FOR AUTOIMMUNE ILLS, BIOLOGICS BRING PROMISE—AND PROBLEMS

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Value-Based Care ..................................... 13
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Significantly more patients with intermediate-2-risk or high-risk myelofibrosis receiving Jakafi® (ruxolitinib) achieved the primary end point compared with placebo (COMFORT-I*) or best available therapy† (COMFORT-II‡).1-3

The primary end point was the proportion of patients achieving a ≥35% reduction in spleen volume from baseline at week 48 as measured by CT or MRI1,3

**COMFORT-I Primary End Point: Spleen Volume Reduction at Week 241,2**

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Jakafi (n = 155)</th>
<th>Placebo (n = 154)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥35% Spleen Volume Reduction From Baseline</td>
<td>42% (n = 65)</td>
<td>0.7% (n = 1)</td>
</tr>
</tbody>
</table>

**COMFORT-II Primary End Point: Spleen Volume Reduction at Week 481,3**

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Jakafi (n = 146)</th>
<th>BAT (n = 73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥35% Spleen Volume Reduction From Baseline</td>
<td>29% (n = 41)</td>
<td>0% (n = 0)</td>
</tr>
</tbody>
</table>

* 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 and high-risk myelofibrosis.1,2
† Best available therapy in COMFORT-II included hydroxyurea (46.6%) and glucocorticoids (16.4%), as well as no medication, anagrelide, epoetin alfa, thalidomide, lenalidomide, lenalidomide, mercaptopurine, thioguanine, danazol, peginterferon alfa-2a, interferon-α, melphalan, acetylsalicylic acid, cytarabine, and colchicine.4
‡ 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 and high-risk myelofibrosis.1,3

**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 × 10^9/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. Continuing 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.
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 thrombocytopenia myelofibrosis.

Overall survival was a prespecified secondary end point in COMFORT-I and COMFORT-II¹

- **COMFORT-I**: At 3 years, survival probability was 70% for patients originally randomized to Jakafi and 61% for those originally randomized to placebo⁴

- **COMFORT-II**: At 3 years, survival probability was 79% for patients originally randomized to Jakafi and 59% for those originally randomized to best available therapy¹

Because of progression-driven events or at the physician’s discretion, patients randomized to placebo (COMFORT-I) or best available therapy (COMFORT-II) who crossed over to receive Jakafi continued to be grouped within their original randomized assignment for analysis purposes⁴

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

**Brief Summary:** For full prescribing information, see package insert.

**CONTRAINDICATIONS:**
- None.

**WARNINGS AND PRECAUTIONS:**
- **Thrombocytopenia, Anemia, and Neutropenia:** Treatment with Jakafi can cause thrombocytopenia, anemia, and neutropenia. [See Dosage and Administration (2.1) in Full Prescribing Information] Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary [see Dosage and Administration (2.1.1) and Adverse Reactions (6.1) in Full Prescribing Information]. Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi. Severe neutropenia (WBC less than 0.5 X 10^9/L) was generally reversible by withholding treatment until recovery [see Adverse Reactions (6.1) in Full Prescribing Information]. Perform a pre-treatment complete blood count (CBC) and monitor CBC every 2 to 4 weeks until doses are stabilized, and then clinically indicated [see Dosage and Administration (2.1.1) and Adverse Reactions (6.1) in Full Prescribing Information].

**Risk of Infection:** Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting therapy with Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. Tuberculosis Tuberculosis infection has been reported in patients receiving therapy with Jakafi. Consult a physician with expertise in the treatment of tuberculosis before starting Jakafi. The decision to continue Jakafi during treatment of active tuberculosis should be based on the overall risk-benefit determination. PML Progressive multifocal leukoencephalopathy (PML) has occurred with ruxolitinib treatment for myelofibrosis. If PML is suspected, stop Jakafi and evaluate. Herpes Zoster Adverse events of herpes zoster and to seek treatment as early as possible if suspected [see Adverse Reactions (6.1) in Full Prescribing Information]. Hepatitis B Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infection taking Jakafi. The effect of Jakafi on viral replication in patients with chronic HBV infection is unknown. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines. Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi: Following discontinuation of Jakafi, symptoms from myeloproliferative neoplasms may return to pretreatment levels over a period of approximately one week. Some patients with myelofibrosis have experienced one or more of the following adverse events after discontinuing Jakafi: fever, respiratory distress, hypoxia, DIC, or multi-organ failure. If one or more of these occur after active disease has been controlled or following interruption or discontinuation of treatment with Jakafi, consider tapering the dose of Jakafi gradually rather than discontinuing abruptly. Non-Melanoma Skin Cancer: Non-melanoma skin cancers (including basal cell, squamous cell, and Merkel cell carcinoma) have occurred in patients treated with Jakafi. Perform periodic skin examinations. Lipid Elevations: Treatment with Jakafi has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined in patients treated with Jakafi. Assess lipid parameters approximately 6-12 weeks following initiation of Jakafi therapy. Monitor and treat according to clinical guidelines for the management of hyperlipidemia.

**ADVERSE REACTIONS:** The following serious adverse reactions are discussed in greater detail in other sections of the labeling: Thrombocytopenia, Anemia, and Neutropenia [see Warnings and Precautions (5.1) in Full Prescribing Information], Risk of Infection [see Warnings and Precautions (5.2) in Full Prescribing Information], Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi [see Warnings and Precautions (5.3) in Full Prescribing Information], Non-Melanoma Skin Cancer [see Warnings and Precautions (5.4) in Full Prescribing Information]. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Clinical Trials Experience in Myelofibrosis: The safety of Jakafi was assessed in 617 patients in six clinical studies with a median duration of follow-up of 10.9 months, including 301 patients with myelofibrosis in two Phase 3 studies. In these two Phase 3 studies, patients had a median duration of exposure to Jakafi of 9.5 months (range 0.5 to 17 months), with 89% of patients treated for more than 6 months and 25% treated for more than 12 months. One hundred and eleven (111) patients started treatment at 15 mg twice daily and 190 patients started at 20 mg twice daily. In patients starting treatment with 15 mg twice daily (pretreatment platelet counts of 100 to 200 X 10^9/L) and 20 mg twice daily (pretreatment platelet counts greater than 200 X 10^9/L), 65% and 25% of patients, respectively, required a dose reduction below the dose increase within the first 8 weeks of therapy. In a double-blind, randomized, placebo-controlled study of Jakafi, among the 155 patients treated with Jakafi, the most frequent adverse drug reactions were bruising, dizziness and headache [see Table 1]. Discontinuation for adverse events, regardless of causality, was observed in 11% of patients treated with Jakafi and 11% of patients treated with placebo. Table 1 presents the most common adverse reactions occurring in patients who received Jakafi in the double-blind, placebo-controlled study during randomized treatment.

**Thrombocytopenia:**
- 23% of patients treated with Jakafi and 15% of placebo patients experienced Grade 3 or higher thrombocytopenia during the double-blind, placebo-controlled study during randomized treatment.
- Median number of units transfused per month was 1.2 in patients treated with Jakafi and 1.7 in placebo treated patients.
- Table 1: Myelofibrosis: Adverse Reactions Occurring in Patients on Jakafi in the Double-blind, Placebo-controlled Study During Randomized Treatment

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jakafi (N=151)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bruisinga</td>
<td>23</td>
<td>&lt;1</td>
<td>0</td>
</tr>
<tr>
<td>Dizzinessb</td>
<td>18</td>
<td>&lt;1</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Urinary Tract Infectionsc</td>
<td>9</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>7</td>
<td>&lt;1</td>
<td>1</td>
</tr>
<tr>
<td>Flatulence</td>
<td>5</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Herpes Zosterd</td>
<td>2</td>
<td>0</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

**Contraindications:**
- Patients with myelofibrosis have experienced one or more of the following adverse events after discontinuing Jakafi: fever, respiratory distress, hypoxia, DIC, or multi-organ failure. If one or more of these occur after active disease has been controlled or following interruption or discontinuation of treatment with Jakafi, consider tapering the dose of Jakafi gradually rather than discontinuing abruptly.
- Non-Melanoma Skin Cancer: Non-melanoma skin cancers (including basal cell, squamous cell, and Merkel cell carcinoma) have occurred in patients treated with Jakafi. Perform periodic skin examinations.
- Lipid Elevations: Treatment with Jakafi has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined in patients treated with Jakafi. Assess lipid parameters approximately 6-12 weeks following initiation of Jakafi therapy. Monitor and treat according to clinical guidelines for the management of hyperlipidemia.

**Adverse Drug Reactions:**
- The three most frequent non-hematologic adverse reactions were bruising, dizziness and headache [see Table 1]. Discontinuation for adverse events, regardless of causality, was observed in 11% of patients treated with Jakafi and 11% of patients treated with placebo. Table 1 presents the most common adverse reactions occurring in patients who received Jakafi in the double-blind, placebo-controlled study during randomized treatment.

**Tuberculosis:**
- 23% of patients treated with Jakafi and 15% of placebo patients experienced Grade 3 or higher tuberculosis during the double-blind, placebo-controlled study during randomized treatment.
- Median number of units transfused per month was 1.2 in patients treated with Jakafi and 1.7 in placebo treated patients.

**Laboratory Parameter | All Grades | Grade 3 | Grade 4 |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Jakafi (N=151)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>35</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>30</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Jakafi (N=151)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevations</td>
<td>19</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Placebo (N=151)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevations</td>
<td>19</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

- *Presented values are worst Grade values regardless of baseline
- **National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
- Includes contusion, ecchymosis, hematoma, injection site hematoma, perifocal edema, punctate subcutaneous hematoma, increased tendency to bruise, petechiae, purpura
- Includes dizziness, postural dizziness, vertigo, balance disorder, Meniere's Disease, labyrinthish
- Includes urinary tract infection, cystitis, urethritis, urinary tract infection bacterial, kidney infection, pyuria, bacteria urine identified, nitrite urine present
- Includes weight increased, abnormal weight gain
- Includes herpes zoster and post-herpetic neuralgia

**Description of Selected Adverse Drug Reactions:**
- Anemia: In the two Phase 3 clinical studies, 2 dose levels were evaluated on a weekly basis. One patient (<1%) discontinued treatment because of anemia. In patients receiving Jakafi, mean decreases in hemoglobin reached a nadir of approximately 1.5 to 2.0 g/dL below baseline after 6 to 8 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 1.0 g/dL below baseline. This pattern was observed in patients regardless of whether they had received transfusions during therapy. In the randomized, placebo-controlled study, 60% of patients treated with Jakafi and 38% of patients receiving placebo had received red blood cell transfusions during randomized treatment. Among transfused patients, the median number of units transfused per month was 1.2 in patients treated with Jakafi and 1.7 in placebo treated patients.
- Thrombocytopenia: In the two Phase 3 clinical studies, in patients who developed Grade 3 or 4 thrombocytopenia, the median time to onset was approximately 6 weeks. Thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above 50 X 10^9/L was 14 days. Platelet transfusions were administered to 5% of patients receiving Jakafi and 4% of patients receiving control regimens. Discontinuation of treatment because of thrombocytopenia occurred in <1% of patients receiving Jakafi and <1% of patients receiving control regimens. Patients with a platelet count of 100 X 10^9/L to 200 X 10^9/L, before starting, had a higher frequency of Grade 3 or 4 thrombocytopenia compared to patients with a platelet count greater than 200 X 10^9/L. (17% versus 7%). Neutropenia: In the two Phase 3 clinical studies, 1% of patients reduced or stopped Jakafi because of neutropenia. Table 2 provides the frequency and severity of clinical hematology abnormalities reported for patients receiving treatment with Jakafi or placebo in the placebo-controlled study.

**Table 2: Myelofibrosis: Worst Hematology Laboratory Abnormalities in the Placebo-Controlled Study**
The Cmax and AUC of ruxolitinib decreased 32% and 61%, respectively, following concomitant administration with mild or moderate CYP3A4 inhibitors. Concomitant administration with strong CYP3A4 inhibitors increased 33% and 91%, respectively following concomitant administration with the strong CYP3A4 inhibitor. The AUC of ruxolitinib is predicted to increase by approximately 100% to 300% following concomitant administration with the combined CYP3A4 and CYP2C19 inhibitor. The AUC of ruxolitinib decreased 32% and 61%, respectively, following concomitant administration with fluconazole doses of greater than 200 mg daily.

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>Adverse Events</th>
<th>Jakafi (N=110)</th>
<th>Best Available Therapy (N=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>14%</td>
<td>20%</td>
</tr>
<tr>
<td>Abdominal Paina</td>
<td>15%</td>
<td>15%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15%</td>
<td>7%</td>
</tr>
<tr>
<td>Dizzinessb</td>
<td>15%</td>
<td>13%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15%</td>
<td>15%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>14%</td>
<td>23%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>13%</td>
<td>3%</td>
</tr>
<tr>
<td>Muscle Spasms</td>
<td>12%</td>
<td>5%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>Constipation</td>
<td>8%</td>
<td>3%</td>
</tr>
<tr>
<td>Cough</td>
<td>8%</td>
<td>5%</td>
</tr>
<tr>
<td>Edema</td>
<td>8%</td>
<td>7%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>7%</td>
<td>11%</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Herpes Zosterf</td>
<td>6%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Nausea</td>
<td>6%</td>
<td>4%</td>
</tr>
</tbody>
</table>

- National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
- Includes abdominal pain, abdominal pain lower, and abdominal pain upper
- Includes dizziness and vertigo
- Includes dyspepsia and dyspepsia esophageal
- Includes edema and peripheral edema
- Includes herpes zoster and post-herpetic neuritis

Other clinically important treatment emergent adverse events observed in less than 6% of patients treated with Jakafi were: Weight gain, hypertension, and urinary tract infections. Clinically relevant laboratory abnormalities are shown in Table 4.

Table 4: Polycythemia Vera: Selected Laboratory Abnormalities 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>Jaifikasi</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best Available Therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>72%</td>
<td>&lt;1%</td>
<td>58%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>27%</td>
<td>5%</td>
<td>24%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3%</td>
<td>0%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>35%</td>
<td>0%</td>
<td>8%</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>25%</td>
<td>&lt;1%</td>
<td>16%</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>23%</td>
<td>0%</td>
<td>23%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15%</td>
<td>0%</td>
<td>13%</td>
</tr>
</tbody>
</table>

- Presented values are worst Grade values regardless of baseline
- National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0

DRUG INTERACTIONS Drugs That Inhibit or Induce Cytochrome P450 Enzymes Ruxolitinib is metabolized by CYP3A4 and to a lesser extent by CYP2C19. CYP3A4 inhibitors: The Cmax and AUC of ruxolitinib increased 33% and 91%, respectively following concomitant administration with the strong CYP3A4 inhibitor ketoconazole in healthy subjects. Concomitant administration with mild or moderate CYP3A4 inhibition did not result in an exposure change requiring intervention [see Pharmacokinetics (12.3) in Full Prescribing Information]. When administering Jakafi with strong CYP3A4 inhibitors, consider dose reduction [see Dosage and Administration (2.3) in Full Prescribing Information]. Fluconazole: The AUC of ruxolitinib is predicted to increase by approximately 100% to 300% following concomitant administration with the combined CYP3A4 and CYP2C19 inhibitor. The AUC of ruxolitinib decreased 32% and 61%, respectively, following concomitant administration with fluconazole doses of greater than 200 mg daily [see Dosage and Administration (2.3) in Full Prescribing Information].

CYP3A4 inducers: The Cmax and AUC of ruxolitinib decreased 32% and 61%, respectively, following concomitant administration with strong CYP3A4 inducer rifampin in healthy subjects. No dose adjustment is recommended; however, monitor patients frequently and adjust the Jakafi dose based on safety and efficacy [see Pharmacokinetics (12.3) in Full Prescribing Information].

