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FDA APPROVED FOR INTERMEDIATE OR HIGH-RISK MYELOFIBROSIS

in COMFORT-I* and COMFORT-II, Jakafi® (ruxolitinib) significantly reduced spleen volume compared with patients receiving placebo or best available therapy, respectively.

* COMFORT-I (Controlled MyeloFibrosis study with ORal JAK inhibitor Treatment-I) was a randomized, double-blind, placebo-controlled phase 3 study with 309 patients with intermediate-2–risk or high-risk myelofibrosis.

† COMFORT-II (Controlled MyeloFibrosis study with ORal JAK inhibitor Treatment-II) was a randomized, open-label phase 3 study with 219 patients with intermediate-2–risk or high-risk myelofibrosis.

‡ Best available therapy in COMFORT-II included hydroxyurea (46.6%) and glucocorticoids (16.4%), as well as no medication, anagrelide, epoetin alfa, thalidomide, lenalidomide, mercaptopurine, thioguanine, danazol, peginterferon alfa-2a, interferon-alfa, cytarabine, and colchicine.

Important Safety Information

- Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated.
- Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary.
- Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi.
- Severe neutropenia (ANC <0.5 × 10⁹/L) was generally reversible by withholding Jakafi until recovery.
- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly.
- Tuberculosis (TB) infection has been reported. Observe patients taking Jakafi for signs and symptoms of active TB and manage promptly. Prior to initiating Jakafi, evaluate patients for TB risk factors and test those at higher risk for latent infection. Consult a physician with expertise in the treatment of TB before starting Jakafi in patients with evidence of active or latent TB. Continuation of Jakafi during treatment of active TB should be based on the overall risk-benefit determination.
- Progressive multifocal leukoencephalopathy (PML) has occurred with ruxolitinib treatment for myelofibrosis. If PML is suspected, stop Jakafi and evaluate.
- Advise patients about early signs and symptoms of herpes zoster and to seek early treatment.
- Increases in hepatitis B viral load with or without associated elevations in alanine aminotransferase and aspartate aminotransferase have been reported in patients with chronic hepatitis B virus (HBV) infections. Monitor and treat patients with chronic HBV infection according to clinical guidelines.

Jakafi is a registered trademark of Incyte Corporation. © 2016, Incyte Corporation. All rights reserved. 12/16
Indications and Usage
Jakafi is indicated for treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post–polycythemia vera myelofibrosis and post–essential thrombocythemia myelofibrosis.

Overall survival was a prespecified secondary end point in COMFORT-I and COMFORT-II.

- COMFORT-I: At 3 years, survival probability was 70% for patients originally randomized to Jakafi and 61% for those originally randomized to placebo.

- COMFORT-II: At 3 years, survival probability was 79% for patients originally randomized to Jakafi and 59% for those originally randomized to best available therapy.

Because of progression-driven events or at the physician’s discretion, patients randomized to placebo (COMFORT-II) or best available therapy (COMFORT-II) who crossed over to receive Jakafi continued to be grouped within their original randomized assignment for analysis purposes.

All patients in the placebo group either crossed over or discontinued.

When discontinuing Jakafi, myeloproliferative neoplasm-related symptoms may return within one week. After discontinuation, some patients with myelofibrosis have experienced fever, respiratory distress, hypotension, DIC, or multi-organ failure. If any of these occur after discontinuation or while tapering Jakafi, evaluate and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi without consulting their physician. When discontinuing or interrupting Jakafi for reasons other than thrombocytopenia or neutropenia, consider gradual tapering rather than abrupt discontinuation.

Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred. Perform periodic skin examinations.

Treatment with Jakafi has been associated with increases in total cholesterol, low-density lipoprotein cholesterol, and triglycerides. Assess lipid parameters 8-12 weeks after initiating Jakafi. Monitor and treat according to clinical guidelines for the management of hyperlipidemia.

The three most frequent non-hematologic adverse reactions (incidence >10%) were bruising, dizziness and headache.

A dose modification is recommended when administering Jakafi with strong CYP3A4 inhibitors or fluconazole or in patients with renal or hepatic impairment. Patients should be closely monitored and the dose titrated based on safety and efficacy.

Use of Jakafi during pregnancy is not recommended and should only be used if the potential benefit justifies the potential risk to the fetus. Women taking Jakafi should not breast-feed.

Please see Brief Summary of Full Prescribing Information for Jakafi on the following pages.

To learn more about Jakafi, visit Jakafi.com/HCP.

Jakafi®
ruxolitinib

e is used to narrow the risk of serious complications of myelofibrosis. If PML is suspected, stop Jakafi and evaluate.

Full Prescribing Information

of follow-up of 10.9 months, including 301 patients with myelofibrosis in two Phase 3 studies. In these two Phase

Risk of Infection Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting

ADVERSE REACTIONS

with myelofibrosis have experienced one or more of the following adverse events after discontinuing

Table 1: Myelofibrosis: Adverse Reactions Occurring in Patients on Jakafi in the Double-blind,

Placebo-controlled Study During Randomized Treatment

Table 2: Myelofibrosis: Worst Hematology Laboratory Abnormalities in the Placebo-controlled Study

Additional Data from the Placebo-controlled Study 25% of patients treated with Jakafi and 7% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in alamine transaminase (ALT). The incidence of greater than or equal to Grade 2 elevations was 2% for Jakafi with 1% Grade 3 and 0 Grade 4 ALT elevations. 17% of patients treated with Jakafi and 6% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in aspartate transaminase (AST). The incidence of Grade 2 AST elevations was <1% for Jakafi with no Grade 3 or 4 AST elevations. 17% of patients treated with Jakafi and <1% of patients treated with placebo developed newly occurring or worsening Grade 1 elevations in cholesterol. The incidence of Grade 2 cholesterol elevations was <1% for Jakafi with no Grade 3 or 4 cholesterol elevations. Clinical Trial Experience in Polycythemia Vera in a randomized, open-label, active-controlled study, 110 patients with polycythemia vera resistant to or intolerant of hydroxyurea received Jakafi and 111 patients received best available treatment (see Clinical Studies (4.2) in Full Prescribing Information). The most frequent adverse drug reaction was anemia. Table 3 presents the most frequent non-hematologic treatment emergent adverse events occurring up to Week 32. Discontinuation for adverse events, regardless of causality, was observed in 4% of patients treated with Jakafi.
managed according to clinical guidelines. Periodic skin examinations should be performed in patients treated with Jakafi. The most frequent adverse drug reaction was anemia. Table 3 presents the most frequent laboratory abnormalities in the open-label, active-controlled study up to Week 32 of randomized treatment.

Table 3: Polycythemia Vera: Treatment Emergent Adverse Events Occurring in ≥ 6% of Patients on Jakafi in the Open-Label, Active-controlled Study up to Week 32 of Randomized Treatment

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jakafi (N=110)</td>
<td>Best Available Therapy (N=111)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Anemia** | 72 | <1 | 1 | 58 | 0 | 0
- **Thrombocytopenia** | 27 | 5 | <1 | 24 | 3 | <1
- **Neutropenia** | 3 | 0 | <1 | 10 | 1 | <1

- **Hematology**

- **Hypertension** | 35 | 0 | 0 | 8 | 0 | 0
- **Elevated ALT** | 25 | <1 | 1 | 16 | 0 | 0
- **Elevated AST** | 23 | 0 | 0 | 23 | <1 | 0
- **Hyperuricemia** | 15 | 0 | 0 | 13 | 0 | 0

**DRUG INTERACTIONS**

* Jakafi interacts with other medications and can markedly change the concentration of other drugs. Consult with your healthcare provider before starting Jakafi.

**Pharmacokinetics**

Ruxolitinib is metabolized by CYP3A4 and to a lesser extent by CYP2C9. Ruxolitinib is not removed by dialysis; however, some active metabolites by dialysis cannot be removed.

**Adverse Events**

- **Headache** | 16 | <1 | 19 | 16 | <1 | 12
- **Abdominal Pain** | 15 | <1 | 15 | <1 | 15 | <1
- **Diarrhea** | 15 | 0 | 7 | <1 | 15 | 0
- **Dizziness** | 15 | 0 | 10 | 13 | 0 | 0
- **Fatigue** | 15 | 0 | 15 | 3 | 15 | 0
- **Pruritus** | 14 | <1 | 23 | <1 | 23 | <1
- **Dyspepsia** | 13 | 3 | 4 | 0 | 0 | 0
- **Muscle Soreness** | 12 | <1 | 5 | 0 | 0 | 0
- **Nasopharyngitis** | 9 | 0 | 8 | 0 | 0 | 0
- **Constipation** | 8 | 0 | 3 | 0 | 0 | 0
- **Cough** | 8 | 0 | 5 | 0 | 0 | 0
- **Edema** | 8 | 0 | 7 | 0 | 0 | 0
- **Arthralgia** | 7 | 0 | 6 | <1 | 0 | 0
- **Anemia** | 7 | 0 | 11 | 12 | 0 | 0
- **Epistaxis** | 6 | 0 | 3 | 0 | 0 | 0
- **Hepatic Zoster** | 6 | <1 | 0 | 0 | 0 | 0
- **Nausea** | 6 | 0 | 4 | 0 | 0 | 0

* National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0

**Use of Jakafi**

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**References**

- U.S. Patent Nos. 7,586,931; 7,732,815; 7,628,930; 8,024,981; 8,825,013; 9,079,012
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Psoriasis: Changing Approaches to the Treatment of Moderate to Severe Disease
The Payer’s Perspective

Gary M. Owens, MD

For a CME/CNE version of this article, please go to www.namcp.org/cmeonline.htm, and then click the activity title.

Summary
The landscape for treating psoriasis has changed dramatically with the introduction of biologic and nonbiologic agents which are effective for moderate to severe psoriasis but have high annual costs. In part, because of these newer agents, the cost of treating psoriasis has the attention of many managed care plans. Payers are implementing different strategies to contain costs of psoriasis treatment.

Key Points
• Those with moderate to severe psoriasis have higher health care costs and utilization.
• Treatment selection should be based on disease severity.
• Managed care uses many strategies to control costs for psoriasis treatment.

Psoriasis, the most common autoimmune disease, affects 2 to 3 percent of the adult population (7.5 million in the United States). Forty percent of those affected have a positive family history, and there is significant genetic overlap with inflammatory bowel disease. Psoriasis affects approximately 3.6 percent of Caucasians and 1.9 percent of African Americans, who are more likely to have moderate to severe disease.1

Psoriasis can present at virtually any age, but there are two peak age groups for presentation - 20 to 30 and 50 to 60 years. There are various types of psoriasis including plaque, pustular, inverse, erythrodermic, and guttate. Plaque psoriasis represents about 85 to 90 percent of the cases. Two-thirds of patients with plaque psoriasis have mild to moderate disease and one-third have a more severe presentation.

Psoriasis appears to be caused by localized and systemic inflammation caused by defects in T cell regulation. There is upregulation of Th-1 and Th-17 cells, antigen presenting cells, and cytokines. It is associated with increased C reactive protein and other markers of inflammation. The result is epidermal hyperproliferation that is clinically appreciated as scaling and cracking. Psoriasis is associated with elevated uric acid, oxidative stress, and angiogenesis from increased circulating vascular endothelial growth factor (VEGF).

Several immunologic factors are known to occur in psoriasis. There is a significant reduction in the number and percentage of CD4+ T cells in the peripheral blood, whereas they are found throughout the skin lesions. Dendritic cells present an unknown antigen to CD4+ cells within the skin, leading to T cell activation. Fibroblasts have an increased proliferative activity and the capability to secrete increased amounts of interleukin one (IL-1), IL-6, and platelet-derived growth factors and increased levels of leukotriene B4.

Psoriasis is not just a skin disease but is a systemic
inflammatory disease. Because of increased inflammation, psoriasis patients are more likely to have associated comorbidities, including cardiovascular disease, psoriatic arthritis, depression, obesity, diabetes, hypertension, and cancer. Someone with psoriasis is 58 percent more likely to have a major cardiac event and 43 percent more likely to have a cerebrovascular vascular accident. Patients with moderate to severe psoriasis incur significantly higher health care utilization and higher health care costs compared with those with mild disease (Exhibit 1).2

Goals of therapy include gaining initial rapid control of the disease, maintaining the patient in long-term remission and avoiding relapse, avoiding adverse effects as much as possible, and improving the patient’s quality of life. Patients present with a broad spectrum of symptoms and severity. A variety of treatment options are available and must be tailored to the patient needs.

Traditional treatment followed a stepwise progression. Patients had to fail the prior step of therapy before moving onto more aggressive therapy. In one patient survey study, 46 percent of people felt that psoriasis therapies were worse than the disease itself.4 Eighty-five percent felt that there is a real need for additional therapies. Therapy has moved to severity-based treatment (Exhibit 2).5

Several new agents for psoriasis have been approved in recent years. One nonbiologic systemic therapy, apremilast (Otezla®) is an oral agent FDA approved for treatment of moderate to severe plaque psoriasis and active psoriatic arthritis. This agent is a phosphodiesterase-4 (PDE4) inhibitor that reduces inflammation. Treatment with this agent results in 33 percent of patients achieving a 75 percent reduction in their Psoriasis Area and Severity Index score (PASI-75) compared with a 5 percent response with placebo.6

Biologics have revolutionized the treatment of moderate to severe plaque psoriasis. Those approved include etanercept (Enbrel®), adalimumab (Humira®), infliximab (Remicade®), ustekinumab (Stelara®), secukinumab (Cosentyx®), and ixekizumab (Taltz®). All of these, except infliximab, are given as subcutaneous injections with varying dosing schedules. Infliximab is given as an intravenous infusion. All of the biologics significantly improve the PASI-75 score in short-term trials.

Etanercept, adalimumab, infliximab are all anti-tumor necrosis factor (TNF) agents. Ustekinumab is an anti-IL-12 and 23 agent. Secukinumab, an anti-IL-17A agent, is one of the two newest agents. In trials, it has produced superior results to etanercept and ustekinumab.7 A second anti-IL-17A agent, ixekizumab, was approved in early 2016 and was also shown superior to etanercept.8

In general, specialty drug management, which includes the biologics, is posing multiple challenges to managed care (Exhibit 3).9 Treatment of inflammatory conditions including psoriasis is the largest category of specialty spending. According to Express Scripts, in 2015, inflammatory conditions were the most expensive specialty therapy class for the seventh year in a row.10 The per-member-per-
In treating psoriasis, it is still about the right therapy for the right patient while being fiscally responsible. Management strategies to control psoriasis costs include step therapy through nonbiological immune-modifiers before biologicals, prior authorization of biological agents, preferred biological agents, limiting prescribing of biologicals to appropriate specialists, guideline-based management, and managing site of service. Other payer strategies in 2016 and beyond include newer benefit designs, multiple tiers of specialty benefit, consideration of the emerging biosimilar marketplace, specialty specific formularies, and alignment of patient incentives. And things will get more complicated as more agents are approved.

There are numerous additional biologic agents in the pipeline for psoriasis treatment. Some include brodalumab, an IL-17 blocker; guselkumab, an anti-IL-23p19; tildrakizumab, an anti-IL-23p19; and risankizumab, an anti-IL-23. Brodalumab was recommended for FDA approval in July 2016 by the Dermatologic and Ophthalmic Drugs Advisory Committee; however, at the time of this writing, it has not yet been FDA approved. It binds to the in-
terleukin-17 (IL-17) receptor and inhibits inflammatory signaling by blocking the binding of several types of IL-17 to the receptor. By stopping IL-17 from activating the receptor, brodalumab prevents the body from receiving signals that may lead to inflammation. The IL-17 pathway plays a central role in inducing and promoting inflammatory disease processes.

**Conclusion**

Those with moderate to severe psoriasis have higher health care costs and utilization. To cost effectively manage those with significant disease, treatment selection should be based on disease severity rather than force patients through a stepped approach. Because of the cost of the newer agents for moderate to severe disease, managed care has implemented many strategies to control costs for psoriasis treatment. Additional biologics are on the horizon which will continue to be costly.

Gary M. Owens, MD, is President of Gary Owens Associates.

**References**

3. Thompson Medstat Marketscan Research Database
IN THE LAST 45 YEARS, THERE HAS BEEN A significant decline in deaths from many diseases, including some cancers. Unfortunately, the same cannot be said for deaths related to smoking. Although not all are attributable to smoking, there are more than 220,000 new cases of lung cancer annually and over 158,000 deaths. Lung cancer accounts for 28 percent of all deaths from cancer. Forty-eight percent of new lung cancer cases are in women.

Overall, there have been some minor improvements in five-year survival for lung cancer. It has increased from 12 percent in 1975 to 1977 to 18 percent in 2004 to 2010. Although Stage IV lung cancer cannot be cured, improvements have been made in survival even for this advanced disease stage. With new targeted treatments, median survival for Stage IV has increased from four to five months with no treatment to 24 months with targeted therapy.

The landscape of Stage IV treatment has been changing since the early 2000s. The treatment of lung cancer, like many other cancers, began changing with the identification of genetic mutations in tumors. Prior to this, lung cancer was simply divided by histology as small cell or non-small cell lung cancer (NSCLC). NSCLC includes adenocarcinoma, squamous cell, and large cell. Precision cancer medicine, or personalized medicine, is treatment planning based on detection of tumor growth and survival.

### Summary

The field of personalized therapy in advanced non-small lung cancer (NSCLC) continues to expand. There are now treatments targeting specific genetic mutations and therapies to activate the immune system against the tumor. Each of these types of therapies are helping to improve survival in advanced disease.

### Key Points

- Next-generation sequencing should be used to identify driver mutations in NSCLC.
- Targeted therapy and immune checkpoint therapy are both improving survival in Stage IV NSCLC.
- Liquid biopsy for identifying genetic mutations is on the horizon.

### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ALK</td>
<td>anaplastic lymphoma kinase</td>
</tr>
<tr>
<td>BRAF</td>
<td>v-Raf murine sarcoma viral oncogene homolog B</td>
</tr>
<tr>
<td>DOR2</td>
<td>discoidin domain-containing receptor tyrosine kinase 2</td>
</tr>
<tr>
<td>EGFR</td>
<td>epidermal growth factor receptor</td>
</tr>
<tr>
<td>ERBB2</td>
<td>erb-b2 receptor tyrosine kinase 2</td>
</tr>
<tr>
<td>FGFR/FGF</td>
<td>fibroblast growth factor receptor/fibroblast growth factor</td>
</tr>
<tr>
<td>HER</td>
<td>human epidermal growth factor receptor</td>
</tr>
<tr>
<td>KRAS</td>
<td>V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog</td>
</tr>
<tr>
<td>MEK1</td>
<td>mitogen-activated protein kinase</td>
</tr>
<tr>
<td>MET</td>
<td>MET proto-oncogene, receptor tyrosine kinase</td>
</tr>
<tr>
<td>NRAS</td>
<td>neuroblastoma Ras viral oncogene homolog</td>
</tr>
<tr>
<td>PDGFR</td>
<td>platelet-derived growth factor receptor alpha</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha</td>
</tr>
<tr>
<td>RET</td>
<td>RET proto-oncogene</td>
</tr>
<tr>
<td>ROS1</td>
<td>proto-oncogene tyrosine-protein kinase ROS</td>
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driver mutations. Driver mutations confer growth advantage and are causal to cancer development versus passenger mutation which are biologically neutral with no growth advantage. Driver mutations occur in genes that encode signal proteins critical for cellular proliferation and survival. Most driver mutations have been identified in adenocarcinomas.

In a landmark publication, the Lung Cancer Mutation Consortium found that 25 percent of adenocarcinomas had KRAS mutations (Exhibit 1). Unfortunately, there are no approved treatments yet targeting KRAS mutations. EGFR, ALK, ROS1, and MET mutations are the ones which have current approved targeted therapies. Therapy is being developed to target many of these known mutations.

Targeted therapy has made a significant difference in survival. In one database, presence of a driver mutation and targeted therapy led to a longer median survival (3.5 years) compared with those who did not have a driver mutation (2.1 years) and those with driver mutation who did not receive targeted therapy (2.4 years).

According the National Comprehensive Cancer Network (NCCN) guidelines, optimal genetic testing in lung cancer before treatment should include testing for at least the top eight mutations - EGFR, KRAS, ALK, ROS1, RET, MET, BRAF, and HER2. EGFR mutations are estimated to occur in 18,000 cases in the United States (U.S.) per year and ALK mutation in 9,000. Likely because of reimbursement issues, in clinical practice, testing is done for the top four and when those come back negative, the limited amount of tissue available is sent for additional testing.

Next-generation sequencing (NGS) can test for 300 or so genes at one time using one sample. Cutting-edge institutions are doing NGS with their lung cancer biopsy samples; however, everyone should be doing NGS. In one trial, it was found that 26 percent of patients had a treatable mutation that was only detected by NGS and another 39 percent had a mutation for which there were effective agents or trials ongoing in which they could be enrolled.

Before targeted therapy, chemotherapy was the front-line treatment for adenocarcinoma. If an EGFR mutation is present, targeted therapy is superior to chemotherapy for progression-free survival (PFS). Tyrosine kinase inhibitors (TKIs, erlotinib, gefitinib) are now first-line therapy for Stage IV adenocarcinoma that has activating mutations. The five-year survival for EGFR mutation-positive disease treated with a TKI is 14.6 percent and median overall survival is 30.9 months.

After about a year of therapy with an EGFR targeting TKI, the tumor will develop resistance to therapy. The most common mechanism in tumors that started with an EGFR mutation is development of a T790M mutation. This mutation occurs in about 60 percent of those who develop resistance to an EGFR TKI. Agents are being developed specifically to target this mutation and one has made it to market. Osimertinib (Tagrisso®) leads to 2.8 months benefit in PFS in those with T790M mutation.
The second most common mutation in adenocarcinoma is ALK rearrangements. Crizotinib (Xalkori®) targets the ALK mutation. Response to this agent tends to be dramatic and occurs within a few weeks of starting therapy. Unfortunately, resistance develops in nine to 12 months. Second-line ALK inhibitors include ceritinib (Zykadia®) and alectinib (Alecensa®). About 50 percent of patients will respond to second-line therapy. Alectinib penetrates the central nervous system (CNS) much better than crizotinib and provides great CNS response rates. Although not FDA approved as first-line therapy, clinicians will likely be choosing it first in patients who present with CNS metastases. Brigatinib is another second-line ALK targeting agent, and it was granted orphan drug designatin by the FDA in May 2016. Lorlatinib is an investigational, third-generation agent. All of the agents that work for ALK-positive lung cancer are also effective for MET and ROS1 mutations.

Clinicians are now doing sequential therapy for patients with ALK rearrangements — a patient is treated with one agent until resistance occurs and then a different agent is started. Because tumors are constantly changing, patients can be cycled back to an agent previously used and have a tumor response. With sequential targeted therapy, some types of lung cancer are becoming a chronic disease.

MET exon 14 skipping mutations are recently recognized mutations found in some lung cancers. Additionally, there are gain of function alterations in MET that include gene amplification and protein over expression. The overall incidence of MET mutations is 3 percent in squamous cell and 8 percent in adenocarcinoma. Four percent of adenocarcinomas have MET exon 14 skipping mutations. Identification of these mutations requires NGS. An early report found effectiveness with crizotinib and carboplatin (investigational) in those with exon 14 skipping mutation.

Although the focus of targeted therapy in NSCLC has been on adenocarcinomas, research is underway for targeted therapy in squamous cell disease. Exhibit 2 illustrates the potential targets in squamous cell lung cancer. The early results of targeted therapy in squamous disease have not been as exciting as results in adenocarcinoma. There is now an EGFR targeted monoclonal antibody, necitumumab (Portrazza®), approved as first-line therapy in Stage IV squamous disease. This agent produces a 1.6 month improvement in median survival.

The immune checkpoint agents are the hottest class of agents in oncology. Essentially these agents activate the immune system to attack tumors by activating T cells. Nivolumab (Opdivo®), an anti-programmed death-1 (PD-1) agent, is approved as second-line therapy in advanced NSCLC. This agent improved one-year survival by 18 percent. Even in heavily treated patients, there are a group of patients who respond long term to nivolumab and clinicians are finding that patients can even go off of therapy.

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**Exhibit 2: Squamous Cell Cancer: Potential Targets**

- FGFR1 amp
- FGFR2/FGFR3 mut
- DDR2 mut
- PIK3CA mut
- PDGFRA amp
- BRAF mut
- EGFR amp
- ERBB2 amp
- Unknown

---

![Graph illustrating potential targets in squamous cell lung cancer. The largest segments are for unknown, DDR2 mut, PDGFRA amp, PIK3CA mut, and ERBB2 amp.](image-url)
for several years and still maintain response. Pembrolizumab (Keytruda®), another anti PD-1 agent, is approved for second-line therapy in advanced NSCLC without sensitizing mutations. There are a large number of other immune checkpoint agents under investigation for lung cancer.

Additional ways to identify genetic mutations in various cancers are also under investigation. The majority of testing failures for genetic testing are due to insufficient tumor tissue in a biopsy sample. Liquid biopsy is a way to overcome the need for tissue biopsy and the related risks such as lung collapse. Tumor cells release free DNA into the blood. Blood samples can identify both genetic and epigenetic aberrations of cancers and can be used to systematically track genomic changes in the tumor over time. Early trials are finding decent sensitivity, specificity, and positive predictive value. This type of noninvasive testing is likely to be widely adopted in the future.

Conclusion
Improvements in survival for Stage IV NSCLC continue to be made with development of additional targeted therapies. Next-generation sequencing should be used initially to identify as many genetic mutations in lung cancer biopsies as possible. Additional therapies such as check point agents are producing exciting results in those with advanced disease.

James R. Jett, MD, is Professor of Medicine Emeritus at National Jewish Health and Chief Medical Officer of Oncimmune LLC.

References
MULTIPLE MYELOMA (MM) IS A CANCER OF the plasma cell characterized by excessive numbers of abnormal plasma cells in the bone marrow. In 2016, 30,330 new myeloma cases and 12,650 deaths were predicted.\(^1\)\(^2\) Myeloma accounts for 1 percent of all cancer cases but 2 percent of deaths. The median age at diagnosis is 69 years and median age of death is 75 years.\(^2\)

Prognosis has significantly improved, with median survival estimated between seven to 10 years with use of the newer therapies and myeloma specific care. The five-year survival rate is 48.5 percent.\(^2\) The pool of patients with MM is increasing because patients are living longer with the disease. There are approximately 300,000 with MM currently in the United States, and this number is expected to double in the next five years.

Multiple myeloma is sensitive to treatment, but curable only in a small subset of patients. Progression is inevitable, requiring multiple lines of therapy. All patients will need salvage therapies eventually.

There is controversy over early treatment of MM versus waiting for symptoms to develop. The older treatments were much more toxic, whereas the newer treatments are better tolerated. It is now recommended that patients with high risk for conversion to symptomatic myeloma be treated early.

After successful first-line therapy, most patients with MM will eventually have a relapse. Exhibit 1 outlines the current treatment approach to relapsed/refractory MM.\(^3\)\(^4\) Novel agents for MM include immunomodulators [lenalidomide (Revlimid®), pomalidomide (Pomalyst®), daratumumab (Darzalex®), elotuzumab (Empliciti®), panobinostat (Farydak®)] and proteasome inhibitors [bortezomib (Velcade®), carfilzomib (Kyprolis®), ixazomib (Ninlaro®)]. These agents are used in various combinations with and without dexamethasone,
which by itself has some efficacy against myeloma cells. Other treatment options include chemotherapy, novel agents in combination with chemotherapy combinations, allogeneic stem cell transplant (SCT), salvage autologous stem cell transplant, and clinical trials. In patients who may be candidates for stem cell transplants, exposure to myelotoxic agents has to be limited to avoid compromising stem cell reserve.

The recommended treatment regimens for relapsed/refractory disease vary depending on prior treatments and patient factors (Exhibits 1 and 2). 

Primary therapy can be repeated if relapse occurred longer than six months since completion and there are no other contraindications. There are now numerous agents indicated for relapsed/refractory disease, so a patient can be treated with multiple lines of therapy.

Bortezomib has been the proteasome inhibitor of first choice, but subsequent lines of therapy include the other two newer agents – carfilzomib and ixazomib. Carfilzomib, a selective irreversible proteasome inhibitor, is approved for treatment of relapsed/refractory MM. Given intravenously, it resulted in a 23.7 percent overall response rate in a heavily pretreated population. The response lasts a median of 3.7 months with overall survival (OS) of 15.6 months. The major distinction from bortezomib, a reversible proteasome inhibitor, is a lower rate of peripheral neuropathy.

Ixazomib (Ninlaro®), the first oral proteasome inhibitor, is indicated in combination with lenalido-
Ixazomib and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy. This agent is a once-weekly pill. It was approved based on data showing progression-free survival (PFS) benefits of 4.5 months. At a median follow-up of approximately 23 months, the median overall survival had not been reached in either study group (ixazomib or placebo), and follow-up is ongoing.6

Lenalidomide has been the initial choice for immunomodulation, but there are now several other agents which can be used in those who have progressed on lenalidomide. Pomalidomide, an immunomodulatory lenalidomide analogue, is indicated for patients with MM who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on therapy or within 60 days of completion of the last therapy. When studied in a heavily pretreated population, 31 percent of patients achieved an overall response rate with pomalidomide in combination with dexamethasone and PFS was four months compared with 1.9 months for dexamethasone alone.7 Overall survival was also longer with the combination (12.7 vs 8.1 months).

Daratumumab is the first monoclonal antibody approved for treating MM and is an antibody against CD38 protein expressed on MM cells. It is FDA approved for use in those who have received at least three prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent or who are double refractory to combination of those two types of agents. Median PFS and OS was 4.0 months and 20.1 months, respectively, with daratumumab treatment.8

Elotuzumab is a monoclonal antibody directed against cell surface 1 (CS1), a member of the signaling lymphocyte activation molecule family (SLAMF). CS1 is present on MM cells in more than 95 percent of patients with primary MM. The mechanism of action of this agent appears to antibody dependent cellular cytotoxicity mediated by natural killer cells. It is approved in combination with lenalidomide and dexamethasone for the treatment of patients with MM who have received one to three prior therapies. The median PFS in the elotuzumab-containing arm was 19.4 months and 14.9 months in the lenalidomide plus dexamethasone alone arm.9

Panobinostat, the first approved histone deacetylase (HDAC) inhibitor, is given orally. It appears to slow the over-development of plasma cells in MM or cause these cells to die. It is indicated for use in combination with bortezomib and dexamethasone for those who have received at least two prior regimens, including bortezomib and an immunomodulatory agent. Median overall survival was 40.3 months in those who received panobinostat, bortezomib, and dexamethasone versus 35.8 months in

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**Exhibit 2: Determinants of Choice of Therapy at Relapse**

<table>
<thead>
<tr>
<th>Symptomatic Relapse</th>
<th>Consider clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapsed myeloma (prior lines of therapy 1-3)</td>
<td>Transplant based (in suitable pts)</td>
</tr>
<tr>
<td></td>
<td>Bortezomib/ixazomib based regimen</td>
</tr>
<tr>
<td></td>
<td>• Greater than median PFS post prior auto SCT</td>
</tr>
<tr>
<td></td>
<td>• No prior auto SCT (collect and store pts)</td>
</tr>
<tr>
<td></td>
<td>• Primary induction failure (cytoreduction followed by auto SCT +/- maintenance)</td>
</tr>
<tr>
<td></td>
<td>Lenalidomide Based regimen</td>
</tr>
<tr>
<td></td>
<td>• Prior IMiD</td>
</tr>
<tr>
<td></td>
<td>• Good response to prior BTZ therapy and relapsed at least 6 months after prior BTZ exposure</td>
</tr>
<tr>
<td></td>
<td>• Combination with HDAC inhibitors in PI resistance</td>
</tr>
<tr>
<td></td>
<td>• Renal insufficiency</td>
</tr>
<tr>
<td></td>
<td>• High risk cytogenetics, t(4;14)</td>
</tr>
<tr>
<td></td>
<td>Carfilzomib based regimens</td>
</tr>
<tr>
<td></td>
<td>• BTZ resistant pts</td>
</tr>
<tr>
<td></td>
<td>• LEN/THAL resistant pts Renal insufficiency</td>
</tr>
<tr>
<td></td>
<td>• Prior PI therapy</td>
</tr>
<tr>
<td></td>
<td>• Peripheral neuropathy (ixazomib may be considered)</td>
</tr>
<tr>
<td></td>
<td>• Partner for elotuzumab</td>
</tr>
<tr>
<td></td>
<td>High risk cytogenetics (combination with POM)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• High risk cytogenetics 17p (+/- combination with PI)</td>
</tr>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Currently approved as single agent for patients that have received 3 lines of therapy.</td>
</tr>
<tr>
<td></td>
<td>• Good safety profile and can combine with other agents</td>
</tr>
<tr>
<td></td>
<td>• Good preliminary activity among high risk pts</td>
</tr>
</tbody>
</table>

BTZ = bortezomib; CFZ = carfilzomib; LEN = lenalidomide; POM = pomalidomide; THAL = thalidomide; PFS = progression free survival; SCT = stem cell transplant; IMiD = immunomodulatory drugs; PI = proteasome inhibitor; HDAC inhibitors = histone deacetylase inhibitors
those who received placebo, bortezomib, and dexamethasone. This agent has a boxed warning about severe diarrhea and severe and fatal cardiac events including arrhythmias.

Despite major advances and newer options, clinicians face many challenges in optimizing therapy in MM. One issue is how to sequence the available regimens. Clinicians need to better understand how to tailor therapy to minimize toxicity yet retain efficacy, especially in heavily pretreated patients. Currently, there are no biomarkers for therapy personalization to maximize benefit from a given agent, but these will likely be available in the near future. There are numerous other agents under investigation for MM which target other cell surface receptors and proteins.

Conclusion
Novel agents in combination can achieve prolonged responses even in relapsed/refractory disease. Novel targeted therapies include agents targeted to cell surface receptors, HDAC inhibitors, cell-signaling inhibitors, and others. Novel agents are improving the survival of patients with relapsed/refractory MM; however, there are still issues to be resolved.

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References
THERE IS A TREMENDOUS BURDEN OF hepatitis C virus infection (HCV) in the United States (U.S.). The true prevalence of HCV is unknown, but there are thought to be over five million people chronically infected (Exhibit 1).\(^1\)\(^-\)\(^3\) Only about 25 percent of those with chronic infection have been diagnosed and, even worse, only 7 to 11 percent get treated.

The majority of people who get infected with HCV acutely will develop chronic HCV (75-85%). Sixty to 70 percent of those with chronic HCV will develop liver fibrosis and 25 percent will go on to develop cirrhosis. Cirrhosis can take up to 20 years from initial infection to develop. Those with cirrhosis are more likely to develop decompensated cirrhosis and hepatocellular carcinoma (HCC, 1-4%). HCV infection is the reason for 60 percent of all cases of HCC in the U.S.

The U.S. health care system is currently in a crisis of HCV-induced cirrhosis and its complications (hepatic decompensation, portal hypertension, ascites, variceal bleed, and encephalopathy), as a consequence of underdiagnosis and undertreatment of HCV. The peak of chronic HCV prevalence was in 2001. Because of the time lapse for development, the highest prevalence of cirrhosis is projected to be in 2020 when one million persons will have cirrhosis.\(^4\)

As mentioned before, there are a significant number of undiagnosed cases of HCV, and what is undiagnosed cannot be treated. Unfortunately, about one-third of undiagnosed Americans are estimated to have advanced fibrosis/cirrhosis.\(^4\) Primary care providers (PCPs) have a major opportunity to make a diagnosis of HCV early and refer for treatment before the development of cirrhosis and its complications. Early diagnosis and treatment can improve survival, improve quality of life, and will reduce the economic burden of HCV and result in cost savings.

Seventy-five percent of HCV cases are found in baby boomers (born between 1945-1965).\(^1\) The

**Summary**

With many new medication combinations, this is an exciting time to be involved in treating hepatitis C virus infection (HCV). These new therapies have very high cure rates and cause few adverse effects. Overall, care needs to be individualized to achieve cure.

