PCORI HEALTH CARE HORIZON SCANNING SYSTEM

High Potential Disruption Report
November 2019

Prepared for:
Patient-Centered Outcomes Research Institute
1828 L St., NW, Suite 900
Washington, DC 20036

Contract No. MSA-HORIZSCAN-ECRI-ENG-2018.7.12

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Patient-Centered Outcomes Research Institute (PCORI) Health Care Horizon Scanning System, operated by ECRI Institute under contract to PCORI, Washington, DC (Contract No. MSA-HORIZSCAN-ECRI-ENG-2018.7.12). The findings and conclusions in this document are those of the authors, who are responsible for its content. No statement in this report should be construed as an official position of PCORI.

An intervention that potentially meets inclusion criteria might not appear in this report simply because the horizon scanning system has not yet detected it or it does not yet meet inclusion criteria outlined in the PCORI Health Care Horizon Scanning System: Horizon Scanning Protocol and Operations Manual. Inclusion or absence of interventions in the horizon scanning reports will change over time as new information is collected; therefore, inclusion or absence should not be construed as either an endorsement or rejection of specific interventions.

A representative from PCORI served as a contracting officer’s technical representative and provided input during the implementation of the horizon scanning system. PCORI does not directly participate in horizon scanning or assessing leads or topics and did not provide opinions regarding potential impact of interventions.

Financial Disclosure Statement

None of the individuals compiling this information have any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The PCORI Health Care Horizon Scanning System (HCHSS) conducts horizon scanning of new and emerging health care technologies and innovations with high potential for disruption to the current standard of care to better inform patient-centered outcomes research investments at PCORI. The HCHSS provides PCORI with a systematic process to identify and monitor technologies and innovations in health care that are in PCORI’s priority areas of interest and to create an inventory of interventions that have the highest potential for disruption to the current standard of care in terms of patient outcomes, health disparities, care delivery, infrastructure, access, and/or costs. It is also a tool for the public to identify information on selected new health care technologies and interventions. Any investigator or funder of research can use the PCORI HCHSS to help select research topics.

The health care technologies and innovations of interest for horizon scanning are those that have yet to become part of established health care practices. These interventions are in late stages of research and development or very early phases of adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the National Academy of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, PCORI is interested—at the outset of this project—primarily in innovations in drugs and biologics, medical devices, and procedures within its selected priority areas of interest for horizon scanning. PCORI may choose, upon future consideration, to expand its focus to include a wider range of interventions (eg, systems innovations).

Horizon scanning involves 2 processes. The first is identifying and monitoring new and evolving health care interventions that purportedly hold potential to diagnose, treat, or otherwise manage a disease or condition or to improve care delivery. The second is analyzing the relevant health care context in which these new and evolving interventions would exist to understand their potential for disruption to the standard of care. The goal of PCORI HCHSS is not to predict future utilization and costs of any health care intervention; rather, the reports are intended to help inform and guide planning and prioritization of research resources.

This edition of the High Potential Disruption Report is the second of 2 editions planned for 2019 and includes topics (ie, interventions intended for a specific use within a specific patient population) and trends (ie, high-level disruptions occurring within or across clinical areas from a combination of factors that, taken together, create a paradigm shift) that have been identified by stakeholders and the horizon scanning team as having high potential to cause disruption to health care. We welcome comments on this report. Send comments by mail to William Lawrence, MD, MS, Patient-Centered Outcomes Research Institute, 1828 L St., NW, Suite 900, Washington, DC 20036, or by email to horizonscan@pcori.org.
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Artificial Intelligence-Enabled Precision Medicine for Cancer Prognosis and Treatment Decisions

Artificial Intelligence for Image Triage to Prioritize Emergency Cases

Artificial Intelligence Systems for Early Detection of Acute Kidney Injury Risk in High-risk Patients

Artificial Intelligence Voice Assistants for Patient-oriented Health Care Applications

Complete Omics Monitoring: Metabolomics, Proteomics, Genomics, and Transcriptomics for Disease Prevention and Treatment

Comprehensive Genomic Profiling in Patients Who Have Cancer to Identify Personalized Targeted Therapy

Direct-to-Consumer Genetic Testing Partnerships With Pharmaceutical Companies to Facilitate Drug Development and Treatment

Fecal Microbiota Transplantation to Treat Diseases Associated With Disturbances in Gut Microbiome (Gut Dysbiosis)

Gene Editing to Prevent or Treat Disease

Integrated Electronic Health Solutions to Improve Cardiovascular Care

Psychedelic Drugs to Treat Mental Health Conditions

Smart Device Applications to Improve Mental Health

Smartphone-guided Medical Examinations and Diagnostics for Use by Patients and Caregivers

Tissue of Origin-Agnostic, Molecularly Targeted Oncology Drugs

References
Introduction

Background

Horizon scanning identifies technology and systems innovations that could disrupt or cause significant shifts in health care. In health care, horizon scanning can identify new (and new uses of existing) diagnostic tests and procedures, health care delivery innovations, medical devices, mental and behavioral health interventions, pharmaceuticals, public health and health promotion activities, rehabilitation interventions, and therapeutic interventions.

Health care horizon scanning has typically been performed to inform a variety of strategic planning activities. Public and private entities around the world have long used formal or informal health care horizon scanning programs for purposes including commercial, financial, or operational planning; prioritization of health services research; controlled diffusion of technologies; and provision of information to policy makers, purchasers, and providers of health care.

System Overview

The PCORI Health Care Horizon Scanning System (HCHSS) identifies and monitors topics (ie, interventions intended for a specific use within a specific patient population) likely to be available for clinical use (ie, outside the research environment) within 3 years and likely to cause significant disruption (ie, change or shift) in one or more key dimensions of health care in the United States. Examples of these dimensions include patient health outcomes, access to care, care setting and delivery processes, disparities, and costs of care. HCHSS continues to monitor topics for up to 1 year after initial clinical availability.

Initially, PCORI has defined its project scope as interventions with high potential for disruption in 5 priority areas: Alzheimer’s disease and other dementias, cancer, cardiovascular diseases, mental and behavioral health conditions, and rare diseases. In addition, the system captures high-level disruptive trends across all clinical areas, which may lead PCORI to expand the project scope to include other priority areas in the future.

We scan information sources broadly within each priority area to detect leads for potential topics meeting criteria as described above. Analysts review leads to discover potential topics and, if they meet inclusion criteria, create topic records encompassing PICO (intended patient population, intervention, comparators to the intervention, and patient-oriented outcomes of interest) information and key regulatory information (if the topic is subject to a regulatory pathway).

Analysts present potential topics at topic nomination meetings. After a brief presentation and discussion, HCHSS team members vote in blinded fashion to include or exclude the topic based on criteria described in the PCORI Health Care Horizon Scanning System: Horizon Scanning Protocol and Operations Manual. All included topics are reported in the quarterly Status Report (see the most recent volume, September 2019 Horizon Scanning Status Report).

Included topics with late-phase clinical data are further developed as topic profiles—reports that rely on focused searches and more robust analysis. Each topic profile is sent to stakeholders for comment with the goal of obtaining a maximum of 9, but at least 5, sets of comments before a topic is eligible for consideration for this report. Stakeholders provide varied perspectives.
and/or areas of knowledge in health care (eg, clinical, health systems, research, nursing), ideally including at least one patient, patient representative, or caregiver. The commenter reads the topic profile and completes a 6-question survey, which elicits ratings—on a scale of 1 (low disruption potential) to 4 (high disruption potential)—about the intervention’s potential to disrupt a number of key areas of health care. Commenters provide a written rationale for each rating.

It is possible, even likely, that a particularly knowledgeable expert or patient commenter could have a personal, intellectual, or financial conflict of interest related to a topic on which he or she provides comments. Commenters are asked to declare all potential conflicts of interest on the structured comment form we send to record their ratings and comments. Those who declare potential conflicts of interest for a topic are not necessarily disqualified from participating. Their views are balanced by inputs from other neutral parties, including ECRI Institute experts.

Individuals with vested interests in new technologies, services, and innovations typically provide critical insights and information about the areas in which they have a vested interest. Their perspectives may include their vision and plans for how they intend to adopt a technology, service, or innovation.

From the total number of commenters per topic (5 to 9), we limit the number of participants with potential conflicts of interest to 2. Equally important is identifying whether any commenters represent special interests against a technology or service. If they are involved in some manner in developing a competing intervention, their views must be balanced by other commenters without special interests.

Twice a year, analysts review all topics for which stakeholder comments have been received in the previous 15 months. Based on stakeholder rationales and ratings, analysts nominate topics deemed to have the highest potential for disruption to be included in the High Potential Disruption Report. See Report Methods below for a detailed description of the process.

At any point, an included topic may be archived for one or more of the following reasons: (1) Comments from stakeholders overwhelmingly suggest that the intervention is unlikely to cause significant disruption in US health care; (2) development of the intervention has ceased; or (3) the intervention has been clinically available outside the clinical research environment for longer than 1 year.

**Report Methods**

A primary goal of the PCORI HCHSS is to identify health care interventions likely to cause significant disruption to patient health care in the United States. To that end, twice a year the Horizon Scanning team prepares a High Potential Disruption Report detailing interventions from among those it has identified and is monitoring that are deemed to have high potential to cause disruption.

Every 6 months, all actively monitored topics that received at least 5 sets of stakeholder comments and ratings (described above) within the past 15 months are considered for inclusion in a High Potential Disruption Report. Stakeholder comments and ratings serve as critical input into the HCHSS process for determining which interventions have the highest potential for disruption. Several weeks before delivery of each High Potential Disruption Report, the horizon scanning team reviews all stakeholder comments and ratings, then convenes to decide which topics to include in the report.

To provide an initial sorting order for the data, ECRI Institute calculates the mean and median ratings for each of the 6 parameters that commenters provided for each eligible topic.
The summary data are exported to a spreadsheet for the analysts, who assess the comments for each eligible topic as a starting point. Comments take priority over ratings because prior HCHSS experience has shown that individual commenters with similar rationales may rate a topic differently. Thus, ratings are used only as a preliminary signal of potential for disruption. Furthermore, comments for all eligible profiles are read—including those whose ratings are below the mean or median in a priority area—to ensure that no topic with important potential is missed because of a rating anomaly.

After review of stakeholder comments, the HCHSS team meets to decide which topics have the highest potential for disruption. The analyst for each priority area presents the results of the comments and ratings on all their respective topics that have at least 5 sets of stakeholder comments from the prior 15 months. Analysts make recommendations based on ratings and comments. Rating scores alone are not the sole criterion for inclusion; rather, commenter rationales are the main drivers for consideration of the topic’s disruption potential. All topics chosen for inclusion in this report have rating scores and/or supporting rationales at or above the average for all topics considered for inclusion in this priority area.

Each team member votes using a blinded voting system (simple majority rules) on topics to include in the report. The current voting team includes 10 to 12 participants. A vote to include indicates that the voter thinks the intervention has high potential for disruption, based on stakeholder ratings/comments and available data at the time. The decision data for each topic that an analyst presents are recorded, as is the reason for exclusion or changes to the topic. If the topic was included in a High Potential Disruption Report but is subsequently excluded, the reason for the change is recorded and stated in the current report. Topics selected for inclusion are subject to updated searches for the latest information and are assigned to analysts for report drafting. Trends are also selected for inclusion at this time.

After the decision meeting, analysts synthesize the stakeholder comments in a written analysis on each topic to compose the chapter(s) in their respective priority areas. This analysis provides a brief overview (see Report Period Summary) of each priority area and all the topics considered, followed by more detailed information on each topic or trend designated as having high potential for disruption. The project manager, medical copyeditor, senior technical advisor, and project director carefully review each chapter before it undergoes final preparation for delivery.

For additional details on methods, please refer to the PCORI Health Care Horizon Scanning System: Horizon Scanning Protocol and Operations Manual.

**Reporting Period Summary**

The PCORI HCHSS began operating in December 2018. Since then, review of about 2300 leads has led to the identification of about 380 potential topics across the 5 PCORI priority areas and 60 high-level trends occurring in all areas of health care.

As of October 1, 2019, after subjecting the potential topics to our inclusion criteria and nomination process, 259 topics have been selected. Of these, 212 topics are being actively monitored in the system; 47 topics have been archived. These 212 topics represent 125 diseases/conditions and span the PCORI-defined priority areas as follows:

- Alzheimer’s disease and other dementias: 7 topics (3%)
- Cancer: 74 topics (35%)
- Cardiovascular diseases: 23 topics (11%)
- Mental and behavioral health conditions: 15 topics (7%)
- Rare diseases: 93 topics (44%)

Across all priority areas, the 212 monitored topics represent the following therapeutic classes:

- Cell therapy: 20 topics (9%)
- Device (nonimplantable): 10 topics (5%)
- Gene therapy: 19 topics (9%)
- Immunotherapy: 3 topics (1%)
- Implant: 6 topics (3%)
- Monoclonal antibody: 4 topics (2%)
- Other biotechnology: 16 topics (8%)
- Pharmaceutical: 124 topics (58%)
- RNA interference: 3 topics (1%)
- Surgical procedure: 1 topic (0.4%)
- Viral vector therapy: 6 topics (3%)

Note: Total does not equal 100% because of rounding.

Of these 212 actively monitored topics, we have selected—based on the procedure described in Report Methods—36 topics for inclusion in this report, distributed across the PCORI priority areas as follows:

- Alzheimer’s disease and other dementias: 1 topic (3%)
- Cancer: 11 topics (31%)
- Cardiovascular diseases: 5 topics (14%)
- Mental and behavioral health conditions: 3 (8%)
- Rare diseases: 16 topics (44%)

Likewise, as of October 1, 2019, after subjecting potential trends to our inclusion criteria and nomination process, 22 trends occurring across clinical areas or within a clinical area that can potentially create a paradigm shift in health care (ie, large, high-level disruptions) have been selected and are being actively monitored in the system. Among these 22 trends, 3 themes have emerged, which together represent nearly 70% of the included trends:

- Artificial intelligence and machine learning: 7 trends (32%)
- Proteomics, genomics, and personalized medicine: 4 trends (18%)
- Health information technology, apps, and smart devices: 4 trends (18%)

Of these 22 trends, we have selected 15 trends that the horizon scanning team unanimously agreed have high potential for disruption for inclusion in this report.
Chapter 1. Alzheimer’s Disease and Other Dementias

Chapter Summary

For the Alzheimer’s disease and other dementias priority area, we considered for inclusion one topic for which (1) preliminary phase III data for drugs, phase II (or equivalent) data for devices and procedures, or some human data for off-label uses or programs were available; (2) information was compiled and sent for stakeholder comment before October 1, 2019; and (3) we received at least 5 sets of comments and ratings from stakeholders between April 1, 2019, and October 10, 2019.

As of October 1, 2019, we were monitoring 7 topics in this priority area, including the topic considered for inclusion in this report. These 7 topics will be listed in the December 2019 PCORI Health Care Horizon Scanning System: Horizon Scanning Status Report. We also archived one topic in May 2019. A description of that topic and the reason it was archived can be found in Section 3 of the June 2019 Status Report.

The 7 monitored topics encompass pharmaceuticals and biotechnologies for treating Alzheimer’s disease (AD) and/or related symptoms (eg, agitation). Of these, 6 topics are too early in development to meet criteria (as outlined above) for eligibility for this report.

Topic Considered for Inclusion in This Report

Table 1.1 lists the single topic selected for inclusion during the High Potential Disruption Report decision meeting. A majority of the horizon scanning team voted that it had high potential for disruption, based on stakeholder ratings and comments and available data.

Table 1.1 Included Topic for Priority Area: Alzheimer’s Disease and Other Dementias

<table>
<thead>
<tr>
<th>Topic Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periodic Therapeutic Plasma Exchange (Alzheimer’s Management by Albumin Replacement Protocol) to Treat Mild to Moderate Alzheimer’s Disease</td>
</tr>
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Topic Summary

Periodic Therapeutic Plasma Exchange (Alzheimer’s Management by Albumin Replacement Protocol) to Treat Mild to Moderate Alzheimer’s Disease

Highlights

Periodic therapeutic plasma exchange (Alzheimer’s management by albumin replacement [AMBAR] protocol) is intended to slow cognitive decline and the progression of mild to moderate AD, which affects millions of Americans, particularly adults between the ages of 55 and 85 years. In a recent clinical trial, treatment with plasma exchange reduced the disease progression by 61%.
compared with placebo. The 10 stakeholders commenting on this topic generally agreed that this treatment could meet an important unmet need and positively disrupt patient-oriented health outcomes, including quality of life (QoL), given the significant illness and burden that patients and caregivers experience due to the lack of effective treatments. However, most commenters thought that factors surrounding cost and delivery of the treatment (eg, infusion center resources, intravenous immunoglobulin [IVIG] shortage) might create disparities in access to care and/or add to the burden of care for these patients.

**Patient Population**

Periodic therapeutic plasma exchange is intended for adults aged 55 to 85 years with mild to moderate AD.

**Intervention**

AD is the leading cause of dementia and has no effective cure and limited options for symptom management. No disease-modifying treatments are available.\(^1\)

Many investigational agents testing small-molecule drugs and immunotherapies have failed to reduce amyloid-β peptide (Aβ) levels in the brain, which some in the research community believe are associated with AD progression and cognitive decline.\(^2\) These failures have led researchers to explore new strategies for AD aimed at lowering Aβ accumulation in the brain by altering the transportation of Aβ through the blood–brain barrier.