USE IN SPECIFIC POPULATIONS Pregnancy Pregnancy Category C: Risk Summary There are no adequate and well-controlled studies of Jakafi in pregnant women. In embryofetal toxicity studies, treatment with ruxolitinib resulted in an increase in late resorptions and reduced fetal weights at maternally toxic doses. Jakafi should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Androgens: Ruxolitinib plasma AUC values of ruxolitinib were greater than 100% following administration of androgens and decreased following administration of combined CYP3A4 and Aromatase inhibitors. The AUC of ruxolitinib is predicted to increase by approximately 100% to 300% following concomitant administration with the combined CYP3A4 and Aromatase inhibitor. The AUC of ruxolitinib decreased 32% and 61%, respectively following concomitant administration with androgens.

OVERDOSAGE There is no known antidote for overdoses with Jakafi. Single doses up to 200 mg have been given with acceptable acute tolerability. Higher than recommended repeat doses are associated with increased myelosuppression including leukopenia, anemia, and thrombocytopenia. Appropriate supportive treatment should be given. Hemodialysis is not expected to enhance the elimination of ruxolitinib.

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I met Anthony DeAngelis a couple of years ago when I wrote some patient profiles for the Brigham and Women's Crohn's and Colitis Center in Boston. 

I suppose I have interviewed hundreds of patients over the years. But Anthony stuck with me. He was intelligent and informed. And he had this amazing family—his wife, Melissa, and two adorable daughters, Stella, now 7, and Tessa, now 4, who has Rett syndrome.

Now 41, Anthony was diagnosed with Crohn's when he was 15. He has endured pain, nausea, malnutrition, fistulas, and a schedule that must take into account the need for marathon bathroom sessions.

He has been on about 30 different medications. Patient assistance programs have saved him thousands in out-of-pocket expenses. “That’s money for Tessa or a summer family vacation,” he told me in a recent phone call. But Anthony is not naïve. Drug companies don’t have these programs simply for charitable purposes: “They know they can get more out of the insurance companies if they cover the drugs.”

Avoiding surgery had been a goal. But in April, Anthony had emergency surgery to remove part of his small intestine after a blockage and strictures caused a perforation. He is hoping that the ileostomy is temporary and that he’ll have surgery to get “rehooked up” soon.

All of this was conveyed without a trace of self-pity.

The autoimmune diseases discussed in this issue are less lethal than cancer, but they are heartless robbers of normal good health in the prime of life. Anthony DeAngelis is a reminder to me of how many people in this world shoulder huge burdens with a dignity and grace to which I can only aspire.

Anthony DeAngelis and his family.

Dignity and Grace Personified

By Peter Wehrwein
Managing Care publishes original papers and feature articles dealing with diverse elements of the health care system. Among these are impartial peer-reviewed research and review articles examining clinical and financial aspects of managed care.

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Independence Blue Cross

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The ConfluenceElite Group, LLC
West Chester, Pa.

JAN BERGER, MD, MJ
President
Health Intelligence Partners
Chicago, Ill.

THOMAS BODENHEIMER, MD
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University of California–San Francisco
San Francisco, Calif.

PETER BOLAND, PhD
President, Boland Healthcare
Berkeley, Calif.

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All About Autoimmune Disease

Biologics Bring Promise, But Also Problems  
These medications revolutionized the treatment of conditions like rheumatoid arthritis. But they can break budgets, and watch out for those side effects.

Product Preferencing is a Common Tactic  
Biologic drugs for autoimmune disease are a big ticket item, so payers are using product preferencing, other tactics to rein in costs.

Attention Switches to Progressive MS  

Autoimmune Diseases Can Rack Up Costs  
Rheumatoid arthritis, psoriasis, and inflammatory bowel disease suck up almost as many health care dollars as stroke and lower back pain.

New Psoriasis Drug Seems a Winner  
Eli Lilly’s Taltz achieves higher remission rates than a competitor, but it’s associated with a slightly higher risk of infection.

Hub Programs Are on the Defensive  
They can help patients, but some programs have led to federal kickback investigations and major settlements.

Original Research

Coaches Can Create a Collaborative Culture  
This program used team meetings followed by coaching to help initiate best practices for patients with chronic conditions and/or end-of-life care needs.

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Autoimmune drug sales trending up.

The digital edition does not contain some of the advertising pages that appear in the print edition.
Gout, Rheumatoid Arthritis Charting Different Courses

This is a tale of two diseases affecting the joints that are on vastly different trajectories. While hospitalizations for rheumatoid arthritis (RA) have dropped considerably, those for gout soared, according to a research letter in the June 7 issue of JAMA.

The annual hospitalization rate for people with RA dived 67%, from 13.9 per 100,000 American adults in 1993 to 4.6 in 2011. Meanwhile, the hospitalization rate for those with gout doubled, from 4.4 to 8.8 per 100,000 Americans adults, according to researchers at the Massachusetts General Hospital in Boston.

For RA, the inflation-adjusted hospital costs per 100,000 U.S. adults dropped from $83,101 to $55,988. For gout, those costs increased from $34,457 to $58,003.

Researchers examined data from the Nationwide Inpatient Sample compiled by the Agency for Healthcare Research and Quality. They investigated overall rates of hospitalizations, rates of surgery related to either condition, and inflation-adjusted hospital costs.

“The findings may reflect suboptimal care received by gout patients and its increasing prevalence,” the research letter stated. But they reflect good news about rheumatoid arthritis. Lead author Hyon K. Choi, MD, of Harvard Medical School, said in a press release that widespread use of effective medications for rheumatoid arthritis—including methotrexate and the newer, genetically engineered biologics—along with better management and earlier treatment have contributed to a reduced incidence of complications requiring hospitalizations, including those for systemic complications and major joint surgeries.

Choi told Managed Care that gout, which affects more than 8 million Americans, can be tied to lifestyle. “The continued Western lifestyle (e.g., consumption of fatty and meaty meals with sugary soda or alcohol), growing obesity epidemic, increased frequency of risk factors such as hypertension and chronic kidney disease, and increased use of low-dose aspirin and diuretics (which elevate uric acid levels) all contribute to the increased incidence of gout,” Choi said in an email.

So although there is a genetic component to gout, there’s a great deal of good evidence for risk factors that are nongenetic and modifiable.

Furthermore, Choi said that almost 9 out of 10 hospitalizations for gout are preventable and can be traced back to inadequate or inefficient care. For example, only a small proportion of people who might benefit from uric acid-lowering medications take them.

And many physicians do not monitor the uric acid levels of their patients who are taking uric acid-lowering prescriptions to make sure they are working and that people are taking them as prescribed.

Choi told Managed Care that the “key approach of ‘treating-to-target’ with urate-lowering drugs (to a baseline serum uric acid [SUA] target of <6.0 mg/dL at a minimum) as advocated by rheumatology guidelines has not been implemented as a standard by primary care physicians in gout care—this needs to be aggressively adopted in PCP care.”

Ninety percent of gout patients are managed by PCPs, and other providers need to be engaged, Choi said. “Results have been impressive for clinical models that share some aspects of broadly employed anticoagulation and hyperlipidemia management and monitoring clinics.”

For instance, a recent study at a specialty clinic for gout proved that good results can be achieved with nurse-led caregiving teams.
ACA Premium Hikes Called Very Likely

It’s going to be ugly next year when it comes to premiums on the ACA exchanges, according to Marilyn Tavenner, CEO of America’s Health Insurance Plans. And although Tavenner speaks for the premier health plan lobbying organization, she was there at the creation of the exchanges in her then role as head of CMS.

CMS officials want Tavenner and others to calm down, pointing out that the dire predictions for 2016 did not pan out with the average premium rates increasing only about 4% for consumers, instead of the double-digit increase that had been expected.

But Tavenner tells Morning Consult, an online newspaper and media outlet, that in addition to the old reliable increases in medical and pharmacy costs, some new factors are in play. She referred to the fact that two of the three “risk mitigation” programs established under Obamacare will end in 2017, reinsurance and risk corridors. Risk adjustment will continue. The idea was that after three years, they could be done away with because marketplaces would be more stable and insurers would have a better grasp on the health status of enrollees. “Reinsurance and risk corridors could end without much ado. But that hasn’t happened,” according to Morning Consult.

Perhaps more vexing is the special enrollment period (SEP), to be used for those who did not enroll during the open enrollment period (OEP) but then found a need for coverage, such as losing their job and health benefits. Insurers argue that the SEPs allow consumers to enter a market only when they’re sick.

AHIP paid Oliver Wyman to crunch the numbers, and they don’t look good. SEP enrollees are more than 40% more likely to let their coverage lapse, thus increasing churn that helps to increase premiums.

Oliver Wyman examined data from 13 health insurers’ premiums of about $27 billion from January 2014 through June 2015, and about $26 billion paid in allowed claims, using claims filed during the same period and paid through October 2015.

The per-member, per-month claim costs during the first three months of enrollment in 2014 were 24% higher for SEP beneficiaries than OEP beneficiaries.

The Oliver Wyman study asserted that CMS’s efforts to crack down on misuse of SEPs has so far not been encouraging, as witnessed by the withdrawal from the exchanges by UnitedHealthcare and other insurers. “Through regulation and guidance, the eligibility categories allowing an individual to qualify for an SEP have expanded to include over 30 different criteria and there is considerable concern among issuers that individuals are using SEPs to delay purchasing health insurance until a need arises.”

CMS is not deaf to these concerns. In May it announced that it has eliminated some of the SEPs and will begin requiring documentation for some of the more common SEPs.

Antiplatelet Misuse Down, Not Gone

Perfection is unreachable but that shouldn’t stop the health care system for reaching anyway. Take the issue of patients undergoing percutaneous coronary intervention (PCI). When patients have certain conditions (e.g., end-stage renal disease or a recent stroke), they should not get certain antiplatelet medications. For the most part, doctors hold the line, according to a study in Circulation: Cardiovascular Quality and Outcomes.

Only 1.1% of 64,294 patients who had PCI performed from 2007 to 2013 received contraindicated antiplatelet medications. The data were taken from the Veterans Affairs Clinical Assessment, Reporting, and Tracking Program.

About 18% of patients undergoing PCI had contraindications to common antiplatelet medications, the study stated, and roughly 6% of those patients received contraindicated medication that could have caused bleeding. Fortunately, though, the contraindicated medications did not result in a significantly higher risk of 30-day mortality.

The contraindicated drugs that were used the most often were eptifibatide (Integrilin) (13.7%) and abciximab (Reopro) (4.6%). One of the problems, say the University of Michigan researchers who conduct-
Narcolepsy is an often misdiagnosed, incurable, chronic and potentially disabling neurologic disorder, and is associated with high medical comorbidity burdens and reduced daily function. Narcolepsy has also been shown to have substantial socioeconomic burden resulting from increased healthcare resource utilization and lower work productivity relative to those without narcolepsy.
The study, is that PCIs “are often performed urgently or emergently … antiplatelet medications are often administered before they are entered into the medical chart in response to verbal orders given during the procedure, potentially limiting the ability for an EMR-triggered alert to prevent the use in patients with a known contraindication.”

Therapeutic Subs Called Money-Saver

The call to expand therapeutic substitution for brand-name drugs got louder recently thanks to a study in *JAMA Internal Medicine* that said that therapeutic substitution could have saved the health care system $73 billion from 2010 to 2012.

Therapeutic substitution means replacing a drug that does not have a generic equivalent with a similar drug within the same general drug class. It’s controversial, raising concerns about efficacy, drug interactions, and adverse effects. In addition, said the researchers from Ohio State University who conducted the study, most physician organizations oppose therapeutic substitution and view it as undermining physician autonomy.

The study estimates that out-of-pocket expenses for patients for branded drug overuse came to almost $25 billion in the same period.

The researchers looked at data on 107,132 people, about 62% of who reported use of any prescribed medication. The survey design included payer expenditures, demographic characteristics, prescription drug info, and self-reported medical conditions.

The drug classes with the highest excess expenditures according to the study were statins ($10.9 billion), atypical antipsychotics (also known as second-generation antipsychotics: $9.9 billion), proton pump inhibitors ($6.1 billion), selective serotonin reuptake inhibitors ($6 billion), and angiotensin receptor blockers ($5.5 billion).

Though these were the leaders, excess expenditure “was identified throughout different aspects of medicine,” accounting for 1 in 10 dollars spent on prescribed medications. “Although therapeutic substitution is controversial, it offers a potential mechanism to decrease drug costs if it can be implemented in a way that does not negatively affect quality of care,” the study states.

It can get tricky, according to Joseph S. Ross, MD, of Yale, who wrote an accompanying editorial. If a doctor prescribes Zocor, for instance, a pharmacist can automatically substitute it for the generic simvastatin.

“Where generic substitution becomes more complicated is when a prescription names a brand-name drug for which there is no FDA-approved generic, but there is an approved generic version of another drug within the same class,” Ross wrote.

State laws vary on whether pharmacists can substitute within therapeutic classes.

Briefly Noted

Poorer adults are more likely to visit doctors or stay overnight in a hospital in states that have expanded their Medicaid programs under the ACA compared with states that did not expand Medicaid, according to a study in the *Annals of Internal Medicine*. Kaiser Health News reported that the authors found no improvement in people’s self-assessment of their health. Why? Increased contact with the health care system and new knowledge about their health status may affect people’s perception of how healthy they are… Opioids aren’t the only problem: deaths from overdosing on anti-anxiety medication are also on the rise, reports STAT. In 2013, more than 22,000 people died of drug overdoses in the United States and 31% of those involved benzodiazepines such as Xanax and Valium.

— Frank Diamond

Children’s, psychiatric hospitals EHRs lag behind

Though hospital adoption of EHR technology keeps growing, there’s a gap in how much that’s happened depending on the type of hospital. Still, the news is good according to the Office of the National Coordinator for Health Information Technology (ONC). Basic EHR technology in hospitals grew from 75.5% in 2014 to 83.8% last year. Basic EHRs include functionalities, such as viewing imaging results, which are not included in certified EHRs, according to an ONC data brief. Hospital adoption of EHRs with more advanced functionality is increasing while adoption of EHRs with less advanced functionality is declining.

Children’s and psychiatric hospitals have much lower rates of basic EHR adoption. “This is not altogether surprising as only 69% of children’s hospitals successfully attested to Stage 1 of the CMS Medicaid EHR Incentive Program and psychiatric hospitals are not eligible for the CMS Medicaid or Medicare EHR Incentive Program,” the study states.

Percent of non-federal acute care hospitals with adoption of at least a basic EHR system by hospital specialty

<table>
<thead>
<tr>
<th></th>
<th>2008</th>
<th>2015</th>
</tr>
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<tbody>
<tr>
<td>Psychiatric</td>
<td>7%</td>
<td>10%</td>
</tr>
<tr>
<td>Children’s</td>
<td>10%</td>
<td>12%</td>
</tr>
<tr>
<td>General medicine</td>
<td>15%</td>
<td>55%</td>
</tr>
</tbody>
</table>

Source: Office of the National Coordinator for Health Information Technology, Data Brief 35, May 2016
Bernie Sanders’ erstwhile presidential bid has been credited—or blamed, depending on your perspective—with making Hillary Clinton tack to the left on some issues, most notably health care.

And it may have worked—at least in the primary season. While Sanders made "Medicare for All" a centerpiece of his campaign, Clinton has shifted to the left somewhat by supporting a “public option”—it appears in quote marks on her website—and building on the ACA. She would let states set up their own public option choices, and her campaign has also floated the idea of letting Americans "55 or 50 and up" buy into Medicare.

These talking points have made for a good story line in preaching to the Democratic choir, but turning them into reality if she wins the White House will be quite another story.

While the Medicare idea is a bit vague at this point, and it hasn’t made it onto her campaign website yet, Jonathan Oberlander, chair of social medicine at the University of North Carolina, thinks it was a smart move on Clinton’s part to reach out to Sanders’ supporters, who proposed the liberal dream of a federally administered single-payer system that would foot the country’s entire health care bill.

Medicare for more not all

Oberlander dubs Clinton’s idea “Medicare for more,” and he believes it was Clinton’s way of offering something to liberal Democrats who want something more than just a to-be-continued ACA.