**Key Points**

- The morbidity and mortality of chronic HCV can be reduced with successful treatment.
- Primary care physicians should screen all patients with risk factors, all baby boomers, and everyone with elevated liver function tests for HCV.
- High cure rates, short duration of treatment, and few adverse effects are all possible with new all-oral combinations.
- Oral therapy costs are offset by future savings through the prevention of liver-related complications.
rates are very high in baby boomers because HCV was not even diagnosed when this population was young, the blood supply was contaminated and there was no way to screen blood products, and there were no universal precautions in health care settings. The Centers for Disease Control and Prevention (CDC) and the U.S Preventive Services Task Force (USPSTF) recommend a one-time screening for all baby boomers.5,6

 Patients infected with HCV do not seek medical attention because they are usually asymptomatic and unaware of the risk factors (Exhibit 2).5 Fifty-six percent of infected people are asymptomatic. Overall, PCPs should screen all baby boomers, all patients with risk factors regardless of age, and all patients with elevated liver function tests.

 Once chronic HCV is identified, the patient should be evaluated for treatment. Previous history of any treatments, the genotype of the virus, and the disease stage are all important in treatment selection. The majority of cases in the U.S. are genotype 1 (70%).7 The other five genotypes are less common and some are more difficult to eradicate.7

 Chronic HCV is staged from F0 to F4. With F0 disease, there is no current evidence of fibrosis. As the disease progresses, fibrosis increases and spreads. At the F4 stage, the patient has cirrhosis with very little normal liver tissue.

 Disease staging has traditionally been done with a liver biopsy, but there are disadvantages of this method. It only samples a very small portion of the liver, is anxiety provoking, can have complications, and is costly ($2,500 to $3,000). Noninvasive options are becoming the standard, when available. Fibroscan and Aixplorer are devices that measure the velocity of the ultrasonic shear wave as the wave passes through the liver. The propagation velocity of the shear wave correlates with the elasticity of tissue. The velocity increases with increased stiffness of the liver parenchyma. Blood fibrosis tests (FibroSure, FibroTest, Hepascore, and Fibrospect) measure variations in biomarkers caused by changes in liver stiffness. These are good for staging patients with zero or minimal fibrosis and those with advanced fibrosis or cirrhosis but are less accurate for assessing mid-range fibrosis.

 Treatment guidelines from the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) in collaboration with the International Antiviral Society–USA (IAS–USA) provide guidance on HCV treatment.8 The goal of HCV treatment is to reduce all-cause mortality and liver-related health adverse consequences such as end-stage liver disease and HCC by achievement of virologic cure or sustained virologic response (SVR). A SVR is an undetectable HCV RNA three months after completion of treatment. An SVR is synonymous with “cure.” SVR rates with current recommended oral regimens are greater than 96 percent in those who have never been treated before (treatment naïve).

 HCV infection needs to be treated early for several reasons. It is a progressive disease that increases morbidity and mortality, which can be reduced with

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Exhibit 1: The Burden of Chronic HCV in the U.S.1-3

- 5.1 million estimated true prevalence (1.6%)
- 3.9 million CDC NHANES estimate (1%)
- 25% HCV detected
- 7% to 11% treated

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successful treatment. Treatment delays can decrease the benefit of SVR and allow for the development of severe liver disease and liver-related complications. Many insurance companies will only pay for treatment of those with advanced fibrosis. The guidelines state that treatment deferral practices based on fibrosis stage alone are inadequate and shortsighted. Curbing HCV at any stage, regardless of baseline fibrosis, results in decreased all-cause mortality, liver-related death, need for liver transplantation, hepatocellular carcinoma rates, and liver-related complications and improvement or prevention of extrahepatic complications and quality of life.

The guidelines no longer recommend prioritizing patients for treatment. Because of the many benefits associated with successful HCV treatment, treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCC. All patients should be treated as promptly as feasible to improve health and to reduce HCV transmission.

Interferon and ribavirin were the first two therapies approved for HCV management. The unsatisfactory response rate in genotype 1 (54-56%) to these two agents and significant adverse effects with interferon led to the development of the direct-acting antivirals (DAAs) that directly inhibit viral replication. The DAAs have revolutionized chronic HCV therapy by being oral agents and very tolerable, having high cure rates, and being aimed at very specific targets in the life cycle of the HCV virus. In 2014, the holy grail of hepatology was achieved with the introduction of interferon-free regimens for genotype 1.

There are four classes of DAAs (Exhibit 3). To prevent emergence of resistance, a combination of DAAs must be used. Most of these combinations only need to be given once a day, which enhances adherence. Some are as two separate tablets or a single tablet.

Because therapy for HCV is changing rapidly, the AASLD, IDSA, and IAS-USA have developed a web-based process for the rapid formulation and dissemination of evidence-based, expert-developed recommendations for HCV management. These up-to-date guidelines can be found at hcvguidelines.org. Because the recommendations change rapidly, a table of recommended regimens is not published here.

With many different choices for HCV treatment, clinicians can use several factors for individualizing care. These include genotype and subtype, naïve or prior treatment experience, presence or absence of cirrhosis, presence of harder-to-treat conditions, and presence or absence of baseline nonstructural protein 5A (NS5A) resistance-associated variants (RAVs). About 10 to 15 percent of HCV genotype 1 patients, without prior exposure to NS5A inhibitors, will have detectable NS5A RAVs prior to treat-
ment. This causes a large reduction in the activity of NS5A inhibitors. Currently, baseline testing for NS5A RAVs is only recommended if the elbasvir/grazoprevir (EBV/GZV) combination is selected for genotype 1a treatment. This is an evolving area, so recommendations for testing will likely change.

The standard of care for treating HCV infection in treatment naïve patients is an all-oral regimen of at least two agents; ribavirin is recommended to be added in some instances. The current duration of therapy is eight to 24 weeks, depending on which therapy is selected and presence of cirrhosis. An eight-week duration of treatment can be considered when sofosbuvir/ledipasvir is used in treatment-naïve patients without cirrhosis with genotype 1 who have pre-treatment HCV RNA less than 6 million IU/mL. Regimens for the various genotypes, those with cirrhosis, and those who are naïve or have had prior treatment are specified in the treatment guidelines.

Hard to treat populations include those with decompensated cirrhosis, renal impairment, genotype 3 HCV infection, HCV/HIV coinfection, and post-liver transplant. Patients with decompensated cirrhosis ideally should be treated in a liver transplantation center because they can become ill quickly. The SVR rates in this population are 83 to 86 percent, but achieving a SVR improves survival in those with decompensated cirrhosis. This is an area where new regimens are needed. Two regimens, paritaprevir/ritonavir/ombitasvir/dasabuvir (PrOD) and paritaprevir/ritonavir/ombitasvir (PrO), which can cause further decompensation need to be avoided in these patients.

At lower levels of renal function, medication doses may need to be adjusted. At levels of 30 ml/min and above, most agents can be used and only ribavirin requires dosage adjustment. Sofosbuvir is not recommended for use in patients with renal function of less than 30 ml/min. Safety and efficacy of many of the medications have not been determined at very low levels of renal function (<15 ml/min). EBZ/GZV is the only regimen that does not require any renal dosage adjustment.

Genotype 3 has been the most difficult genotype to treat. Fibrosis progression occurs more rapidly than with other genotypes, and there is a higher prevalence of severe steatosis and higher incidence of hepatocellular carcinoma in those infected with genotype 3. The SVR rates with DAA combinations for genotype 3 are lower than with genotype 1 (82-96% vs 95-98%).

The same treatment recommendations (naïve and treatment experienced), as in patients without HIV, are recommended for those coinfected with HIV. The primary consideration in selecting a HCV treatment in a coinfected patient is potential drug-drug interactions with antiretroviral therapy. It is important that treatment is coordinated with the patient’s HIV specialist.

Post-liver transplant is the last hard to treat population. HCV accounts for almost 50 percent of liver transplants in the U.S. All patients with detectable HCV RNA at the time of transplant will infect the graft liver. Reinfection occurs as soon as reperfusion of the allograft takes place in the operat-
ing room and viral titers reach pretransplant levels within 72 hours. The likelihood of developing cirrhosis in the newly transplanted liver over three to five years post-transplant is 10 to 30 percent. The goal in those who are awaiting transplant is to suppress HCV RNA to an undetectable level for at least 30 days prior to transplant to prevent the graft liver from becoming infected with the HCV virus. Patients with longer periods of undetectable HCV RNA prior to transplant have better post-transplantation SVR rates. Patients who continue to have HCV post-transplant can be treated; the guidelines provide recommended regimens which can achieve SVR rates of 94 to 96 percent.

The safety profiles of all the recommended regimens are excellent. Across numerous Phase III programs, less than 1 percent of patients without cirrhosis discontinued treatment early and adverse events were mild. Most adverse events occurred with ribavirin-containing regimens. Discontinuation rates were higher for patients with cirrhosis but still very low (approximately 2% for some trials). Drug interactions are another safety consideration in managing DAA therapy. All of the DAAs interact with at least a few medications. Sofosbuvir has the fewest drug interactions.

Curing HCV can be very expensive in terms of medication costs and have led to significant debate about the costs of treatment. When considering the costs of HCV treatment, the cost of not treating the infection is important to consider. While the prevalence of HCV infection is declining from its peak, the incidence of advanced liver disease, cirrhosis, and HCC and associated health care costs continue to rise. HCV health care costs are substantial and will continue to increase exponentially through 2030 due to progressive liver disease.10,11

Although the DAA regimens are expensive in terms of acquisition costs, they are cost effective. Curing HCV markedly reduces the national cost of treating cirrhosis and hepatocellular carcinoma ($30,000-$70,000 annual cost x 5 to 10 years/patient) and markedly reduces need for liver transplantation ($350,000-$577,000/transplant + $145,000 year maintenance). On an individual health plan basis, the per member per month health care costs are 24 to 35 percent lower in those who receive treatment compared to an untreated population.12

Early treatment of HCV is financially beneficial. Fewer patients will progress to more advanced fibrosis and end-stage liver disease; the cost for treating HCV is significantly higher for those with more severe disease.13 A SVR in non-cirrhotic HCV patients prevents the development of cirrhosis and its complications. A SVR in compensated cirrhosis lowers the rate of complications, liver cancer, and transplant. Overall, SVR improves all-cause mortality, quality of life, and increases life expectancy.14-16

The U.S. is unique among Western countries in that it does not regulate drug prices. Actual U.S. drug costs paid are rarely known by consumers. Pharmaceutical companies determine the wholesale acquisition cost (WAC) of a drug; pharmacy benefit managers and insurance companies negotiate for rebates and discounts that decrease the actual price paid. Negotiations of drug prices are considered confidential business contracts, so there is almost no transparency regarding the actual prices paid. Market-based competition has driven down the cost of HCV drugs. Recently approved EBV/GZV has a WAC of $54,600, about the same price as average discounted ledipasvir/sofosbuvir (LED/SOF) and ProD.

Cost-effectiveness studies published in 2015, even using the higher WAC prices, have shown that DAA regimens are cost effective for most patients, within the range of other accepted medical therapies. Cost-effectiveness does not take into account affordability.

Affordability refers to whether a payer has sufficient resources in its annual budget to pay for a therapy for all who need it. The challenge is to pay for HCV drugs which have high upfront costs incurred over a short period of time. Many payers have limited coverage to only those with advanced fibrosis and cirrhosis because of budgetary constraints. Many clinicians and bioethics professionals have called this rationing.

HCV coverage limitations have raised some serious ethical questions. There are a large number of people with HCV for which we have a cure for almost everybody, yet many are not being treated. There are not many other curable conditions where many patients are told that they have to be sicker before they can be treated. Limiting access as a way to cope with price is not the answer; driving down the price is a likely option. Insurers, government, and pharmaceutical companies should work together to bring medication prices to the point where all of those in need of treatment are able to afford and readily access it.

There are more DAAs under study which will hopefully continue to raise the SVR rates closer to 100 percent, further reduce adverse effect rates, allow increasingly shorter treatment regimens, and be effective for all six genotypes (pangenotypic). There is hope that in the future we can treat people for as little as four weeks to produce a cure.

**Conclusion**

HCV is a major cause of chronic liver disease, cirrhosis and hepatocellular carcinoma. Clinicians
should screen all patients with risk factors and all baby boomers for HCV. A dramatic paradigm shift in HCV treatment is here, with new DAA combinations that promise higher cure rates, shorter treatment duration and fewer side effects. Virtually every patient with chronic HCV should be treated.

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References
MULTIPLE SCLEROSIS (MS) IS A NEURODEGENERATIVE DISORDER OF THE CENTRAL NERVOUS SYSTEM (CNS) THAT IS PRESUMED TO BE AUTOIMMUNE. THE WORLDWIDE INCIDENCE IS 0.1 PERCENT, AND IT OCCURS MORE OFTEN IN WOMEN (1 IN 200) THAN IN MEN (1 IN 400). THE RATE IN WOMEN HAS BEEN INCREASING BUT MEN TYPICALLY HAVE A MUCH WORSE PROGNOSIS. APPROXIMATELY 400,000 PEOPLE HAVE MS IN THE UNITED STATES. THERE IS A HIGHER INCIDENCE IN THOSE OF NORTH-EASTERN EUROPEAN DESCENT AND IN TEMPERATE CLIMATES, BUT THE LATITUDE GRADIENT IS DECREASING. THE AGE AT DIAGNOSIS IS BETWEEN 20 AND 40.

In MS, the immune system attacks the nervous system, forming plaques or lesions commonly involving brain white matter. These attacks destroy oligodendrocytes causing demyelination (Exhibit 1). Remyelination occurs in the early phase of the disease but not completely. Repeated attacks lead to less remyelination.

Both T and B cells appear involved in the pathogenesis of MS. The currently predominant hypothesis of MS is that autoreactive T lymphocytes cross the blood-brain barrier (BBB) and trigger inflammatory events which results in axonal demyelination and neuronal damage. Normally, the BBB prevents entrance of T cells into the nervous system. Infection or another environmental trigger decreases the integrity of the BBB allowing T cell entry.1 When the blood–brain barrier regains its integrity, usually after the inciting event has cleared, the T cells are trapped inside the brain. T cell attacks on myelin trigger additional inflammatory processes, stimulating other immune cells and soluble factors like cytokines and antibodies. Leaks form in the BBB causing swelling, activation of macrophages, and more activation of cytokines and other destructive proteins.

B cells are also involved in the pathophysiology of MS.2 The level of B cell involvement may vary in...
MS patients. The most frequently found pattern of lesion pathology is characterized by significant antibody deposits and complement activation, suggesting that the locally produced antibody response by B cells may indeed contribute to CNS demyelination. Besides differentiating into antibody-secreting plasma cells, B cells may contribute to the development and progression of CNS autoimmune disease as antigen-presenting cells for activation of T cells.

MRI scans have become the tool for diagnosis of MS because lesions, even subclinical ones, can be seen in the brain. The brain will demonstrate lesions termed T1 and T2. T1 lesions are new or acute lesions that appear as dark areas on the scan. These typically disappear within three months but may also remain showing an area of total destruction of neurons. T1 lesions correlate with disease acuity. T2 lesions, white areas on the scan, loosely correlate with disease burden.

Clinically isolated syndrome (CIS) is the first MS attack experienced by a patient. CIS can be optic neuritis, transverse myelitis, or isolated brain stem cerebellar syndrome. Patients can be classified as low or high risk for developing clinically definite MS based on brain MRI findings of silent lesions.

Several subtypes of clinically definite MS are recognized. Eighty-five to 90 percent of MS cases at onset are characterized by episodes of relapse (relapsing-remitting multiple sclerosis, RRMS). The remaining 10 to 15 percent of patients will have primary-progressive MS. These patients have a slow worsening from disease onset. Primary-progressive MS has about equal gender onset and a decade later age of onset than RRMS. These patients may have superimposed relapses. Secondary-progressive MS is when an initial relapsing patient transitions to slow worsening disease. The natural history of RRMS is to start out as relapsing, then transition to the secondary-progressive subtype.

With increasing understanding of the underlying pathophysiology of this disease, several disease-modifying therapies (DMT) for RRMS have been developed since the early 1990s (Exhibit 2). All of these FDA approved agents reduce the annualized relapse rate (ARR), disability, and MRI evidence of disease in RRMS. The first-generation agents – interferon beta-1a, interferon beta-1b, and glatiramer acetate – have years of patient experience for MS and still have a large number of users and new starts. These agents are many times termed platform agents because they tend to be the first agents started.

Interferon beta (Avonex®, Betaseron®, Extavia®, Rebif®, Plegridy®) is administered by self-injection in varying regimens of once daily to once every two weeks, depending on the product. The newest interferon product, peginterferon beta-1A (Plegridy®), is only injected every two weeks. Interferon diminishes the ability of activated T cells to cross the blood-brain barrier and enter the CNS. Injection site necrosis and flu-like symptoms are potentially limiting adverse events.

Glatiramer acetate (Copaxone®) is a self-injected polymer of four amino acids that compete with antigen-presenting cells for binding to the T cell. This
agent is an inducer of specific T helper 2 type suppressor cells. Injection site reactions, chest pain, flushing, dyspnea, and palpitations may be adverse events.

Mitoxantrone (Novantrone®), a chemotherapy agent, is FDA approved for MS treatment. It was originally suggested for highly active RRMS and possibly early progression and results in a 50 percent reduction in ARR. The issue with this agent is the adverse effects of cardiotoxicity and promyelocytic leukemia. Because the newer agents are safer and more effective, there is minimal current use in MS of mitoxantrone.

Natalizumab (Tysabri®), an integrin α4 blocker, stops circulating lymphocytes from entering the CNS. Monthly infusions of natalizumab provide effective relapse suppression (68% reduction). Progressive multifocal leukoencephalopathy (PML) is a rare adverse effect that occurs in about 0.1 percent of patients treated with this agent. This potentially fatal adverse effect occurs in people infected with John Cunningham virus (JC virus). The JC virus is a polyomavirus and infection is almost universal; however, the virus is dormant in the majority of the adult population. Risk of PML can be assessed with JC virus testing. The risk of PML appears to increase with time on treatment; the rate is very low in the first year and increases after two or more years of treatment.

The next generation of MS treatments began with the approval of oral agents. Fingolimod (Gilenya®), an oral sphingosine-1-phosphate receptor modulator, induces rapid and reversible sequestration of lymphocytes in lymph nodes and prevents activated and autoreactive cells from migrating to the CNS. Lymphocytes remain functional and may still be activated as part of an immune response. This agent crosses the BBB and may have neuroprotective properties. The first dose must be given in the hospital due to potential for bradycardia and atrioventricular block. Other adverse effects of concern are macular edema and hypertension. Relapse reduction is 55 percent with this agent.

