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Special Report: Six Fatal Condition Treatment Updates
EXPERIENCE IMBRUVICA® (ibrutinib):

• ORAL, ONCE-DAILY DOSING
• APPROVED IN 6 INDICATIONS
• MORE THAN 40,000 US PATIENTS HAVE BEEN TREATED ACROSS ALL INDICATIONS SINCE APPROVAL

Visit IMBRUVICAHCP.com and discover more reasons to make IMBRUVICA® your choice.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients treated with IMBRUVICA®. Grade 3 or higher bleeding events (intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post-procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with IMBRUVICA®.

The mechanism for the bleeding events is not well understood. IMBRUVICA® may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding.

Consider the benefit-risk of withholding IMBRUVICA® for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding.

Infections: Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 14% to 29% of patients. Cases of progressive multifocal leukoencephalopathy (PML) and Pneumocystis jirovecii pneumonia (PJP) have occurred in patients treated with IMBRUVICA®.

Monitor and evaluate patients for fever and infections and treat appropriately.

Cytopenias: Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 13 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 13%) based on laboratory measurements occurred in patients with B-cell malignancies treated with single agent IMBRUVICA®.

Monitor complete blood counts monthly.

Cardiac Arrhythmias: Fatal and serious cardiac arrhythmias have occurred with IMBRUVICA® therapy. Grade 3 or greater ventricular tachyarrhythmias occurred in 0 to 1% of patients, and Grade 3 greater atrial fibrillation and atrial flutter occurred in 0 to 6% of patients. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias.

Periodically monitor patients clinically for cardiac arrhythmias. Obtain an ECG for patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arrhythmias appropriately, and if it persists, consider the risks and benefits of IMBRUVICA® treatment and follow dose modification guidelines.


Please see additional Important Safety Information and Brief Summary on the following pages.
IMBRUVICA®: HELPING PATIENTS ACROSS 6 INDICATIONS¹

INDICATIONS
IMBRUVICA® (ibrutinib) is a once-daily oral therapy indicated for the treatment of adult patients with:
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)
- CLL/SLL with 17p deletion
- Waldenström’s Macroglobulinemia (WM)
- Chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy
- Mantle cell lymphoma (MCL) who have received at least one prior therapy
- Marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy
- Accelerated approval was granted for the MCL and MZL indications based on overall response rate. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials

IMPATIENT SAFETY INFORMATION (CONT’D)
WARNINGS AND PRECAUTIONS (CONT’D)

Hypertension: Hypertension (range, 6 to 17%) has occurred in patients treated with IMBRUVICA® with a median time to onset of 4.6 months (range, 0.03 to 22 months). Monitor patients for new onset hypertension or hypertension that is not adequately controlled after starting IMBRUVICA®.

Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

Second Primary Malignancies: Other malignancies (range, 3 to 16%) including non-skin carcinomas (range, 1 to 4%) have occurred in patients treated with IMBRUVICA®. The most frequent second primary malignancy was non-melanoma skin cancer (range, 2 to 13%)

Tumor Lysis Syndrome: Tumor lysis syndrome has been infrequently reported with IMBRUVICA® therapy. Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions.

To learn more, visit IMBRUVICAHCP.com

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA® can cause fetal harm when administered to a pregnant woman. Advise women to avoid becoming pregnant while taking IMBRUVICA® and for 1 month after cessation of therapy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Advise men to avoid fathering a child during the same time period.

ADVERSE REACTIONS

B-cell malignancies: The most common adverse reactions (≥20%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were thrombocytopenia (62%)*, neutropenia (61%)*, diarrhea (43%), anemia (41%)*, musculoskeletal pain (30%), bruising (30%), rash (30%), fatigue (29%), nausea (29%), hemorrhage (22%), and pyrexia (21%).

The most common Grade 3 or 4 adverse reactions (≥5%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia (39%)*, thrombocytopenia (16%)*, and pneumonia (10%).
Approximately 6% (CLL/SLL), 14% (MCL), 11% (WM) and 10% (MZL) of patients had a dose reduction due to adverse reactions. Approximately 4%-10% (CLL/SLL), 9% (MCL), and 9% (WM [6%] and MZL [13%]) of patients discontinued due to adverse reactions.

**cGVHD:** The most common adverse reactions (≥20%) in patients with cGVHD were fatigue (57%), bruising (40%), diarrhea (36%), thrombocytopenia (33%)*, stomatitis (29%), muscle spasms (29%), nausea (26%), hemorrhage (26%), anemia (24%)*, and pneumonia (21%).

The most common Grade 3 or 4 adverse reactions (≥5%) reported in patients with cGVHD were fatigue (12%), diarrhea (10%), neutropenia (10%)*, pneumonia (10%), sepsis (10%), hypokalemia (7%), headache (5%), musculoskeletal pain (5%), and pyrexia (5%).

Twenty-four percent of patients receiving IMBRUVICA® in the cGVHD trial discontinued treatment due to adverse reactions. Adverse reactions leading to dose reduction occurred in 26% of patients.

**DRUG INTERACTIONS**

**CYP3A Inhibitors:** Dose adjustment may be recommended.

**CYP3A Inducers:** Avoid coadministration with strong CYP3A inducers.

**SPECIFIC POPULATIONS**

**Hepatic Impairment** (based on Child-Pugh criteria): Avoid use of IMBRUVICA® in patients with severe baseline hepatic impairment. In patients with mild or moderate impairment, reduce IMBRUVICA® dose.

Please see the Brief Summary on the following pages.
INDICATIONS AND USAGE
IMBRUVICA® (ibrutinib) capsules are indicated for:
- Treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) with 17p deletion.
- Treatment of adult patients with Waldenström's macroglobulinemia (WM) and have received at least one prior anti-CD20-based therapy.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Hypertension: Fatal bleeding events have occurred in patients treated with IMBRUVICA. Grade 3 or higher bleeding events (intracranial hemorrhage indicates the patient), gastrointestinal bleeding, hematuria, and post-procedural hemorrhage have occurred in up to 6% of patients. The mechanism for the bleeding events is not well understood. IMBRUVICA may increase the risk of hemorrhage in patients receiving anti-platelet or anti-coagulant therapies and patients should be monitored for signs of bleeding.

Antihypertensive medications and/or initiate antihypertensive treatment that is not adequately controlled after starting IMBRUVICA. Adjust existing antihypertensive medications as appropriate.

Infections: Grade 3 or greater infections have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 0 to 1% of patients, and Grade 3 or greater atrial fibrillation and ventricular arrhythmias have occurred in up to 6% of patients. The risks and benefits of IMBRUVICA treatment and follow dose modification guidelines [see Warnings and Precautions].

Cardiac Arrhythmias: Treatment-emergent Grade 3 or 4 arrhythmias including atrial fibrillation occurred in 0 to 6% of patients. These events have occurred in patients with cardiac risk factors, hypertension, acute infections, and post procedural hemorrhage. Monitor patients clinically for cardiac arrhythmias appropriately, and if it persists, consider the risks and benefits of IMBRUVICA treatment and follow dose modification guidelines [see Warnings and Precautions].

Cytopenias: Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 13 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 13%) based on laboratory measurements occurred in patients with B-cell malignancies treated with single agent IMBRUVICA.

Monitor complete blood counts monthly.

Tumor Lysis Syndrome: Tumor lysis syndrome has been infrequently reported with IMBRUVICA therapy. Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions. Monitor patients closely and treat as appropriate.

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Avoid IMBRUVICA in pregnant women. If this drug is used during pregnancy or the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus [see Use in Specific Populations].

ADVERSE REACTIONS
The following adverse reactions are discussed in more detail in other sections of the labeling:

- Hemorrhage [see Warnings and Precautions]
- Infections [see Warnings and Precautions]
- Cytopneas [see Warnings and Precautions]
- Cardiac Arrhythmias [see Warnings and Precautions]
- Hypertension [see Warnings and Precautions]
- Second Primary Malignancies [see Warnings and Precautions]
- Tumor Lysis Syndrome [see Warnings and Precautions]

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates of clinical trials of another drug and may not reflect the rates observed in practice.

Mantle Cell Lymphoma: The data described below reflect exposure to IMBRUVICA in a clinical trial (Study 1104) that included 111 patients with previously treated MCL treated with 560 mg daily with a median treatment duration of 8.3 months.

The most commonly occurring adverse reactions (≥20%) were thrombocytopenia, diarrhea, neutropenia, anemia, fatigue, musculoskeletal pain, peripheral edema, upper respiratory tract infection, nausea, bruising, dyspnea, constipation, rash, abdominal pain, vomiting and decreased appetite (see Tables 1 and 2).

The most common Grade 3 or 4 non-hematological adverse reactions (≥5%) were pneumonia, abdominal pain, atrial fibrillation, diarrhea, fatigue, and skin infections.

Fetal and serious cases of renal failure have occurred with IMBRUVICA therapy. Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 9% of patients.

Adverse reactions from the MCL trial (N=111) using single agent IMBRUVICA have occurred in 0 to 6% of patients.

| Body System | Adverse Reaction | Grade 3 or 4 (%)
|-------------|------------------|------------------|
| Gastrointestinal disorders | Diarrhea | 51
| | Nausea | 31
| | Constipation | 25
| | Abdominal pain | 24
| | Vomiting | 23
| | Stomatitis | 17
| | Dyspepsia | 11

| Infections and infestations | Upper respiratory tract infection | 34
| | Urinary tract infection | 14
| | Pneumonia | 14
| | Skin infections | 14
| | Sinusitis | 13

| General disorders and administration site conditions | Fatigue | 41
| | Peripheral edema | 35
| | Pyrexia | 18
| | Asthenia | 14

| Skin and subcutaneous tissue disorders | Bruising | 30
| | Rash | 25
| | Petechiae | 11

| Musculoskeletal and connective tissue disorders | Musculoskeletal pain | 37
| | Muscle spasms | 14
| | Arthralgia | 11

| Respiratory, thoracic and mediastinal disorders | Dyspnea | 27
| | Cough | 19
| | Epistaxis | 11

| Metabolism and nutrition disorders | Decreased appetite | 21
| | Dehydration | 12

Table 1: Non-Hematologic Adverse Reactions in ≥10% of Patients with MCL (N=111)
Ten patients (9%) discontinued treatment due to adverse reactions in the trial (N=111). The most frequent adverse reaction leading to treatment discontinuation was subdural hematoma (1.8%). Adverse reactions leading to dose reduction occurred in 14% of patients. Patients with MCL who develop lymphocytosis greater than 400,000/mcL have developed intracranial hemorrhage, lethargy, gait instability, and headache. However, some of these cases were in the setting of disease progression. Forty percent of patients had elevated uric acid levels on study including 15% of patients.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: The data described below reflect exposure in one single-arm, open-label clinical trial (Study 1102) and three randomized controlled clinical trials (RESONATE, RESONATE-2, and HELIOS) in patients with CLL/SLL (n=1278 total and n=668 previously treated CLL/SLL, RESONATE included 391 randomized patients older with treatment naïve-CLL or SLL who received single agent IMBRUVICA or ofatumumab, RESONATE-2 included 269 randomized patients 65 years or older with treatment naïve-CLL or SLL who received single agent IMBRUVICA in combination with bendamustine and rituximab or placebo in combination with bendamustine and rituximab, and HELIOS included 578 randomized patients with previously treated CLL or SLL who received IMBRUVICA in combination with bendamustine and rituximab or placebo in combination with bendamustine and rituximab.

