting up a pathway to deliver targeted messages to the broader population will open more possibilities for incorporating personalization for each patient. Basing messages in free text or operating live chats with health-care practitioners can allow for tailored interactions with a patient and move exchanges beyond simple, one-size-fits-all, automatic replies.

Videoconferencing

Those patients who may not prefer text messaging as a means of communication need not be excluded from using advanced technologies. Online video capabilities, for example, allow for face-to-face counseling between clinicians and patients.

Video calls combine videoconferencing, online meetings, and mobile collaboration into one platform. This tool allows for personalized and more meaningful patient engagement, enables clinicians to pick up on cues that cannot be captured over the phone, supports visual monitoring of side-effect symptoms, and

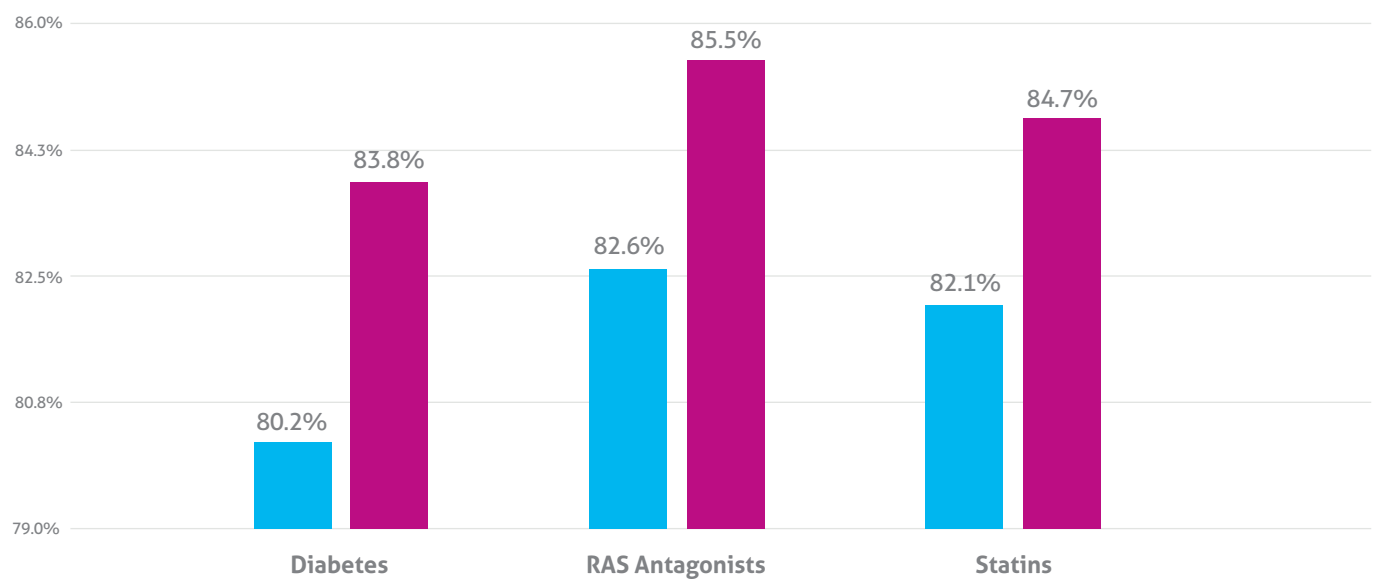
Figure 2: Results — Proportion of Days Covered (PDC)



Source: MRx internal Data, 2017–2018

Control Intervention

Figure 3: Results — Proportion of Members with PDC ≥80%



Source: MRx internal Data, 2017–2018

Control Intervention



There are numerous services, including cloud-based telehealth services, currently available based around the idea of allowing a physician, physician's assistant, or nurse practitioner to conduct consultations and examinations of patients in a similar manner. If the concept works in a medical office scenario, then the same may be leveraged for pharmacists and/or nurses to relay patient education.

even allows for virtual hands-on trainings, such as injection techniques. Video calls may be valuable in helping patients visually connect with their pharmacists, even if the pharmacists are available virtually and not in person at a physical location.

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Artificial Intelligence

Incorporating artificial intelligence into the analytic process presents the opportunity to develop predictive models based on historical data that can identify potential trends and forecast which patients may or may not be prone to specific issues, like poor adherence. These models can incorporate a variety of factors, such as characteristics or trends that are specific to medications

and conditions, as well as geographic, economic, and social factors, helping payers with budgeting resources narrow their focus to the most at-risk of patients within a given population.

Healthcare apps can also help solve patient-facing issues, supporting patients by providing education and reminders. Digital modules can walk patients through self-paced journeys of behavior changes, potentially covering topics such as smoking cessation, insomnia, and chronic pain. The wearable and portable devices mentioned earlier can, with patient permission, be reviewed to collect data on patients, including their behavior as consumers. This data could allow for interventions to be provided in a timely manner, potentially helping to reduce use of urgent care and emergency departments.

In a more advanced application of technology, there may be a benefit to using facial recognition to identify patients, identify a tablet or capsule, or confirm dose administration to monitor adherence. Even more advanced digital pills are now an option. Their role in therapy is still emerging, but they may offer yet another enhanced method of improving and measuring adherence.

Video on Demand

YouTube videos are viewed from mobile devices an average of 1 billion times per day.¹³ Translating this information to healthcare, we must recognize that today's patient is resourceful. With endless references available to them at the click of a button, patients will ultimately find the answers they are seeking. As subject matter experts, health plans and healthcare providers are now tasked with helping provide access to the accurate and valuable information patients desire in order to reduce the risk of patients tracking down less accurate or unreliable information on their own. Not all resources on the internet carry the same level of credibility, and there can be great benefit in claiming control and establishing healthcare experts as the keepers and source for this vital information.