What works in primary season often gets jettisoned in the summer and fall of an election year as candidates attempt to gain supporters beyond their base. “It remains to be seen in a general election how much she emphasizes this issue, but I don’t think the politics in the general election are bad either, necessarily,” says Oberlander. “The public likes Medicare.”

But the politics of “Medicare for more” are daunting. Not only will Clinton have to defeat Donald Trump in November (as we went to press, she was favored in most polls), she will need to pull enough Democrats into the House and Senate with her—and they will have to be the kind of Democrats who are willing to take on the political risks of health care reform. The lumps that President Obama took to get the ACA passed may scare them off, although the Medicare-for-more proposal is the kind of incremental change to health care coverage that has gone over well in the past. Think Part D prescription coverage and before that, the Children’s Health Insurance Program.

One of the important story lines this year that hasn’t gotten enough attention in the press is that Congress is also up for grabs, says Nicholas Bagley, a health law specialist at the University of Michigan Law School. Of course every member of the House is up for re-election and a third of the Senate. But depending on how the partisan composition of both houses of Congress shift, it’s going to either open or close the windows of political opportunity when it comes to health care, says Bagley.

Consider this: It has been six years since the ACA was signed into law, and Republican opposition has not relented. Clinton would likely need the full-throated support of every Democrat in Congress to get something like a Medicare buy-in passed, says Bagley. That’s a tough proposition, unless health care becomes a priority in the early days of a Clinton administration, when the “wind is at her back,” as Bagley says. “A president can only put the full weight of her office behind a small number of major legislative initiatives,” he adds.

Yet many Sanders supporters will say that...
a Medicare-for-more doesn’t go nearly far enough. Physicians for a National Health Plan is a nonpartisan organization, but the single-payer plan that Sanders called for falls in line with the organization’s goals. Adam Gaffney, MD, a critical care physician at Massachusetts General Hospital and the group’s president, sees problems with the Medicare buy-in.

On the surface, extending Medicare might look like a way to move higher-risk people out of the exchanges and help moderate premiums there, but that could spell adverse selection problems for Medicare, in Gaffney’s opinion. “If you have a Medicare buy-in program that’s optional, what could wind up happening is that the better risk population will be covered by the private insurance industry and many of the worst risks could get relegated into the public system,” he says.

Bagley says the risk profile of the individual purchasers of Medicare would depend on the structure of the buy-in. “It’s too soon to model the economic consequences of all this,” he says. “Older people, as a general rule, are more expensive than younger people in terms of insurance, but sicker people are much more expensive than healthy people, and there are sick people at every step of the age hierarchy. A lot would depend on whether the Medicare buy-in is attractive to sick people or whether it’s attractive to healthy people.”

### Three ACA complications

The Committee for a Responsible Federal Budget has analyzed how each candidate’s plans would impact the federal budget, but this “Medicare for more” idea throws a curveball into its calculations. Marc Goldwein, senior vice president of the group, recalls earlier proposals for a Medicare buy-in that would be “pretty close” to budget neutral. “Before ACA, the idea was rather simplistic: People younger than age 65 would be charged the average premium of everyone who bought in, and Medicare would adjust rates in the next year to cover losses or account for surpluses.”

Now Goldwein sees three ACA-related problems with Medicare expansion. The first is the ACA subsidies for anyone with income up to 400% of the poverty rate. “Would that buy-in also have that subsidy?” Goldwein asks. “If it does, is the subsidy scaled up or down to adjust for Medicare or is it exactly the same subsidy you would get in the exchanges? Depending on the answer, this could end up costing us money in subsidies.”

The second complication: Who’s going to want to buy into Medicare rather than buy a plan on the exchanges? The ACA places age bands on premiums for exchange plans that limit the age differential to a 3-to-1 ratio. “For that reason, it’s hard for me to imagine a Medicare premium that’s going to do better than that,” says Goldwein. “I don’t know how Medicare is going to be competitive for most people compared to the exchanges.” And the third: How would the Medicare buy-in work with the employer and individual mandates? That’s a huge unknown, Goldwein says.

### What’s realistic?

Clinton has other ideas to build on the ACA that would, as she sees it, move the country closer to universal coverage. She would extend tax credits to offset out-of-pocket costs, boost tax credits for health exchange premiums, and fix the “family glitch,” so people can get coverage when their employer’s family plans are too expensive. She would offer federal support to states that expand Medicaid to cover the full costs for the first three years and spend up to $500 million a year on navigators to draw in the 16 million Medicaid-eligible people who have not enrolled. Clinton has also talked about reining in drug spending, but she hasn’t offered any specifics.

“She could try to implement some of these changes on her own administratively. But those efforts are less likely to prove effective in the absence of new legislation,” says Bagley.

Still, she has levers to pull, notes Bagley. Those levers might be a salve for the lumps a truculent Congress could inflict, but first she has to get them within her reach. MC
Over the past two decades, a lot of low-hanging fruit has been lopped off health care costs. Inpatient days per thousand have come down by about one third. Generic drug utilization has reached 90% in some classes. And yet, there has been no appreciable bend in the health care spending curve. In the search for savings, what’s been more or less overlooked is care that is of little or no value. A few years ago, the Institute of Medicine labeled more than a third of health care spending as wasteful. Subtract out the subset that represents fraud and abuse, and you still wind up with about 30 cents on the dollar that goes to low-value or no-value care.

What do those terms really mean? It’s not just unnecessary tests or overuse of antibiotics. It’s unwarranted variation in care—a culprit studied for years by the folks who produce the Dartmouth Atlas. The classic example is low-back pain: Regardless of whether most patients try stretching and weights, visit a pain management specialist, or choose surgery, outcomes are roughly the same—though the cost of each differs dramatically.

“We’ve always known there’s a ton of variation, but under fee for service, nobody cared,” says Joshua Rosenthal, chief scientific officer at RowdMap. The shift to value-based payment and risk-bearing schemes has changed all that, he says. “Being able to get rid of that 30 cents is really, really important. Essentially, as population increases and expenditure decreases, you have two choices: start rationing needed care or get rid of the unneeded care.”

Formula for building networks
With offices in the heart of Louisville’s Whiskey Row, RowdMap is a young company full of data scientists and smart hipsters who are exploiting CMS’s so-called data liberation movement, one of the largest releases of government-held data ever. CMS is also making much more provider-level information public through the Physician Compare and Hospital Compare websites and nearly a half dozen other databases. As payers divert compensation from fee-for-service to risk-bearing models, providers will need all the practice data they can get. Having the data is one thing. Knowing how to use it is another. Applying its computational power to the data, RowdMap puts providers into high-, medium-, and low-value buckets compared with peers in their markets, using specific benchmarks to show why outliers differ from the norm. RowdMap has developed “no-value care” and population-health profiles for every physician and hospital in the country.

“It’s not just summary benchmarks; it’s literally about how they practice. How they spend their time. What they bill for and associated costs,” says Rosenthal. “That allows you to do some pretty interesting things.”

Like working with payers to help them develop high-value provider networks. For one Northern California health plan, the average provider in its network cost the plan $274 per member per year (PMPY). Using RowdMap’s provider profiles, the plan removed from its network 101 physicians whose profiles suggested that they provided an excess of low-value care,
replacing them with 121 high-value physicians. Over 12 months, the average PMPY cost across the plan’s provider panel fell to $179, according to RowdMap.

“We can say ‘Per patient, per interaction, the difference in the dollars you pay to this ortho specialist compared with the average ortho specialist could be a thousand dollars,’” says Rosenthal.

As you might imagine, that kind of information can be explosive—which is why the Northern California plan will remain anonymous—so a lot of RowdMap’s work is intentionally low profile. However, at the Health Datapalooza conference in May, one payer openly shared how it works with RowdMap to pool publicly available information with its own internal data and analyze it to accomplish two very different ends.

Stephen Ondra, MD, who oversees medical policy for Health Care Service Corp. (HCSC), the parent company of Blues plans in Illinois, Montana, New Mexico, Oklahoma, and Texas, uses that information to create networks that are narrow—not by discount but by the value providers bring to patient care.

“Who are the desirable providers you want in your network? Who aren’t? How many do you need and where do you need them?” Ondra told a session at Health Datapalooza. “Is there a mismatch of disease burden and provider availability?”

That’s not only an issue of access, it’s one of unnecessary costs, said Ondra, a neurosurgeon by training. “As a surgeon, when you’re busy, your criteria for surgery get really narrow. When you hit those lulls, your criteria broaden. Not inappropriately, but enough to fill out the OR schedule. … When you have too many providers in an area, they’re going to do things on the margin—not inappropriate, not abusing people, but low-value things that fill their time.”

In contrast to HCSC, CareFirst, the Blues affiliate serving Maryland, Washington, D.C., and two counties in Northern Virginia, is building an expansive provider network. CareFirst says it is using publicly available cost-efficiency informa-

### Connecting the dots

RowdMap, a Louisville, Ky., health information company, uses publicly available data to create reports on physician efficiency and readiness to take on risk. The chart below is an illustrative example. Color-coded dots signify values relative to their peers, and the dotted line in the middle is the midpoint and benchmark. The red and orange dots represent performance below the benchmark and the green and blue dots, performance above it.

#### Physician risk-readiness report

| Doctor 1 | Doctor 2 | Doctor 3 | Doctor 4 | Doctor 5 | Doctor 6 | Doctor 7 | Doctor 8 | Doctor 9 | Doctor 10 | Doctor 11 | Doctor 12 | Doctor 13 | Doctor 14 | Doctor 15 | Doctor 16 | Doctor 17 | Doctor 18 | Doctor 19 | Doctor 20 | Doctor 21 | Doctor 22 | Doctor 23 | Doctor 24 | Doctor 25 | Doctor 26 |
|----------|---------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
| Procedure efficiency | Referral efficiency | Rx efficiency | Visit intensity | Overall efficiency |

Source: RowdMap
tion to help primary care physicians understand the cost implications of their referral patterns.

CareFirst leaves the judgment of a specialist’s quality up to the referring physician, says Jonathan Blum, CareFirst’s executive vice president for medical affairs. “We’re using this concept to help primary care physicians understand who are the best partners in order to manage care.”

That’s critical information for any physician or group looking to evaluate its own readiness for risk, says Rosenthal. “Providers ask, ‘How much low-value care am I creating? Why am I creating it? And which partners would be best for my value chain?’” Similarly, data can help physicians understand which flavor of risk matches their style: “Should I pick an MSSP or a Next Gen ACO?”

**Eye-popping data**

Using Dartmouth Atlas definitions and public data, RowdMap benchmarks physicians against their peers in four areas: visit intensity, procedural efficiency, pharmacy efficiency, and referral intensity. For each of these measures, a physician is given color-coded dots, signifying high, medium, or low value relative to peers. Physicians are also graded on their overall efficiency.

“Green or red doesn’t mean you have better or worse clinical outcomes; it means you practice higher-intensity treatment,” says Rosenthal. “So, what is the cause of that? Is it your referral pattern? Prescriptions? A particular drug? Is it variations within your practice?”

Specifically, visit intensity refers to the number of patient encounters for an episode, procedural efficiency is indicative of the intensity of a procedure, and pharmacy efficiency is suggestive of the cost of prescriptions written for a patient’s condition. The fourth measure, referral intensity, can be a big cost driver—a concern especially for primary care physicians in risk-bearing networks.

“If you come in with low-back pain, do I refer you to a higher-intensity service like a pain management specialist or an ortho? And if I refer you to an ortho, do I refer you to a surgeon or someone else? Do I refer you to a green dot or a red dot surgeon? Do I refer you to someone who is low or high value?” asks Rosenthal. “Docs’ eyes pop out of their heads when they see all that red.”

The beauty of it all is that as fee for service fades into the rearview mirror, the road ahead is paved not only with good intentions but with data that are publicly available, waiting to be harnessed and not locked away in a proprietary database. Rosenthal sees American health care as preparing to leave fee for service behind and readying itself for a value-based present and future.

“The world that was is about fee for service. There is a data architecture and a business mindset associated with fee for service. It was really about claims and reconciliation. Maximize as much stuff as you can get, lock your data away, don’t share it, sell the secret sauce. That’s the playbook for how to do it.”

“In the world that is, where it’s all about pay for value, there’s a data architecture that matches it and a business mindset that matches it. The data architecture is about taxonomy and interconnected meta-data, and the question is, ‘How do I statistically normalize a hospital referral region to Medicare contracts?’ So our data architecture looks different, and five years ago, it would have been impossible to do what we are doing now in a meaningful way.”

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FOR AUTOIMMUNE ILLS, BIOLOGICS BRING PROMISE—AND PROBLEMS

These medications have revolutionized the treatment of conditions like rheumatoid arthritis. But they are budget busters and have a tricky side effect profile.

By Katherine T. Adams and Peter Wehrwein

When rock musician Glenn Frey of the Eagles died at age 67 in January, the band’s website said the cause was complications of rheumatoid arthritis (RA), acute ulcerative colitis and pneumonia. But some media outlets ran with quotes from his longtime manager that blamed Frey’s death on unspecified medications he was taking. “The colitis and pneumonia were side effects from all the meds,” Irving Azoff was quoted as saying. “He died from complications of ulcer [sic] and colitis after being treated with drugs for his rheumatoid arthritis which he had for over 15 years.”

Of course, every treatment takes patients for a ride on a risk–benefit teeter-totter, although you hope the latter far outweighs the former. And it’s often a secondary complication such as pneumonia that brings death. But Frey’s illness and death—or at least how they were portrayed—hit a special chord in some circles. Writing on the TheMighty.com, a website where people with chronic and mental illness post firsthand accounts, Jessica Hawk-Tillman, a young woman with RA, described vividly the risk–benefit dilemma posed by biologic medications like the ones Frey used: “Without biologic drugs, many people with these diseases cannot perform daily tasks or even get out of bed. With them, our immune systems are suppressed, so we are at a greater risk of developing other illnesses.” Moreover, wrote Hawk-Tillman, biologics often provide just partial relief—and even that modest goal may require enduring the ups and downs of trial and error.

“Given all of this, it’s easy to understand the love/hate relationship autoimmune patients have with these powerful drugs,” she wrote.

The body attacks itself

There are about 80 different autoimmune diseases—conditions in which the immune system becomes confused and unleashes its immunological forces on the body itself. The autoimmune diseases range from the fairly common and familiar like rheumatoid ar-
thritis, multiple sclerosis, psoriasis, and inflammatory bowel disease to the rare and obscure like pemphigus, a group of autoimmune diseases that cause blistering of the skin and mucous membranes, and granulomatosis with polyangiitis (also called Wegener’s) that causes inflammation of the blood vessels in the nose, sinuses, throat, lungs, and kidneys.

Researchers have different estimates for the prevalence of autoimmune disease, ranging from as little as 3.2% up to 9.4%. The higher percentage would mean that at any given time roughly 30 million Americans have an autoimmune disease. That’s more than double the number of Americans living with cancer. The American Autoimmune Related Diseases Association, an advocacy organization, says the actual number of Americans affected is closer to 50 million when you factor in the conditions for which the epidemiologic evidence is less certain. Autoimmune disease comes in such a variety because of differences in how the immune system is dysregulated and the many different parts of the body that are affected. Rheumatoid arthritis damages the joints; psoriasis, the skin and sometimes the joints; and type 1 diabetes, the insulin-producing islet cells of the pancreas.

Treatment tactics are as varied as the underlying pathophysiology and are often guided by complicated decision trees that branch off in multiple directions depending on the person’s response to a certain medication and the severity of the disease. Particularly in mild cases, symptom management may be the goal; for example, people with Crohn’s disease may take loperamide for diarrhea and those with psoriasis may get some relief by using topical corticosteroids and moisturizers. But the armamentarium for autoimmune diseases also includes agents that go after the underlying problem of a misdirected and overactive immune response. For example, methotrexate, which is also used in the treatment of certain cancers, is an immunosuppressant and a mainstay in treating rheumatoid arthritis and several other autoimmune diseases.