The most commonly occurring adverse reactions in Studies 1102, RESONATE, RESONATE-2, and HELIOS in patients with CLL/SLL receiving IMBRUVICA (≥ 20%) were neutropenia, thrombocytopenia, anemia, diarrhea, musculoskeletal pain, nausea, rash, bruising, fatigue, pyrexia and hemorrhage. Four to 10 percent of patients receiving IMBRUVICA in Studies 1102, RESONATE, RESONATE-2, and HELIOS discontinued treatment due to adverse reactions. These included pneumonia, hemorrhage, atrial fibrillation, rash and neutropenia (1% each). Adverse reactions leading to dose reduction occurred in approximately 6% of patients.

Study 1102: Adverse reactions and laboratory abnormalities from the CLL/SLL trial (N=51) using single agent IMBRUVICA 420 mg daily in patients with previously treated CLL/SLL occurring at a rate of ≥ 10% with a median duration of treatment of 15.6 months are presented in Tables 3 and 4.

### Table 1: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with MCL (N=111) (continued)

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Platelets Decreased</td>
<td></td>
<td>57</td>
<td>17</td>
</tr>
<tr>
<td>Neutrophils Decreased</td>
<td></td>
<td>47</td>
<td>29</td>
</tr>
<tr>
<td>Hemoglobin Decreased</td>
<td></td>
<td>41</td>
<td>9</td>
</tr>
</tbody>
</table>

* Based on laboratory measurements and adverse reactions

Table 2: Treatment-Emergent* Hematologic Laboratory Abnormalities in Patients with MCL (N=111)

<table>
<thead>
<tr>
<th>Percent of Patients (N=111)</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets Decreased</td>
<td>57</td>
<td>17</td>
</tr>
<tr>
<td>Neutrophils Decreased</td>
<td>47</td>
<td>29</td>
</tr>
<tr>
<td>Hemoglobin Decreased</td>
<td>41</td>
<td>9</td>
</tr>
</tbody>
</table>

Table 3: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL/SLL (N=51) in Study 1102

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>59</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Stomatitis</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
<td>12</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infection</td>
<td>47</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Sinusitis</td>
<td>22</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Skin infection</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection</td>
<td>12</td>
<td>2</td>
</tr>
</tbody>
</table>

### Table 3: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL/SLL (N=51) in Study 1102

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>48</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>26</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Stomatitis*</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Pyrexia</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>26</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Stomatitis*</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>14</td>
<td>0</td>
</tr>
</tbody>
</table>

### Table 4: Treatment-Emergent* Hematologic Laboratory Abnormalities in Patients with CLL/SLL (N=51) in Study 1102

<table>
<thead>
<tr>
<th>Percent of Patients (N=51)</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets Decreased</td>
<td>69</td>
<td>12</td>
</tr>
<tr>
<td>Neutrophils Decreased</td>
<td>53</td>
<td>26</td>
</tr>
<tr>
<td>Hemoglobin Decreased</td>
<td>43</td>
<td>0</td>
</tr>
</tbody>
</table>

* Based on laboratory measurements per IWCLL criteria and adverse reactions.

**RESONATE:** Adverse reactions and laboratory abnormalities described below in Tables 5 and 6 reflect exposure to IMBRUVICA with a median duration of 8.6 months and exposure to ofatumumab with a median of 5.3 months in RESONATE in patients with previously treated CLL/SLL.

Table 5: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>IMBRUVICA (N=195)</th>
<th>Ofatumumab (N=191)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>48</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>26</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Stomatitis*</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>14</td>
<td>0</td>
</tr>
</tbody>
</table>

### Table 6: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>IMBRUVICA (N=195)</th>
<th>Ofatumumab (N=191)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td>Pyrexia</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>26</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Stomatitis*</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>14</td>
<td>0</td>
</tr>
</tbody>
</table>

**Skin and subcutaneous tissue disorders**

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>IMBRUVICA (N=195)</th>
<th>Ofatumumab (N=191)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash*</td>
<td>24</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Petechiae</td>
<td>14</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Bruising*</td>
<td>12</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
### Table 5: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE (continued)

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA (N=195)</th>
<th>Ofatumumab (N=191)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>28</td>
<td>2</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contusion</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vision blurred</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

Subjects with multiple events for a given ADR term are counted once only for each ADR term.

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

* Includes multiple ADR terms

### Table 6: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with CLL/SLL in RESONATE

<table>
<thead>
<tr>
<th>ADR Term</th>
<th>IMBRUVICA (N=195)</th>
<th>Ofatumumab (N=191)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils Decreased</td>
<td>51</td>
<td>23</td>
</tr>
<tr>
<td>Platelets Decreased</td>
<td>52</td>
<td>45</td>
</tr>
<tr>
<td>Hemoglobin Decreased</td>
<td>36</td>
<td>21</td>
</tr>
</tbody>
</table>

### Table 7: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE-2

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA (N=135)</th>
<th>Chlorambucil (N=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>42</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>36</td>
<td>4</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Dry eye</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Lacrimation increased</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

Subjects with multiple events for a given ADR term are counted once only for each ADR term.

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

* Includes multiple ADR terms

### HELIOS: Adverse reactions described below in Table 8 reflect exposure to IMBRUVICA + BR with a median duration of 14.7 months and exposure to placebo + BR with a median of 12.8 months in HELIOS in patients with previously treated CLL/SLL.

### Table 8: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients with CLL/SLL in HELIOS

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>Ibrutinib + BR (N=287)</th>
<th>Placebo + BR (N=287)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Neutropenia*</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia*</td>
<td>34</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash*</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>Bruising*</td>
<td>20</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>12</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Ibrutinib + BR (N=287)</td>
<td>Placebo + BR (N=287)</td>
</tr>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td></td>
<td>Neutropenia*</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia*</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>Rash*</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>Bruising*</td>
<td>20</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>12</td>
</tr>
</tbody>
</table>
Adverse reactions leading to discontinuation were interstitial lung disease, 11% discontinued treatment due to adverse reactions. The most common adverse reactions in Studies 1118 and 1121 were thrombocytopenia, diarrhea, neutropenia, fatigue, bruising, and nausea.

The most commonly occurring adverse reactions in Studies 1118 and 1121 were thrombocytopenia, diarrhea, neutropenia, fatigue, bruising, hemorrhage, anemia, rash, musculoskeletal pain, and nausea. Nine percent of patients receiving IMBRUVICA across Studies 1118 and 1121 discontinued treatment due to adverse reactions. The most common adverse reactions leading to discontinuation were interstitial lung disease, diarrhea and rash. Adverse reactions leading to dose reduction occurred in 10% of patients.

Study 1118: Adverse reactions and laboratory abnormalities described below in Tables 9 and 10 reflect exposure to IMBRUVICA with a median duration of 11.7 months in Study 1118.

### Table 8: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients with CLL/SLL in HELIOS (continued)

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>Ibrutinib + BR (% N=287)</th>
<th>Placebo + BR (% N=287)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>25 (% 4)</td>
<td>22 (% 2)</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>19 (% 2)</td>
<td>9 (% 1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 (% 5)</td>
<td>5 (% 2)</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td>13 (% 2)</td>
<td>10 (% 3)</td>
</tr>
<tr>
<td>Skin infection*</td>
<td>10 (% 3)</td>
<td>6 (% 2)</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>10 (% 2)</td>
<td>6 (% 0)</td>
</tr>
</tbody>
</table>

The body system and individual ADR terms are sorted in descending frequency order. * Includes multiple ADR terms.

### Table 9: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with WM in Study 1118 (N=63) (continued)

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>37</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Stomatitis*</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Gastroesophageal reflux disease</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash*</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Bruising*</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Pruritus</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and administrative site conditions</td>
<td>Fatigue</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Muscle spasms</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Arthropathy</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infection</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Sinusitis</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Pneumonia*</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Skin infection*</td>
<td>14</td>
<td>2</td>
</tr>
</tbody>
</table>

The body system and individual ADR preferred terms are sorted in descending frequency order.

### Table 10: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with WM in Study 1118 (N=63)

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets Decreased</td>
<td>43</td>
<td>13</td>
</tr>
<tr>
<td>Neutrophils Decreased</td>
<td>44</td>
<td>19</td>
</tr>
<tr>
<td>Hemoglobin Decreased</td>
<td>13</td>
<td>8</td>
</tr>
</tbody>
</table>

### Study 1121: Adverse reactions and laboratory abnormalities described below in Tables 11 and 12 reflect exposure to IMBRUVICA with a median duration of 11.6 months in Study 1121.

### Table 11: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with MZL in Study 1121 (N=63)

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>43</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Stomatitis*</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain upper</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>General disorders and administrative site conditions</td>
<td>Fatigue</td>
<td>44</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Peripheral edema</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Bruising*</td>
<td>41</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Rash*</td>
<td>29</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Pruritus</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Musculoskeletal pain*</td>
<td>40</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Arthralgia</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Muscle spasms</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infection</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Sinusitis*</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Bronchitis</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Pneumonia*</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Decreased appetite</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Hyperuricemia</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Hypoalbuminemia</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Hypokalemia</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hemorrhage*</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Hypertension*</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Dyspnea</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Anxiety</td>
<td>16</td>
<td>2</td>
</tr>
</tbody>
</table>

The body system and individual ADR preferred terms are sorted in descending frequency order.

* Includes multiple ADR terms.
IMBRUVICA® (ibrutinib) capsules

Table 12: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with MZL in Study 1121 (N=63)

<table>
<thead>
<tr>
<th>Percent of Patients (N=63)</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets Decreased</td>
<td>49</td>
<td>6</td>
</tr>
<tr>
<td>Hemoglobin Decreased</td>
<td>43</td>
<td>13</td>
</tr>
<tr>
<td>Neutrophils Decreased</td>
<td>22</td>
<td>13</td>
</tr>
</tbody>
</table>

Chronic Graft versus Host Disease: The data described below reflect exposure to IMBRUVICA in an open-label clinical trial (Study 1129) that included 42 patients with cGVHD after failure of first line corticosteroid therapy and required additional therapy.

The most commonly occurring adverse reactions in the cGVHD trial (≥ 20%) were fatigue, bruising, diarrhea, thrombocytopenia, stomatitis, muscle spasms, nausea, hemorrhage, anemia, and pneumonia. Atrial fibrillation occurred in one patient (2%) which was Grade 3.

