CAR T-Cell Therapy
Life-saving treatment, huge price tag

CANCER CARE IN THE NEXT DECADE
TOP ONCOLOGY DRUG APPROVALS
NEW ONCOLOGY PAYMENT MODELS

AND
New C-suite positions
Accomplish more in less time
**YES** CAR T IS HERE

YESCARTA®, THE FIRST CAR T THERAPY FOR CERTAIN TYPES OF RELAPSED OR REFRACTORY LARGE B-CELL LYMPHOMA

The following data reflect results from the ZUMA-1 pivotal trial*1

**// PROVEN EFFICACY**

51%

Patients achieved a best response of complete remission (CR) (52/101)

**// CYTOKINE RELEASE SYNDROME**

13% 94%

Grade ≥3 incidence Overall incidence

**// RAPID & RELIABLE MANUFACTURING**

17 DAYS

Median turnaround time †

**// NEUROLOGIC TOXICITIES**

31% 87%

Grade ≥3 incidence Overall incidence

**VISIT YESCARTAHCP.COM/CENTERS TO FIND A LIST OF AUTHORIZED TREATMENT CENTERS**

*ZUMA-1 was an open-label, single-arm study in 101 adult patients who received YESCARTA® therapy. Patients received lymphodepleting chemotherapy prior to a single infusion of YESCARTA® at a target dose of 2 x 10⁶ viable CAR T cells/kg body weight (maximum of 2 x 10⁸ viable CAR T cells). Patients had refractory disease to their most recent therapy, or had relapsed within 1 year after autologous hematopoietic stem cell transplantation.

†The median time from leukapheresis to product delivery.

**INDICATION**

YESCARTA® is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

**LIMITATION OF USE:** YESCARTA® is not indicated for the treatment of patients with primary central nervous system lymphoma.

**IMPORTANT SAFETY INFORMATION**

**BOXED WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGIC TOXICITIES**

- Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving YESCARTA®. Do not administer YESCARTA® to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.

- Neurologic toxicities, including fatal or life-threatening reactions, occurred in patients receiving YESCARTA®, including concurrently with CRS or after CRS resolution. Monitor for neurologic toxicities after treatment with YESCARTA®. Provide supportive care and/or corticosteroids as needed.

- YESCARTA® is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA® REMS.

Important Safety Information continued on adjacent page.
YESCARTA® REMS: Because of the risk of CRS and neurologic toxicities, YESCARTA® is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA® REMS. The required components of the YESCARTA® REMS are: Healthcare facilities that dispense and administer YESCARTA® must be enrolled and comply with the REMS requirements. Certified healthcare facilities must have on-site, immediate access to tocilizumab, and ensure that a minimum of 2 doses of tocilizumab are available for each patient for infusion within 2 hours after YESCARTA® infusion, if needed for treatment of CRS. Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense or administer YESCARTA® are trained about the management of CRS and neurologic toxicities. Further information is available at www.YESCARTAREMS.com or 1-844-454-KITE (5483).

HYPERSENSITIVITY REACTIONS: Allergic reactions may occur. Serious hypersensitivity reactions including anaphylaxis may be due to dimethyl sulfoxide (DMSO) or residual gentamicin in YESCARTA®.

SERIOUS INFECTIONS: Severe or life-threatening infections occurred. Infections (all grades) occurred in 38% of patients, and in 23% with ≥ Grade 3. Grade 3 or higher infections with an unspecified pathogen occurred in 16% of patients, bacterial infections in 9%, and viral infections in 4%. YESCARTA® should not be administered to patients with clinically significant active systemic infections. Monitor patients for signs and symptoms of infection before and after YESCARTA® infusion and treat appropriately. Administer prophylactic anti-microbials according to local guidelines. Febrile neutropenia was observed in 36% of patients and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids and other supportive care as medically indicated. Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs directed against B cells. Perform screening for HBV, HCV, and HIV in accordance with clinical guidelines before collection of cells for manufacturing.

PROLONGED CYTOPENIAS: Patients may exhibit cytophenias for several weeks following lymphodepleting chemotherapy and YESCARTA® infusion. Grade 3 or higher cytophenias not resolved by Day 30 following YESCARTA® infusion occurred in 28% of patients and included thrombocytopenia (18%), neutropenia (15%), and anemia (13%). Monitor blood counts after YESCARTA® infusion.

HYPOGAMMAGLOBULINEMIA: B-cell aplasia and hypogammaglobulinemia can occur. Hypogammaglobulinemia occurred in 15% of patients. Monitor immunoglobulin levels after treatment and manage using infection precautions, antibiotic prophylaxis and immunoglobulin replacement. The safety of immunization with live viral vaccines during or following YESCARTA® treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during YESCARTA® treatment, and until immune recovery following treatment.

SECONDARY MALIGNANCIES: Patients may develop secondary malignancies. Monitor life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact Kite at 1-844-454-KITE (5483) to obtain instructions on patient samples to collect for testing.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES: Due to the potential for neurologic events, including altered mental status or seizures, patients are at risk for altered or decreased consciousness or coordination in the 8 weeks following YESCARTA® infusion. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, during this initial period.

ADVERSE REACTIONS: The most common adverse reactions (incidence ≥ 20%) include CRS, fever, hypotension, encephalopathy, tachycardia, fatigue, headache, decreased appetite, chills, diarrhea, febrile neutropenia, infections-pathogen unspecified, nausea, hypoxia, tremor, cough, vomiting, dizziness, constipation, and cardiac arrhythmias.

Please see Brief Summary of Prescribing Information, including BOXED WARNING, on the following pages.
1 INDICATIONS AND USAGE
YESCARTA is a CD19-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Limitation of Use: YESCARTA is not indicated for the treatment of patients with primary central nervous system lymphoma.

2 DOSAGE AND ADMINISTRATION

2.2 Administration: YESCARTA is for autologous use only. The patient’s identity must match the patient identifiers on the YESCARTA cassette and infusion bag. Do not infuse YESCARTA if the information on the patient-specific label does not match the intended patient [see Dosage and Administration (2.2, 2.3), Warnings and Precautions (5.1)].

Preparation for YESCARTA Infusion: Confirm availability of YESCARTA prior to starting the lymphodepleting regimen. Pre-treatment: Administer a lymphodepleting chemotherapy regimen of cyclophosphamide 500 mg/m² intravenously and fludarabine 30 mg/m² intravenously on the fifth, fourth, and third day before infusion of YESCARTA. Premedication: Administer acetaminophen 650 mg PO and diphenhydramine 12.5 mg intravenously or PO approximately 1 hour before YESCARTA infusion. Avoid prophylactic use of systemic corticosteroids, as it may interfere with the activity of YESCARTA.

Preparation of YESCARTA for Infusion: Confirm the timing of YESCARTA thaw and infusion. Confirm the infusion time in advance, and adjust the start time of YESCARTA thaw such that it will be available for infusion when the patient is ready. Confirm patient identity. Prior to YESCARTA preparation, match the patient’s identity with the patient identifiers on the YESCARTA cassette. Do not remove the YESCARTA product bag from the cassette if the information on the patient-specific label does not match the intended patient. Once patient identification is confirmed, remove the YESCARTA product bag from the cassette and check that the patient information on the cassette label matches the bag label. Inspect the product bag for any breaches of container integrity such as breaks or cracks before thawing. If the bag is compromised, follow the local guidelines (or call Kite at 1-844-454-KITE). Place the infusion bag inside a second sterile bag per local guidelines. Thaw YESCARTA at approximately 37°C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Gently mix the contents of the bag to disperse clumps of cellular material. If visible cell clumps remain, continue to gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. Do not wash, spin down, and/or re-suspend YESCARTA in new media prior to infusion. Once thawed, YESCARTA may be stored at room temperature (20°C to 25°C) for up to 3 hours.

Administration: For autologous use only. Ensure that tocilizumab and emergency equipment are available prior to infusion and during the recovery period. Do NOT use a leukodepleting filter. Central venous access is recommended for the infusion of YESCARTA. Confirm the patient’s identity matches the patient identifiers on the YESCARTA product bag. Prime the tubing with normal saline prior to infusion. Infuse the entire contents of the YESCARTA bag within 30 minutes by either gravity or a peristaltic pump. YESCARTA is stable at room temperature for up to 3 hours after thaw. Gently agitate the product bag during YESCARTA infusion to prevent cell clumping. After the entire content of the product bag is infused, rinse the tubing with normal saline at the same infusion rate to ensure all product is delivered. YESCARTA contains human blood cells that are genetically modified with a replication incompetent retroviral vector. Follow universal precautions and local biosafety guidelines for handling and disposal to avoid potential transmission of infectious diseases.

Monitoring: Administer YESCARTA at a certified healthcare facility. Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of CRS and neurologic toxicities. Instruct patients to remain within proximity of the certified healthcare facility for at least 4 weeks following infusion.

2.3 Management of Severe Adverse Reactions

Cytokine Release Syndrome (CRS): Identify CRS based on clinical presentation [see Warnings and Precautions (5.1)]. Evaluate for and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, manage according to the recommendations in Table 1. Patients who experience Grade 2 or higher CRS (e.g., hypotension, not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function. For severe or life-threatening CRS, consider intensive care support therapy.

Table 1. CRS Grading and Management Guidance

<table>
<thead>
<tr>
<th>CRS Grade</th>
<th>Tocilizumab</th>
<th>Corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Administer tocilizumab (c) 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.</td>
<td>Manage per Grade 3 if no improvement within 24 hours after starting tocilizumab.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Per Grade 2 Administer methylprednisolone 1 mg/kg intravenously twice daily or equivalent dexamethasone (e.g., 10 mg intravenously every 6 hours).</td>
<td>Continue corticosteroids use until the event is Grade 1 or less, then taper over 3 days.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Per Grade 2 Administer methylprednisolone 1000 mg intravenously per day for 3 days; if improves, then manage as above.</td>
<td></td>
</tr>
</tbody>
</table>

(a) Lee et al 2014. (b) Refer to Table 2 for management of neurologic toxicity. (c) Refer to tocilizumab Prescribing Information for details

Neurologic Toxicity: Monitor patients for signs and symptoms of neurologic toxicities (Table 2). Rule out other causes of neurologic symptoms. Patients who experience Grade 2 or higher neurologic toxicities should be monitored with continuous cardiac telemetry and pulse oximetry. Provide intensive care supportive therapy for severe or life-threatening neurologic toxicities. Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis for any Grade 2 or higher neurologic toxicities.
The required components of the YESCARTA REMS are:
- Healthcare facilities that dispense and administer YESCARTA must be enrolled and comply with the REMS requirements. Certified healthcare facilities must have on-site immediate access to tocilizumab, and ensure that a minimum of two doses of tocilizumab are available for each patient for infusion within 2 hours after YESCARTA infusion, if needed for treatment of CRS.
- Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense or administer YESCARTA are trained about the management of CRS and neurologic toxicities.

Further information is available at www.YescartaREMS.com or 1-844-454-KITE (5483).

5.4 Hypersensitivity Reactions: Allergic reactions may occur with the infusion of YESCARTA. Severe hypersensitivity reactions including anaphylaxis, may be due to dimethyl sulfoxide (DMSO) or residual gentamycin in YESCARTA.

5.5 Serious Infections: Severe or life-threatening infections occurred in patients after YESCARTA infusion. In Study 1, infections (all grades) occurred in 38% of patients. Grade 3 or higher infections occurred in 23% of patients. Grade 3 or higher infections with an unspecified pathogen occurred in 16% of patients, bacterial infections in 19%, and viral infections in 4%. YESCARTA should not be administered to patients with clinically significant active systemic infections. Monitor patients for signs and symptoms of infection and manage with broad spectrum antibiotics, fluids and other supportive care as medically indicated. Viral Reactivation: Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs directed against B cells. Perform screening for HBV, HCV, and HIV in accordance with clinical guidelines before collection of cells for manufacturing.

5.6 Prolonged Cytopenias: Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and YESCARTA infusion. In Study 1, Grade 3 or higher cytopenias not resolved by Day 30 following YESCARTA infusion occurred in 26% of patients and included thrombocytopenia (18%), neutropenia (15%), and anemia (3%). Monitor blood counts after YESCARTA infusion.

5.7 Hypogammaglobulinemia: B-cell aplasia and hypogammaglobulinemia can occur in patients receiving treatment with YESCARTA. In Study 1, hypogammaglobulinemia occurred in 15% of patients. Monitor immunoglobulin levels after treatment with YESCARTA and manage using infection precautions, antibiotic prophylaxis and immunoglobulin replacement. The safety of immunization with live viral vaccines during or following YESCARTA treatment has not been studied. Vaccine with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during YESCARTA treatment, and until immune recovery following treatment with YESCARTA.

5.8 Secondary Malignancies: Patients treated with YESCARTA may develop secondary malignancies. Monitor life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact Kite at 1-844-454-KITE (5483) to obtain instructions on patient samples to collect for testing.

5.9 Effects on Ability to Drive and Use Machines: Due to the potential for neurologic events, including altered mental status or seizures, patients receiving YESCARTA are at risk for altered or decreased consciousness or coordination in the 8 weeks following YESCARTA infusion. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, during this initial period.

6 ADVERSE REACTIONS: The following adverse reactions are described in Warnings and Precautions: Cytokine Release Syndrome, Neurologic Toxicities, Hypersensitivity Reactions, Serious Infections, Prolonged Cytopenias, Hypogammaglobulinemia.

6.1 Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of YESCARTA cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety data described in this section reflect exposure to YESCARTA in the clinical trial (Study 1) in which 108 patients with relapsed/refractory B-cell NHL received CAR-positive T cells based on a recommended dose which was weight-based (see Clinical Trials (14)). Patients had a history of CNS disorders (such as seizures or cerebrovascular ischemia) or autoimmune disease, requiring systemic immunosuppression were ineligible. The median duration of follow up was 8.7 months. The median age of the study population was 58 years (range: 23 to 76 years); 68% were men. The baseline ECOG performance status was at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of neurologic toxicities. Monitor patients for signs or symptoms of neurologic toxicities for 4 weeks after infusion and treat promptly. See Management of Cytokine Release Syndrome (CRS); Neurologic Toxicities (2.2).
43% with ECOG 0, and 57% with ECOG 1. The most common adverse reactions (incidence ≥ 20%) include CRS, fever, hypotension, encephalopathy, tachycardia, fatigue, headache, decreased appetite, chills, diarrhea, febrile neutropenia, infections-pathogen unspecified, nausea, hypoxia, vomiting, dizziness, constipation, and cardiac arrhythmias. Serious adverse reactions occurred in 52% of patients. The most common serious adverse reactions (≥ 2%) include encephalopathy, fever, lung infection, febrile neutropenia, cardiac arrhythmia, cardiac failure, urinat tract infection, renal insufficiency, aphasia, cardiac arrest, Clostridium difficile infection, delirium, hypotension, and hypoxia. The most common (≥ 10%) Grade 3 or higher reactions include febrile neutropenia, fever, CRS, encephalopathy, infections-pathogen unspecified, hypotension, hypoxia, and lung infections. Forty-five percent (49/108) of patients received tocilizumab after infusion of YESCARTA.

**Summary of Adverse Reactions Observed in at Least 10% of the Patients Treated with YESCARTA in Study 1**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Any Grade (%)</th>
<th>Grades 3 or Higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>57</td>
<td>2</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>23</td>
<td>7</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>38</td>
<td>4</td>
</tr>
<tr>
<td>Nausea</td>
<td>34</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>Constipation</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>86</td>
<td>16</td>
</tr>
<tr>
<td>Fatigue</td>
<td>46</td>
<td>3</td>
</tr>
<tr>
<td>Chills</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>Edema</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td><strong>Immune system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytokine release syndrome</td>
<td>94</td>
<td>13</td>
</tr>
<tr>
<td>Hypogammaglobulinemia</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections-pathogen unspecified</td>
<td>26</td>
<td>16</td>
</tr>
<tr>
<td>Viral infections</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>Bacterial infections</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>44</td>
<td>2</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Dehydration</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor dysfunction</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Back pain</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Muscle pain</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>57</td>
<td>29</td>
</tr>
<tr>
<td>Headache</td>
<td>45</td>
<td>1</td>
</tr>
<tr>
<td>Tumor</td>
<td>31</td>
<td>2</td>
</tr>
<tr>
<td>Dizziness</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>Aphasia</td>
<td>18</td>
<td>6</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delirium</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoxia</td>
<td>32</td>
<td>11</td>
</tr>
<tr>
<td>Cough</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td><strong>Renal and urinary disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>57</td>
<td>15</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>10</td>
<td>1</td>
</tr>
</tbody>
</table>

The following events were also counted in the incidence of CRS: tachycardia, arrhythmia, fever, chills, hypoxia, renal insufficiency, and hypertension. For a complete list of events that contributed to the incidence of certain adverse reactions, please see footnote Table 3 in Section 6.1 of the Full Prescribing Information.

Other clinically important adverse reactions that occurred in less than 10% of patients treated with YESCARTA include the following: blood and lymphatic system disorders: coagulopathy (2%); cardiac disorders: cardiac failure (6%) and cardiac arrest (4%); immune system disorders: hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) (1%); hypersensitivity (1%); infections and infestations disorders: fungal infections (5%); nervous system disorders: ataxia (6%), seizure (4%), dyscalculia (2%), and myoclonus (2%); respiratory, thoracic and mediastinal disorders: pulmonary edema (9%); skin and subcutaneous tissue disorders: rash (9%); vascular disorders: capillary leak syndrome (3%).

**Grade 3 or 4 Laboratory Abnormalities Occurring in ≥ 10% of Patients in Study 1 with YESCARTA**

- Lymphopenia 100%, Leukopenia 96%, Neutropenia 93%, Anemia 66%
- Thrombocytopenia 56%, Hypophosphatemia 50%, Hypotrombinaemia 13%, Uric acid increased 13%, Direct Bilirubin increased 13%, Hypokalemia 10%, Alamine Aminotransferase increased 10%.

6.2 Immunogenicity: YESCARTA has the potential to induce anti-product antibodies. The immunogenicity of YESCARTA has been evaluated using an enzyme-linked immunosorbent assay (ELISA) for the detection of binding antibodies against FMO63, the originating antibody of the anti-CD19 CAR. Three patients tested positive for pre-dose anti-FMO63 antibodies at baseline and Month 1, 3, or 6 in Study 1. There is no evidence that the kinetics of initial expansion and persistence of YESCARTA, or the safety or effectiveness of YESCARTA, was altered in these patients.

**8 USE IN SPECIFIC POPULATIONS**

8.1 Pregnancy: Risk Summary: There are no available data with YESCARTA use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with YESCARTA to assess whether it can cause fetal harm when administered to a pregnant woman. It is not known if YESCARTA has the potential to be transferred to the fetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause fetal toxicity, including B-cell lymphocytopenia. Therefore, YESCARTA is not recommended for women who are pregnant, and pregnancy after YESCARTA infusion should be discussed with the treating physician. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% - 4% and 15% - 20%, respectively.

8.5 Geriatric Use: Clinical trials of YESCARTA did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently or have different safety outcomes as compared to younger patients.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide). Ensure that patients understand the risk of manufacturing failure (1% in clinical trial). In case of a manufacturing failure, a second manufacturing of YESCARTA may be attempted. In addition, while the patient awaits the product, additional chemotherapy (not the lymphodepletion) may be necessary and may increase the risk of adverse events during the pre-infusion period. Advise patients to seek immediate attention for any of the following: Cytokine Release Syndrome, Neurologic Toxicities, Serious Infections, Prolonged Cytopenia [see Warnings and Precautions (5.1, 5.2, 5.3, 5.5) and Adverse Reactions (6) for more information and signs and symptoms]. Advise patients for the need to: Refrain from driving or operating heavy or potentially dangerous machinery after YESCARTA infusion until at least 8 weeks after infusion [see Warnings and Precautions (5.2)]. Have periodic monitoring of blood counts. Contact Kite at 1-844-454-KITE (5483) if they are diagnosed with a secondary malignancy [see Warnings and Precautions (5.8)].

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Financial Toxicity of Cancer Treatment

Our cancer care challenge

In 1975, a cancer diagnosis of any kind meant a patient had less than a 50% chance of surviving more than five years. Today, that five-year survival rate is closing in on 70%. And the rate is much higher for certain cancer sites, so long as the cancer is detected at an early stage.