Très expensive

The development of recombinant DNA and other technologies has added a whole new dimension to the treatment of autoimmune disease. The biological products of these technologies have proven to be effective at interfering with crucial steps in the immune response that result in bringing the autoimmune attack on the body at least partially under control, stabilizing the diseases that tend to worsen. Especially in cases when the traditional treatments don’t work or have been tried and have stopped working, the advent of the biologics has filled a void.

But they are the kind of progress we expect these days—not a steady march of improvement but halting steps that come with caveats, drawbacks, and often with a hefty price tag.

For payers, the biologics have changed autoimmune diseases from being a peripheral concern to a central one. There’s no shortage of evidence about their financial impact. For example, a 2014 report by Decision Resources Group said that medications for autoimmune disease are the most expensive category of drugs when you organize pharmaceuticals by the disease they treat. And they’re an expense that shows no signs of abating.

A report that the IMS Institute for Healthcare Informatics (IMSIHI) issued this April said that spending on specialty drugs for autoimmune disorders more than doubled between 2011 and 2015 (Figure 1), and that last year the $30.5 billion spent on medications...
for autoimmune disease accounted for roughly 20% of the $150 billion spent on specialty drugs. It’s no surprise, then, that by IMSIHI’s reckoning, three of the biologics for autoimmune disease ranked among the nation’s top sellers, as measured by nondiscounted spending (see Figure 2).

It looks like the spending will continue to go up. GBI Research, a London-based health information firm, estimates that the market in this country for RA treatment alone will increase to $9.3 billion by 2020. About 1.3 million Americans have RA, and an estimated 2 out of 3 of them take a biologic.

All the dollars going out the door have not gone unnoticed; payers are taking steps to slow the exodus. Magellan’s Medical Pharmacy Trend Report for 2015, which came out a couple of months ago and is based on a survey of payers and claims data, found that biologics for autoimmune diseases were the most managed of the drugs billed through the medical benefit. For example, more payers (67%) had product referencing in place for biologics for autoimmune disease than for any other category (for more on the Magellan report, see page 21). Even more (88%) had prior authorization for biologics, and about half had

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**SOME OF THE BIOLOGICS USED TO TREAT AUTOIMMUNE DISEASE**

<table>
<thead>
<tr>
<th><strong>TNF inhibitors</strong></th>
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<tbody>
<tr>
<td>adalimumab (Humira)</td>
<td>Administered subcutaneously; over $10 billion in sales in 2015.</td>
</tr>
<tr>
<td>certolizumab (Cimzia)</td>
<td>Administered subcutaneously; pegylated humanized antibody FAB fragment that is linked to polyethylene glycol.</td>
</tr>
<tr>
<td>etanercept (Enbrel)</td>
<td>Administered subcutaneously. Indicated as a treatment for rheumatoid arthritis, plaque psoriasis, ankylosing spondylitis, and other conditions. Over $6 billion in sales in 2015. The golfer Phil Mickelson has been featured in ads for Enbrel.</td>
</tr>
<tr>
<td>infliximab (Remicade)</td>
<td>Administered intravenously over a period of at least two hours. Effective for moderate-to-severe Crohn’s disease that has not responded to other treatment. FDA approved a biosimilar for infliximab in April 2016.</td>
</tr>
<tr>
<td>golumimab (Simponi)</td>
<td>Approved for treatment of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis.</td>
</tr>
</tbody>
</table>

**Interleukin-1 inhibitors**

| anakinra (Kineret)          | Approved in 2001. Indications include rheumatoid arthritis and cryopyrin-associated periodic syndromes, one of autoinflammatory conditions that affect a different part of the immune response than the classic autoimmune diseases like rheumatoid arthritis and psoriasis. |
| canakinumab (Ilaris)        | Received FDA breakthrough therapy designation in April 2016 for three periodic fever syndromes.                             |

**Interleukin-6 inhibitors**

| tucilizumab (Actemra)       | Approved in 2010. Indications include rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, and systemic juvenile idiopathic arthritis. |

**Costimulation blockade**


**B-cell depletion**

| belimumab (Benlysta)        | Approved in 2011 as a treatment for lupus.                                                                               |
| rituximab (Rituxan)         | Approved for rheumatoid arthritis. A monoclonal antibody comprising both mouse and human portions. Approved for us with methotrexate in patients who have not responded to an TNF inhibitor. |

**Janus kinases (JAKs) inhibitors**

| tofacitinib (Xeljanz)       | Approved in 2012 as a treatment for rheumatoid arthritis in patients who did not respond well to methotrexate. Has a black box warning about serious infections and checking for latent tuberculosis before the patient starts the drug. |
| ruxolitinib (Jakafi)        | Approved in 2011 as a treatment for myelofibrosis and in 2014 as a treatment for polycythemia vera. Researchers have reported positive results for autoimmune disease. |

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*Not every biologic is listed.

**Agents that work by blocking stimulation of T cells.
step-edit requirements. The Managed Care Biologics and Injectables Index from Zitter Health Insights, a health care research and business intelligence firm in Livingston, N.J., also shows that autoimmune diseases (particularly RA) are very much on the cost-management radar. Among payers who say they’re trying to control the cost of treating the various autoimmune diseases, the primary methods used include transferring more of those costs onto patients and waiting for biosimilars to hit the market. When prompted, roughly 84% of commercial payers who answered the 2015 survey said that they were likely to leverage biosimilar drugs to negotiate deeper discounts or rebates from manufacturers.

**Different modes of action**

The creation of separate utilization management categories may be another way payers try to exercise some control over their mounting biologics bills. The TNF inhibitors have dominated the biologics, but agents with different modes of action, such as the JAK inhibitors like Xeljanz (tofacitinib) and interleukin-6 inhibitors like Actemra (tocilizumab), may be favored by payers over the current market leaders, Humira (adalimumab) and Enbrel (etanercept). The introduction of biosimilars may increase the chances of this happening, according to Zitter’s survey as 80% of payers who indicated either neutrality or a low likelihood of dividing their management of the RA category said that they would at least consider doing so after introduction of biosimilars.

Aside from the financial impact, biologics also present providers and payers with adherence challenges. These are drugs that people may take for years, sometimes during periods when they are feeling OK and just need to lower the risk of a relapse. Zitter Health Insights has data suggesting that nonadherence hovers around 20%. “Patients generally stick to their dosing as prescribed, but there’s certainly room for improvement,” say Zitter researchers Pamela Morris and Marie Hollowell. For patients with multiple sclerosis, RA and psoriasis, they found that there is often a gradual lead-up over time to nonadherence rather than a sudden event.

The biologics have a complicated side effect profile, and that’s one reason people may have a hard time sticking with them. Interfering with a system as complex as the immune system—a welter of feedback loops and interconnected pathways—is bound to have varied and somewhat unpredictable consequences.

In some cases, for example, the immune system reacts to the biologic by unleashing antibodies against it. Those antibodies can cause an allergic reaction. They also can put the biologic itself out of commission and render it less effective. It makes sense that studies have shown an association between higher levels of antibodies and discontinuation of the medication.

The evidence so far is that Remicade and Humira are more likely to provoke this kind of an antibody response than Enbrel and, furthermore, the anti-Enbrel antibodies don’t impair the effectiveness of the drug very much. Remicade is a chimeric antibody that’s about 75% human sequence and 25% mouse. It’s primarily the mouse part that stirs up the immune system and its legions of antibodies. The symptoms are similar, but most of the acute infusion reactions to Remicade are not your classic IgE-mediated allergic reactions but anaphylactoid reactions produced directly by the substance. One tactic for reducing the immunogenicity of Remicade is to have patients on a regimen that also includes methotrexate or azathioprine.

In some cases, the immune response the biologics stir up is strong and misguided enough that the patient develops another autoimmune disease. So while it’s impossible to be sure just from press reports whether Glenn Frey’s manager was right about Frey developing colitis in response to his medications, it’s a possibility.

By some accounts, the most common drug-induced autoimmune conditions associated with the TNF inhibitors are vasculitises—particularly cutaneous vasculitis—lupus and lupus-like syndrome, and psoriatic skin conditions. Sometimes the autoimmune disease comes on almost right away but people can be taking biologics for years before they are affected. There’s no doubt that medication-induced autoimmune diseases

---

**FIGURE 2**

*Three biologics for autoimmune disease rank among the 6 best-selling prescription drugs in the U.S. in 2015*

<table>
<thead>
<tr>
<th>Drug</th>
<th>2015 Billions $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harvoni</td>
<td>16</td>
</tr>
<tr>
<td>Humira</td>
<td>14</td>
</tr>
<tr>
<td>Enbrel</td>
<td>12</td>
</tr>
<tr>
<td>Crestor</td>
<td>10</td>
</tr>
<tr>
<td>Lantus</td>
<td>8</td>
</tr>
<tr>
<td>Remicade</td>
<td>6</td>
</tr>
</tbody>
</table>

occur, but they are relatively rare events. Whether they will become more common as more biologics are introduced and people take them for long periods of time remains to be seen. A Mayo Clinic study of 500 patients who were followed for a median of 17 months and received a median of three infusions of Remicade, found that three patients developed lupus and one a demyelination disorder. Data from a French registry showed that the incidence of drug-induced lupus among patients taking Remicade or Enbrel was about 0.2%. The good news is that autoimmune disease from biologics can often be remedied by discontinuing the drug that is provoking the immune response. Some research has shown that more than 80% of cases of medication-induced autoimmune disease have a favorable outcome.

Another untoward consequence of biologics is an increased risk of infection for reasons that are just opposite to the immunological overreaction that manifests itself as another autoimmune disease. By interfering with some aspect of the immune system, the biologics, particularly the TNF inhibitors, sometimes lower the body's defenses against bacterial and fungal infections.

Studies have come up with different estimates about how great the added risk of infection is. A 2015 meta-analysis that included 106 randomized trials of RA patients delivered a split decision. The study found an increased risk of serious infections among patients taking standard doses of biologics compared with traditional nonbiologic regimens but found no increase in the risk of serious infections from lower doses. The infection risk is real, though. The FDA has added a boxed warning about the risk of Legionella infection on all the TNF inhibitors. Patients are also supposed to be screened for tuberculosis, hepatitis B, and hepatitis C before starting a TNF inhibitor because the medication may disrupt an immune response that has been keeping a latent infection in check.

**Entering a new era**

Anne Pollock, an associate professor of science, technology and culture at Georgia Tech, wrote a memorable article for the *Atlantic* magazine in 2013 titled, “Enbrel and the autoimmune Era.” In the piece, Pollock argued that with Enbrel—and by extension, all the biologics—pharmaceuticals are entering a new phase. Antibiotics conquered infections but weren’t necessarily the best business proposition because once cured, “your customers no longer need your drugs.” The drugs developed to reduce the risk of hypertension and high cholesterol and the “lifestyle” drugs like Viagra have been better for the pharmaceutical industry because people take them for years.

In Pollock’s telling, Enbrel has the characteristics of both a risk-reducing drug—for people with rheumatoid arthritis, it’s prescribed to fend off further damage to their joints—and a lifestyle drug—because “it is meant to enhance life rather than extend it.” Casting the biologics as lifestyle drugs goes against the common meaning of the term and could be taken to mean that they aren’t needed or that autoimmune diseases aren’t serious.

Pollock’s point, though, was that they are not curative, and she argued that the new “autoimmune era” encompasses the three prior eras (antibiotics, risk-reducing, and lifestyle) all at once. She also noted that the biologics are harder to copy than the small-molecule medications produced by chemical processes. Harder does not mean impossible, and biosimilars may yet bring some price competition to biologics.

Robert Aronowitz, MD, chair of the History and Sociology of Science Department at the University of Pennsylvania and the author of *Risky Medicine: Our Quest to Cure Fear and Uncertainty*, has a similar analysis. “The objective is to not get worse,” he says. “Keep the patient comfortable and manage the risk. That hasn’t always been true with medicines. For example, you get a bacterial infection, take an antibiotic, and, within a couple of weeks, it’s gone. But with autoimmune diseases, there is no promissory note.”

Aronowitz argues that physicians today increasingly focus on reducing the probability of a bad outcome as opposed to interventions that treat symptoms or alter physiological processes doing harm in the body. “Making life more comfortable is not a bad thing,” he says, but he quickly points out that there is much more profit to be made when pharmaceutical companies and device makers develop interventions aimed at producing comfort or reducing risk, rather than shooting higher and going for a cure.

Aronowitz says he is “spooked” by the direct-to-consumer ads for biologics that are designed to stoke demand for the expensive drugs. “I worry about misuse,” he says. “And I worry that the Chinese menu-style of diagnosing RA and other autoimmune diseases makes increasing sales all too easy.” He says we need to find the best possible evidence that these biologics work, which means investing in knowledge production in the form of clinical trials and showing some discipline about prescribing expensive new drugs as a society through the insurers, government regulation, medical authorities, and, mostly, the doctor–patient relationship. 

"Katherine T. Adams is a health care journalist in the Philadelphia area. Peter Wehrwein is editor of Managed Care."
Rheumatoid arthritis is the single biggest drug expense category for most plans, which is why these treatments are managed so closely, explained Roger Longman, who is chief executive at Read Endpoints, a market research firm that focuses on pharmaceutical reimbursement. “So to try to get a handle on the medical benefits side—you’d go first to the biggest category, which is the anti-inflammatory drug.”

This brings us to Johnson & Johnson’s Remicade, which rang a lot of registers last year, generating more than $6.5 billion in sales. Because the drug is purchased—and infused—by physicians, payers know they will pay more for this medication than the other drugs, Rubinstein notes, since they have less control over its use. “This is a very high visibility item on their budgets,” says Elan Rubinstein of EB Rubinstein Associates, a pharmaceutical consultant. “If a plan were to force Remicade out of the hospital outpatient department, there’s no evidence that you would be reducing quality of care. You’re just making things cheaper” for the plan.

This helps explain why payers report they received more rebates for BDAIDs than any other type of medication. Rubinstein noted this can reflect a site of care issue—if a doctor prescribed Remicade and it’s administered in a hospital outpatient facility, a health plan may require prior authorization.

The Magellan survey found that 80% received rebates last year for medications in the BDAID category, which has been the therapeutic category with the highest number of rebates since 2013. Meanwhile, in 2015, erythropoiesis-stimulating agents was a distant second, with 57% of payers getting rebates. The reason for implementing a step edit was because it was required in order to receive a rebate, according to the Magellan survey. Longman posited that Johnson & Johnson offers “some kind of rebate, but it’s not as big as a plan is getting, in total, from AbbVie and Amgen.”

But there may be room for optimism. The FDA recently approved a biosimilar version of Remicade that is manufactured by South Korea’s Celltrion, Rubinstein notes. Once that becomes available, payers may have still more opportunity to cite their preferences.

For the longest time, payers have been talking about ways to control drug spending in medical benefits plans. Now, there are signs that many are starting to become more assertive.

It’s rare for commercial payers to have drug formularies for medical benefits, but a recent survey found that 92% of payers do use product preferencing in hopes of lowering costs. And this includes such familiar tools as step edits and prior authorizations, as well as guideline criteria. What’s more, 96% of smaller plans—which were defined as those covering fewer than 500,000 lives—take this approach, according to Magellan Rx Management. The pharmacy benefits manager queried medical, pharmacy, and network directors from 59 commercial payers—not just its own clients—that cover about 130 million covered lives.

In effect, health plans are, in some way, choosing drugs they prefer, based on their judgments about safety and efficacy, as well as availability, lowest net cost, and how a drug is administered, according to Casandra Stockman, a vice president of medical pharmacy strategy at Magellan.

Product preferencing was used more for biologic drugs for autoimmune disorders (BDAIDs) than for any other type of medicine. The survey found that 67% of payers use this tactic for those treatments, greatly exceeding other therapeutic categories. For instance, 43% of payers use preferencing for hyaluronic acids (used to treat knee osteoarthritis) and multiple sclerosis drugs, and 37% use it for bone resorption inhibitors for osteoporosis.