Twenty-four percent of patients receiving IMBRUVICA in the cGVHD trial discontinued treatment due to adverse reactions. The most common adverse reactions leading to discontinuation were fatigue and pneumonia. Adverse reactions leading to dose reduction occurred in 26% of patients.

Adverse reactions and laboratory abnormalities described below in Tables 13 and 14 reflect exposure to IMBRUVICA with a median duration of 4.4 months in the cGVHD trial.

The system organ class and individual ADR preferred terms are sorted in descending frequency order.

* Includes multiple ADR terms.

Table 13: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with cGVHD (N=42)

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue</td>
<td>57</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Edema peripheral</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Bruising*</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Rash*</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>36</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Stomatitis*</td>
<td>29</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Muscle spasms</td>
<td>29</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Musculoskeletal pain*</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hemorrhage*</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Pneumonia*</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Upper respiratory tract infection</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Sepsis*</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Fall</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Dyspnea</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Hypokalemia</td>
<td>12</td>
<td>7</td>
</tr>
</tbody>
</table>

Table 14: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with cGVHD (N=42)

<table>
<thead>
<tr>
<th>Percent of Patients (N=42)</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets Decreased</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>Neutrophils Decreased</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Hemoglobin Decreased</td>
<td>24</td>
<td>2</td>
</tr>
</tbody>
</table>

Additional Important Adverse Reactions: Cardiac Arrhythmias: In randomized controlled trials (n=1227; median treatment duration of 13.1 months for patients treated with IMBRUVICA and 9.0 months for patients in the control arm), the incidence of ventricular tachyarrhythmias (ventricular extrasystoles, ventricular arrhythmias, ventricular fibrillation, ventricular flutter, and ventricular tachycardia) of any grade was 1.0% versus 0.2% and of Grade 3 or greater was 0.2% versus 0% in patients treated with IMBRUVICA compared to patients in the control arm. In addition, the incidence of atrial fibrillation and atrial flutter of any grade was 7% versus 1.5% and for Grade 3 or greater was 2.8% versus 0.3% in patients treated with IMBRUVICA compared to patients in the control arm.

Diarrhea: Diarrhea of any grade occurred at a rate of 43% (range, 36% to 59%) of patients treated with IMBRUVICA. Grade 2 diarrhea occurred in 9% (range, 3% to 14%) and Grade 3 in 3% (range, 0 to 5%) of patients treated with IMBRUVICA. The median time to first onset of any grade diarrhea was 10 days (range, 0 to 627), of Grade 2 was 39 days (range, 1 to 719) and of Grade 3 was 74 days (range, 3 to 627). Of the patients who reported diarrhea, 82% had complete resolution, 1% had partial improvement and 17% had no reported improvement at time of analysis. The median time from onset to resolution or improvement of any grade diarrhea was 5 days (range, 1 to 418), and was similar for Grades 2 and 3. Less than 1% of patients discontinued IMBRUVICA due to diarrhea.

Visual Disturbance: Blurred vision and decreased visual acuity of any grade occurred in 10% of patients treated with IMBRUVICA (9% Grade 1, 2% Grade 2). The median time to first onset was 85 days (range, 1 to 414). Of the patients with visual disturbance, 61% had complete resolution and 38% had no reported improvement at time of analysis. The median time from onset to resolution or improvement was 38 days (range, 1 to 360).

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of IMBRUVICA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hepatobiliary disorders: hepatic failure
- Respiratory disorders: interstitial lung disease
- Metabolic and nutrition disorders: tumor lysis syndrome
- Immune system disorders: anaphylactic shock, angioedema, urticaria
- Skin and subcutaneous tissue disorders: Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis
- Infections: hepatitis B reactivation

DRUG INTERACTIONS

Effect of CYP3A Inhibitors on Ibrutinib: The coadministration of IMBRUVICA with a strong or moderate CYP3A inhibitor may increase ibrutinib plasma concentrations [see Clinical Pharmacology (12.3) in Full Prescribing Information]. Increased ibrutinib concentrations may increase the risk of drug-related toxicity.

- Avoid concomitant use of other strong CYP3A inhibitors. Interrupt IMBRUVICA if these inhibitors will be used short-term (such as anti-infectives for seven days or less) [see Dosage and Administration (2.4) in Full Prescribing Information].

Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain strong or moderate inhibitors of CYP3A.

Effect of CYP3A Inducers on Ibrutinib: The coadministration of IMBRUVICA with strong CYP3A inducers may decrease ibrutinib concentrations. Avoid coadministration with strong CYP3A inducers [see Clinical Pharmacology (12.3) in Full Prescribing Information].

USE IN SPECIFIC POPULATIONS

Pregnancy: Risk Summary: IMBRUVICA, a kinase inhibitor, can cause fetal harm based on findings from animal studies. There are no available data on IMBRUVICA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In animal reproduction studies, administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis at exposures up to 2-20 times the clinical doses of 420-560 mg daily produced embryofetal toxicity including structural abnormalities [see Animal Data]. If IMBRUVICA is used during pregnancy or if the patient becomes pregnant while taking IMBRUVICA, the patient should be apprised of the potential hazard to the fetus.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage is clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Animal Data: Ibrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 10, 40 and 80 mg/kg/day. Ibrutinib at a dose of 80 mg/kg/day was associated with visceral malformations (heart and major vessels) and increased resorptions and post-implantation loss. The dose of 80 mg/kg/day in rats is approximately 14 times the exposure (AUC) in

or greater.
patients with MCL or MZL and 20 times the exposure in patients with CLL/SLL or WM administered the dose of 560 mg daily and 420 mg daily, respectively. Ibrutinib at doses of 40 mg/kg/day or greater was associated with decreased fetal weights. The dose of 40 mg/kg/day in rats is approximately 4 times the exposure (AUC) in patients with MCL administered the dose of 560 mg daily. Ibrutinib was also administrated orally to pregnant rabbits during the period of organogenesis at doses of 5, 15, and 45 mg/kg/day. Ibrutinib at a dose of 15 mg/kg/day or greater was associated with skeletal variations (fused sternebrae) and ibrutinib at a dose of 45 mg/kg/day was associated with increased resorptions and post-implantation loss. The dose of 15 mg/kg/day in rabbits is approximately 2.0 times the exposure (AUC) in patients with MCL and 2.8 times the exposure in patients with CLL/SLL or WM administered the dose of 560 and 420 mg daily, respectively.

Lactation: Risk Summary: There is no information regarding the presence of ibrutinib or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. The development and health benefits of breastfeeding should be considered along with the mother’s clinical need for IMBRUVICA and any potential adverse effects on the breastfed child from IMBRUVICA or from the underlying maternal condition.

Females and Males of Reproductive Potential: Pregnancy Testing: Verify the pregnancy status of females of reproductive potential prior to initiating IMBRUVICA therapy.

Contraception
Females: Advise females of reproductive potential to avoid pregnancy while taking IMBRUVICA and for up to 1 month after ending treatment. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus. Males: Advise men to avoid fathering a child while receiving IMBRUVICA, and for 1 month following the last dose of IMBRUVICA.

Pediatric Use: The safety and effectiveness of IMBRUVICA in pediatric patients has not been established.

Geriatric Use: Of the 905 patients in clinical studies of IMBRUVICA, 62% were ≥ 65 years of age, while 21% were ≥75 years of age. No overall differences in effectiveness were observed between younger and older patients. Anemia (all grades) and Grade 3 or higher pneumonia occurred more frequently among older patients treated with IMBRUVICA.

Hepatic Impairment: Avoid use of IMBRUVICA in patients with severe hepatic impairment (Child-Pugh class C). The safety of IMBRUVICA has not been evaluated in patients with mild to severe hepatic impairment by Child-Pugh criteria. Dose modifications of IMBRUVICA are recommended in patients with mild or moderate hepatic impairment (Child-Pugh class A and B). Monitor patients for adverse reactions of IMBRUVICA closely [see Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in Full Prescribing Information].

Plasmapheresis: Management of hyperviscosity in WM patients may include plasmapheresis before and during treatment with IMBRUVICA. Modifications to IMBRUVICA dosing are not required.

PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Patient Information).

- Hemorrhage: Inform patients of the possibility of bleeding, and to report any signs or symptoms (severe headache, blood in stools or urine, prolonged or uncontrolled bleeding). Inform the patient that IMBRUVICA may need to be interrupted for medical or dental procedures [see Warnings and Precautions].
- Infections: Inform patients of the possibility of serious infection, and to report any signs or symptoms (fever, chills, weakness, confusion) suggestive of infection [see Warnings and Precautions].
- Cardiac Arrhythmia: Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, and chest discomfort [see Warnings and Precautions].
- Hypertension: Inform patients that high blood pressure has occurred in patients taking IMBRUVICA, which may require treatment with antihypertensive therapy [see Warnings and Precautions].
- Second primary malignancies: Inform patients that other malignancies have occurred in patients who have been treated with IMBRUVICA, including skin cancers and other carcinomas [see Warnings and Precautions].
- Tumor lysis syndrome: Inform patients of the potential risk of tumor lysis syndrome and to report any signs and symptoms associated with this event to their healthcare provider for evaluation [see Warnings and Precautions].
YOU&i™ Support Program

ELEVATING PATIENT SUPPORT

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Your eligible commercially insured patients pay $10 PER PRESCRIPTION* of IMBRUVICA®

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*Eligible patients may qualify for $10 per prescription of IMBRUVICA® until the maximum limit of $24,600 per calendar year is reached. The Instant Savings Program applies to commercial insurance co-pay, deductible, and coinsurance medication costs for IMBRUVICA®. This program cannot be used with any other federally-funded prescription insurance plan which includes Medicare Part D, Medicare Advantage Plan, Medicaid, TRICARE, or any other federal or state health care plan, including pharmaceutical assistance programs.

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The Disruptive Catalyst We’ve Long Awaited: Artificial Intelligence

While you’re reading this opening sentence, AI is quietly disrupting the practice of medicine as we know it.

In fact, AI (which we write about extensively in this issue’s cover story, pg. 20) is about to do what we hoped to see technology do in the last decade for the health industry: Empower organizations and clinicians to improve the health, outcomes, and experience of care for more people in less time and at lower cost. It’s happening now in fits and starts, but, eventually, as AI becomes invisibly woven into the fabric of our work and lives, the practice of medicine will become astonishingly more efficient, effective, and, ironically—more human.

And that’s good news for the U.S. health industry that’s known for its overachievement in inefficiency and consumer unfriendliness.

It’s also good news for clinicians that are legitimately skeptical of highfalutin promises of new technologies. They’re skeptical because their experiences with EHRs have left them feeling hindered more than helped by computers. Some studies have shown that up to half of their day is now spent facing a computer screen instead of patients.