Teriflunomide (Aubagio®) inhibits pyrimidine synthesis and binds dihydroorotate dehydrogenase, the fourth enzyme in de-novo pyrimidine synthesis thus inhibiting T cell division. Its parent compound, leflunomide, is used in treatment of rheumatoid arthritis. It reduces ARR in RRMS by 31 percent.

Fumarate is a naturally occurring molecule that is essential for cellular oxidative respiration (citric acid cycle). Dimethyl fumarate’s (Tecfidera®) proposed mechanism of action is a direct antioxidant effect with normalization of energy metabolism, inhibition of inflammation, and repair/degradation of damaged proteins and DNA. This agent reduces ARR in RRMS by 50 percent.

The oral agents have the advantages of oral convenience, very good efficacy, and good tolerability. On the negative side, there is limited experience with using the oral agents and no long-term safety or efficacy data. This data are being accumulated now.

Two additional injectable agents have also been approved as next-generation agents. Alemtuzumab (Lemtrada®) is a recombinant humanized mono-

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Exhibit 2: Relapsing/Remitting MS Drug Treatment Timeline

<table>
<thead>
<tr>
<th>First Generation Therapies</th>
<th>Next Generation Therapies</th>
</tr>
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<tbody>
<tr>
<td>Betaseron®</td>
<td>Tecfidera®</td>
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<tr>
<td>Avonex®</td>
<td>Zinbryta®</td>
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<tr>
<td>Copaxone®</td>
<td>Aubagio®</td>
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clonal antibody that targets CD52, a glycoprotein present at high levels on the surface of mature T and B lymphocytes. Treatment with alemtuzumab produces a very rapid and almost complete depletion of circulating CD52 positive cells. ARR is reduced by 49 percent with alemtuzumab. Due to its cell-depleting effect, alemtuzumab is also FDA approved for the treatment of B cell chronic lymphocytic leukemia (marketed as Campath®).

Alemtuzumab is administered as an intravenous injection over two hours daily for five days. A second course of three doses is given 12 months after the first. Black box warnings for alemtuzumab include cytopenias, infusion reactions, and infections. Premedicating with an oral antihistamine and acetaminophen prior to dosing and monitoring closely for infusion-related adverse events is required. Treated patients require anti-infective prophylaxis to reduce risk of infection due to the severe and prolonged lymphopenia.4

T cell depletion for alemtuzumab is long lasting. In trials, CD4+ cells were depleted for a median of five years and CD8+ cells for 2.5 years. Monocytes and B cells return to normal more quickly, usually within three months. B cell counts then continue to increase and still exceed pretreatment levels by approximately 124 percent nearly two years later. These differing temporal patterns in immune cell repopulation result in a skewed immune repertoire. This is presumed to result in the paradoxical development of new autoimmune disorders in approximately 30 percent of MS patients treated with alemtuzumab in clinical trials. Because of its safety risk, this agent is generally reserved for patients who have had an inadequate response to two or more therapies.

Daclizumab (Zinbryta®), an interleukin-2 receptor blocking antibody, was approved for RRMS in 2016. Like alemtuzumab, this agent is labeled for use in people who have not had therapeutic success with two or more other agents. Autoimmune hepatitis and other immune-mediated disorders can occur; thus, this agent carries both a black box warning and is only available through a restricted distribution Risk Evaluation and Mitigation Strategies (REMS) program. It is given by self-injection once monthly and reduces ARR by 54 percent.

DMT in RRMS currently is selected based on patient and neurologist preference, clinical symptoms and MRI findings. Clinicians do not yet know how to individualize therapy using biomarkers. Establishing satisfactory biomarkers for MS has proven to be very difficult, due to the clinical and pathophysiological complexities of the disease. Potential new biomarkers are divided into three subgroups – genetic-immunogenetic, laboratory, and imaging. Example biomarkers under study include chemokine and cytokine, adhesion molecules, genetic markers, vitamin D, T and B cell characteristic markers, natural killer cell markers, markers...
of BBB disruption, and myelin basic proteins. The ultimate goal would be better predictors for prognosis, medication selection, disability progression, and adverse event prediction.

There is currently insufficient Class I evidence for a detailed MS treatment algorithm. The lack of definitive clinical evidence to guide MS treatment decisions has become increasingly important as the number of therapeutic options continues to increase annually. Payers struggle with which drug is right for which patient, while balancing costs, outcomes and access. In an effort to control costs, most payers have a contracted interferon because there are multiple products.

One approach by payers was presented in a study that used a modified Delphi process to develop consensus statements regarding MS management approaches. In a live consensus meeting with 14 panel members who were experts in managed care, eight pharmacy directors and six medical directors from 12 U.S. health plans, one specialty pharmacy, and one consulting company were represented. All were presently or previously involved in the formulary decision-making process at their organization. This group did produce several consensus recommendations but did not agree on a standardized treatment approach (Exhibit 3). These recommendations were made before several of the newer medications were approved.

One of the important recommendations made by the previously discussed study was that there is a need for patient compliance and support while on disease-modifying therapy. Payers make a large lifetime investment in MS treatments. Adherence to therapy in MS, like all chronic diseases, can be an issue, especially if the disease is controlled and the patient does not understand the reason for continuing therapy. If a patient does not appropriately use their therapy, money is being wasted.

MS patients may stop their medications for many different reasons. Factors that can influence adherence to DMT include medication tolerability, patient physical and cognitive decline, frequency and complexity of the dosing regimen, duration of the disease and treatment, patient perceptions of medication benefits and risks, and economic burden associated with medication. Interventions aimed at optimizing medication adherence by a patient with MS need to incorporate new and creative approaches that take individual patient needs and lifestyle into account. When considering a DMT, it is important to evaluate the safety and tolerability profile of the drug, the individual patient’s needs and lifestyle, and how the specific requirements and characteristics of the drug intersect with the individual patient’s profile.

There are numerous agents in the drug development pipeline for MS. Ofatumumab (Arzerra®) is currently used for chronic lymphocytic leukemia and is being investigated for MS. It depletes B cells via antibody-dependent cell-mediated toxicity and complement-dependent cytotoxicity. Ocrelizumab is a humanized anti-CD20 monoclonal antibody that targets mature B lymphocytes and hence is an immunosuppressive drug. Treatment with this agent has demonstrated a statistically significant reduction in disease activity as measured by brain lesions (measured by MRI scans) and relapse rate compared to placebo. It has been given a breakthrough therapy designation for primary-progressive MS, but is not yet FDA approved.

Conclusion

The MS therapeutic arena continues to expand and the expense of these agents prompts managed care to pay close attention to them. Many clinicians start with the traditional first-line therapies because of the length of experience with them, saving the newer agents for later use, but there are no consensus guidelines for selecting therapy. Clinical symptoms and MRI findings remain mainstay methods for selecting and monitoring therapy but biomarkers are under study for this purpose. Most importantly, with these expensive but effective therapies, long-term adherence needs to be facilitated.

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References
IN 2016, MELANOMA WAS THE FIFTH AND sixth most common type of cancers in men and women, respectively.\(^1\) There has been a significant increase (~3.1% per year) in the incidence of melanoma since the 1960s.\(^2\) This increase is partially due to increased sun exposure. Tanning beds are a significant cause in young women. In the United States (U.S.), lifetime risk of melanoma is one in 36 for men and one in 57 for women. Overall, one person dies every hour in the U.S. from melanoma.

Overall survival of patients treated with different therapies for melanoma varies by the extent of the disease. Those with metastatic disease have the worst prognosis. Before the development of agents targeting the immune system, the median survival with a metastatic melanoma diagnosis was eight to 12 months with single agent and doublet chemotherapy treatment, respectively.\(^3\) Interferon and interleukin-2 in combination with chemotherapy produced a similar median survival. Unfortunately, none of these improved overall survival (OS). Agents approved since 2011 have begun to improve median and overall survival in metastatic disease.

Melanoma is one cancer that is highly immunogenic - the immune system can be manipulated against the disease. Because of this, the treatment of melanoma is moving to strategies that target the immune system. Exhibit 1 illustrates how these strategies act to win the host versus tumor battle.

Supplementing the immune system is one avenue for stimulating the immune system to work against melanoma. Treatment with high-dose interleukin-2 (IL-2) does result in a durable response in a small percentage of patients (15-18%). If a patient responds to IL-2 and stays in remission for 24 months, they can be considered cured. While IL-2 can cure some, it is a very toxic therapy. It is toxic to virtually every organ system and needs to be administered in specialized centers in an ICU-like setting with continuous cardiac monitoring. Patients must clear...
several hurdles before being approved for this therapy, including normal nuclear stress tests, pulmonary function tests, and brain imaging.

The second way to target melanoma with the immune system is to block suppressive elements. The activity of the T cells is controlled by a series of regulatory molecular interactions, including those between cytotoxic T cell lymphocyte–associated antigen 4 (CTLA-4) and antigen presenting cells (APC) and between programmed death-1 (PD-1) and its main ligand, PD-L1 on the melanoma cell. CTLA-4 and PD-1 are the brakes on the immune system; they prevent the immune system from being overactive and leading to autoimmune disease. Shutting down these checkpoints on the immune system allows T lymphocytes to recognize and destroy melanoma cells.

Ipilimumab (Yervoy®) is an anti-CTLA-4 antibody. In trials it improves median OS by three to four months. This was the first agent shown to provide any improvement in median OS in metastatic melanoma. With ipilimumab, a cure of metastatic disease is possible. In one study, the three-year survival rate was 22 percent. The longest survival in published data has been almost 10 years. Like with IL-2, not everyone responds to ipilimumab.

The other checkpoint therapy is anti-PD-1. Nivolumab (Opdivo®) was the first agent in this class. It results in a three-year survival rate of 42 percent and 32 percent at four years, even in heavily pretreated patients. It is now approved as first-line therapy in metastatic melanoma. Pembrolizumab (Keytruda®) is the second anti-PD-1 agent. In two trials for FDA approval, pembrolizumab was superior to ipilimumab.

Given that only a percentage of patients respond to checkpoint therapy, clinicians began studying the combination of agents. Combining ipilimumab and nivolumab is superior to ipilimumab alone, but the increases in median survival come at a cost. The combination leads to significantly higher rates of high grade adverse effects (54 vs 24%) and therapy discontinuation. The adverse effects come from unleashing the immune system. It is not known if the combination is better than nivolumab alone because this was not studied.

Provider and patient education and communication is key to early recognition and treatment of immune reactions with checkpoint therapy. Dermatitis, colitis, hypophysitis (pituitary gland inflammation and failure), and hepatotoxicity are the major toxicities. Grade 3 and 4 reactions have to be treated early and aggressively with steroids. Steroid use is not believed to hamper the therapeutic effect of checkpoint therapy. Treatment may also require additional immune suppression with infliximab. Importantly, the checkpoint therapy has to be stopped until the reaction is resolved.

Low grade dermatitis can be treated with topical steroids and antihistamines while also continuing the checkpoint therapy. If grade 3 or 4 (more than 30% of body) dermatitis occurs, and it has to be
treated systemically and with checkpoint therapy interruption.

Pembrolizumab and nivolumab cause grade 1 and 2 colitis in 8 to 20 percent of patients. One to 3 percent will have a grade 3 to 4 reaction. Ipilimumab causes higher rates (23-35% grade 1-2 and 2-9% grade 3-4). Grade 1 to 2 colitis (<6 stools/day) can be managed with an anti-diarrheal and holding checkpoint therapy. If diarrhea continues for over a week with minimal improvement, then oral prednisone is given. Grade 3 to 4 colitis (>7 stools/day) treatment requires holding checkpoint treatment and oral prednisone tapered over one month. If diarrhea persists despite high-dose steroids, infliximab infusions are given to suppress the immune system.

Checkpoint therapy can take some time to be effective. Clinicians have found that combining it with radiation leads to an improved response.

Four cancer centers around the U.S. (Moffitt, University of Pennsylvania, National Cancer Institute, University of Washington) are doing clinical trials of adoptive cell transfer, which is a method of generating autologous tumor infiltrating lymphocytes (TILs). A resected melanoma specimen is divided into multiple tumor fragments that are individually grown in IL-2 (Exhibit 2). The lymphocytes overgrow, destroy tumors within two to three weeks, and generate pure cultures of lymphocytes that can be tested for reactivity in co-culture assays. Individual cultures of TILs are then rapidly expanded. By approximately five to six weeks after resecting the tumor, up to 1011 TILs can be obtained for infusion into patients who have been treated with chemotherapy to suppress their immune system.

Activating mutations in BRAF (v-Raf murine sarcoma viral oncogene homolog B) are present in 40 to 60 percent of melanomas. Vemurafenib (Zelboraf®) was the first BRAF inhibitor approved by the FDA. About 60 percent of patients will initially respond to a BRAF inhibitor but the tumor becomes resistant to the therapy after about six to 12 months. The combination of BRAF and MEK (mitogen-activated protein kinase) inhibition [dabrafenib (Tafinlar)/trametinib (Mekinist®) or vemurafenib/cobimetinib (Cotellic®)] is now the standard therapy for BRAF- mutated disease to prevent development of resistance.

The cost of treating melanoma is significant. In melanoma, one course of IL-2 can cost $100,000. A course of ipilimumab can cost $159,000, pembrolizumab $83,000 and dabrafenib/trametinib $226,000. The median out-of-pocket cancer expenses in the
U.S. are $1,730 to $4,727 per year. In addition to the direct costs of care, the indirect costs of disability, medical-related absenteeism lost productivity, and travel/accommodation costs have to be considered. Cancer can be a financially toxic disease.

Risk factors for financial distress include younger age at diagnosis, low income or low savings, patients with dependent children, and patients lacking adequate social support. Only 15 percent of oncologists are cognizant of their patient’s financial well-being. The solution needs to come from physicians, patients, industry, policy makers, health care stakeholders, and third-party payers.

Dose rounding with ipilimumab is one way to save some money for health plans. The FDA approved dose is 3mg/kg/dose. For an 80kg person, the acquisition cost at this dose is $115,200 per course. This medication is supplied in 50 and 200mg vials, but any unused medication has to be discarded. In one trial, dose rounding to the nearest 50mg (up or down) resulted in significant cost savings. This trial estimated that dose rounding could save $22 million per year in the U.S.12

Another option is shortening the infusion time of ipilimumab from the FDA labeled 90 minutes to 30 minutes. Thirty-minute infusions improve patient convenience and are a more efficacious use of infusion centers. Shortening the infusion time has been studied and found to be safe for the lower approved dose of 3 mg/kg.13 The incidence of infusion-related reactions is slightly higher with 30 minutes infusion, but not statistically significant.

The optimal dose and duration for checkpoint therapy is not known. Clinicians are studying this to maximize outcome while minimizing costs. Intermittent dosing is also being studied to delay the development of resistance.

Conclusion
While the survival curves in metastatic melanoma have been shifted significantly, there is still a need for continued improvement, especially for those patients who have been on every available therapy or have no response to the therapies. Immunotherapy is potentially curative; yet, not all will benefit. Toxicity management requires concerted education and communication. The challenge for better pharmaco-economic value in cancer care must be a shared undertaking.

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References
Optimizing Treatment Strategies to Improve Outcomes in the Management of Cystic Fibrosis

Seth Walker, MD, FCCP, FAAP

For a CME/CNE version of this article, please go to www.namcp.org/cmeonline.htm, and then click the activity title.

**Summary**

With increased understanding of the pathophysiology of cystic fibrosis (CF), therapies targeting the underlying issues with sodium and chloride transport are now available. These therapies increase lung function and reduce exacerbations by targeting the defects in the CF transmembrane conductance regulator (CFTR).

**Key Points**

- Loss of CFTR activity is the underlying cause of CF.
- The F508del mutation is the most common CFTR mutation in the world.
- Two therapies are available that target CFTR activity.

**ALTHOUGH LONG THOUGHT OF AS A DISEASE OF CHILDREN, CYSTIC FIBROSIS (CF) IS NOW AN ADULT DISEASE.** About half of the CF patients in the United States are over the age of 18. There is even a larger majority of adults in some European countries. Two reasons for the adult population growth are increases in survival with good care and more cases being identified as testing has improved. Some of the chronic bronchitis and severe asthma patients in the past were really CF patients.

Cystic fibrosis (CF) is a genetic disease that causes severe lung and digestive problems and results in early death. It is caused by abnormalities in the CF transmembrane conductance regulator (CFTR) gene. There are over 2,000 mutations on the CFTR gene which have been identified and which lead to malfunctioning CFTR protein. Not all CFTR mutations are created equal; the CFTR protein could be completely nonfunctional or have limited functional ability (Exhibit 1). The CFTR protein functions as a channel across the cell membrane in cells that produce mucus, sweat, saliva, tears, and digestive enzymes. Class I mutations result in no production of the CFTR protein. Class II mutations result in an improperly folded protein that is destroyed by the cell and never makes it to the luminal surface. With Class III mutations, the protein is folded almost right, but it cannot be unfolded correctly. In Class IV mutations, the protein opens on the luminal surface but is not open long enough or large enough for chloride to pass through. Lastly, Class V mutations produce a completely normal protein, but there is just not enough of it. Often these mutations are not in the coding section of the gene but are in the promoter section, so there is little transcription.

Unfortunately, genotype does not predict phenotype in CF; therefore, one cannot tell, based on genotype, how severe someone’s disease will be. Most of the time if the patient has two mutations of Class I, II, or III that will be more severe disease versus Class IV and V, which are partial function mutations. Also, patients can have more than one mutation.

In the lungs, the primary purpose of CFTR is to regulate sodium and water passage in the airways. When CFTR works correctly, mucous in the airways floats on top of a layer of fluid which covers the
cilia, allowing them to move correctly to clear airways. When there is a malfunction, the airway becomes dehydrated, the mucus becomes very thick, and the cilia are unable to function correctly, creating a perfect environment for infection and eventually damage to the airways.