Educational videos can be accessed several ways. Some pharmacies append prescription labels with QR codes, which provide one-click access to refills and videos about the patient's medication and its proper usage. For patients or caregivers who prefer an alternate way to access video, a video link can be provided via email or embedded in a central location, like a member portal.

These videos serve as one aspect of a larger initiative to help payers, providers, and others in healthcare go paperless. Use of portals and electronic methods of communication help reduce the need for printing and postage and reduce the costs associated with each.

Table 2: Results — Endpoints

Modality	Control Group	Intervention Group	Difference (%)
Average Days to Refill	6.9 days	6 days	13%
Percent Filling Within 3 Days of Intervention	53.1%	60%	6.9%
Reach Rates (Telephonic)	60.4%	64%	3.6%
Engagement Rates (Telephonic)	36.8%	43.8%	7%

Source: MRx Internal Data, 2017–2018

Potential Challenges in Adopting and Implementing Digital Health Solutions Within a Managed Care Organization

There are, of course, potential challenges to integrating new technologies into the healthcare system. These considerations include, but are not limited to, implementation costs, system integration, data transfer, licensing agreements, privacy considerations, and potential changes to an entity's liability. Patients and providers may not immediately accept all the changes associated with adopting new technologies, which may affect workflow and require development, implementation, and learning of new systems. These technologies may be faced with skepticism, as change is unfamiliar and may require time and education, especially for patients and providers with less overall familiarity with technology.

New Technologies in Practice and Impacts on Engagement and Adherence

Case Study: Star Adherence — SMS Refill-Reminder Pilot Program (Current Program)

Magellan Rx is currently implementing a Star Adherence pilot program that leverages SMS texting to improve adherence rates through the use of refill reminders. The program is specifically intended to reduce the number of days between refills and improve



Magellan Rx is currently implementing a Star Adherence pilot program that leverages SMS texting to improve adherence rates through the use of refill reminders. The program is specifically intended to reduce the number of days between refills and improve health plan star ratings for adherence measures to select therapies.

health plan star ratings for adherence measures to select therapies (diabetes, RAS antagonists, and cholesterol medications). Ultimately, this program aims to improve engagement by directly communicating through SMS to improve adherence among hard-to-reach members.

Limitations to the current program include the reactive process of waiting for populations to be prioritized based on proportion of days covered (PDC) calculations. The pilot program will look to overcome this limitation by proactively reminding patients to refill their medication before they become nonadherent.

The pilot program was implemented using specific identification criteria. Patients chosen had one of a group of specified disease states (hypertension, diabetes, or hyperlipidemia) as inferred from prescription data; were a specified number of days early or late for refill (between four days late and three days early); and had a valid phone number available for the member. Contact via SMS texting was made weekly.

The contact was initiated with a welcome message, which gave participants the ability to opt out of future messaging. Following the welcome message, refill reminders were sent along with a required date-of-birth verification to control for release of Protected Health Information. The refill reminder included medication class, drug name, and the pharmacy name and phone number. The SMS texting program included a number of automatic replies which were developed to handle a majority of common replies that may be sent by members, such as, "Who is this?", "Thank you", and "HELP." Automatic replies provided the member with contact information for the Magellan Rx call center and triaged the member case to a specific queue to address their unique response or inquiry.

Results: Initial Pilot — Version 1.0 (10 weeks)

The initial pilot, which lasted 10 weeks and included 3,045 enrolled members, saw a 25.9% engagement rate (791 members) and a 16.8% opt-out rate (513 members). Overall, member satisfaction with the program was poor. The key learnings from the initial pilot were the importance of ensuring accurate data, accurately identifying membership, and verifying correct medications. Adjustments to messaging content were also identified as being necessary and crucial to program success.

Results: Updated Pilot — Version 2.0

Utilizing the key learnings from Version 1.0, necessary alterations and enhancements were made to the pilot, including updated



analytics (i.e., Generic Sequence Number/Generic Product Identifier vs. National Drug Code) and additional reminders to reply at various intervals — two hours from the time of initial messaging and then again at 24 hours to boost patient engagement. Finally, messaging content was adjusted to include an option allowing members to re-enter the program after they had previously opted out.

The modifications improved outcomes. Version 2.0 had a total of 9,536 initially enrolled members with a 32% engagement rate (3,056 members) and 12.2% opt-out rate (1,164 members). Reports of patient satisfaction also improved. The proportion of days covered (PDC) was higher across all three intervention groups who received both phone calls and texts, as compared to control groups, who received phone calls only (Figure 2). The proportion of members with a PDC greater than or equal to 80% was higher in the intervention group than in the control group (Figure 3).

Members participating in the SMS refill-reminder program refilled their prescriptions approximately 20% earlier than members in the control group. Within the intervention group, this resulted in a shorter number of average days to refill, and a higher percentage of patients refilling within three days of intervention. Additionally, better telephonic-reach rates and engagement rates were demonstrated by members of the intervention group (Table 2).

Key Takeaways

While effective, traditional patient engagement strategies present certain limitations. Various technologies can be leveraged to enhance patient experience and improve outcomes. Offering alternative ways to connect with patients through technology was shown to be effective in this case study. Mobile devices have become a part of the everyday routine for most adults of all ages. Using these devices for communications other than phone calls has been shown to be a preferred and effective means to improve medication-refill adherence.

Despite the challenges associated with implementation of new strategies, data demonstrates that with experience and refinement, it is possible to utilize technology to positively influence members participating in these initiatives. Program success and favorable impact on health outcomes— in this case therapy adherence — are possible when innovative programs are effectively implemented by MCOs.