Reasons for optimism

AI, (think of it as a mostly invisible machine with human-like abilities to perceive, read, speak, and learn, and analyze), is wildly different from any technology we’ve experienced before.

Why? First, because it is more like us. It can sense, converse, work, and act for us, on our behalf. In contrast, the EHR is more like a complex tool that requires special training and repetitive use to build the skills required to master the tool. The more you use it, of course, the more adept at it you become, and the more good things you can do with the tool. But the learning curve is long and painful. Thankfully, AI is almost the exact opposite. It requires almost no training to use because it can adapt to the way we think and work.

Second, AI delivers a big advantage over EHRs. It doesn’t just work on our behalf. It works on our behalf without getting in our way like the keyboards and displays that EHRs require. That’s because AI hardware is usually hidden in the cloud, out of sight. So, there’s no hardware to get between the patient and clinician

Lastly, unlike humans, AI works tirelessly, instantly, and can analyze thousands of data points at the same time. This means that AI can work on behalf of clinicians behind the scenes, vastly expanding their capacity to act. This frees them to do more important things, like care for patients, sleep, and improve their work-life balance.

To be sure, AI will never get a chance to earn its keep unless health organizations and clinicians choose to adopt it. Fortunately, health organizations will rapidly adopt it because, with operating cost growth overtaking revenue growth, it won’t be long before they won’t be able to afford to operate without it. And, unlike past technologies that took years to see any results, AI will prove its value almost instantly by finding its way into existing work flows. And don’t worry about clinicians adopting AI. When clinicians experience how it amplifies their productivity and expands their capacity to act, they’ll want more of it, not less.

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Board members share what other industries can teach healthcare, PAGE 32
ESSENTIALS
13 Payers Save Money by Doling Out Incentives
Approach steers patients to low-cost providers
15 Doctor Diversity Grows
More women, minorities flock to med school
16 Fewer Consumers Trust Health Organizations
How to turn the tide

17 Ten Wearables To Watch
Tech collaborations make devices more robust

24 Advance Your Career
Don’t miss your next opportunity

26 Fight Against Six Fatal Conditions
Treatment developments show promise

30 Next Up in the Quest to Cut the Fat
Two changes needed to tackle healthcare costs

COMMENTARY
10 The Disruptive Catalyst We’ve Long Awaited
by Dennis Schmuland, MD, FAAFP

DEPARTMENTS
11 Board Members
32 What Other Industries Can Teach Us
33 The Bottom Line

COVER STORY
Artificial Intelligence
Real Industry Benefits
Trailblazers reap clinical, administrative rewards
PAGE 20

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Health Management

BEST PRACTICES FOR OPTIMAL OUTCOMES

Payers Save Money by Doling Out Incentives

Approach steers patients to low-cost providers by KAREN APPOLD

Some health insurers are giving members cash rewards when they choose less-expensive providers or have procedures or tests performed at lower-priced facilities. Health Care Service Corporation, a health insurer in Chicago, is one of them. Its member rewards program is available through its "Provider Finder" tool and customer advocate resources, making it simple to compare costs for procedures and see which facility selections will lead to rewards, says Tom Meier, vice president of Market Solutions.

If members choose a more cost-effective, quality facility, they receive a check ranging from $25 to $500. The greater the savings, the greater the reward, says Meier. Priority Health, a health insurer based in Grand Rapids, Michigan, is another example. It has a "cost estimator" tool that informs members what their specific out-of-pocket costs will be based on their plan benefits, and it shows them how they can save money.

Savings generated for members depend on their plan, how much they have paid toward their deductible, and if they have a coinsurance amount, says Nathan Foco, senior director of Market & Sales Intelligence. If the member has a high-deductible plan and hasn't met the deductible, the savings applies to the member only. If the member has met the deductible, Priority Health and the member split the savings.

Members receive a Visa gift card with $50, $100, or $200 depending on the procedure and facility selected. Procedures such as total cataract surgery, shoulder and knee arthroscopy, and ear tubes fall within the $200 rewardable category; MRIs, heart echo imaging, and Doppler heart exams are in the $100 category; and computed tomography and bone density scans are in the $50 category.

Give a little, save a lot
Some insurers are also using incentives to meet volume commitments to specific healthcare providers, especially for certain higher-volume procedures, says Stuart Hanson, senior vice president and general manager, Consumer Payment Solutions, Change Healthcare, a healthcare technology company. They typically put these arrangements in place with high-quality providers for frequent procedures such as labs or diagnostic imaging.

Insurers could reap big rewards for helping patients make more cost-conscious decisions, he says. "An insurer may recognize reduced recovery time, improved overall results, fewer return visits to the emergency room, and so forth from a certain provider that could result in improved outcomes for the patient as well as reduced expenses for both the patient and insurer."

Foco, of Priority Health, believes that the more informed and engaged members are, the better their outcomes will be. "If we didn’t offer cash incentives, we wouldn’t get the level of engagement that we have," he says.

Use of Priority Health’s tool has reached 10% for group and individual members, including those with marketplace plans. Foco
believes the high engagement is because the tool provides customized information. “We continue to enhance the tool to meet members’ demands, and recently added prescription costs,” he says.

**Getting buy in**

It can be difficult to teach members to shop for services rather than simply going to the facility that their trusted physician recommends, says Suzannah Gill, JD, benefits strategy consultant, EPIC Insurance Brokers & Consultants, an employee benefits insurance brokerage and consulting firm.

“It goes against the general practice to question a physician’s recommendation, so people need to be trained and motivated to do so,” she says. “Cash-back incentives provide the carrot to encourage people to be smarter healthcare consumers.”

Of course, for these initiatives to be effective, patients and employees need to know that their health insurer offers incentives and then be able to determine which provider to select. In order to reap the savings, Health Care Service Corporation members can check with their employer’s human resources group to understand what programs and benefits are available. “We work directly with employers to develop engagement plans and use direct marketing to encourage members to shop for care,” Meier says. “We send monthly emails and postcards to members, and communications to members through their employers.”

Karen Appold is a medical writer in Lehigh Valley, Pennsylvania.

**Costly variations**

The cost for the same quality of medical care can vary drastically across healthcare facilities, particularly for services such as diagnostic imaging and surgical procedures like hip and knee replacements, says Meier. Foco agrees, noting that the price of a colonoscopy in Michigan can range from $1,200 to $4,500.
Doctor Diversity Grows

More women, minorities flock to med school

by JENNIFER NELSON

Medical school enrollment has traditionally been dominated by men—until now. The number of women enrolling surpassed men for the first time last year, according to the Association of American Medical Colleges (AAMC).

Women represented 50.7% of the 21,338 med school enrollees in 2017. Female matriculants increased by 3.2%, while male matriculants declined by 0.3%. The overall number of U.S. med school matriculants rose 1.5% with total enrollment at 89,904 students.

“It’s important because women have been underrepresented in medicine for a long time, and we really strive to have a workforce that reflects the general working population,” says Alison Whelan, MD, chief medical education officer at the AAMC. “Overall, a workplace that reflects a 50-50 balance is reasonable, so we should continue the effort to maintain this balance, and make sure it’s not just a one-time blip and then goes back down again.”

Trickle-down effect

Entering classes at the nation’s medical schools continue to diversify. From 2015 to 2017, African American matriculants increased by 12.6%, and Hispanic, Latino, and matriculants of Spanish origin rose by 15.4%.

It’s no surprise women followed suit. Pipeline programs that encourage young women and girls to enroll in medicine as well as other sciences, where they’ve been traditionally underrepresented, are paying off. These K-12 STEM (science, technology, engineering, and mathematics) programs encourage gender equality. Whelan says medical schools are working to foster more diversity as well.

As more women enter the field, more changes such as acceptance of alternate career paths in medicine, time out for family care, structured mentoring, and addressing the gender differences that impact the experiences of women in medicine are occurring.

“This is important because women in medicine have long played a major part in innovation, clinical care, and the education of trainees and students in the health sciences,” says Pamela B. Davis, MD, dean of the school of medicine and senior vice president for medical affairs at Case Western Reserve University.

The AAMC survey also uncovered that more students indicate having a work-life balance is essential to their paths after medical school. And nearly 30% say they plan to work in underserved areas.

As a culture, society has embraced both working women and working mothers over the past several decades, which may have given rise to these promising numbers. A few short decades back, women may have been more reticent to enter the medical field because of its arduous nature, long hours, and male-centric focus.

More changes coming

Experts think as more women populate medical specialties and higher rungs on the medical academia ladder, women physicians will continue to bring new perspective and address issues like balancing work and family life, paving the way for more women doctors.

“Women have historically been an underrepresented part of medicine,” says Linda Mehta, MD, associate dean for admissions at Case Western University. “While our numbers are increasing, our voices and recognition of our contributions have yet to be fully recognized. We have so much talent and perspective to add to the medical landscape, and this must be recognized, celebrated, and encouraged.”

Jennifer Nelson is a Florida-based freelance healthcare writer. This article originally appeared in our sister publication, Medical Economics.
Consumer Trust Falls
How to turn the tide

 TRACEY WALKER

U.S. trust in healthcare is dropping—a warning sign to executives across the industry. The 2018 Edelman Trust Barometer found that trust in healthcare declined nine points this year, making it the least trusted of the 15 sectors Edelman studies.

In addition, for the first time since 2015, every health subsector studied dropped in trust. Compared to the previous year:

- Pharma lost 13 points (score of 38 out of 100);
- Insurance lost nine points (score of 46);
- Biotech/life Sciences and consumer health each lost seven points (scores of 55 and 56; respectively) and
- Hospitals dropped one point (score of 70).

WHY IT’S FALLING
“One hypothesis we have is that the ongoing blame game over the high cost of healthcare had an overall negative impact on all industries,” says Susan Isenberg, Edelman’s global health chair. “Edelman data shows no health subsector is coming out ahead in this argument. We believe that instead it has served to amplify that healthcare costs are rising with no solution yet in sight.”

Hospitals/clinics on the frontlines of delivering care have consistently been the most trusted subsector in healthcare, according to previous Edelman studies. “This is the first year we have ever seen a decline in trust in this subsector in the U.S.,” Isenberg says. “While a trust score of 70 in the U.S. is still largely positive, any decline in trust must be addressed in today’s polarized environment.”

Edelman hypothesizes that hospitals tend to maintain a higher level of trust because providers have a direct relationship with patients, according to Isenberg. “However, this year we believe that has not spared hospitals from the cost debate.”

Tracey Walker is content manager for Managed Healthcare Executive.

Most distrusted sector Pharma is the most blamed among the list of players in the industry for high healthcare costs. Both global and U.S. data from the Trust Barometer found most respondents agreed that pharmaceutical companies put profit ahead of patients.