Two new medications have been FDA approved for treating CF in the presence of specific genetic mutations. Ivacaftor (Kalydeco®) is a potentiator of CFTR. It initially showed promise in G551D-CFTR, the most common Class III mutation. This mutation occurs in about 3 percent of the CF population. It is FDA approved for patients ages 2 and older who have one of the following mutations: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549ER. It is available as an oral tablet given as 150 mg every 12 hours and granules in 50 and 75 mg doses for children ages 2 to 6. In patients with moderate to severe homozygous G551D CF, those who received ivacaftor had a 10 percent increase in lung function, improvement in symptoms scores, reduced exacerbations requiring antibiotics, and weight gain (3–3.5 kg).1 Decreased weight is associated with worsened lung function and prognosis, so weight gain is typically a desired endpoint in those with CF. Similar results have been seen in patients with only one copy of defective gene and less severe disease.2–4 The benefits of ivacaftor have been shown to persist out to three years.5

Ivacaftor can lead to elevated liver transaminases, which occurs more frequently in 2 to 5 year olds. It has significant drug–drug interactions with CYP3A4 substrates. The major controversy with this agent is its cost. It costs about $800 per day of therapy, which is about $300,000 annually for the rest of someone’s life. This price was negotiated with insurers before the agent was approved.

The F508del is the most common mutation in those with CF, occurring in about 50 percent of patients. In those with the Class II F508del mutation, correction of the protein being transported to the luminal surface and potentiation of its effect are both needed. Lumacaftor/ivacaftor (Orkambi®) is a combination of corrector and potentiator for patients homozygous for F508del. In vitro studies have shown that CFTR function goes from almost zero to about 25 percent when these two agents are given. It is an oral regimen taken as two tablets every 12 hours.

More than 1,000 patients ages 12 and older with homozygous for F508del and forced expiratory volume in one second (FEV1) at 40 to 90 percent predicted (mean 61%) were in the two Phase III trials that led to FDA approval of lumacaftor/ivacaftor.6 Over 24 weeks, the combination improves FEV1 modestly (~2%) and increases the time to pulmonary exacerbation (hospitalization requiring intravenous antibiotics) in this population. Over 24 weeks, there was a 25 percent reduction in exacerbations, which is a number needed to treat of three to prevent one exacerbation.

Adverse effects with the combination include frequent chest tightness/shortness of breath and elevated transaminases. Pulmonary symptoms occur most commonly at the beginning of therapy and may lead to withdrawal from treatment. Approximately 10 percent of patients have significant shortness of breath and may require slow-dose titration to be able to tolerate the medication. Some have such significant symptoms they have to stop the medication. Elevated transaminases are more common than with ivacaftor alone. Drug–drug interactions also are an issue with this combination. Lumacaftor upregulates CYP3A4 metabolism of ivacaftor, so higher doses are required when the combination is used. Lumacaftor also makes hormonal contracep-
tives ineffective, so patients need to use other types of contraception.

With CF therapies that were available before these CFTR agents, the best adherence was about 50 percent. Even with this generally poor rate of adherence, there have been improvements in life expectancy in CF.

Given the cost of the CFTR therapies and the lifetime use, it is important to optimize patient adherence. Standard strategies include verbal and written education, a review of refill records, and questioning at each visit. It is especially important in adults who, unlike children, often do not have someone else to manage their therapy. Patients need to understand how these agents work, how they provide benefit, and that modulators are not a cure. Patients may stop their other therapies because they think these medications are curing their disease. The CFTR therapies were tested in addition to the standard CF regimens, so to get benefit the standard therapies need to be continued. To maximize benefit of these agents, they need to be taken every 12 hours for optimal CFTR functioning and have to be taken with food for absorption. If taken on an empty stomach, the absorption is almost nonexistent.

Optimizing patient safety can be accomplished with reviewing for drug-drug interactions and keeping up with the recommended lab schedules for the first year of therapy. A repeat hepatic panel should be done in two weeks if transaminase levels go above five times the upper limit of normal. Therapy should be stopped if they reach eight times normal. Once transaminases return to baseline, the medication can be restarted. Patients should be educated to call their CF provider before starting any new medications. Because of some concerns about cataracts in animal studies, most clinicians will do annual eye exams, regardless of age. A baseline eye exam should be done before therapy is started.

**Conclusion**

New therapies targeting the underlying pathophysiology of CF are now available. These agents provide both improvements in lung function and reductions in hospitalizations for exacerbations. As more data are gathered on these agents, additional benefits may be seen.

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**References**

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) is the most prevalent leukemia in adults in the United States. Approximately 19,000 cases occur each year, with a median age at diagnosis of 72 years. It occurs in men twice as often as in women. CLL tends to be an indolent disease; many patients are asymptomatic when diagnosed and do not immediately require therapy. When they do require therapy, CLL is treatable but typically relapses and is incurable.

CLL is diagnosed based on peripheral blood flow cytometry. A bone marrow biopsy is required for determining cytogenetics, which are an important predictor of overall survival, and the degree of bone marrow involvement. CT scans are done for staging the disease. Certain genetic features are associated with more favorable long-term survival. Those who have del (13q14) have the best survival, even better than those with normal cytogenetics, whereas those with other mutations (NOTCH1 M/SF3B1 M/del(11q22–q23 or TP53 DIS/BIRC3 DIS) have much worse survival rates. Those with the poor prognosis mutations do not respond well to chemoimmunotherapy. In CLL, clonal evolution can occur in response to treatment, so cytogenetics have to be repeated when patients relapse.

Indications for treatment of CLL include persistent night sweats, fatigue, fevers, chills, unexplained weight loss. Additional indications include autoimmune anemia or thrombocytopenia not responsive to steroids, rapidly rising white blood cell count, and/or rapidly progressive lymphadenopathy or splenomegaly. The goals of treatment are outlined in Exhibit 1. The aggressiveness of treatment will depend on the patient’s age, current organ function, comorbidities, and functionality. For a patient who is younger and in relatively good health other than CLL, aggressive treatment with higher toxicities would be initiated to try and achieve a deep remission with essentially undetectable disease. In an older patient with reduced organ function and
poor performance status, the goal is to do no harm. The therapies selected are more palliative and chosen to minimize toxicity. Many patients are somewhere in the middle of the aggressive and palliative spectrum—a tolerable regimen that achieves a good response is sought.

In the past, chlorambucil, an alkylating agent, was used; this agent produced about a 30 percent response rate. Because it is well tolerated, it is still commonly used in elderly patients with other comorbidities. Fludarabine came into use in the early 1990s and produced higher complete response (CR) rates. Chemotherapy regimens for treatment-naïve CLL have changed significantly since early 2000 with the addition of immunotherapy agents. The first revolutionary immunotherapy agent approved was rituximab (Rituxan®), a monoclonal antibody against the protein CD20, which is primarily found on the surface of immune system B cells. Chemoimmunotherapy with rituximab added to fludarabine produced overall response rates (ORR) of 90 percent, CR of 47 percent, and an improvement in overall survival (OS, 7 months). In younger patients (median age 58), triple therapy fludarabine, cyclophosphamide, and rituximab (FCR) produced good responses (ORR 90%, CR 44%, median progression-free survival [PFS] 57 months) but has a much higher toxicity rate compared with a rituximab/fludarabine combination. Bendamustine combined with rituximab (BR) produces comparable response to FCR with less toxicity and is an option for older patients or those with comorbidities.

Because the CR rates were still not great with the available regimens, the search for better agents examined other ways to target lymphocytes or ways to improve upon rituximab. Ofatumumab (Arzerra®) and obinutuzumab (Gazyva®) are two additional anti-CD20 monoclonal antibodies. Ofatumumab is a type I fully human antibody that binds a unique epitope of CD20, which is different from the mechanism of action of rituximab, and has better complement-dependent cytotoxicity than rituximab. It is FDA approved, in combination with chlorambucil, for the treatment of previously untreated patients with CLL for whom fludarabine-based therapy is considered inappropriate, in combination with fludarabine and cyclophosphamide for the treatment of patients with relapsed CLL, for extended treatment of patients who are in complete or partial response after at least two lines of therapy for recurrent or progressive CLL, and for the treatment of patients with CLL refractory to fludarabine and alemtuzumab.

Obinutuzumab, a type II glycoengineered humanized monoclonal antibody against CD20, was superior to rituximab in preclinical studies including whole blood B-cell depletion assays, human lymphoma xenograft mice models, and nonhuman primates. It is FDA approved, in combination with chlorambucil, for the treatment of patients with previously untreated CLL. This agent in combination with chlorambucil produced higher ORR and CR compared to rituximab/chlorambucil (ORR: 78% vs. 65%, CR: 21% vs. 7%). Obinutuzumab does cause higher
rates of infusion reactions than rituximab.

Overall, the combination of an anti-CD20 antibody and chlorambucil is an effective regimen but not comparable to more aggressive chemoimmuno-therapy (FCR or BR) in terms of response. These regimens do produce less toxicity than more aggressive regimens including less cytopenias and infection. This combination is indicated for the elderly, frail patient, or those with multiple comorbidities.

Beyond targeting cell surface proteins like CD20, signaling pathways within the B lymphocytes can also be targeted (Exhibit 2). Various oral agents have been developed or are under development to target these pathways. Three compounds, which have been approved to date, are ibrutinib (Imbruvica®), idelalisib (Zydelig®), and venetoclax (Venclexta®).

Ibrutinib is a Bruton’s tyrosine kinase (BTK) inhibitor approved for first-line treatment of CLL, with or without a 17p deletion. It results in good ORR (90%), CR, and one-year PFS (94%). In relapsed/refractory CLL, it can be combined with BR or rituximab alone (ORR 95%, CR 8%, 18 mo PFS 78%).

In addition to reduced blood cell counts (thrombocytopenia, anemia, and neutropenia), ibrutinib can cause hemorrhage because it affects platelet function through von Willebrand factor. The other unusual adverse effect is atrial fibrillation in 6 to 9 percent of patients.

Second-generation BTKs under investigation include acalabrutinib, ONO-4059, and spebrutinib (CC-292). The first is the closest to market.

Idelalisib, a potent selective inhibitor of a key kinase, the phosphatidylinositol 3-kinase (PI3K) delta isomform, is FDA approved for relapsed CLL, in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities and two types of lymphoma. In combination with rituximab, an ORR of 97 percent, CR of 19 percent, and 90 percent PFS at 36 months were achieved. The problematic adverse effects are severe diarrhea, liver function test elevations, and pneumonitis. Idelalisib has been studied in combination with BR, in the relapsed/refractory setting.

Venetoclax (Venclexta®) is the most recently approved agent. It is a B-cell lymphoma-2 (BCL-2)
inhibitor indicated for the treatment of patients with 17p deletion who have received at least one prior therapy. It blocks anti-apoptotic BCL-2 protein, leading to programmed cell death of CLL cells. In early research, single doses of this agent led to a greater than 95 percent reduction in lymphocytosis within 24 hours in two patients. There was a rapid reduction in palpable lymphadenopathy, but a dose-limiting laboratory tumor lysis syndrome (TLS) was found. TLS secondary to this agent caused fatalities in some of the studies with venetoclax. TLS occurrence led to a recommended weekly step-wise dose escalation. An ORR of 79 percent and 7.5 percent CR was seen in a trial of those with 17p deletion with relapsed/refractory CLL. This agent has been studied as monotherapy in patients who were refractory to ibrutinib and idelalisib and in various combinations in the relapsed/refractory setting. Several combination trials are ongoing.

The last area to discuss is altering the tumor microenvironment. It is known that many factors outside the tumor cell affect the growth of tumors and their ability to survive. The best studied agent for affecting the tumor microenvironment is lenalidomide (Revlimid®), which is already approved for their ability to survive. Pembrolizumab (Keytruda®) and nivolumab activate T cells, anti-programmed death one (PD-1) antibodies are approved for treating multiple myeloma and mantle cell lymphoma. Lenalidomide is an immune modulator with numerous effects on the microenvironment of tumors. Although good results are being seen, it is still under investigation for CLL and the packaging labeling suggests it only be used for CLL in the setting of a clinical trial.

In many cancers, T cells are “turned off” and do not recognize and destroy tumor cells. Agents that activate T cells, anti-programmed death one (PD-1) antibodies, are approved for treating some cancers. Pembrolizumab (Keytruda®) and nivolumab (Opdivo®) are both under investigation for CLL.

Chimeric antigen receptor (CAR) modified T cells are also being studied in CLL and other cancers. These combine an antigen recognition domain of an antibody with intracellular signaling domains into a single chimeric protein. Gene transfer is used to reengineer a patient’s T cells to express CAR; the CAR-modified T cells are then infused into the patient to fight tumor cells. A small early study in 14 patients found a decent ORR (57%) and CR (29%).

**Conclusion**

Several new targeted therapies with unique mechanisms of action are now available to treat CLL. These therapies have potential for greater specificity and less nonspecific toxicity than chemotherapy regimens used in past. Targeted therapy has efficacy in high-risk and aggressive disease. Clinicians are learning how to integrate these therapies with chemoimmunotherapy, and how to incorporate them into current treatment algorithms. Overall, treatment is shifting toward safe, multitargeted regimens in the hope of a personalized cure.

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**References**

Improving Patient Outcomes in the Management of Hemophilia

Mark T. Reding, MD

For a CME/CNE version of this article, please go to www.namcp.org/cmeonline.htm, and then click the activity title.

Summary

Hemophilia is an expensive, rare, and difficult to manage condition. New long-acting factors are changing how many patients are managed and will hopefully improve long-term outcomes by improving patient adherence. Additional new therapies are on the horizon which will continue to change the management of hemophilia.

Key Points

- Reliable access to safe factor replacement therapy exists today.
- Aside from development of inhibitors, hemophilic arthropathy is currently the most significant complication of hemophilia.
- Strict adherence to long-term prophylaxis is the only way to prevent hemophilic arthropathy and its devastating consequences.
- New treatments are beginning to address many of the barriers to effective prophylaxis.
- New treatments for personalized prophylaxis has made clinical decision making much more complex.
- Resources and expertise necessary for optimal management of hemophilia in the current era do not exist outside of hemophilia treatment centers.

HEMOPHILIA IS A CONGENITAL BLEEDING disorder due to deficiency or absence of a coagulation cascade protein. Hemophilia A is a factor VIII deficiency, whereas hemophilia B is a factor IX deficiency, but the clinical phenotypes are indistinguishable. Both are treated almost identically with factor replacement.

Hemophilia is rare; it only affects about 20,000 Americans, but there are more than 500,000 hemophiliacs worldwide. There are few other diseases with as much economic impact on both the health care system and patient as hemophilia. Unlike other blood diseases, like sickle cell disease, hemophilia affects all racial groups equally. The majority of cases are found in the 2- to 19-year-old age group, but there are patients in all age groups.1

Genes for factors VIII and IX are located on the X chromosome; thus, females are carriers and are by and large unaffected, whereas males are affected. Because of spontaneous mutations, approximately 30 percent of those affected have no family history of hemophilia. Many times these patients with no family history get misdiagnosed as infants as victims of child abuse because of bleeding or severe bruising.

Patients can have mild, moderate, or severe factor deficiency; the severity of bleeding tendency depends on the degree of factor deficiency. Those with severe factor deficiency have less than 1 percent of normal factor levels. These patients have frequent spontaneous bleeding and are usually diagnosed early in childhood. Typically, the diagnosis will be made once a child with severe disease begins learning to walk. Moderate factor deficiency is defined as factor levels between 1 and 5 percent. These patients
will bleed after injury or surgery and may have occasional spontaneous bleeding. Those with mild disease (>5% factor levels) bleed only after severe injury, trauma, or surgery and may not be diagnosed until adulthood. It is important to note that patients do not have to have a very high level of normal clotting factors to avoid bleeding.

Clinicians unfamiliar with hemophilia may expect to see major bruising in those affected but the majority of major complications are typically inside the body and not in the skin. The major complications of hemophilia are hemarthrosis, deep muscle bleeds, intracranial bleeds, and soft tissue bleeds. Death can result from major bleeds.

Hemarthrosis, primarily involving the ankles, knees, and elbows, is the most common complication of hemophilia. Hemarthrosis is bleeding into a joint which is very painful and results in significant damage and disability because of the inflammatory effect of blood in the joint space. Even one severe joint bleed can lead to end-stage joint disease. Forty-five percent of those with hemophilia, not on factor replacement, experience their first joint bleed within the first year of life. Ninety percent have at least one joint bleed by 4 years of age. Ninety percent of those with severe hemophilia have chronic degenerative changes involving at least one joint by age 25. Around 40 percent of those with hemophilia report restricted physical activities due to arthropathy. Joint damage and destruction leads to immobility, which leads to obesity in many patients with hemophilia. Joints that do not move also lead to difficulties in holding a job. The key in newly diagnosed patients is to prevent hemarthrosis from ever occurring. Factor replacement can prevent much of the joint disability related to hemophilia.

Since 1968, hemophilia has been treated with factor concentrate infusion, which has led to significant improvements in life expectancy (Exhibit 1). The modern era of treatment began in the 1990s with the development of recombinant factor VIII and factor IX. In addition to the older plasma-derived products, there are now four generations of recombinant factor concentrates. Among these products, there is no major difference in how they work or in their efficacy.

Factor replacement can be given by self-infusion; the goal of therapy is for every child with hemophilia to learn self-infusion. This allows the individual to be independent and have a normal life.

Factor replacement is given on demand or as prophylaxis. On demand is treatment of bleeds with factor replacement when bleeds occur. This method is good at stopping bleeds after they start, but does not prevent bleeds. The benefits of on-demand administration include fewer infusions and greater patient convenience. The problems with on-demand use includes bleeds are not prevented, joint damage is ongoing, end-stage arthropathy is unavoidable resulting in long-term functional disability, and bleeds may become more difficult to control over time. The lifetime costs of on-demand therapy are much greater than prophylaxis because of the disability. Prophylaxis consists of regular factor administration to prevent bleeds from occurring with a goal of no bleeds. Older prophylactic therapies require frequent infusions, venous access, and time commitment for patients but, they have been proven to prevent bleeds. Preventing bleeds keeps joints healthy and may delay progression of existing arthropathy. It also provides protection from traumatic and unexpected bleeds.

Exhibit 1: Historical Overview

- 1900 – 1940s: Hemophilic life expectancy 25 – 30 years, usually disabled by age 20
- 1960: Life expectancy increased to 40 years due to transfusions of whole blood and plasma, but most hemophiliacs still severely disabled and unemployed
- 1968: First commercially available factor VIII concentrate
- 1980: Life expectancy reaches 60 years
- 1982: First reported cases of AIDS in hemophilia patients. More than 50% ultimately infected with HIV and more than 75% infected with viral hepatitis
- 1985: Virally inactivated factor concentrates introduced
- 1992: Recombinant factor VIII
- 1997: Recombinant factor IX

Prophylactic therapy in children was pioneered in Sweden in the 1960s and became standard of care.
with introduction of recombinant factor concentrates in the 1990s. It is initiated after the first joint bleed or before age 3. In children, prophylactic therapy has been shown to decrease bleeding frequency and to prevent joint damage.