A plan’s pharmacy department can more easily control access to some rheumatoid arthritis drugs directly—AbbVie’s Humira and Amgen’s Enbrel—because they are typically part of a pharmacy benefit, and patients administer the medicines themselves.

**Drug categories with the most product preferencing in place, 2015 (% of payers)**

<table>
<thead>
<tr>
<th>Drug category</th>
<th>% of payers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biologic drugs for autoimmune disorders</td>
<td>67%</td>
</tr>
<tr>
<td>Viscosupplementation (hyaluronic acid)</td>
<td>43%</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>43%</td>
</tr>
<tr>
<td>Bone resorption inhibitors for osteoporosis</td>
<td>37%</td>
</tr>
<tr>
<td>Erythropoiesis-stimulating agents</td>
<td>33%</td>
</tr>
</tbody>
</table>

Source: Magellan Rx Management Medical Pharmacy Trend Report 2015

Ed Silverman founded the Pharmalot blog and has covered the pharmaceutical industry for 20 years.
Finally, Attention Switches To Progressive Multiple Sclerosis

A surge of new MS treatments have been for the relapsing-remitting form of the disease. A new drug that targets CD20-positive B cells may change that.

By Thomas Reinke

Therapy for multiple sclerosis (MS) has been on a roll. Since 2009, a steady stream of more effective medications has been introduced for the autoimmune disease that attacks the myelin sheaths of nerve cells. The FDA approved the latest agent, daclizumab (Zinbryta) in May. The medication, marketed by Biogen and AbbVie, has many of the same characteristics as other recent therapies for MS. Daclizumab is a monoclonal antibody requiring less frequent dosing (monthly). It targets a unique set of immunological cells that cause the disease. And like other recently approved therapies, it’s superior to traditional “disease-modifying agents” in achieving the current MS treatment goal of “no evidence of disease activity,” or NEDA for short.

But here’s the thing: While daclizumab and its ilk can greatly improve the quality of life for MS patients, all of these new drugs are approved for only one form of the disease.

The blood–brain barrier

MS comes in several varieties. Most new patients are diagnosed with relapsing-remitting multiple sclerosis, which is characterized by flare-ups of inflammation that produce brain lesions and vision, bladder, and muscle coordination problems.

A relatively small minority of between 10% and 15% of newly diagnosed MS patients are diagnosed with a different form of the disease called primary progressive multiple sclerosis. It’s a silent thief of vitality that produces slow and steady neurodegeneration affecting motor skills and cognition, absent the acute exacerbations that occur with the relapsing-remitting MS. Over time as many as 80% of relapsing-remitting patients transition to secondary progressive MS, which also brings relentless neurodegeneration.

There are currently no FDA-approved medications for primary progressive MS, which is the more challenging variant of the disease. And there is only an old standby, mitoxantrone, approved for secondary progressive MS.

This skewed MS drug development reflects both the complex nature of the disease and an understanding of its pathology that is still incomplete.

The pathogenic pathways of relapsing and progressive MS seem to be quite different. The relapsing form of MS occurs when immune system cells and other factors, which normally protect the body from infections and cancers, go rogue. They manage to leave the bloodstream and cross the blood–brain barrier to attack the protective myelin covering of nerve cells in the brain and spinal cord.

In contrast, in progressive disease the flow of these immune cells from the circulation into the brain is less prominent. Instead, there is compartmentalization of T and B cells and aberrant cytokines that activate microglia, T and B cells in the central nervous system. In progressive MS, there’s also more degeneration and loss of neural cells and nerve fibers that cause permanent disability.

The treatment of progressive MS is complicated by the fact that the blood–brain barrier, a kind of biological moat that defends the central nervous system from all manner of pathogens, also keeps medications at bay, so they can’t enter the central nervous system. Researchers face the problem of not having a good animal model for the disease.

The absence of treatments for primary progressive MS may be about to change with a new monoclonal antibody rushing through FDA approval. In February, the FDA granted breakthrough status to ocrelizumab, which is being developed by Genentech, a member of the Roche Group. In a Phase 3 trial called ORATORIO, ocrelizumab was studied in 732 patients with

Gray matter atrophies in primary progressive multiple sclerosis.
primary progressive multiple sclerosis. The drug was administered intravenously, as two infusions of 300 mg given two weeks apart every six months. At the end of the study period, ocrelizumab significantly reduced disability progression sustained for at least 12 weeks by 24% compared with placebo as measured by the expanded disability status scale. The scale is based on physical and neurological exams of vision, coordination, limb movement, strength, thinking abilities, bowel and bladder control, sensation, and walking ability.

Ocrelizumab has also been tested in two Phase 3 trials for relapsing MS. Those results show that it was superior to interferon beta-1a, reducing the annualized relapse rate by nearly 50% over a two-year treatment period. So ocrelizumab may be effective as a treatment for both forms of MS, and Roche has said it will apply for the dual indications. The breakthrough status, however, applies only to primary progressive MS.

Targeting B cells

Researchers involved in ocrelizumab’s clinical trials say we may now have our foot in the door with primary progressive MS. Suhayl Dhib-Jalbut, MD, says that ocrelizumab has helped researchers cross an important threshold in MS drug development by identifying and targeting a new subset of MS-causing immune cells. Dhib-Jalbut is a professor and chair of the neurology departments at both of the Rutgers medical schools, Robert Wood Johnson Medical School and the New Jersey Medical School, and past president of the Americas Committee for Treatment and Research in Multiple Sclerosis. Relapsing and progressive MS are thought to be caused by T and B cells that attack the central nervous system. The prevailing wisdom is that aberrant versions of these cells and the signaling molecules that they produce breach the blood–brain barrier and attack the protective myelin sheath around nerve fibers as well as the nerve fibers themselves. An MS attack or relapse results in brain cell inflammation that shows up as lesions on MRI scans. There is an alternative theory that an abnormality in the central nervous system itself causes demyelination and neurodegeneration and that inflammation is just a byproduct.

For many years the research and drug development focused primarily on T cells, says Dhib-Jalbut. The drugs that work in relapsing MS either kill those T cells or sequester them in the body and prevent them from getting into the brain. Daclizumab, for example, targets CD25, a component of the interleukin-2 receptor on T cells that promotes their growth. “But in the majority of patients we have a growing understanding that MS is mediated by T and B cells; both coordinate the attack on the nervous system,” says Dhib-Jalbut. And some agents do target both types of cells, including natalizumab (Tysabri), alemtuzumab (Lemtrada), and fingolimod (Gilenya).

Ocrelizumab is novel and achieved its breakthrough designation because it selectively binds to and depletes CD20-positive B cells. Results from preclinical studies show that while ocrelizumab binds to the CD20 proteins expressed on aberrant B cells, it does not latch onto stem cells or plasma cells, and therefore important functions of the immune system may be preserved.

Dhib-Jalbut explains how ocrelizumab’s focus on CD20-positive B cells makes it the potential first in class agent for progressive MS. He says that the meninges, the protective brain covering, is rich in B cells that may contribute to progressive MS by passing through the blood–brain barrier when they’re aberrant. By homing in on CD20-positive B cells, ocrelizumab is able to knock them out and other aberrant B cells circulating in the bloodstream, explains Dhib-Jalbut.

This recent crop of MS drugs is an important step forward for MS patients but work remains. MS has many potential causes. It is known to occur more frequently in areas that are farther from the equator, and epidemiologists have found that vitamin D levels, which decrease with lack of exposure to sunlight, are deficient in MS patients.

As far as medications are concerned, researchers say that we need a wider set of therapies, drugs that protect the nervous system from attack and others that repair damage once it has happened.
The Disease Burden of the Most Common Autoimmune Diseases

They are far less common than many chronic conditions. But by some measures, the financial and health toll from inflammatory bowel disease, rheumatoid arthritis, and psoriasis is comparable to stroke and lower back pain.

Rheumatoid arthritis (RA), psoriasis, and inflammatory bowel disease (IBD), which includes Crohn’s disease (CD) and ulcerative colitis (UC), are among the most common autoimmune diseases. Collectively, they affect about 10 million patients in the United States. They are chronic conditions characterized by immune-mediated inflammation of unknown etiology and for which there is no cure. Substantial morbidity, shortened survival, and diminished health-related quality of life (HR-QOL) are associated with these diseases during the many decades that patients cope with them.

The chief goal of therapy is to suppress disease flares and extend periods of remission if remission is attainable. Biologics are the mainstay of treatment for severe disease, and the extent to which they are used reflects the disease burden associated with autoimmune diseases.

Three of the top six best-selling prescription drugs in 2015 were biologics used to treat autoimmune disorders. In 2015, spending on drugs for autoimmune disorders accounted for 20% of all specialty drug spending.

Diminished HR-QOL and the inability to work at full productivity are among the negative consequences of moderate to severe autoimmune disease. A survey of a major self-insured employer (Navistar) found self-reported prevalence of RA, psoriasis, and IBD in 2009 was 4.2%, 3%, and 1.2%, respectively (Allen 2012). An important finding in this study was that if mild autoimmune disease stayed mild, the productivity of employees remained comparable to that of employees without autoimmune disease.

Inflammatory bowel disease

About 1.2 million Americans have IBD (Table 1). The age of onset for IBD occurs in two peaks, the first between ages 15 and 30 and a second peak between

---

### TABLE 1

**Differences between the major inflammatory bowel diseases**

<table>
<thead>
<tr>
<th></th>
<th>Crohn’s disease</th>
<th>Ulcerative colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>US prevalence, estimated</td>
<td>565,000</td>
<td>593,000</td>
</tr>
<tr>
<td>Commercially insured pediatric</td>
<td>58 per 100,000</td>
<td>34 per 100,000</td>
</tr>
<tr>
<td>Commercially insured adult</td>
<td>241 per 100,000</td>
<td>243 per 100,000</td>
</tr>
<tr>
<td>Anatomical regions typically involved</td>
<td>Any part of the intestine, usually ileum and colon</td>
<td>Rectum and part or all (pancolitis) of colon</td>
</tr>
<tr>
<td>Disease pattern</td>
<td>Discontinuous</td>
<td>Uninterrupted</td>
</tr>
<tr>
<td>Typical extent of inflammation</td>
<td>Transmural</td>
<td>Mucosal only</td>
</tr>
<tr>
<td>Presence of granulomas, strictures, fistulas</td>
<td>Typical</td>
<td>Atypical</td>
</tr>
<tr>
<td>Risk associated with cigarette smoking</td>
<td>Increased risk, increased severity</td>
<td>Decreased risk (increased risk in former smokers and nonsmokers)</td>
</tr>
<tr>
<td>Genetic factors</td>
<td>More prominent</td>
<td>Less prominent</td>
</tr>
</tbody>
</table>

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Involvement of autophagy gene ATG16L1 in pathogenesis</td>
<td>Yes</td>
</tr>
<tr>
<td>Involvement of genes regulating interleukin 23-Th17 pathway</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Sources: Abraham 2009, Friedman 2015, Kappelman 2013
60 and 80 years. The signs and symptoms of IBD are severe diarrhea, abdominal pain, blood in the stool, fatigue, and weight loss. They are similar to the signs and symptoms of other diseases, so clinicians sometimes have difficulty diagnosing IBD. When IBD is diagnosed, in about 15% of cases it is not possible to further classify the disease as CD or UC. Such cases are known as indeterminate colitis (Friedman 2015). As time goes by, it eventually becomes clear whether indeterminate colitis is CD or UC. In mild to moderate disease of either kind, some of the treatments are the same.

About a third of IBD patients have one or more extraintestinal manifestations of their disease. These complications may involve the skin (e.g., erythema nodosum, pyoderma gangrenosum), bone and joints (e.g., peripheral arthritis, ankylosing spondylitis, low bone mass), eyes (e.g., conjunctivitis, uveitis), liver (e.g., fatty liver, gallstones), genitourinary system (e.g., calculi, ureteral obstruction), and cardiovascular system (e.g., venous and arterial thrombosis).

In addition to taking drugs to control their disease and the comorbid conditions associated with it, patients with IBD may take drugs to manage comorbid conditions that are common in the general population. An analysis of insurance claim records for 150 million individuals showed that many comorbidities were much more prevalent among patients with IBD than matched members in the general population, such as deficiency anemias (21.2% vs 6.7%), fluid and electrolyte disorders (12.5% vs 3.5%), weight loss (6.4% vs 1.2%), liver disease (4.6% vs 1.3%), and RA (4.1% vs 1.3%) (Buckley 2013). With all this comorbidity, as well as their disease, it’s not surprising that patients with IBD had more prescriptions than matched members: 38% of patients with IBD had 10–19 prescriptions compared with 22.5% of matched members, and 16.3% of IBD patients had 20 or more prescriptions compared with 5.5% of matched members (Buckley 2013). Polypharmacy of this magnitude puts people at risk for becoming nonadherent to their drug regimens as well as for experiencing drug interactions.

An analysis of data from the Medical Expenditure Panel Surveys showed that insurers’ expenditures for patients with UC and CD are 64% and 124% higher, respectively, than for patients without the conditions (Figure 1). The same analysis also showed that aggregate incremental per-patient costs for UC and CD are comparable to those for major chronic conditions (Figure 2).

The common pattern with milder forms of IBD is occasional periods of relapse amid longer periods of relatively normal health, so many patients with IBD can work full-time, even if their productivity is somewhat impaired compared with workers without IBD. During disease flares, however, patients with IBD are twice as likely as people without IBD to be out of the labor force (Jacobs 2011).

**Psoriasis**

Estimates of psoriasis prevalence range from 0.95% to 3.2%. Prevalence in the middle of this range—2.2%—translates into an estimate of about 5.3 million Americans having psoriasis in 2013 (Vanderpuye-Orgle 2015). There are several subtypes of psoriasis, the most common of which is plaque psoriasis. Plaque psoriasis is characterized by plaques—elevated, inflamed areas of the skin—that are often itchy and painful. They tend to stay roughly the same size and appear on the scalp, knees, elbows, lower back, palms, and soles.

The National Psoriasis Foundation defines psoriasis severity in terms of percentage of the body surface area (BSA) covered: mild, <3%; moderate, 3–10%; severe, >10%. (NPF 2016). A more complicated measure commonly used in clinical research but not in clinical practice is the Psoriasis Area and Severity Index [PASI], in which scores ≤10 indicate...
mild disease; 11–20, moderate; and >20, severe. In the United States, comparative rates of psoriasis severity are 83%, 11%, and 5% for mild, moderate, and severe disease, respectively (Vanderpuye-Orgle 2015). Treatments are determined by disease severity, with topical treatments and phototherapy usually used for mild localized psoriasis and systemic medications for moderate to severe disease, especially if it is resistant to other treatments. Systemic medications may also be used if the disease is substantially impairing the patient’s quality of life (e.g., psoriasis that affects the soles or palms).

Common comorbidities among patients with psoriasis are psoriatic arthritis, which develops in up to 30% of patients with psoriasis, and metabolic syndrome, which in turn is associated with increased risk for cardiovascular disease, stroke, and diabetes. In an analysis of a large managed care database (Kimball 2011), the psoriasis-associated comorbidities with the highest average incremental six-month costs were cerebrovascular disease, peripheral vascular disease, cardiovascular disease, depression, and diabetes. The three most costly comorbidities were also the ones with the highest rates of inpatient care or emergency care. For the comorbidities of cardiovascular, cerebrovascular, and peripheral vascular disease, the inpatient incidence rate ratios (IRR) compared with psoriasis patients without the comorbidity were 4.19, 3.74, and 3.22, respectively; for emergency care (the combination of inpatient and emergency department services), the IRRs for the same three comorbidities were 3.06, 3.21, and 2.67, respectively. Depression was the comorbidity resulting in the highest IRR for outpatient care, 1.82.