Addressing the problem
To improve trust, the health industry must show how it is part of the solution to high costs, Isenberg says. Here are her suggestions:

Every healthcare company needs to be a “publisher.”
There is ample room to share messaging through a company’s own channels, particularly as the report found that trust in the media declined in 2018, yet consumers trust content provided by health companies. “This is a clear opportunity for health companies to leverage their own media channels and share their stories through interactive, creative content,” says Isenberg.

Use a chorus to tell the story.
“The industry can move toward trust by activating both their experts—a spokesperson group that is once again viewed as credible—and their employees, who can speak to company news in authentic and local voices,” Isenberg says.

Sell more than the product.
“Patients are looking to health companies to build and create solutions beyond the pill,” Isenberg says. “Our data also show the general population has generally positive sentiment toward the future of health technology. While developing new treatments is expected of the health industry, providing holistic solutions will further build trust.”

Humanize your approach.
For example, Isenberg says, humanize what happens in the laboratory by showcasing the real scientists behind a breakthrough, or create a campaign where patients are heard and can contribute rather than just feeling they are simply the target of promotions.
Ten Wearables to Watch

Tech collaborations make devices more robust  by DONNA MARBURY

The healthcare wearables market experienced a boost in 2017, with more than 10% market growth between 2017 and 2018. As more apps come to market, users are looking for more sophisticated devices, says Ramon T. Llamas, research director for wearables at the International Data Corporation (IDC), a market intelligence firm.

Vendors, including start-ups, have created devices with features and services that make wearables more advanced, says Llamas. “Going forward, the next generation of wearables will make the ones we saw as recently as 2016 look quaint.”

Smartwatches continue to be the most popular kind of wearable device, taking up about 33% of the market this year, according to IDC. In total, IDC estimates that 132.9 million wearables will be shipped this year.

Many tech companies are thriving by integrating their devices with other organizations that already have a footprint in the healthcare industry. For example, Fitbit announced a collaboration with Google in April 2018, giving Fitbit the ability to connect its fitness data with EHRs secured by Google. In March 2018, Apple announced a partnership with 40 health systems that will allow patients to access their medical records via their iPhones, integrating Apple Health data from fitness and wellness apps.

Wearables are having an immediate impact on patient care because of their quick adoption, says Ilan Reingold, vice president of business development and marketing at Altair Semiconductor. Altair has collaborated with Ericsson and Sony Mobile to create a continuous glucose monitor (CGM) that utilizes cloud technology not dependent on mobile connectivity.

Reingold says that low power, more affordable technology that easily integrates with existing health technology will allow for wearables to be more accessible and meaningful to users. “The core connectivity technologies powering health wearables are integral for providing low-power, highly integrated solutions that enable users to benefit from longer battery life,” Reingold says. “Health monitors will continue to become easier to use and remain connected anytime, anywhere.”

Here are 10 wearables to watch

**E-vone smartshoe**
The E-vone smartshoe is for seniors and others susceptible to falls. It notifies family and caregivers in case of abnormal movements or inaction. The shoe is equipped with a GPS monitor, motion sensors, and a vibration point. If the shoe perceives an abnormal movement such as a fall, caregivers (predetermined in advance by users) are alerted. So far, the shoe can be monitored in more than 120 countries. The company says the shoe will be available to purchase in the U.S. in the first quarter of 2019.
Technology

**Byteflies Sensor Dot**
This device measures a user’s vital signs. It can be used on different areas of the body depending on the use. Current uses include heart information (electrocardiogram and blood flow), respiration, motion, electrodermal activity, and muscle activity (electromyogram). The device can transfer the user’s data to cloud-based applications via a docking station but can also store data on the device. Byteflies provides raw data to healthcare organizations that utilize the devices for their patients, and provides data analytics and machine learning to derive clinical insights.

**Motiv fitness ring**
This waterproof ring measures activity, sleep, and heart rate. In April 2018, Motiv announced the ring is integrated with Amazon Alexa, and users can ask Alexa about their heart rate. Further developments will allow questions about sleep and other high-level metrics. Motiv, which launched integrating with Apple platforms, announced a move to launch its system in Android in 2018. Consumers can receive a ring-size kit to ensure a correct fit before ordering the ring. Motiv also plans to roll out its rings in retail locations this year.

**Aira**
Using smartglasses and a mobile app, Aira connects users to agents who can help low vision or blind people navigate the world. The glasses are video equipped with artificial intelligence and augmented reality technology that allows users to access a voice-enabled assistant named Chloe, similar to Alexa or Siri, for real-time assistance. Users also have the option to press a button on the side of the device to access a live agent who can view their environment through the lenses and offer assistance or answer questions. The glasses come with a subscription-based plan, priority WiFi service in public places, and insurance for the hardware.

**Oska Pulse**
Oska Pulse, a palm-sized patch, is used to alleviate chronic pain and reduce the need for opioid use. The device can work on multiple parts of the body, such as knees, the back, and other muscles and joints, for chronic pain relief. It uses pulsed electromagnetic fields (PEMF) to dilate blood vessels and help reduce inflammation and pain. Aside from slight warming due to increased blood flow, Oska developers say users don’t feel much from the patch during 30-minute therapy sessions. A mobile app, called Oska Pulse Active, works remotely with the wearable and features a pain tracker that allows users to track pain management on the app and through a web portal. Oska Pulse is FDA registered as a wearable device that delivers PEMF at a safe rate for home use and is on the market.

**Kardia Mobile**
Using a mobile app and a fingerpad that’s smaller than a credit card, this device provides medical-grade single-lead EKG result in 30 seconds. Users can use a fingerpad to receive instant analysis for detecting atrial fibrillation and normal sinus rhythm. The FDA-cleared device gives users four results: normal, possible atrial fibrillation, unreadable due to too much interference during the recording, or unclassified (when the reading doesn’t easily fit into any of the other categories; if this occurs, users can send the analysis directly to the Kardia app or share it with a medical professional). The fingerpad and mobile device is currently available and offers a subscription service that stores unlimited EKG recordings and a monthly report. Kardia is also developing a medical-grade EKG band for the Apple Watch.
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UV Sense
Cosmetic company L’Oreal has partnered with the La Roche-Posay skin care brand to develop wearable technology to help users track ultraviolet exposure and decrease overexposure to sun rays that can lead to skin damage. The UV Sense can fit on a thumbnail without the use of additional adhesives and works with a mobile app to track up to three months of data on UVA and UVB exposure. Data is transferred from the patch to the user’s mobile app, which compiles the data in a profile to help users change habits that could lead to sun damage. The UV Sense will be available in small quantities in summer 2018, with wide release in 2019, according to the company. A slightly larger version using the same technology, called My UV Patch, is currently on the market.

My BP Lab
After a pivot to focus on healthcare technology, Samsung is engaged in several healthcare wearable product integrations using virtual reality and mobile connectivity. My BP Lab mobile app utilizes the optical sensor embedded in the Samsung Galaxy S9 and S9+ phones. The app allows for real-time monitoring of the demand placed on the user’s heart and is monitored through a University of California, San Diego program. To take part in the program, users must be 18 years old, fit certain health criteria, and opt in. Blood pressure is measured directly through the device without the use of external hardware. Samsung aims to give users more accurate feedback on how daily habits can affect blood pressure and stress levels. Through the app, the partners also hope to use the data of thousands of real-world participants to better understand blood pressure readings.

At the HIMSS conference in March 2018, Samsung announced plans to make the Samsung Health service more robust. This includes more options on the Gear S3 Smartwatch and the GearVR virtual reality headset, including a program to help people with type 2 diabetes that is currently available. The all-inclusive Samsung Health platform tracks fitness and wellness measures including weight management, caloric intake, and sleep, and integrates with more than 140 health and wellness apps.

iTBra
Aimed at helping women with dense breast tissue detect cancer earlier, the device consists of two, wearable breast patches that monitor circadian temperature changes within the breast tissue. The devices communicate with Cyrcadia Health’s core lab for analysis. Cyrcadia Health states that wearing the patches for two to 12 hours a day can be as effective as a highly-accurate monthly breast exam. The device has received premarket clearance from the FDA and is currently working toward full clearance for marketing purposes by 2019.

Ericsson, Sony Mobile, and Altair Continuous Glucose Monitor (CGM) wristband
The result of a collaboration between technology and healthcare companies, this CGM will alert users to potential problems with blood sugar. The wristband will display glucose levels, activity, sleep information, and heart rate. Using Sony cloud technology and a smartphone app, users will be alerted if glucose levels drop. Altair’s technology, called LTE-M, allows the device to communicate through the Sony cloud without a mobile phone for connectivity. The LTE technology allows for affordable, low-powered use of end-to-end connectivity that could help expand the electronic health and wearables market, according to the wristband’s creators. The device was prototyped at the Mobile World Congress in February 2018, with plans to hit the market in 2019.

Donna Marbury is a writer in Columbus, Ohio.
Artificial intelligence (AI) in healthcare is no longer a futuristic idea. Organizations are benefiting—on administrative and clinical levels—from practical adoptions that make cost savings and better patient care a reality. But industry experts say there’s still a lot of untapped potential to look forward to, which will only be realized when trust in AI is more firmly established and when healthcare organizations become more skilled at integrating it into their daily work flows.

“In other industries where the stakes are lower, the trust is higher,” says Dan Housman, chief technology officer of ConvergeHEALTH by Deloitte and managing director of Deloitte Consulting LLP. “AI deals with ambiguity, but in medicine the rules are

WHAT IS AI?

AI encompasses a broad range of technologies that can:

- Perceive images and sounds and understand them;
- Learn from these inputs and interactions and get better over time; and
- Reason over large amounts of data to identify patterns.

“While there is strong interest in the topic of AI, many business leaders and teams are trying to determine how to think about AI relative to their industry and/or company,” Doyle says. Schmuland says the concepts and abilities of AI are still widely misunderstood. “AI isn’t something you can see or touch, and you may not even realize you are using it,” he says. “In fact, most of us are probably relying on technology that uses AI every day, without even knowing it. If you used Microsoft’s Bing search engine or built a PowerPoint presentation, you may well have used AI. If you dictated a text into your phone, you were probably relying on AI.”

WHAT IS HEALTHCARE AI?

There are three categories of healthcare AI, says Housman:

- Automation
  Processing clinical and administrative documentation.

- Engagement
  Handling patient issues and responding to behaviors.

- Insight
  Finding patterns in data that are hard to see with traditional analytics.
clear cut. There needs to be work on both sides (with technology companies and healthcare organizations) to make sure AI tools are easier to understand and the healthcare community is more comfortable with a fully untraceable answer. For example, while consumers embrace AI voice-enabled technology devices like Siri and Alexa, Housman says they, and providers, may not be as accepting of an AI-assisted speaker at the patient’s bedside because the consequences of error are greater.

Here are some of the most noteworthy ways AI is being used in healthcare, and how organizations could use it in the future.