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Diabetes Update

Treatment Guidelines and Managed Care Implications



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Current Treatment Guidelines and Clinical Considerations

According to the 2017 National Diabetes Statistics Report, 30.3 million people have diabetes — an estimated 9.4% of the U.S. population.¹ Of these, 7.2 million individuals are undiagnosed.¹ Approximately 40% of Americans with diabetes are aged 65 years or older, and 25% of all U.S. adults over age 65 have diabetes.¹ The total direct and indirect estimated costs for diagnosed diabetes in the U.S. in 2012 was \$245 billion, and those with diagnosed diabetes had an average medical expenditure 2.3 times that of those without diabetes.¹

Lifestyle modifications including diet and exercise play a large part in helping patients manage their diabetes. Most individuals with Type 2 diabetes (T2DM) require the addition of oral and injectable medications, possibly including insulin therapy, to reach appropriate diabetes management goals. The specific therapeutic goals vary according to an individual's current health status, comorbidities, and the specific lens used for assessment. The National Committee for Quality Assurance uses its Healthcare Effectiveness Data and Information Set (HEDIS) guidelines to evaluate patient outcomes on a yearly basis: A1c and blood pressure outcome values are assessed, while LDL cholesterol management is credited based on the testing being completed rather than the outcome value. The American Diabetes Association (ADA), the American Association of Clinical Endocrinologists (AACE), and the American College of Endocrinology (ACE) all maintain and update recommended goals for clinical practice. These focus on the outcome values for A1c, blood pressure, and LDL cholesterol. The goals listed in Table 1 should be adjusted based on individual patient history and comorbidities.

Achieving these goals is just one aspect of the complex management of patients with diabetes. Morbidity and mortality due to diabetic complications continues to rise with 7 of 10 patients with diabetes dying from some type of heart disease.⁵ The Food and Drug Administration (FDA) is now requiring diabetic clinical trials to include the three-point composite endpoint major adverse cardiac events, looking at nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death. These additional endpoints have brought to light positive effects for patients with cardiovascular disease (CVD), kidney disease, and weight-management issues. These positive endpoints have shown the most promise in two classes of antidiabetic medications: glucagon-like peptide-1 receptor agonists (GLP-1 RA) and sodium-glucose cotransporter 2 inhibitors (SGLT2 inhibitors).

Table 1: Clinical Outcomes for Patients with Diabetes^{2, 3, 4}

Clinical Organization	A1c	Blood Pressure	LDL Cholesterol
HEDIS	<7%*, <8%*	<140/90 mmHg	Yearly assessment
ADA	<7%, <8%	<140/90 mmHg	<70mg/dL
AACE/ACE	<6.5%–8%	<130/80 mmHg	<100mg/dL**

Source: MRx Internal Data, 2017–2018

In the fall of 2018, the ADA and the European Association for the Study of Diabetes convened a panel to update their 2012 and 2015 position statements on the management of T2DM in adults. The panel agreed upon multiple consensus recommendations related to lifestyle modifications, diabetes self-management education and support, obesity and weight management, and medication management with a focus on patients with cardiovascular and renal comorbidities. The panel also considered patient preference in treatment options and the cost associated with such options. Highlights of the consensus recommendations are as follows:

- Metformin is the preferred initial glucose-lowering medication for most people with T2DM.⁵
- The stepwise addition of glucose-lowering medication is generally preferred to initiating treatment with combination therapy.⁵
- The selection of medication added to metformin is based on patient preference and clinical characteristics. Important clinical characteristics include the presence of established atherosclerotic cardiovascular disease (ASCVD) and other comorbidities such as heart failure (HF) or chronic kidney disease (CKD); the risk for specific adverse medication effects, particularly hypoglycemia and weight gain; as well as safety, tolerability, and cost.⁵
- Intensification of treatment beyond dual therapy to maintain glycemic targets requires consideration of the impact of medication side effects on comorbidities, as well as the burden of treatment and cost.⁵
- In patients who need the greater glucose-lowering effect of an injectable medication, GLP-1 receptor agonists are the preferred choice to insulin. For patients with extreme and symptomatic hyperglycemia, insulin is recommended.⁵
- Patients who are unable to maintain glycemic targets on basal insulin in combination with oral medications can have treatment intensified with GLP-1 receptor agonists, SGLT2 inhibitors, or prandial insulin.⁵