Clearly, we’ve come a long way in 40 years—but we still have a long way to go. Cancer care needs to be more collaborative and evidenced-based. It needs to be more focused on prevention and psychosocial wellness. And on top of all that, it needs to be more affordable and accessible.

So how do we get there?

Personalized care. When we speak of "personalized medicine" in the context of cancer care, we’re often referring to next-generation genomic sequencing, data science, targeted therapies, and immunotherapies.

And those are vitally important weapons in our ongoing fight against cancer. But personalized care is much bigger than that—it’s about a holistic approach to multidisciplinary care coordination. From the moment of diagnosis to a patient’s final treatment, at every point along the care continuum—surgery, radiation, pathology, imaging, chemotherapy, dietary, rehab—the care needs to be precisely organized around the patient’s convenience, preferences, and best interests.

I’ll give you an example: In recent years, some health systems (including ours) have opened after-hours oncology clinics. Many cancer patients experience side effects to their care—nausea, pain, fever and more—and if the symptoms hit after 4 p.m., those patients may require a trip to the emergency room. But an ER is the last place a cancer patient should be, because of increased susceptibility to the types of infections that are often present in a hospital emergency setting.

These after-hour oncology centers are open late (and in some cases, 24/7), and they provide safe care alternatives for cancer patients with urgent symptoms. This leads to better outcomes.

Provider-payer collaborations. Providing comprehensive cancer care is an all-in effort that, increasingly, requires investment and creative thinking from payers, too. Over the last several years, insurers across the country have become more involved, and it’s a trend that will accelerate.

“We’ve made remarkable progress in understanding and treating cancer, but the truth is that our current delivery models provide those treatments at an unsustainable cost.”

The partnerships make sense. Insurers have a wealth of claims data that can be beneficial to oncologists, and oncologists possess the clinical data and up-to-date technical knowledge that is required to make timely treatment decisions. Carriers have also developed bundled payment models for clinics that adhere to certain best practices, as determined through real-time collaboration with staff oncology experts. And some insurers are considering payments for remote oncology care and out-of-the-office triage, which allows practices to deploy clinical resources in nontraditional ways.

Financial wellness. It’s no secret that cancer care is expensive, in America and around the world. Yes, we’ve made remarkable progress in understanding and treating cancer, but the truth is that our current delivery models provide those treatments at an unsustainable cost.

A lot of that cost is tied up in the latest oral medicines and cell-based therapies, which can run hundreds of thousands of dollars per year (or per even dose). But there are other, systemic costs that we as providers and insurers must work to address if we want to reduce the budget stress and “financial toxicity” of cancer treatment. Our challenge in the years ahead is to ensure that cost of care reflects the value of care—because when the cost of cancer care is prohibitive, we’re doing a poor job of serving our patients and their families.

Cynthia Hundorfean, a Managed Healthcare Executive editorial advisor, is president and CEO of Allegheny Health Network (AHN), an integrated healthcare delivery system that serves Western Pennsylvania. AHN is part of the Highmark Health family of companies.
Mission Managed Healthcare Executive provides healthcare executives at health plans and provider organizations with analysis, insights, and strategies to pursue value-driven solutions.

Roy Beveridge, MD is senior vice president and chief medical officer for Humana, where he’s responsible for developing and implementing Humana’s clinical strategy with an emphasis on advancing the company’s integrated care delivery model.

Mark Boxer, PhD is executive vice president and global chief information officer for CGI, where he is responsible for driving the company’s worldwide technology strategy.

Joel V. Brill, MD is the chief medical officer for Predictive Health, LLC, which partners with stakeholders to improve coverage of value-driven care that optimizes health for people.

David Calabrese, RPh, MHP, is senior vice president and chief pharmacy officer at OptumRx, a pharmacy benefits firm that provides pharmacy care services for more than 65 million lives nationally.

Douglas L. Chaet, FACHE is chief managed care officer, Sentara Healthcare, and chairman, American Association of Integrated Healthcare Delivery Systems.

Perry Cohen, PharmD is chief executive officer of The Pharmacy Group and the TPG family of companies, which provides services to associations, healthcare and information technology organizations, payers and pharmaceutical companies.

Darnell Dent is president and CEO of FirstCare Health Plans, a provider-sponsored health plan serving local communities in West Texas with offices in Abilene, Amarillo, and Lubbock; and, corporate offices in Austin, Texas.

Don Hall, MPH is principal of DeltaSigma LLC, a consulting practice specializing in strategic problem solving for managed care organizations. He most recently served as president and chief executive officer of a nonprofit, provider-sponsored health plan.

Daniel J. Hilferty, MPA is president and CEO, Independence Health Group, a leading health insurance organization headquartered in Southeastern Pennsylvania with nearly 4.5 million members in 24 states and Washington, D.C.

Cynthia Hundorfean is president and CEO of Allegheny Health Network (AHN), an integrated healthcare delivery system that serves Western Pennsylvania. AHN is part of the Highmark Health family of companies.

John Mathewson is chief operating officer for America’s Health Insurance Plans (AHIP), the national trade association that advocates for the health insurance community and the consumers they serve across the nation.

Margaret A. Murray, MPA is the founding chief executive officer of the Association for Community Affiliated Plans, which represents 54 nonprofit safety net health plans in 26 states.

Kevin Ronneberg, MD is vice president and associate medical director for health initiatives at HealthPartners, an integrated, nonprofit healthcare provider and health insurance company located in Bloomington, Minnesota.

David Schmidt is president of the TPG International Health Academy, which hosts trade/study missions around the world for U.S. healthcare executives. He also provides strategic consulting to health plans and health systems.

Dennis Schmuland, MD is chief health strategy officer, U.S. Health & Life Sciences division of Microsoft Corp., where he is responsible for setting the company’s strategy and overseeing solutions for the managed care industry.

Paul J. Setlak, PharmD, MBA is director of field health outcomes at AstraZeneca, where he is responsible for leading field-based clinical and health outcomes activities with payers, integrated delivery networks, health systems, and other groups.

Amy Shin is the CEO of Health Plan of San Joaquin, a not-for-profit plan serving 350,000 Medicaid members in San Joaquin and Stanislaus counties of California. Amy has 20 years of progressive Medicare, Medicaid and commercial managed care leadership experience.
The global medical foods market is expected to be worth $24.4 billion by 2025, according to Grand View Research. Despite its significant size, less is understood about these products than about nutraceuticals, which include dietary supplements, functional foods, botanicals/herbals, vitamins, and minerals.

David Doman, MD, clinical professor of medicine at George Washington University School of Medicine and a gastroenterologist in Silver Spring, Maryland, says medical foods are a gray area when trying to distinguish them from nutraceuticals, creating problems for coverage by insurers, most of whom do not include medical foods as a benefit.

Gayle Scott, PharmD, assistant professor, Virginia Commonwealth University, Medical College of Virginia and School of Pharmacy, says, “Medical foods should be used when regular food does not provide enough nutritional benefit.”

As defined in the Orphan Drug Act of 1988, minimal requirements for a product to be considered a medical food are:

1. The product is a food specially formulated and processed for oral or tube feeding.
2. It is used for dietary management of a medical disorder, disease, or condition with distinctive nutritional requirements.
3. The product should be used under medical supervision, and is primarily obtained through hospitals, clinics, and other medical and long-term care facilities.

Examples include CerefolinNAC (L-methylfolate with B vitamins) for mild-to-moderate cognitive impairment; Limbrel (flavocoxid) for osteoporosis; Vasculera (diosmiplex) for chronic venous insufficiency; and low-protein products for phenylketonuria, an inherited disorder.

Medical foods are not subject to any regulatory requirements like drugs are; may be labeled for specific conditions, unlike dietary supplements that cannot make claims to treat or prevent a disease, and follow labeling requirements dictated by the Federal Food, Drug, and Cosmetics Act. However, they must comply with applicable FDA requirements for foods and with the Current Good Manufacturing Practice regulations.

The FDA does not require a warning of adverse effects on medical foods nor information on how much of each ingredient is in a product—just the total amount—Scott adds.

Varying rules, coverage
Each state can decide how to cover medical foods, placing limits on what kinds of foods fall into the category, the conditions they address, route of administration, and eligibility. The regulations, which vary widely, most often apply to employer-sponsored insurance coverage and less to self-funded Employee Retirement Income Security Act (ERISA) plans that are generally exempt from state-mandated benefits, according to the National Coordinating Center.

A number of national bills have been proposed to provide for the coverage of medically necessary food and vitamins for digestive and inherited metabolic disorders under federal health programs and private health insurance, but none of these bills have come to fruition.
The American Medical Association supports legislation to establish a uniform requirement that health plans—both federal insurance programs and ERISA plans—offer coverage of medical foods and foods modified to be low protein for those conditions recommended by the HHS.

**Dietary management: A first step**

Although most insurers have put medical products on the back burner without coverage, some sponsor programs to address chronic conditions by providing and funding nutritional, specially tailored meals.

The Metropolitan Area Neighborhood Nutrition Alliance (MANNA), which targets the greater Philadelphia area, serves as a successful model providing nutritious, medically appropriate meals and nutrition counseling to people battling life-threatening illnesses.

**HPP promotes nutrition**

In February 2015, as part of a strategy to promote nutrition at its Philadelphia-based, MCO, HPP developed a pilot program with 30 people with diabetes. It proved to be so successful that after a few months, it became an established program. Enrollees receive three medically tailored meals a day delivered weekly to their homes. Case managers support patients through regularly scheduled phone calls.

Although the meal program is not a covered benefit, HPP reimburses MANNA for meals for some of the most chronically ill Medicaid and Medicare members, hoping to reduce emergency room visits and hospitalizations, improve health, and ultimately save money, says HPP CEO and President William Daugherty, CEO of MANNA, calls the organization "a pharmacy for diets."

"While it might be common practice for a healthcare professional to prescribe a specialized diet, there hasn't been much thought or attention paid to where an individual would access that diet and who would pay for it," Daugherty says, outlining one of the reasons MANNA has partnered with MCOs.

**Study: High Healthcare Users Benefit from Medically Tailored Food Programs**

Medicare and Medicaid beneficiaries participating in certain food delivery programs have fewer costly emergency department visits and hospital admissions, according to a new study in Health Affairs, "Meal Delivery Programs Reduce the Use of Costly Health Care in Dually Eligible Medicare And Medicaid Beneficiaries."

The study, published in April, found that Medicare and Medicaid dual eligibles who participate in either a medically tailored meals program or a non-tailored food program stay healthier.

The study, funded by AARP Foundation in partnership with Massachusetts General Hospital and the community-based health plan Commonwealth Care Alliance, is the first to demonstrate how this specialized intervention can lead to fewer costly emergency department visits and hospital admissions. "Individuals dually eligible for Medicare and Medicaid often face significant clinical and social risk, and consequently often have high levels of emergency department use, along with other associated health services such as inpatient admissions," says lead study author Seth A. Berkowitz, MD, MPH, assistant professor of general medicine and clinical epidemiology in the UNC School of Medicine. During the time of the study, he was an assistant professor at Massachusetts General Hospital/ Harvard Medical School, in Boston.

Berkowitz and colleagues examined two meal programs and medical claims data for adults who were dually eligible for Medicaid and Medicare coverage from January 1, 2014, to January 1, 2016. One group received home-delivered meals from Community Servings, whose meals are medically tailored meals to fit the medical and nutritional needs of those with diabetes, HIV/AIDS, cancer, heart disease, kidney disease, and other life-threatening illnesses. The other group was given a non-tailored meal program like Meals on Wheels. Both groups were compared to a control group of patients with similar demographics and illness profiles.

The researchers found that participants in both meals programs experienced fewer emergency department visits and emergency transportation services, but only Community Servings clients who received medically tailored meals had fewer inpatient admissions, resulting in a 16% net reduction in healthcare costs, according to the authors. Average monthly medical costs for medically tailored meal participants was $843, compared to $1,413 for the control group, reflecting gross savings of $570 per month, or net savings (factoring in the cost of the meals) of $220 per month.
Average HbA1c Test Results Six Months after MANNA

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<td>441</td>
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<td>107</td>
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George.

George was attracted to the program because of a family history of diabetes and an opportunity for the plan to manage diabetes patients’ diets. HPP is a plan of choice for those with diabetes; more than 13% of the Medicare/Medicaid plan members have the condition, he says.

HPP eligibility criteria include:

- Must be in active case management for one or multiple chronic conditions and demonstrate willingness to change behavior.
- Must be willing to make the appropriate dietary changes to gain control of their medical condition and be committed to work with their HPP care manager.
- Must be prepared to understand the necessity of portion control and the role it plays in health outcomes.

As of July 31, HPP has delivered 610,500 meals to more than 2,400 members. Participants enroll for a six-week cycle and may continue for an additional two cycles depending on the severity of their condition and following an assessment by a case manager.

Dependent children of members who are under 18 and spouses with a serious illness who are dependent on a member for shopping and cooking also receive meals.

The pilot studied HbA1c results six months after the program (see chart). The program also measured medical use costs six months before the program, during, and after the conclusion for hospital readmissions, emergency room visits, and appointments with primary care physicians and specialists.

Based on May 2017 data on 194 participants, admissions dropped 27.7%, emergency room visits declined by 6.9%, primary care visits fell 15.9%, and specialist visits decreased 7.08%.

As with most new programs, the pilot is not without challenges. George says that as a government-funded plan, HPP is highly regulated, with limits on what it is allowed to do. HPP also had to train MANNA staff to create and submit claims electronically, something entirely new for MANNA.

Statewide endeavor supports food as medicine

The Food is Medicine Coalition, a California State-funded pilot under the auspices of six nonprofit agencies, including Project Angel Food and Project Open Hand, started in May 2018. Over the pilot’s three years, it anticipates enrolling 1,000 low-income patients with congestive heart failure (CHF). The pilot is modeled after MANNA.

The program, which provides low-sodium meals, will study 30-day hospital readmissions, emergency room visits, and hospital lengths of stay.

“Our goal is to reduce costs for CHF patients by keeping them out of the hospital, and deliver return on investment to the state so that a medically tailored food program could become a covered Medicaid benefit, in which foods could be written as a prescription by physicians,” says Richard Ayoub, executive director, Project Angel Food. “Other states could potentially adopt the program.”

Participants must:

- Be covered under Medi-Cal, California’s Medicaid program, for an entire year without interruption. Ayoub says this requirement presents the biggest challenge to the program.
- Be considered “frequent fliers,” i.e., have more than two but fewer than six hospitalizations a year.
- Not have kidney failure.

In addition, the first meal must be delivered to enrollees within seven days of hospital discharge to measure hospital use.

LA Care Health Plan is participating in California’s pilot under the umbrella of Project Angel Food, with a state directive of serving 60 Medi-Cal patients the first year.

David Kagan, MD, medical director, utilization management for the health plan, outlines the program’s goals:

1/ Change healthcare policy so that meals become a reimbursable expense for insurers; and
2/ Provide all patients discharged from the hospital with daily meals, hoping to reduce readmission rates by 50%.

He sees the $6 million program as a tradeoff between paying $2,000 per day per person for hospital care versus a year’s worth of meals.

Kagan recognizes the challenges associated with eating a proper and nutritious diet. "Most people don’t understand what are the ‘right’ foods, how to cook them, and how important they are," he says. "They also have to get over the hump that medical foods don’t taste good. That takes education and hand holding by dieticians, who are part of our disease management programs."
New C-suite Positions

Four roles you may want to add  

by KAREN APPOLD

The C-suite at healthcare organizations is expanding. New roles, however, do not diminish the more traditional roles of chief financial officer, chief medical officer, chief operations officer, and chief information officer, rather, they augment them. “A chief executive officer must have a more diverse team to address the rising complexity and velocity of healthcare,” says David Gallegos, senior vice president of consulting services at Change Healthcare, a healthcare consultancy.

Here are four positions that managed care organizations may want to seriously consider:

**Chief People Officer (CPO).** Traditionally, the human resources function has been distanced from the C-suite and limited to handling the basics of hiring, performance reviews, and benefits. In contrast, today’s CPOs are more closely aligned with talent recruitment, development, and retention as strategies for overall business success. A CPO is data driven, possesses a strategic mindset, and is highly analytical of the organization’s future needs. “They are masterful at developing and implementing a fully integrated, strategically aligned talent plan throughout an organization,” says Mary Herrmann, MS, managing director of executive coaching at BPI group, a leadership, talent, and career transition consultancy.

The best CPOs in the healthcare space are comfortable with ambiguity as they lead employees through instability and make related decisions. “As the demand for great talent continues to grow, they are constantly conceiving of new ways to attract and engage top talent to differentiate the organization and fill future skills gaps,” Herrmann says. They also possess a strategic and highly analytical mindset as they consider their organization’s future direction, and have a strong handle on industry trends so they can stay ahead of competitors.

**Chief Digital Transformation Officer (CDTO).** This person is responsible for bringing together all of sectors of an organization in order to fundamentally change the way the company interacts with consumers and agents, as well automate old-school manual processes, says Bill Fox, JD, MA, chief strategist of global healthcare, life sciences, and insurance at MarkLogic, an enterprise database company. The CDTO needs to ascertain consumers’ experience when using the patient portal, using the company’s website, calling a representative, and using the company’s mobile app in order to increase acquisition and retention, he says.

These individuals also need to be able to relate that information back to the company’s technology and business investments to make sure there’s a return on their investment, which will only happen if they positively affect customers, Fox says. This requires an excellent understanding of technologies, i.e., artificial intelligence, machine learning, and bots, and includes what tools are available in marketing, mobile technologies, the patient portal, and the call center that can be used to transform the consumer experience.

A CDTO also needs excellent networking and cultural skills to bring together executives, information technology, actuaries, agents, and managers and ensure they stick to their mission, he says.

“Executives and managers at all levels need to embrace and adapt to how technology is going to change their roles.”

ASHRAF SHEHATA, KPMG

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Chief Customer Experience Officer (CXO). Increased accountability for customer satisfaction has created the need for this position. A CXO is charged with making every customer’s experience positive, and creates new ways to improve customer experience and increase satisfaction scores.

“Today’s customers have choices regarding which health plans they choose to enroll in,” says Diane Doherty, MS, CPHRM, senior vice president of Chubb Insurance, a property and casualty insurer based in New York. Having a dedicated executive who understands the customer experience and exactly what consumers value most is critical to ensuring that the organization designs their services in a way that is user friendly and easy for consumers to navigate. The position also highlights a health plan’s commitment to positive customer experiences.

The typical responsibilities of a CXO may include leading, coordinating, and overseeing a program to improve the customer experience and promote an organization-wide approach to customer-centeredness and engagement, Doherty says. The CXO serves as a change agent and works closely with the executive leadership team in identifying priority areas, developing goals, planning improvement, and measuring effectiveness.

Chief Quality Officer (CQO). With the federal government, state regulators, and purchasers of health insurance (including large employer groups or purchasing consortia) pushing for improved health outcomes, health plans can reap benefits by hiring a CQO. “There is renewed emphasis to directly tie quality care outcomes to plan reimbursement as evidenced by the largest payer of all, CMS, and its Five Star Medicare Advantage Plan,” says Dennis Eder, MBA, MA, cofounder and managing partner of Strategic Health Group, a healthcare consultancy.

A CQO is charged with ensuring high-quality standards are maintained and continuously improved through the introduction of new quality-focused programs and the refinement of quality measurement tools, Eder says. In achieving this goal, the CQO heads internal multidisciplinary teams that focus on quality, and he or she interacts with the plan’s chief compliance officer and regulators while working directly with provider partners to maximize the delivery of both clinical care and the overall member experience.

More Chief Technology Roles
Emerging technologies such as artificial intelligence, data and analytics, telehealth, and robotics are changing the nature of work at all businesses. While this work has traditionally been overseen by a chief technology officer, technologies are now influencing all parts of organizations. As a result, over the past few years, more technology-driven roles are emerging at health insurance companies, such as chief of healthcare informatics officer and chief information security officer. “Executives and managers at all levels need to embrace and adapt to how technology is going to change their roles,” says Ashraf Shehata, MHA, principal at KPMG and a member of the firm’s Global Healthcare Center of Excellence. “These executives will make decisions regarding the pace of adaptation and how quickly an organization will invest in new technologies.”