AMBAR is a novel therapeutic approach under study that involves performing plasma exchange, using albumin to replace the plasma volume that is removed.\(^3\) Researchers theorize that such replacement can lead to a shift of the dynamic equilibrium that exists between brain and plasma Aβ, thereby improving symptoms and delaying progression of cognitive decline in adults with mild to moderate AD.\(^3\)

In the AMBAR protocol, an initial phase of large-volume plasma exchanges through plasmapheresis is used to replace the removed plasma volume with a commercial albumin solution (Albutein). This is called the intensive treatment period. Then, a periodic maintenance period starts during which IVIG or intravenous (IV) albumin is used to replace the plasma removed during the exchange.\(^3\)

Researchers assert that AMBAR may remove Aβ from the brain because of the dynamic equilibrium that exists between Aβ in plasma (most of which is bound to albumin) and the cerebrospinal fluid (CSF) of the central nervous system.\(^2\) Albumin infused as volume replacement would theoretically be able to bind and capture additional free-circulating Aβ. These processes purportedly reduce levels of free Aβ in plasma, resulting in a diffusion gradient that draws Aβ from the CSF and slows the progression of Aβ-driven AD pathogenesis.\(^3\)

A neurologist refers a patient to an infusion center for the plasma exchange. During the 6-week intensive period, patients undergo weekly total plasma exchange (2.5 to 3 L plasma removal) and volume replacement with a 5% albumin solution. A 12-month maintenance phase follows, during which patients undergo monthly low-volume plasma exchange (650 to 880 mL plasma removal) and volume replacement with a 20% albumin solution or IVIG.\(^4\)

Three regimens are being tested that use some combination of albumin with or without IVIG as the replacement:\(^4\):

- Three 4-month cycles consisting of 20 g IVIG in month 1 and 40 g albumin in months 2 to 4
- Three 4-month cycles consisting of 10 g IVIG in month 1 and 20 g albumin in months 2 to 4
- Twelve 1-month cycles consisting of 20 g albumin

The [Alzheimer’s Association website](https://www.alz.org) offers more information about AD.
Evidence Development Summary

Investigators have reported results from a single trial of AMBAR (NCT01561053) to treat mild to moderate AD using albumin infusion combined with IVIG.\(^5\) In the phase III AMBAR randomized controlled trial (RCT), adults (n = 347) aged 55 to 85 years who had mild to moderate AD were assigned to albumin replacement with or without IVIG. The trial evaluated the safety and efficacy of albumin replacement in slowing disease progression.\(^6\)

The investigators reported a statistically significant reduction of 61% in disease progression in 2 primary efficacy endpoints, ADAS-Cog (Alzheimer’s Disease Assessment Scale – Cognitive) and ADCS-ADL (Alzheimer’s Disease Cooperative Study – Activities of Daily Living) scales. Some improvement was noted in language and processing speed in patients with mild AD as well. Also, the CDR-Sb (Clinical Dementia Rating – Sum of Boxes) scale, which assesses memory, orientation, judgment, community affairs, home and hobbies, and personal care, showed a statistically significant 65% to 71% lower declination compared with placebo (sham-simulated plasma exchange without fluid replacement) at 14 months. Further analysis showed a decline of 53% in patients with moderate-stage disease, while patients with mild-stage disease showed an improvement that was interpreted as a higher treatment effect for earlier Alzheimer’s stages. From the analysis of the ADCS-CGIC (Alzheimer’s Disease Cooperative Study – Clinical Global Impression of Change) scale, which assesses several cognition domains, daily functioning, and behavior from both the patient and the caregiver perspective, the investigators reported similar improvement in all treated patients with respect to placebo.\(^6\)

Manufacturers and Regulatory Status

The Albutein and IVIG (Flebogamma 5% DIF) treatment protocol (Grifols, SA, Barcelona, Spain) was evaluated in a phase II/III clinical trial for treating mild to moderate AD.\(^5\) FDA has not approved Albutein to treat AD, but it has been commercially available since 1978 and is FDA approved for use in several other indications.\(^7\) IVIG also is not labeled for use in AD but is indicated for treating primary (inherited) immunodeficiency in adults and pediatric patients aged 2 years or older.\(^8\) Albutein and IVIG, as used in the AMBAR protocol, could be administered as an off-label treatment for mild to moderate AD.

Cost Information

According to ECRI Institute’s PriceGuide database, member hospitals reported a median price paid of about $34 for 250 mL of 5% Albutein, $36 for 50 mL of 25% Albutein, and $836 for 10 g of 5% Flebogamma IVIG (as of August 29, 2019).\(^9\)-\(^11\) Using these figures, the drug cost for 14 months would range from $5474 to $8501, depending on the prescribed dosing regimen.\(^4\),\(^9\)-\(^11\) These costs do not include the costs of administration and other fees associated with an infusion procedure.

Results and Discussion of Stakeholder Comments

Ten stakeholders reflecting caregiver, clinical, research, and health systems perspectives provided comments and ratings on this periodic plasma exchange treatment.\(^12\)-\(^21\) We have organized the following discussion of stakeholder comments by the parameters on which they commented.

Patient outcomes, quality of life, and overall health: Most commenters agreed that data reported from the clinical trial\(^5\) show that AMBAR has the potential to slow cognitive decline and improve QoL for patients, their caregivers, and families. A clinician expressed concerns that the data may be misrepresented because other trials using IVIG treatment have yielded negative results.\(^18\) Commenters thought that, in the absence of other options for slowing the progression of AD, this treatment would likely positively disrupt patient health outcomes and QoL.
**Health disparities:** All commenters noted that the high cost of this treatment along with logistic difficulties for patients may increase disparities. A caregiver thought if the insurance companies and government supported this therapy for AD treatment, it could increase the patient’s overall healthy years enough to offset AD-associated nursing home and hospitalization costs. A clinician noted that a current IVIG shortage would likely lead to extremely high costs for this treatment, which is unlikely to be covered by insurance companies and would be difficult for patients of low economic status or limited resources to afford.

**Health care delivery system:** Two clinicians and a researcher thought that AMBAR administration would likely increase demands at infusion centers and in the overall health care delivery system, because current AD management involves use of outpatient medications and possibly cognitive training. Conversely, a commenter with a health systems perspective noted that this intervention would not disrupt patient management, clinician, or health systems current practices if side effects associated with this infusion are low.

**Current paradigm of patient care:** Most commenters thought this intervention has moderate to high potential to disrupt treatment paradigms. On the other hand, the health systems commenter did not think this would disrupt the current paradigm of care because infusion-based treatments are common for other neurologic disorders; however, this commenter expressed concerns about possible infusion-related complications, such as bloodstream infections, infusion site infections or infiltration, or air emboli.

**Health care costs:** Most commenters agreed that this therapy would likely disrupt costs for payers and health care facilities. They also agreed that the extent of cost disruptions would depend on whether and how much insurance would reimburse for the therapy and the copayments required of patients. However, several commenters stated that this treatment would save costs due to decreased needs for home health aides or long-term care facilities.

**Overall disruption potential:** Most commenters, noting that no other disease-modifying treatments are available for slowing mild to moderate AD, thought that AMBAR has large overall potential to disrupt health care delivery, particularly regarding patient health outcomes and QoL. A clinician, a caregiver, and a health systems commenter expressed concerns about the long-term effectiveness (beyond 14 months) of this treatment as well as the purported mechanism of action of lowering cerebral amyloid.
Chapter 2. Cancer

Chapter Summary

For the cancer priority area, we considered for inclusion 24 topics for which (1) preliminary phase III data for drugs, phase II (or equivalent) data for devices and procedures, or some human data for off-label uses or programs were available; (2) information was compiled and sent for stakeholder comment before October 1, 2019; and (3) we received at least 5 sets of comments and ratings from stakeholder commenters between April 1, 2019, and October 10, 2019.

As of October 1, 2019, we were monitoring 74 topics in this priority area, including those considered for inclusion in this report. These 74 topics will be listed in the December 2019 PCORI Health Care Horizon Scanning System: Horizon Scanning Status Report. We also have archived 9 topics since May 2019 (2 in May, 1 in June, and 6 in August). Descriptions of those topics and the reasons they were archived can be found in Section 3 of the 2019 editions of the June, September, and December Status Report, which lists archived topics.

The 74 monitored topics encompass pharmaceuticals, gene and cellular therapies, and devices intended to treat 38 cancers and/or related conditions. One topic, UGN-101 (MitoGel) to Treat Low-grade Upper Tract Urothelial Cancer, is currently undergoing stakeholder comment; however, fewer than 5 sets of stakeholder comments were received for the topic before October 1, and it was not considered for inclusion in this report. The remaining 49 topics are too early in development to meet criteria (as outlined above) for eligibility for this report.

Topics Considered for Inclusion in This Report

Table 2.1 lists 11 topics selected for inclusion during the High Potential Disruption Report decision meeting. A majority of the horizon scanning team voted that these topics had high potential for disruption, based on stakeholder ratings and comments and available data. Topics are listed and discussed alphabetically by title.

Table 2.1 Included Topics for Priority Area: Cancer

<table>
<thead>
<tr>
<th>Topic Title</th>
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<tbody>
<tr>
<td>ABI-009 (Tarzifyx) to Treat Locally Advanced or Metastatic Perivascular Epithelioid Cell Tumor</td>
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<tr>
<td>Atezolizumab (Tecentriq) as First-line Treatment for Locally Advanced or Metastatic Triple-negative Breast Cancer</td>
<td></td>
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<tr>
<td>Avapritinib (BLU-285) to Treat Advanced Systemic Mastocytosis</td>
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<tr>
<td>DCVax-L to Treat Newly Diagnosed Glioblastoma Multiforme</td>
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<tr>
<td>Lifileucel (LN-144) as Second-line Treatment for Newly Diagnosed Glioblastoma Multiforme</td>
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<tr>
<td>MDNA55 to Treat First Recurrence of Recurrent Glioblastoma Multiforme</td>
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<tr>
<td>Oprotuzumab Monatox (Vicinium) for Treatment-resistant, Recurrent, or High-risk Non-Muscle Invasive Bladder Cancer</td>
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<tr>
<td>Pembrolizumab (Keytruda) as First-line Treatment for Locally Advanced or Metastatic, Recurrent Head and Neck Squamous Cell Carcinoma</td>
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<tr>
<td>Pexidartinib (Turalio) to Treat Tenosynovial Giant Cell Tumors</td>
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Table 2.2 lists 13 topics considered, but not selected, for inclusion during the High Potential Disruption Report decision meeting. A majority of the voting team agreed that these topics lacked high potential for disruption, based on stakeholder ratings and comments and available data. Each record contains a note explaining the reasons for exclusion.

### Table 2.2 Topics Considered but Not Included for Priority Area: Cancer

<table>
<thead>
<tr>
<th>Topic Title</th>
<th>Exclusion Reason(s) and Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpelisib (Piqray) to Treat Locally Advanced or Metastatic Estrogen Receptor (ER)-positive Breast Cancer Harboring PIK3CA Gene Alterations (Second-line Setting)</td>
<td>Stakeholder commenters agreed that alpelisib has the potential to improve patient health outcomes; however, because of a 40% response rate and 25% discontinuation rate due to adverse events, it will not likely be the preferred regimen for most. Commenters also stated that this treatment is likely to increase overall health care costs due to the combined cost of alpelisib–fulvestrant and an increase in hospital visits due to treatment-related adverse events.</td>
</tr>
<tr>
<td>Atezolizumab (Tecentriq) to Treat Extensive-stage Small Cell Lung Cancer (First-line Setting)</td>
<td>Stakeholder commenters generally agreed that combining atezolizumab with standard first-line chemotherapy resulted in only an incremental improvement to health outcomes. Commenters also considered atezolizumab to be a very expensive therapy, which would limit its diffusion, and they did not think that its modest effectiveness justified such a high cost.</td>
</tr>
<tr>
<td>Avapritinib (BLU-285) to Treat Locally Advanced or Metastatic Gastrointestinal Stromal Tumors</td>
<td>Stakeholder commenters thought that the data from a phase I clinical trial for avapritinib showed incremental benefit in a small percentage of patients with gastrointestinal stromal tumors. Commenters thought avapritinib will not likely disrupt the current treatment pathway or health care delivery system due to comparable efficacy to existing oral drugs, as well as low quality of life in trial patients based on incidence of reported adverse events such as memory impairment (29%).</td>
</tr>
<tr>
<td>Enfortumab Vedotin (Adcetris) to Treat Advanced or Metastatic Urothelial Cancer (Third-line Setting)</td>
<td>Stakeholder commenters thought that early clinical trial results for enfortumab vedotin suggest a small improvement to patient health outcomes. Comments suggested the IV dosing would not change the treatment paradigm or disrupt the health care delivery system. Commenters indicated that results from an ongoing phase III clinical trial need to be reviewed for overall survival and progression-free survival to determine the potential for disruption.</td>
</tr>
<tr>
<td>Erdafitinib (Balversa) to Treat Metastatic or Surgically Unresectable Urothelial Cancer (Second-line Setting)</td>
<td>Stakeholder commenters agreed that results from an ongoing phase III trial are needed to determine whether this intervention has potential for disruption in patients with advanced urothelial cancer. We continue to actively monitor this topic.</td>
</tr>
<tr>
<td>Topic Title</td>
<td>Exclusion Reason(s) and Notes</td>
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<tr>
<td>Ivosidenib (Tibsovo) to Treat Acute Myeloid Leukemia (First-line Setting)</td>
<td>Stakeholder commenters generally agreed that ivosidenib demonstrated encouraging preliminary efficacy results; however, they thought the benefits would not likely outweigh the risks. Ivosidenib has a black box warning from FDA stating that about 20% of patients experience dedifferentiation syndrome, which is associated with life-threatening complications (eg, pulmonary infiltrates, pleural effusions). Commenters also thought its high cost would limit its availability and adoption.</td>
</tr>
<tr>
<td>Melflufen (Ygalo) to Treat Relapsed and Refractory Multiple Myeloma</td>
<td>Stakeholder commenters thought the risk-to-benefit ratio for melflufen was too high, which would limit the likelihood of its approval and uptake. In addition, most commenters thought that any potential benefit from melflufen would be incremental and that its overall potential for disruption to patient health and care paradigms was low.</td>
</tr>
<tr>
<td>NovoTTF-100L to Treat Locally Advanced or Metastatic Malignant Pleural Mesothelioma (First-line Setting)</td>
<td>Stakeholder commenters expressed doubts about this technology's purported underlying mechanism of action and its ability to improve outcomes, noting that test group data were compared with historical control group data that were more than 15 years old. They further noted that the intervention is an adjunct to, not a replacement for, chemotherapy, so it is unlikely to substantially disrupt care paradigms.</td>
</tr>
<tr>
<td>Olaparib (Lynparza) to Treat Germline BRCA Mutated Metastatic Pancreatic Cancer (Maintenance Setting)</td>
<td>Stakeholder commenters thought that olaparib might improve short-term health outcomes (eg, progression-free survival); however, because there was no significant improvement in overall survival or quality-of-life (QoL) scores, they agreed that overall disruption potential is small. Commenters also noted that the higher incidence of adverse events (reported in the POLO clinical trial) would also slow or prevent adoption.</td>
</tr>
<tr>
<td>Pembrolizumab (Keytruda) to Treat Metastatic Renal Cell Carcinoma (First-line Setting)</td>
<td>Stakeholder commenters generally agreed that preliminary results from pembrolizumab plus axitinib were positive but that it provided only incremental improvement in outcomes compared with standard care. They also thought its overall disruption potential was low because of other, more promising experimental treatments in development.</td>
</tr>
<tr>
<td>Polatuzumab Vedotin (Polivy) to Treat Relapsed or Refractory Diffuse Large B-cell Lymphoma (Third-line Setting)</td>
<td>Stakeholder commenters agreed that polatuzumab vedotin provided only incrementally improvements in treatment response, overall survival, and quality of life for patients compared with standard of care. In addition, they thought it could add substantial cost burden to an already costly area of treatment, thereby limiting its use.</td>
</tr>
<tr>
<td>Ruxolitinib Phosphate (Jakafi) to Treat Steroid-refractory Acute Graft-Versus-Host Disease</td>
<td>Some stakeholder commenters cited study results, which revealed that treatment with ruxolitinib resulted in a 6-month survival rate of 79% compared with a historical 6-month survival rate of about 50%. However, most commenters thought that these improvements were likely incremental since the data were limited to single-arm observational case series with a relatively small number of patients. Commenters agreed that data are needed from a prospective controlled trial. We continue to monitor this topic.</td>
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</table>

**Table Notes:**
- **Topic Title:** The name of the drug and the indication for treatment.
- **Exclusion Reason(s) and Notes:** The reasons why the drug was excluded from the disruption report, along with any relevant notes or considerations.
### Topic Summaries

We present below 11 summaries on topics deemed to have high potential for disruption.

**ABI-009 (Tarzifyx) to Treat Locally Advanced or Metastatic Perivascular Epithelioid Cell Tumor**

**Highlights**

Perivascular epithelioid cell sarcoma (PEComa) is a rare soft-tissue sarcoma with no FDA-approved therapy. ABI-009 is a novel formulation of an inhibitor that targets a molecular pathway known as the mammalian target of rapamycin (mTOR) pathway. This pathway is involved in cell proliferation, and ABI-009 is intended to treat locally advanced or metastatic PEComa tumors. Most of the 7 stakeholders commenting on this topic agreed that ABI-009 has the potential to improve health outcomes for patients with PEComas, a disease for which no FDA-approved treatments are available. Most commenters also expected ABI-009 to be costly, possibly creating disparities for uninsured patients or those who cannot afford deductibles and/or copayments. ABI-009 is given intravenously and is unlikely to disrupt delivery or care paradigms because it will use infrastructure that is already in place for IV treatments.