In a study that compared the effect of psoriasis on productivity with the effect of other costly diseases (atrial fibrillation, neck or lower back pain, and stroke), mean work impairment costs for patients with psoriasis were comparable to those for the other conditions (Table 2). Presenteeism accounted for most of the productivity costs associated with psoriasis (Carter 2011). Among patients with psoriatic arthritis, lost productivity because of absenteeism and presenteeism was substantially higher, such that only neck or lower back pain re-
sulted in a greater productivity burden. In a Finnish study enrolling only patients with moderate to severe psoriasis, absenteeism and presenteeism accounted for 38% of costs attributed to lost productivity, with the remaining 62% of productivity loss attributed to other medical issues (Mustonen 2015).

In the United States, the total annual cost of psoriasis has been estimated at $35 billion (Figure 3), including $12 billion in direct costs and $23 billion in indirect costs (Vanderpuye-Orgle 2015). As in other studies, presenteeism was a greater contributor to lost productivity than was absenteeism.

**Rheumatoid arthritis**
About 1.5 million U.S. adults are living with RA (NIAMSD 2014). The disease affects peripheral joints in a symmetrical fashion, usually beginning with inflammation of synovial tissue in the small joints of the hands and feet. RA often is accompanied by extreme unremitting fatigue, depression, and cognitive dysfunction. The clinical course of RA is highly variable. Up to 10% of patients who meet the diagnostic criteria for RA will experience spontaneous remission within six months, but most patients will develop progressive disease whose intensity varies over time. Other patients experience recurring cycles of very active disease and minimally active disease (Shah 2015).

The goal of contemporary treatment is to halt or slow the progression of RA before joint damage occurs. Prior to the biologic era, a highly aggressive form of RA led to severe joint destruction. Treatment with disease-modifying antirheumatic drugs (DMARDs), especially the biologic DMARDs, in the early stages of RA has made this outcome less common. Not all patients respond to DMARDs, either the conventional or biologic variety. Although there is no cure for RA, early diagnosis followed by effective treatment lets many patients pursue usual activities because their disease activity has been minimized.

Compared with the general population, patients with RA have twice the mortality rate, with median life expectancy reduced by seven and three years in men and women, respectively (Shah 2015). Compared with the general population, patients with RA are at twice the risk of CVD, partly due to the prevalence of multiple common CVD risk factors and possibly because of the interaction of systemic inflammation with CVD risk factors (Cutolo 2014). The increased risk for myocardial infarction among people with RA is similar to the increased risk among those with diabetes.

Other comorbidities include osteoporosis (prevalence 20% to 30%), often as a consequence of prolonged use of prednisone and subsequent hip fracture;
infection; subcutaneous nodules, once found in up to 40% of patients, especially those with very active disease; Sjögren’s syndrome (characterized by dry eyes or dry mouth), occurring in about 10% of patients with RA; lung disorders (e.g., pleuritis, interstitial lung disease, lung nodules); and lymphoma, which occurs two to four times as often in people with RA as in the general population (Shah 2015).

If left untreated or poorly controlled, RA limits the ability of patients to function well in domestic or vocational settings. Research has shown that up to half of such patients leave the workforce less than 10 years after disease onset and up to 90% have stopped working prior to age 65 (Birnbaum 2010). From a societal perspective, the total cost of RA in the U.S. has been estimated at $39 billion in 2005 dollars (Birnbaum 2010). About half of the total was attributed to intangible costs—diminished QOL ($10 billion) and premature mortality ($10 billion)—and half to direct ($9 billion) and indirect costs ($10 billion). Direct medical costs were evenly divided between employer-provided health insurance and Medicare and Medicaid (Figure 4).

References


In a Rare Head-to-Head Matchup, New Psoriasis Drug Seems a Winner

Studies show Eli Lilly’s Taltz achieves higher remission rates than its main competitor but is also marked by slightly more infections.

Thomas Morrow, MD

Back in 2003, in just its second installment, this column highlighted upcoming therapies for psoriasis, a relatively common chronic inflammatory skin disease characterized by red scaly plaques that can be accompanied by joint involvement. At that time, the only biologic medication approved for the condition was alefacept, sold as Amevive. Etanercept, marketed as Enbrel, was approved only for those with psoriatic arthritis, not for those whose psoriasis was limited to skin. Two other TNF inhibitors, adalimumab (Humira) and inflixiimab (Remicade), were being studied. The FDA was considering efalizumab (Raptiva), another biologic that was developed as a treatment for psoriasis. These drugs carried a yearly price tag of $16,000 to $20,000.

What a difference 13 years have made!

As it turned out, Raptiva and Amevive were abandoned and are no longer on the market. But other biologics have taken their place, and the menu of available agents and the mechanisms of action they use is growing. Also growing, and by leaps and bounds: the prices. They have more than doubled.

Human genome studies have uncovered a host of polymorphisms in numerous genes regulating the immune system. Those discoveries have led to the development of drugs targeting not just the legacy TNF pathway but also various interleukin pathways.

The interleukins, of course, are a family of cytokines, those swarms of messenger com-

pounds that allow the various parts of the immune system to communicate. So far 36 different interleukins have been described. These remarkable proteins promote the differentiation of T and B lymphocytes and hematopoietic cells and influence numerous other pathways. They interact in an amazingly complex manner throughout the immune system. Teasing out their individual roles is almost as difficult as trying to isolate the sound of one instrument in the New York Philharmonic.

Direct comparison

Ixekizumab, sold as Taltz, is the latest biologic to be approved. It is a humanized IgG4 monoclonal antibody that selectively binds with interleukin 17A and, in so doing, inhibits its interaction with the IL-17 receptor. It is hitting the market with three randomized, double-blind, multicenter phase 3 studies under its belt, two of which compared results against etanercept in treating psoriasis.

Taltz is indicated for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. It is delivered as a subcutaneous injection. Dosing starts with two 80-mg injections the first week, followed by 80-mg injections at Weeks 2, 4, 6, 8, 10, 12 and then an 80-mg injection every four weeks. This schedule makes it a bit more complicated to use than some of the competitors, at least for the first three months.

The agent comes as either a pre-filled syringe or an autoinjector and can be self-injected after proper training and with physician supervision.

Taltz is accompanied by a warning about an increased risk of infections including upper respiratory tract infections, oral candidiasis, conjunctivitis, and tinea (ringworm). It does not, however, have the black box warning common to many drugs used to treat autoimmune dis-

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that about 70% achieved a PASI score of 90.

In short, this drug rocks!

Other drugs also demonstrate high efficacy but due to differences in selection criteria and study design it is virtually impossible to directly compare two different drugs for psoriasis (or any other disease for that matter) based on separate trials. This is where Taltz stands out because of the two pivotal trials that included an etanercept arm. Those two trials randomized subjects to a dosing schedule of either every two weeks or every four weeks for Taltz, placebo, or etanercept. Remember that the FDA approval for Taltz sets the dosage frequency at every four weeks after the initial period of more frequent injections.

In an article published in *Lancet* last year, Christopher E. M. Griffiths and his colleagues reviewed both of the head-to-head studies. They found that Taltz demonstrated greater efficacy than the placebo and etanercept over the 12-week study period. The comparison of the study subjects that experienced complete resolution is telling: 35% of those receiving Taltz every four weeks and 38% to 41% of those getting it every two weeks achieved complete resolution as compared with 5% to 7% of those receiving etanercept (p<0.0001). Obvious differences in response between Taltz and etanercept occurred as early as Week 1.

To be fair, the new drug does have a slight downside. Griffiths and company noted that overall infections occurred more frequently in patients taking Taltz than those randomized to receive etanercept or placebo. Twenty-six percent of those taking Taltz developed an infection compared with 22% in the etanercept group and 21% in the placebo group. However, the authors note that less than 1% of patients in all the treatment groups had serious infections and there were no notable differences among them.

Using the GoodRx app with Atlanta as the location, the monthly maintenance price of Taltz is about $4,200 per 80-mg syringe. That’s about 10% more expensive than the price that GoodRx had for etanercept.

While cost remains a challenge, things are changing fast in the treatment of psoriasis. The approval of Taltz suggests that the bar for treatment is getting set higher, so patients (and their doctors) may soon be expecting, if not complete remission, then something very close to it.
Workers not getting help they need to navigate the health care system

The workplace might seem like the perfect place to educate employees about how to access health care, but there doesn’t seem to be much movement on that front, according to a survey of 550 benefit managers conducted by Optum, a subsidiary of UnitedHealth Group.

Only 20% of employers strongly believe that their workers know how to navigate the health care system, yet wellness programs do not focus much on this aspect of employees’ well-being, the survey found.

Health advocacy services connect employees with advisers who can answer questions and provide advice about using the often-Byzantine health care system. The number of companies offering such services has remained stagnant at about 24% since 2013, according to Optum, and it’s a minority of companies that provide other kinds of help for dealing with the health care system.

Lack of takers may be a factor. When employers offer health advocacy services, just 26% of employees (on average) take advantage of them, the survey found.

The survey, which was conducted in December, found that most wellness programs continue to focus on physical health, despite the push for a more holistic approach that takes into account financial and social needs.

Companies are using financial incentives to coax employees into wellness programs. The survey found that employers spent $403 per participant per year on average. Most employers dangled premium discounts and contributions to health savings accounts in front of employees. The authors of the Optum white paper noted that premium discounts can mean a year-long wait for a reward. They said employers should use nonfinancial rewards like social recognition and time off to complement programs that depend on premium discounts.

Current wellness programs offered

<table>
<thead>
<tr>
<th>Program</th>
<th>Physical health</th>
<th>Behavioral health</th>
<th>Social health</th>
<th>Financial health</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flu shots</td>
<td>85%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employee assistance program</td>
<td>84%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health and wellness website</td>
<td>67%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Gym membership discounts</td>
<td>61%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tobacco cessation program</td>
<td>61%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health or fitness challenges</td>
<td></td>
<td>58%</td>
<td></td>
<td></td>
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<tr>
<td>Wellness coaching</td>
<td></td>
<td>54%</td>
<td></td>
<td></td>
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<tr>
<td>Health biometric screenings</td>
<td></td>
<td>54%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight management program</td>
<td></td>
<td></td>
<td></td>
<td>51%</td>
</tr>
<tr>
<td>On-site fitness center</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease management programs</td>
<td></td>
<td>41%</td>
<td></td>
<td></td>
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<tr>
<td>On-site stress-reduction activities</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Healthy pregnancy programs</td>
<td></td>
<td>29%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case management programs</td>
<td></td>
<td>27%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On-site medical clinics</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Health care financial education</td>
<td></td>
<td>23%</td>
<td></td>
<td>21%</td>
</tr>
<tr>
<td>Sleep health program</td>
<td></td>
<td></td>
<td></td>
<td>7%</td>
</tr>
</tbody>
</table>

Current penetration of programs designed to help employees navigate the health system

- Case management programs: 27%
- Transparency tools: 25%
- Health advocacy service: 24%
- Telemedicine: 20%
- Musculoskeletal or orthopedic programs: 8%

Boosting a Drug’s Market Share Can Cross a Dangerous Line

Hub programs are growing in popularity as a way for pharmaceutical companies to combat the clout of employers, health plans, and PBMs. But they spell trouble if they spark collusion, threaten patients, or waste federal dollars.

By Thomas Reinke

Selling branded drugs, never smooth sailing, is an especially tough business these days. Well-established generics and brand names often have a lock on whatever drug class they fall into. Employers, health plans, and PBMs frequently put hurdles in the way of newcomers, using higher copays, prior authorization requirements, and step therapy policies that put less-established products at a distinct disadvantage. Drug manufacturers grouse about a lack of “market access” and a playing field that is far from level—especially with new drug launches, where long-term success depends on how much of a market share a drug can grab after it goes on sale.

One remedy, pharmaceutical companies believe, is hub programs. They're gaining traction as a way to push into markets and counter the clout of the payers and PBMs. Hub programs group packages of services (thus the term hub) designed to drive the marketing, sales, and utilization of a drug. Hub programs as a business have grown in tandem with the limited distribution agreements some manufacturers have with a select group of specialty pharmacies. Services include benefits investigations, prior authorization negotiations, delivery services, care management, and managing copayments and coinsurance issues for patients. Some simple hub programs zero in on just one aspect of a drug, while more comprehensive programs exert tight control over every aspect of a drug’s revenue cycle. Some drug manufacturers create and manage their own hub programs. The more common approach is for a drug manufacturer to partner with a consulting firm to perform administrative tasks while a pharmacy, specialty pharmacy, or pharmacy network fills prescriptions and works with patients to keep them adherent.

Hub programs have emerged as a profitable new line of business in the sales and distribution side of the pharmaceutical industry that has got more than its fair share of wheeling and dealing. For the consulting companies, the programs mean multi-year contracts (thus the term hub) designed to drive the marketing, sales, and utilization of a drug. Hub programs as a business have grown in tandem with the limited distribution agreements some manufacturers have with a select group of specialty pharmacies. Services include benefits investigations, prior authorization negotiations, delivery services, care management, and managing copayments and coinsurance issues for patients. Some simple hub programs zero in on just one aspect of a drug, while more comprehensive programs exert tight control over every aspect of a drug’s revenue cycle. Some drug manufacturers create and manage their own hub programs. The more common approach is for a drug manufacturer to partner with a consulting firm to perform administrative tasks while a pharmacy, specialty pharmacy, or pharmacy network fills prescriptions and works with patients to keep them adherent.

Hub programs have emerged as a profitable new line of business in the sales and distribution side of the pharmaceutical industry that has got more than its fair share of wheeling and dealing. For the consulting companies, the programs mean multi-year contracts and for specialized pharmacies they can be more profitable than the contracts they have with PBMs. And a lot of drug manufacturers believe that an in-house hub program has the potential to generate more business than the old-school way of getting market share for a product—the hard slog of negotiating prices, rebates, and formulary placement with payers.

Two faces of hubs

The hub business is one with two very different personas. Health plans and drug manufacturers have used them to good effect to inject some reality into the much-talked about “patient-centered” approach. Health plans have used them to optimize therapy management for specialty medicines or rare diseases. They are also useful for accomplishing some important steps in drug development and post-market safety and outcomes studies.

But there’s also a darker side. Manufacturers have used hub programs to muscle the sales of their products through alternative channels that are really all about sales and not what’s best for the patient. These programs start with marketing the drug to patients
and physicians. They often add on a coupon program to reduce out-of-pocket costs and get patients locked into a drug. Once the patient is enrolled, the hub program does the billing, monitors refill rates, collects detailed patient data, and follows up with an adherence program designed to build "loyalty," a favorite term of the hub industry.

The industry's reputation has been tainted by some deceitful if not illicit hub programs that captured national attention. The dealings between Valeant Pharmaceuticals and Philidor RX Services LLC, which ran a number of hub programs for Valeant, have come under Congressional scrutiny. News reports have described byzantine money flows and shady business relationships. According to Bloomberg and other news outlets, documents released by the Senate Special Committee on Aging in May showed that Valeant and Philidor had an undisclosed contract that dangled millions of dollars of bonus money in front of Philidor if it hit certain sales targets. Bloomberg reported last year that Philidor employees were instructed to change codes on prescriptions so it would look like the prescriber had asked for Valeant brand-name drug. Valeant, CVS, and Express Scripts cut all their ties with Philidor, and the company went out of business late last year.

Still, the hub industry is still growing. New companies are entering the business, and some of the existing ones are consolidating. The big three pharmaceutical distribution companies—AmerisourceBergen, Cardinal Health, and McKesson—and the largest PBMs—Express Scripts and CVS Health—are major players. Each of these companies has a subsidiary that provides the infrastructure for hub programs as well as a specialty pharmacy for distribution and patient services.

The most clearly documented case of a hub program gone awry involves Novartis and Exjade (deferasirox), a drug approved by the FDA for treatment of elevated iron levels caused by blood transfusions. In November 2015, Novartis agreed to pay $392 million to settle a Department of Justice lawsuit alleging that the drug manufacturer's hub program paid illegal kickbacks to the pharmacies. Separately Accredo and Bioscrip agreed to pay $60 million and $15 million, respectively, to settle allegations of their illegal activities in the scheme. The Lash Group in Charlotte, N.C., which is part of AmerisourceBergen, administered the program but was not named in the lawsuit or part of the settlement. The settlement also included Myfortic (mycophenolic acid), an immunosuppressant drug marketed by Novartis, but the settlement focuses mainly on the hub services for Exjade.