Along these lines, disrupting trends in healthcare have created a demand for highly skilled leaders who can navigate the conversion of clinical, strategic, and informational domains to determine the best applications of technology and data science within a healthcare organization, says Steve Whitehurst, CEO, Health Fidelity, a healthcare technology startup. An organization might enlist a chief data strategist or chief innovation officer to thoughtfully approach and test the role of artificial intelligence and data science to problem-solving and interventions to ensure that all stakeholders understand how and why a technology is being used, before using it.

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

The percentage of respondents to Managed Healthcare Executive’s 2018 State of the Industry Survey who said improving customer/patient satisfaction is their top patient-centered area of focus. Other responses included more cost/quality transparency (30%) and providing more financial counseling (4%).

Full survey findings will be released in the December issue.
A t a time when primary healthcare in the United States is more dependent than ever on foreign-trained doctors, the programs that permit those doctors to practice in this country face an uncertain future under the Trump administration.

Uncertainty, red tape, and anti-immigration policies have some primary care physicians contemplating leaving the U.S. for more welcoming countries, while some international medical graduates are reconsidering whether they want to practice here.

A decline in the number of international medical graduates would worsen the already serious shortage of primary care doctors, particularly because they tend to choose primary care specialties and many of them work in medically underserved areas.

“We are making healthcare more accessible, but we are subject to such uncertainty that some of us are rethinking whether we have a future here,” says Ram Sanjeev Alur, MD, an Indian-born internist in Marion, Illinois, who’s thinking of leaving the country.

The impact of international medical graduates

According to the American Immigration Council (AIC), just over one-quarter of doctors (247,449) in the U.S. were foreign-trained as of 2017, meaning they received their medical degrees from schools outside the country. A small percentage are U.S. citizens who went abroad to medical school, but most are not.

The percentage of these doctors in primary care is even higher. The same study found that nearly a third (31.8%) of physicians specializing in family medicine, internal medicine, or pediatrics are foreign-trained.

International medical graduates are more likely to serve in low-income areas, as well. More than half (53.4%) of all such doctors work in areas where the population has a per-capita income of $30,000 or less, according to the AIC. In areas where per-capita income is below $15,000 a year, these graduates account for 42.5% of all doctors.

In areas where 75% or more of the population is non-white, 36% of the doctors are trained outside the U.S. They also make up greater shares of all doctors serving populations with lower educational attainment.

With the Association of American Medical Colleges (AAMC) predicting a shortage of primary care physicians of up to 49,300 by 2030, the AIC and other organizations are raising concerns about...
the future of primary care.

“International medical graduates serve a very important purpose in providing primary healthcare in this country, particularly in light of the physician shortage,” said Ana Maria Lopez, MD, MPH, FACP, president of the American College of Physicians (ACP). The ACP and other healthcare organizations have lobbied Congress and regulators to ease some policies that made it more difficult for internationally trained physicians to practice here.

One couple’s story
The difficulties of those policies are well known to Narayanan Krishnamoorthy, MD, and Chitra Mony, MD, a husband and wife practicing in Tallahassee, Florida. They went to medical school in India, then trained in Scotland.

In 2006, Mony matched with Tallahassee Memorial HealthCare’s

How international doctors are licensed to practice in the U.S.

For international medical graduates, getting approval to practice in the U.S. is a long and complicated procedure:

1. They must complete an accredited residency program in the United States or Canada. But first, the Educational Commission on Foreign Medical Graduates must certify the foreign national is academically prepared and has passed the first three components of the U.S. Medical Licensing Examination. Then, the physician must match into a residency program.

2. Once matched, the physician must obtain a visa to participate in medical training. This is usually the J-1 visa, which is limited to seven years, long enough for a residency and a fellowship for a sub-specialty training.

3. After completing residency, J-1 visa holders usually must return to their home countries for two years before they can re-enter the United States, often on an H-1B visa. International residency or fellowship graduates willing to work in medically underserved areas or with underserved patients for three years can apply for a federal waiver of the two-year residency requirement. The biggest sponsor of these waivers is the Conrad 30 program, which allows states to sponsor up to 30 waivers annually. Physicians who obtain clinical J-1 waivers can apply for a temporary H-1B visa in order to work in the United States but must work for the employer sponsoring them for three years. After three years, the physician can apply for permanent resident status (lawful permanent resident, or LPR, status).

4. Doctors may qualify for a temporary H-1B visa to complete U.S. residency training but need a residency program to sponsor them, which many programs won’t do. In addition, to qualify for the H-1B, the physician must generally have passed all three steps of the U.S. medical licensing exam, something that many physicians just beginning residency have not done. The maximum six-year duration of the H-1B can be a problem for physicians who wish to complete both residency and fellowship training in the United States, since that training can take six years, leaving the physician with no time left to practice medicine following training.

5. Whether the physician trains in J-1 status and then obtains a waiver of the two-year home residency requirement, or trains in H-1B status, LPR status following training is not guaranteed. Doctors may qualify for LPR, but an eligible family member or employer must sponsor them. This can take years to complete, especially if the physician is from a country with substantial backlogs like India.
A year later, Krishnamoorthy matched with the same hospital and joined his wife in Florida. Mony, who entered on a national interest visa, was required to work for three years in an underserved area. Krishnamoorthy switched from an H-1B visa, which binds him to one employer, to an H4 visa Employment Authorization Document (EAD) work permit, which allows him more flexibility in working as the spouse of an H-1B visa recipient. They have both applied for green cards to become permanent residents but are in a quota-restricted waiting line that could take decades.

In the meantime, the couple fills multiple gaps in primary care in their community. She is a family practitioner at Tallahassee Memorial. He works four-and-a-half days a week as an internist at a large medical practice while also treating his patients who are admitted to the local hospital and rehabilitation center. He also works half a day a week at a wound treatment center and volunteers to train physician assistants and nurse practitioners, as well as medical students.

The couple have a 13-year-old daughter, who was born in Scotland, and an 8-year-old son, who was born in the United States. They say they want to stay in Tallahassee, but, after 12 years here, their future is still unsettled.

As part of its overhaul of immigration, the Trump administration has announced it intends to end the H4 visa EAD program, which allows H-1B visa spouses, like Krishnamoorthy, to work. He had his H4 visa renewed for three years in April and hopes he will be grandfathered in until 2021 if the program is ended. If not, he would have to apply again for an H-1B visa and return to work for the hospital system or another sponsoring employer.

That could put an end to his practice with the medical group, a practice he says he has built up to 2,000 patients, many of them Medicare recipients who turned to him after two other primary care doctors retired. If that happens, the couple is thinking of relocating to another country with a more welcoming immigration policy for doctors, such as Canada, Australia, or the United Kingdom.

“We are deeply rooted in this community, but what do I say to my 2,000 patients [if I leave]? I want people to know these things are happening,” Krishnamoorthy says. “We have always played by the rules and done everything right, but we might still have to leave.”

### An immigration debate

Most Americans agree that the country needs more international medical graduates, but their fate is tangled up in the larger debate over immigration. Many enter the country on H-1B visas, the same as other highly skilled foreign professionals, particularly IT workers who have drawn the fire of immigration critics.

Bureaucratic restrictions and backlogs have existed for a long time, but critics say it’s gotten worse under President Trump, who has made reducing immigration—legal and illegal—a centerpiece of his administration. Under the Trump administration, H-1B visa approval rates declined from more than 90% in fiscal 2017 to less than 85% in the first two months of fiscal 2018.

U.S. Citizenship and Immigration Services (USCIS) has become more demanding and less respon-

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### Targeted by Trump

Fourteen million doctors’ appointments are provided annually by physicians from Iran, Libya, Somalia, Sudan, Syria, and Yemen—countries targeted by the Trump administration’s travel ban. These doctors provide:

- **1.2 million** appointments per year in Michigan
- **880,000** appointments per year in Ohio
- **700,000** appointments per year in Pennsylvania
- **210,000** appointments per year in West Virginia

The five cities with the highest share of doctors from targeted countries are:

1. **Detroit, Mich.**
2. **Toledo, Ohio**
3. **Los Angeles, Calif.**
4. **Cleveland, Ohio**
5. **Dayton, Ohio**

Source: Immigrant Doctors Project
sive to non-native doctors who want to practice in this country, say Jennifer Minear, JD, and Greg Siskind, JD, immigration attorneys who represent such doctors and the U.S. healthcare organizations that want to hire them.

“Th is is an administration that has a general hostility to immigration, no matter the occupation,” says Siskind. “The overall goal of the administration, I think, is to make the system as unpleasant as possible and try to reduce the number of applicants. I think that is their tactic.”

Minear says USCIS is making it more difficult and time-consuming to renew work visas through “requests for evidence,” demanding proof of everything from doctors’ salaries to their work schedules. From January to November of 2017, USCIS issued around 40 percent more requests than in all of 2016. Minear says USCIS has even challenged whether physicians meet the H-1B requirement that they be “highly skilled.”

“How anyone can assert that a job as a physician doesn’t require a college degree, I don’t know,” she says. “It’s almost like there’s been some sort of internal decision to deny those claims.”

The delays and increased scrutiny are difficult and expensive for the healthcare systems and practices that want to hire the doctors, Siskind says. Uncertainty over when a visa will be approved makes it hard for employers to know when an international medical graduate can be added to a rotation, he says. While visas are eventually renewed, it’s taking its toll. “There are doctors asking themselves whether the U.S. is a home where they want to practice.”

### Data on internationally trained physicians

Percentage of internationally trained doctors by region

- **Northeast**: 32%
- **Midwest**: 24%
- **West**: 20%
- **South**: 24%

### Specialty

Specializations of internationally trained doctors by % of overall U.S. physicians

- **Geriatrics**: 52.7%
- **Endocrinology/diabetes/metabolism**: 40.9%
- **Internal medicine**: 38.6%
- **Oncology**: 34.4%
- **Cardiology**: 34%
- **Pediatrics**: 26.5%
- **Family medicine**: 24.6%

*Source: American Immigration Council*
“How anyone can assert that a job as a physician doesn’t require a college degree, I don’t know. It’s almost like there’s been some sort of internal decision to deny those claims.” JENNIFER MINEAR, JD, IMMIGRATION ATTORNEY

“good long-term bet,” he says.

In June, the U.S. Supreme Court upheld the administration’s travel ban, which severely restricts immigration from Iran, Libya, North Korea, Somalia, Syria, Venezuela, and Yemen. This policy could worsen the shortage of doctors.

According to the Immigrant Doctors Project, which opposes the travel ban, there are more than 7,000 doctors from the targeted countries practicing in the U.S. The travel restrictions will make it harder for physicians from those countries to work here and could impose hardships on those already here who will not risk traveling home for fear of not being able to return.

**State programs**

Some states have stopped waiting for the government to act and started their own programs to make it easier to practice within their borders.

The Minnesota Department of Health’s Office of Rural Health and Primary Care in 2015 began its own program to help offset a projected shortage of 2,000 primary care physicians by 2025. So far, the initiative has funded six residency programs for non-native doctors with the requirement that they practice in underserved areas for five years after graduation.

“We really need (international medical graduates) to provide primary care and we need primary care,” says Yende Anderson, JD, head of the program.

Funding two residencies a year isn’t making a dent in the need, Anderson says, so she is trying to raise $3 million to $4 million a year from foundations and corporations to pay for 10 residencies annually.

UCLA has a program specifically for graduates of medical schools in Latin America. It allows qualified graduates who legally reside in the United States to get the same hands-on training with California physicians as UCLA medical school students.

More programs like that are needed to bring in Hispanic physicians, says Elena Rios, MD, MSPH, FACP, president of the National Hispanic Medical Association. Immigrant Hispanic communities are more likely to trust and seek treatment from doctors of similar backgrounds, she says.

“When people get sick, they want to be treated by someone they’re comfortable with, someone who speaks Spanish,” she says.

**Pushing back**

As the primary care shortage worsens, healthcare organizations are calling for reform, but so far, progress has largely been limited to fighting to keep a faulty system from getting worse. For example, the AAMC, ACP, and other groups in June persuaded USCIS to reverse its decision to no longer accept AAMC resident stipend data for prevailing wage information on H1-B visas. That had resulted in the denials of visa requests from IMGs scheduled to begin work in residency programs July 1.

Some Indian-born physicians have formed Physicians for American Health Care Access to advocate that Congress create a separate path for doctors to obtain green cards. They also want reform of the rule that says no more than 7% of H-1B visas may be issued to natives of any one country in a year. That quota is largely responsible for the backlog of physicians from India, which accounts for more applicants than any other country.

One of the group’s founders is Alur, an internist at Marion Veterans Affairs Medical Center in southern Illinois. He has to renew his H-1B visa every three years and faces a decades-long wait for a green card. “I’m 42,” he says. “I can’t be doing this in my fifties and sixties. If things don’t go right then my job is in peril and my life here is in peril.”

James F. Sweeney, is a frequent contributor to Medical Economics, our sister publication, in which this article first appeared.
Receiving a cancer diagnosis can be a stressful experience not only for the patient, but also for their family members. In addition to the shock of receiving the diagnosis, patients may also be concerned about their financial obligations regarding their treatment plan.

That’s why Bensalem, Pennsylvania-based Alliance Cancer Specialists provides patients and family members with access to a social worker (who is imbedded at one of the oncology group’s 11 practices) to help them navigate through their emotional journey and the financial impacts of oncology treatment, says Ann Marie Edwards, CEO.

This social worker is funded through the group’s participation in CMS’ Oncology Care Model. Under this model, physician practices have entered into payment arrangements that include financial and performance accountability for episodes of care surrounding chemotherapy administration to cancer patients. CMS is also partnering with commercial payers in the model.

Another benefit of its involvement in CMS’ Oncology Care Model is having access to data—although “it’s usually about a quarter behind”—on its patients’ total cost of care. This information allows the oncology group to identify its highest-cost patients and work to curb some of those costs. For example, it can focus more efforts on helping certain patients avoid emergency room visits, she says.

Edwards notes that Alliance Cancer Specialists also receives data feeds from Philadelphia’s HealthShare Exchange, a regional health information exchange (HIE) that links the EHRs of different hospitals and health systems, medical centers, and clinics, in addition to claims data from payers. These data feeds include real-time updates when one of the oncology group’s patients presents at a regional hospital emergency room, when the patient is discharged, and if the patient is going to a rehabilitation facility.

In the future, Edwards would like this information to flow directly from the regional HIE to the practice’s EHR. For now, her group uses a population health platform from HealthEC, which provides value-based care solutions and services, that sends email notifications to Alliance Cancer Specialists when its patients experience a healthcare-related event.

Data about discharge and care transition episodes allows the oncology group to know when its patients return home from the hospital or if they’re going to a rehabilitation facility, which trig-

### Payer Incentives

Here are three reasons Edwards says private payers should be interested in partnering with community oncology practices on value-based care contracts:

1. **Community oncology settings are lower-cost settings** when compared to cancer centers that are being acquired by hospital networks, where the cost of care will likely increase, she says. That’s particularly the case in Philadelphia, adds Edwards, “where everybody is being bought by hospitals.”

2. **More proactive information between community practices and payers will lead to savings.**

3. **Value-based care can also help retain members.** “Creativity is required for payers that want to engage in covering high-cost diseases,” says Edwards. “It’s not by bundling the total cost, but by lowering costs while giving patients value that will retain members.”

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**New Oncology Payment Models in Action**

**Why more payers might want to get involved**

**by AINE CRYS**
Many patients weren’t attributed to the practice for follow-up care.

**Upside for payers**

At press time, Edwards has been unsuccessful at getting private payers to work with the group on value-based contracts. Those payers could be missing out.

Ron Barkley, MS, JD, president of the Cancer Center Business Development Group, which consults with oncology providers on value-based care arrangements, estimates that payers could stand to save 12% by engaging in value-based contracts for cancer care. Despite the upside, many payers are locked into legacy technology systems, “where they can’t deal with anything but claims data, and that prevents them from engaging with providers on value-based contracts for cancer care,” Barkley says.

In addition to technology hurdles, he says many payers are unwilling to be transparent about their total spend on cancer treatment for patients.

Still, he’s bullish on value-based care for cancer treatment. Here’s his advice for payers who haven’t yet offered value-based contracts to oncology providers:

**Give a little.** There’s a huge opportunity for providers to reduce total spend by using care management techniques to prevent patients’ unnecessary visits to the emergency room, says Barkley. Through monthly payments to oncology providers, payers can partially subsidize the cost of hiring a care manager who can reach out to patients within 48 hours of their treatment. And the oncology provider can use insight gained from calls to patients to determine if they need a prescription for anti-nausea medication or if a same-day appointment with an oncology nurse is appropriate.

**Encourage performance transparency.** “If there’s evidence-based medicine and documentation that these are the drugs that should be used for this condition, why would you not follow that?” asks Barkley.

But changing providers’ behavior can be difficult. Key to making changes to cancer treatment is provider engagement, says Mah-Jabeen Soobader, PhD, chief analytics officer at Archway Health, which consults with providers, payers, and employers on value-based care programs.

She recommends tapping into physicians’ competitive nature and being transparent about the data associated with their performance when compared to other oncologists in their group or department. “Most times, they self-correct after looking at the data,” she says.

**Work with providers to help them manage patient expectations.** Oncology providers need to be disciplined around terminal, end-of-life issues and educating patients and their family members about the true side effects of treatments, says Barkley.

That means providers shouldn’t be providing chemotherapy two hours before death or sending the patient to the intensive care unit for three days. Instead, oncology providers should be using palliative care and hospice, he adds.

**Learn from other programs.** Barkley describes CMS’ Oncology Care Model as “very well received,” with participation from approximately 190 organizations nationwide.

“A positive of (the Oncology Care Model) is having a large-scale opportunity to start to understand the total cost that goes into cancer and the opportunity to reduce the spend with care management,” he says.

Still, the oncology care model performance-based payment methodology/prediction model is a “very aggressive, large program which is overly complex,” says Barkley.

The first indication of model deficiencies became apparent with the February 28 release of initial performance-based payment calculations for the first performance period, says Barkley. Reportedly, only 20% of oncology care model participants earned performance-based payment in the first payment period, he says.

Three of the challenges associated with the oncology care model’s predictive model, according to Barkley, include:

- Many patients weren’t attributed accurately to the providers delivering their oncology treatment.
- Statistical bias in the methodologies for treating prostate and bladder cancer.
- Lack of statistical adjustment for novel therapies, such as immunotherapies to treat leukemia and lymphoma, which were introduced after the 2012 to 2015 baseline price period.

CMS is aware of these challenges and is making updates to the model to address these issues, says Barkley.

Aine Cryts is a writer based in Boston.
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Five Questions You Should Be Asking

If you’re not asking the right questions, your healthcare organization could be missing out. by TRACEY WALKER

Q: Do we need to redefine innovation?
“Incumbents start out as innovators, but as they grow and scale, they become comfortable with the status quo, which ultimately leads to their demise. Every incumbent healthcare industry player should be asking whether they need to redefine their historical definition of innovation within the context of their industry to ignite future growth.”
—Ruchin Kansal, author of “Redefining Innovation” and leader of the digital business strategy group, healthcare, insurance, and life sciences sectors, at Virtusa, a digital engineering and outsourcing services provider

Q: What is our strategy for organic vs. inorganic growth?
“Most health systems are looking to M&A as a growth driver, but many struggle to answer how they can drive sustainable growth through their existing services and footprint. This will typically require improvements in patient engagement and access and new approaches to service line and contracting strategies.”
—Liam Walsh, line of business leader for Healthcare & Life Sciences at KPMG, a tax, audit and advisory firm

Q: Should the customer experience we provide consumers really differ from the experience they receive from other businesses?
“Why would people treat interactions with their healthcare providers any differently than their other consumer-oriented interactions? Could they afford to manage those high-stakes healthcare interactions via the same convenient channels they use to handle oil changes and retail experiences? Would they be willing to try? They certainly would and have. As we’ve seen consumerism influence the direction of healthcare technology, a once potentially ‘dumb’ question has paved the way for an improved patient experience and outcomes.”
—Josh Weiner, COO of Solutionreach, a healthcare technology company

Q: How do you describe your value proposition?
“When we meet prospective clients, our first question is usually: ‘Does your product work well and is it safe?’ The response from company senior leadership is often convoluted and guarded. In some cases, there are concerns about overstating efficacy or safety benefit. But often there has been no focus on building a clear product value story. Without a strong value message, there can be considerable challenges in communications, marketing, patient and clinician education, engagement with payers, and other areas.”
—Bill Berry, president, Berry & Company, a healthcare public relations agency

Q: What exactly do you mean by improved healthcare quality?
“I asked my team this question after a health plan CMO asked us to explain to them how our population health management services improve quality. This led to a robust discussion on the definition of quality, the detail of which we ultimately shared with the health plan.”
—Christopher Long, CEO, AxisPoint Health, a population health management company

Two questions to ask vendors
CAR T-cell Therapy

Payers react to new life-saving treatment with huge price tag

By AINE CRYTS

How CAR T-cell therapy works

This treatment involves taking a patient’s own blood and genetically modifying the immune cells—also called T cells—in a lab and then returning the modified cells to the patient’s body, says Catherine Bollard, MD, director of the Center for Cancer and Immunology Research at Washington, D.C.-based Children’s National Health System.