**Patient Population**

ABI-009 is intended for adults aged 18 years or older with locally advanced or metastatic PEComa.

**Intervention**

PEComa is a rare sarcoma that originates in the soft tissues of the stomach, intestines, lungs, and genitourinary organs. Although most PEComas are noncancerous (ie, benign) tumors that grow slowly and are unlikely to spread to other organs, some are malignant with potential to spread to other parts of the body (for more information see the National Cancer Institute’s Physician Data Query). No targeted therapies are approved by FDA to treat malignant PEComas, and the tumors usually do not respond well to chemotherapy. Therefore, patients need new treatment options that can improve outcomes.\(^{22}\)

The mTOR pathway is a molecular pathway involved in cell proliferation and frequently activated in PEComas by genetic variations in the tuberous sclerosis complex genes, \(TSC1\) and \(TSC2\).\(^{22}\) Off-label use of commercially available drugs that inhibit the mTOR pathway has shown some benefit for these patients. However, these mTOR inhibitors distribute widely in the body and affect normal cells as well as tumor cells, leading to adverse events.\(^{22,23}\)
ABI-009 is different because it purportedly accumulates preferentially in cancer cells. The drug is a nanoparticle suspension, and each nanoparticle consists of several molecules of an mTOR inhibitor, sirolimus, that is bound to human albumin and called nab-sirolimus.\textsuperscript{23,24}

Cancer cells take up blood albumin to support protein synthesis, and albumin might act as a carrier that helps sirolimus accumulate preferentially in tumor tissues.\textsuperscript{24} Once the nab-sirolimus nanoparticles enter cells and inhibit the mTOR pathway, ABI-009 purportedly prevents tumor cell growth, proliferation, nutrient metabolism, and blood vessel formation.\textsuperscript{22,23}

An oncologist prescribes ABI-009 to be given at an infusion center. An infusion nurse administers IV ABI-009 weekly at a dose of 100 mg/m\textsuperscript{2} in a 2-weeks-on, 1-week-off schedule until disease progression or intolerable toxicity.

Evidence Development Summary

ABI-009 is being studied in the phase II AMPECT (NCT02494570) clinical trial for treating locally advanced or metastatic PEComas. AMPECT is a nonrandomized, single-group assignment, open-label trial to evaluate the safety and effectiveness of intravenous ABI-009 given to patients (n = 34) weekly at a dose of 100 mg/m\textsuperscript{2} in a 2-weeks-on, 1-week-off schedule. The primary endpoint is objective response rate (ORR) and the secondary endpoints are overall survival (OS), progression-free survival (PFS), duration of response (DOR), and adverse events.\textsuperscript{25}

The ORR rate among 31 patients with evaluable responses was 42%, with 13 patients achieving partial response, 11 with stable disease, and 7 with progressive disease. At the time of assessment, 69% patients had ongoing partial responses, of which 5 had responded for more than 1 year and 2 for more than 2 years. The median PFS was 8.9 months and the 6-month PFS was 66%, but DOR was not reached. The most common ABI-009–associated grade 3 adverse events were mucositis (18%) and anemia (12%).\textsuperscript{25}

Among 25 patients with known TSC gene status, 5 harbored TSC1 gene variants and 9 had TSC2 gene variants with no overlap. Based on the status gene variants, partial responses were reported in 100% (9 of 9) of patients with TSC2 mutations, in 20% (1 of 5) with TSC1 mutations, and in 9% (1 of 11) without mutations. Disease control was observed in 93% (13 of 14) of patients with TSC1 or TSC2 variants and in 55% (6 of 11) of patients without the variants.

Manufacturers and Regulatory Status

Investigators at Aadi Bioscience, Inc (Pacific Palisades, California) are studying ABI-009 in a phase II clinical trial. FDA granted ABI-009 Orphan Drug, Fast Track, and Breakthrough Therapy designations to treat patients with PEComa.\textsuperscript{26,27} Based on results from the phase II AMPECT trial, Aadi Bioscience plans to submit a New Drug Application to FDA during the fourth quarter of 2019 or the first quarter of 2020.\textsuperscript{27,28}

Results and Discussion of Stakeholder Comments

Seven stakeholders, reflecting clinical, health systems, nursing, physical therapy, and research perspectives, provided comments and ratings on ABI-009 to treat PEComas.\textsuperscript{29-35} We have organized the following discussion of stakeholder comments by the parameters on which they commented.

**Patient outcomes, quality of life, and overall health:** Most commenters agreed that ABI-009 use shows potential to improve health outcomes of patients with PEComa, who are in need of effective treatments. Four commenters—a physical therapist, a health systems commenter, a
clinician, and a researcher—pointed out that \textit{TSC1} or \textit{TSC2} genetic variants might be biomarkers that predict response to ABI-009.\textsuperscript{29-31,33} Three commenters—the health systems commenter, a nurse, and a researcher—thought that additional patient-oriented outcomes, preferably from larger studies, are needed to evaluate ABI-009’s potential to improve health outcomes.\textsuperscript{31,32,35}

**Health disparities:** A physical therapist and a researcher thought ABI-009 use could reduce disparities by offering a possible treatment option for PEComas.\textsuperscript{29,34} In contrast, a health systems commenter and 2 researchers expected ABI-009 to be expensive and cause disparities for patients without health insurance who cannot afford to pay for treatment.\textsuperscript{31,33,35} These commenters indicated that ABI-009 use could also affect insured patients who cannot afford the associated deductibles and copayments. A clinician explained that PEComas can be misclassified as sarcomas because diagnosis requires appropriate testing and an experienced pathologist, and such pathologists are not available in every health center. Therefore, only patients in whom a PEComa has been correctly diagnosed will be eligible to receive ABI-009.\textsuperscript{30}

**Health care delivery system:** Most commenters agreed that, because it is an IV intervention, ABI-009 has little potential to disrupt the health care delivery system. One clinician thought that centers adopting ABI-009 would need to change personnel and infrastructure to correctly diagnose PEComas.\textsuperscript{30}

**Current paradigm of patient care:** Most commenters did not anticipate ABI-009 use being any more disruptive than current IV treatments. Three commenters—a physical therapist, a clinician, and a nurse—also pointed out that patients have no effective treatment options available, and if ABI-009 proves to be effective, its adoption has the potential to disrupt the paradigm of care.\textsuperscript{29,30,32}

**Health care costs:** While most commenters anticipated ABI-009 would be expensive, their opinions differed on ABI-009’s potential to disrupt health care costs. A physical therapist, a health systems commenter, and a researcher were unsure whether insurance companies would cover ABI-009, leaving patients and families who cannot afford the treatment with an economic burden.\textsuperscript{29,31,34} Two researchers expected ABI-009 would have a small impact on health care costs overall because PEComas are very rare.\textsuperscript{33,35} A clinician and a researcher also indicated that ABI-009 use could disrupt costs, because it is much more expensive than other generic mTOR inhibitors.\textsuperscript{30,33}

**Overall disruption potential:** Most commenters indicated that ABI-009’s overall disruption potential was based on the lack of treatment options for PEComas. Four commenters—a physical therapist, a clinician, and 2 researchers—thought preliminary results for ABI-009 showed that it was a well-tolerated and promising treatment for PEComas by at least causing tumors to shrink.\textsuperscript{29,30,33,34} Three researchers emphasized the need for long-term, patient-oriented outcomes to further evaluate ABI-009’s potential to improve health outcomes.\textsuperscript{33-35}
Atezolizumab (Tecentriq) as First-line Treatment for Locally Advanced or Metastatic Triple-negative Breast Cancer

Highlights

Triple-negative breast cancer (TNBC) constitutes about 15% of all breast cancers, and metastatic TNBC is associated with poor outcomes and limited treatment options. Atezolizumab (Tecentriq) is an immune checkpoint inhibitor that is intended to treat metastatic TNBC. In a single clinical trial, treatment with the combination of atezolizumab and nab-paclitaxel showed improved PFS and OS. The 8 stakeholders commenting on this topic generally thought that the combination of atezolizumab with nab-paclitaxel, if effective, could largely and positively disrupt outcomes for patients who have TNBC with PD-L1–positive tumor expression. Most commenters also stated that this combination therapy would disrupt costs because it adds to overall costs for other drugs that patients might need to resolve unanticipated side effects. A few commenters were concerned that the treatment might be inaccessible to minorities with TNBC, which might influence disparities and limit its overall disruption potential.36-38

Patient Population

Atezolizumab is intended for adults aged 18 years or older who have locally advanced or metastatic TNBC and have had no previous systemic therapy. Like other cancer indications for drugs targeting the programmed death-1/PD-1 ligand 1 (PD-1/PD-L1) immune checkpoint, atezolizumab’s use in TNBC might require that a patient’s tumor exhibit PD-L1 expression, and genetic testing might be needed to establish eligibility for the drug.

Intervention

TNBC is a type of breast cancer that lacks overexpression of the protein receptors estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2, which typically drive growth of and provide therapeutic targets in other types of breast cancer. TNBC constitutes about 15% of all breast cancers. These advanced forms of TNBC are typically treated with systemic therapy (for more information, see Breastcancer.org).

Atezolizumab is a humanized monoclonal immunoglobulin G4 (IgG4) antibody that selectively binds to PD-L1, an inhibitory ligand expressed by tumor cells.39 Tumor cells have developed immune-tolerance mechanisms that involve the overexpression of ligands that limit T-cell responses to avoid detection and destruction by the immune system.

One of these checkpoint pathways is PD-1, a cell receptor expressed by many immune system cells, including high expression on activated T cells, which has a central role in T-cell downregulation. In many types of cancer, PD-L1 is highly expressed by cells in the tumor. Binding of PD-L1 to PD-1 is thought to induce T-cell anergy (ie, diminished response to persistent antigen exposure), limiting tumor rejection by tumor-specific T cells in the effector phase of the immune response.40 Although TNBC tumors have relatively high PD-L1 expression, they are mostly devoid of infiltrating cytotoxic T cells, which might explain their limited response to monotherapy with a PD-1/PD-L1 immune checkpoint inhibitor.39,41 Atezolizumab binding to PD-L1 purportedly prevents its interaction with the coinhibitory receptor PD-1, inhibiting the immune checkpoint pathway and leading to an increase in anticancer immune response to TNBC tumors.39,40 PD-L2 is a ligand expressed in various cell types, including breast cells, involved in maintaining immune tolerance through interaction with PD-1. Because
atezolizumab binds PD-L1 and not PD-L2, it prevents any toxicity associated with PD-L2 inhibition. Atezolizumab’s Fc region has also been modified to reduce the induction of antibody-dependent cellular toxicity and complement mediated toxicity to prevent immune cell depletion, of T cells in particular, which also express high levels of PD-L1.41,42

An oncologist prescribes atezolizumab for administration in an infusion center. An infusion center nurse administers 840 mg of IV atezolizumab on day 1 and 15 of each 28-day cycle until disease progression or unacceptable toxicity. Atezolizumab is used in combination with IV nanoparticle albumin-bound paclitaxel (nab-paclitaxel; at a dose of 100 mg/m²) or paclitaxel (at a dose of 90 mg/m²) on day 1, 8, and 15 of each 28-day cycle.

Evidence Development Summary

The manufacturer continues to evaluate atezolizumab in combination with nab-paclitaxel in 2 ongoing phase III clinical trials, IMpassion130 (NCT02425891) and IMpassion131 (NCT03125902).

In November 2018, Schmid et al43 reported the preliminary results from the IMpassion130 phase III double-blind RCT to evaluate the safety and effectiveness of atezolizumab in combination with nab-paclitaxel in patients with TNBC. Patients were assigned to receive either IV atezolizumab (840 mg on day 1 and 15 of each 28-day cycle) or placebo in combination with IV nab-paclitaxel (100 mg/m²) in a 1:1 ratio. The investigators included 451 patients (median follow-up = 12.9 months) in each group.

In the intention-to-treat analysis, the median PFS was reported as 7.2 months in the atezolizumab plus nab-paclitaxel group and 5.5 months in the placebo plus nab-paclitaxel group (hazard ratio [HR] for progression or death = 0.80; 95% confidence interval [CI], 0.69-0.92; \( P = .002 \)). Patients with PD-L1–positive tumors showed a median PFS of 7.5 months vs 5.0 months, respectively (HR = 0.62; 95% CI, 0.49-0.78; \( P < .001 \)).43

Investigators also reported the median OS as 21.3 months for the atezolizumab plus nab-paclitaxel group vs 17.6 months in the placebo plus nab-paclitaxel group (HR for death = 0.84; 95% CI, 0.69-1.02; \( P = .08 \)). Patients with PD-L1–positive tumors showed a median OS of 25.0 months vs 15.5 months, respectively (HR = 0.62; 95% CI, 0.45-0.86). Adverse events that led to treatment discontinuation occurred in 15.9% of patients in the atezolizumab plus nab-paclitaxel group and 8.2% in the placebo plus nab-paclitaxel group.43

Manufacturers and Regulatory Status

On March 11, 2019, FDA granted accelerated approval to atezolizumab in combination with nab-paclitaxel for first-line treatment of patients with locally advanced or metastatic TNBC.44 The approval was based on PFS results from the phase III IMpassion130 trial. Atezolizumab is being developed by Genentech, Inc (South San Francisco, California), a subsidiary of F Hoffman-La Roche AG (Basel, Switzerland).45

Cost Information

According to a US-based online aggregator of prescription drug prices, Drugs.com, atezolizumab’s retail price as of October 2019 was about $6600 for one vial of 840 mg, which is half the amount a patient would use for each 28-day cycle. Thus, if a patient continued on treatment for a full year, the retail cost would be about $171 600 (13 cycles at $13 200 per cycle).46
According to Drugs.com, patient assistance programs are available, and discounts might be available in the form of coupons, rebates, savings cards, and trial offers. The company offers a Tecentriq Genentech BioOncology Co-pay Card. Eligible patients pay $5 per prescription and can receive annual savings up to $25,000.

Results and Discussion of Stakeholder Comments

Eight stakeholders, reflecting caregiving, clinical, nursing, patient, and research perspectives, provided comments and ratings on the combination of atezolizumab with nab-paclitaxel to treat TNBC that cannot be treated surgically. We have organized the following discussion of stakeholder comments by the parameters on which they commented.

**Patient outcomes, quality of life, and overall health:** Commenters agreed that the preliminary data from the phase III IMpassion130 trial show moderate potential to improve health outcomes and QoL for patients with localized or metastatic TNBC that cannot be treated surgically. A caregiver, a nurse, and a researcher thought that the potential benefit could be limited to patients with PD-L1–positive tumor expression. A patient shared that many patients in this category are younger or belong to racial or ethnic minorities whose disease might go undiagnosed because of limited access to medical care. Another commenter with a health systems perspective thought that the data show moderate short-term improvement; however, since the drug does not stop the tumor from producing antibodies, it has low potential for disruption over the long term.

**Health disparities:** Most commenters agreed that disruption to health disparities would depend on health insurance coverage, especially for patients who are not covered under Medicare, Medicaid, or Veterans Administration/Department of Defense insurances, and that this intervention would most likely not widen disparities more than what already exists. A patient and a clinician also added that TNBC is disproportionately diagnosed in the minority population and, for some, the drug might be unattainable and, therefore, not disruptive to those most in need.

**Health care delivery system:** Commenters generally agreed that this intervention would not disrupt the health care delivery system, because it is administered at an infusion center, which is similar to other types of chemotherapy. Conversely, a patient stated that this intervention would moderately disrupt how health care providers support and engage patients with a diagnosis of TNBC.

**Current paradigm of patient care:** Most commenters agreed that this intervention would moderately disrupt current treatment paradigms for patients with TNBC, based on clinician ease of use, patient ease of acquisition, and minimal learning curve for medical oncologists and clinical staff, who are already using similar therapies for patients. Four commenters—a caregiver, a nurse, a patient, and a researcher—noted the need for further research to evaluate the effectiveness and side effect profile of this combination therapy.

**Health care costs:** Most commenters thought this combination therapy has high potential to disrupt ongoing costs for payers and patients because this adds to costs as a combination therapy and might incur additional costs of drugs involved in managing side effects. Conversely, a caregiver and a clinician stated that the cost disruption would be small since the cost for this treatment is similar to other first-line cancer treatments.
Overall disruption potential: Most commenters thought that this treatment has moderate to large overall potential to disrupt the paradigm of care for first-line treatment of TNBC, patient-oriented health outcomes, and QoL. On the contrary, a caregiver and a researcher thought that this treatment would be disruptive in only a small population of patients with TNBC and would not address long-term survival when the disease progresses. Other commenters, with nursing, patient, and research perspectives, noted that cost will be a huge deterrent in terms of this treatment’s adoption; however, this treatment offers the first immunotherapy option that might prolong OS in this patient population.

Avapritinib (BLU-285) to Treat Advanced Systemic Mastocytosis

Highlights

Advanced systemic mastocytosis (SM) is a rare blood cancer that lacks safe and effective treatment options. Avapritinib is a small-molecule inhibitor of the receptor tyrosine kinase KIT and is under study for treating advanced SM. The 9 stakeholders commenting on this topic generally agreed that avapritinib use has moderate to large potential to disrupt the treatment of advanced SM. They indicated that the preliminary clinical data for avapritinib suggest it might be more effective than current treatments for advanced SM and so has substantial potential to improve health outcomes for a patient population with a debilitating disease. Multiple commenters suggested that avapritinib would become the standard of care for these patients. However, commenters also cautioned that this interpretation was based on a small amount of data from a small clinical trial with no control arm and that avapritinib’s effectiveness would need to be demonstrated in further studies. Multiple commenters also noted that the magnitude of avapritinib’s impact on the health care system would be limited by the small number of patients affected by advanced SM.