**CURRENT USES**

Many organizations are partnering with tech companies to tackle clinical issues with AI. In March 2018, the Mayo Clinic and IBM Watson announced that using IBM’s clinical trial matching AI platform, Mayo Clinic increased enrollment for breast cancer clinical trials by 80%, and reduced screening time for patients looking for clinical trial matches. This is an important development, as only 5% of cancer patients participate in clinical trials, and low attendance leads to many trials being incomplete or cancelled, according to Mayo Clinic.

“Novel solutions are necessary to address this unmet clinical need, advance cancer research and treatments, and, in turn, improve the health outcomes of patients,” says Tufia Haddad, MD, a Mayo Clinic oncologist and physician leader for the Watson for Clinical Trial Matching project.

Mayo Clinic is also using AI and machine learning to make stroke diagnoses quicker and more efficient (use of AI to read CT scans decreases the time needed by at least 30 minutes, according to Mayo Clinic). With physicians estimating that 1.9 neurons die each minute during a stroke, the more precise scans can lead to life-saving interventions.

Another example is Microsoft’s partnership with Ochsner Health System in Louisiana to use AI to create predictive models that foresee patient deterioration. Using Microsoft’s cloud service, Azure, the models communicate directly with Ochsner’s rapid response team through its Epic EHR, allowing clinicians to make early interventions. Within a 90-day trial period, the technology was able to reduce codes, or emergency cardiac events, by 44%.

“By working side-by-side with the healthcare industry’s most pioneering players, we are bringing Microsoft’s capabilities in groundbreaking research and product development to help healthcare providers, biotech companies, and organizations around the world use AI and the cloud to innovate,” says John Doyle, director of Worldwide Health for Microsoft Corporation.

On the administrative side, the technology company CrossChx is using its AI-assisted automation tool called Olive in a partnership with Meadows Health in Georgia. Olive is called a
“digital employee” and automates order management, eligibility, prior authorizations, and claims processing tasks for the health system. By logging into EHRs and other existing technology, Olive can learn through previous human processes and optimize them to make them more efficient. Working with Olive, Meadows Health created an automation support operations center, and has identified more than 35 processes that can be automated within the organization.

Because of the increase in automation, CrossChx reports that Meadows Health has been able to train staff to focus on more direct patient interaction, especially in their understaffed call center. CrossChx also works with Hancock Regional Hospital in Indiana to optimize the eligibility process, and reports that the hospital has cut the patient billing cycle from 30 days to three days.

Sean Lane, CEO of CrossChx, says that innovative AI solutions can also work “out of the box” for healthcare organizations. “These AI solutions need to get to work right away,” Lane says. “In the beginning of implementing AI, it’s important to address the administrative tasks, though the clinical AI tools have all of the sex appeal.”

CRITICAL CONSIDERATIONS
Though partnerships with AI companies are becoming more prevalent and the availability of AI tools is growing, healthcare executives still need to be cautious about jumping all in. “It’s essential that everyone is aligned in the C-suite,” Lane says. “Remember that healthcare organizations are not tech companies. AI solutions that require a lot of AI engineering take healthcare organizations away from their first obligations.”

Managed Healthcare Executive Editorial Advisor Dennis Schmuland, MD, FAAFP, chief health strategy officer of U.S. health and life Sciences for Microsoft Corporation, says healthcare executives must consider how AI tools will change hiring decisions, finance, safety, and security, and how their organization might grow in the next few years based on future needs. “These rapid technology changes also raise complex questions about the impact they will have on other aspects of society: jobs, privacy, safety, inclusiveness, and fairness.”

DENNIS SCHMULAND, MD, MICROSOFT CORPORATION

FIVE MUST-HAVES
Schmuland says the following should serve as foundation of the development and deployment of AI-powered solutions:

FAIRNESS
“When AI systems make decisions about medical treatment or employment, for example, they should make the same recommendations for everyone with similar symptoms or qualifications. To ensure fairness, we must understand how bias can affect AI systems.”

SUFFICIENCY
“AI systems must be designed to operate within clear parameters and undergo rigorous testing to ensure that they respond safely to unanticipated situations and do not evolve in ways that are inconsistent with original expectations.”

TRANSPARENCY
“As AI increasingly impacts people’s lives, we must provide contextual information about how AI systems operate so that people understand how decisions are made and can more easily identify potential bias, errors, and unintended outcomes.”

PRIVACY AND SECURITY
Like other cloud technologies, AI systems must comply with complex privacy laws of healthcare that regulate data collection, use, and storage, and ensure that personal information is used in accordance with privacy standards and protected from theft.

ACCESS
AI solutions must address a broad range of human needs and experiences through inclusive design practices that anticipate potential barriers in products or environments that can unintentionally exclude people.

“These rapid technology changes also raise complex questions about the impact they will have on other aspects of society: jobs, privacy, safety, inclusiveness, and fairness.”

DENNIS SCHMULAND, MD, MICROSOFT CORPORATION

Artificial Intelligence
vacy, safety, inclusiveness, and fairness,” he says. “When AI augments human decision making, how can we ensure that it treats everyone fairly, and is safe and reliable? How do we respect privacy? How can we ensure people remain accountable for systems that are becoming more intelligent and powerful?”

While Microsoft’s focus has been working on building AI platforms and services and infusing AI into existing technology and creating AI business solutions, Doyle says it is important to keep AI adoption in step with the availability of people who can administer these tools.

Schmuland agrees. “Today it’s still difficult for organizations to find and hire people who are versed in the science of AI,” he says. “Previous AI systems were primarily sophisticated rules-based engines, but with the growth and success of deep neural networks [a set of algorithms made to mimic the human brain and recognize patterns], and the ability to rapidly test and deploy AI algorithms, the baseline background for AI practitioners has changed. As a result, the state of the art for AI is quickly advancing, making it harder to find people who can be subject matter experts across the growing set of AI capabilities.”

One problem healthcare organizations tend to face when implementing AI is a lack of data governance, says Housman. “AI is highly dependent on available, nicely-packed data, and the state of data in healthcare is still very poor,” he says, referring to clinical and financial data. “If the data is not ready yet, there needs to be an investment in making sure there is tagged data and data governance.”

However, Lane says healthcare organizations don’t always have to have a ton of data to see an impact in AI. “One of the biggest myths in AI adoption is that a prerequisite is that you need to have a data lake or warehouse and be prepared for intense integrations,” Lane says. “The right solutions shouldn’t require a ton of prepopulated data, they should just come in and work.”

Lane cautions against getting caught up in “brain in a jar” AI solutions that are attractive, but don’t add any real value. “A lot of AI solutions make a lot of work for humans, and the output is a report or a heat map that doesn’t affect work flow,” he says. “AI solutions shouldn’t be ‘human heavy.’”

Lane says Olive’s ability to operate without previous data organization, such as a data warehouse or data lake, makes it accessible to smaller health systems. “There’s a misconception that the only groups that will have access to AI are the large health systems. But mid-sized organizations can implement AI today,” Lane says. “My argument is that AI has more impact to the smaller organizations than the ones at the top.”

FUTURE CAPABILITIES

The healthcare AI market will reach $6.6 billion by 2021—up from $600 million in 2014, according to Accenture. Though many experts agree that the increase in AI will affect clinical and administrative processes, they don’t expect a massive decrease in healthcare jobs. “Every single healthcare system has 150 important things to do, but the capacity to do 75 of those things. One of our goals is to take the robot out of humans. That can lead to a significant change in how healthcare is delivered,” Lane says. “AI will give humans the freedom to innovate, think, and increase quality of care delivery.”

Housman says, in the near future, AI will give healthcare organizations the ability to look at specific diseases and know which prescription drugs and treatments will help patients the fastest.

“Using AI and machine learning, we will be able to build models of a patient journey. We can’t infer things easily from data without AI,” he says. “We will be able to bring data sets together in a way never seen before.”

There’s still a lag between how healthcare is using AI compared to other industries. As noted earlier, that could change as patients and providers become more comfortable with the technology. “Ultimately, for AI to be trustworthy, we believe that it must be human-centered—designed in a way that augments human ingenuity and capabilities,” says Doyle. “Its development and deployment must be guided by ethical principles that are deeply rooted in timeless values.”

Donna Marbury is a writer in Columbus, Ohio.

“...impact to the smaller organizations than the ones at the top.”

SEAN LANE, CROSSCHX

AI in breast cancer clinical trials

Mayo Clinic, using IBM’s clinical trial matching AI platform, increased enrollment for breast cancer clinical trials by 80% and reduced screening time for patients looking for clinical trial matches.
Leadership Skills
HELP YOUR ORGANIZATION SUCCEED

Advance Your Career
Don’t miss your next opportunity by AINE CRYTS

Thirty-seven percent of healthcare executives are considering a career change within a year and 9% are considering an immediate career change, according to a 2018 career report from healthcare executive search firm B.E. Smith. Even if you’re not ready to make a transition right now, it’s always important to keep your resume polished and your networking skills on point. The industry is changing rapidly, and new opportunities may arise unexpectedly. Here’s advice from experts.

Connect in person
Twenty-eight percent of LinkedIn users have between zero and 300 connections, according to a 2016 report from Statista. Twenty-seven percent have between 500 and 999 connections. And 1% have more than 10,000 connections. Consider your own page. How many of your connections have you actually interacted with one-on-one?

Christina Maley Higley, owner and CEO of Rochester, New York’s MedSense Recruiting, says sending a LinkedIn connection request to a useful new contact, such as a chief operating officer at a nearby hospital, is a smart tactic. But that’s only half the battle. After the person accepts your request, follow up with a personal note.

Be bold, Maley Higley says. “Ask him if he’d like to meet for coffee and chat further about his position. Tell him you’d like to learn more about what he does.”

A lot of people are willing to meet for 15 minutes in person, so it’s worth a try, says Maley Higley. Once you are chatting, set the right tone by saying something like, “Hey John, I’ve really taken an interest in what you do at your organization. I’m thinking about my next career steps and bettering myself. How did you get to this point in your career?”

Look laterally
Cody Burch, executive vice president at B.E. Smith, notes the large transformation occurring in healthcare. Take, for example, CVS Health’s move to acquire Aetna, Geisinger’s shift to serve as provider and payer, and UnitedHealthcare’s OptumCare’s 2017 acquisition of Surgical Care Associates.

He recommends healthcare executives embrace this transformation and consider it when planning their career trajectory. For example, a lateral role at a payer organization could be a good career move if you have years of experience on the provider side.

“Don’t see your next step as a ladder,” he says. “You need to think of opportunities as a lattice. Even if one role feels like a lateral move, you can learn and grow and be better prepared.”

Healthcare executives also need to “demonstrate the ability to change,” says Burch. “With consolidation and all the things that are associated with that, healthcare organizations need executives who can be flexible and adaptable to those changes.”