Chemotherapy kills patients’ healthy and cancerous cells, whereas CAR T-cell therapy is much more targeted and only kills cancer cells, says Bollard.

CAR T-cell therapy is a new cancer treatment that’s already saving lives. But it comes with significant costs.

Yescarta (axicabtagene ciloleucel), approved by the FDA for adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, racks up $373,000 per treatment. Kymriah (tisagenlecleucel), approved for patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia that’s refractory or in second or later relapse, amounts to $475,000 per treatment.

There’s also additional costs to consider, such as responding to adverse events that can occur, which can include ICU visits to treat symptoms associated with cytokine release syndrome and administering and monitoring treatments. Those costs can reach up to $1 million, according to experts.

Cytokine release syndrome can cause fever, nausea, headache, rash, rapid heartbeat, low blood pressure, and trouble breathing. While most patients have a mild reaction, other patients can have a severe response to the treatment, and some may even die, according to the National Cancer Institute.

Costs aside, Frederick Locke, MD, a medical oncologist and translational researcher at Moffitt Cancer Center in Tampa, Florida, enthuses that, with a single infusion of CAR T cells, 83% of patients in the ZUMA-1 clinical trial for the treatment of patients with chemorefractory-aggressive B-cell non-Hodgkin lymphoma had a measurable response with Yescarta. More than 50% experienced a complete disappearance of their lymphoma. Even more promising, after a median follow-up at nearly nine months, 44% of those patients whose lymphoma had disappeared remained in remission. Locke was a principal investigator for the clinical trial.

The 101 patients included in the trial had tumors that were growing, despite chemotherapy treatments, prior to the new treatment. It’s likely that these patients wouldn’t have lived more than six months, says Locke. And even more remarkable, the patients, prior to the new treatment, stood less than a one in 10 chance of having their lymphoma disappear.

In June, Novartis revealed 14-month results from a clinical trial of Kymriah. According to an announcement, “ongoing durable responses are achievable with Kymriah (tisagenlecleucel) when administered to adult patients with relapsed or refractory diffuse large B-cell lymphoma.” The overall response rate was 52% among 93 evaluable patients who had been followed for three months or more or discontinued earlier. Forty percent of patients experienced a disappearance of their cancer, whereas 12% achieved a partial response.

The company highlighted that patients had a 65% chance of being disease-free one year after
onset of response; 54% of patients who initially achieved a partial response later experienced a complete response. In addition, response rates remained consistent with previous reports and the safety profile was maintained with no emergence of new safety signals, according to Novartis.

UPFRONT INVESTMENT
The cost to develop in-house capabilities to administer these immunotherapies can be significant. Providing the therapy requires removing cells from patients and then having them shipped properly to a facility where they can be combined with the CAR T-cell product. Then the healthcare facility needs to be able to receive the final CAR T-cell product, which involves having experts who understand cellular therapy. Preparation of the treatment also requires the ability to properly freeze and thaw cells.

For this reason, providers of CAR T-cell therapy must make significant infrastructure investments and secure the appropriate clinical and administrative expertise, says Locke. Facilities and physician groups that have similar expertise already, such as with stem-cell transplants, will be able to launch these therapies more quickly and more easily, he says.

Healthcare facilities involved in CAR T-cell therapy also need to invest in the care to treat patients’ side effects. They need physicians who are familiar with the therapy and nurses who know how to manage the toxicities, says Locke. Facilities also need to be able to retain databases on patient outcomes. Alternatively, they could contract this work out to a blood marrow treatment center, he says.

Providers should also recognize the need for accreditation. The ASCO Post reports that the Foundation for the Accreditation of Cell Therapy (FACT) has played a pivotal role in “advancing the safe and effective delivery of immune effector (e.g., CAR T-cell) therapy.” Locke points to FACT accreditation as key to providing the therapy at a provider organization.

Legal and risk-management teams at provider organizations also need to be involved, because delivering this treatment requires risk assessment, he says. Legal teams need to ensure that patient confidentiality is maintained, and that the organization is protected if that information is breached. Issues can also occur when transferring

Types of Adoptive T-Cell Therapy
There are three main types of adoptive T-cell therapy (177) As of July 31, 2018, only one type, chimeric antigen receptor (CAR) T-cell therapy, had been approved by the U.S. Food and Drug Administration.

CAR T-cell therapy. T cells are harvested from a patient’s blood and genetically modified in the laboratory to have a new gene that encodes a protein called a CAR. The T cells are expanded in number and infused back into the patient. The CAR modification targets the T cells specifically to the patient’s cancer cells and triggers them to attack when they get there.

T cell receptor (TCR) T-cell therapy. T cells are harvested from a patient’s blood and genetically modified in the laboratory to have a new gene that encodes a protein called a TCR. The T cells are expanded in number and infused back into the patient. The TCR modification targets the T cells specifically to the patient’s cancer cells and triggers them to attack when they get there.

Tumor-infiltrating lymphocyte (TIL) therapy. T cells are harvested directly from a patient’s tumor, expanded in number in the laboratory, and infused back into the patient. Many of these T cells naturally recognize and kill the patient’s cancer cells.

American Association for Cancer Research (AACR) Cancer Progress Report 2018
Payer and provider representatives say organizations typically coordinate payment for this treatment with customized agreements on a per-patient basis.

Deirdre Saulet, a consultant at the Advisory Board Company, agrees. “My sense is that the vast majority of private payers are paying for this. It’s just burdensome,” she says.

As CAR T-cell therapy momentum grows, payers are approving the therapy more quickly, says Saulet. When she started talking to providers about their experience with payers in February, it took them many weeks to secure approval; now it’s taking three to four weeks, she says. Still Saulet says it could take regional payers without the depth of expertise covering CAR T-cell therapies longer to negotiate these per-patient agreements with providers.

Providers that have secured timely coverage of this treatment have been transparent about the cost to treat previous patients, she says. But most providers don’t have the volume of patients to provide an average estimate of treatment costs. Most of the provider organizations Saulet has talked to have only provided CAR T-cell therapy to between five to 10 patients.

Saulet says one of the provider organizations she works with has been providing the treatment to Medicaid patients free of charge. While admirable, it’s not sustainable for the long term.

**BROADER USES**

Jennie Crews, MD, a medical oncologist at the Seattle Cancer Care Alliance Survivorship Clinic, says there’s potential for CAR T-cell therapy to expand into treatment of solid cancers, such as lung and breast cancer.

Crews is also interested in the ability to combine CAR T-cell therapy with other expensive treatments, such as checkpoint inhibitors. That’s because combining the therapies would help oncologists engage more effectively with the immune system, she says.

Also on Crews’ radar are efforts to develop off-the-shelf CAR T-cell products, such as Allogene Therapeutics’ UCART19, which could be used to produce “universal” T cells, she says. This has the potential to decrease the cost and increase access to this therapy, she says. The product wouldn’t require an individual patient’s cells to tailor the therapy on a per-patient basis. Instead, it would use genetically modified T cells from a healthy donor, which could then be used to treat patients.

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Aine Cryts is a writer based in Boston.
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Ten years from now, driverless cars might be the norm. Service bots might perform jobs that humans would prefer not to do. And what about cancer care? If a cure hasn’t been found for this deadly disease by then, what type of changes will have occurred? Several positive ones, say cancer care experts. For more on the shifting cancer care landscape, and how it will impact healthcare quality and costs, we asked experts to weigh in. Here, they share their predictions.

**Prediction #1**

**More precise treatments**

Carlos L. Arteaga, MD, director at UT Southwestern Simmons Cancer Center in Dallas, which provides care to more than 105,000 hospitalized patients and oversees approximately 2.4 million outpatient visits annually, expects widespread use of precision cancer medicine, which is using a cancer’s molecular profile to determine the best therapy approach for individual patients, such as single-targeted therapies or a combination. The therapy will be applicable to most solid tumors, such as those in the breast, colon, lung, and ovaries. Consequently, traditional chemotherapy will be used less frequently.

Precision medicine also includes collecting big data sets on individuals and populations and integrating that data to better predict, prevent, diagnose, and treat cancer, says Jeffrey Golden, MD, chair of pathology at Brigham and Women’s Hospital in Boston, which includes 150 outpatient practices with more than 1,200 physicians. Golden is also professor of pathology at Harvard Medical School, which serves as a home base for more than 10,000 physicians and scientists with faculty appointments. Information would include biologic data such as a patient’s genome and other large data sets, as well as routine chemistry, hematology, and microbiology lab test results.

“Recent innovations help to detect tumor cells and tumor DNA in patients’ blood, known as a ‘liquid biopsy,’ without the need for invasive procedures such as surgery.”

JEFFREY GOLDEN, MD, BRIGHAM AND WOMEN’S HOSPITAL

**Prediction #2**

**More effective approaches**

Ten years from now, fundamental knowledge about using immunotherapy to treat cancer will provide scientists with a much better understanding of why some patients respond to this treatment while others don’t. “This knowledge—drawn from data from the more than 4,000 immunotherapy clinical trials ongoing today as well as academic centers of excellence where in-depth laboratory analyses are carried out parallel to clinical trials—will affect how treatment decisions are made,” says Jill O’Donnell-Tormey, PhD, CEO, and director of scientific affairs at the Cancer Research Institute in New York, which supports more than 3,000 scientists globally. “These sources will also provide insight into strategies for improving immunotherapy’s effectiveness in more patients and in diverse cancers.”

It may become possible, for example, to draw a patient’s blood and know precisely why their immune system is not keeping their cancer under control. “Armed with this knowledge, doctors will be able to develop personalized treatment regimens that include combinations of drugs designed to counter whatever is preventing the immune system from attacking the cancer,” O’Donnell-Tormey says.

**Prediction #3**

**Broader use of T-cell based therapies**

These therapies will be more effective and more widely used across hematological cancers as
well as solid tumors, says O’Donnell-Tormey. Research and engineering technologies will allow for the creation of either autologous (coming from the patient) or off-the-shelf (mass produced) T cells that can recognize multiple targets on cancer cells, making them more specific to cancer and thus reducing damage to normal cells, she says. Advances in genetic engineering will also enable the inclusion of “safety switches” that allow oncologists to control the rate of T-cell expansion or deactivate T cells entirely when they have finished the job of eliminating cancer cells. This also will reduce T-cell therapy’s toxicity and side effects, while maintaining its ability to attack cancer cells.

**Prediction #4**

**Earlier detection**

Advanced single-cell (or smaller numbers of cells) and single molecule (or smaller numbers of molecules) analytics will drive improved diagnostics, prognostics, treatment stratification, and more precise entry into clinical trials leading to novel and improved therapies, Golden says. “Recent innovations help to detect tumor cells and tumor DNA in patients’ blood, known as a ‘liquid biopsy,’ without the need for invasive procedures such as surgery,” he says. Through a simple blood draw, tumors are being detected and specific mutations identified. Today this technology is primarily assisting in monitoring therapy; essentially evaluating if treatment is reducing tumor burden, without the need for imaging or other tests. These advances will likely provide improved diagnostics as well as early detection for cancer, or possibly even new prevention strategies.

Kevin Hrusovsky, founder of Powering Precision Health and chairman and CEO of Quanterix, a company focused on advancing the science of precision health, says studies show promise for the reliability of specific biomarkers, which are found in blood—such as PSA—in determining if a patient has a recurrence of cancer at its earliest stages, while other markers show promise for detecting cancers long before any symptoms present. While blood tests for early cancer detection today are primarily used in research environments, he foresees a day when they will be offered as point-of-care tests and be available in doctors’ offices on a routine basis.

Hrusovsky expects biomarker readings to be part of routine physicals. By taking a baseline reading of a person’s biomarker levels via a blood test, doctors will be able to detect changes to these levels, indicating that diseases like cancer may be emerging, helping doctors potentially catch it before stage one. Consequently, doctors will be able to diagnose and treat cancer earlier, he says.

**Prediction #5**

**More artificial intelligence applications**

Digital pathology, which entails creating digital images from glass slides, will advance cancer care by developing artificial intelligence algorithms, Golden says. Recent advances, empowered by technical innovations in computer science, have permitted the analysis of data from digital images, advancing pathologists’ ability to more accurately, more safely, and with higher quality provide additional information regarding the biologic behavior of many abnormal growths.

Golden also predicts better forecasting of growth rates, metastatic potential, and even where cancer might develop. The positioning of artificial intelligence in the pathologist’s arsenal also has promise for clinical trials; improved patient selection will likely better define appropriate therapeutics and ultimately improve the approval of pharmaceuticals by identifying the patient population most likely to respond. Finally, digital images in combination with artificial intelligence will play an essential role in the research, development, and implementation of immunotherapy, he says.

**Prediction #6**

**Drug development changes**

Biomarkers will change the way pharmaceutical companies develop drugs, especially for oncology, says Hrusovsky. There’s already evidence of a growing openness to utilizing precision medicine approaches. The National Comprehensive Cancer Network (NCCN) has already embraced biomarkers, says Hrusovsky, and predicts they will become standard of care, just as all cancer will be personalized.

“Precision medicine approaches can be game changers in oncology treatment, because not all cancers are alike and drugs perform differently depending on the patient and prognosis.”

KEVIN HRUSOVSKY, POWERING PRECISION HEALTH
to using biomarkers for drug development as a complement to symptomatic clinical endpoints, which are measured in clinical research to determine if a drug is working, with recent new guidance from FDA Commissioner Scott Gottlieb that biomarkers can be a reliable tool for advancing clinical trials, he says. By using biomarkers, researchers have the potential to see a drug’s effect on the body long before traditional symptomatic or imaging endpoints could reveal the drug’s effect.

Pharmaceutical researchers will also increasingly use biomarkers to measure certain drugs’ efficacy and toxicity on individual patients. “Precision medicine approaches can be game changers in oncology treatment, because not all cancers are alike and drugs perform differently depending on the patient and prognosis,” Hrusovsky says.

**Prediction #7**

**Personalized cancer vaccines**

Cancer vaccines will become an integral part of patients’ treatment protocols, especially vaccines that provide the immune system with specific cancer targets that are unique to an individual patient’s tumors, O’Donnell-Tormey says. These targets, known as neoantigens, have been shown to stimulate spontaneous anti-cancer immune responses in cancer patients and hold great potential as therapeutic targets. Advances in computational prediction of neoantigen expression will enable doctors to design personalized vaccines that drive the immune system to seek out and destroy unique antigens that are likely to appear in patients’ tumors, says O’Donnell-Tormey. Vaccines will likely be given in combination with other immunotherapies designed to overcome immune suppression at the tumor site and facilitate a targeted immune response.

**Prediction #8**

**More reliance on nonphysicians**

Advanced practice providers, e.g., nurse practitioners and physician assistants, will provide care to many more cancer patients, particularly at academic centers, says Arteaga. This will occur due to more treatment options, the significant prolongation of patient survival, and decreased treatment time due to better therapies, as well as a huge emphasis on cancer prevention.

Already, the use of advanced practice providers in oncology practices is growing—from 52% in 2014 to 81% in 2017—according to the American Society of Clinical Oncology’s annual Practice Census.

Arteaga says advanced practice providers will also provide care to cancer survivors, who will require an increasing use of telemedicine because physical cancer facilities may not be able to accommodate the large number of survivors.

*Karen Appold is a medical writer in Lehigh Valley, Pennsylvania.*
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Make Tech a Priority

Top advice from tech leaders by DONNA MARBURY

Leading the technology department of a healthcare organization comes with unique challenges. While technology trends in other industries can move at lightning speeds, striking a balance between innovation, corporate culture, and security concerns can lead to technology lags in healthcare.

To minimize disruptions and ensure healthcare organizations can move quickly when new technology innovations arrive, strong partnerships and communication between technology leaders and other C-suite executives are key.

Mark Lantzy, senior vice president and chief information officer (CIO) of Indiana University Health in Indianapolis, the largest health system in Indiana, says CIOs and chief technology officers (CTOs) have two main priorities:

1. Educating executives about the important role that technology has across all business lines; and
2. Aligning IT with business priorities.

“Packaging IT strategy and IT initiatives into language that is consumable and actionable by the C-suite is an under-rated skill set among CIOs and their chief medical informatics partners,” says Lantzy.

Ensuring technology aligns with business and clinical strategies is paramount, says Jayashree Raman, senior vice president and CIO at Cooper University Health Care, an academic health system in New Jersey. “It’s our responsibility to provide accurate information and educate the decision makers about the integration requirements, support costs, risks, and security implications of their decisions,” Raman says. “This enables them to be an informed decision maker as they continue to grow and run the business.”

Building relationships

Strong partnerships between organization leaders is vital to ensure priorities are aligned, says Steve Betts, senior vice president and CIO of Health Care Service Corp., a health plan that serves Illinois, Montana, New Mexico, Oklahoma, and Texas.

Betts says that although the technology team at Health Care Services Corp. is embedded in all departments, the department has increased its strategy and development with front lines of business, including group and retail departments.

“This is because the capabilities that we bring to market to our members through technology are increasingly important to our customer-facing parts of the business. This is more so than it has been historically,” Betts says.

Paul Browne, CIO at Henry Ford Health System, which includes more than 1,200 physicians in the Detroit region, says his relationships with clinical leaders ensure tech strategy is aligned with patient needs.

Close relationships with the financial leadership are also essential, since technology initiatives are expensive, he says.

In order to build those relationships, Browne is active in several committees, including the capital allocation, health system strategic plan, and health system quality committees.

“We don’t have very many technology-specific meetings,” he says. “What I try to do is use other forums and opportunities to educate people about the technologies that are important to the topic we’re discussing.”

He also helps temper expectations when other health system leaders read about new technology trends.

“Usually there’s a lot of hype around new technology and a lot of fanciful thinking about all the problems that technology will be able to solve,” he says. “Many times new technology can solve a lot of specific and focused problems, but it’s not a silver bullet. I think it’s incredibly important to educate the C-suite about what’s realistic with
new technology and what’s not realistic, so that they can calibrate their expectations appropriately.”

Sharing knowledge
Betts holds monthly meetings that discuss the success and challenges of technology-based strategies being deployed within the organization. But he also regularly discusses with senior leaders how technology can improve the business. Most of those conversations center around data analytics, artificial intelligence, and digital tools.

“Focusing on business outcomes and possibilities that can be driven through technology is the most important thing,” Betts says. “It’s not a point-in-time conversation about technology. It’s really an ongoing conversation about the role technology needs to play in strategy, in addition to supporting other non-traditional strategies.”

Betts adds that his team has created an interactive PDF called Health Tech Radar that discusses current technologies, those that are important to the future, and those being piloted by the organization. It is updated regularly and is available to all employees and executives to help them stay abreast of the technology strategy.

“What we’ve done is make this a dynamic tool so that each technology has a video explanation and our point of view on how we would use it in healthcare,” Betts says. “We also have some information that ties to broader themes in healthcare, not just one kind of technology. It’s an interactive, immersive tool that executives and other employees can use to really get their wheels turning on how emerging technology can drive business in the future.”

Securing funding is a top challenge
Working within the regulatory and financial restraints of a healthcare organization creates unique challenges for technology leaders. For example, Raman says that one challenge is securing technology resources as the payment landscape changes in healthcare.