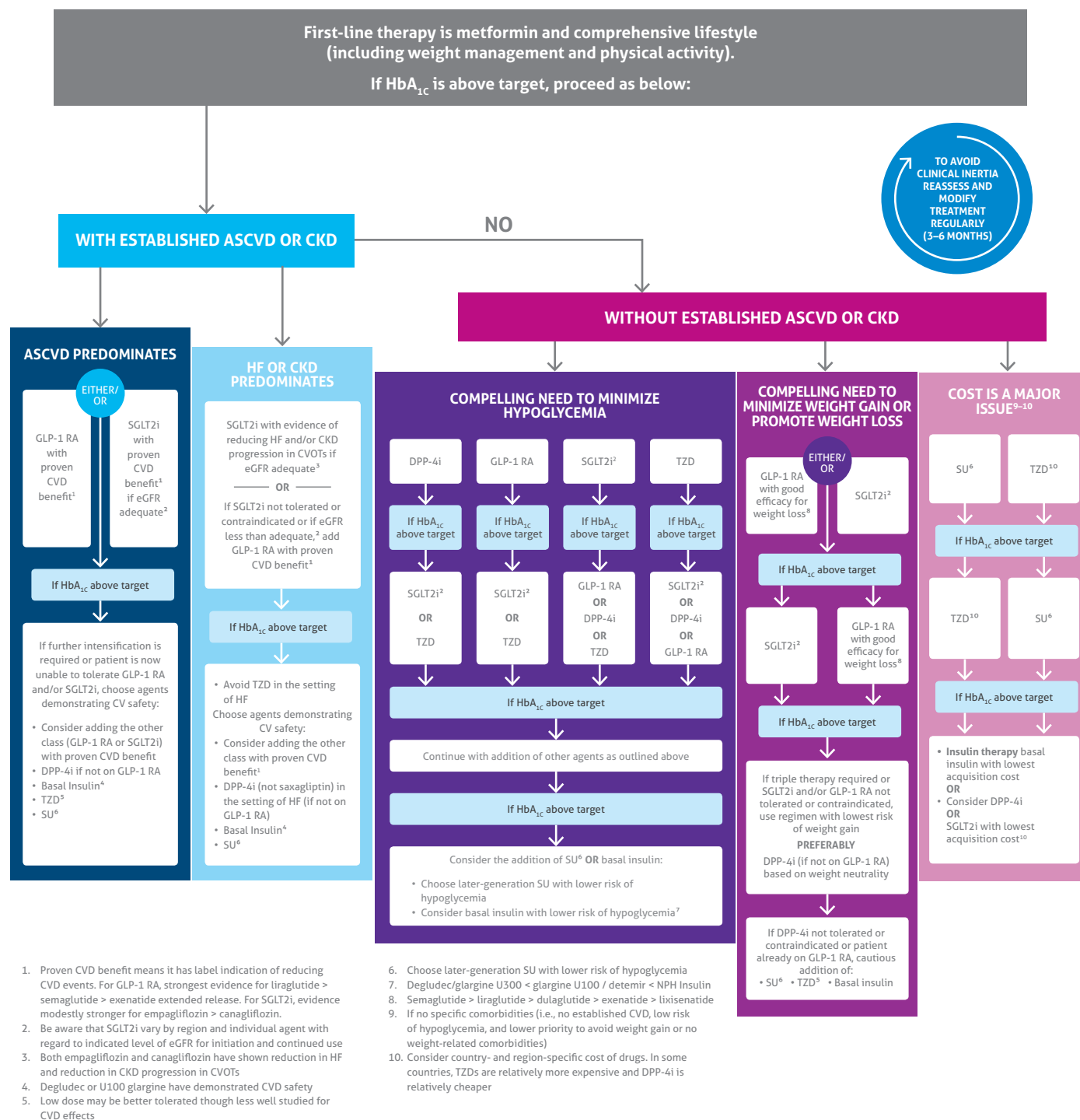
- Access, treatment cost, and insurance coverage should all be considered when selecting glucose-lowering medications.⁵

The ADA's 2019 Standards of Medical Care in Diabetes³ has adopted the above recommendations for medications used as second- and third-line therapies to include considerations for the presence of CVD, ASCVD, and CKD. This is a significant change from the 2018 guidelines, which focused on the comorbidity of hypertension. Some additional revisions to the guidelines include considering financial costs of diabetes to individuals and society, highlighting the importance of weight loss, and encouraging the comprehensive medical evaluation and assessment of comorbidities and diabetes in older adults³ (Figure 1).



The panel agreed upon multiple consensus recommendations related to lifestyle modifications, diabetes self-management education and support, obesity and weight management, and medication management with a focus on patients with cardiovascular and renal comorbidities.

Figure 1: Glucose-lowering medication in Type 2 diabetes: overall approach:³



Abbreviations: CVOTs = cardiovascular outcome trials; DPP-4i = dipeptidyl peptidase 4 inhibitors; SU = sulfonylurea; TZD = thiazolidinediones

Figure 2: GLP-1 RAs and Weight Changes⁶



p-values are for statistical superiority (unless noted for noninferiority): *p = not significant, †p = 0.0005, ‡p-value not reported for weight difference of 1.02 kg (95% confidence interval 0.456–1.581), §p <0.0001, ¶p <0.001 dulaglutide 0.75 mg versus exenatide bid, **p = not significant between dulaglutide 1.5 mg versus exenatide bid, ††p = 0.011.

First-Line Therapy

When diet and exercise prove insufficient in achieving the desired glycemic control, metformin should be added.³ Most patients do well on metformin if they can tolerate the early onset gastrointestinal (GI) side effects. GI side effects can be avoided by initiating therapy at a lower dose and titrating slowly to the desired goal. If glycemic control is not achieved, additional therapy should be considered.³