Patient Population

Avapritinib is intended for adults aged 18 years or older with advanced SM, including aggressive SM (ASM), SM with an associated hematologic neoplasm (SM-AHN), and mast cell leukemia (MCL).

Intervention

Avapritinib is a small-molecule inhibitor of the receptor tyrosine kinase KIT that is being developed to treat advanced SM, a rare type of hematologic malignancy characterized by mast cell accumulation in skin, bone marrow, and internal organs (eg, gastrointestinal tract, liver, lymph nodes, spleen). SM is divided into 5 subtypes based on symptoms, presentation, and severity, with indolent SM and smoldering SM representing mild subtypes and ASM, SM-AHN, and MCL representing severe subtypes. For more information, see the National Institutes of Health Genetic and Rare Diseases Information Center.

SM is a clonal mast cell disease characterized by activating genetic variations in the proto-oncogene c-kit. These variants lead to decreased cell death (ie, apoptosis) and increased cell proliferation in malignant mast cells. Tyrosine kinase inhibitors (TKIs) capable of inhibiting the KIT protein (eg, imatinib, midostaurin) are used in treating SM; however, available TKIs have significant shortcomings. For instance, imatinib is ineffective against a KIT variant (KIT D816V) that is present in more than 90% of SM cases; therefore, imatinib is suitable for use only in the
minority of SM cases that test negative for KIT D816V. Although midostaurin has activity against KIT D816V, it is a nonselective TKI whose off-target effects on other tyrosine kinases are associated with adverse events including hematologic toxicity, gastrointestinal upset, and rare but serious cases of interstitial lung disease and pneumonitis. Therefore, new treatment options are needed for SM that have the potential to treat a larger percentage of patients with an improved safety profile.

Avapritinib is highly selective for KIT and is designed to act against a wide range of KIT-activating variants, including the D816V KIT isoform associated with imatinib resistance. Avapritinib purportedly inhibits KIT with high selectivity and low off-target activity to prevent SM cell proliferation, spread, and survival. An oncologist prescribes avapritinib, an oral therapy that patients take themselves once daily at a dose of 200 or 300 mg until disease progression or intolerable toxicity.

**Evidence Development Summary**

Investigators presented data from the phase I EXPLORER trial at the 24th European Hematology Association Congress in June 2019. This trial enrolled 69 patients with SM (7 ASM, 37 SM-AHN, 9 MCL, and 16 indolent SM/smoldering SM); 39 of these patients (3 ASM, 28 SM-AHN, and 8 MCL) were evaluable by modified International Working Group (mIWG) criteria at the time of data reporting. All patients received avapritinib, and the overall response rate in evaluable patients was reported as 77% (complete response or complete response with partial hematologic recovery in 23% of patients). Additionally, the response rate in the subset of mIWG-eligible patients (n = 7) previously treated with midostaurin was reported as 86%. Among the 60 patients with advanced SM, the OS time had reportedly not been reached yet; however, the estimated 24-month OS rate was reported as 100% in patients with ASM, 70% in patients with SM-AHN, and 88% in patients with MCL.

Investigators also reported safety results for 67 patients. The most common treatment-emergent adverse events (all grades; grade 3 or higher) included periorbital edema (67%; 4%), anemia (52%; 26%), fatigue (37%; 7%), nausea (36%; 4%), diarrhea (34%; 1%), peripheral edema (34%; 0%), thrombocytopenia (31%; 17%), vomiting (28%; 2%), and cognitive effects (28%; 1%). Investigators reported that 3 patients discontinued because of treatment-related adverse events (ascites, encephalopathy, and intracranial bleed).

**Manufacturers and Regulatory Status**

Avapritinib is being developed by Blueprint Medicines Corp (Cambridge, Massachusetts) and is under study in phase I (EXPLORER, NCT02561988) and II (PATHFINDER, NCT03580655) clinical trials. FDA granted avapritinib Breakthrough Therapy designation to treat severe subtypes of advanced SM that include ASM, SM-AHN, and MCL. Based on results from the phase I EXPLORER trial, Blueprint Medicines plans to submit a New Drug Application to FDA in the first quarter of 2020. Blueprint Medicines is also developing avapritinib for use in treating gastrointestinal stromal tumors (GIST). The manufacturer submitted a New Drug Application to FDA for this indication in June 2019, which could lead to commercial availability of the drug before FDA approval for an SM indication.
Results and Discussion of Stakeholder Comments

Nine stakeholders, reflecting clinical, physician assistant, nursing, research, and health systems perspectives, provided comments and ratings on this treatment.58-66 We have organized the following discussion of stakeholder comments by the parameters on which they commented.

**Patient outcomes, quality of life, and overall health:** Commenters were unanimous in suggesting that avapritinib use has a moderate to large potential to improve patient health outcomes. They noted the shortcomings of existing targeted therapies in treating SM, the solid preclinical premise upon which avapritinib is based, and the promising preliminary results observed in the EXPLORER clinical trial as factors supporting its potential to improve patient health outcomes. However, most commenters also noted the small number of patients who had been studied in these trials and suggested these preliminary results would need to be supported by additional follow-up and additional trials.

**Health disparities:** Commenters suggested that avapritinib use would have a minimal effect on health disparities. Commenters who saw some potential for disruption suggested that the likely high cost of avapritinib could exacerbate socioeconomic disparities and access to the treatment.

**Health care delivery system:** Most commenters did not envision that adoption of avapritinib would substantially disrupt the health care delivery system. Commenters with health systems and research perspectives cited the familiar routine of orally administered tyrosine kinases already used in treating some patients with advanced SM as a factor that would limit the disruptive potential of avapritinib.58,64,65 Also, commenters with health systems and research perspectives noted that no additional staff or facilities changes would be needed for this drug58,66 and that only a small number of patients are affected by the condition.60,63 A clinician, a physician assistant, and 2 researchers noted that the potential effectiveness of avapritinib could reduce the need for health care facility resources used in managing patients with advanced SM (eg, hospitalizations and clinic visits, steroid infusions, hematopoietic stem cell transplants), which could cause a minor disruption to the health care delivery system.59,61,64,66

**Current paradigm of patient care:** Most commenters indicated that avapritinib use has moderate to large potential to disrupt the current paradigm of treatment for advanced SM. These commenters—a physician assistant and 2 health systems commenters—indicated that avapritinib would displace current treatments for advanced SM, potentially improving outcomes and/or reducing side effects.60,61,63 One researcher suggested that avapritinib would likely be adopted in lieu of existing treatments but indicated that the drug’s disruption potential was only small because using avapritinib instead of other TKIs would not represent a substantial shift in the patient management paradigm.64 Another researcher, who also suggested that avapritinib use would have only a small effect on the patient management paradigm, indicated that the limited amount of data available for avapritinib prevented a more positive assessment of disruption potential.65 Yet another researcher suggested that, although avapritinib could reduce some symptoms of advanced SM, patients would likely still require close monitoring of disease progression and potentially serious side effects and, therefore, the drug would not dramatically alter the overall care paradigm for these patients.66
**Health care costs:** Most commenters indicated that avapritinib use has moderate to large potential to disrupt health care costs. They suggested that, if approved, avapritinib would likely be costly, similar to other molecularly targeted therapies and so its adoption would increase the cost of care for this patient population. Two researchers who rated avapritinib’s cost impact as small also suggested that it would likely increase the cost of care for these patients, but the impact to the health system generally would be small because of the small number of patients affected by this condition.65,66 A physician assistant suggested that avapritinib would not substantially disrupt the cost of care because the drug is similar in cost to currently used treatments for advanced SM. This commenter also noted that improved patient outcomes could reduce other health care costs associated with managing advanced SM symptoms.61

**Overall disruption potential:** Overall, most commenters suggested avapritinib use has moderate to large potential to disrupt the treatment of advanced SM. These commenters indicated that the preliminary clinical data suggest that it might be more effective than current treatments and, therefore, has substantial potential to improve health outcomes for a patient population with a debilitating disease. Multiple commenters suggested that avapritinib use would become the standard of care.59,60,64 However, commenters also cautioned that this interpretation was based on a small data set from a small clinical trial with no control arm and that avapritinib would need to demonstrate efficacy in further studies. Multiple commenters noted that the magnitude of avapritinib’s impact on the health care system would be limited by the small number of patients affected by advanced SM.

**DCVax-L to Treat Newly Diagnosed Glioblastoma Multiforme**

**Highlights**

Glioblastoma multiforme (GBM) is a malignant brain cancer associated with limited treatment options, poor outcomes, and short survival times. DCVax-L is an immunotherapy made from activated dendritic cells derived from the patient’s monocytes obtained during pheresis. The cells are loaded with patient-derived tumor antigens that were obtained from the patient’s tumor during surgery. The therapy is intended as an adjunct to standard first-line therapy for newly diagnosed GBM. Most of the 8 stakeholders commenting on this topic agreed that DCVax-L use has the potential to improve outcomes, QoL, and overall health of patients with GBM. Because DCVax-L cost is anticipated to be high relative to standard of care, it also has the potential to disrupt health care costs for patients and payers. DCVax-L’s high cost might also increase disparities because copayments even for insured patients could be high, and uninsured and underinsured patients could have difficulty accessing DCVax-L.

**Patient Population**

DCVax-L is intended for adults aged 18 to 70 years with newly diagnosed, unilateral, stage IV GBM, astrocytoma, or glioma. Patients must not have had disease progression after completing primary therapy consisting of surgical resection (gross or near total resection) and external beam radiation therapy with or without concurrent temozolomide chemotherapy.

**Intervention**

GBM is a malignant brain cancer associated with poor outcomes and high mortality. GBM begins as a stage IV disease with no evidence of a lower-grade precursor (the American Brain
Tumor Association offers more information about GBM). Patients who have undergone primary treatment including surgery, radiation, and temozolomide chemotherapy typically experience disease recurrence in about 7 months and have a median OS between 14 and 17 months. An unmet need exists for new GBM treatments capable of delaying disease recurrence and extending survival.67,68

DCVax-L is an autologous immunotherapy that consists of activated dendritic cells loaded with patient-derived tumor antigens. DCVax-L is manufactured from monocytes obtained from the patient through leukapheresis (ie, extracted from the patient’s blood) at a hospital, cancer center, or blood center (eg, the American Red Cross).69 The sample is collected using a kit containing a shipping box and a special grinder vial (that grinds and homogenizes the sample) prefilled with enzymes. After tumor excision, a nurse or technician places the tissue sample into the vial and ships the sample to the manufacturer.69 The isolated monocytes are differentiated into dendritic cells in the laboratory, activated and loaded with tumor-derived antigens obtained from a lysate of the surgically resected GBM tumor,70 frozen into single doses, and shipped back to the treatment facility. The product must remain frozen until just before it is given to the patient.69 According to the manufacturer, facilities might need to “adopt new requirements for handling, distribution and delivery of DCVax.”69

When DCVax-L is injected into the patient, the tumor lysate–pulsed dendritic cells purportedly activate T cells and B cells to elicit an adaptive immune response against GBM tumor cells.70 Intended as an adjunct to standard first-line therapy for newly diagnosed GBM, DCVax-L use could disrupt patient management and improve health outcomes.67,70

At least 2 weeks after patients undergo primary therapy, a clinician administers DCVax-L as an intradermal injection in the upper arm at days 0, 10, and 20 and at weeks 8, 16, 32, 48, 72, 96, and 120. DCVax-L is intended to be used in combination with adjuvant temozolomide chemotherapy. Patients take oral tablets of adjuvant temozolomide (150-200 mg/m²) for 5 days every 28 days until disease progression or development of intolerable toxicity.

**Evidence Development Summary**

DCVax-L is being evaluated (NCT00045968) for treating newly diagnosed GBM. The GBM trial is a phase III quadruple-blinded RCT to evaluate the safety and effectiveness of DCVax-L. Patients (n = 348) are randomly assigned in a 2:1 ratio to DCVax-L plus temozolomide or placebo plus temozolomide. Upon disease progression, patients in the placebo arm cross over to the DCVax-L arm. The primary endpoint is PFS, and the secondary endpoints are OS and time to disease progression.

Preliminary results from the GBM trial67 reported a median OS of 23.1 months from surgery in intention-to-treat patients (n = 331). However, about 90% of intention-to-treat patients have received DCVax-L because of the trial’s crossover design. At the time of analysis, of 223 patients whose surgery was at least 30 months prior, 67 (30%) lived 30 months or more. Among 182 patients whose surgery was at least 36 months prior, 44 (24.4%) lived 36 or more months. The median OS was 34.7 months for patients (n = 131) in whose tumors the promoter driving O⁶-methylguanine-DNA methyltransferase (MGMT) expression was methylated, which is associated with a better prognosis. The median OS was 40.5 months in a subpopulation (n = 100) of extended survivors with currently unknown prognostic factors. Grade 3 or 4 adverse events were reported in 7 (2.1%) patients.

The primary endpoint of PFS had not yet been evaluated and will be the subject of later analyses by an expert panel. Because PFS can be complex to determine and pseudo-progression
is a known confounding phenomenon in patients with GBM, researchers have called for investigators to perform a central and multifactorial assessment that uses criteria emerging as appropriate for immune therapy.

Manufacturers and Regulatory Status

Northwest Biotherapeutics, Inc (Bethesda, Maryland) is developing DCVax-L, which is being evaluated in a phase III trial.

Results and Discussion of Stakeholder Comments

Eight stakeholders, reflecting clinical, health technology, health systems, nursing, and research perspectives, provided comments and ratings on the topic of DCVax-L to treat newly diagnosed GBM.\(^{71-78}\) We have organized the following discussion of stakeholder comments by the parameters on which they commented.

Patient outcomes, quality of life, and overall health: A clinician emphasized the unmet need for this patient population: “In spite of advances in earlier diagnosis, the standard of care and adjuvant therapy for GBM have remained essentially the same since 2005. The continued absence of preventive measures, poor prognosis and relatively young age at presentation, for many in their mid-50s, with a mean OS for newly diagnosed GBM of 14 to 15 months and mean OS of 7 to 8 months for recurrent GBM makes this disease not only devastating for the individual and family, but socioeconomically significant.”\(^{72}\) Basing their opinions on preliminary results and the poor prognosis of patients with GBM, 6 commenters thought DCVax-L has the potential to improve patient health outcomes.\(^{71-73,75,77,78}\) But a commenter with a health systems perspective thought that available results suggest DCVax-L use has a small potential to improve health outcomes. Still, this commenter indicated that if the mature data demonstrate better effectiveness, DCVax-L use could have greater impact on health outcomes.\(^{74}\)

Health disparities: Commenters unanimously agreed that DCVax-L use has no potential to improve health disparities. Six commenters—2 clinicians, 2 health systems commenters, 1 nurse, and 1 researcher—anticipated that DCVax-L would be very expensive; even if insurance offers reimbursement, copayments could be high for anyone with insurance, and uninsured and underinsured patients with low socioeconomic status especially would have difficulty paying for DCVax-L.\(^{72-77}\) In terms of geographic access, a health systems commenter and a researcher suggested that DCVax-L use might initially be limited to large research or academic medical centers. Thus, many patients, especially those living in rural areas, might have difficulty accessing hospitals that offer DCVax-L treatment, thought a health systems commenter and a researcher.\(^{71,77}\)

Health care delivery system: Most commenters thought DCVax-L use has small to no potential to disrupt the health care delivery system, indicating that DCVax-L would not be burdensome because it is administered as an intradermal injection in combination with standard adjuvant therapy. But a clinician expected DCVax-L implementation to cause a moderate disruption in restructuring of multifunctional staff and clinical facilities in hospitals, which would be similar to changes experienced by hospitals employing immunotherapy protocols.\(^{72}\)

Current paradigm of patient care: DCVax-L is administered via intradermal injection and would be used in addition to standard therapy instead of as a replacement, and because of that, most commenters expected DCVax-L to have small to no potential to disrupt current patient care
paradigms. A clinician suggested that as a personalized medicine, DCVax-L might cause specific adverse effects that clinicians will need to monitor closely.

**Healthcare costs:** Although 4 commenters, with health systems and research perspectives, expected DCVax-L would add significant cost to standard care, 3 other commenters, with clinical and nursing perspectives, indicated that they could not directly comment on DCVax-L’s potential to disrupt healthcare costs. Two researchers specified that DCVax-L is likely to disrupt costs for the affected patients and payers, but because the overall population eligible for DCVax-L treatment is not large, it will likely have less impact on health care providers and facilities.

**Overall disruption potential:** Four commenters—a clinician, a health systems commenter, a nurse, and a researcher—thought that DCVax-L would be more likely to disrupt patient health outcomes (by potentially improving them) than any other aspect of health care delivery. A health systems commenter, a nurse, and a researcher noted that DCVax-L has the potential to improve survival of patients with this difficult-to-treat disease. Still, the nurse pointed out that if a patient lives longer with DCVax-L than with standard of care, but treatment causes serious adverse events (SAEs), DCVax-L use would not benefit the patient. A clinician indicated the therapy could improve outcomes, thereby being a positive disruption. Based on the way DCVax-L was developed, resection of a patient’s tumor is essential, and DCVax-L must be administered in combination with standard adjuvant therapy. Because DCVax-L is considered an immunotherapy, it purportedly elicits an adaptive immune response against GBM tumor cells. However, the biology of immune responses in the brain involving B cells, T cells, and circulating tumor cells is not well understood. With the available clinical data, 4 commenters, with clinical, health systems, and research perspectives, thought that additional results from the ongoing trial are needed to fully assess DCVax-L’s potential for disruption.