“As the payment models shift, we all have to continue to do more with less. We are competing for the same limited dollars with departments that are involved in direct patient care,” Raman says. “So, do we spend to replace an outdated MRI machine, or should we attempt to introduce some new IT technology?”

Browne says that due to constantly changing technology, it is more difficult to get leaders to agree on which technologies to invest in.

“There are so many different ways to use technology to improve healthcare,” he says. “It’s often very difficult to get all the key leaders in an organization to agree on priority and what specific problems we want to solve with technology.”

Donna Marbury is a writer in Columbus, Ohio.

Raman holds IT governance meetings regularly to educate leaders on technology and get input from across departments. “If virtual visits are part of the strategic plan, we need to bring forward the different technology options to support the strategic plan,” she says. “As technology continues to be used for competitive advantages, it’s all the more important for helping the C-suite connect the dots.”

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Introducing

Delstrigo™
doravirine/lamivudine/
tenofovir disoproxil fumarate
100 mg/300 mg/300 mg tablets

Please read the adjacent Brief Summary of the Prescribing Information, including the Boxed Warning about posttreatment acute exacerbation of Hepatitis B.
Brief Summary of the Prescribing Information for DELSTRIGO™ (doravirine, lamivudine, and tenofovir disoproxil fumarate) tablets, for oral use

WARNING: POSTTREATMENT ACUTE EXACERBATION OF HEPATITIS B
Severe acute exacerbations of hepatitis B (HBV) have been reported in patients who are coinfected with HIV-1 and HBV and who discontinue lamivudine-containing antiretroviral therapy (ART), which are components of DELSTRIGO. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue DELSTRIGO. If appropriate, initiation of anti-HBV therapy may be warranted.

INDICATIONS AND USAGE
DELSTRIGO is indicated as a complete regimen for the treatment of HIV-1 infection in adult patients with no prior antiretroviral treatment history.

DOSEAGE AND ADMINISTRATION
Testing When Initiating and During Treatment with DELSTRIGO
Prior to or when initiating DELSTRIGO, test patients for HIV infection.
Prior to or when initiating DELSTRIGO, and during treatment with DELSTRIGO, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus.

Recommended Dosage
DELSTRIGO is a fixed-dose combination tablet and the dosage of lamivudine and TDF cannot be adjusted. DELSTRIGO is not recommended in patients with estimated creatinine clearance less than 50 mL/min.

Dosing Adjustment with Rifabutin
If DELSTRIGO is co-administered with rifabutin, take one tablet of DELSTRIGO once daily, followed by one tablet of doravirine 100 mg (PIFELTRO™) approximately 12 hours after the dose of DELSTRIGO for the duration of rifabutin co-administration.

DOSAGE FORMS AND STRENGTHS
DELSTRIGO film-coated tablets are yellow, oval-shaped, debossed, with the corporate logo and 776 on one side and plain on the other side. Each tablet contains 100 mg doravirine, 300 mg lamivudine, and 300 mg tenofovir disoproxil fumarate (equivalent to 245 mg of tenofovir disoproxil).

CONTRAINDICATIONS
DELSTRIGO is contraindicated when co-administered with drugs that are strong cytochrome P450 (CYP) inducers. Because of DDI risk, do not co-administer with drugs that are strong CYP3A inhibitors or inducers. In addition, DELSTRIGO is contraindicated in patients with a previous hypersensitivity reaction associated with lamivudine.

WARRIORS AND PRECAUTIONS
Severe Acute Exacerbation of Hepatitis B in Patients Coinfected with HIV-1 and HBV
All patients with HIV-1 should be tested for the presence of HBV before initiating antiretroviral therapy.

Severe acute exacerbations of hepatitis B (e.g., liver decompensation and liver failure) have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued current ART and TDF and may occur with discontinuation of DELSTRIGO. Patients who are coinfected with HIV-1 and HBV who are taking DELSTRIGO should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment with DELSTRIGO. If appropriate, initiation of anti-HBV therapy may be warranted, especially in patients with advanced liver disease or cirrhosis, since post-treatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure.

New Onset or Worsening Renal Impairment
Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of TDF, a component of DELSTRIGO.

DELSTRIGO should be avoided with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple nonsteroidal anti-inflammatory drugs [NSAIDs]). Cases of acute renal failure after initiation of high-dose or multiple NSAIDs have been reported in HIV-infected patients with risk factors for renal dysfunction who appeared stable on TDF. Some patients required hospitalization and renal replacement therapy. Alternatives to NSAIDs should be considered, if needed, in patients at risk for renal dysfunction.

Persistent or worsening bone pain, pain in extremities, fractures, or muscle weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function in at-risk patients.

Risk of Adverse Reactions or Loss of Virolologic Response Due to Drug Interactions
The concomitant use of DELSTRIGO and certain other drugs may result in known or potentially significant drug interactions, some of which may lead to:
- Loss of therapeutic effect of DELSTRIGO and possible development of resistance.
- Possible clinically significant adverse reactions from greater exposures of a component of DELSTRIGO.

See Table 5 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during DELSTRIGO therapy, review concomitant medications during DELSTRIGO therapy, and monitor for adverse reactions.

Bone Loss and Mineralization Defects
Bone Mineral Density
In clinical trials in HIV-1 infected adults, TDF (a component of DELSTRIGO) was associated with slightly greater decreases in bone mineral density (BMD) and increases in biochemical markers of bone metabolism, suggesting increased bone turnover relative to comparators. Serum parathyroid hormone levels and 1,25-Vitamin D levels were also higher in subjects receiving TDF. The effects of TDF-associated increases in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. Assessment of BMD should be considered in HIV-infected adult patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation with calcium and Vitamin D was not studied, such supplementation may be beneficial in all patients. If bone abnormalities are suspected, then appropriate consultation should be obtained.

Mineralization Defects
Cases of osteomalacia associated with proximal renal tubulopathy, manifested as bone pain or pain in extremities and which may contribute to fractures, have been reported in association with the use of TDF. Arthralgias and muscle pain or weakness have also been reported in cases of proximal renal tubulopathy.

Hypophosphatemia and ostteomalacia secondary to proximal renal tubulopathy should be considered in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving products containing TDF.

Immune Reconstitution Syndrome
Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections such as Mycobacterium avium infection, cytomegalovirus, Pneumocystis jirovecii pneumonia (PCP), or tuberculosis, which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves’ disease, polymyalgia, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable and can occur many months after initiation of treatment.

ADVERSE REACTIONS
The following adverse reactions are discussed in other sections of the labeling:
- Severe Acute Exacerbation of Hepatitis B in Patients Coinfected with HIV-1 and HBV
- New Onset or Worsening Renal Impairment
- Bone Loss and Mineralization Defects
- Immune Reconstitution Syndrome

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 to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions in Adults with No Prior Antiretroviral Treatment History
The safety assessment of DELSTRIGO is based on Week 48 data from two Phase 3, randomized, international, multicenter, double-blind, active-controlled trials. A total of 747 subjects received doravirine either as the sole entity in combination with other antiretroviral drugs as background regimens (n=383) or as the fixed-dose DELSTRIGO (n=364), and a total of 747 subjects were randomized to control arms.

In DRIVE-AHEAD (Protocol 021), 728 adult subjects received either DELSTRIGO (n=364) or EFV/FTC/TDF once daily (n=364). By Week 48, 3.3% in the DELSTRIGO group and 6% in the EFV/FTC/TDF group had adverse events leading to discontinuation of study medication.

Adverse reactions reported in greater than or equal to 5% of subjects in any treatment group in DRIVE-AHEAD are presented in Table 1.

Table 1: Adverse Reactions* (All Grades) Reported in ≥5% of Subjects in Any Treatment Group in Adults with No Antiretroviral Treatment History in DRIVE-AHEAD (Week 48)

<table>
<thead>
<tr>
<th>Reaction</th>
<th>DELSTRIGO On Once Daily</th>
<th>EFV/FTC/TDF On Once Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=364</td>
<td>N=364</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7%</td>
<td>32%</td>
</tr>
<tr>
<td>Nausea</td>
<td>5%</td>
<td>7%</td>
</tr>
<tr>
<td>Abnormal Dreams</td>
<td>5%</td>
<td>9%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>3%</td>
<td>7%</td>
</tr>
<tr>
<td>Rash‡</td>
<td>2%</td>
<td>12%</td>
</tr>
</tbody>
</table>

*Frequencies of adverse reactions are based on all adverse events attributed to trial drugs by the investigators.

No adverse reactions of Grade 2 or higher (moderate or severe) occurred in ≥2% of subjects treated with DELSTRIGO.

Rash includes: rash, erythematous rash, generalized rash, macular, maculopapular, papular, or pruritic.

The majority (65%) of adverse reactions associated with DELSTRIGO occurred at severity Grade 1 (mild).

Neuropsychiatric Adverse Events
For DRIVE-AHEAD, the analysis of subjects with neuropsychiatric adverse events by Week 48 is presented in Table 2. The proportion of subjects who reported one or more neuropsychiatric adverse events were 24% and 57% in the DELSTRIGO and EFV/FTC/TDF groups, respectively.

A significant, numerically lower proportion of neuropsychiatric adverse drug reactions occurred in subjects treated with EFV/FTC/TDF compared to EFV/FTC/TDF-treated subjects reported neuropsychiatric adverse events by Week 48 in the three pre-specified categories of dizziness, sleep disorders and disturbances, and altered somnolence.

Table 2: DRIVE-AHEAD - Analysis of Subjects with Neuropsychiatric Adverse Events*(Week 48)

<table>
<thead>
<tr>
<th>Reaction</th>
<th>DELSTRIGO On Once Daily</th>
<th>EFV/FTC/TDF On Once Daily</th>
<th>Treatment Difference (DELSTRIGO vs EFV/FTC/TDF)* Estimate (95% CI)§</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=364</td>
<td>N=364</td>
<td></td>
</tr>
<tr>
<td>Sleep disorders and disturbances*</td>
<td>12%</td>
<td>26%</td>
<td>-13.5 (-19.1, -7.9)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9%</td>
<td>37%</td>
<td>-28.3 (-34.0, -22.5)</td>
</tr>
<tr>
<td>Altered somnolence*</td>
<td>4%</td>
<td>8%</td>
<td>-3.8 (-7.6, -0.3)</td>
</tr>
</tbody>
</table>

*All causality and all grade events were included in the analysis.

§Predefined using MedDRA preferred terms including: altered state of consciousness, lethargy, somnolence, syncope.

Neuropsychiatric adverse events in the pre-specified category of depression and suicide/self-injury were reported in 4% and 7% of subjects, in the DELSTRIGO and EFV/FTC/TDF groups, respectively.

In DRIVE-AHEAD through 48 weeks of treatment, the majority of subjects who reported neuropsychiatric adverse events reported events that were mild to moderate in severity (97% [3386] and 96% [19802]) in the DELSTRIGO and EFV/FTC/TDF groups, respectively, and the majority of subjects reported these events in the first 4 weeks of treatment (72% [6286] in the DELSTRIGO group and 86% [1771/207] in the EFV/FTC/TDF group).
Brief Summary of the Prescribing Information for DELSTRIGO™ (doravirine, lamivudine, and tenofovir disoproxil fumarate) tablets, for oral use (continued)

Neuropsychiatric adverse events led to treatment discontinuation in 1% (2/364) and 1% (5/364) of subjects in the DELSTRIGO and EFV/FTC/TDF groups, respectively. The proportion of subjects who reported neuropsychiatric adverse events through Week 4 was 17% (82/364) in the DELSTRIGO group and 49% (177/364) in the EFV/FTC/TDF group. At Week 48, the prevalence of neuropsychiatric adverse events was 12% (44/364) in the DELSTRIGO group and 22% (81/364) in the EFV/FTC/TDF group.

Laboratory Abnormalities

The percentages of subjects with selected laboratory abnormalities (that represent a worsening from baseline) who were treated with DELSTRIGO or EFV/FTC/TDF in DRIVE-AHEAD are presented in Table 3.

Table 3: Selected Laboratory Abnormalities Reported in Adult Subjects with No Antiretroviral Treatment History in DRIVE-AHEAD (Week 48)

<table>
<thead>
<tr>
<th>Laboratory Parameter Preferred Term (Unit/Limit)</th>
<th>DELSTRIGO Once Daily</th>
<th>EFV/FTC/TDF Once Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>&gt;1.1 - &lt;1.6 x ULN</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>&gt;1.6 - &lt;2.0 x ULN</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1.3 - 1.8 x ULN or increase of &gt;0.3 mg/dL above baseline</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>&gt;1.8 x ULN or increase of 3.1.5 x above baseline</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Aspartate aminotransferase (IU/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;2.5 - &lt;5.0 x ULN</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>&gt;5.0 x ULN</td>
<td>0%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Alanine aminotransferase (IU/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;2.5 - &lt;5.0 x ULN</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>&gt;5.0 x ULN</td>
<td>0%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Alkaline phosphatase (IU/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;2.5 - &lt;5.0 x ULN</td>
<td>0%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>&gt;5.0 x ULN</td>
<td>0%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Lipase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1.5 - &lt;3.0 x ULN</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>&gt;3.0 x ULN</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Creatine kinase (IU/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;6.0 - &lt;10.0 x ULN</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>&gt;10.0 x ULN</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Cholesterol, fasted (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;300 mg/dL</td>
<td>2%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>LDL cholesterol, fasted (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;190 mg/dL</td>
<td>0%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Triglycerides, fasted (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;500 mg/dL</td>
<td>0%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>ULN = Upper limit of normal range.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Change in Lipids from Baseline

For DRIVE-AHEAD, changes from baseline at Week 48 in LDL-cholesterol, non-HDL-cholesterol, total cholesterol, triglycerides, and HDL-cholesterol are shown in Table 4. The LDL and non-HDL comparisons were pre-specified and are summarized in Table 4. The differences were statistically significant, showing superiority of DELSTRIGO for both parameters. The clinical benefit of these findings has not been demonstrated.

Table 4: Mean Change from Baseline in Fasting Lipids in Adult Subjects with No Antiretroviral Treatment History in DRIVE-AHEAD (Week 48)

<table>
<thead>
<tr>
<th>Laboratory Parameter Preferred Term</th>
<th>DELSTRIGO Once Daily</th>
<th>EFV/FTC/TDF Once Daily</th>
<th>Difference Estimates (DELSTRIGO - EFV/FTC/TDF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=320</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in LDL-Cholesterol (mg/dL)*</td>
<td>91.7</td>
<td>-2.1</td>
<td>-93.8 (-138.3, -67.7)</td>
</tr>
<tr>
<td>Change in Non-HDL-Cholesterol (mg/dL)*</td>
<td>114.7</td>
<td>-4.1</td>
<td>-118.8 (-208.8, -13.0)</td>
</tr>
<tr>
<td>Change in Total Cholesterol (mg/dL)*</td>
<td>156.8</td>
<td>-2.2</td>
<td>-159.0 (-268.0, -50.0)</td>
</tr>
<tr>
<td>Change in Triglycerides (mg/dL)*</td>
<td>118.7</td>
<td>-12.0</td>
<td>-130.7 (-240.7, -20.8)</td>
</tr>
<tr>
<td>Change in HDL-Cholesterol (mg/dL)*</td>
<td>42.1</td>
<td>1.8</td>
<td>43.9 (4.8, 82.9)</td>
</tr>
</tbody>
</table>

Subjects on lipid-lowering agents at baseline were excluded from these analyses (DELSTRIGO n=15 and EFV/FTC/TDF n=10). Subjects initiating a lipid-lowering agent post-baseline had their last fasted on-treatment value (prior to starting the agent) carried forward (DELSTRIGO n=3 and EFV/FTC/TDF n=4). P-value for the pre-specified hypothesis testing for treatment difference was <0.0001. *Not pre-specified for hypothesis testing.

Postmarketing Experience

The following adverse reactions have been identified during postmarketing experience in patients receiving lamivudine- or TDF-containing regimens. Because postmarketing 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.

Lamivudine:
- Body as a Whole: redistribution/accumulation of body fat
- Endocrine and Metabolic: hyperglycemia
- General: Weakness
- Hematologic: anemia (including pure red cell aplasia and severe anemias progressing on therapy)

Hepatic and Pancreatic: lactic acidosis and hepatic steatosis, posttreatment exacerbations of hepatitis B

Hypersensitivity: anaphylaxis, urticaria

Musculoskeletal: muscle weakness, CPK elevation, rhabdomyolysis

Skin: alopecia, pruritus

TDF:
- Immune System Disorders: allergic reaction, including angioedema
- Metabolism and Nutrition Disorders: lactic acidosis, hypokalemia, hypophosphatemia
- Respiratory, Thoracic, and Mediastinal Disorders: dyspnea

Gastrointestinal Disorders: pancreatitis, increased amylase, abdominal pain

Hepatobiliary Disorders: hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT, gamma GT)

Skin and Subcutaneous Tissue Disorders: rash

Mucositis and Connective Tissue Disorders: rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy

Renal and Urinary Disorders: acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria

General Disorders and Administration Site Conditions: asthenia

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia, hypokalemia, muscular weakness, myopathy, hypophosphatemia.

Drug Interactions

Concomitant Use with Other Antiretroviral Medications

Because DELSTRIGO is a complete regimen for the treatment of HIV-1 infection, co-administration with other antiretroviral medications for treatment of HIV-1 infection is not recommended. Information regarding potential drug interactions with other antiretroviral medications is not provided.

Effect of Other Drugs on DELSTRIGO

Co-administration of DELSTRIGO with a CYP3A inducer decreases doravirine plasma concentrations, which may reduce DELSTRIGO efficacy.

Co-administration of DELSTRIGO and drugs that are inhibitors of CYP3A may result in increased plasma concentrations of doravirine.

Table 5 shows the significant drug interactions with the components of DELSTRIGO. The drug interactions described are based on studies conducted with either DELSTRIGO or the components of DELSTRIGO as individual agents.

Table 5: Drug Interactions with DELSTRIGO*

<table>
<thead>
<tr>
<th>Concomitant Drug Class</th>
<th>Drug Name</th>
<th>Effect on Concentration</th>
<th>Clinical Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androgen Receptors</td>
<td>enzalutamide</td>
<td>↓ doravirine</td>
<td>Co-administration is contraindicated with enzalutamide. At least a 4-week cessation period is recommended prior to initiation of DELSTRIGO.</td>
</tr>
<tr>
<td>Anion Exchangers</td>
<td>carbasalate</td>
<td>↓ doravirine</td>
<td>Co-administration is contraindicated with these anticonvulsants. At least a 4-week cessation period is recommended prior to initiation of DELSTRIGO.</td>
</tr>
<tr>
<td>Antimycobacterials</td>
<td>rifabutin¹</td>
<td>↓ doravirine</td>
<td>If DELSTRIGO is co-administered with rifabutin, one tablet of doravirine (PIFELTRO™) should be taken approximately 12 hours after the dose of DELSTRIGO. At least a 4-week cessation period is recommended prior to initiation of DELSTRIGO.</td>
</tr>
<tr>
<td>Cytotoxic Agents</td>
<td>mitotane</td>
<td>↓ doravirine</td>
<td>Co-administration is contraindicated with mitotane. At least a 4-week cessation period is recommended prior to initiation of DELSTRIGO.</td>
</tr>
<tr>
<td>Hepatitis C Antiviral Agents</td>
<td>sofosbuvir/ledipasvir</td>
<td>↑ tenofovir</td>
<td>Monitor for adverse reactions associated with TDF.</td>
</tr>
<tr>
<td>Herbal Products</td>
<td>ledipasvir/sofosbuvir</td>
<td>↑ sorbitol</td>
<td>Monitor for adverse reactions assoicated with TDF.</td>
</tr>
</tbody>
</table>

Table 6: Preferred Terms and Concentration Clinical Comment

<table>
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<th>Effect on Concentration</th>
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†Not pre-specified for hypothesis testing.

1The interaction between doravirine and the concomitant drug was evaluated in a clinical study.

All other drug-drug interactions shown are anticipated based on the known metabolic and elimination pathways.
Co-administration of DELSTRIGO with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of lamivudine, tenofovir, and/or other renally eliminated drugs. Some examples of drugs that are eliminated by active tubular secretion include, but are not limited to, acyclovir, adefovir, ganoclovir, valacyclovir, valganclovir, emiclovir, and high-dose or multiple NSAIDs.