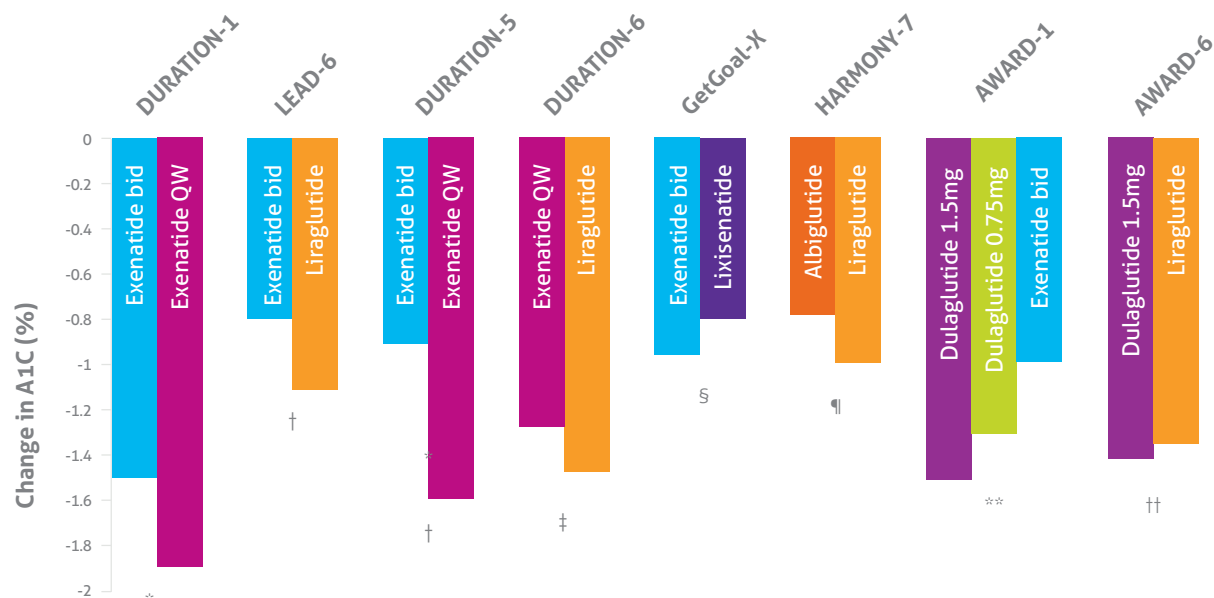
Second-Line Therapy

When considering second-line therapy, guidelines now include consideration of the presence of ASCVD and/or CKD in the decision-making tree, as mentioned previously.³ If ASCVD and/or CKD is/

are present, studies have shown the benefit of the addition of a GLP-1 RA or a SGLT2 inhibitor to the patient's regimen.³ GLP-1 RAs work in multiple sites within the body to decrease appetite, slow gastric emptying, stimulate insulin secretion, and suppress glucagon secretion.⁶ The greatest cardiovascular benefit within the GLP-1 RA class was seen with Victoza® (liraglutide) and Ozempic® (semaglutide).⁶ Other medications in this class of drug therapy include Trulicity® (dulaglutide), Bydureon® (exenatide extended release), and Adlyxin® (lixisenatide).⁶

SGLT2 inhibitors work within the kidney to block sugar from being absorbed into the bloodstream to improve glycemic control.⁷ CVD benefit was seen with Jardiance® (empagliflozin), Invokana® (canagliflozin), and Farxiga® (dapagliflozin).⁷ Another medication within this class is Steglatro™ (ertugliflozin).⁷

Figure 3: GLP-1 RAs and A1c Changes⁶



p-values are for statistical superiority unless otherwise noted as non-inferiority: *p < 0.0025, †p < 0.0001, ‡p = 0.02, \$p = not significant, noninferiority p-value not reported (95% confidence interval 0.033–0.297, meeting predefined noninferiority margin), ¶noninferiority p-value = 0.0846 (not meeting predefined noninferiority margin), **p < 0.001 for both doses of dulaglutide versus exenatide bid, ††p = not significant, noninferiority p-value < 0.0001 (meeting predefined noninferiority margin).

For patients with HF or CKD, SGLT2 inhibitors are preferred if tolerated and the patient's estimated glomerular filtration rate is within prescribing range for the specific agent chosen. GLP-1 RAs can be used with this population if SGLT2 inhibitors are not tolerated or appropriate.

In addition to producing positive outcomes for CVD, GLP-1 RAs and SGLT2 inhibitors have been shown to promote weight loss and improve A1c. In a comparison of head-to-head trials including GLP-1 RAs, a reduction in weight and A1c was seen across all agents. The greatest weight loss was seen with exenatide, taken twice daily, with a decrease in weight of 3.8 kg (Figure 2).⁶ The largest reduction in A1c was seen with exenatide weekly at -1.9% (Figure 3).⁶

Additional Therapeutic Options

For patients without ASCVD, HF, or CKD, the therapies discussed above may be determined by their physician to be the most appropriate, but there are also other options when contraindication or cost is an issue³. Dipeptidyl peptidase-4 inhibitors,



Although the economics of diabetes care is complex and ideally should include consideration of the costs of diabetic complications and long-term outcomes, cost of drugs and affordability of treatment are often the primary basis for treatment selection.

Table 2: Wholesale Acquisition Cost of New GLP-1 RAs and SGLT-2 Inhibitors

Drug Name	Dosing Frequency	Wholesale Acquisition Cost (WAC)/Month*
GLP-1 Receptor Agonists		
dulaglutide (Trulicity®) 1.5mg/0.5 ml 4 pens	Once weekly	\$759
exenatide ER (Bydureon®) 4 pens	Once weekly	\$700
liraglutide (Victoza®) 6 mg/1 ml 3 pens	Once daily	\$922
lixisenatide (Adlyxin®) 100mcg/ml 2 pens	Once daily	\$620
semaglutide (Ozempic®) 2mg/1.5 ml 1 pen	Once weekly	\$386
SGLT-2 Inhibitors		
canagliflozin (Invokana®) 100 mg/30 tablets	Once daily	\$494
dapagliflozin (Farxiga®) 10 mg/30 tablets	Once daily	\$492
empagliflozin (Jardiance®) 25 mg/30 tablets	Once daily	\$493
ertugliflozin (Steglatro™) 15 mg/30 tablets	Once daily	\$281

*Source: Micromedex Red Book, accessed May 2, 2019

thiazolidinediones, and sulfonylureas can be considered as treatment options for patients depending on the level of glycemic control needed, comorbidities, and the risk of hypoglycemia.³

Implications for Managed Care and Economic Considerations

The economics of diabetes care are complex and ideally should include consideration of the costs of diabetic complications and long-term outcomes, yet cost of drugs and affordability of treatment are often the primary basis for treatment selection.⁵ While the cost of newer agents is higher than previous therapies, these

agents may improve compliance by decreasing dosing frequency or offering alternative routes of administration. The cost of a treatment should be evaluated against the backdrop of the financial implications of uncontrolled diabetes and associated comorbidities that may result from ineffective management.⁸ Table 2 captures the cost of the injectable agents in the GLP-1 RAs class and the oral agents in the SGLT-2 inhibitor class cost per month.