In adults, prophylactic therapy is increasingly used, with support from recent clinical trials. It decreases bleeding frequency and improves quality of life but has not been shown to definitively prevent progression of arthropathy. Children who enter adulthood on regular prophylaxis, with preserved joints, are usually kept on prophylaxis.

Hemophilia carries a significant economic burden, with factor concentrates accounting for the majority of the cost of treating hemophilia. Routine prophylaxis for severe hemophilia A, dosed at 25-40 IU/kg three times per week, can annually cost an estimated $78,000 to $124,800 for a 5-year-old child and $312,000 to $499,200 for an adult.

Factor VIII replacement has typically been given every 48 to 72 hours. A typical schedule would be Monday, Wednesday, and Friday, with a larger dose on Friday to cover the weekend. Factor IX has a longer half-life so it can be given twice a week. Patients will do a Monday/Thurs or Tuesday/Friday schedule. Bleeding risk increases with less than perfect adherence, especially with twice weekly dosing.

Unfortunately, the immune systems of some hemophilia patients “see” factor VIII or factor IX as a foreign protein leading to production of antibodies. Antibodies (inhibitors) directed against factor VIII or factor IX neutralize the procoagulant effect and render standard treatment useless. Development of inhibitors is currently the most serious complication of factor replacement therapy. About 25 percent of hemophilia A patients develop inhibitors, as do 3 to 5 percent of hemophilia B patients.

Typically, inhibitors are seen in those with severe hemophilia, but there is increasing recognition that inhibitors develop in mild or moderate hemophilia, usually after intense factor exposure related to trauma or surgery. Luckily, development of inhibitors is no longer associated with increased mortality. However, in those with inhibitors, bleeding is more difficult to control because the treatments are not as effective as standard factor replacement, devastating joint disease and disability can occur, and major clinical and economic challenges occur. Those who develop inhibitors develop end-stage joint damage at a much earlier age (20s) than those who do not (40s).

Treatment of inhibitor patients is very complicated, extremely expensive, and absolutely requires hemophilia treatment center (HTC) expertise because these patients are rare and treatment options have significant limitations. Factor replacement therapy is not possible; treatment options are currently limited to bypassing agents. Bypassing agents, such as activated prothrombin complex concentrates (aPCC) and recombinant factor VIIa (rFVIIa), are used to treat acute bleeding in people with high antibody titers. These agents have incomplete (75 – 90%) and unpredictable efficacy. No standard laboratory monitoring for this therapy exists and thrombosis is a real risk.

Issues with the older factors have led to the development of extended half-life factor concentrates. The half-life of the factors is extended by modifying the recombinant factor VIII and IX proteins through Fc fusion, albumin fusion, and PEGylation. Longer half-life means less frequent infusions, which means improved adherence and better protection from bleeding. This should translate to improved outcomes. For example, long-acting factor IX has a half-life of 80 to 90 hours compared with 18 to 24

<table>
<thead>
<tr>
<th>Product</th>
<th>Mean Half-Life (hours)</th>
<th>Prophylactic Dose</th>
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</thead>
<tbody>
<tr>
<td>Factor VIII</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eloctate</td>
<td>19.7</td>
<td>50 U/kg every 4 days, then adjust dose by 25 – 65 U/kg and interval by 3 – 5 days</td>
</tr>
<tr>
<td>Adynovate</td>
<td>14.7</td>
<td>40 - 50 U/kg 2x/week</td>
</tr>
<tr>
<td>Factor IX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alprolix</td>
<td>86</td>
<td>50 U/kg every 7 days, OR 100 U/kg every 10 days; then adjust based on individual response</td>
</tr>
<tr>
<td>Idelvion</td>
<td>104</td>
<td>25-40 U/kg every 7 days; If well controlled, may try 50-75 U/kg every 14 days</td>
</tr>
</tbody>
</table>
hours for the non-long-acting product. This results in an initial dosing regimen for long-acting factor IX of every seven to 10 days compared with every three days. The first to market were Alprolix® (Factor IX, March 2014) and Eloctate® (Factor VIII, June 2014), which are Fc fusion products where the factor molecule is linked to a protein fragment, Fc, which is found in antibodies. Adynovate (Nov 2015) is PEGylated factor VIII and Idelvion (March 2016) is an albumin fusion factor IX. There are three more PEGylated long-acting products likely to be approved within the next few years.

When considering whether a long-acting factor is best for a given patient, clinicians have to consider age, adherence, venous access, activity types and patterns, baseline bleeding phenotype, peak/trough factor levels needed to protect based on activity pattern, and joint status. Annualized bleeding rate (ABR) is another factor to consider. For example, a young man with an ABR of zero on shorter-acting recombinant factor replacement has no room for improvement. If the reason he is not bleeding is that he spends all his time sedentary, he may benefit from a change in treatment that will allow an increase in function. Similarly, an adult who is currently active and very functional but has an ABR of 2 will become sedentary and nonfunctional over time without a change in therapy.

With the long-acting factors, it is known they are highly effective for prophylaxis, acute bleeds and surgery with safety comparable to existing products. There has been a high degree of patient satisfaction with the long-acting factors and adherence has generally improved. There are not a lot of data on use of long-acting factors in previously untreated patients. The data so far appear good in these patients. Ongoing challenges include whether patients need management of acute bleeds with long-acting agents, their role in inpatient settings, and cost. The combination of short- and long-acting products may become the standard; this would be similar to regular and long-acting insulin in a diabetic. The short-acting factors would be used for acute bleeds and long-acting for routine prophylaxis. In the inpatient setting, continuous infusion of short-acting factors has been used for managing acute bleeds. Where the long-acting factors fit in for treatment of acute bleeds is unknown. The factors are expensive and more expensive than short-acting factors.

It is important to note that the long-acting factors are not interchangeable like the short-acting factors. Unlike standard half-life factor products, the extended half-life agents have clinically meaningful pharmacokinetic differences and more complex and varied dosing schedules (Exhibit 2). This has made product selection much more complicat-
AbbVie
Acelity (KCI)
Acorda Therapeutics
Actelion Pharmaceuticals US, Inc.
Allergan
Amarin Corporation
Ambry Genetics
AmerisourceBergen
Amgen Inc.
Apobologix
Ariad Pharmaceuticals
Assurex Health
Astellas Pharma US, Inc.
Bayer Healthcare Pharmaceuticals
Biodesix
BioFire Diagnostics
Bioventus, LLC
Boston Scientific
Braeburn Pharmaceuticals
Bristol-Myers Squibb Company
CareNational
Castle Biosciences
Celgene Corporation
Courtagen Life Sciences
Eisai
Exact Sciences
Foundation Medicine
Genentech
Genomic Health
Genoptix
Gilead Sciences
HeartFlow
Heron Therapeutics
Incyte Corporation
Infinity Pharmaceuticals
InSightec
Intarcia Therapeutics
J & J Health Care Systems, Inc.
Janssen Biotech
Jazz Pharmaceuticals
Kite Pharmaceuticals
Lilly Oncology
Lilly USA, LLC
LIM Innovations
Merck & Co, Inc.
Merrimack Pharmaceuticals
Merz North America
Myriad Genetic Laboratories
Natera
Novartis Oncology
Novo Nordisk
NovoCure
Pfizer Inc.
PharMedQuest
Philips Healthcare
Regeneron Pharmaceuticals
Sandoz Pharmaceuticals
Seattle Genetics
Sunovion Pharmaceuticals
Taiho Oncology
Teva Pharmaceuticals
VITAS Healthcare Corporation
Veracyte, Inc.
Vermillion
Woundtech
Developments in the management and treatment of asthma include recognition of multiple phenotypes and asthma COPD overlap syndrome. With increasing recognition of the different types of asthma, personalized medicine may be on the horizon. For now, clinicians still select therapy based on symptoms and the degree of disease control. Eventually, phenotypes and biomarkers will be used for therapy selection.

Key Points
- Asthma is a complex group of diseases with multiple phenotypes and treatments.
- Asthma severity is an intrinsic characteristic that guides therapy.
- Asthma control can be influenced by a number of important modifiable factors.
- Asthma and chronic obstructive pulmonary disease (COPD) can coexist in a significant proportion of patients.

Asthma used to be easy for clinicians to understand; someone had it or they did not. As various phenotypes are being recognized, the disease has become more complicated to understand and manage (Exhibit 1). These phenotypes are based on inflammation and other factors and do overlap. Patients in the type 2 high phenotype are those with more allergic asthma. The severe asthma phenotype program has developed a method for clustering patients by phenotype based on a number of factors (Exhibit 2). The clusters have prognostic indications and patients can move between categories. Because patients may have clinical or pathologic features of more than one phenotype, there is limited ability to use these in general clinical practice at this time.

Practically, asthma is classified based on severity as intermittent, mild persistent, moderate persistent, or severe persistent. The thought with this type of classification is there are intrinsic factors that determine severity. A difficulty is that the same symptoms used to determine severity are also used to determine disease control (controlled versus uncontrolled). This can make it difficult to distinguish whether a patient is severe persistent or moderate persistent but is uncontrolled. There is not a blood test or definitive clinical test for asthma severity.

Many clinicians will only focus on asthma control rather than also considering severity. Several factors affect asthma control, including perception (locus of control, cultural), adherence, comorbidities (gastroesophageal reflux disease, sinus disease, allergic rhinitis), and triggers (tobacco smoke, pets, cockroaches, pollution, poor quality housing). PACT is an easy mnemonic to remember these factors. Socioeconomics is a major factor in achieving asthma control. For example, a homeless mother’s first priority is not whether her child has good asthma control. The best designed management plan is not going to overcome socioeconomic issues.

The Global Initiative for Asthma (GINA) is a similar program to the Global Initiative for Chronic Obstructive Lung Disease (GOLD). GINA published updated asthma guidelines in 2016. Exhibit 3,
from the GINA guidelines, provides a way to help distinguish between uncontrolled disease and severe asthma.\(^4\)

Treatment is based on the severity classification and disease control. The GINA asthma management guidelines recommend stepwise therapy based on classification, similar to the Expert Panel guidelines.\(^3,4\) The stepwise progression begins with low-dose inhaled corticosteroids (ICS) and progresses in dose and the addition of a long-acting beta agonist (LABA) inhaler. The last step (Step 5) in the recommendations is referral to an asthma specialist for consideration of higher level therapies.

The management of asthma is a continuous process of assessment, adjustment, and review (Exhibit 4).\(^4\) Unfortunately, asthma control assessment in the community is sparse. Clinicians don’t ask about, patients don’t report, and clinicians don’t document. Asthma control can be assessed at each visit with simple patient questionnaires.

Review of all of the patient’s medications and adherence at each visit is important. Patients need to understand the difference between rescue inhalers and controller medications and to recognize the importance of continuing controller medications, even when they feel good. Many patients may believe that no symptoms equals no asthma.

Appropriate medication adherence is vital for asthma control. It is especially important to assess that patients are using their inhalers correctly. Overall, efficient inhaler technique occurs in 46 to 59 percent of patients. Mistakes in metered-dose inhaler inhalers occur in about 37 percent of patients and in 35 percent with dry-powder inhalers.\(^5\)

It is important that patients understand how to use an inhaler, whether new or a refill. Inhaler technique should be evaluated at each visit as part of medication reconciliation. Inhaler videos are available for instructing patients. These videos are available on the websites of inhaler manufacturers and on the American Association of Respiratory Care website (http://www.nationalasthma.org.au/managing-asthma/how-to-videos/using-your-inhaler). New ones available on the website were specifically developed for primary care.

Managed care policies can contribute to loss of asthma control. Automatic switching of inhalers because of formulary issues may result in loss of asthma control.
In addition to treating modifiable risk factors such as GERD, clinicians can improve asthma control by several actions. Clinicians can teach skills and provide support for guided asthma self-management. This comprises self-monitoring of symptoms and/or lung function, a written asthma action plan, and regular medical review. Medications or regimens proven to minimize exacerbations should be prescribed. Inhaled corticosteroid-containing controller regimens reduce risk of exacerbations. All asthmatics should be encouraged to avoid tobacco smoke. For current smokers, smoking cessation advice and resources should be provided at every visit. Clinicians also need to look for occupational exposures which may be triggering or exacerbating the disease. Occupational asthma should be considered in those with adult-onset asthma. About 20 to 30 percent of adult onset asthma is thought to be due to occupational exposures.

Patients who are not controlled should have their asthma treatment stepped up. This should be a sustained step-up, for at least two to three months if asthma is poorly controlled. Before stepping up therapy it is important to check that the symptoms are not due to something other than asthma, poor inhaler technique, or nonadherence. For patients with a viral infection or seasonal allergy exposure, a short-term step-up, for one to two weeks for example, may be needed. Patients with a written asthma action plan can do their own short-term increases in therapy.

Once a patient has good disease control maintained for three months, the clinician can consider stepping down asthma treatment. The goal is to find each patient’s minimum effective dose, which controls both symptoms and exacerbations and minimizes the risk of adverse effects. Stepping down ICS doses by 25 to 50 percent at three-month intervals is feasible and safe for most patients. Completely stopping the ICS is not recommended in adults with asthma.

The recommended treatment option at Step 5 is referral for a specialist investigation and consideration of add-on treatment. Add-on biologic therapy is an option for patients with moderate or severe eosinophilic asthma or severe asthma that is uncontrolled on Step 4 treatment. Other add-on treatment options at Step 5 include tiotropium for adults, sputum-guided treatment available in specialized centers, or add-on low-dose oral corticosteroids (≤7.5 mg/day prednisone equivalent). Tiotropium, a long-acting anticholinergic, now has an asthma in-
ication. It is appropriate as add-on therapy for adult patients with a history of exacerbations. The dosing is half the dose used for COPD. Oral corticosteroid regimens may benefit some patients, but have significant systemic side-effects. These should be avoided if possible. Bronchial thermoplasty is approved for severe and persistent asthma not well controlled with an ICS and LABA combination.

Biologic agents available for severe eosinophilic asthma include omalizumab (Xolair®) and mepolizumab (Nucala®), and reslizumab (Cinquair®). Omalizumab is an anti-IgE antibody given as a
Subcutaneous injection every four weeks. Mepolizumab and reslizumab are anti-interleukin-5 monoclonal antibodies given as a subcutaneous injection and an intravenous infusion, respectively, every four weeks. The biologics are expensive ($10,000 – $30,000 yearly) but do reduce exacerbations and steroid dosing. There are many more therapies targeted at various immune factors under investigation. None of the biologic agents currently available or under study are “curative” for asthma at this time.

There is ongoing work in moving to personalized medicine in severe asthma. Use of biomarkers to identify particular phenotypes and which patients are more likely to respond to a particular therapy are under study.

There is significant overlap between asthma and COPD, which now is called ACOS—asthma COPD overlap syndrome (Exhibit 5). There are probably two to four million people in the United States with ACOS. ACOS is defined by low lung function, episodic wheezing, nocturnal symptoms, eosinophilia, gastroesophageal reflux disease, limited reversibility of airflow limitation, hyperinflation, abnormal body composition, coexisting cardiac conditions, infection, and dyspnea. A patient can start with either asthma or COPD and evolve into ACOS. Generally, patients are treated with medications for both.

**Conclusion**

Asthma is a complex group of diseases with multiple phenotypes and treatments. Asthma severity is an intrinsic characteristic that guides therapy. Asthma control can be influenced by a number of important modifiable factors. Asthma and COPD can coexist in a significant proportion of patients.

**References**

Summary

Approximately 700 regenerative medicines are en route to market, some of which hold the potential to transform patient care or even cure disease. These therapies are currently in their early days and are poised to enter payer and provider systems that may be ill prepared to receive them. This paper is a sentinel survey of the managed care state of the union and perspectives surrounding regenerative therapy by the National Association of Managed Care Physician’s Genomics Biotech and Emerging Medical Technology Institute. Key questions are proposed and value demonstration, patient access, reimbursement and pricing considerations and solutions are discussed.

Introduction

Existing biopharmaceutical treatments have addressed a large number of unmet medical needs and improved patient outcomes over the past quarter century. With optimal use, these medicines have been shown to improve health outcomes of many chronic conditions such as diabetes, hypertension, and heart failure and helped to reduce the need for costly health care services, such as emergency room admissions, hospital stays, surgeries, and long-term care.1-4 In addition, there are now more than 250 biotechnology health care products available to patients, many for previously untreatable diseases. These biotechnology advances are saving millions of lives and changing the odds of serious, life-threatening conditions such as cancer and rare disease affecting millions around the world.5 Treatment approaches such as personalized medicine have also improved upon conventional drug models by focusing treatment expenditures in a more controlled manner to enable provision of treatment to the right patient at the right time. Biopharmaceuticals can currently remediate some of society’s most intractable illnesses, but once diffused into the broader clinical community, they are subject to the characteristic challenges of traditional pharmaceuticals, namely overuse, underuse, and requirements for chronic treatment or uncertain medication switching decisions.6 Biopharmaceuticals also present challenges to the broader health care system in terms of increased cost burdens, long-term administration of non-curtative treatments, variable effectiveness in broader populations, treatment resistance, and adherence challenges.

Regenerative medicines (e.g., tissue, cell, and gene-engineered therapies) are poised to have a similar influence on health care as monoclonal antibody (mABs) based biopharmaceuticals and precision medicine. By leveraging the body’s innate reparative machinery, regenerative medicines have the potential to impact multiple physiological mechanisms in a broader fashion to regenerate, repair or possibly cure disease. The primary difference is that while biopharmaceuticals are increasingly pursuing more targeted approaches, regenerative medicines, in contrast to past therapies, promise treatment benefits that are not frequently seen in the context of modern medicine.