No clinically significant changes in concentration were observed for doravirine when co-administered with the following agents: TDF, lamivudine, elbasvir and grazoprevir, ledipasvir and sofosbuvir, ritonavir, ketoconazole, aluminun hydroxide/magnesium hydroxide/simethicone containing antacid, pantoprazole, or methadone.

No clinically significant changes in concentration were observed for tenofovir when co-administered with tacrolimus or entecavir.

Effect of DELSTRIGO on Other Drugs
No clinically significant changes in concentration were observed for the following agents when co-administered with doravirine: lamivudine, TDF, elbasvir and grazoprevir, ledipasvir and sofosbuvir, stavudinast, an oral contraceptive containing ethinyl estradiol and levonorgestrel, metformin, methadone, or midazolam.

No clinically significant drug interactions have been observed between TDF and the following medications: entecavir, methadone, oral contraceptives, simethicone, or midazolam. It is unlikely that clinically significant drug interactions will occur through these pathways.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to DELSTRIGO during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Registry (APR) at 1-800-258-4263.

Risk Summary
There is insufficient prospective pregnancy data from the APR to adequately assess the risk of birth defects and miscarriage. Doravirine use in individuals during pregnancy has not been evaluated; however, lamivudine and TDF use during pregnancy has been evaluated in a limited number of individuals reported to the APR. Available data from the APR show no difference in the overall risk of major birth defects for lamivudine and TDF compared with the background rate for major birth defects of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MADCDP) (see Data). The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in the clinically recognized pregnancies in the U.S. general population is 15-20%. Methodological limitations of the APR include the use of MACDP as the external comparator group. The MACDP population is not disease-specific, evaluates individuals and infants from the limited geographic area, and does not include outcomes for births that occurred at less than 20 weeks gestation.

In animal reproduction studies, oral administration of lamivudine to pregnant rabbits during organogenesis resulted in embryolethality at systemic exposure (AUC) similar to the recommended clinical dose; however, no adverse development effects were observed with oral administration of lamivudine to pregnant rats during organogenesis at plasma concentrations (Cmax) 35 times the recommended clinical dose. No adverse developmental effects were observed when doravirine and TDF were administered separately at doses/exposures 0.8 (doravirine) and 8 (TDF) times those of the recommended human dose (RHD) of DELSTRIGO (see Data).

Data

Human Data
Lamivudine: The APR has received a total of over 12,000 prospective reports with follow-up data of possible exposure to lamivudine-containing regimens; over 5,400 reports in the first trimester; over 5,500 reports in the second trimester; and over 1,800 reports in the third trimester. Birth defects occurred in 151 of 5,008 (3.0%, 95% CI: 2.6% to 3.5%) live births for lamivudine-containing regimens (first trimester exposure); and 35 of 1,570 (2.2%, 95% CI: 1.6% to 3.1%) live births for TDF-containing regimens (second/third trimester exposure). Among pregnant mothers in the U.S. reference population, the background rate of birth defects is 2.7%. There was no association between lamivudine and overall birth defects observed in the APR.

TDF: The APR has received a total of over 5,500 prospective reports with follow-up data of possible exposure to tenofovir disoproxil-containing regimens; over 3,900 reports in the first trimester; over 1,000 reports in the second trimester; and over 500 reports in the third trimester. Birth defects occurred in 62 of 3,325 (3.3%, 95% CI: 1.9% to 2.9%) live births for TDF-containing regimens (first trimester exposure); and 35 of 1,570 (2.2%, 95% CI: 1.6% to 3.1%) live births for TDF-containing regimens (second/third trimester exposure). Among pregnant mothers in the U.S. reference population, the background rate of birth defects is 2.7%. There was no association between tenofovir and overall birth defects observed in the APR.

Animal Data
Doravirine: Doravirine was administered orally to pregnant rabbits (up to 300 mg/kg/day) on gestation days (GDB) 7 to 20; and rats (up to 450 mg/kg/day on GDB 6 to 20 and separately from GDB 6 to lactation/postpartum day 20). No significant toxicological effects on embryo-fetal (rats and rabbits) or pregestational (rats) development were observed at exposures (AUC) approximately 9 times (rats) and 8 times (rabbits) the exposure in humans at the RHD. Doravirine was transferred to the fetus through the placenta in embryo-fetal studies, with fetal plasma concentrations of up to 40% (rabbits) and 52% (rats) that of maternal concentrations observed on gestation day 20.

Lamivudine: Lamivudine was administered orally to pregnant rats (at 90, 600, and 4,000 mg per kg per day) and rabbits (at 90, 300, and 1,000 mg per kg per day and at 15, 40, and 90 mg per kg per day) during organogenesis (on gestation Days 7 through 16 [rat] and 8 through 20 [rabbit]). No evidence of fetal malformations due to lamivudine was observed in rats and rabbits at doses producing plasma concentrations (Cmax) approximately 35 times higher than human exposure at the recommended daily dose. Evidence of early embryolethality was seen in the rabbit at system exposures (AUC) similar to those observed in humans, but there was no indication of this effect in the rat at plasma concentrations (Cmax) 35 times higher than human exposure at the recommended daily dose. Studies in pregnant rats showed that lamivudine is transferred to the fetus through the placenta. In the fertility/pre- and postnatal development study in rats, lamivudine was administered orally at doses of 180, 900, and 4,000 mg per kg per day (from prior to mating through postnatal Day 20). In the study, development of the offspring, including fertility and reproductive performance, was not affected by maternal administration of lamivudine.

TDF: Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of harm to the fetus.

Lactation

Risk Summary
The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking potential transmission of HIV-1 infection. Based on limited published data, both lamivudine and tenofovir are present in human milk. It is unknown whether doravirine is present in human milk, but doravirine is present in the milk of lactating rats. It is not known whether DELSTRIGO or the components of DELSTRIGO affects human milk production, or has effects on the breastfed infant. Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) serious adverse reactions in a breastfed infant, instruct mothers not to breastfeed if they are receiving DELSTRIGO.

Data
Doravirine: Doravirine was excreted into the milk of lactating rats following oral administration (450 mg/kg/day) from gestation day 6 to lactation day 14, with milk concentrations approximately 1.5 times that of maternal plasma concentrations observed 2 hours post dose on lactation day 14.

Pediatric Use

Safety and efficacy of DELSTRIGO have not been established in pediatric patients less than 18 years of age.

Geriatric Use
Clinical trials of doravirine, lamivudine, or TDF did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration of DELSTRIGO in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Renal Impairment
Because DELSTRIGO is a fixed-dose combination tablet and the dosage of lamivudine and TDF, both components of DELSTRIGO, cannot be altered, DELSTRIGO is not recommended in patients with estimated creatinine clearance less than 50 mL/min.

Hepatic Impairment
No dosage adjustment of DELSTRIGO is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. DELSTRIGO has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

OVERDOSAGE
No data are available on overdose of DELSTRIGO in patients and there is no known specific treatment for overdose with DELSTRIGO. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required.

Doravirine: There is no known specific treatment for overdose with doravirine.

Lamivudine: Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event.

TDF: TDF is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of TDF, a 4-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

For more detailed information, please read the Prescribing Information.

Data uspi-m1439a-t-1808r000

Revised: 08/2018
Nine Ways to Deal with Escalating Drug Costs

Hospitals share successful strategies

BY KEITH LORIA

As drug costs continue to increase at an unsustainable rate, many industry insiders believe the current trajectory of pharmaceutical expenses will eventually bankrupt the U.S. healthcare system.

Girish Dighe, PharmD, MS, director of pharmacy, business services, at OhioHealth, a not-for-profit system of hospitals and healthcare providers in Columbus, notes that there are fundamental flaws within the healthcare system causing vastly complex challenges to drug pricing.

“The multitude of stakeholders involved in the drug channels for bringing patients access to medications (manufacturers, insurers, pharmacy benefit managers (PBMs), providers, retail pharmacies, wholesalers) revolves around financial incentives driving each stakeholder,” Dighe says. “The growing spread between pharmaceutical list price and net price negotiated by drug channel stakeholders has negatively impacted patients’ out-of-pocket costs.”

According to a recent survey from NORC at the University of Chicago and the West Health Institute, 75% of Americans believe prescription drug prices are unreasonably high.

President Donald Trump took a big stance against rising drug prices early in his tenure and since then some drug companies—Pfizer, Novartis, Sanofi, Roche, and Merck among them—have announced that they’re freezing or even lowering drug costs.

Alex Azar, HHS secretary, recently announced that the administration is also working to stop drug rebates to PBMs.

The Pharmaceutical Care Management Association (PCMA), which represents pharmacy benefit managers, issued a report recently blaming high drug prices on drug makers, not PBMs.

In the report, Mark Merritt, PCMA’s president and CEO, said the findings supported the belief that drug makers set and raise prices unrelated to the rebates they negotiate with PBMs.

“Drug companies keep raising prices even when rebates go down,” he says. “Simply eliminating plans’ ability to negotiate price concessions would enrich drug makers at the expense of patients, who would not only face higher prices, but also higher premiums and out-of-pocket costs.”

Amy Beatty, PharmD, BCPS, OhioHealth’s clinical director of pharmacy services, says medication shortages are to blame for some drug price escalations.

“When lower-cost generic medications enter shortage status, providers are faced with selecting more expensive alternatives,” she says. “This pattern of drug shortages has continued to the point where many organizations are now funding positions and teams to manage the fragile supply chain.”

As drug costs continue to escalate, many hospitals feel a challenge will be access to important medications, since they cannot always get what they need when they need it. That’s why many hospitals, such as OhioHealth, have begun rationing drugs in certain situations and some larger healthcare systems have even started producing their own medications to address both cost and supply concerns (see sidebar, “Hospitals Form Own Drug Company”).
Earnest Alexander, PharmD, assistant director, clinical pharmacy services, Tampa General Hospital, a teaching hospital for the USF Health Morsani College of Medicine, and co-editor of the peer-reviewed *AACN Advanced Critical Care*, notes that hospitals and pharmacy departments work closely with group purchasing organizations, which negotiate lower drug prices for member organizations, to monitor and attempt to predict inflation trends. This isn’t an exact science and can vary based on several factors, such as changes in formulary and clinical practice, drug shortages, and alterations in competition in the marketplace for drugs.

For example, a decade ago, yearly inflation would range 3% to 5%, he says. In the last five years, this has more than doubled to 8% to 12% increases in cost yearly.

“Interestingly, the number of drug shortages has skyrocketed in the past five to 10 years, resulting in decreased supply and sharply climbing costs for the remaining drugs available for patient care,” Earnest says. “Challenges exist because there is a constantly shrinking margin, which poses operational issues for facilities.”

John M. Allen, PharmD, clinical assistant professor, College of Pharmacy, University of Florida, and co-editor of *AACN Advanced Critical Care*, says rising drug costs are certainly not a new phenomenon; however, the price of several medications that have few alternatives and that are commonly used in the care of critically ill patients, including epinephrine, vasopressin, and calcitonin, has risen recently. Historically, these agents had relatively low prices and had minimal cost increases year after year.

“Hospital pharmacies routinely monitor for changes in drug pricing and evaluate different ways to mitigate the impact of increasing drug prices without sacrificing patient care,” he says. “Some strategies may include establishing criteria for using more expensive drugs, development of order sets to drive appropriate use, and prospective drug audits.”

Here are some other avenues that hospitals are exploring to alleviate high costs.

1 **PROPER USE OF DRUGS**

When price simply cannot be negotiated, appropriate use of drugs is the only pathway to manage escalating drug costs, says Linda Huang, PharmD, OhioHealth’s...
Civica Rx, the new not-for-profit generic drug company formed by a consortium of health systems, could help alleviate shortages of certain critical drugs in hospitals.

The company will initially manufacture 14 hospital-administered generic drugs that have suffered from supply shortages, and then will expand production to other medications. The organization is not naming the drugs it will manufacture for competitive reasons, according to a statement.

Civica Rx says it expects to save the U.S. healthcare system hundreds of millions of dollars annually. “Research into the actual costs of manufacturing and distributing generic drugs suggests that, in many instances, prices for generic drugs used in hospitals can be reduced to a fraction of their current costs,” the organization says.

The seven initial governing members of Civica Rx—which represent about 500 U.S. hospitals—are: Catholic Health Initiatives, HCA Healthcare, Intermountain Healthcare, Mayo Clinic, Providence St. Joseph Health, SSM Health, and Trinity Health. More than 120 other health organizations could also become involved.

“The fact that a third of the country’s hospitals have either expressed interest or committed to participate with Civica Rx shows a great need for this initiative. This will improve the situation for patients by bringing much needed competition to the generic drug market,” says Martin VanTrieste, Civica Rx’s CEO and former chief quality officer for Amgen, in a statement.

VanTrieste agreed to lead the new organization without compensation.

Civica Rx will be an FDA-approved manufacturer that will manufacture some drugs itself and will subcontract manufacturing for others. It says it expects to have some medications available as early as next year.

Hospitals Form Drug Company  by Christine Blank

USE PHARMACOGENOMICS

Houda Hachad, PharmD, chief science
officer at Translational Software Inc., which provides recommendations based on genetic data to more than 20,000 clinicians, says DNA-guided prescribing/pharmacogenomics (PGx) is a great way to improve treatment efficacy and costs.

“We now have data that shows if you implement pharmacogenetics approaches in different specialties, they result in optimizing different metrics that can be used to assess medication optimization,” Hachad says. “These include fewer emergency room visits and fewer hospitalizations, and some of them have shown reduction in total costs compared to standard approaches.”

She explains that using genetic tests can help healthcare workers ascertain the best medication and appropriate dosage based on a patient’s DNA before prescribing, which not only improves the effectiveness of treatment, but lowers drug costs by identifying the medication that works best for each patient.

Hachad co-developed a PGx knowledge-base and a drug interaction database that are used by pharmaceutical companies, regulatory agencies, commercial laboratories, and academic healthcare organizations.

4 CONSIDER ANALYTICS

Analytics can help healthcare systems monitor their drug costs and find opportunities to reduce their spending without reducing the quality of care. Western Maryland Health Systems (WMHS), which offers healthcare services to those in Allegany and Garrett counties in Maryland and surrounding counties in West Virginia and Pennsylvania, presents an excellent example.

It began using Dimensional Insight’s Diver platform after the cost of the IV form of acetaminophen jumped 250%, to $35 per vial, says George Dealy, vice president of healthcare applications at the analytics company. It used the platform to examine whether the IV drug actually produced better outcomes than the oral version, justifying the increased cost.

After examining various surgical procedures, patient lengths of stay, and number of opiates given, WMHS found no significant difference in patient outcomes with IV acetaminophen, says Dealy. As a result, the health system sharply decreased the amount of the drug it purchased, reducing its spending by 78% over two years, from nearly $250,000 in FY15 to just over $55,000 in FY17.

5 ANALYZE COST DATA

Alexander says the most critical step to dealing with escalating drug costs is a proactive review of the spend/cost data that can aid in spotting issues and altering purchasing on an ongoing basis.

“For example, identifying the best price available for agents along with benchmarking prices is a critical ongoing step in the assessment,” he says. “Because there is constant fluctuation and changes within the market, this requires increased resources within the pharmacy department devoted to purchasing and business analysis.”

These resources can be leveraged to create competition through comparable analysis of agents and also through contract maintenance, he says.

Allen adds that knowing a facility’s drug spend, particularly those medications that account for most spending, and being aware of recent trends can help facilities develop plans to curb inappropriate or unnecessary drug use.

“Having data for the prescriber level can also help to identify opportunities to engage with individual clinicians,” he says. “Peer institution benchmarking is helpful to gain insight on potential opportunities for reducing drug spend.”

Allen says another proven method shown to improve care, and reduce both drug and overall hospital cost, is a robust antimicrobial stewardship program.

“Many institutions now use electronic
surveillance programs to promote streamlined antimicrobial use and reduce the development of antimicrobial-related adverse events such as *Clostridium difficile* infection, or multi-drug resistant infections,” he says. “Investment in these types of surveillance programs to strengthen your antimicrobial stewardship program can generate a significant return on investment for some facilities.”

**DIVERSIFY MANUFACTURERS**

For many hospital and healthcare systems, managing the supply chain of pharmaceutical sourcing and contracting is a key focus area for drug cost savings. OhioHealth, for example, has found that multiple vendor contracting has demonstrated effective cost management and flexible options for sourcing.

“In today’s environment, drug shortages continue to burden drug channels and access,” Dighe says. “Ensuring a robust supply chain will keep health systems in a strong position to identify the most cost-effective drug sourcing opportunities, while continuing to drive high-quality healthcare delivery.”

**USE MARKET INTELLIGENCE**

Huang also recommends staying current on what is coming down the pipeline in terms of new products, biosimilars, and generics.

“The traditional method of finding this information is by enrolling in multiple listservs and newsletters from the FDA, national group purchasing organizations, wholesale drug distributors, and/or national medical or pharmacy organizations,” she says, warning that a lot of this information is incomplete and requires a lot of labor to piecemeal from multiple sources to understand the changing landscape.

“Our health system chose to subscribe to a third-party market intelligence company that provides a database of pipeline information (i.e., new products or alternatives, projected launch dates and probability, competitive strategies, etc.), as well as medical experts to help digest this into actionable information,” Huang says.

**EXPLORE AUTOMATION TECHNOLOGY**

A recent strategy employed at Tampa General is intravenous compounding automation/robotic technology, which allows facilities to move away from more expensive ready-made products and shift toward an internally compounded product that is purchased in bulk.

“There is a learning curve associated with this technology, and it’s a capital expense that requires budgetary approval,” Alexander says. “Also, it is important to note that the return on investment can occur quickly, in a matter of months, due to flexible financing options, such as hardware leases instead of upfront, out-of-pocket hardware purchases.”

Allen adds that increasingly, hospitals are scrutinizing the use of high-cost biological agents in their outpatient infusion centers. Many of these agents can be administered in a physician’s office, and do not require administration via an outpatient infusion center.

“Completing a profit/loss evaluation on specific high-cost biological agents, with potential re-evaluation of formulary status, may be another way for hospitals to reduce the impact of rising drug costs,” he says.

**ENCOURAGE MEDICATION USE INITIATIVES**

OhioHealth’s Beatty notes that the healthcare system recognized several years ago that managing medication costs solely through contracting, inventory strategies, and substitutions would not provide the cost-effective care that would be needed in the future.

“Health systems need to be willing to look at and capture cost-avoidance through medication use initiatives,” she says. “These initiatives should look at the right medication for the right patient for the right reasons; executing on this tactically can take many forms.”

For instance, the electronic medical record can help drive decision making, or focused project groups might dig deep into a specialty area.

“We have found clinical pharmacists and coordinators to be a key component of our use strategy,” Beatty says. “These pharmacists work alongside prescribers and help manage the medication plan, including evaluating less-costly alternatives that will retain or improve quality. This is especially necessary in complex fields like oncology, critical care, or infectious disease.”