Important factors to consider when weighing benefit versus cost of newer agents include but are not limited to:

- Improved adherence to diabetes medications contributed to higher drug cost but has been associated with lower inpatient,

Table 3: Diabetes Mellitus Pipeline Drug List¹¹

Name	Manufacturer	Clinical Use	Dosage Form	Approval Status	Expected FDA Approval
Nasal Glucagon	Eli Lilly	Improved glycemic control in Type 1 and Type 2 diabetes	Intranasal	Pending	Q2 2019
G-Pen (glucagon)	Xeris	Improved glycemic control in Type 1 and Type 2 diabetes	Subcutaneous	Pending	Q3 2019
NN9924 (semaglutide)	Novo Nordisk	Improved glycemic control in Type 1 and Type 2 diabetes	Oral	Pending	Q3 2019

outpatient, and emergency room costs.⁸

- The effect of hypoglycemia on cost depended on patient severity and the cost category being analyzed, but in general, hypoglycemia was associated with higher costs.⁸
- Higher hemoglobin A1c levels were associated with higher overall total costs, since patients with poor glucose control tended to use more healthcare resources than patients whose A1c is at target levels did.⁸

Diabetes-related direct and indirect costs in the U.S. are projected to reach \$622.3 billion in 2030, to include \$472 billion in annual medical costs.⁹ The estimated additional lifetime cost of treating a T2DM patient and their associated complications in the U.S. differs based on gender and age at diagnosis. For men, lifetime costs range from \$54,700 for those diagnosed at age ≥ 65 years to \$124,700 for those diagnosed at between age 25 and 44 years.⁹ For women, lifetime costs range from \$56,600 for patients diagnosed at age ≥ 65 years to \$130,800 for those diagnosed at between age 25 and 44 years.⁹ Hospital admissions and readmissions account for most of a diabetic patients' healthcare costs.⁹

The increased risk of comorbidities from uncontrolled diabetes can influence a patient's quality of life. Health-related quality of life was noted to decrease as medical expenses for diabetes increased.⁹ A one-year post-diagnosis follow-up period for T2DM patients showed costs were 32% higher for patients with an A1c>7% relative to patients with an A1c<7% (\$1,540 versus \$1,171 per patient).⁹ This same study correlated a 1% increase in A1c with a patient incurring a 4% increase in diabetes-related medical cost (translating to an annual cost increase of \$250 per year).⁹



There are also alternative treatments on the horizon. Table 3 lists new drugs expected in 2019 and early 2020 to treat diabetes mellitus. Two new glucagon products, one additional injectable, and a new addition to the class in the form of inhaled glucagon will offer additional options to treat hypoglycemia.

Diabetes Pharmaceutical Pipeline: What's On the Horizon?

There are also alternative treatments on the horizon. Table 3 lists new drugs expected in 2019 and early 2020 to treat diabetes

mellitus. Two new glucagon products, one additional injectable, and a new addition to the class in the form of inhaled glucagon will offer additional options to treat hypoglycemia. Eli Lilly's inhaled glucagon product would offer a new, alternative route of administration to the currently available glucagon injection.¹⁰ Also in the pipeline is an oral GLP-1RA, a new dosage form in this class of previously only injectable medications. The addition of an oral dosage form could increase the number of patients willing to try this class of medications, since there would be no need for injections. Novo Nordisk released results from their PIONEER 1 study in fall 2018 indicating the oral version of semaglutide showed both glycemic and nonglycemic benefits.¹⁰ These results also showed no unexpected safety or tolerability issues.¹⁰

The benefit of having a variety of therapies available to address the unique needs of individuals with uncontrolled T2DM is underscored by the changes to the 2019 ADA guidelines. As the number of patients diagnosed with T2DM continues to grow, health-care costs are projected to rise, for newly diagnosed patients and for those who were previously diagnosed but are not attaining A1c goals. Newer therapies, though more expensive, may be considered together with existing lower-cost treatments as part of an overall strategy to improve the management and overall health of this patient population.