For this paper, the term “regenerative medicine” includes technologies comprising cell therapies (in-
cluding cell therapy vaccines), gene therapies, and other biological materials (e.g., tissue-engineered materials, biological matrices, cell-derived regenerative components) that aim to restore functionality to damaged tissue.2 Cell therapies may either be autologous (collected from one patient and returned to that same patient) or allogeneic (collected from one patient or source [including embryonic sources] and then transferred to another patient). Cells can be taken from a variety of sources (e.g., bone marrow, peripheral blood, umbilical cord, adipose tissue), though we remain at early stages of understanding whether certain cell lines or sources have inherent benefits (e.g., greater persistence or potency) and risks (e.g., down-stream cancer development or immune rejection) than others. In some cases the cells are purified “as is” and in other cases cells may be modified, differentiated, transdifferentiated, or expanded in cell culture to increase the number of cells that may be administered in a dose. In rare cases, some treatment platforms involve genetic manipulation of cells to address some naturally occurring defect (e.g., replacing inherited genetic abnormalities that cause disease with functionally normal ones, among other types of molecular genetic engineering). Likewise, there are many variants of gene therapy in pipeline development today and gene editing and related emerging approaches have enabled evolution of current technologies with potential to overcome limitations of initial experimental therapies. Administration of regenerative therapies can occur in many ways, though most commonly involve either infusion, simple injection (e.g., treatment site is intramuscular) or complex administration (e.g., use of novel catheter delivery systems or surgical implantation of biocompatible matrices that hold cells in place). All said, this is a complex and rapidly evolving area where many approaches are currently being advanced.

While regenerative medicine therapies bear similarities to conventional biopharmaceuticals, they also differ in material ways that matter to managed care including:10

1. **Potential to cure some diseases or have a more sustained duration of therapeutic effect** beyond conventional biopharmaceuticals.

2. **More complex value drivers**, given often greater procedural complexity associated with, for example, obtaining cells, purifying or manipulating cells or genes, gene editing, and administering them to the desired target treatment site.

3. **Attributes of both medical devices/procedures and biologicals** (i.e., more like logics in terms of mechanism of action, but often more characteristic of devices or procedures in terms of administration and system “fit”), resulting in more difficult integration into existing reimbursement mechanisms that are not built to easily accommodate such “hybrid” therapies. In addition, current coding and payment structures such as DRGs did not anticipate therapies with true transformative potential and often do not fit regenerative technologies from their novelty, procedural complexity and cost of therapy perspectives.

4. **Functional components can span entire episodes of care and can include requirements for reimbursement of related procedural steps**, for some of the more complex therapies, to achieve successful reimbursement of the overall procedure/episode of care.

5. **Complex administration considerations** - (sometimes) requiring special provider training or facilities. Also, many therapies are currently developed as single administration therapies, versus today’s recurrent dosing regimes. On the one hand, single administration would simplify treatment and access processes, but also would challenge current value creation models and disrupt existing health incentive structures.

Innovator technologies such as regenerative medicines will be pressed to prove their value in an increasingly challenging and restrictive health environment as United States (U.S.) and global health decision makers are pushed to balance quality vs. cost and seek improved efficiency in health prevention and treatment.31 In scenarios where regenerative therapies offer long-term treatment of disease or cure disease altogether, such outcomes would also challenge our ideals around clinical and economic benefits, including how we value, pay for and manage such therapies, including consideration of novel value recognition and payment models such as amortization or “pay-for-outcomes as you go” models that may flow from curative or nearly curative therapies.12 Such benefits, if established by this vanguard of regenerative medicine technologies, may also enable redeployment of scarce health resources in increasingly restrictive payer and risk-based provider organizations.

Some health technology assessment and payer groups, such as the National Institute for Health and Clinical Excellence (NICE), are taking stock of regenerative medicines, identifying over 35 near-term pipeline technologies in this category, and are beginning to consider how value assessment processes would change in light of technologies that may
forestall traditional treatments or remove the need for subsequent treatments altogether.\textsuperscript{12} This is a fraction of the more than 700 regenerative technologies en route to market. According to the Alliance for Regenerative Medicine, almost 200 technologies have advanced to Phase II development, promising a surge of technologies that will rival anything that we have seen from conventional biologics to date.

In order to gain a better understanding of early U.S. payer perspectives surrounding regenerative medicines, a targeted Internet-based survey was conducted by the Genomics, Biotech, and Emerging Medical Technologies Institute (GBEMTI) of the National Association of Managed Care Physicians (NAMCP) member medical directors. The following paper provides results of this survey and considers early issues surrounding integration of a new wave of regenerative medicine technologies into managed care medicine.

Methods

The GBEMTI was established in 2011 as an institute of the NAMCP. The NAMCP represents medical directors from payer, purchaser (employers), and provider systems such as IPAs, ACOs, PHOs and medical groups. The goal of the GBEMTI is to support and characterize the value of genomics, biotechnology, regenerative medicines and medical technologies as these new modalities enter and impact the health care system. The GBEMTI seeks to support collaborative stakeholder engagement around emerging health technologies to consider their potential to improve patient outcomes, impact on managed care management practices and value to the health care market place. The Institute is guided by an Executive Leadership Council (ELC), comprising approximately 100 payer and manufacturer members. The GBEMTI is unique in that it is a multi-stakeholder group centered around bringing medical director decision makers and manufacturers together to address key trends and topics that are transforming U.S. health care and explore means to improve managed care decision making and patient access to emerging health technologies.

The GBEMTI is divided into four key technology divisions:

- Biopharmaceuticals, Orphan and Specialty Products
- Diagnostics and Personalized Medicine
- Emerging Medical Devices and Combination Products, including emerging e-connective applications
- Regenerative Medicine

To address the objectives of the Institute, each division is focusing on unique questions and developing a series of perspective papers. The goal of this series of papers is to evaluate payer/managed care perspectives and implications for improving managed care processes, policies, and patient outcomes for each core emerging technology area. Perspectives and implications of regenerative medicines was chosen as an initial topic of the GBEMTI because of the future potential of these technologies to alter managed care practice and reflect the emphasis of the GBEMTI on the intersection of cutting-edge technology issues, managed care improvement and identification of rational policy solutions. This paper and prior ones published by the Institute have been

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**Exhibit 1: Technology Types with the Greatest Potential to Impact Quality and Cost of Care**

1 = Lowest Impact
10 = Highest Impact
n = 56
Exhibit 2: Overall Impact that Regenerative Medicine Technologies May Have on the Health Care Practice

- 28% Transformative, offering options not possible with conventional biopharmaceuticals
- 6% Significant impact, but few may be transformative
- 6% Comparable to existing standards of care
- 61% No impact

Findings and Implications

Potential Impact of Regenerative Medicine

The survey asked respondents to consider a range of technology types that have the greatest potential to impact quality and cost of care; around 55 percent of payer respondents indicated that cell and gene therapies ranked as very high or high (Exhibit 1). This overall favorable ranking is comparable to novel medical devices and small molecules and just below personalized medicine and molecular diagnostics. Vaccines (including immunotherapies) and biologicals ranked the highest, perhaps because of the growing number of high impact technologies in these categories versus the relatively limited on-market examples seen in regenerative medicines to date. While payer respondents appear to be generally favorable in terms of the potential value of innovative health technologies, the question did not consider evidence and cost parameters or differential acceptance drivers.

When asked more specifically about the overall impact potential of regenerative medicines, greater than 60 percent of respondents viewed regenerative medicines to have significant impact potential, but perceived that few would emerge as transformative (Exhibit 2). This is in light of the fact that most payer/provider respondents are unlikely to be aware of the approximately 700 pipeline regenerative technologies currently en route to market. A significant minority, around 30 percent, considered the overall category to be potentially transformative, changing practice of medicine, or enabling treatment outcomes not possible with conventional pharmaceuticals. This suggests that managed care decision makers are hopeful that regenerative medicines can offer important improvements in care delivery and outcomes, but given the sparse number of currently marketed technologies, most are reserving judgment until there is a stronger basis for appraising the promise of this novel treatment category.

Given the nascence of the field of regenerative medicine, respondents were asked where efforts to develop new technologies would best be deployed. As might be expected, payer responses were heterogeneous in terms of advancing “one single disease” that should be targeted by regenerative medicines, but generally focused on (a) chronic and/or costly conditions.
illnesses with high unmet need (e.g., diabetes) or (b) debilitating and degenerative diseases that lack disease-modifying treatment options (e.g., spinal injury or chronic kidney disease) (Exhibit 3). Orphan or rare diseases were not raised by payer respondents, which is not a reflection of the relative importance of advancing potentially life-altering/saving therapies in this category – NAMCP payers are uniform in their acknowledgement of the need for advances in this area – but instead, the areas suggested reflect need in terms of both financial impact and unmet need. Of the categories specifically advanced by respondents, diabetes, neurodegenerative disease, and arthritic or related conditions represented the greatest fraction at 20 percent each respectively. GBEMTI ELC feedback further suggested that factors such as patient population size, unmet need, effectiveness/safety of available alternatives, and cost offset potential are general factors that would be considered in assessing the value of any new therapy, including in
particular regenerative medicines that were viewed as having potentially higher costs compared with conventional alternatives.

**Current Landscape for Regenerative Medicines**

Of the areas where regenerative medicines have received coverage in the U.S. according to payer respondents, the majority have been in bone marrow transplant, cancer immunotherapies, and wound care (Exhibit 4). The remaining covered regenerative therapies encompass a wide array of disease areas. From the survey it is unclear whether these covered therapies are still in clinical research where some costs of research are covered or are fully covered therapies (including potentially non-commercial therapies administered in a hospital). This is in stark contrast to the areas indicated by payers as representing the greatest unmet need, including stroke, heart failure and diabetes. However, the reality is that cell therapies are currently being developed for an array of diseases, ranging from broad indications (e.g., cardiovascular and neurology) to specialty areas (e.g., Parkinson’s disease) and orphan diseases.

A targeted search of available U.S. payer coverage policies was also conducted to support this publication and provide a view into the current U.S. situation for in-line regenerative products already available for use in the marketplace (Exhibit 5). This search was not intended to capture all available U.S. policies on regenerative technology applications, but should provide a comprehensive and representative sample of the current U.S. coverage landscape for regenerative medicines. Results of this assessment show that coverage across existing regenerative medicine applications is highly variable and a significant number of regenerative technologies or applications are considered non-covered and investigational/experimental. In scenarios where coverage was rejected, the most common rational cited by payers included poor study design (including sample size, patient characteristics, lack of sufficiently robust trial design to reduce potential for bias and confounding, gaps in evidence, and primary endpoint selection) and unclear or inconsistent outcomes. One unusual observation is that some policies categorically include non-coverage of a wide range of regenerative treatment applications in scenarios where commercially marketed products do not yet appear to exist. Discussion with ELC and national medical directors of some leading commercial plans clarified that this finding does not indicate that such technologies will not be covered in the future, but does reflect two issues (a) regenerative medicine is on the payer radar and (b) there is a significant concern that some regenerative therapies which can be developed as “home brews in hospital” will be used via existing billing codes without appropriate quality controls or sufficient evidence backing them. Payer conversations beyond the survey clarified that if the evidence of the value of regenerative medicines will live up to the promise, payers would welcome those technologies that have the potential to substantially improve patient outcomes. Deeper review of policies confirmed that in areas where specific technologies have developed robust, quality evidence demonstrating clear and consistent outcomes benefits, coverage has been achieved. This also reflects that novelty of regenerative technology alone is insufficient to achieve reimbursement and that regenerative medicine manufacturers are well warranted to carefully consider payer and other stakeholder decision drivers and align evidence development plans early in development to address key clinical issues and unmet need in target disease areas.

**Evidence for Assessment of Regenerative Medicines and Potential Management Models**

The most important factors for assessing regenerative medicine, not surprisingly, included effectiveness measures (i.e., outcome-based, comparative, and durable), safety, scientific rationale, and cost (Exhibit 6), with durable effectiveness rated as most important by approximately 50 percent of respondents. Interestingly, when one considers responses that received at least a 70 percent or higher response, a broader view of what payers are looking for to value regenerative medicines becomes clearer. Approximately 90 percent of respondents indicated that efficacy with hard outcomes (e.g., measurement of mortality or key morbidity metrics) was the most important consideration; however, 50 percent of this category also noted that surrogate outcomes may also be important in more fully characterizing therapy value, though they should ideally be incorporated into a more comprehensive value story. Other areas that emerged as very important included durability of treatment effect, safety, comparative effectiveness and rationale for clinical response. Medical society support, while very important to some payers, ranked lowest of the tested variables, though clinical guidelines were noted as particularly persuasive in ELC discussions. Overall, these results indicate that a variety of factors will be critical for manufacturers to consider and address in establishing plans for value demonstration of regenerative medicine pipeline assets.

Expanding upon survey findings on durability of treatment effect, payers from the ELC clarified that the core value argument for regenerative medicine is that the therapy not only provides substantial clini-
cally relevant improvement over alternatives, but that it also works for a meaningfully longer time vs. conventional drug treatments. ELC members clarified that even a curative therapy may be viewed as having limited value in a scenario where the treatment effect would not last much longer than that achieved with standard of care (SOC) therapies and cost of re-administration is higher. In open discussion, payers also generally held a view that regenerative medicines will be significantly more costly than available therapies, reflecting a potential need for industry to communicate that this is not necessarily the case as treatments continue to emerge. Several payers voiced strong concerns about affordability of potentially curative therapies, citing the substantial cost burden associated with recent potentially curative hepatitis C therapies. Additionally, ELC members indicated that since these therapies are truly novel, information about benefits/risks (versus other regenerative platforms) and long-term safety effects is also important, a minority citing concerns about downstream cellular rejection (and treatment with immunosuppressive agents) and oncology risks. This uncertainty is something that the vanguard of regenerative medicine product manufacturers should consider in articulating their value propositions to payers.

In reference to management models, the majority of payer respondents (90 percent replied greater than 7 out of 10) indicated that evaluation of comparative effectiveness to standard of care/ existing therapies would be considered in the context of regenerative medicine (Exhibit 7) and that payers would evaluate the entire regenerative procedure/episode of care and not just consider management of the cells alone. This suggests that manufacturers should (a) consider ways to assemble comparative evidence (e.g., indirect treatment comparisons) because the payers will look for this information or assemble it on their own and (b) consider framing the episode of care that the procedure entails in articulating the regenerative therapy's additive value proposition beyond SOC or in-line alternatives.

Payers would also consider limitations on repeat administration and, though the survey was unclear, some may potentially consider additional administrations as part of the initial procedural payment established for the therapy (depending upon timing). This would be a key consideration for any regenerative treatments that have a single-time administration, including emerging gene therapies and gene-modified and cell-based immunotherapies, as such a provision could limit payment to manufacturers and providers for a re-administration event. Discussions with ELC members indicate that similar policies have been associated with some traditional bone marrow transplant and other inpatient procedures, but are usually time-limited where additional care (e.g., hospitalizations) is absorbed into the initial diagnosis related group (DRG) payment.

Coverage with evidence development and new co-pay models were also noted as strong possibilities for regenerative medicine, given potential for prolonged duration of treatment effect or a cure. The possibility of establishing long-term duration of effect by following every patient that receives the therapy was not explicitly discussed with payers, but is likely a preferable means of establishing a long-term or curative claim versus “back end” approaches such as coverage with evidence development that are likely to reflect disconnects between evidence of value and pricing potential at launch. This highlights a key opportunity in regenerative medicine and/or for potentially curative therapies for manufacturers to have open collaborative discussions where new payment models would be supported by evolving evidence of product value. While risk sharing agreements were the least likely to be considered by U.S. payer respondents, this finding should be considered in the context that such models are rarely applied in the U.S. compared with non-U.S. markets like the United Kingdom and Italy. Novel payer-manufacturer or provider-manufacturer partnerships were not considered explicitly in the survey, but may represent a collaborative opportunity to characterize real-world treatment value if the treatment in question is targeted towards an area of high unmet need or limited cost-effectiveness/impact from the payer’s or provider’s perspective.

Complexities Associated with Reimbursement of Regenerative Medicines

In terms of their effectiveness, usage, and pricing characteristics, the most complex regenerative medicines are comparable to the best and worst of biologicals and devices. The survey explored a few of these issues, which are addressed in the following two broad categories.

1. Regenerative medicine technologies may involve multiple therapeutic steps involving cell extraction, processing/purification and administration, which complicate reimbursement. Discussions of accommodating emerging regenerative medicine therapies with the current coding platforms (e.g., inpatient and outpatient) in ELC meetings suggested that existing coding systems may not be sufficiently established to easily support cell therapies. For example, existing payments for inpatient treatment scenarios may not anticipate or
### Exhibit 5: Overview of U.S. Commercial Payer Coverage Policies on Regenerative Medicines

<table>
<thead>
<tr>
<th>Disease Area/Application</th>
<th>Technology Description</th>
<th>Coverage Position</th>
<th>Rationale</th>
</tr>
</thead>
</table>
| Critical limb ischemia/PAD\(^{14,35}\) | • Autologous, including studies representing multiple cell sources | • Non-covered, investigational | • Studies small and poorly powered  
• Study designs were non-randomized, non-controlled  
Guidelines did not address cellular therapies |
| Cardiovascular applications (e.g., congestive heart failure, myocardial ischemia/infarction)\(^{15,19,20,21,22}\) | • Autologous, including studies representing multiple cell types | • Non-covered, investigational | • Not specified in policy |
| Diabetes and metabolic disease applications\(^{16,41}\) | • Autologous or cadaveric pancreatic islet cells | • Covered for patients receiving total or near-total pancreatectomy for severe chronic pancreatitis | • Evidence suggests that the treatment prevents or addresses surgical diabetes by enabling patients to produce their own internal insulin  
• Support from the American Diabetes Association  
• NICE report supporting therapy |
| Orthopedic applications\(^{17,18}\) | • Mesenchymal cell therapy and various allograft or bone graft substitutes | • Non-covered, investigational | • Studies small and poorly powered  
• Study designs were non-randomized, non-controlled  
Some products did not have FDA clearance |
| Spinal Fusion\(^{33}\) | • Stem cells for spinal fusion | • Non-covered, experimental | • No randomized controlled trials (RCTs)  
• Insufficient evidence  
• No statistically significant improvements in neurological function after stem cell treatment |
| Sickle Cell Disease and Thalassemia Major\(^{34}\) | • Allogenic hematopoietic stem cell transplantation | • Covered for myeloablative applications with HLA matched donor  
• Non covered non-myeloablative applications | • Small and/or poorly designed studies  
• Heterogenous conditioning regimens |
| Autoimmune Diseases - including\(^{36,38}\) | • Hematopoietic stem cell transplantation to HLA-matched donor | • Non-covered, investigational | • Small and/or poorly designed studies  
• Inconclusive results  
• Insufficient trial durations  
• Insufficient overall evidence base |
accommodate costs of the cell/gene therapy component beyond existing alternatives. Alternatively, outpatient scenarios where the cells may achieve separate payment, may involve multiple therapy steps ranging from cell extraction and processing to administration (e.g., some autologous methods involve cell mobilization, separation, purification, administration, and patient monitoring steps that in some reimbursement models may be separately payable), all of which must achieve acceptable reimbursement to optimize access and uptake. This means that regenerative medicine technology manufacturers will need to be particularly diligent in early product coding assessments to understand if existing structures fit the regenerative application, as well as in planning for building a case to support novel coding, where appropriate. In other scenarios, payers understood that some treatments in this category would be less complex and more similar to conventional biologicals from a coding and payment perspective (e.g., emerging monoclonal antibody immunotherapies).