**Lifileucel (LN-144) as Second-line Treatment for Locally Advanced or Metastatic Melanoma**

**Highlights**

Patients with metastatic melanoma need more effective options after standard second-line therapies have failed. Lifileucel is a cell-based therapy that uses the patient’s own immune cells to enhance antitumor immune responses against melanoma. Most of the 7 stakeholders commenting on this topic thought lifileucel has the potential to improve patient health outcomes as a treatment option for progressive disease or after standard-of-care treatment. As a personalized cell-based therapy, lifileucel would be offered at relatively few health centers, creating disparities that would restrict access for some patients. Because lifileucel is also expected to be very expensive, patients will likely have difficulty paying for it, even if covered by insurance.

**Patient Population**

Lifileucel is intended for adults aged 18 years or older who have unresectable or metastatic melanoma that has progressed after one or more lines of systemic therapy, including an immune checkpoint inhibitor. Patients with disease containing a BRAF (B homolog of the rapidly accelerated fibrosarcoma) gene V600 variation are given a BRAF inhibitor alone or in

**Intervention**

Melanoma is a type of skin cancer that originates from melanocytes, responsible for making the pigment melanin. Among skin cancers, melanoma is less common, but it is most likely to spread to other parts of the body (for more information on melanoma, see the [American Cancer Society](https://www.cancer.org/cancer/melanoma-skin-cancer/index)).

Lifileucel (LN-144) is an autologous T-cell therapy that uses tumor-infiltrating lymphocytes (TILs), which are naturally occurring T cells that are embedded in and directed against the patient’s melanoma tumor. To produce lifileucel, a patient’s tumor sample is shipped to a centralized manufacturing facility where TILs are isolated from the sample and expanded (ie, multiplied) in vitro until a certain number (ie, $1 \times 10^9$ to $1 \times 10^{11}$ TILs) are generated. The company states that its manufacturing process takes 22 days from biopsy receipt at the manufacturing facility to shipping lifileucel back to the treating institution. The patient is then given a pretreatment chemotherapy (fludarabine and cyclophosphamide), which neither destroys bone marrow nor reduces lymphocytes, to reduce the immunosuppressive tumor environment before giving the TIL infusion.

The TILs are expected to be of sufficient number and physiologic state to effectively target, infiltrate, and induce tumor responses against the primary melanoma and any metastases. Physicians also prescribe up to 6 doses of interleukin 2 (IL-2) immediately after infusing lifileucel to support TIL growth, activation, and efficacy.

The manufacturer asserts that TILs are a new therapeutic paradigm for treating solid tumors because they might address some of the following key challenges encountered in treatment: (1) tumor cells that vary in makeup, with multiple gene variants driving the cancer; (2) critical gene variants that drive the cancer and are potential treatment targets but that are unclear to physicians; (3) tumors that resist treatments targeting a single variant; (4) tumor mechanisms that reduce immunosuppression (ie, the body’s immune response); and (5) immunosuppression that arises from standard-of-care treatment options.

The one-time cellular therapy is intended to enhance the effectiveness of the patient’s antitumor immune response via an activated, expanded, and polyclonal (ie, targeting multiple tumor antigens) TIL repertoire, while mitigating the long-term side effects associated with current treatments.

**Evidence Development Summary**

Lifileucel is being studied in the innovaTIL-01 (NCT02360579) clinical trial to treat locally advanced or metastatic melanoma that has progressed after one or more lines of systemic therapy, including an immune checkpoint inhibitor or a BRAF inhibitor alone or in combination with a MEK inhibitor. It is a phase II nonrandomized, parallel-assignment, open-label, multicohort trial to evaluate lifileucel’s safety and effectiveness in patients with melanoma. Cohort 1 is testing lifileucel without cryopreservation, cohorts 2 and 4 are testing cryopreserved lifileucel, and cohort 3 consists of eligible patients from cohorts 1, 2, and 4 who are being retreated with cryopreserved lifileucel. After lifileucel infusion, patients receive up to 6 doses of IL-2 to stimulate TILs. The primary endpoint is ORR and secondary endpoints are DOR, disease control rate (DCR), PFS, OS, and adverse events.
Cohort 1 included patients (n = 9) with tumors harboring wild-type or variant \(\textit{BRAF}\). Although 8 patients received all 6 doses of IL-2, all 9 had TILs present at 14 days after the infusion. At the time of assessment, lifileucel’s ORR was 33%; 1 patient achieved complete response, 2 had partial response, and 2 had progressive disease. No patients died or discontinued treatment because of lifileucel-associated SAEs. The most common nonhematologic grade 3 to 4 adverse event reported was hypophosphatemia.

Cohort 2 included patients (n = 55) with locally advanced or metastatic melanoma who had received a mean of 3.1 previous therapies that included anti-PD-1 (100%), anti-CTLA-4 (80%), and/or \(\text{BRAF}/\text{MEK}\) inhibitors (24%). Lifileucel’s DCR was 76% and ORR was 38%; 2 patients achieved complete response, 18 had partial response, and 1 had unconfirmed partial response. At median follow-up of 7.4 months, 4 of 21 responders had disease progression, but in some patients improved responses were observed with longer follow-up times. The reported adverse events resolved within 2 weeks of receiving a one-time TIL infusion.

Manufacturers and Regulatory Status

Iovance Biotherapeutics, Inc (San Carlos, California), in collaboration with the National Cancer Institute at the National Institutes of Health (Bethesda, Maryland), is studying lifileucel in a phase II clinical trial. The company reported receiving Fast Track designation and Regenerative Medicine Advanced Therapy designation from FDA for treating advanced melanoma. In an end-of-phase-II meeting, FDA recommended amending the ongoing innovaTIL-01 trial to add the registration-enabling cohort 4. After collecting and analyzing these data, Iovance plans to submit a Biologics License Application to FDA in the second half of 2020.

Results and Discussion of Stakeholder Comments

Seven stakeholders, reflecting clinical, health systems, nursing, patient advocate, and research perspectives, provided comments and ratings on lifileucel for treating locally advanced or metastatic melanoma in the second-line setting. We have organized the following discussion of stakeholder comments by the parameters on which they commented.

Patient outcomes, quality of life, and overall health: Most commenters believed that lifileucel showed potential to improve health outcomes. Two clinicians thought that, compared with second-line standard of care, lifileucel might become a treatment option after progression on first-line treatments. Four commenters—a clinician, a nurse, and 2 researchers—pointed out that available data on lifileucel are preliminary, and patient-oriented outcomes would help with its evaluation. Among these, one researcher emphasized that favorable response rates do not always correlate with patient survival, but this commenter expected the ongoing phase II trial to address evidence gaps.

Health disparities: Two clinicians and a researcher thought that lifileucel would be available only at large medical centers experienced in providing immunotherapies. Four commenters, with clinical, health systems, nursing, and research perspectives, anticipated lifileucel to be expensive and likely to create disparities for patients of low socioeconomic status, who will likely have limited access to the drug. Among these, a health systems commenter and a nurse both pointed out that even patients with insurance are likely to incur added costs in the form of high copayments and coinsurance.
Health care delivery system: A health systems commenter and 2 researchers thought that in order to administer lifileucel, several steps are required, including tumor resection and sample shipping, TIL isolation and proliferation, pretreatment chemotherapy, lifileucel infusion, and IL-2 treatment, all of which are more disruptive than receiving an IV medication at an infusion center. Two clinicians and a nurse anticipated lifileucel’s potential to disrupt health care delivery to be low because most health centers have the infrastructure to offer the therapy.

Current paradigm of patient care: Most commenters anticipated that lifileucel would disrupt the paradigm of patient care. Only one commenter with a health systems perspective thought that lifileucel would be administered in a similar way as standard-of-care comparators. Besides performing a successful tumor biopsy and preparing TILs, facilities must monitor patients for adverse events associated with immune responses, noted a clinician, a nurse, a patient advocate, and a researcher. Another clinician expected lifileucel to become a new treatment option for patients who have few effective second-line treatment options.

Health care costs: All commenters expected lifileucel to be very expensive, which is likely to be a significant cost burden to patients and payers. In addition to increasing out-of-pocket expenses and insurance copayments, lifileucel use will also increase costs associated with hospitalization and patient monitoring, one clinician pointed out. One nurse also indicated that patients of low socioeconomic status would be further burdened with costs after struggling to pay for expensive treatments in the first-line setting.

Overall disruption potential: Four commenters—a clinician, a nurse, a patient advocate, and a researcher—indicated that lifileucel use has the potential to positively disrupt the current standard of care by improving health outcomes in heavily treated patients whose disease has failed to respond to previous lines of therapy and who lack effective treatment options. Excluding the clinician, these commenters added that lifileucel use has the potential to be negatively disruptive because of its high cost and treatment-related adverse events. A researcher indicated lifileucel has the potential to benefit patients with limited treatment options, but evidence supporting this claim is currently lacking. A clinician thought that lifileucel use will likely benefit a very specific patient population, but because of its limited reach, it has low disruptive potential.

MDNA55 to Treat First Recurrence of Recurrent Glioblastoma Multiforme

Highlights

Patients with recurrent GBM have poor outcomes and short survival, and lack effective treatment options for recurrent disease. MDNA55 is a genetically engineered therapy composed of a protein that binds the IL-4 receptor (IL4R) and a bacteria-derived endotoxin to kill cancer cells and immunosuppressive cells overexpressing IL4R. Most of the 8 stakeholders commenting on this topic agreed that MDNA55 offers a novel approach to treat GBM, with potential to improve patient health outcomes. Some commenters also thought MDNA55 has the potential to disrupt delivery and paradigms of care because health centers offering MDNA55 would require changes in infrastructure, personnel, and care setting. While there is a need for effective treatments for GBM, MDNA55’s high cost might create disparities that will limit its access to
some patients. Some commenters thought that although available data seem promising, additional data from larger studies are needed to assess MDNA55’s potential for disruption.

**Patient Population**

MDNA55 is intended for adults aged 18 years or older with recurrent or progressive GBM.

**Intervention**

GBM is a malignant brain cancer associated with poor outcomes and high mortality. GBM begins as a stage IV disease with no evidence of a lower grade precursor (the American Brain Tumor Association offers [more information about GBM](#)). Patients who have undergone primary treatment composed of surgery, radiation, and temozolomide chemotherapy typically experience disease recurrence in about 7 months. Even with treatment, patients with recurrent GBM have a median OS of 15 months and a 2-year survival rate of 27%, emphasizing the need for new therapies capable of treating recurrent disease and extending survival.

MDNA55 is a novel, genetically engineered fusion protein composed of a circularly permuted IL-4 (cpIL-4) molecule fused to exotoxin A (ETA), a *Pseudomonas*-derived protein-synthesis inhibitor. MDNA55 is designed to specifically target IL4R, a cell surface receptor overexpressed in various types of cancer stem cells and immunosuppressive cells composing the tumor microenvironment. MDNA55 functions like a “molecular Trojan horse” because cpIL-4 binding to IL4R triggers receptor-mediated endocytosis to deliver the cytotoxic ETA payload into the target cell cytoplasm. Via IL4R targeting, MDNA55 purportedly kills GBM stem cells and immunosuppressive cells in the tumor microenvironment with high specificity.

A neuro-oncologist prescribes MDNA55, which is administered in a hospital by a neurosurgeon during a minimally invasive surgical procedure using a technique (ie, convection-enhanced delivery) that allows delivery of the drug through a thin tube (ie, cannula) inserted directly into the tumor under stereotactic guidance. The starting dose is 63 μg. Depending on response to the initial dose, patients may be eligible for a second MDNA55 infusion.

**Evidence Development Summary**

MDNA55 is being studied in the phase II nonrandomized, single-group MDNA55-05 ([NCT02858895](#)) clinical trial for treating recurrent or progressive GBM. Enrollment will be 42 patients. The primary endpoint is OS, and the secondary endpoints are PFS, ORR, and adverse events.

In patients treated with low doses of MDNA55 (median 63 μg; n = 21), median OS was 11.8 months. When patients were stratified by IL4R status, median OS was 7 months longer in patients (n = 8) with IL4R\text{High} than in patients (n = 10) with IL4R\text{Low} (15.2 months vs 8.1 months).94 Treatment with MDNA55 also improved the 12-month survival rate in patients with IL4R\text{High} compared to patients with IL4R\text{Low} (55% vs 30%).95

In the total population (n = 42) treated with MDNA55, irrespective of IL4R status, DCR of patients showing tumor shrinkage or stabilization was 83% (n = 35). Treatment also caused no systemic toxicity and no treatment-related deaths.94

**Manufacturers and Regulatory Status**

[Medicenna Therapeutics Corp (Toronto, Ontario, Canada)](#) is developing MDNA55 in an ongoing phase II trial. FDA has granted MDNA55 Orphan Drug and Fast Track designations for treating patients with recurrent GBM.93,96
Results and Discussion of Stakeholder Comments

Eight stakeholders, reflecting clinical, health systems, nursing, and research perspectives, provided comments and ratings on MDNA55 to treat recurrent GBM.97-104 We have organized the following discussion of stakeholder comments by the parameters on which they commented.

**Patient outcomes, quality of life, and overall health:** Most commenters agreed that MDNA55 use represents a new treatment approach with potential to improve health outcomes for patients with recurrent GBM, a disease with a high mortality rate and short life expectancy. A researcher also noted that MDNA55 use might also improve QoL by causing fewer adverse events than standard therapies.103 However, 4 commenters—a nurse, a health systems commenter, and 2 researchers—argued that evidence is promising but insufficient to fully support MDNA55’s potential to improve overall health.100,101,103,104 Additional data, preferably from larger studies, are needed to confirm MDNA55’s potential to improve health outcomes.

**Health disparities:** Three commenters—a systems commenter, a nurse, and a researcher—pointed out that MDNA55 use has the potential to create health disparities, because delivery requires trained personnel and equipment.99,101,103 A clinician noted that MDNA55’s delivery via convection-enhanced delivery would be more disruptive than drugs taken orally.97 A commenter with a health systems perspective expected MDNA55 to be prohibitively expensive, thereby creating health disparities.100

**Health care delivery system:** Two clinicians and one health systems commenter anticipated that because of a lack of effective treatments for GBM, MDNA55 might replace current treatments.97-99 Five commenters—2 clinicians, 1 nurse, and 2 researchers—thought that MDNA55’s delivery setting and trained personnel requirement might disrupt health care delivery.97,98,101,103,104 However, one of these researchers thought that GBM’s low prevalence might decrease MDNA55’s potential to disrupt health care delivery.104 Another researcher did not expect MDNA55 use to be disruptive because it would be given to patients in existing clinical facilities.102

**Current paradigm of patient care:** Four commenters—2 clinicians, a health systems commenter, and a researcher—expected that MDNA55 use will disrupt the current care paradigm because its administration requires special changes in infrastructure, care setting, and personnel.97-99,103 A nurse thought that MDNA55’s potential to disrupt paradigms of care relies on its ability to improve health outcomes.101 This nurse further indicated that successfully treated patients might not need follow-up chemotherapy or radiation therapy and are less likely to be readmitted to the hospital for treatment-related complications.

**Health care costs:** Two clinicians and 2 health systems commenters thought that, similar to many new specialty drugs and biologics, MDNA55 could be very expensive.97-100 Three commenters—2 clinicians and 1 nurse—anticipated that the added costs in the procedures and personnel required to administer MDNA55 are also likely to disrupt health care costs.97,98,101 However, 2 researchers indicated MDNA55 use is unlikely to disrupt health care costs.102,104 One of these researchers foresaw MDNA55 having poor adoption104, the other did not expect it to cost any more than other GBM interventions.102

**Overall disruption potential:** Most commenters agreed that if MDNA55 proves to be effective, it will have high overall potential to disrupt how GBM is treated. A commenter with a health systems perspective expected a high demand for MDNA55 but thought that lack of
insurance or discount programs would restrict its access for some patients.\textsuperscript{99} Two researchers pointed out that patients with GBM are desperate for new therapies because the current standard of care offers limited benefits.\textsuperscript{102,103} However, 3 commenters—2 clinicians and a researcher—were concerned that MDNA55, like other FDA-approved drugs for GBM, would offer patients only an incremental health benefit.\textsuperscript{97,98,104}

Oportuzumab Monatox (Vicinium) for Treatment-resistant, Recurrent, or High-risk Non–Muscle Invasive Bladder Cancer

\textbf{Highlights}

Non–muscle invasive bladder cancer (NMIBC) is usually treatable in early stages, but some disease is resistant to standard care, is high risk for metastasis, or recurs after initial treatment. Treatment options are limited and surgery (ie, cystectomy) has a high risk of complications. New, effective, nonsurgical options are desired. Oportuzumab monatox (Vicinium) is a protein fusion drug, intended to treat NMIBC that has not responded to bacillus Calmette-Guérin (BCG) treatment or has recurred after at least 2 courses of BCG. The 5 stakeholders commenting on this topic generally agreed that oportuzumab monatox use, if effective, might be highly disruptive in this patient population, especially for patients who are not candidates for surgery. Most commenters thought that there would not be a major disruption to health systems because of this treatment’s administration in an outpatient setting. However, commenters thought that oportuzumab monatox use might create disparities due to its anticipated high cost and added burden of cystectomy for patients who do not respond to this treatment.