Program designed to boost sales

Novartis's admissions demonstrate how hub programs can be primarily focused on the drug, not the patient (see sidebar). According to the settlement, Novartis used pay-for-performance incentives and scorecards of refill and patient adherence rates to steer patients to the pharmacies with the highest rates. There is nothing wrong with scorecarding and programs to promote adherence, but the settlement paints a less flattering picture of a program focused on boosting sales.

"The underlying problem in this case was greed," says Scott Lampert, a federal investigator with the HHS Office of Inspector General. "In the end all of the activities were based on greed, both on the part of Novartis and on the part of the three specialty pharmacies." HHS was involved in the case because the lawsuit was brought under the federal Anti-Kickback Statute, which is written explicitly to protect federal health care programs from bribery.

"The aggregate settlement in the Novartis case of $465 million is the largest settlement in a False Claims Act case based solely on a kickback theory" notes Shelley Slade, the attorney who represented the whistleblower who initially brought the lawsuit. Slade's
**Legal settlement sheds light on hub program**

The lawsuit against Novartis and three specialty pharmacies—Accredo, BioScrip, and US Bioservices—alleged that the hub program violated two closely related federal laws, the False Claims Act and the Anti-Kickback Statute. These laws are intended to protect federal programs from business arrangements that would inappropriately increase costs to the federal government. The kickback law prohibits anyone from offering, paying, soliciting, or receiving compensation or financial incentives to induce or reward referrals to any federal program.

The Department of Justice asserted that Novartis pressured the specialty pharmacies to start and keep Medicare and Medicaid patients on Exjade which increased costs to government. The kickoff that Novartis provided, the lawsuit claimed, was a larger number of Exjade prescriptions to fill. Under the law the three pharmacies were prevented from receiving these incentives, and the arrangement between the parties was banned even though Medicare patients may have needed the drug.

Novartis’s hub program activities began in 2006 and continued into 2012. At one point the case included allegations of illegal hub activities for six drugs and a much larger group of companies including Aetna, Caremark, Cigna, Curascript, and Walgreens SPP, according to court documents.

The hub program contained all of the elements that demonstrate how hub programs can work against the best interests of patients. The following details are taken from the signed stipulation and order of settlement.

Novartis created an exclusive distribution network with the three pharmacies for Exjade called Exjade Patient Assistance and Support Services, or EPASS. The network was administered by the LASH Group, a hub services vendor owned by AmerisourceBergen that provides an IT platform for hub programs. Doctors who prescribed Exjade submitted a patient registration form and the prescription to LASH for fulfillment. LASH distributed the prescriptions among the three EPASS pharmacies, tracked and reported detailed patient information including data on the reasons for discontinuation, and provided the data to Novartis on a regular rate basis.

In 2007, the discontinuation data the pharmacies submitted to LASH showed that physicians and patients were discontinuing Exjade because of serious side effects. In 2007, Novartis added warnings to the drug’s label for renal failure, thrombocytopenia, and hepatic failures to its drug label.

Novartis kept monthly scorecards on the pharmacies that measured patient adherence scores and in 2007 told Bioscrip that its “refill rates and other adherence metrics” were below those of the other two pharmacies. Novartis told Bioscrip that if it did not improve its performance Novartis would terminate the distribution relationship or reduce the number of prescriptions that LASH assigned to it.

In response Bioscrip initiated a recovery program for patients who had stopped ordering Exjade. Bioscrip told Novartis that it would tell patients that they “should continue taking Exjade” because “undetected or untreated excess iron kills after inflicting injury to a variety of body organs.”

In 2008, Novartis took further steps to incentivize all three pharmacies distributing Exjade to increase prescription refill levels by allocating 60% of unassigned patients to the pharmacy with the highest “adherence” metric (as measured based on the number of refills) and paying additional rebates to the pharmacies for meeting quarterly shipment goals based on Novartis’s sales targets.

“We alleged that the pharmacies would be penalized on the scorecards even for patients who were taken off the drug by their doctor and those who experienced side effects and chose to stop the medication,” says Shelley Slade, the attorney who represented the whistleblower who initially brought the lawsuit against Novartis.

Novartis’s signed admissions state that it pushed US Bioservices and Accredo to implement adherence im-

continues
Legal settlement, continued

Act for Trileptal (oxcarbazepine), an anticonvulsant, and five other drugs. As part of the settlement Novartis was required to set up a five-year corporate integrity program designed to prevent future violations of federal health care and kickback regulations. In 2013, the Department of Justice sued Novartis again, this time for violating the Anti-Kickback statute. A press release about the legal action said the company paid doctors to speak about certain drugs (two hypertension drugs, Lotrel [a combination of amlopidine and benazepril] and Valturin [a combination of aliskiren and valsartan that has been pulled from the market], and a diabetes drug, Starlif [nateglinide], are mentioned) at “events that were often little or nothing more than social occasions for the doctors.” In an email response to an inquiry about its current hub programs, Novartis said that its patient access and support programs can serve an important function for patients. The company said it is committed to improving and extending patient lives by delivering better outcomes while complying with all applicable laws. Novartis also said that it has expanded its corporate integrity program as a means to prevent future problems.

warning shots

Lampert says that the pharma sector and hub programs are now on the federal government’s radar screen. The red flags the government looks for include “anything that indicates interference with the traditional doctor-patient relationship or increases health care costs.”

“Federal scrutiny of expensive hub perks is mount-

-ing and costly prosecutions and civil actions are warn-
ing shots of heightened scrutiny of pharma hub perks,” agrees James Quiggle with the Coalition Against Insurance Fraud, an alliance of insurers, consumer groups, and government agencies. Court actions have alerted the hub industry to the legal difference between honest, profit-making arrangements and illegal backroom deal-making, he adds.

A month before it settled with Novartis, the Department of Justice reached a $9.25 million settlement with PharMerica, a nursing home pharmacy headquartered in Louisville, Ky. The department accused the company of soliciting bribes from Abbott for recommending that physicians prescribe Depakote (valproic acid), its antiseizure medication. Abbott settled with the federal government and individual states four years ago.

PBMs and health plans are also responding to hub programs that depend on “captive pharmacies” that make drugs available only through certain handpicked pharmacies. Express Scripts, CVS, and Optum all excluded Philidor from their networks within days after its hub program with Valeant was revealed.

Meanwhile, some drug manufacturers and hub vendors have taken steps to avoid the kind of legal hot water that Novartis got into. Many hub programs now exclude patients who have coverage through Medicare, Medicaid, and the federal employee benefit plans, so the Anti-Kickback Statute and the Federal False Claims Act, that were the basis of the Novartis lawsuit, don’t apply. Lawsuits would have to be brought under different laws but the burden of proof is higher. Kickback cases take years to resolve and the government has limited resources to pursue them so it chooses its battles carefully. NC

Feedback Please!

Any thoughts about this article? Let us know. Send responses to Managing Editor Frank Diamond at fdiamond@medimedia.com.
Faced with a limited ability to raise premiums, health plans must continue to advance cost-effective health care delivery. Palliative care, which focuses on relieving the pain, symptoms and stress of a serious illness, is an important opportunity for implementing such care. In recent years, palliative care has become America’s fastest growing medical specialty. There are now more than 6,500 physicians and 13,500 nurses certified in palliative care, and palliative care teams available in more than 80% of American hospitals with more than 50 beds.

Unlike hospice care, which is intended for dying patients who forgo all other treatments, palliative care is appropriate for patients at any stage of a serious illness. It can be provided alongside curative or life-prolonging treatment.

There’s a great need for palliative care. Roughly 46 million Americans have both a serious illness and some functional dependency, meaning they rely on a caregiver to help with one or more daily activities such as bathing, dressing, or eating. This is the population most in need of palliative care. Without it, these patients can experience unmanageable pain and symptom crises, resulting in 911 calls, emergency department visits, and repeated hospitalizations.

\[\text{Palliative care in US hospitals with 50 or more beds, 2000–2013}\]

Multiple studies have demonstrated that palliative care adds a layer of support that both helps improve the quality of care and makes it more cost effective.

The managed care industry is taking note. Aetna, Highmark, Cambia Health Solutions, and other leading health plans have achieved impressive results with palliative care programs. Take Aetna’s Compassionate Care Program for example. It resulted in improved member satisfaction, an 81% decrease in inpatient days, and net savings of $12,000 per participating member (Spettell 2009).

Other health plans are now developing similar programs.

\[\text{Palliative care improves quality}\]

Palliative care addresses two areas that have long been weak spots in American health care: effective pain and symptom management and the expertise needed for long, often difficult communications about prognosis and goals of care.

This translates into better results on quality ratings used to calculate HEDIS measures and Medicare Stars.

- **Satisfaction scores.** Home-based palliative care teams significantly improved seriously ill, non-terminal patients’ satisfaction with access, technical quality, communication, and interpersonal relationships, as well as overall satisfaction scores (Hughes 2000).
- **Emergency department use.** Home-based palliative care reduces emergency department visits by nearly 30% (De Jonge 2002).
- **Hospital readmissions.** Home-based palliative care consultations significantly reduce the likelihood of a 30-day readmission, along with a 60% reduction in total hospital days (Lukas 2013).
Another outcome that surprises many is that palliative care prolongs survival. Researchers at the Dana-Farber Cancer Institute conducted a randomized trial that added palliative care to usual cancer care for newly diagnosed lung cancer patients. When compared with a control group of patients receiving only the best cancer care, patients receiving palliative care lived an average of 2.7 months longer, as well as experiencing improved mood and quality of life. Their health care costs were also lower than those of patients in the control group (Temel 2010).

**Palliative care is cost-effective care**
Palliative care is cost-effective care because it produces improvements in quality that lead to lower overall health care costs. Health care utilization declines for two reasons: pain and symptom management that reduces exacerbations and crises, and attention to relieving the stress of patients and their caregivers.

A randomized controlled study of Kaiser Permanente members found that, compared to patients in usual care, patients in the palliative care program not only had statistically significant improved satisfaction scores and reduced hospital days, but also found that costs were lower by a full 33% (Brumley 2007).

A comparative analysis at Sharp Healthcare, presented at an industry conference in February, found that its home-based palliative care program achieved average net savings of more than $4,500 per member per month (Cassel 2016).

**How can managed care organizations use these findings?**
One of the most important steps to improve the care of persons living with serious illness is to correctly identify them. They are the sickest 5% of enrollees whose care accounts for 60% of health care spending. When Amy Kelley and her colleagues at Mount Sinai Medical Center analyzed 12 years of the Health and Retirement Study, they found that patients diagnosed with a serious illness, who also had prior hospitalizations or nursing home stays, and limitations in one or more of the activities of daily living were four times more likely to be hospitalized, covering nearly half of all hospitalizations (Kelley 2016). One way to capture this information is to design, implement and analyze more comprehensive health risk assessments for beneficiaries that would include questions about functional and cognitive abilities. Another would be to incorporate information from the clinical record in the screening algorithm.

Health plans have chosen to increase access to palliative care for these high-risk beneficiaries in a variety of different ways. Members with serious illness can be provided with specially trained care management resources, delivered over the phone or in person. Plans can expand coverage and benefits policies to include full-fledged palliative care team support and home-based primary and palliative care. Support tools to build member awareness of palliative care and its benefits can support these efforts. Practical services such as transport or meal delivery can also be included. Furthermore, plans can design their provider networks to help direct members to specialty palliative care when it’s needed and require that hospitals, home health agencies, and primary care providers in a network obtain certifications in palliative care.

Providers, payers and policymakers are all pursuing value in health care. Palliative care provides a pathway to value for our sickest and most vulnerable patients: high quality care that also reduces costs. MD

Saskia Siderow is a research analyst at the Center to Advance Palliative Care. Allison Silvers is vice president of payment and policy at the Center. Diane E. Meier, MD, is director of the Center and a professor of geriatrics and palliative medicine at Icahn School of Medicine at Mount Sinai Hospital in New York.

Further information and tools are available at the Center to Advance Palliative Care’s website, www.capc.org

**References**


Connected Health Summit: Engaging Consumers will be held August 30 - September 1, 2016, at The Omni Hotel in San Diego. This event analyzes the role of innovative connected health solutions in driving changes in consumer behaviors.

The core themes:
- Role of healthcare in the connected home
- Impact of technology innovations and disruptions
- Success stories in expanding accountability and consumer engagement
- Transformative business models for providers

Keynotes

**Medtronic**
Annette Brüls
President, Diabetes Service and Solutions Medtronic

**Samsung**
David Rhew
Chief Medical Officer and Head of Healthcare and Fitness Samsung

Session Topics

**Technology Strategies**
- Innovative Devices for Consumer Care: IoT and Healthcare Services
- Enabling Better Care: Integrated Technology and Data Platforms
- Sensors and IoT Technologies for Connected Care

**Business Strategies and Partnerships**
- Partnerships in the Connected Health and IoT Market
- From Selling Products to Selling an Integrated Care Experience
- From Fee-for-Service to Pay-for-Performance: Success Stories

**Consumer Engagement**
- Effective Population Health Management Strategies: Success and Lessons Learned
- Engaging Caregivers for Coordinated Care
- Bring Doctors to your Home: Virtually and in Person

**Disruptive Business Models**
- IoT: Integrating Smart Home Solutions into Connected Health Experience
- Everything Disruptive: What Can Consumers Expect From Care Innovators
- Venture Capital and Investment Trends in Consumer Health

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A Strategy for Identifying and Disseminating Best Practice Innovations in the Care of Patients with Multiple Chronic Conditions or End-of-Life Care Needs

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¹Division of Geriatrics, Department of Medicine, David Geffen School of Medicine, University of California–Los Angeles; ²SCAN Health Plan; ³VA Greater Los Angeles Healthcare System

INTRODUCTION

Health care organizations continuously strive to achieve the “Triple Aim” of improving patients’ experience of care and their health outcomes while simultaneously lowering the costs of such care (Berwick 2008). Achieving the Triple Aim among older patients is especially challenging because of the number of patients with multiple chronic conditions and those with end-of-life care needs (Berwick 2008). High costs and the need for skilled coordination of care and provider training are associated with these two types of care.

More specifically, patients with multiple chronic conditions (e.g., ischemic heart disease, arthritis, diabetes, chronic kidney disease, dementia, and depression) often require care from multiple specialists and may experience a multitude of care transitions across different care settings. Without appropriate care management and care coordination, the care of this population not only is very costly but also may result in poor patient experience and patient outcomes (Hong 2015).

The documented high cost of attempted life-prolonging treatments in acute care settings is an issue in end-of-life care. Moreover, the care is often inconsistent with the individual’s and family’s goals and preferences and with the individual’s prognosis (Sabatino 2014). Discussions of end-of-life care preferences, standardized documentation of these preferences, accessibility of these documents across care settings, adherence to advance directives, and availability of palliative care and hospice referrals are all consistent with patient-centered care, yet they are not always common in practice (IOM 2014).

Successful innovative programs that provide better care to these patient populations with high needs and high costs are often localized and not actively disseminated to other settings. In academic settings, there are incentives to publish descriptions of innovations that improve care but few incentives to disseminate these innovations into practice. Conversely, in community practices, there is little incentive to publish but often considerable incentive to disseminate within a health care system. Neither setting offers incentives to disseminate innovations to other health systems.

To address the gap between community practices and academic researchers, the SCAN Health Plan...
has partnered with the UCLA Multicampus Program in Geriatric Medicine and Gerontology. Together, they have developed a quality improvement project to identify local innovations aimed at improving the care of older adults with multiple chronic conditions and those with end-of-life care needs, and to facilitate the diffusion of those practices across medical groups that partner with SCAN Health Plan. More specifically, the SCAN–UCLA project developed a process to identify the leading innovations in practice among SCAN-partnered medical groups, created a platform to share and disseminate these best practices, and facilitated the adoption of successful practices across other medical groups in the SCAN Health Plan network.