<table>
<thead>
<tr>
<th>Exhibit 5: Overview of U.S. Commercial Payer Coverage Policies on Regenerative Medicines (cont.)</th>
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</thead>
<tbody>
<tr>
<td><strong>Disease Area/Application</strong></td>
</tr>
<tr>
<td>autoimmune hemolytic anemia</td>
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<tr>
<td>autoimmune hepatitis</td>
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<tr>
<td>celiac disease</td>
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<tr>
<td>Crohn’s disease</td>
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<tr>
<td>cryptogenic cirrhosis</td>
</tr>
<tr>
<td>dermatomyositis</td>
</tr>
<tr>
<td>immune vasculitis</td>
</tr>
<tr>
<td>juvenile idiopathic arthritis</td>
</tr>
<tr>
<td>multiple sclerosis</td>
</tr>
<tr>
<td>neuromyelitis optica</td>
</tr>
<tr>
<td>polymyositis</td>
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<tr>
<td>rheumatoid arthritis</td>
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<tr>
<td>systemic lupus erythematosus</td>
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<tr>
<td>systemic sclerosis, also known as scleroderma</td>
</tr>
<tr>
<td>thrombotic thrombocytopenia purpura</td>
</tr>
<tr>
<td>type I diabetes mellitus</td>
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<tr>
<td>ulcerative colitis</td>
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</tbody>
</table>

Inherited Metabolic Disorders - including:
- Alpha mannosidosis
- Cerebral X-linked Adrenoleukodystrophy
- Farber disease type 2/3
- Gaucher disease types I and 3
- Hunter syndrome (MPS-II), attenuated form
- Hurler syndrome (MPS-IH)
- Krabbe disease (globoid leukodystrophy, GLD)
- metachromatic leukodystrophy (MLD)
- Maroteaux-Lamy syndrome (MPS-VI)
- Sly syndrome (MPS VII)
- Wolman disease
- Niemann-Pick disease type B
- Scheie syndrome (MPS-IIS)
- Niemann-Pick disease type A
- Hunter syndrome (MPS-II), severe form
- Sanfilippo disease (MPS-III)

• Hematopoietic stem-cell transplantation to HLA-matched donor | • All with the exception of Scheie syndrome (MPS-IIS), Niemann-Pick disease type A, Hunter syndrome (MPS-II) severe form, and Sanfilippo disease (MPS-III) are covered as medically necessary | • Extremely rare nature of these conditions was taken into account, though sufficient evidence was deemed available for covered indications | • Non-covered diseases had little or no available evidence supporting stem cell transplantation |
Coding for multi-step treatments may represent a particular challenge because most coding systems have not anticipated regenerative medicines that may involve either multiple codes or closely blend device, drug, and other steps in completion of a procedure. Some therapies that are more “drug-like” such as intramuscular injection or infusion of cells or genes may more closely fit conventional biological coding models, whereas more complex autologous therapies may not readily fit available coding schemes (because they do not anticipate such cross-functional or complex therapies that can blend drug and device components), representing a potential reimbursement risk with payers and an adoption barrier for providers. Some commercial payer respondents (variable by plan) did indicate that they can establish episode of care payments to cover the entire procedure for promising applications in the absence of appropriate existing coding structures. This reflects a need for the regenerative medicine industry to channel resources to education around regenerative medicines and evaluation of current payment models at both stakeholder and policy levels to help prepare the marketplace for the hundreds of pipeline therapies currently in development.

2. Regenerative medicine technologies have the

<table>
<thead>
<tr>
<th>Disease Area/Application</th>
<th>Technology Description</th>
<th>Coverage Position</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular Conditions - including [^{39,40}]</td>
<td>Limbal stem cell transplantation</td>
<td>Covered when medical management has failed, is contraindicated, or not tolerated</td>
<td>No specific rationale on coverage cited in policy</td>
</tr>
<tr>
<td>Wound Healing [^{45,46,47,48}]</td>
<td>Autologous, allogeneic, and xenograft-based products</td>
<td>Highly variable, with some products covered and others considered investigational</td>
<td>Rationale supporting coverage and non-coverage of individual technologies based on rationale on quality and sufficiency of available evidence</td>
</tr>
<tr>
<td>Gene Therapy [^{42}]</td>
<td>Gene therapy</td>
<td>Non-covered, investigational</td>
<td>No specific rationale on coverage cited in policy</td>
</tr>
<tr>
<td>Cancer Vaccines [^{43,44}]</td>
<td>Cell therapy or gene-modified cell therapy vaccines</td>
<td>Non-covered, investigational</td>
<td>Trial results not yet sufficiently conclusive Substantial variations in available trial results for some applications Use of cancer vaccines not recommended in clinical practice guidelines</td>
</tr>
</tbody>
</table>

Exhibit 5: Overview of U.S. Commercial Payer Coverage Policies on Regenerative Medicines (cont.)
potential to offer a longer duration or therapeutic effect or even a cure for disease in some cases.

Regenerative therapies promise prolonged duration of therapeutic effect or disease cures. The longer a regenerative therapy provides evidence that the therapy is still working, the more valuable it may become – this is particularly true in competitive indications or scenarios where standard of care is particularly expensive. Chronic immunological conditions like multiple sclerosis, rheumatoid arthritis or Crohn's disease, which require long-term biological therapies, would be a prime example.

The survey responses suggest that conventional studies of six months to a year may be inadequate to characterize the value of regenerative therapies and that registries to follow patients up to two or more years may be necessary to support or optimize reimbursement potential (Exhibit 8). The responses also suggest that coverage with evidence development or risk sharing schemes may be appropriate to consider if duration of effect is believed to be longer term, though payers indicated uncertainty around engaging in such approaches, stating that administrative approaches would need to be simple and easily actionable to be acceptable. Designing Phase I/II and II studies to collect outcomes data may be the most efficient and affordable bridge to help better address payer needs and establish duration of effect.

Regenerative medicine administration schedule was also highlighted in the context of duration of

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**Exhibit 6: Rated Factors in Terms of Level of Importance Regarding Assessment of Regenerative Medicines for Coverage**

<table>
<thead>
<tr>
<th>Factor</th>
<th>1 - 2</th>
<th>3 - 4</th>
<th>5 - 6</th>
<th>7 - 8</th>
<th>9 - 10</th>
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</thead>
<tbody>
<tr>
<td>Effectiveness - based on hard outcomes</td>
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<tr>
<td>Durability of treatment effect</td>
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<tr>
<td>Evidence of safety (including treatment related)</td>
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<tr>
<td>Comparative effectiveness vs. SOC alternatives</td>
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<tr>
<td>Established scientific rationale for clinical response</td>
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<tr>
<td>Cost of the cell/gene therapy component</td>
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<tr>
<td>Overall procedure costs</td>
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<tr>
<td>Quality of life impacts</td>
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<tr>
<td>Availability of long-term data</td>
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<tr>
<td>Effectiveness - based on surrogate outcomes</td>
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<tr>
<td>Physician/medical society support</td>
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1 = Lowest Rate  
10 = Highest Rate

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**Exhibit 7: Rated Likelihood of Approaches to be Applied to Novel Regenerative Medicine Technologies**

<table>
<thead>
<tr>
<th>Approach</th>
<th>1 - 2</th>
<th>3 - 4</th>
<th>5 - 6</th>
<th>7 - 8</th>
<th>9 - 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparative effectiveness</td>
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<tr>
<td>Limits on repeat administration</td>
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<tr>
<td>Coverage with Evidence Dev’t</td>
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<tr>
<td>New patient co-pay/coinsurance models</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Risk sharing agreements</td>
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1 = Lowest Rate  
10 = Highest Rate

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therapeutic effect. Some treatments may be completed with a single administration of the regenerative medicine – where view of value and differentiation will be linked to whether the regenerative therapy is administered a single time, via a couple of doses or multiple times (similar to conventional drug models). ELC members were interested in evaluating the value of single administration schedules and would consider the cost of additional administrations in value and annual cost assessments when reviewing alternative conventional therapies, as noted above. However, single administration models are unfamiliar and reflect value capture risks to manufacturers, as existing payment mechanisms do not anticipate such a scenario.

The potential for curative therapies was also discussed. Though ELC members did acknowledge that the definition of what constitutes “a cure” is a moving target by disease and would be open to debate, they generally felt that a cure would involve no need for re-administration of standard of care/alternative therapies (during duration of effect) that the regenerative therapy would replace. Introduction of purportedly curative treatments for hepatitis C, though not classified as regenerative medicine, was significant to this industry because it brought the issues of pricing and payment for curative therapies to the forefront of global debate in 2014 and 2015, though therapy cost levels have since more than halved versus initial market entry due to competition and other factors. EU entrance of one orphan regenerative gene therapy in 2014 (i.e., Glybera) of more than one million euros with an unclear value proposition supported by a surrogate endpoint (chylomicron levels) was also folded into this discussion as an example of scenarios that managed care may increasingly face in the future. The possibility of a cure has introduced early discussions of how new
Payment models may be required to accommodate truly curative therapies, including novel payment approaches such as milestone payments with claw-back provisions, amortization and issuance of bond-like payback approaches. While no conclusion in the debate around payment of curative therapies has been reached, emerging treatments may (a) push evolution of both the working definition of curative in a managed care context and (b) evolution of new payment approaches that address the potential affordability challenges of curative therapies. While payers may prefer a longer-term payout approach to spread finances and cap risks, manufacturers will be equally motivated to accrue payment upfront or in the most compacted timeframe possible to address their own revenue risks and ensure practical and viable business models. Other U.S. and EU payers, under current system constraints, may need to rely on an upfront payment approach due to system constraints, despite interests in other payout models. How curative therapy payment models will evolve for regenerative medicines remains a moving target and in early stages of debate and will vary by market and stakeholder (e.g., in scenarios where regional- or local-level contracting routes may offer reasonable channels to market). Manufacturers would be warranted to model various scenarios and understand their viability among different markets and market archetypes.

Payer respondents in the survey did indicate that they would be willing to pay more for regenerative therapies that would represent a cure or prolonged duration of therapeutic effect. More than 60 percent of the sample indicated that premiums of 50 to 100 percent (or higher) over existing treatments might be possible in the case of a disease cure and around 55 percent of the sample indicated that 26 to 50 percent premiums may be possible for therapies that deliver a complete ablation of symptoms or disease progression for two to three years or more. While actual payment levels for curative or prolonged duration of therapeutic effect scenarios may exceed that covered in the survey based on question composition, it is an indicator that payers are willing to reimburse at premium levels those treatments that bring transformative value to patient care situations and areas of high unmet need.

Conversely, therapies that only improve outcomes for six to 12 months would, as anticipated, result in a lower perception of achievable premium. This result may also in part be influenced by several factors, including a) payer perspectives that regenerative medicines have the potential to be more costly than standard of care, b) uncertainty about the safety and effectiveness of these new therapies, and c) perceptions that a key benefit will be prolonged duration of therapy to justify any higher price versus standard of care.

The severity of the disease was found to have a lower effect on payer perspectives regarding willingness to pay premium prices. Around 30 percent of payers indicated that they would more heavily consider a premium for regenerative medicines for fatal disease compared to around 20 percent for chronic/degenerative diseases. However, a majority of payers, around 55 percent, would not consider differences in premium payment justified under these conditions. This suggests that other factors besides disease severity, such as unmet need, level of competition, and availability of alternatives will also factor into pricing perceptions for regenerative medicines.
Study Limitations
Limitations of this analysis may include respondent bias, as it was not possible to determine whether respondents held a particular interest in regenerative medicine and/or are early adopters. Based on the limited number of respondents, survey findings may not be fully representative of U.S. medical director perspectives, but do point to trends in payer and provider views on regenerative medicine.

Conclusions
As regenerative medicines continue to enter the marketplace, payers are optimistic that many of these technologies will have significant impact on patient outcomes. However, as the science evolves faster than highly-regulated, resource-constrained health systems can adapt to absorb some of these technologies, the following key areas will be critical to ensure appropriate uptake and value realization:

Education on the unique aspects of regenerative medicines:
The simple fact is that from a technological standpoint, this industry is complex, with the scientific principles underlying these therapies representing a pinnacle of our understanding of genetics, physiology and systems biology. Manufacturers would be remiss in thinking that substantial educational efforts will be not required to prepare payers, providers and patients for this coming wave of technological evolution. Practical issues such as how the therapy interacts with the body, whether gene-based therapies alter patients genetic makeup in a harmful manner or not, and whether the technology can be “turned off” in the event of a safety risk, and potential for long-term risks/complications (e.g., requirements for immunosuppression, potential of oncology or other physiological risks) are particularly important in this space. Although payers typically are ambivalent to mechanism of action provided that therapy works well and is safe, characterization of the risks and benefits of the myriad emerging platforms upon which regenerative medicines are built will also be critical in this educational cascade. Additionally, manufacturers must consider education and awareness-building for payers about the political and patient advocacy dynamics that surround novel technologies, and particularly those with potential to provide curative outcomes. This dynamic has tremendous implications for influence by third-parties (such as regional and national legislators, national advocacy leadership, and other public service/public health advocates) on payer decision-making. And to a lesser extent, the role of media and public awareness and perceptions for curative technologies should not be overlooked and can present unanticipated challenges and opportunities to motivate payers and other decision makers.

Collect data early and post-market:
In the U.S. market, and particularly given that substantial investment is already going into early and pivotal trials, manufacturers would be advised to integrate outcomes/economic thinking and patient follow-up that involves all patients who may receive the therapy. This approach enables a more cohesive value proposition to be established around duration of effect or curative potential. Otherwise, payers are left with no means to validate such claims. Likewise, these therapies will certainly be subject to post-market requirements. The longer they are shown to work, the more valuable they will become, in some cases potentially jumping to front-line therapies in the case of fatal or degenerative diseases with substantial unmet need. The incremental investment in this strategy is minor compared to the overall investment in clinical evidence and potential to demonstrate transformative benefits of these therapies.

Ensure a sufficiently comprehensive and clear value demonstration strategy:
Some of the disease areas that are being targeted by regenerative medicines involve surrogate or other outcomes as primary outcomes that may not be sufficiently clear to payers. This research suggests that payers consider many dimensions of value and regenerative medicine; treatment developers would be well warranted to approach value demonstration in a comprehensive manner. Given the state of the industry and fact that most developers are currently small to mid-sized companies, it is also important to develop and pressure test evidence optimization plans and stakeholder acceptance potential early on to appropriately align development efforts to stakeholder core needs/questions and to differentiate “nice to know” versus “got to have” differentiation requirements. Payer scrutiny of these novel technologies will be high and manufacturers in this space will need to clearly demonstrate value beyond current treatments to secure a successful future for this industry.

Greater clarity on evidence expectations for long-term effective and curative therapies:
The primary driver of regenerative medicine value proposition is that it will work better and longer than conventional therapies. To date, in the practice of medicine, it has rarely been necessary to define a “cure,” but this industry will certainly push those boundaries. The definition of cure may differ by disease and be driven by many factors such as etiol-
ogy, effectiveness of alternatives and other factors. Likewise, the duration of therapy’s effect must stand out from conventional therapies and be considered carefully. Technologies that are viewed to have marginal effect and also enter at high cost are highly likely to stumble and fail. Manufacturers should consider what would be required for development of “transformative” technologies that will justify higher development investments and associated pricing of these therapies to optimize uptake.

**Evaluation of novel payment models for long-term effective and curative therapies, particularly under single administration scenarios:**

Currently, there is much debate around how single administration therapies with curative potential will be paid for. The extent to which up-front, single payment, amortized payment or either of these approaches with clawback or similar provisions will be acceptable under current systems is only at the earliest stages of being established. Single administration models pose challenges for both payer and provider systems (e.g., ACO models) that are not geared to handle hefty front-loaded payments or in the context of rapid beneficiary churn, as well as manufacturers who must establish a sufficient ROI to be able to offer transformative therapies to the marketplace. ROI models currently appear daunting to all stakeholders in the value chain. Nevertheless, functional payment models for these therapies will be material to enabling patient access and ensuring incentives for the regenerative medicine industry to bring forth the best and most transformative treatments for patient care.

**Consider policy implications of regenerative medicine:**

There are a range of policy factors that must be considered for regenerative medicines, spanning value demonstration, coding, coverage and payment. Evidentiary requirements for demonstrating a “needle moving” duration of therapeutic effect or a cure should be considered, along with how to address scenarios in which current procedural coding or payment mechanisms fail short in terms of addressing the realities of regenerative medicine technologies that do not fit in the conventional “box.” Factors such as rapid approval, patient follow-up requirements, differential HTA considerations and allocation of funding to the fraction of therapies that may emerge as truly curative in this area are also key areas in the debate.

In order to help managed care organizations prepare for and adapt to regenerative medicines, manufacturers in this space would benefit from engaging in education around emerging approaches (including benefits, risks and differentiation characteristics, value demonstration and reimbursement/payment issues). Payers and financially at-risk providers on the other hand (e.g., under IDN and ACO models) should clearly articulate how such technologies may enter a U.S. environment where bundling, accountable care and other health system changes are driving new differentiation and acceptance models, including in the context of single administration potentially curative therapies. Given the complexity of this emerging life sciences technology area, as well as its promise and potential, open stakeholder collaborative interaction and planning are of paramount importance to address the value demonstration, practice and policy evaluation required to ensure that the truly transformative technologies in this category will be available to patients in need of such solutions.

**References**


Spring Managed Care Forum

April 27-28, 2017
Rosen Shingle Creek
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