\textbf{Patient Population}

Oportuzumab monatox is intended for adults aged 18 years or older who have NMIBC that has not spread to any nearby tissues or has a high risk of spreading and those whose disease has not responded to treatment with BCG or has recurred after at least 2 courses of BCG.

\textbf{Intervention}

NMIBC is one of the most common forms of cancer. It occurs when cells in the bladder’s inner layers become malignant.\textsuperscript{105} The \textit{Urology Care Foundation website} offers more information on NMIBC. Oportuzumab monatox is a new gene combination protein consisting of a humanized monoclonal infection-fighting fragment specific for the epithelial cell adhesion molecule (EpCAM) connected via a peptide to a shortened form of \textit{Pseudomonas aeruginosa} ETA.\textsuperscript{106} EpCAM is purportedly highly expressed by more than 98% of high-grade NMIBCs, making it an attractive target for therapy.\textsuperscript{45,106}

The manufacturer designed the drug to selectively bind NMIBC cells through its EpCAM antibody fragment region and deliver the anticancer exotoxin directly into tumor cells. The cytotoxic part of the drug, ETA, purportedly inhibits tumor protein synthesis by deactivating the translation factor elongation factor-2, which purportedly kills both rapid-growing and slow-growing cancer cells.\textsuperscript{106}

In an ongoing phase III trial, a clinician delivers the drug in an outpatient setting directly into the bladder using a sterile urethral catheter. The dose is 30 mg in 50 mL buffered saline. Patients receive the drug twice a week for 12 weeks (induction therapy), then once every 2 weeks for up to 2 years (maintenance therapy).\textsuperscript{106}
Evidence Development Summary

Investigators have reported results from 2 clinical trials: a phase II trial (NCT00462488) and the phase III VISTA trial (NCT02449239). The phase II open-label trial enrolled adults (n = 46) aged 18 years or older with NMIBC (recurrent or unresponsive to BCG treatment). The patients were assigned to cohort 1 for a 6-week induction regimen or cohort 2 for a 12-week induction regimen. Investigators reported that a complete response to oportuzumab monatox was seen in 9 of 22 patients (41%) in cohort 1 and 9 of 23 (39%) in cohort 2 at 3-month follow-up. Twenty patients (44%) achieved a complete response. The investigators added that 2 other patients without carcinoma in situ (CIS) who achieved a complete response were excluded from the trial due to the development of noninvasive papillary (Ta) disease. The median time to recurrence in patients who achieved a complete response was 274 and 408 days in cohorts 1 and 2, respectively. Overall, 7 patients (16%) remained disease free at 12 to 13 weeks. An assessment after the trial demonstrated that these patients remained disease free at their last follow-up (18-25 months). Investigators also reported mild to moderate reversible bladder symptoms as the most commonly occurring adverse event.

The phase III VISTA RCT enrolled adults (n = 134) aged 18 years or older who have NMIBC that has recurred or has not responded to BCG treatment. Enrolled patients were assigned to 1 of 3 cohorts: Cohort 1 had patients with CIS with or without papillary disease that did not respond to BCG treatment or recurred within 6 months of their last course of adequate BCG; cohort 2 had patients with CIS with or without papillary disease that did not respond to BCG treatment or recurred 6 to 11 months after their last course of adequate BCG; cohort 3 had patients who had high-risk papillary disease without CIS that did not respond to BCG treatment or recurred within 6 months of their last course of adequate BCG.

Results from pooled cohorts 1 and 2 (n = 93) showed complete response rates as follows:

- At 3 months, 39% (95% CI, 29%-49%)
- At 6 months, 28% (95% CI, 19%-38%)
- At 9 months, 21% (n = 92; 95% CI, 13%-30%)
- At 12 months, 15% (n = 91; 95% CI, 9%-24%)

Using the Kaplan-Meier method, the DOR for cohort 1 (n = 86) was reported as 287 days (95% CI, 127-NA). The secondary endpoint analysis showed the time to disease recurrence for patients in cohort 3 (n = 40) as 402 days (95% CI, 170-NA), and the time to cystectomy across all 133 patients treated with oportuzumab monatox to be approximately 2.5 years for more than 75% of patients. Based on reported data from March 1, 2019, about 30% of all 133 patients treated with oportuzumab monatox were estimated to remain event free, using the Kaplan-Meier method. Of all 133 patients treated with oportuzumab monatox, 91% had an OS of >2.5 years.

In this trial, investigators reported that 78% of the common adverse events in patients across all cohorts (n = 133) were grade 1 or 2 and included painful urination (13%), blood in the urine (12%), and urinary tract infection (11%). Furthermore, 5 patients (4%) discontinued treatment due to an adverse event, while SAEs were reported in 14% of patients. Investigators reported 4 treatment-related SAEs: acute kidney injury (grade 3), fever (grade 2), cholestatic hepatitis (grade 4), and kidney failure (grade 5).
Investigators also reported recurrence-free rates in cohort 3 (n = 40) as follows\textsuperscript{108}:

- At 3 months, 68% (95% CI, 51%-81%)
- At 6 months, 56% (n = 39; 95% CI, 40%-72%)
- At 9 months, 42% (n = 38; 95% CI, 26%-59%)
- At 12 months, 35% (n = 36; 95% CI, 21%-54%)

**Manufacturers and Regulatory Status**

Sesen Bio (Cambridge, Massachusetts) is assessing the therapy in a phase III trial.\textsuperscript{45} FDA is considering this drug under an accelerated approval pathway with rolling review of accumulating data. The manufacturer announced plans to initiate a Biologics License Application in the fourth quarter of 2019.\textsuperscript{110} In August 2018, FDA also granted Fast Track designation.\textsuperscript{111}

**Results and Discussion of Stakeholder Comments**

Five stakeholders, reflecting clinical, nursing, research, and health systems perspectives, provided comments and ratings on this treatment.\textsuperscript{112-116} We have organized the following discussion of stakeholder comments by the parameters on which they commented.

**Patient outcomes, quality of life, and overall health:** Commenters agreed that the preliminary data from the phase III VISTA trial showed that oportuzumab monatox use has the potential to improve health outcomes and QoL for patients with NMIBC whose disease has recurred or did not respond to BCG treatment. A clinician highlighted the need for more adoptable treatments in this population, since the alternative is surgery (ie, cystectomy) that is risky, with a death rate of 2% and a complication rate of 50% to 60%.\textsuperscript{113} Other commenters, with nursing, research, and health systems perspectives, also thought that this intervention might obviate the need for radical surgery, which would likely positively disrupt patient health outcomes and QoL in this population.\textsuperscript{112,114-116}

**Health disparities:** Most commenters agreed that health disparities associated with this therapy would depend on health insurance coverage and that this intervention would most likely not widen existing disparities. A health systems commenter added that Medicare beneficiaries might face lower out-of-pocket costs than younger patients due to caps on those costs. Out-of-pocket costs to patients with private insurance would depend on the level of coverage, but copayments for this new therapy could be substantial.\textsuperscript{114}

**Health care delivery system:** A clinician, a researcher, and a health systems commenter thought that this intervention would not disrupt the health care delivery system due to its administration in an outpatient setting.\textsuperscript{113,114,116} Conversely, another health systems commenter was concerned that although educated patients might demand this treatment, health systems might not adopt it because of additional training in outpatient settings that would increase burden on the system.\textsuperscript{112}

**Current paradigm of patient care:** Most commenters thought oportuzumab monatox use has small potential to disrupt treatment paradigms based on ease of acquisition and a minimal learning curve for clinicians compared with invasive approaches. However, a clinician and a health systems commenter agreed that being able to delay cystectomy even for 2 to 3 years could disrupt current treatment paradigms for patients.\textsuperscript{112,113}
Health care costs: Most commenters agreed that oportuzumab monatox use would disrupt costs because of increased out-of-pocket costs for patients from insurance coverage limits. One clinician stated that this treatment could have a large cost disruption since patients who do not respond well to this treatment will then require cystectomy, which could increase overall costs of care for this disease.113

Overall disruption potential: Most commenters thought that oportuzumab monatox use has moderate overall potential to disrupt the paradigm of care, patient-oriented health outcomes, and quality of life by avoiding or delaying the need for cystectomy. A clinician added that this intervention would benefit many affected patients who are older and are poor candidates for radical surgery like cystectomy.113 Conversely, a researcher noted that the potential for overall disruption would depend on the cost of treatment, as well as the results from comparative studies that would validate the initial data reported.116

Pembrolizumab (Keytruda) as First-line Treatment for Locally Advanced or Metastatic, Recurrent Head and Neck Squamous Cell Carcinoma

Highlights

Effective treatments are lacking for recurrent or metastatic head and neck cancers, which are associated with poor outcomes. Pembrolizumab is an immune checkpoint inhibitor that prevents tumor cells from downregulating cancer-specific immune responses. It is intended as a first-line therapy for treating locally advanced or metastatic, recurrent head and neck squamous cell carcinoma (HNSCC). Most of the 8 stakeholders commenting on this topic agreed that pembrolizumab’s potential for disruption is based on it being a much-needed and important advancement for treating HNSCC and improving patient health outcomes. However, additional data on short- and long-term adverse events are needed to further assess whether pembrolizumab’s benefits as a monotherapy or in combination with chemotherapy outweigh its risks. Most commenters also agreed pembrolizumab’s high cost has the potential to disrupt health care costs. Some commenters pondered whether payers would reimburse an expensive intervention such as pembrolizumab. If they do not, only patients of high socioeconomic status would be able to pay for treatment. Pembrolizumab’s high cost could also lead to increased disparities in access to care.

Patient Population

Pembrolizumab is intended for adults aged 18 years or older with previously untreated, unresectable, or metastatic, recurrent HNSCC located in the oral cavity, larynx, hypopharynx, or oropharynx. Patients with recurrent HNSCC who completed postoperative systemic therapy more than 6 months earlier, given as part of multimodal treatment for locally advanced disease, are also eligible. The therapy may be used as a single agent or in combination with chemotherapy. As a monotherapy for HNSCC, it requires the patient’s tumor to exhibit expression of PD-L1, which requires genetic testing.
Intervention

Head and neck cancers encompass tumors that develop in the oral cavity, nasal cavity, paranasal sinuses, larynx, oropharynx, hypopharynx, nasopharynx, and salivary glands. Most head and neck cancers originate from the flat squamous cells on the surface of the structures in the head and neck (for more information about HNSCC, see the American Society of Clinical Oncology).

Cancer cells have developed immune-tolerance mechanisms to avoid detection and destruction. These mechanisms involve the overexpression of ligands that limit the immune responses of T cells. These so-called immune checkpoints are thought to have evolved to prevent runaway immune responses; however, by aberrantly activating these immune checkpoints, cancers reportedly can reduce the body’s anticancer immune response.

One of these checkpoint pathways is PD-1, a cell receptor expressed by many immune system cells, including high expression on activated T cells, which has a central role in T-cell downregulation. In many types of cancer, PD-L1, the ligand for PD-1, is highly expressed by cells in the tumor. Binding of PD-L1 to PD-1 causes the inactivation of cancer-specific T cells, which allows the tumor to evade immune responses.40

HNSCC tumors can reduce anticancer immune responses because they express high levels of PD-L1, thus preventing T cells from targeting tumor cells.117 A potential therapeutic target that prevents the interaction between PD-L1 in tumor cells and PD-1 in T cells could potentially induce an immune response against HNSCC by preventing T-cell downregulation.40,117

Pembrolizumab is a humanized monoclonal IgG4 antibody that binds the PD-1 coinhibitory receptor expressed in activated T cells. Animal cancer models have shown that antibody-mediated inhibition of the PD-1/PD-L1 pathway increases T-cell antitumor response. Pembrolizumab binding to PD-1 purportedly prevents interaction between PD-1 and its ligands, inhibiting the immune checkpoint pathway and leading to an increase in anticancer immune response to HNSCC tumors.40,117 Because antibody binding to PD-1—expressing immune cells has the potential to deplete these immune cells, pembrolizumab’s Fc region has also been modified to reduce the induction of antibody-dependent cellular cytotoxicity and complement mediated cytotoxicity.40

For several indications, pembrolizumab has been jointly approved with the PD-L1 IHC 22C3 pharmDx companion diagnostic test. Most of the KEYNOTE trials of pembrolizumab, including KEYNOTE-048, have used PD-L1 IHC 22C3 pharmDx to determine the PD-L1 status (combined positive score [CPS] ≥ 1) of tumors. The companion diagnostic test is billed separately from pembrolizumab.118

An oncologist prescribes pembrolizumab and refers the patient to an infusion center. An infusion nurse will administer 200 mg of IV pembrolizumab on day 1 of each 21-day cycle for up to 24 months.119 Pembrolizumab may be administered in combination with IV cisplatin (100 mg/m² on day 1) or carboplatin (area under the curve [AUC] 5 on day 1) plus 5-fluorouracil (1000 mg/m² from day 1 to 4) for up to 6 cycles.

Evidence Development Summary

Pembrolizumab is being studied in the KEYNOTE-048 (NCT02358031) clinical trial for treating locally advanced or metastatic, recurrent HNSCC in the first-line setting. KEYNOTE-048 is a phase III unblinded RCT. Patients (n = 882) are randomly assigned in a 1:1:1 ratio to pembrolizumab, pembrolizumab in combination with a platinum agent plus 5-fluorouracil (P+C),
or the EXTREME regimen (5-fluorouracil plus cetuximab and cisplatin or carboplatin). The primary endpoints are OS and PFS and the secondary endpoints are ORR and health-related QoL.

Although the KEYNOTE trial is still ongoing, published results are available. Patients were stratified by PD-L1 (CPS ≥ 20, CPS ≥ 1, and CPS < 1), derived from the PD-L1 IHC 22C3 pharmDx test to evaluate PD-L1 expression in both tumor cells and tumor-associated immune cells. The second interim analysis demonstrated that in the pembrolizumab vs EXTREME groups, pembrolizumab was superior in patients (n = 255) with CPS ≥ 20 (median OS 14.9 vs 10.7 months; HR = 0.61; 95% CI, 0.45-0.83; \( P < .0007 \)). Patients (n = 512) with CPS ≥ 1 had median OS of 12.3 vs 10.3 months (HR = 0.78; 95% CI, 0.64-0.96; \( P = .009 \)).

In this trial, pembrolizumab did not prolong PFS in patients with CPS ≥ 20 (\( P = .45 \)), and PFS was not analyzed in patients with CPS ≥ 1. Although pembrolizumab did not demonstrate better ORR than the EXTREME regimen in the CPS ≥ 20 (23% vs 36%) and CPS ≥ 1 (19% vs 35%) groups, it improved DOR for patients with CPS ≥ 20 (23.4 vs 4.5 months) and with CPS ≥ 1 (22.6 vs 4.5 months).

In a subsequent survival analysis, P+C was also superior to the EXTREME regimen in patients (n = 236) with CPS ≥ 20 (median OS 14.7 vs 11.0 months; HR = 0.60; 95% CI, 0.45-0.82; \( P < .0004 \)) and in patients (n = 477) with CPS ≥ 1 (median OS 13.6 vs 10.4 months; HR = 0.65; 95% CI, 0.53-0.80; \( P < .0001 \)). In patients in the P+C group with CPS ≥ 20 and CPS ≥ 1, PFS did not achieve statistical significance compared with the EXTREME regimen group.

Treatment with P+C also did not improve ORR or DOR.

In the total population (n = 601), OS for pembrolizumab and P+C was noninferior to the EXTREME regimen. Although patients treated with pembrolizumab experienced fewer grade 3 or higher adverse events than those treated with the EXTREME regimen (54.7% vs 83.3%), P+C increased the rate of grade 3 or higher adverse events (85.1% vs 83.3%).

**Manufacturers and Regulatory Status**

Merck & Co, Inc (Kenilworth, New Jersey) manufactures pembrolizumab. On June 11, 2019, FDA approved pembrolizumab, based on results from the KEYNOTE-048 trial, for the following indications:

- As first-line monotherapy for patients with unresectable or metastatic, recurrent HNSCC whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test (ie, the companion diagnostic test PD-L1 IHC 22C3 pharmDx [Agilent Technologies, Inc])
- In combination with 5-fluorouracil plus a platinum agent as first-line therapy for patients with unresectable or metastatic, recurrent HNSCC, regardless of PD-L1 expression

FDA had previously granted accelerated approval to pembrolizumab to treat recurrent or metastatic HNSCC that has progressed on or after platinum-based chemotherapy (ie, second-line setting). According to Merck, results from the KEYNOTE-048 trial also served as confirmatory results to support pembrolizumab’s full approval in the second-line setting. FDA has also approved pembrolizumab to treat more than a dozen other cancer types. For FDA-approved indications, see FDA prescribing information.

**Cost Information**

According to a US-based online aggregator of prescription drug prices, GoodRx, pembrolizumab’s retail price as of October 2019 was about $9000 for 4 vials of 50 mg, which is the amount (200 mg) a patient would use for each 3-week cycle. Thus, if a patient continued on treatment for a full year, the cost would be about $153,000 (17 cycles at $9000 per cycle).
Results and Discussion of Stakeholder Comments

Eight stakeholders, reflecting clinical, health systems, nursing, patient, and research perspectives, provided comments and ratings on pembrolizumab to treat locally advanced or metastatic, recurrent HNSCC.123-130 We have organized the following discussion of stakeholder comments by the parameters on which they commented.