**BACKGROUND**

The SCAN Health Plan is a California-based, not-for-profit Medicare Advantage plan that serves approximately 170,000 members. SCAN Health Plan began a provider integration initiative in which leaders of medical groups meet to discuss and address performance concerns. The idea of sharing innovations that were then implemented in community-based practices stemmed from these meetings and also led to this project and partnering with the UCLA Multicampus Program in Geriatric Medicine and Gerontology, a national leader in academic geriatrics.

The medical groups involved in this project were located in both northern and southern California. They are organized in a variety of ways and include independent practice associations (IPAs), staff models (i.e., physicians are employees of the medical group), and mixed models with some practices operating independently and others employing their providers. The medical groups ranged in level of expertise and experience in quality improvement and in inclination toward innovation; while some groups can be considered innovators and are willing to lead the field in trying new innovations, others range from early adopters to cautious late adopters that require progressively higher rigor of evidence before trying out a new innovation to laggards, groups that resist change (Rogers 1995).

**METHODS**

To identify existing best practices addressing the two patient populations—those with multiple chronic conditions and those with end-of-life care needs in community settings—we used existing data on quality measures and surveyed medical groups.

**Quality measures**

To identify medical groups with high quality of care, we used scores for two consecutive years of the Centers for Medicare and Medicaid Services (CMS) Five-Star Quality Rating System for Medicare Advantage Plans. The star ratings are derived from four sources of data: (1) CMS administrative data on plan quality and member satisfaction; (2) the Consumer Assessment of Healthcare Providers and Systems (CAHPS) survey; (3) Healthcare Effectiveness Data and Information Set (HEDIS) measures; and (4) the Health Outcomes Survey (HOS). The Star ratings are scored 1, 2, 3, 4, and 5, representing poor, below average, average, above average, and excellent performance, respectively. These ratings are tied to financial incentives in the form of bonus payments (Jacobson 2011). We identified groups for which quality measures were uniformly high or quality measures had improved significantly, possibly indicating implementation of an effective innovation.

**Survey and interviews**

To identify specific best practices for patients with multiple chronic conditions and end-of-life care needs among the high-achieving groups, we collected data from key informants using focused surveys and interviews. Data collected included background information on the structure of the organization (medical group, IPA, etc.) and the processes used to identify and disseminate best practices.
Identifying and Disseminating Best Practice Innovations

management services organization), types of innovations used in treating the two focused types of populations, how the medical group delivered these innovations to patients, and measures used to assess the innovation outcomes. Ten of the 16 groups contacted provided data (Figure 1).

**Selection of best practices**

Once the 10 potential best practices were identified, the SCAN and UCLA team convened a judging panel composed of UCLA faculty coaches, SCAN coaches, and SCAN steering committee members. That panel selected the five most promising best practices. To evaluate the best practices fairly, a scoring matrix was developed based on several criteria with a rating system that scored unsatisfactory as 0, satisfactory as 1, and excellent as 2. The scoring matrix included six components, including the degree to which the innovation addressed an established need, its effects on achieving the Triple Aim, how well the best practice could be adapted to other settings (scalability), and how sustainable the best practice would be over the long term (Table 1, page 46) (Berwick 2008).

Of the five best practices, two innovations addressed care of patients with multiple chronic conditions: (1) enhanced care coordination for high-risk patients with multiple chronic conditions, and (2) a virtual interdisciplinary care team for patients with multiple chronic conditions.

The remaining three focused on caring for patients with end-of-life care needs, including (1) a nursing approach to introducing palliative care in a hospital setting, (2) outpatient palliative care using multidisciplinary home visits, and (3) advance care planning (ACP) for high-risk patients.

**Disseminating best practices**

A one-day summit was used as the platform for sharing the selected best practices. Ten of the 14 medical groups approached regarding best practices sent representatives to the meeting (Figure 1). Two additional groups were invited by SCAN, so a total of 12 groups were represented at the event and 75 individuals attended.

The objective of the summit was for each of the participating medical groups to leave the meeting with a decision on a specific innovation to adopt and a specific implementation plan. More specifically, the objectives included:

- Identifying a specific evidence-based best practice to adopt in

---

**FIGURE 1**

Total number of medical groups participating in the program

<table>
<thead>
<tr>
<th>Medical groups contacted to participate in project (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responded to survey and interview request (n=10)</td>
</tr>
<tr>
<td>Selected as summit speaker (n=5)</td>
</tr>
<tr>
<td>Interviewed but not selected as summit speaker (n=5)</td>
</tr>
<tr>
<td>Attended summit (n=12)</td>
</tr>
<tr>
<td>Completed action plan (n=11)</td>
</tr>
<tr>
<td>Active implementation with coaching calls (n=5)</td>
</tr>
<tr>
<td>Active implementation without coaching calls (n=2)</td>
</tr>
<tr>
<td>Did not complete action plan (n=1)</td>
</tr>
<tr>
<td>No implementation (n=4)</td>
</tr>
</tbody>
</table>

---
Identifying and Disseminating Best Practice Innovations

After hearing the three presentations, participants from each attending organization picked one innovation to adopt.

**Process and content coaching**
Preparation for implementation of the chosen best practice was facilitated through process and content coaching. Trained researchers and clinicians with experience in implementing innovations and quality-improvement projects served as process coaches. Before the summit, the process coaches were given detailed information regarding the best practices and were asked to familiarize themselves with the innovations.

At the summit, each implementation team from an adopting medical group was assigned a specific process for each of the five best practices selected for presentation, a representative from the medical group initially presented a brief description of the innovation to the entire audience. Following these general presentations, the attendees selected three best practices to learn about in greater depth. A subsequent 15-minute in-depth presentation of each best practice innovation was conducted in a round-robin format; each innovation was presented three times, allowing attendees to attend three different presentations and ask questions of the presenters regarding implementation.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Criteria for selecting best practices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selection criteria</td>
<td>Unsatisfactory (0 points)</td>
</tr>
<tr>
<td>Need identified</td>
<td>1. Incomplete QI plan</td>
</tr>
<tr>
<td>How effectively does this best practice address an identified need within the medical group?</td>
<td>2. No or little data</td>
</tr>
<tr>
<td>Quality of care is measurable (patient satisfaction)</td>
<td>1. No evidence of improvement</td>
</tr>
<tr>
<td>Does the best practice measurably improve the quality of care received by the patient?</td>
<td>2. No or little data</td>
</tr>
<tr>
<td>Cost savings per patient is measurable</td>
<td>1. No evidence of cost savings</td>
</tr>
<tr>
<td>Does the best practice measurably lower the per capita cost of treating the patient?</td>
<td>2. No or little data</td>
</tr>
<tr>
<td>Demonstrates improvement in health</td>
<td>1. No or low evidence</td>
</tr>
<tr>
<td>Does the best practice measurably improve target population health?</td>
<td>2. No or little data</td>
</tr>
<tr>
<td>Easily adaptable to many settings</td>
<td>1. No, too specific to one care setting</td>
</tr>
<tr>
<td>Is this best practice unique to the setting where it was developed, or can the principles be adopted in other care settings?</td>
<td></td>
</tr>
<tr>
<td>Sustainability</td>
<td>1. Demonstration project/pilot only</td>
</tr>
<tr>
<td>Is this intervention sustainable in the medical group?</td>
<td></td>
</tr>
</tbody>
</table>

the area of care for patients with multiple chronic conditions and/or end-of-life care
- Developing an action plan for adoption of the selected best practice with specific goals and timelines to achieve the goals
- Outlining the potential barriers to achieving the action plan and identifying strategies to address and overcome these barriers
- Identifying appropriate measures and data-collection plans for tracking progress and documenting outcomes

To achieve these objectives, the agenda for the summit began by introducing the concepts of best practices and quality improvement, followed by presentations of the best practices by each speaker and dedicated time for the medical groups to meet with quality improvement coaches from SCAN and UCLA to develop their implementation plan.

For each of the five best practices selected for presentation, a representative from the medical group initially presented a brief description of the innovation to the entire audience. Following these general presentations, the attendees selected three best practices to learn about in greater depth. A subsequent 15-minute in-depth presentation of each best practice innovation was conducted in a round-robin format; each innovation was presented three times, allowing attendees to attend three different presentations and ask questions of the presenters regarding implementation.

After hearing the three presentations, participants from each attending organization picked one innovation to adopt.
coaches spent two hours guiding following components:

- A clearly articulated statement of the planned innovation, based on the implementation team’s selected best practice or components of a best practice
- A statement of the overarching goal of the innovation and its intended outcomes
- A description of the target population or patients affected by this innovation
- Three Specific, Measurable, Achievable, Realistic/Results Oriented, and Time-Dated (SMART) Goals (CDC 2009) related to innovation adoption or implementation
- An assessment plan including quality improvement methods to study the project
- A measurement plan including quality-improvement tools to measure the project’s outcomes and achievement of SMART goals
- A plan for achieving commitment from the organization’s leadership including identification of key stakeholders in the organization and a concrete plan of achieving their support
- Resources needed to accomplish the plan
- Anticipated barriers and obstacles to implementation
- Strategies to overcome barriers
- A time frame with specific tasks that need to take place in the six-month implementation period

Eleven of the 12 groups that attended the summit completed an action plan for a new best practice. One group chose to focus its efforts on further improvement of an innovation it had already developed. Two groups declined coaching because they had sufficient resources and in-house expertise in quality improvement, and the remaining four were not able to pursue the innovations for a variety of reasons.

**Implementation**

The UCLA coaching model involved an intense postsummit coaching component, conducted through regularly scheduled 30-minute conference calls, usually twice a month, during the six months of the implementation process. The calls included key personnel from the implementation team, the assigned process coach, and the UCLA program manager.

Before each call, the implementation team completed a best practices adoption dashboard tool (available upon request and as online supplementary material, Appendix 3†), which included prompts regarding progress on the SMART goals outlined in the action plan, barriers to completing the goals, and questions or requests for the coach. The tool served as a quick self-assessment for the implementation team, as a reminder of the planned call, and as a communication method between the coach and team to allow efficient work during the conference call. Eleven teams completed an action plan and five participated in coaching calls (Figure 1, page 45).

The post-summit process coaching supported the implementation teams in several ways. First, it provided a mechanism for keeping the teams on track and facilitating a timely and structured implementation. Second, the process coaches provided the teams with information regarding implementation details as needed. Finally, drawing on their experience in quality improvement projects, the process coaches provided in-time assistance in overcoming unanticipated barriers during implementation. In addition to the scheduled calls with process coaches, implementation teams had phone conversations and email exchanges with content coaches from the groups that had developed the innovations, as well as with other

* managedcaremag.com/bpi-1
† managedcaremag.com/bpi-2
groups that chose the same innovation to adopt.

The process coaches met monthly on a conference call to review progress and to leverage their combined experience. The coaches’ call provided an opportunity for the coaches to support each other through the process and provide suggestions to one another on how to help their respective teams. A feedback tool (available upon request and as online supplementary material, Appendix 4) was developed for coaches to report on team progress, assessments of barriers, and ratings of medical group engagement and communication. Coaches completed the feedback tool monthly and the responses were used to guide the discussions about successes and progress, communication problems, structural challenges, and changes in selected practice innovations and level of engagement in coaching.

Discussion
This paper documents a process designed to identify and disseminate successful innovations in the care of older adults with multiple chronic conditions or end-of-life care needs. One of the barriers to innovation dissemination is the competing time demands placed on medical groups’ leadership and the need to focus on pressing concerns such as performance measures and other operational and clinical concerns. Recognizing this barrier, SCAN Health Plan developed its provider integration initiative, in which leaders of the various groups meet periodically to discuss common concerns.

Building upon this collaborative culture, SCAN teamed up with UCLA to further encourage the groups to share and learn from one another with the ultimate goal of improving the quality of care provided for the two clinical populations of interest.

Disseminating successful innovations requires an awareness of the intervention (achieved through presentations at the summit) and following principles of decision adoption (e.g., relative advantage, compatibility, complexity, trialability, and observability) (Rogers 1995). The criteria we developed to judge each of the innovations (Table 1) helped select promising interventions that fit these principles.

A common barrier to dissemination is implementing an innovation in a different setting, which often requires adaptation and possibly additional resources. Moreover, despite best intentions, without guidance and support, it is sometimes difficult to carry out even a very detailed action plan because of competing demands on time, shifting organizational priorities, unexpected barriers, lack of resources, and a variety of factors. To overcome these barriers, we developed a structured system of support and guidance to assist teams with the adoption of these best practices by experienced coaches both during a summit-like meeting to introduce and explain best practices and during the six months following the adoption of the best practice. In our project, 5 of the 11 participating implementation teams chose to receive coaching support following the summit.

Dissemination of complex innovations is challenging. Even if the outcomes under “as usual” conditions are suboptimal, changing systems of care to make improvements may be more difficult than keeping the status quo. Few health care systems have the resources and “know how” to identify, adapt, and implement innovations that have worked in other systems. We have described a process that can help overcome the inertia and resource barriers to dissemination. However, it must be recognized that even with the substantial guidance provided by this system, fewer than half of the medical practices were able to implement desired innovations in their practices. Additional incentives will be needed. Once those incentives are in place, the process of selecting innovations and coaching through the implementation stages may be very valuable.

REFERENCES

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4 managedcaremag.com/bpi-4
The worldwide market for medications for autoimmune disorders is expected to grow from $61.5 billion in 2015 to $74.2 billion in 2022, according to GBI Research, a health care information and data company headquartered in London. The company expects Eli Lilly’s biologics, baricitinib and ixekizumab (Taltz), to be particularly strong sellers. GBI also predicted in a November 2015 report that APB-501—the provisional name for Amgen’s biosimilar to AbbVie’s Humira (adalimumab)—will generate annual revenues of almost $1 billion by 2022.

These rosy predictions for sales may take on a different hue from the patient perspective. A study published last year in *Arthritis & Rheumatology* looked at 2,737 formularies for Medicare Part D plans in 50 states and Washington, D.C., from 2013. The researchers found that nearly all plans required coinsurance and that translated into an average out-of-pocket expense of about $2,700.

Changes to the coverage gap in the Part D plans—often referred to as the donut hole—might help ease the out-of-pocket burden. The ACA gradually lowers the patient share of drug expenses during the donut hole phase. This year, seniors are paying 45% of the price of brand-name drugs while they are in the donut hole and 65% of generics, compared with 47.5% and 79%, respectively, in 2013. By 2020, the patient share for both brand-name and generic drugs is scheduled to be 25%.

### Projected worldwide sales of autoimmune disease medications*

<table>
<thead>
<tr>
<th>Year</th>
<th>Market size ($bn)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td></td>
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<tr>
<td>2021</td>
<td></td>
</tr>
<tr>
<td>2022</td>
<td></td>
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</tbody>
</table>

* GBI’s forecast includes biologics, other medications, and drugs in the development pipeline. Medications for inflammatory bowel disease (Crohn’s disease and ulcerative colitis), multiple sclerosis, and type 1 diabetes are not included in this forecast.


### Filling in the donut hole

<table>
<thead>
<tr>
<th>Year</th>
<th>Patient share brand-name drugs in coverage gap</th>
<th>Patient share generic drugs in coverage gap</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>45%</td>
<td>65%</td>
</tr>
<tr>
<td>2016</td>
<td>45%</td>
<td>58%</td>
</tr>
<tr>
<td>2017</td>
<td>40%</td>
<td>51%</td>
</tr>
<tr>
<td>2018</td>
<td>35%</td>
<td>44%</td>
</tr>
<tr>
<td>2019</td>
<td>30%</td>
<td>37%</td>
</tr>
<tr>
<td>2020</td>
<td>25%</td>
<td>25%</td>
</tr>
</tbody>
</table>

Source: CMS, “Closing the Coverage Gap,” January 2015
NOW APPROVED

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