Don’t rope yourself in
Given the blending between payers and providers, build your skill sets in both areas. For example, a provider executive working in hospital operations could get involved in

“Don’t see your next step as a ladder . . . You need to think of opportunities as a lattice.”
CODY BURCH, B.E. SMITH

Build your personal brand

Healthcare executives should post regularly to their professional social media channels and be mindful that the content is timely, relevant, and informative—because that’s how you’ll build your following and your personal brand, says Fahey-Kaiser. Suitable updates to post to LinkedIn include executive board involvement or recent presentations at industry events, she says.

Burch advises using LinkedIn’s built-in features to ensure you have a robust profile. When you view your profile, the site will inform you if you’re at the beginner, intermediate, or “all-star” level. All-star profiles are 27 times more likely to be found in recruiter searches, according to the website.

Additional advice from Burch:

- **Use appropriate keywords.** This is the best way to demonstrate all of your capabilities. So, if you have a Six Sigma Certification, for example, note it. A hiring manager or recruiter might search under that term and find you.
- **Focus on your results.** Instead of just updating your profile to include job titles and responsibilities, list the results or achievements you’ve had in these roles.

### Percentage of healthcare executives considering a job change:

- Immediate: 8.6%
- 6 months: 11.8%
- 1 year: 16.5%
- 3 years: 23.3%
- No change: 39.9%

### Percentage of healthcare executives approached about a job opportunity in the past year:

- Yes, considered and pursued: 18.8%
- Yes, but did not pursue: 57.7%
- No: 24.2%


#### Keep your eyes open

Kasey Fahey-Kaiser, director of the payer-healthcare IT practice at Solon, Ohio-based Direct Recruiters, says new “opportunities can come in disguise or at inopportune times.” Don’t be so heads down that you miss out on what’s going on around you, she says.

While you don’t have any control over an unforeseen retirement or move at your organization, the best way to position yourself for success is to excel in your current role and exceed expectations, says Fahey-Kaiser.

“Down the road, those former colleagues, clients, and managers will be the meaningful references and relationships leveraged to help [you] achieve [your] dreams,” she says. To ensure you’re ready for an unexpected opportunity, she suggests continually tracking your quantifiable accomplishments and keeping an updated resume.

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**Aline Cryts** is a writer based in Boston.

**What to do today**

Pitching yourself for advancement isn’t easy. A good way to start is by “working above your day job,” and asking to be assigned to cross-organizational teams that are solving your organization’s toughest problems, says Burch.

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Managed Healthcare Executive.com
Fight Against Six Fatal Conditions

Treatment developments show promise

BY KAREN APPOLD

Prostate, colorectal, and lung cancer remain among the most common diseases in men while breast cancer, maternal mortality, and Alzheimer’s disease often affect women. Researchers and scientists continue to develop and test new treatments for these fatal conditions.

MEN

PROSTATE CANCER

Safer radiation therapy

Radiation therapy is a common and highly effective treatment for prostate cancer. However, it can unintentionally injure surrounding healthy tissues resulting in bowel, urinary, and sexual function disorders.

SpaceOAR Hydrogel is a new treatment that acts as a spacer between the rectum and prostate. This reduces the chances that the rectum is exposed to harmful radiation, explains Steven E. Finkelstein, MD, director, Advanced Urology Institute/Bay Regional Cancer Center, Panama City, Florida.

Before starting radiation treatment, the physician injects the hydrogel between the prostate and rectum. The material quickly solidifies into a soft gel that expands in the space, creating a barrier.

Each year more than 160,000 men in the United States are diagnosed with prostate cancer, and one in nine will be diagnosed in their lifetime.

- The American Cancer Society
The hydrogel remains in this space until radiation therapy is completed and then the body eliminates it. SpaceOAR is the first and only prostate cancer spacing device to receive FDA clearance, in April 2015. Clinical data has highlighted the long-term bowel and sexual quality of life benefits, and results from three and five-year post treatment studies support the use of SpaceOAR during radiotherapy.

**Radiopharmaceutical treatment**

Michigan Institute of Urology in Detroit, Michigan, offers a radiopharmaceutical treatment called Xofigo, which can help extend life by more than 30% in men whose prostate cancer no longer responds to medical or surgical treatment and has spread to the bone. “Xofigo gives off a strong energy that is deadly to cancer cells in the bones, but does limited damage to nearby healthy cells,” says Kenneth Kernen, MD, partner, urologist, and director of research. As a radiopharmaceutical, when it is injected into the vein it is radioactive. It goes to areas in the bone where prostate cancer has spread and attacks those cells, Kernen says.

**COLORECTAL CANCER**

**Immunotherapy**

In the past few years, Eyal Meiri, MD, interim chief of medical oncology, medical oncologist, Cancer Treatment Centers of America in Atlanta, reports more use of immunotherapy in individuals with colorectal cancer. The treatment uses the body’s immune system to identify and attack cancer cells. One type of immunotherapy involves using innovative medications called checkpoint inhibitors. Checkpoint inhibitors release immune T-cells to recognize and attack cancer cells, Meiri says.

In 2017, the FDA approved two checkpoint inhibitors, pembrolizumab and nivolumab for eligible patients. More than 80% of patients benefited from the therapy in one trial of patients with MSI-H colorectal cancer, says Meiri. “These treatments hold promise due to their low toxicity and long-lasting benefits,” Meiri says. The lack of nausea, hair loss, fatigue, and many other side effects of chemotherapy make this treatment option attractive.

Colorectal cancer is the third most common cancer in the United States. The lifetime risk of developing colon cancer in a U.S. male is one in 22, or 4.5%. There are approximately 140,000 new cases per year. The overall incidence of colorectal cancer is approximately 30% higher in men than women. - The American Cancer Society.

**TransAnal minimally invasive surgery (TAMIS)**

This newer approach to remove rectal tumors and polyps is a safe, effective option for select patients with early stage rectal cancers and precancerous growths, according to a recently released study. TAMIS, developed in 2009 by Sam Atallah, MD, director, colorectal surgery, Oviedo Medical Center in Oviedo, Florida, and two other surgeons, allows surgeons to perform surgery through a natural orifice without any scars and with minimal or no pain afterward.

TAMIS uses laparoscopic equipment, high-definition cameras, and a specialized insufflation system. The recent study published monitored 200 cases over a six-year period and found that the procedure helped patients maintain organ preservation.

**LUNG CANCER**

**Immunotherapy**

In patients with inoperable stage 3 lung cancer that has spread to the lymph nodes in the center of the chest, immunotherapy after chemotherapy and radiation has delayed recurrence of cancer in many patients by over 10 months, says Jorge E. Gomez, MD, director of thoracic oncology, Mount Sinai Hospital, New York, and member of the American Lung Association’s Lung Cancer Expert Medical Advisory Panel.

Immunotherapy has been able to improve the “progression-free survival rate,” the length of time between treatments where the cancer doesn’t grow, he says. One clinical trial showed that the progression free survival was 16.8 months compared to 5.6 months with a placebo.

Lung cancer is the second most common cancer in men and women. Approximately 121,000 men will be diagnosed with lung cancer in 2018. It is also the most common cause of cancer death. - The American Cancer Society, the National Cancer Institute.
**PD-1 inhibitors**

Norman Edelman, MD, senior scientific advisor to the American Lung Association and professor of preventive medicine, internal medicine, physiology, and biophysics at Stony Brook University in Stony Brook, New York, has seen success reported in the scientific literature in using PD-1 inhibitors to reactivate the immune system to seek and destroy cancerous cells. These drugs work in the most common form of lung cancer and have been shown to increase survival rates within one year.

**WOMEN BREAST CANCER**

**Partial breast irradiation treatment**

One standard treatment for early stage breast cancer after removing the breast tumor (lumpectomy) is whole breast radiation. Asal Rahimi, MD, MS, assistant professor and director of clinical research, University of Texas Southwestern, Dallas, Texas, and her medical group, are among the pioneers of a new partial breast irradiation technique called stereotactic partial breast irradiation. It entails treating a focused portion of the breast where the tumor was removed. During lumpectomy surgery, the breast surgeon places small markers in the breast to indicate where treatment should be delivered.

The group developed and conducted a clinical trial to deliver partial breast irradiation non-invasively for five days. "By increasing the radiation dose and pinpointing it, we are able to reduce the number of radiation sessions to the area where the tumor was removed," says Rahimi.

Early results of the study demonstrated outstanding tumor control, while giving women more flexibility in their daily routines during treatment for early stage breast cancer, she says.

**Proton therapy**

Henry K. Tsai, MD, radiation oncologist, ProCure Proton Therapy Center, Somerset, New Jersey, treats patients with proton therapy—an advanced form of radiation treatment that reduces radiation exposure to normal, healthy organs. "This is especially important if a woman is diagnosed with left-sided breast cancer, as the cancer is very close to critical organs such as the heart and lungs," he says. A recent study showed that patients with left-sided breast cancer may be more likely than patients with right-sided breast cancer to develop cardiovascular diseases after receiving radiation treatment.

Proton therapy and X-ray radiation therapy both treat breast cancer by killing cancer cells when they attempt to divide and multiply. However, unlike X-ray radiation which releases radiation as it passes through the body beyond the tumor and exposes more tissue to unwanted radiation, proton therapy delivers most of the radiation exactly at the tumor site and then stops, Tsai says.

**MATERNAL MORTALITY**

**Perinatal software**

One contributing factor to maternal mortality stems from the fact that clinicians integrate a myriad of information points as they continuously revise their assessments during childbirth. "Medical judgment is prone to lapses and biases, especially when coupled with fatigue or distractions," says Steven L. Clark, MD, professor of obstetrics and gynecology, Maternal Fetal Medicine, and program director for the Maternal Fetal Medicine Fellowship at Baylor College of Medicine, Houston.

A perinatal software solution (PeriGen), used at Baylor College of Medicine, incorporates artificial intelligence to enhance

**Approximately 268,670 women will be diagnosed with breast cancer in 2018, and 40,920 women will die of the disease this year. The average risk for a woman in the United States to develop breast cancer in her lifetime is about 12%. This means a one in eight chance of developing breast cancer.**

*The American Cancer Society*

**Each year, more than 700 U.S. women die from complications related to pregnancy. About 60% of deaths are potentially preventable. Another 50,000 women experience life-threatening complications.**

*CDC*
early recognition of worsening conditions and standardization of care during childbirth. “This solution provides a single, time-aligned color-coded view of critical data over many hours showing how the mother and baby are tolerating labor with respect to expected norms,” says Clark. It provides a consistent unbiased analysis of key developments that are usually scattered throughout the medical record. “When early warning signs have been identified, specific treatment can be tailored,” Clark says. According to research by MedStar, a health system, when using PeriGen’s decision support software solutions over a 10-year period, there was a 54% reduction in the use of cardiopulmonary resuscitation, assisted ventilation, or intubation; a 52% decline in unanticipated neonatal intensive care unit transfers; and stabilized Cesarean rates.