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Keith Loria is an award-winning journalist who has been writing for major newspapers and magazines for close to 20 years.
Top Oncology Drug Approvals

Eight promising therapies by ERIN BASTICK, PHARMD, RPH

Kymriah (tisagenlecleucel) from Novartis
Drug Class: CD19-directed genetically modified autologous T-cell immunotherapy
Indications: Acute lymphoblastic leukemia—relapsed or refractory, diffuse large B-cell lymphoma—relapsed or refractory
Cost: $475,000 per treatment of advanced pediatric B-cell precursor ALL (money-back guarantee to hospitals if it does not work by the end of the first month of therapy); $373,000 per treatment of adults with relapsed large B-cell lymphoma
Impact: "This first-ever approved CAR T-cell product is a highly effective therapy for patients who are completely refractory to chemotherapy or who experience a second relapse."
—Gerry Messerschmidt, MD, FACP, chief medical officer at Precision for Medicine Oncology and Rare Disease, and Suzana Corritori, MD, PhD, senior vice president, Strategic Drug Development Solutions at Precision for Medicine Oncology and Rare Disease

Poteligeo (mogamulizumab-kpc) from Kyowa Hakko Kirin
Drug Class: Humanized monoclonal antibody that selectively binds to chemokine receptor type 4 (CCR4)
Indication: Mycosis fungoides—relapsed or refractory; Sézary syndrome—relapsed or refractory
Cost: Rx price for 5 mL of 20 mg/5 mL in major pharmacies is $3,700 to $4,200
Impact: "Mycosis fungoides and Sézary syndrome are rare, hard-to-treat types of non-Hodgkin lymphoma and the approval of Poteligeo fills an unmet medical need for these patients."
—Messerschmidt and Corritori

Tibsovo (ivosidenib) from Agios
Drug Class: Oral isocitrate dehydrogenase 1 (IDH1) inhibitor
Indication: Relapsed or refractory acute myeloid leukemia (AML) with IDH1 mutation
Cost: $26,115 for 30-day supply
Impact: "This is a significant step forward in the treatment of AML and it is anticipated that combinations in earlier subjects will be of tremendous interest, a shift in the current treatment paradigm for patients with the specific IDH-1 mutation."
—Messerschmidt and Corritori

Lutathera (lutetium Lu 177 dotatate) from Advanced Accelerator Applications
Drug Class: Beta- and gamma-emitting radionucleotide that binds to somatostatin receptors
Indication: Somatostatin receptor-positive gastroentero-pancreatic neuroendocrine tumors
Cost: $47,500 per dose, with usual treatment period including four doses for a total of $190,000
Impact: "This is a major advance for patients with neuroendocrine tumors and provides a new treatment alternative for a good number of patients who do not respond to other treatments."
—Messerschmidt and Corritori

Yescarta (axicabtagene ciloleucel) from Kite Pharma Inc./Gilead Sciences Inc.
Drug Class: CD19-directed genetically modified autologous T-cell immunotherapy
Indication: Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma
Cost: 373,000 per treatment, on an outpatient basis
Impact: "Use of this agent has the potential to prolong survival in heavily pre-treated patients and/or those with highly aggressive disease trials are planned or ongoing for other CAR T products in other hematological malignancies and solid tumors."
—Jonathan R. Ptachcinski, PharmD, BCPS, BCOP, clinical pharmacist practitioner, University of North Carolina Medical Center
Drugs In The Pipeline

**Erleada** (apalutamide) from Janssen
**Drug Class:** Nonsteroidal androgen receptor inhibitor
**Indication:** Non-metastatic, castration-resistant prostate cancer
**Cost:** About $11,000 per month of therapy, duration of therapy is until disease progression or unacceptable toxicity
**Impact:** "This therapy has the potential to prolong metastasis-free survival in men who are at high risk of developing metastases.”
—Ptachcinski

**Yervoy** (ipilimumab) from Bristol-Myers Squibb
**Drug Class:** Recombinant human IgG1 immunoglobulin monoclonal antibody that binds to the cytotoxic T-lymphocyte associate antigen 4 (CTLA-4)
**Indication:** This is not a newly approved agent, but received an expanded indication for progression of microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) metastatic colorectal cancer, in combination with Opdivo (nivolumab)

**Cost:** Combination therapy with Yervoy plus Opdivo is approximately $228,000
**Impact:** “While conventional chemotherapy has been the foundation of first-line treatment of various cancers historically, there are various researchers trying to bypass this potentially toxic and modestly effective approach. Chemotherapy involved drugs that are cytotoxic—while they destroy rapidly dividing cancer cells, they are non-specific and do not target any particular cancer biomarker. In comparison, immunotherapies employ antibodies targeting certain biomarkers in cancer cells and boost the patient’s immune response.”
—Rajiv Kalia, associate vice president of Healthcare Research, MarketsandMarkets

**Fulphila** (pegfilgrastim-jmdb) from Mylan
**Drug Class:** First biosimilar to Neulasta (pegfilgrastim)
**Indication:** Prevention of chemotherapy-induced neutropenia
**Cost:** Wholesale acquisition cost per manufacturer of $4,175 per syringe (compared to $6,231 for Neulasta)
**Impact:** “Neulasta has been one of the top oncology drug spends for its use in preventing chemotherapy-induced neutropenia; the emergence of biosimilars and competition within this space will benefit patients and help reduce the overall cost of care in oncology.”
—Jeremy Whalen, PharmD, BCOP, specialty clinical program director, oncology, Prime Therapeutics

Oncology Pipeline Predictions

This year has been another year full of oncology approvals, proving that the oncology pipeline is robust with first-of-the kind molecules, competitor products for existing agents, and biosimilars, according to Whalen.

“As more is being discovered and understood within the tumor micro-environment and specific cancer genomics, it is being paired with the emerging precision oncology practice,” Whalen says. “Manufacturers are investing in these pathways and targets looking for the next paradigm shifting therapy.”

Prime is actively monitoring 15 products that could receive approval before the end of the 2018. “These would join the additional 13 new products that already received approval this year and the more than 20 products that had expanded approvals,” Whalen says.

Ptachcinski says the oncology pipeline is continuing to be robust with possible upcoming approvals in a variety of both solid hematologic malignancies. “Approvals are anticipated for multiple new agents as well as a number of biosimilar specialty medications which are likely to be approved at the end of 2018 and early 2019,” Ptachcinski says.

One novel mechanism is the one targeted by larotrectinib, (LOXO-101), a pan-TRK inhibitor under FDA priority review for adult and pediatric patients with locally advanced or metastatic solid tumors that harbor a NTRK gene fusion, he says. “Reports from phase 2 data suggest that the benefit is seen across multiple solid tumor types which may help justify acquisition costs,” Ptachcinski says.

The outlook for healthcare executives will continue to focus on balancing the cost of administration of new agents, according to Ptachcinski. “Specifically, I anticipate that they will want to ensure that these new agents possess an improvement in outcomes that is commensurate with the increased cost versus. a small—yet statistically significant—benefit. Also, executives may wish to evaluate whether reimbursement for the cost of new therapies at will least cover drug administration cost or potentially also allow for new bottom-line margin.”

—Jeremy Whalen, PharmD, BCOP, specialty clinical program director, oncology, Prime Therapeutics

Erin Bastick, PharmD, RPh, is a staff pharmacist at Southwest General Health Center, Middleburg Heights, Ohio.
Leadership Skills
HELP YOUR ORGANIZATION SUCCEED

Efficiency Boosters

Tricks to nix those evening and weekend hours

The average CEO works 9.7 hours per weekday and conducts business on 79% of weekend days, putting in an average of 3.9 hours daily. They also work on 70% of vacation days, averaging 2.4 hours daily. That’s according to a recent study of 27 CEOs in the July-August issue of Harvard Business Review.

It’s a grueling schedule, and it’s one that might sound very familiar to you as a healthcare executive. While we can’t help you cut down on your responsibilities, we can help you work more efficiently so hopefully, you won’t need to work so much.

1 Make tough decisions about meetings
You don’t need to attend every meeting to make decisions, says Jess Jones, managing director at Huron Healthcare Consulting. “This behavior both inhibits the growth and diversity of decision making in the organization while also taking up your valuable time,” she says.

How can you tackle this? Review each meeting’s agenda by asking the following questions:

- Am I needed to lead or facilitate the meeting?
- Am I a necessary, key decision maker to move a process along?
- Or am I joining to gain information or to provide occasional input?

If it’s the third bullet, remove yourself from the meeting and empower members of your team to attend, facilitate decision making, and provide weekly updates.

2 Decide on your three most important tasks
Kirsty Boyd, director of process improvement at Newton-Wellesley Hospital, which is part of Boston’s Partners HealthCare, says this will help you focus on your priorities. “You may have 50 things to do, but if you get nothing else done today, what are the three most important things to get accomplished? Then, schedule time today to do them,” she says.

No time on your calendar? Create a “to-not-do” list. That means taking a moment at the start of each week to go through your schedule and determine what’s not in line with your priorities—and cancel or reschedule those activities. This one simple act can help free up your time to focus on your three most important tasks.

3 Make 10, take five, give two
Kalyan Jonnalagadda, a leader in Bain & Company’s healthcare practice advises executives to:

- Make 10 minutes by shortening meetings to 50 minutes versus 60.
- Take five of those minutes and clear your email or think about the one action you can take in an area that matters to you. Perhaps it’s something small but meaningful to inspire your team.
- Give two minutes to exercise mindfulness, recommends Jonnalagadda. “Take deep breaths and center yourself,” she says. “At the end of it, you still have three minutes to walk to your next meeting and not be late.”

4 Carve out time to think big picture
“Forcing this and sticking to keeping those blocks protected will naturally filter out lower priority meetings and calls,” says Jonnalagadda.

5 Ask how critical the issue is
Carol DeVol, chief operating officer for Huntington Beach, California-based Landmark Health, says if it’s something that will affect your metrics, pay attention to it. If not, delegate it to the right team. “Make sure you have the right team in place and trust them to get it right,” she says. “I provide the right direction and input, but I don’t get too far in the details. I admit, this can be a hard thing to do, particularly if you’re moving from a start-up mode to a larger organization, but it’s the only way to scale.”

6 Embrace an “explicit personal agenda”
This tip comes from the Harvard Business Review article referenced previously: Be clear about your agenda so you can optimize your time. If you don’t, the loudest voices will take over, and you won’t get to advance your own agenda.

Also, take a “matrix approach” to agenda setting. This should include strategic areas for improvement and specific items that must be addressed, write Harvard Busi-
ness School professors Michael E. Porter, PhD, and Nitin Nohria, PhD, who ran the study. CEOs have to include both time-bound goals and more open-ended priorities as they set their agendas.

To ensure alignment, you must communicate your agenda to members of your executive team, including your executive assistant.

7 **Follow the two-minute rule**

Boyd says it doesn’t matter if it’s as simple as responding to an email or a voicemail. “Spend no more than two minutes on it,” she recommends.

“Follow the two-minute rule”

8 **Partner with your executive assistant**


That’s because it’s the little things that can have a huge impact on your day—from blocking out your calendar so no one can sneak in a 30-minute meeting to getting you out of your office by scheduling meetings in other people’s offices. Your executive assistant should also block out 30 minutes so you have time for a healthy lunch.

9 **Hire the right people**

Patricia Howard, senior vice president of health plan operations at Pittsburgh-based Highmark Health, says you must commit to hiring people you know can assume ownership and that you can trust to deliver on their responsibilities. Otherwise, you’ll waste your time doing other people’s jobs.

10 **Up collaboration and communication**

Technology helps with this, says Stephen P. Zieniewicz, MPH, president and CEO of Livingston, New Jersey-based Saint Barnabas Medical Center.

For example, one of his priorities is to find and implement the best evidence-based delivery protocols for patients. That means his entire team needs to be on board to get that done successfully and efficiently, says Zieniewicz. The medical center has developed a program for identifying, applying, and tracking best practices more efficiently. Also important here is reducing variation, in addition to maintaining communication with team members.

To streamline adoption of new protocols, they must be hard-wired into the EHR, he advises.

Looking for proof this approach works? Saint Barnabas Medical Center used it to cut its sepsis mortality rate by half in the program’s first year.

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### Q1: How many hours per week do you work, on average?

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<thead>
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<th>Responses</th>
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<tr>
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<td>23%</td>
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<tr>
<td>More than 60</td>
<td>6%</td>
</tr>
</tbody>
</table>

### Q2: Do you often work in the evenings and on the weekends outside of typical work hours?

- **No** 29%
- **Yes** 71%


Managed Healthcare Executive.com
iPhone Emoji Serves Public Health Need

Apple will add a mosquito emoji to its products, giving public health professionals a quick way to communicate with the public about the presence of mosquitoes, and allowing researchers to promote their work around mosquito-borne diseases more easily via social media. “The mosquito [emoji] could stand in for public health alerts, alert to community spraying or the distribution of prevention tools,” according to a proposal from Johns Hopkins Center for Communication Programs, the Bill & Melinda Gates Foundation, and others.

Physicians Identify Top 3 Benefits of Virtual Care

1. Improved access
2. Improved patient satisfaction
3. Staying connected with patients and caregivers

— Deloitte 2018 Survey of U.S. Physicians

Quotable

“Precision medicine approaches can be game changers in oncology treatment, because not all cancers are alike and drugs perform differently depending on the patient and prognosis.”

— Kevin Hrusovsky, Powering Precision Health, page 30

More Consumers Care About Costs

27% of consumers looked up healthcare cost information in 2018, up from 14% in 2015

- Almost 1 in 4 patients looked up a report card for a physician in 2018.
- Half of consumers say they are likely to look up price information in the future.

Deloitte 2018 Health Care Consumer Survey
UNDERSTANDING THE TREATMENT PARADIGM FOR AGE-RELATED MACULAR DEGENERATION

Release Date: November 1, 2018
Expiration Date: November 30, 2019
Estimated Time to Complete Activity: 1.5 hours

Faculty

W. Lloyd Clark, MD (Co-Chair)
Assistant Clinical Professor of Ophthalmology
University of South Carolina
School of Medicine
Retina Specialist, Palmetto Retina Center
Columbia, South Carolina

Winston Wong, PharmD (Co-Chair)
President
W-Squared Group
Longboat Key, Florida

Jeffrey S. Heier, MD
Co-President and Medical Director
Ophthalmic Consultants of Boston
Boston, Massachusetts

Gary Owens, MD
President
Gary Owens Associates
Ocean View, Delaware

This activity is supported by an independent educational grant from Regeneron Pharmaceuticals, Inc.
Target Audience
This activity is intended for managed care clinical and nonclinical executives engaged in the care of patients with neovascular age-related macular degeneration (nAMD).

Educational Objectives
After completing this activity, the participant should be better able to:
• Explain current practice patterns for the treatment of patients with nAMD
• Outline the benefits of collaboration between payers and providers

Joint Accreditation Statement
In support of improving patient care, this activity has been planned and implemented by the Postgraduate Institute for Medicine and MedEdicus LLC. Postgraduate Institute for Medicine is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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Postgraduate Institute for Medicine designates this continuing education activity for 1.5 contact hour(s) (0.15 CEUs) of the Accreditation Council for Pharmacy Education.
(Universal Activity Number - JA4008162-9999-18-408-H01-P)

Type of Activity: Knowledge

ACHE Qualified Education
By attending the Understanding the Treatment Paradigm for Age-Related Macular Degeneration offered by Postgraduate Institute for Medicine, participants may earn up to 1.5 ACHE Qualified Education Hours toward initial certification or recertification of the Fellow of the American College of Healthcare Executives (FACHE) designation.

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Faculty
W. Lloyd Clark, MD
Consulting fees from Genentech, Inc; and Regeneron Pharmaceuticals, Inc
Fees for non-CME/CE services received directly from a commercial interest or their agents (e.g. speakers’ bureaus) from Genentech, Inc; and Regeneron Pharmaceuticals, Inc
Contracted research from Genentech, Inc; and Regeneron Pharmaceuticals, Inc

Jeffrey S. Heier, MD
Consulting fees from Adverum; Apellis Pharmaceuticals; Bayer Corporation; Chengdu Kanghong Pharmaceutical Group Co, Ltd; Daiichi Sankyo Company, Limited; F. Hoffman-La Roche Ltd; Genentech, Inc; Hemera Biosciences; Notal Vision; Novartis Pharmaceuticals Corporation; Regeneron Pharmaceuticals, Inc; Regenxbio Inc; SciFluor Life Sciences, Inc; Stealth BioTherapeutics Inc; and Tyrogenex
Contracted research from Aerpio Therapeutics; Apellis Pharmaceuticals; Concept Therapeutics; Daiichi Sankyo Company, Limited; F. Hoffman-La Roche Ltd; Genentech, Inc; Genzyme Corporation; Hemera Biosciences; Janssen Global Services, LLC; Ophthotech Corporation; Optovue, Incorporated; Regeneron Pharmaceuticals, Inc; Regenxbio Inc; SciFluor Life Sciences, Inc; and Tyrogenex
Ownership interest in Ocular Therapeutix, Inc

Gary Owens, MD
Dr Owens has nothing to disclose.

Winston Wong, PharmD
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For Pharmacists: Upon successfully completing the post-test with a score of 75% or better and the activity evaluation form, transcript information will be sent to the NABP CPE Monitor Service within 4 weeks.

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Neovascular age-related macular degeneration (nAMD) is a leading cause of vision loss among older people in the United States. Its treatment has been revolutionized by anti–vascular endothelial growth factor (VEGF) therapy, but achieving optimal outcomes for individual patients depends on timely initiation of effective therapy and careful follow-up with ongoing treatment to control disease activity. Individualization of treatment plans is a key theme for achieving good outcomes. In real-world settings, however, there are challenges to meeting these needs.

Collaboration between payers and providers is critical for enabling selection of the most appropriate treatment for patients with nAMD and improving overall visual outcomes. It is important that retinal specialists understand the issues payers face in their efforts to balance cost, quality, and access on a population-wide basis. At the same time, there is a need for payers to understand the issues confronting retinal specialists as they try to preserve vision and quality of life of patients with nAMD. Payers must also understand the current landscape of nAMD treatment and the evidence on which it is based so that best clinical practices are incorporated into payer models for covering care.

Background: Prevalence, Treatment, and Health Care Spending

Dr Wong: According to a report in 2010, Medicare spent one-sixth of its part B medication budget on anti-VEGF treatment for nAMD. What is the burden of nAMD in terms of its prevalence or number of affected people?

Dr Heier: Age-related macular degeneration (AMD) is a chronic and potentially progressive disease, of which nAMD is a late, advanced form. Although approximately only 20% of people with AMD develop neovascular disease, 90% of the severe vision loss attributed to AMD is due to nAMD.

A report published in 2004 estimated that AMD affected 14 million people in the United States, of which 1.75 million had an advanced, sight-threatening form of AMD in at least
1 eye, and more than 7 million had features of AMD that put them at increased risk of developing advanced disease in 1 or both eyes. On the basis of the expected growth of the aging population, the study projected that in 2020, nearly 3 million people in the United States would have advanced AMD.

AMD typically does not develop until after age 50, but its prevalence and the prevalence of nAMD increase with age. A recent analysis pooling data from several population-based studies determined that nAMD prevalence increased steadily from 0.14% in people aged < 55 years to 8.5% in people aged ≥ 85 years.

**Dr Clark:** Researchers using data from the phase 3 trials of ranibizumab for nAMD estimated that using the anti-VEGF agent could reduce the number of cases of legal blindness by approximately 75% and the number of cases of visual impairment by approximately 35%.

Before anti-VEGF therapy, the only treatment available for nAMD was photodynamic therapy, but it only slowed the rate of vision loss. Results from clinical trials investigating anti-VEGF therapy showed that for the first time, we could stabilize vision for most patients and even improve vision for a significant minority of patients when they were treated with ranibizumab on a monthly basis or with aflibercept monthly or every other month.

**Clinical Trials vs Real-World Outcomes**

**Dr Wong:** What do the US Food and Drug Administration (FDA) registration trials show about the efficacy of anti-VEGF treatment for nAMD?

**Dr Heier:** The primary end point in the registration trials looked at the proportion of patients with stable vision, defined as losing < 15 letters on an ETDRS (Early Treatment Diabetic Retinopathy Study) eye chart from their baseline visual acuity (VA). Key secondary efficacy end points looked at the proportion of patients with a clinically relevant improvement in vision, defined as gaining ≥ 15 letters from baseline VA, change from baseline VA, change in retinal thickness, and absence of fluid. Results from the registration trials for aflibercept and ranibizumab and from CATT (Comparison of Age-Related Macular Degeneration Treatments Trials), which investigated ranibizumab and bevacizumab, showed that after 1 year, > 90% of patients maintained stable vision, defined as a loss of < 15 ETDRS letters. It is important to realize, however, that these outcomes were achieved in highly selected populations of patients who were managed for a finite duration, followed closely at monthly visits, and received regular treatment. We know from other studies and from clinical experience that in the real world, many patients do not maintain the initial benefit of anti-VEGF therapy. For example, in the SEVEN-UP (Seven-Year Observational Update of Macular Degeneration Patients Post-MARINA/ANCHOR and HORIZON Trials) study that included participants from the ranibizumab registration trials, 37% of eyes were legally blind at 7 years.

**Dr Owens:** What accounts for the discrepancy?

**Dr Clark:** There are several contributing factors. First, as is typical of FDA registration trials, enrolled patients are not fully representative of those seen in the real-world setting. Registration trials enroll a highly selective patient population because these trials use strict inclusion/exclusion criteria. The
cohort of patients encountered in clinical practice is more heterogeneous and might include patients with more complex disease features. Consequently, the response to treatment might be different for patients seen in the real world compared with than in clinical trial participants.