**Patient outcomes, quality of life, and overall health:** Most commenters indicated that pembrolizumab used as a monotherapy or in combination with chemotherapy seems to be an advancement in HNSCC treatment because clinical data show its potential to improve patient health outcomes. However, a clinician and a health systems commenter thought that the 3-month improvement in OS was not meaningful.123,125 A nurse and a researcher pointed out that before pembrolizumab became available, little advancement had been made for treating HNSCC, and it is positive for patients to have new treatment options.126,128 A patient was concerned about the lack of information on short- and long-term adverse events.127

**Health disparities:** Five commenters, with clinical, health systems, nursing, patient, and research perspectives, indicated that pembrolizumab’s high cost would likely create disparities for patients who cannot afford treatment.123,125-127,130 Among these, a clinician, a nurse, and a patient pointed out that, even with insurance, pembrolizumab might be prohibitively expensive for patients. A researcher thought that pembrolizumab would initially be available in large research hospitals, but it might take time to become accessible in smaller rural hospitals.130

**Health care delivery system:** Most commenters agreed that used as an IV drug, pembrolizumab is unlikely to disrupt the health care delivery system and would use the existing infrastructure of hospitals and infusion centers. A nurse pointed out that pembrolizumab’s availability might be limited at rural locations and patients in those locations could need to find time and transportation to receive treatment.126 A researcher also indicated that pembrolizumab’s use might increase in the first-line setting and disrupt treatment offerings in the second-line setting.128

**Current paradigm of patient care:** Most commenters agreed that, because pembrolizumab would be administered intravenously at infusion centers, it is unlikely to disrupt the current paradigm of patient care. Two clinicians indicated that patients might shift to receiving pembrolizumab alone or in combination with chemotherapy in the first-line setting instead of standard chemotherapy.124,125

**Health care costs:** Most commenters agreed that with a cost of about $150,000 per year, pembrolizumab has the potential to disrupt health care costs. A researcher thought that, even with its high price, pembrolizumab’s potential to disrupt health care costs would be low, pointing out that not all patients with HNSCC would receive pembrolizumab in the first-line setting.130 Three commenters—a clinician, a health systems commenter, and a patient—pondered whether payers would reimburse an expensive intervention such as pembrolizumab, indicating that if they did not, only patients with very high socioeconomic status would have access to treatment.123,125,127 If pembrolizumab successfully diffuses, health centers might need to find additional space for infusions and train new staff to offer the drug, which a nurse noted would also increase health care costs.126
Overall disruption potential: Most commenters concluded that much of pembrolizumab’s potential for disruption is based on it being a sorely needed and important advancement for treating HNSCC and improving patient health outcomes. However, a researcher thought that additional data are needed to determine whether pembrolizumab used as a monotherapy or in combination with chemotherapy provides game-changing benefits. A patient indicated that additional data on pembrolizumab’s short- and long-term adverse events are needed to assess whether adverse events outweigh the benefits. Noting its cost, this commenter also thought that pembrolizumab might not be a viable treatment option for patients who cannot afford it.

Pexidartinib (Turalio) to Treat Tenosynovial Giant Cell Tumors

Highlights

Pexidartinib (Turalio) is a multikinase inhibitor to treat tenosynovial giant cell tumors (TGCTs). TGCTs are benign soft-tissue sarcomas that arise from joint tissue. They can significantly deteriorate QoL, and no FDA-approved systemic therapy has been available. The 6 stakeholders commenting on this topic generally agreed that pexidartinib represents the first systemic therapy approved by FDA for treating the rare disease TGCT and, therefore, is likely to cause a paradigm shift in managing these patients. It would do so by providing an option for patients ineligible for surgical resection or as an alternative to surgical resection. However, most commenters voiced concerns regarding toxicity associated with pexidartinib (particularly liver toxicity), with some reviewers suggesting that the risk-to-benefit ratio could limit uptake of pexidartinib.

Patient Population

Pexidartinib is intended for adults aged 18 years or older with a TGCT (also known as a giant cell tumor of the tendon sheath) that is unamenable to surgical resection because surgery would likely cause significant disease burden or functional limitation.

Intervention

Pexidartinib is a multikinase inhibitor under study for treating TGCTs. A type of benign soft-tissue sarcomas, TGCTs arise from joint tissue, particularly the synovium, bursae, and tendon sheath. TGCTs typically remain localized to a single affected joint and are rarely fatal; however, they can be locally aggressive and substantially reduce QoL because of resulting joint pain, inflammation, and dysfunction.

TGCTs are often amenable to treatment by surgical resection, However, patients (in particular, patients with the diffuse type of TGCT, also known as pigmented villonodular synovitis) often experience multiple recurrences, which can lead to substantial disease burden. Up until pexidartinib’s recent FDA approval, patients with TGCT who were ineligible for surgical resection had very few treatment options. For more information on TGCT, see the National Organization for Rare Disorders.

TGCTs are characterized by the overexpression of a cytokine, colony stimulating factor-1 (CSF-1). In many cases, CSF-1 overexpression is caused by a genetic base-pair translocation involving the CSF-1 gene, which causes constitutive expression of the gene by neoplastic TGCT cells. Overexpression of CSF-1 causes recruitment of cells that express colony-stimulating...
factor-1 receptor (CSF-1R), such as macrophages, which compose most of the tenosynovial giant cell tumor’s mass.\textsuperscript{132}

Pexidartinib is a small-molecule inhibitor of multiple receptor tyrosine kinases, including CSF-1R, FLT3, and KIT.\textsuperscript{133} Inhibition of CSF-1R signaling by pexidartinib has the potential to disrupt the paracrine signaling loop that underlies the pathogenesis of TGCTs.\textsuperscript{132}

In clinical trials, pexidartinib was administered as 200-mg oral capsules. Patients take the capsules themselves at a dosage of 1000 mg/day for 2 weeks followed by 800 mg/day for an additional 22 weeks. In the FDA approval, the recommended dose is 400 mg (2 capsules) orally twice daily on an empty stomach.\textsuperscript{134}

**Evidence Development Summary**

Results from the phase III randomized controlled ENLIVEN trial (NCT02371369) were published in 2019.\textsuperscript{135} In this trial, 120 adults aged 18 years or older with symptomatic TGCTs for whom surgery would be associated with reduced joint function or substantial morbidity were randomly assigned to treatment with either pexidartinib (61 patients at 1000 mg/day for 2 weeks followed by 800 mg/day for 22 weeks) or to placebo (59 patients). Patients who completed the randomized controlled portion of the trial were eligible to continue into an open-label extension portion of the trial in which all patients received pexidartinib.

The trial’s primary efficacy endpoint was overall response rate by Response Evaluation Criteria in Solid Tumors (RECIST) in the randomized controlled portion of the trial; 39% of patients receiving pexidartinib achieved a response compared with 0% of patients receiving placebo ($P < .0001$).\textsuperscript{135} Patients in the pexidartinib arm of the trial also experienced increased improvements in measures of joint function such as range of motion (+15.1% pexidartinib vs +6.2% placebo; $P = .004$), PROMIS (Patient-reported Outcomes Measurement Information System) physical function scale (+4.06 vs –0.89; $P = .002$), worst stiffness (–2.45 vs –0.28; $P < .001$), and pain response (31.1% vs 15.3%; 1-sided $P = .03$).\textsuperscript{136}

Hepatic toxicities were observed in patients receiving pexidartinib, and trial enrollment was halted by the trial’s data monitoring committee 6 patients short of the target enrollment after nonfatal, serious hepatic toxicity was reported in 2 patients. In all, 8 patients discontinued pexidartinib treatment because of hepatic toxicity. Other adverse events reported in at least 15% of patients who received pexidartinib included hair-color changes, vomiting, fatigue, dysgeusia (altered taste), and swelling around the eyes (ie, periorbital edema).\textsuperscript{135}

**Manufacturers and Regulatory Status**

Pexidartinib was developed by Daiichi Sankyo (Tokyo, Japan). On August 2, 2019, FDA approved pexidartinib to treat “adult patients with symptomatic tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery.”\textsuperscript{134}

The FDA approval carries a black box warning regarding the potential for serious and fatal liver injury; because of this risk, pexidartinib is available only through a Risk Evaluation and Mitigation Strategy (REMS) program. The REMS requires that prescribing physicians enroll in the REMS and receive training, that patients prescribed pexidartinib enroll in a registry, and that pharmacies be certified by the program.\textsuperscript{137}

FDA had previously granted pexidartinib Breakthrough Therapy designation to treat TGCT.\textsuperscript{138}
Cost Information

According to a US-based online aggregator of prescription drug prices, GoodRx.com, pexidartinib’s retail price, as of November 2019, was about $20,000 for one-hundred twenty 200-mg tablets, which represents a 30-day supply of the drug.\textsuperscript{139} Thus, a 1-year supply of pexidartinib would cost about $240,000. According to the manufacturer website, patient assistance programs are available in the form of copayment assistance, financial assistance for patients without insurance coverage for pexidartinib, and a free trial period for patients with a delay in obtaining a pexidartinib prescription.\textsuperscript{140}

Results and Discussion of Stakeholder Comments

Six stakeholders, reflecting clinical, nursing, research, and health systems perspectives, provided comments and ratings on this TGCT treatment.\textsuperscript{141-146} We have organized the following discussion of stakeholder comments by the parameters on which they commented.

\textbf{Patient outcomes, quality of life, and overall health}: Most commenters thought that pexidartinib use has moderate to large potential to disrupt patient outcomes, citing the limited nonsurgical treatment options for TGCT and the promising response rates observed in patients not amenable to surgery. However, most commenters also noted concerns regarding liver toxicity associated with pexidartinib treatment, which was seen as potentially limiting the patient outcome benefit. One commenter with a health systems perspective suggested that the observed adverse events and the inability to determine which patients would experience them limit the drug’s potential to improve patient outcomes.\textsuperscript{141} One researcher, who indicated that pexidartinib use has small potential to improve patient health outcomes, also noted that TGCT is typically a nonfatal malignancy and, therefore, potential benefits of pexidartinib would extend only to improvements in quality of life and reduced disease burden.\textsuperscript{144}

\textbf{Health disparities}: Most commenters suggested that the drug has the potential to cause a small to moderate increase in health disparities in groups with limited access to the health care system, poor health care coverage, and/or lower economic status. A nurse and a researcher suggested that in addition to the cost burden, the requirement to comply with the REMS, in particular the need for ongoing monitoring of liver toxicity, might impose an additional barrier to adoption by underserved individuals, potentially worsening existing disparities.\textsuperscript{143,144} A commenter with a health systems perspective suggested that some payers might choose to deny pexidartinib coverage because of the risk of severe adverse events, putting a greater burden of the cost of care on patients.\textsuperscript{141} Conversely, a researcher\textsuperscript{144} and a clinician\textsuperscript{142} indicated that coverage and access to the medication for most patients was likely for the FDA-approved indication and based on the inclusion of pexidartinib in clinical practice guidelines for treating TGCT, which could limit the drug’s impact on health disparities.

\textbf{Health care delivery system}: Although most commenters indicated that the availability of pexidartinib would change how patients with TGCT are managed (see below), they thought that any potential disruption would be mitigated by the small number of patients affected and the fact that, as an oral medication patients take themselves, pexidartinib would not require substantial changes in health care delivery.

\textbf{Current paradigm of patient care}: Most commenters thought pexidartinib use would moderately disrupt the current paradigm of TGCT care. Although pexidartinib’s immediate impact would be as the first FDA-approved systemic treatment of TGCTs not amenable to
surgery, a clinician and a researcher suggested that its largest impact might occur if pexidartinib use is extended to patients with resectable TGCT. In particular, the clinician suggested that neoadjuvant (ie, before surgery) use of the drug could make these tumors more amenable to surgical resection and reduce surgery-associated morbidity. Additionally, a nurse and a researcher noted that the requirement to monitor patients for liver function while taking pexidartinib would disrupt current patient management. One commenter with a health systems perspective suggested that pexidartinib use would represent only a small disruption to patient management, suggesting that the high cost of the drug and potential for SAEs would steer patients to more conservative treatment options. Lastly, a researcher suggested that pexidartinib would not disrupt the current paradigm of patient care, citing the ease of administration of an orally administered drug and the off-label use of similar drugs in this disease setting.

Health care costs: Most commenters thought that pexidartinib use would have a small effect on health care costs. One researcher suggested its cost was likely to be high, considering that pexidartinib is a new agent for a rare disease with no existing systemic treatment options. (Note: Cost information was unavailable at the time of stakeholder comments.) This commenter and a nurse also suggested that the required monitoring for liver function could further increase costs associated with pexidartinib treatment. While the costs of pexidartinib were anticipated to be high, a clinician and a nurse noted that the direct cost to patients would likely be mitigated by insurance coverage or manufacturer patient assistance programs for underinsured or uninsured patients. One researcher suggested that, as a factor mitigating the overall cost impact, the low prevalence of TGCTs would limit the financial impact to payers and the health system generally. Additionally, another researcher suggested that an effective, nonsurgical treatment could lower downstream costs associated with managing TGCT-related symptoms.

Overall disruption potential: Most commenters thought that pexidartinib’s overall disruption potential would be moderate to large. These commenters cited the fact that pexidartinib represents the first systemic therapy approved for treating TGCT and that the demonstrated effectiveness of the drug in terms of disease control and symptom management represents a welcome addition to the treatment options. However, several of these commenters also cautioned that the observed adverse events (in particular, serious hepatic toxicity) represent a tradeoff in terms of the risk-to-benefit profile of the drug and could limit its disruptive potential. Commenters disagreed on the extent to which these adverse events would limit pexidartinib’s adoption. A commenter with a health systems perspective suggested that pexidartinib’s potential to cause SAEs would lead patients to seek alternative treatments, substantially limiting the drug’s disruptive potential. Similarly, a nurse suggested that pexidartinib use would be limited to a last resort to manage substantial reductions in QoL caused by TGCTs not amenable to other treatments. Conversely, one researcher suggested that pexidartinib would likely become the standard of care in patients with TGCTs not amenable to surgery and further suggested that future use of pexidartinib could extend to patients whose disease is amenable to surgical resection. Separate from the concerns regarding adverse events, another researcher suggested that pexidartinib has little to no overall disruption potential based on the similarity of pexidartinib to existing receptor TKIs used off label for treating patients with TGCTs.
Remestemcel-L (Prochymal) to Treat Pediatric Steroid-refractory Acute Graft-Versus-Host Disease

Highlights

No FDA-approved therapy exists for children who develop steroid-refractory acute graft-versus-host disease (GVHD) after a bone marrow transplant, and 6-month survival rates are only about 50%, emphasizing the need for more effective treatments. Remestemcel-L (Prochymal) is an off-the-shelf, allogeneic (from a donor) cell therapy under study for treating pediatric patients with steroid-refractory acute GVHD. The 8 stakeholders commenting on this topic indicated that remestemcel-L has substantial potential to improve patient outcomes in cases of steroid-refractory GVHD, based on the available data. But some reservations about the efficacy data remained, given the lack of published results from the phase III trial and the use of historical controls rather than parallel controls in a randomized trial. Commenters did not envision that an off-the-shelf stem cell therapy would cause substantial shifts in the health care delivery system or paradigm of care for these patients. Conversely, commenters suggested that the likely high cost of this cell therapy could have multiple consequences, including the potential for slower adoption and the exacerbation of any existing health disparities based on socioeconomic status and/or access to health insurance coverage.

Patient Population

Remestemcel-L is intended for children aged 2 to 17 years who have developed acute GVHD after a bone marrow transplant and whose GVHD has not responded adequately to steroid treatment.

Intervention

Allogeneic hematopoietic stem cell transplant (allo-HSCT) is used in treating several hematologic malignancies and nonmalignant hematologic and inherited metabolic diseases. While potentially effective for these conditions, allo-HSCT carries a risk of GVHD, which occurs when donor graft components initiate an immune response against the graft recipient’s tissues. Acute GVHD manifests as specific symptoms affecting the skin, gastrointestinal tract, and liver and can occur in the early posttransplantation period (ie, classic GVHD within 100 days of transplant) and later time points (persistent, recurrent, late-onset acute GVHD; overlap syndrome).147-150

Acute GVHD has substantial impacts on patient QoL and is the second leading cause of death in patients who have undergone allo-HSCT (disease recurrence being the leading cause). GVHD accounts for about one-third of deaths that occur after allo-HSCT. First-line treatment of acute GVHD typically uses corticosteroids to suppress the immune system; however, complete responses to corticosteroid treatment occur in only a minority of patients. No FDA-approved therapy exists for patients younger than 12 years with steroid-refractory acute GVHD, and 6-month survival rates are only about 50%.147-150

Remestemcel-L is an off-the-shelf preparation of allogeneic mesenchymal stromal cells (also known as mesenchymal stem cells). These cells purportedly have an immunomodulatory effect, regulating T-cell-mediated inflammation by inhibiting T-cell proliferation and downregulating production of inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interferon gamma. Additionally, remestemcel-L purportedly secretes growth factors that might
facilitate tissue repair. To produce remestemcel-L, allogeneic adult human mesenchymal stem cells are isolated from donor bone marrow and expanded in culture.\textsuperscript{151,152}

In clinical trials, patients receive remestemcel-L by IV infusion at a dose of $2 \times 10^6$ cells/kg twice a week for 4 consecutive weeks. Patients achieving a response at 4 weeks may receive up to 4 additional weekly infusions.\textsuperscript{153}

Evidence Development Summary

The evidence base for use of remestemcel-L in pediatric steroid-refractory acute GVHD consists of a 55-patient phase III trial (NCT02336230) and a 241-patient expanded-access program (NCT00759018). The phase III trial had a single group in which all patients received treatment with remestemcel-L. Results reported in a developer news release indicate that 69\% of 55 patients achieved an overall response at day 28, which compares favorably to a historical control group rate of 45\% ($p = .0003$). Additionally, OS at day 180 was reported as 69\% for all patients and 79\% for patients who had achieved an overall response at day 28.\textsuperscript{154} Similar results have been reported from the expanded-access program. Published results indicate that 65\% of 241 patients achieved an overall response at day 28, and OS at day 100 was reported as 66\% and 82\% for all patients and patients who achieved an overall response at day 28, respectively.\textsuperscript{155}

In a previous placebo-controlled RCT in pediatric and adult patients with steroid-refractory GVHD, remestemcel-L had failed to demonstrate improved outcomes; however, a subgroup analysis of the 28-patient pediatric subgroup showed signs of efficacy.\textsuperscript{156,157}

Manufacturers and Regulatory Status

Remestemcel-L is being developed by Mesoblast, Ltd (Melbourne, Australia), which acquired the product from Osiris Therapeutics, Inc, in 2013. Mesoblast has initiated a rolling Biologic License Application submission to FDA, which the company intends to complete by the end of 2019.\textsuperscript{158} FDA had granted remestemcel-L to treat acute GVHD Fast Track designation in March 2017\textsuperscript{159} and Orphan Drug designation in December 2005.\textsuperscript{160}

Results and Discussion of Stakeholder Comments

Eight stakeholders, reflecting clinical, nursing, research, and health systems perspectives, provided comments and ratings on this GVHD treatment.\textsuperscript{161-168} We have organized the following discussion of stakeholder comments by the parameters on which they commented.