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PIPELINE DRUG LIST

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Name	Manufacturer	Clinical Use	Dosage Form	Approval Status	Expected FDA Approval
selinexor	Karyopharm Therapeutics; Antengene Corporation; Ono Pharmaceutical Company, Ltd.	MM (penta-refractory)	PO	Fast track; orphan drug; priority review	7/5/2019
afamelanotide (Scenesse®)	Clinuvel Pharmaceuticals	Porphyria	ID	Fast track; orphan drug; priority review	7/8/2019
relebactam/imipenem/cilastatin	Merck & Co., Inc.	Intra-abdominal infections; urinary tract and reproductive tract infections	IV	Fast track; qualified infections; priority review	7/16/2019
riluzole (BHV-0223)	Biohaven Pharmaceutical Holding Company Ltd.; Catalent, Inc.; Portage Biotech	ALS	SL	Orphan drug	7/19/2019
apremilast (Otezla®)	Celgene	Behcet's Syndrome	PO	Orphan drug	7/19/2019
ferric maltol (Feraccru®)	Shield Therapeutics plc; AOP Orphan Pharmaceuticals AG; Ewopharma AG	Anemia	PO	Submitted	7/26/2019
filgrastim (biosimilar Neupogen)	Tanvex BioPharma, Inc.	Neutropenia/leukopenia	SQ	Orphan drug	8/1/2019
pexidartinib	Daiichi Sankyo Co., Ltd.	TGCT	PO	Orphan drug; breakthrough therapy; priority review	8/2/2019
cefiderocol	Shionogi & Co. Ltd.; GlaxoSmithKline plc.	Urinary tract and reproductive tract infections	IV	Submitted	8/14/2019
loteprednol etabonate 0.25% (KPI-121 0.25%)	Kala Pharmaceuticals, Inc.	Dry eye	Topical	Submitted	8/15/2019
entrectinib	Genentech; Chugai Pharmaceutical Co. Ltd.; Shanghai Advanced Research Institute	Solid tumors (NTRK fusion positive, locally advanced or metastatic); NSCLC (metastatic, ROS1-positive)	PO	Breakthrough therapy; priority review	8/16/2019
tasimelteon (Hetlioz®)	Vanda Pharmaceuticals, Inc.; Bristol-Myers Squibb	Jet lag disorder	PO	Submitted	8/16/2019
golodirsen	Sarepta Therapeutics, Inc.	DMD	IV	Orphan drug; priority review	8/19/2019

PIPELINE DRUG LIST

PIPELINE DRUG LIST CONT.					
Name	Manufacturer	Clinical Use	Dosage Form	Approval Status	Expected FDA Approval
lefamulin	Nabriva Therapeutics plc; Roivant Sciences, Inc.	CAP (antibacterial)	IV; PO	Fast track; qualified infections; priority review	8/19/2019
polatuzumab vedotin	Roche Holding AG; Chugai Pharmaceutical Co., Ltd.; Seattle Genetics, Inc.	Diffuse large B-cell lymphoma; NHL	IV	Orphan drug; breakthrough therapy; priority review	8/19/2019
upadacitinib	AbbVie, Inc.	RA	PO	Priority review	8/20/2019
quizartinib	Daiichi Sankyo Co., Ltd.	AML (FLT3-ITD mutated)	PO	Fast track; orphan drug; breakthrough therapy; priority review	8/23/2019
istradefylline (Nourias [®])	Kyowa Hakko Kirin Co., Ltd.	Parkinson's disease	PO	Submitted	8/27/2019
oxycodone hydrochloride (Oxycodone ER) (abuse- and alcohol-resistant)	Intellipharmaeueutics International Inc.	Chronic pain	PO	Fast track	8/28/2019
pitolisant	Harmony Biosciences, LLC; BioProject SCR; Endo International plc; Grupo Ferrer Internacional, S.A..	Narcolepsy	PO	Fast track; orphan drug; breakthrough therapy; priority review	July–August 2019
ixekizumab (Taltz [®])	Eli Lilly & Company; Torii Pharmaceutical Co., Ltd.	Axial spondyloarthritis	SQ	Fast track; orphan drug	August 2019
fedratinib	Celgene	Myelofibrosis	PO	Orphan drug; priority review	9/3/2019
tenapanor	Ardelyx, Inc.; Knight Therapeutics Inc.; Kyowa Hakko Kirin Co., Ltd; Shanghai Fosun Pharmaceutical Group Co., Ltd.	IBS (constipation predominant)	PO	Submitted	9/13/2019
nintedanib (Ofev [®])	Boehringer Ingelheim GmbH	Scleroderma	PO	Fast track; orphan drug	9/18/2019
oral semaglutide	Novo Nordisk A/S; Emisphere Technologies, Inc.	Type 2 diabetes mellitus	PO	Priority review	9/20/2019
lumateperone	Intra-cellular Therapies, Inc.; Bristol-Myers Squibb	Schizophrenia	PO	Fast track	9/27/2019

PIPELINE DRUG LIST

PIPELINE DRUG LIST CONT.					
Name	Manufacturer	Clinical Use	Dosage Form	Approval Status	Expected FDA Approval
pretomanid	Mylan N.V.; Global Alliance for TB Development; Novartis AG; Shanghai Fosun Pharmaceutical Group Co., Ltd.	TB	PO	Fast track; orphan drug; priority review	August–September 2019
imvamune	Bavarian Nordic A/S	Smallpox vaccine	SQ	Submitted	September 2019
dapagliflozin (Farxiga®)	AstraZeneca plc; Bristol-Myers Squibb; Ono Pharmaceutical Company, Ltd.; Sun Pharmaceutical Industries, Ltd.	Type I diabetes mellitus	PO	Submitted	September 2019
pegfilgrastim (Ziextenzo™)	Novartis AG	Neutropenia/Leukopenia	SQ	Submitted	10/3/2019
emtricitabine/tenofovir alafenamide	Gilead Sciences, Inc.	HIV prevention	PO	Priority review	10/4/2019
biosimilar teriparatide recombinant	Pfenex, Inc.; Alvogen, Inc.; NT Pharmaceuticals Co., Ltd.	Osteoporosis/osteopenia	SQ	Submitted	10/7/2019
Biosimilar infliximab	Amgen Inc.; Allergan plc; Daiichi Sankyo Co., Ltd.	RA; AS; PSO; PsA; CD; UC	IV	Submitted	10/17/2019
diroximel fumarate (Vumerity™)	Biogen, Inc.; Alkermes plc	Multiple sclerosis (relapsing)	PO	Submitted	10/17/2019
minocycline (FMX101)	Foamix Pharmaceuticals Ltd.	Acne	Topical	Submitted	10/18/2019
triamcinolone acetonide (Xipere™)	Clearside Biomedical, Inc.	Uveitis-associated macular edema	IO	Submitted	10/18/2019
ustekinumab (Stelara®)	Janssen; Bristol-Myers Squibb Company; DRI Capital Inc.; Mitsubishi Tanabe Pharma Corporation	UC	IV; SQ	Orphan drug; priority review	10/18/2019
cosyntropin (synthetic ACTH Depot)	Assertio Therapeutics, Inc.; Slan Medicinal Holdings, Ltd.	Endocrine disorder	Injectable	Submitted	10/18/2019
darolutamide	Bayer AG; Endo International plc; Orion Corporation	Prostate cancer (non-metastatic, castration-resistant)	PO	Fast track; priority review	10/25/2019
Naloxone (Naloxone Symject™)	Adamis Pharmaceuticals Corporation	SUD	IM	Fast track; orphan drug	10/31/2019