**Dr Heier:** Not only were patients in the registration trials and in CATT more ideal with respect to their clinical characteristics, they also received more ideal follow-up and treatment. Patients in the clinical trials had close monthly follow-up and regular treatment with injections given monthly or every other month, depending on the medication. Monthly treatment is generally highly effective for keeping the macula dry and preserving vision, but it can be impractical and a burden for many patients with nAMD, considering their advanced age, likelihood of having comorbidities, dependence on a caregiver for transportation, and the need for some to travel long distances to see a retina specialist.

The data are pretty clear that patients need to receive approximately 6 injections per year to achieve the vision gains seen in the registration trials after 1 year and maintain the benefit in the second year.\(^\text{17,18}\) Compared with the clinical trial participants, real-world patients are not receiving this level of treatment.\(^\text{15}\) In SEVEN-UP, patients followed for up to 7 years were getting just 2 to 3 injections annually.\(^\text{12}\) A study of real-world ranibizumab therapy in treatment-naïve eyes found the median number of injections received in the first, second, and third years was 5, 4, and 4, respectively.\(^\text{15}\)

**Obstacles to Optimizing Outcomes**

**Dr Wong:** Although a monthly injection scheme provides the most opportunity for a patient to retain maximum vision, it is easy to appreciate how patients might not be able to maintain ongoing treatment because of logistic issues that limit their ability to return for monthly visits. We also need to ask if economics is a factor. Do you think high copays play a role?

**Dr Heier:** For some patients, carrying a commercial plan that has a high deductible or lacking a supplemental Medicare coverage plan might limit treatment frequency and choice of the anti-VEGF agent. Although the copay for bevacizumab might just be $15, it could be $400 for aflibercept or ranibizumab. Manufacturer patient-assistance programs and grant money that is available through independent foundations can help reduce the cost burden. But because bevacizumab costs less than ranibizumab and aflibercept, in my experience, some commercial insurers have step-therapy policies that mandate treatment for nAMD be initiated with the off-label use of bevacizumab. According to these policies, coverage for treatment with an FDA-approved drug—ranibizumab or aflibercept—is not allowed without documentation that the patient has a contraindication to bevacizumab or had a trial with bevacizumab and either failed to respond or showed intolerance. Beginning in January 2019, Medicare Advantage plans will also be allowed to implement step therapy for physician-administered and other part B drugs.\(^\text{19}\)

**Dr Wong:** It is interesting to see step-therapy mandates requiring treatment initiation with bevacizumab, essentially a drug with an off-label use and one requiring compounding for an ophthalmic preparation. When claims for bevacizumab treatment of nAMD began being submitted, many of my colleagues were questioning its use because of these 2 aspects. However, at that time, neither ranibizumab nor aflibercept were approved or available. With the approval of ranibizumab, many health plan managers considered a definitive step therapy using bevacizumab first. Some decided not to adopt step therapy beginning with bevacizumab because bevacizumab was off-label and required compounding, the latter of which might be performed in a nonsterile environment and, therefore, raises concerns of contamination risk. Although off-label use is a noncovered service on most benefit plans, managers still elected to continue coverage for bevacizumab to assure that patients received appropriate care at the lowest cost. Evidence from the literature on the efficacy and safety of bevacizumab is what helped to clear the barrier relating to off-label use.\(^\text{10,11}\)

What concerns do retina specialists have with step therapy for nAMD? Are there data to show that the 3 anti-VEGF drugs differ in efficacy, or are there clinical situations in which there is a preference for using a particular anti-VEGF agent?

**Dr Clark:** Step therapy beginning with bevacizumab would be reasonable if bevacizumab had an FDA-approved indication for the treatment of nAMD,\(^\text{20}\) and if it showed similar efficacy and safety compared with ranibizumab or aflibercept in multiple randomized clinical trials with confirmatory results. Because these criteria are not met, establishing bevacizumab as primary therapy for all patients with nAMD is problematic. Although CATT gave us useful information for guiding treatment decisions, it was neither a registration trial nor a confirmatory pivotal trial.\(^\text{10,11}\) In addition, CATT was not powered to evaluate the safety of bevacizumab as treatment for nAMD—a critical measure in the process of FDA approval for a medication. Also, because bevacizumab is not available to retina specialists in single-dose vials, as are ranibizumab and aflibercept, there remains uncertainty regarding the sterility and bioavailability of bevacizumab when delivered in syringes prepared by compounding pharmacies. Finally, recent reports of intravitreal silicone oil droplets after bevacizumab injections create uncertainty for clinicians and their patients.\(^\text{21,22}\)

Although it is true that the 2-year VA outcomes in CATT were similar for bevacizumab and ranibizumab when
comparing the groups treated with the same dosing regimen—bevacizumab monthly vs ranibizumab monthly or bevacizumab as needed vs ranibizumab as needed—patients receiving bevacizumab as needed had the least gain in VA; the bevacizumab-as-needed group also had the greatest lesion growth and the greatest likelihood of having macular fluid (Table). This is an important point because dosing less than once a month probably reflects how patients are treated in the real world. CATT is the only trial that provides data on as-needed treatment with bevacizumab, and its results indicate that this approach compromises outcomes.

Dr Heier: Step therapy for nAMD is concerning because it can interfere with the ability to optimize outcomes for individuals according to their unique clinical characteristics and other circumstances. Because bevacizumab needs to be compounded, there are inherent safety concerns with its use.

I use all 3 anti-VEGF medications to treat nAMD, and I start most patients on bevacizumab. I think bevacizumab can be very appropriate as first-line therapy because it is a very good drug that in many patients is as efficacious as the FDA-approved medications. In my experience, however, it is not more efficacious for every patient than the on-label alternatives.

There are situations in which I would prefer to use aflibercept, either because it can reduce treatment burden or because it has potential benefit in certain hard-to-treat patients. For example, there are cases in which time is of the essence in getting a treatment response. Data from the aflibercept registration trials—VIEW 1 and VIEW 2—provide evidence that it has a more potent and more persistent macular drying effect than does ranibizumab. An integrated analysis of data from the VIEW trials showed that the percentage of patients achieving dry status was higher in the groups receiving aflibercept 2 mg every 4 weeks or 2 mg every 8 weeks than in the group receiving ranibizumab 0.5 mg every 4 weeks (72.4% and 67.7% vs 62%, respectively). In addition, a post hoc analysis considering patients with early persistent retinal fluid found that the mean best-corrected VA gain from baseline to week 52 was greater in eyes treated with aflibercept 2 mg every 4 weeks than in those treated with ranibizumab 0.5 mg every 4 weeks or aflibercept 2 mg every 8 weeks. Patients receiving aflibercept 2 mg every 4 weeks also had the lowest percentage of eyes losing 5 or more letters compared with those receiving ranibizumab or aflibercept 2 mg every 8 weeks (6.5% vs 16.6% and 16.2%, respectively). A step-therapy approach can delay timely use of a more appropriate treatment for a given patient.

Dr Owens: Is there a way to identify the “given” patients for whom aflibercept might be needed so that the step-therapy process could be made more efficient?

Dr Heier: It would be difficult to propose specific criteria for identifying such patients. Rather, these situations reflect the art of practicing medicine and applying clinical judgment.

Dr Wong: Do you see other issues requiring step therapy?

Dr Heier: Step therapy also interferes with patient choice. I inform patients about the efficacy, safety, and cost of the available medications. Some patients prefer to start treatment with bevacizumab because it is the less-expensive drug. Others feel more comfortable being treated with an FDA-approved drug, despite the fact that it might be more expensive, but they might not be allowed to receive the treatment they desire because of their insurance policy.

Dr Wong: I agree that in the area of specialty drugs, physician and patient choice should play a large role. Unfortunately, we live in a world in which economics comes into play. Even if a patient wants the higher-cost drug and authorization is not an issue, he or she might have a fairly significant out-of-pocket cost that might limit access.

Dr Owens: Are you finding that payers are putting a limit on the number of injections patients can receive each year?

Dr Clark: Not currently, which is good for many patients. In the past, there were some problems with insurers refusing to pay for aflibercept administered more often than once every 8 weeks after the initial 3 loading doses, but the issue seems to have been resolved when the original labeling was revised. The labeling now states, “Some patients may need every-4-week (monthly) dosing after the first 12 weeks.”

Dr Wong: This has been a very informative discussion, and I hope my colleagues are gaining an appreciation of some of

### Table. Outcomes in CATT for Patients Maintained on the Same Dosing Regimen for 2 Years

<table>
<thead>
<tr>
<th>Regimen</th>
<th>VA Gain, Letters</th>
<th>Fluid on OCT, %</th>
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<td>Bevacizumab</td>
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P value
- Drug: .21, .0003, .006
- Regimen: .046, < .0001, .0003

Abbreviations: CATT, Comparison of Age-Related Macular Degeneration Treatments Trials; OCT, optical coherence tomography; VA, visual acuity.
the nuances of treating patients with nAMD. Are there other issues that you are encountering that might be impeding your ability to optimize patient outcomes?

Dr Heier: Some insurers have denied payments for anti-VEGF injections given more frequently than every 28 days. Considering practical issues that affect appointment scheduling, it is important to be able to treat patients before 28 days. Trials had a window around the allowable re-injection time, so treating a little sooner than every 28 days can be considered safe. In MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration), for example, retreatment was allowed within 23 days.6

Dr Clark: As another issue, the requirement for prior authorization can delay essential treatment for some patients. Data from clinical trials showing that vision outcomes with anti-VEGF therapy are best when patients are treated when vision is still good and/or the lesion is small support the importance of early treatment.25-27 Furthermore, we know that some patients’ conditions can deteriorate quickly in a very short time. Ideally, therefore, we should be able to initiate treatment on the same day we make the diagnosis of nAMD rather than having to ask a patient to return when we have received authorization for treatment. Getting to the clinic can be a difficult burden for many patients. Same-day treatment can further patient satisfaction because a second trip is avoided and treatment needs are immediately addressed.

Update on the Treat-and-Extend Dosing Scheme to Reduce Treatment Burden and Improve Vision

Dr Wong: Considering all the burdens and the cost of maintaining monthly treatment, is there a treatment strategy that can optimize patient outcomes while balancing costs and convenience?

Dr Heier: Recognition that monthly injections presented a burden and might also be overtreatment for some patients prompted interest in alternative treatment strategies. Initial studies evaluated as-needed approaches, in which patients were treated monthly to achieve disease control—only if they had evidence of recurrent disease activity—and then evaluated at return visits.28-32 Results from studies investigating as-needed treatment clearly showed that it did not provide the same benefit as fixed monthly injections unless patients continued to be followed rigorously with monthly visits.

With an as-needed approach, patients develop disease reactivation time and again, and the exposure to multiple recurrences likely increases the risk for permanent loss of vision.32 Treat-and-extend (TAE) is a strategy for administering anti-VEGF injections that aims to maximize outcomes for patients by maintaining disease control while minimizing the costs and inconvenience of frequent, regular follow-up.

Treat-and-extend is customized to the patient, and, in contrast to an as-needed approach, is designed to limit patient exposure to recurrent disease activity. In TAE, treatment is initiated on a fixed monthly schedule that continues until macular fluid resolves or is stabilized at an improved level. Then, the treatment interval is extended in a stepwise manner as long as there is no active disease. The interval between treatments is usually increased by 2-week increments up to a maximum of 8 to 12 weeks. Patients are evaluated at each visit by clinical examination and imaging with optical coherence tomography (OCT) that can identify macular fluid as a subclinical sign of recurrent activity, before there is a significant decrease in vision that might be irreversible.

For example, once disease activity is controlled with monthly injections, a patient will return after 6 weeks for assessment and treatment. If the nAMD is quiet, the patient will be asked to return again after 8 weeks. If the retina is still dry, the treatment interval can be extended to 10 weeks. If at any follow-up visit there is fluid present on OCT, the interval between visits would be shortened, and the patient would be kept on the more frequent schedule for follow-up and treatment indefinitely or at least for a period of time before trying to extend treatment again.

Dr Clark: I was an investigator in the TREAT-AMD (Treat and Extend Protocol in Patients With Wet Age-Related Macular Degeneration) study, which was a randomized trial of TAE with ranibizumab vs a monthly dosing regimen for patients with nAMD.33 The OCT images and VA data collected at follow-up visits from 1 of the participating patients who was treated by Dr Charles Wykoff provide an excellent illustration of how TAE works (Figure 2).

The initial anti-VEGF injection resulted in dramatic, almost complete resolution of fluid that was accompanied by a 24-letter gain in VA. For this patient, the level of functional improvement brought the vision to a level that was good enough to drive a car. At 12 weeks after starting monthly treatment and having achieved durable disease control, the injection interval was extended to 6 weeks and then extended successfully 2 more times. However, when the patient returned at 10 weeks post-injection, there was recurrence of intraretinal fluid, with a 4-letter decrease in VA. The patient was treated and instructed to return after just 8 weeks. Because there was still fluid on the OCT, and VA had further decreased, the interval between treatments was shortened to 6 weeks. At the next visit, the macula was dry, and the patient’s VA had improved by 2 letters.
You can see from the images in this case that the success of TAE requires the use of OCT at each follow-up visit and intensive review of the images by the retina specialist to identify evidence of subclinical recurrence that cannot be appreciated by clinical examination or VA testing. Although there is cost associated with the required imaging and assessment, because TAE can reduce the frequency of anti-VEGF injections, it can be cost saving. For example, the ability to manage a patient with injections every 6 weeks instead of every 4 weeks reduces the number of injections given per year by 3, which translates to an annual savings of $>6000 for a health plan when a patient is being treated with 1 of the on-label medications. The savings might exceed the costs for reimbursing the diagnostic testing and its interpretation.

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Dr Wong: Is TAE considered standard of care for managing nAMD?

Dr Heier: It has not been endorsed by any practice guidelines. According to recent survey results, however, most retina specialists in the United States are using TAE to manage patients with nAMD.

Dr Clark: Although TAE is widely used, there is limited published level 1 evidence that supports it. Several published studies, anecdotal reports, and a wealth of personal knowledge indicate that outcomes for patients managed by TAE with careful follow-up can be similar to those achieved with fixed monthly dosing. Authors of a systematic review and meta-analysis that included 4 studies using ranibizumab concluded that the evidence suggested TAE is comparable to monthly dosing and superior to as-needed dosing for both efficacy and safety. There are also promising data for aflibercept. There are little data on TAE using bevacizumab. In LUCAS (Lucentis Compared to Avastin Study), in which patients were randomized to a TAE protocol with ranibizumab or bevacizumab, functional and anatomic outcomes after 1 year were similar in the 2 groups, but the
mean number of injections was significantly greater with bevacizumab than with ranibizumab.\textsuperscript{37}

**Dr Heier:** In my personal experience, there is a durability advantage for using aflibercept for TAE. For this reason, I might be able to maintain patients using a longer interval between treatment intervals than I would with bevacizumab. Treat-and-extend with bevacizumab every 5 weeks or with aflibercept every 6 to 8 weeks might provide the same outcome, assuming that both regimens keep the retina dry. The reduced treatment burden that comes with the longer interval between treatments can be important to some patients and can result in better treatment adherence.

**Dr Owens:** Treat-and-extend seems to be a good economic proposition. I think it is important that payers become aware that there is good objective evidence showing that by doing the OCT-guided TAE approach, patients can receive fewer injections without jeopardizing their outcomes.

**Take-Home Points**

AMD is a leading cause of severe vision loss among adults.

- Neovascular AMD accounts for 90% of AMD-related severe vision loss

Visual acuity can be maintained for up to 2 years in > 90% of patients with nAMD who are treated with regular monthly injections of aflibercept, bevacizumab, or ranibizumab.

- Early treatment improves outcomes
- Outcomes in patients treated with anti-VEGF agents in the real world do not match those achieved by clinical trial participants receiving fixed monthly injections

Off-label use of compounded bevacizumab can be effective treatment for many patients.

Evidence from comparative clinical trials suggests that compared with ranibizumab, aflibercept might have a stronger and more persistent drying effect.

As-needed treatment with injections given for recurrent nAMD activity is not as effective as fixed monthly treatment for maintaining early VA gains unless patients receive monthly follow-up.

Treat-and-extend anti-VEGF regimens for nAMD can provide outcomes comparable to those seen with fixed monthly injections, but with fewer visits and fewer anti-VEGF injections.

Open dialogue between payers and providers can keep payers apprised of the latest standards of care and help provide optimal and cost-effective health care services to patients with nAMD.

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**Commentary: Collaboration Through Discussion and Education**

Winston Wong, PharmD

This discussion is an excellent example of how payers and providers can collaborate to deliver optimal health care services. The role of payers is to manage the common health needs of the insured population. Hence, it is imperative that they stay relatively up-to-date on the current standards of care for the most common diseases and medical conditions. It is impossible, however, for payers to be knowledgeable of the latest standards and best practices for every disease, especially specialty diseases such as neovascular age-related macular degeneration. Open dialogues and educational programs that involve both payers and providers go a long way to keep payers well informed and might help payers facilitate the delivery of optimal and cost-effective health care services.

**References**


CME/CE Post-Test Questions

To obtain CME/CE for this activity, complete the CME/CE post-test and course evaluation online at https://tinyurl.com/AMDmanagedcare. Upon successful completion of the post-test and activity evaluation, you will be able to generate an instant certificate of credit.

See detailed instructions at Method of Participation and Request for Credit on page 2.

1. What percentage of patients with AMD have the neovascular form?
   A. 10%
   B. 20%
   C. 50%
   D. 90%

2. In FDA registration studies, vision was maintained or improved at 1 year compared with baseline in approximately ____ of patients treated with ranibizumab or aflibercept.
   A. 10%
   B. 30%
   C. 50%
   D. > 90%

3. Outcomes with anti-VEGF treatment for nAMD in the real world do not match those achieved in the registration trials. Possible explanations include all the following, EXCEPT:
   A. Real-world patients have more complex disease
   B. Real-world patients discontinue treatment more often because of a higher rate of treatment-related complications
   C. Real-world patients receive fewer treatments
   D. Real-world patients receive less regular follow-up

4. At the end of 2 years in CATT, which treatment group had the least gain in VA, the greatest lesion growth, and the greatest likelihood of having macular fluid?
   A. Bevacizumab monthly
   B. Bevacizumab as needed
   C. Ranibizumab monthly
   D. Ranibizumab as needed

5. Data from the aflibercept registration trials (VIEW 1 and VIEW 2) showed that compared with patients receiving ranibizumab 0.5 mg every 4 weeks, those receiving aflibercept 2 mg every 4 weeks or every 8 weeks were more likely to:
   A. Achieve a dry macula
   B. Have more complex clinical characteristics
   C. Lose ≥ 5 letters of VA
   D. Maintain baseline VA

6. In MARINA, the registration trial for ranibizumab, what was the minimum allowed interval between injections?
   A. 21 days
   B. 23 days
   C. 28 days
   D. 30 days

7. The as-needed approach to treating nAMD has been shown to provide the same benefit as fixed monthly treatment if patients are:
   A. Started on treatment when vision is still good (20/40 or better)
   B. Followed monthly
   C. Instructed to return for treatment as soon as they notice a decrease in vision
   D. Treated with aflibercept vs ranibizumab or bevacizumab

8. Which clinical/diagnostic test is the primary tool for guiding decisions on the appropriate treatment interval in a TAE approach?
   A. Fluorescein angiography
   B. OCT
   C. Preferential hyperacuity perimetry
   D. ETDRS VA

9. Results of a meta-analysis found that compared with as-needed dosing, a TAE approach:
   A. Had better efficacy
   B. Had a lower injection burden
   C. Required fewer follow-up visits
   D. All the above

10. Educational programs about nAMD involving payers and providers are important for:
    A. Reducing letters sent by providers to payers calling for step therapy reform
    B. Reducing provider errors in medical claims billing
    C. Facilitating delivery of optimal and cost-effective health care services
    D. Reducing provider requests for prior authorization
UNDERSTANDING
THE TREATMENT PARADIGM FOR
AGE-RELATED MACULAR DEGENERATION