### Bundled care
Ronald E. Iverson, Jr., MD, MPH, vice chair, Obstetrics, Department of OB-GYN, Boston Medical Center, says the center has incorporated obstetric bundled care into its approach to four of the most common causes of maternal death: hemorrhage, hypertension, venous thromboembolism, and opiate use disorder. “Through our collaborative process, we have become completely prepared to prevent, diagnose, and treat patients for the common causes of maternal death and severe illness,” he says. “By working as a team with all of the services involved in maternal care, we have uncovered gaps in our service that we have addressed and improved together.”

### Alzheimer’s Disease

#### Antibodies that break down amyloid
Sharon A. Brangman, MD, is director of Upstate Center of Excellence for Alzheimer’s Disease at SUNY Upstate Medical University, Syracuse, New York. In July 2018, Brangman’s center, along with other sites across the country, began enrolling patients into a clinical trial to evaluate the use of Roche’s drug gantenerumab as a potential treatment for early to mild Alzheimer’s disease.

Gantenerumab is an antibody that helps break down amyloid in the brain, Brangman says. Amyloid is an abnormal protein that builds up in the brain of some people with Alzheimer’s disease, causing brain damage.

Early studies show that the drug is effective, she says. “One of the purposes of this clinical trial is to determine if removing amyloid from the brain slows down or improves the loss of brain function that is seen in people with Alzheimer’s disease.”

#### Evaluating functional brain health
Alzheimer’s disease has recently been referred to as “type 3 diabetes” in research. This is because in brains of individuals with Alzheimer’s disease, a deficiency in insulin, insulin growth factors, and insulin receptors, has been shown.

Evidence also shows that a high fat, low carbohydrate diet can help prevent and improve symptoms as can aerobic and cognitive exercises, says David Traster, DC, functional neurologist, South Florida Integrative Health in Miami. Furthermore, Neurofeedback therapy has also been shown to improve function in Alzheimer’s disease patients, he says. Natural anti-inflammatory supplements such as fish oil, curcumin, and resveratrol may help prevent and improve Alzheimer’s disease, research shows.

Traster’s medical center specializes in evaluating brain. Clinicians customize a treatment plan for each patient, which may consist of nutritional advice, a physical exercise plan, a cognitive exercise program, neurofeedback therapy, and natural anti-inflammatory products.
Next Up in the Quest to Cut the Fat

Two changes needed to tackle healthcare costs

by RACHAEL ZIMLICH, RN

The United States continues to outspend other high-income nations on healthcare without superior outcomes. Outsourcing, streamlining operations, and changing reimbursement models have made some progress in curbing spending, but real improvements are still needed. Here are two of the biggest areas of need, according to two experts.

1 More advanced interoperability

EHRs, which were initiated with the promise of improving care and reducing costs, have not fulfilled that mission as hoped, says Barak Richman, JD, PhD, a member of the Health Sector Management faculty at Duke’s Fuqua School of Business and a senior fellow at the Kenan Institute for Ethics. Richman co-authored a study in JAMA in which he found that EHRs have resulted in little improvement in time and cost associated with various billing and administrative functions.

On the clinical side, Richman says EHRs should make health data more available to patients and physicians to help in diagnosing and identifying the most effective medical regimens. But to do that, these systems need to be rebuilt around the patient, he says. “You have to have an architecture that wherever the patient goes, whoever they see, those records should be readily available,” he says. “And I don’t think we have a health record architecture in this country that can do that.”

Simplification is needed to move forward, he says, pointing to the electronic healthcare cards that contain centralized data that are used by patients in France and other countries. Centralizing and streamlining data would offer patients more control over their health choices and spending, he says. Increased efficiencies through a system that is more user-friendly and allows patients to access and aggregate their own data could save a lot of trouble—and dollars.

“We recognize that the best ideas don’t come from Washington, so it’s important that we hear from the front lines of our healthcare system about how we can improve care,” CMS Administrator Seema Verma wrote in a statement about the poll. “The responses … will help inform and drive our initiatives to transform the health care delivery system with the goal of improving quality of care while reducing unnecessary cost.”

The responses will continue to be reviewed over the next year to develop new models for cost-savings and improved outcomes, says CMS.

New cost-savings models coming

The CMS Innovation Center recently sought suggestions regarding how to promote better patient-centered care, says CMS Public Affairs Specialist William C.F. Polglase. Stakeholders submitted more than 1,000 responses as part of an industry-wide survey. Suggestions included:

- Realigning incentives;
- Streamlining burdensome regulatory requirements; and
- Direct provider contracting.

Direct provider contracting models would put more accountability for cost and quality into the hands of clinicians, with the goal of increasing care while reducing administrative burdens and associated expenses, says CMS.

The responses will continue to be reviewed over the next year to develop new models for cost-savings and improved outcomes, says CMS.

Managed Healthcare Executive.com
Which is a sad irony. You build up this huge infrastructure to do what you want to do, and now we see the best way to do the things you want to do is to work around it."

2 More use of artificial intelligence

Artificial intelligence (AI) is garnering attention in terms of streamlining administrative costs and patient care, says Pamela Hepp, JD, MPH, a healthcare consultant with Buchanan Ingersoll & Rooney. "There are various sources of administrative waste within the healthcare system, including inefficiencies in the delivery of care from duplicative services, medication errors, and other types of clinical errors that lead to additional services and/or increased morbidity."

In addition, physicians report that they are overloaded with data, Hepp says, leading to inefficiencies in care delivery. "Artificial intelligence can winnow down the amount of data necessary to that which is essential for physicians to make decisions," she says.

One example is streamlining the many treatment options physicians face for every patient. "Artificial intelligence can analyze information regarding all patients for which such treatment options have been utilized to predict how patients may react to a given drug or treatment plan, thereby developing a more effective patient-specific treatment plan and improving patient compliance and outcomes," Hepp says. "Artificial intelligence may also help to streamline the clinical trial process by gathering and analyzing data across study sites in a more cohesive and comparative way."

To be successful, the information provided to physicians must be manageable in terms volume as well as understandable and useful, Hepp says. It’s not enough to know how many patients have heart failure, for example. But, knowing which medications and treatment modalities improve outcomes with less hospitalizations is useful. That’s where AI comes in, it can analyze volumes of data to infer evidence-based strategies and functions that help patients and reduce costs, Hepp says.

The artificial intelligence technology of today has a greater capacity to analyze, solve problems, and make decisions, Hepp says. The concern going forward, she says, will be making sure this technology is affordable and secure.

"Value-based payment systems, population health management, and other clinical uses of artificial intelligence require the development and implementation of a technology infrastructure across all providers involved in the care spectrum. Such technology is expensive and there are regulatory constraints as to how such technology can be deployed from a health system to independent providers within the community," Hepp says. "Many providers also view data mining as suspect, and while the use of artificial intelligence for the purposes described can occur in a way that is HIPAA compliant, many providers may be hesitant to share data on a wide scale beyond the traditional treatment, payment, and for their own business operations."

Rachael Zimlich, RN, is a writer in Columbia Station, Ohio.

THE U.S. PAYS MORE FOR:

**Doctors**
The average salary for a general practitioner in the U.S. is **$218,173**, nearly double the average salary across all high-income countries. Specialists and nurses in the U.S. also earn significantly more than in other countries.

**Pharmaceuticals**
The U.S. spends **$1,443** per person on pharmaceuticals, compared to the average cost in all high-income countries of **$749**.

**Healthcare administration**
The U.S. spends **8%** of total national health expenditures on activities related to planning, regulating, and managing health systems and services, compared to an average **3%** spent among all high-income countries.

SPENDING SNAPSHOT  
The U.S. spent **17.8%** of its gross domestic product on healthcare in 2016 compared to an average of **11.5%** in similar nations.  

Source: "Health Care Spending in the United States and Other High-Income Countries," The Commonwealth Fund, March 2018

Source: "Health Care Spending in the United States and Other High-Income Countries," The Commonwealth Fund, March 2018

Source: The Commonwealth Fund
What Other Industries Can Teach Us

by AUBREY WESTGATE

1. **How to incorporate scenario planning.**
   “Southwest Airlines has excelled at envisioning potential changes in their industry and then determining how they would successfully respond to them with tremendous success. Their responses to 9/11 as well as how they handled a significant rise in aviation fuel prices are legendary in their industry. We do far too little of this type of planning in healthcare despite the fact that our future is always a wide range of possible scenarios.” —Don Hall

2. **How to build a platform focused on consumerism.**
   “The retail market and related patient/member education are still relatively new to the healthcare sector and we could learn a great deal from other industries and companies who have excelled in this regard.” —Doug Chaet

3. **How to better manage money.**
   We need to have better cost accounting across the healthcare continuum. —Perry Cohen

4. **How to harness the true power and value of digitization and disruptive transparency.**
   “We can learn a lot from the banking industry when it comes to these critical tools which could help healthcare organizations effectively lower operating costs, improve coordination, personalize customer care and service, and inject a much greater social context into the healthcare experience.”
   —David Calabrese

5. **How to shift the focus to consumers.**
   “Other industries are so much better at being consumer-centric. We get way too involved in the complicated ‘delivery’ and we don’t really understand how consumers view healthcare and what they want from it.” —Amy Shin

6. **How to think much bigger about driving out inefficiencies.**
   “We can learn from Uber and Lyft when it comes to this skill. Healthcare needs to learn how to transform its cost structure from the sharing economy that matches dynamic demand with fixed supply. On the fixed supply side, the health industry needs to think beyond just beds and exam rooms and include expertise that can be delivered virtually, like translation services, dependency services, pharmacist services, and behavioral health services.”
   —Dennis Schmuland

7. **How to infuse quality throughout.**
   “Managed Care needs to view the entire business as a process and begin to seek quality improvement in each step in the process. This model has led to significant productivity gains in many industries.”
   —David Schmidt

**IN CASE YOU MISSED IT**
To learn more about these board members, see PAGE 11
Fewer U.S. Consumers Trust Health Industry

Consumer trust declines by healthcare subsector

Trust score points are out of 100.

Pharma: -13 (38)  Health Insurance: -9  Biotech/Life Sciences: -7 (55)  Hospitals and Clinics: -1 (70)

Three Findings on the State of Value-Based Care

1. **Payers report success in reducing unnecessary medical costs**, with savings topping 5.6% on average, with almost a quarter of respondents noting savings in excess of 7.5%.

2. **Almost 80% of payers report quality improvements**, 64% report provider relationship improvements, and 73% report patient engagement improvements.

3. **For the first time, commercial lines, not government lines of business, are leading adoption, advancement, and innovation of value-based care models** and strategies.


“You have to have an architecture that wherever the patient goes, whoever they see, those records should be readily available. And I don’t think we have a health record architecture in this country that can do that.”

— Barak Richman, JD, PhD, Duke’s Fuqua School of Business, pg 30.

Cost Matters: Diabetes

In a survey of more than 6,600 diabetic patients, **45% have gone without diabetes care at times because they couldn’t afford it.**

— UpWeld