PIPELINE DRUG LIST

PIPELINE DRUG LIST CONT.					
Name	Manufacturer	Clinical Use	Dosage Form	Approval Status	Expected FDA Approval
lasmiditan	Eli Lilly & Company; Ildong Pharmaceutical Co., Ltd.	Migraine and other headaches	PO	Orphan drug	11/14/2019
alpesilib	Novartis AG	Breast cancer	PO	Submitted	11/15/2019
cenobamate	SK Biopharmaceuticals Co.; Arvelle Therapeutics GmbH	Seizure disorders (epilepsy)	PO	Submitted	11/21/2019
riluzole film (Exservan™)	Aquestive Therapeutics, Inc.	ALS	Oral transmucosal	Orphan drug	11/29/2019
cetirizine (QUZYTIR™)	Pfizer, Inc.; JDP Therapeutics	Urticaria	IV	Submitted	October–November 2019
brolocizumab	Novartis AG; Delenex Therapeutics AG	Wet AMD	IO	Priority review	November 2019
methotrexate (RediTrex™)	Cumberland Pharmaceuticals, Inc.	Psoriasis	SQ	Submitted	November 2019
sodium thiosulfate (Pedmark™)	Fennec Pharmaceuticals, Inc.	Chemotherapy-induced hearing loss	IV	Fast track; orphan drug; breakthrough therapy	September–December 2019
dulaglutide (Trulicity®)	Eli Lilly & Company; Lupin Ltd.; Sumitomo Dainippon Pharma Co., Ltd.	Type 2 diabetes CV outcomes	SQ	Submitted	November 2019–January 2020
Biosimilar adalimumab	Pfizer, Inc.	RA; AS; PSO; PsA; JIA; CD; UC	SQ	Submitted	Q3 2019

Abbreviations: ALS = amyotrophic lateral sclerosis; AMD = age-related macular degeneration; AML = acute myelogenous leukemia; AS = ankylosing spondylitis; CD = Crohn's disease; CV = cardiovascular; DMD = Duchenne muscular dystrophy; HIV = human immunodeficiency virus; IBS = irritable bowel syndrome; ID = intradermal; IM = intramuscular; IO = intraocular; IV = intravenous; JIA = juvenile idiopathic arthritis; MM = multiple myeloma; NHL = non-Hodgkin's lymphoma; NSCLC = non-small cell lung cancer; PO = oral; PsA = psoriatic arthritis; PSO = psoriasis; RA = rheumatoid arthritis; SL = sublingual; SQ = subcutaneous; SUD = substance use disorder; TB = tuberculosis; TGCT = tenosynovial giant cell tumors; UC = ulcerative colitis

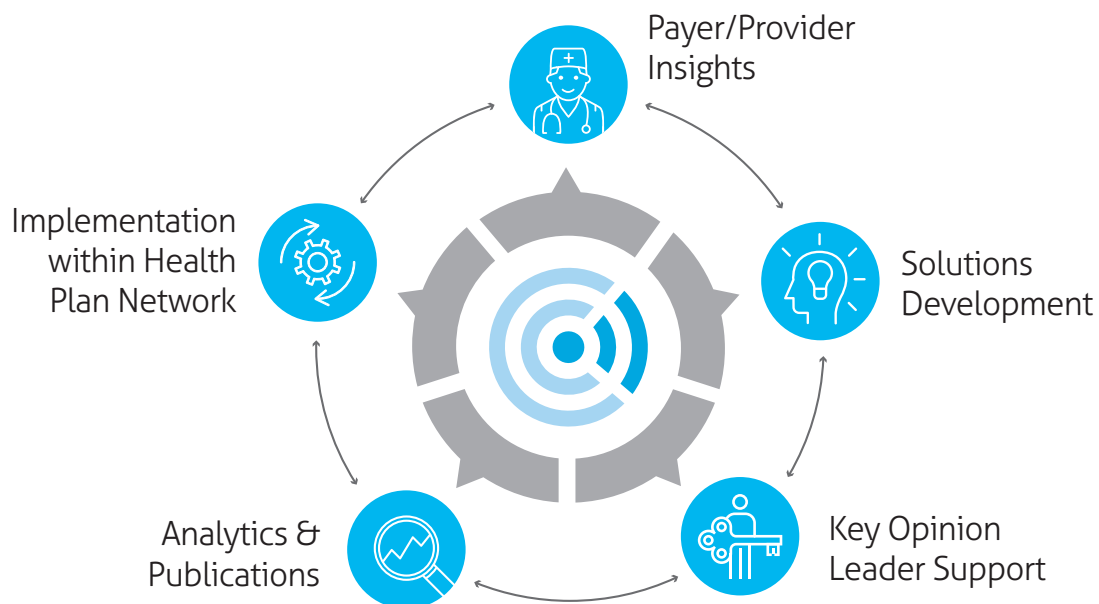


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