**Patient outcomes, quality of life, and overall health:** Most commenters indicated that remestemcel-L use has moderate to large potential to improve patient health outcomes. These commenters cited the lack of existing FDA-approved treatment for pediatric patients with steroid-refractory GVHD,\textsuperscript{161,166-168} promising preliminary results compared with historical controls,\textsuperscript{161,163,164} and an acceptable safety profile.\textsuperscript{166,168} However, one clinician, who indicated that this intervention has only a small potential to improve patient outcomes, was more skeptical about the available data, citing an earlier RCT of remestemcel-L in treating GVHD that failed to demonstrate efficacy in adults and demonstrated a positive effect only in a subset of pediatric patients. This commenter also cautioned against weighing too heavily the comparison with historical data, suggesting that outcomes in steroid-refractory GVHD have improved in recent years.\textsuperscript{162}
**Health disparities:** Most commenters noted that the likely high cost of this therapy would probably exacerbate existing health disparities based on socioeconomic status or access to health care coverage; however, this was seen as representing only a small to moderate disruption in health disparities by most commenters.

**Health care delivery system:** Most commenters indicated that remestemcel-L use would have low potential to disrupt the health care delivery system. These commenters indicated that as a treatment delivered by IV infusion with minimal requirements for monitoring after the infusion, remestemcel-L would easily be incorporated into the established infrastructure for treating patients with GVHD. However, a researcher noted that the cell-based nature of remestemcel-L might require some staff training for proper storage and handling of the cell therapy during administration.\(^{166}\) This commenter also suggested that the need to monitor patients after infusion for side effects (in particular, lung infiltration by infused cells) might require shifts in the health care delivery system.\(^{166}\) Two clinicians suggested that, if effective in treating GVHD, remestemcel-L use could shorten lengths of hospital stay and health care resource use.\(^{162,164}\)

**Current paradigm of patient care:** Most commenters indicated that remestemcel-L use would lead to minimal disruption of the current paradigm of patient care. These commenters cited remestemcel-L’s relatively straightforward mode of administration and suggested that the cell therapy would simply represent another treatment option that would be easily adopted into bone marrow transplant centers. Conversely, a researcher suggested that because of the lack of effective treatment options in steroid-refractory GVHD, remestemcel-L has a large potential to disrupt the treatment paradigm for these patients.\(^{168}\) Commenters with clinical and health systems perspectives noted that the availability and, therefore, the disruption potential could be limited by access issues related to cost and/or payer coverage.\(^{161,162,164}\)

**Health care costs:** Although specific cost information for remestemcel-L is unavailable, most commenters indicated that remestemcel-L use would cause moderate to large shifts in the cost of care for patients with GVHD. Most of these commenters indicated that remestemcel-L would likely be costly and, therefore, increase upfront costs of treating steroid-refractory GVHD compared with the cost of other treatments. A researcher also noted that increased costs might be associated with preparing the cell therapy, in terms of laboratory procedures and specialized staffing.\(^{166}\) Although upfront costs were seen as being likely to increase, 2 clinicians suggested that, if effective, the therapy could decrease long-term costs associated with expensive alternatives to treating this condition.\(^{162,163}\) In contrast to the majority, one commenter with a health systems perspective suggested that remestemcel-L would be priced similarly to other infusion therapies and, therefore, would have only a small impact on health care costs.\(^{161}\)

**Overall disruption potential:** Commenter perspectives varied widely on the overall potential of remestemcel-L use to disrupt treatment of steroid-refractory acute GVHD. A clinician and a nurse suggested that this treatment has no overall potential for disruption, although it would be another option in this space.\(^{163,165}\) Another clinician suggested that this treatment has only a small potential for disruption, noting that while the rationale for treating GVHD appears valid, a more thorough presentation of the data is needed to adequately assess whether remestemcel-L actually improves outcomes.\(^{162}\) Commenters who viewed remestemcel-L’s overall disruption potential more favorably suggested that remestemcel-L represents a promising approach to treating pediatric patients with steroid-refractory GVHD, an indication
with no FDA-approved therapies; however, 2 of these commenters, a clinician and researcher, noted that additional studies would be needed to validate the promising initial results.164,167

Sodium Thiosulfate (Pedmark) to Prevent Pediatric Cisplatin-mediated Ototoxicity

**Highlights**

Pedmark is a proprietary formulation of sodium thiosulfate intended to reduce the risk of cisplatin-induced ototoxicity, which can lead to hearing loss, tinnitus, or vertigo, particularly in children undergoing chemotherapy. No effective treatment is available for chemotherapy-induced ototoxicity. In 2 clinical trials, treatment with sodium thiosulfate significantly reduced hearing loss by 48% and 49%, compared with standard care. The 7 stakeholders commenting on this topic generally agreed that sodium thiosulfate use could meet an important unmet need—given the significant disease burden that children with cisplatin-induced ototoxicity experience and the lack of approved treatments—and that it could positively disrupt patient-oriented health outcomes, including quality of life. However, most commenters thought that factors surrounding delivery of the treatment (eg, the 6-hour wait time after chemotherapy infusion) might create disparities in access to care and/or add to the burden of care for these patients.

**Patient Population**

Pedmark is intended for children aged 1 month to 18 years with localized, nonmetastatic solid tumors eligible for cisplatin chemotherapy.

**Intervention**

Pedmark is a proprietary formulation of sodium thiosulfate intended to reduce the risk of cisplatin-induced ototoxicity.169,170 Development of ototoxicity, which can result in hearing loss, tinnitus, or vertigo, is a well-known risk of using cisplatin chemotherapy for various cancers.171 Protective effects of sodium thiosulfate have been attributed to multiple mechanisms of action—including inactivation of platinum and/or platinum–protein complexes to reduce cisplatin’s direct cytotoxic effects, inactivation of reactive oxygen species (ROS), and/or elevation of levels of endogenous reducing agents (eg, glutathione)—which could inhibit the ROS-induced cell death (ie, apoptosis) induced by cisplatin.170

Because of sodium thiosulfate’s potential to interfere with cisplatin’s cytotoxic activity, sodium thiosulfate administration is delayed to allow cisplatin to exert its anticancer effects while remaining within a time window that allows an otoprotective effect. In clinical trials, sodium thiosulfate is given intravenously, 16 g/m² or 533 mg/kg, 6 hours after the patient receives cisplatin-based chemotherapy. Sodium thiosulfate treatment is given with each round of cisplatin until treatment is complete.169,170

**Evidence Development Summary**

Investigators have reported results from 2 trials of sodium thiosulfate, SIOPEL6 (NCT00652132) and ACCL0431 (NCT00716976), to reduce the risk of cisplatin-induced ototoxicity.

In the phase III SIOPEL6 RCT, pediatric patients (n = 109) aged 1 month to 18 years with stage I to III liver cancer (hepatoblastoma) were assigned to treatment with cisplatin alone or...
cisplatin plus sodium thiosulfate infusion 6 hours after chemotherapy, for 4 preoperative and 2 postoperative courses. The trial evaluated the safety and efficacy of sodium thiosulfate for reducing absolute hearing loss (Brock grade 1 or higher) in patients treated with cisplatin chemotherapy.

The investigators reported that 33% of children receiving cisplatin with sodium thiosulfate experienced hearing loss compared with 63% of children receiving cisplatin alone (48% lower incidence of hearing loss; relative risk, 0.52; \(P = .002\)).

At a median 52 months of follow-up, both groups had similar 3-year, event-free survival rates (cisplatin and sodium thiosulfate 82% [95% CI, 69%-90%] vs 79% for cisplatin alone [95% CI, 65%-88%]). Patients in both groups also had similar 3-year OS rates (98% for cisplatin and sodium thiosulfate [95% CI, 88%-100%] vs 92% for cisplatin alone [95% CI, 81%-97%]).

In the phase III open label, ACCL0431 RCT, pediatric patients (n = 104) aged 1 to 18 years with newly diagnosed germ cell tumor, hepatoblastoma, medulloblastoma, neuroblastoma, osteosarcoma, or other malignancy who were eligible for cisplatin therapy were assigned in a 1:1 ratio to treatment with sodium thiosulfate or observation (control group). The investigators reported hearing loss in 28.6% of patients given sodium thiosulfate compared with 56.4% of patients in the control group (\(P < .001\)), and when adjusted for stratification variables, the likelihood of hearing loss remained lower in the sodium thiosulfate group compared with control (odds ratio [OR] = 0.31; 95% CI, 0.13-0.73; \(P = .004\)).

Of the 194 SAEs reported in patients given sodium thiosulfate, none were attributed to the drug. The most common grade 3 to 4 hematologic adverse event was neutropenia (66% of 178 participant cycles in the sodium thiosulfate group vs 65% of 224 cycles in the control group). The most common nonhematologic adverse event observed was hypokalemia (17% of 149 cycles in the sodium thiosulfate group vs 12% of 187 cycles in the control group).

Manufacturers and Regulatory Status

Sodium thiosulfate is being developed by Fennec Pharmaceuticals, Inc (Research Triangle Park, North Carolina). In December 2018, Fennec Pharmaceuticals initiated a rolling New Drug Application for Pedmark for preventing cisplatin-induced ototoxicity in children aged 1 month to 18 years who have localized, nonmetastatic, solid tumors. In March 2018, FDA granted the drug Breakthrough Therapy designation for preventing cisplatin-related ototoxicity in pediatric patients with standard-risk hepatoblastoma. FDA has also granted sodium thiosulfate Orphan Drug and Fast Track designations for preventing cisplatin-induced ototoxicity in children.

Results and Discussion of Stakeholder Comments

Seven stakeholder commenters, reflecting clinical, nursing, audiology, research, and health systems perspectives, provided comments and ratings on sodium thiosulfate. We have organized the following discussion of stakeholder comments by the parameters on which they commented.

**Patient outcomes, quality of life, and overall health:** Commenters agreed that data from a clinical trial showed that sodium thiosulfate use substantially reduces the incidence of hearing loss in children concomitantly treated with cisplatin. A nurse thought a need exists for a hydration plan accompanying this intervention during the 6-hour waiting period due to the risk of renal toxicity that chemotherapeutic drugs like cisplatin are known to cause. An audiologist and 2 health systems commenters thought that in the absence of other options for preventing
hearing loss, sodium thiosulfate use would likely positively disrupt patient health outcomes and QoL in this population.176,177,182

**Health disparities:** Most commenters noted that the cost of sodium thiosulfate and changes in transportation accommodations due to the 6-hour interval between treatments might be burdensome for some patients and caregivers and thereby increase disparities. However, a clinician and an audiologist thought that sodium thiosulfate use might reduce disparities by alleviating downstream burdens associated with lifelong hearing loss, which could be even more difficult to manage for patients of low economic status or who have limited resources.176,179

**Health care delivery system:** A clinician and a health systems commenter thought that the 6-hour wait between cisplatin and sodium thiosulfate administration would likely lead to longer outpatient infusion visits or hospital stays, increasing demands on the system.179,182 Conversely, an audiologist noted that preventing hearing loss and related lifelong supportive care could substantially improve health outcomes and reduce cost of care and long-term system burden.176

**Current paradigm of patient care:** Most commenters thought sodium thiosulfate has little potential to disrupt treatment paradigms. However, a clinician and a nurse agreed that a longer chemotherapy stay could disrupt current treatment paradigms because treatment with sodium thiosulfate involves keeping children at the facility and occupied.179,180

**Health care costs:** Most commenters agreed that sodium thiosulfate use would be cost saving because the costs for hearing rehabilitation (eg, hearing devices, educational services, speech-language services) would likely outweigh the costs of hearing loss prevention—and hearing technology costs might not be covered by insurance. Two commenters, with health systems and clinical perspectives, thought that disruption in costs would depend on insurance reimbursement for patients and providers for this treatment.177,179

**Overall disruption potential:** Noting that no other options are available for preventing cisplatin-related ototoxicity, most commenters thought that sodium thiosulfate has large overall potential to disrupt health care delivery, particularly regarding patient-oriented health outcomes and QoL. A researcher and a health systems commenter expressed concerns about how quickly this intervention would be adopted by clinicians and patients because of the IV administration route for Pedmark.178,182
Chapter 3. Cardiovascular Diseases

Chapter Summary

For the Cardiovascular Diseases priority area, we considered for inclusion 8 topics for which (1) preliminary phase III data for drugs, phase II (or equivalent) data for devices and procedures, or some human data for off-label uses or programs were available; (2) information was compiled and sent for stakeholder comment before October 1, 2019; and (3) we received at least 5 sets of comments and ratings from stakeholder commenters between April 1, 2019, and October 10, 2019.

As of October 1, 2019, we were monitoring 26 topics in this priority area, including the 8 topics considered for inclusion in this report. These 26 topics will be listed in the December 2019 PCORI Health Care Horizon Scanning System: Horizon Scanning Status Report. We also archived one topic in May 2019. A description of that topic and the reason it was archived can be found in Section 3 of the June 2019 Status Report.

The 26 monitored topics encompass pharmaceuticals, gene and cellular therapies, devices, and implants intended to treat 11 cardiovascular diseases and/or related symptoms. One topic, Bempedoic Acid to Treat High-risk Atherosclerosis With Statin Intolerance, is currently undergoing stakeholder comment; however, fewer than 5 sets of stakeholder comments were received for the topic before October 1, and it was not considered for inclusion in this report. The remaining 17 topics are too early in development to meet criteria (as outlined above) for eligibility for this report.

Topics Considered for Inclusion in This Report

Table 3.1 lists 5 topics selected for inclusion during the High Potential Disruption Report decision meeting. A majority of the horizon scanning team voted that these topics had high potential for disruption, based on stakeholder ratings and comments and available data. Topics are listed and discussed alphabetically by topic title.

Table 3.1 Included Topics for Priority Area: Cardiovascular Diseases

<table>
<thead>
<tr>
<th>Topic Title</th>
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<tbody>
<tr>
<td>Neovasc Reducer to Treat Refractory Angina</td>
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<tr>
<td>Optimizer to Treat Moderate to Severe Chronic Heart Failure</td>
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<tr>
<td>Organ Care System (OCS) Heart to Treat End-stage Heart Failure Requiring Transplantation</td>
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<tr>
<td>Paradise Renal Denervation System to Treat Resistant Hypertension</td>
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<tr>
<td>Tafamidis (Vyndaqel, Vyndamax) to Treat Amyloid Transthyretin-mediated Cardiomyopathy</td>
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Table 3.2 lists 3 topics considered, but not selected, for inclusion during the High Potential Disruption Report decision meeting. A majority of the voting team agreed that these topics lacked high potential for disruption, based on stakeholder ratings and comments and available data. Each record notes the reasons for exclusion.

Table 3.2 Topics Considered but Not Included for Priority Area: Cardiovascular Diseases

<table>
<thead>
<tr>
<th>Topic Title</th>
<th>Exclusion Reason(s) and Notes</th>
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<tbody>
<tr>
<td>Baroreflex Activation Therapy (BAT; Barostim neo) to Treat Heart Failure</td>
<td>Stakeholder commenters generally thought the Barostim neo has small overall potential for disruption, citing doubts about the device’s ability to substantially improve outcomes and maintain long-term effectiveness compared with standard care. Most commenters anticipated low adoption, especially given the device’s history of unsuccessful US development for treating resistant hypertension.</td>
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<tr>
<td>Ischemic Stroke System to Treat Acute Ischemic Stroke</td>
<td>Most stakeholder commenters thought this technology would likely be adopted at specialized stroke centers and would represent a modest addition with small disruptive potential to current resource- and staff-intensive ischemic stroke care. All commenters cited the limited evidence available to adequately evaluate this technology.</td>
</tr>
<tr>
<td>Woven EndoBridge (WEB) Aneurysm Embolization System to Treat Intracranial Wide-necked Bifurcated Aneurysms</td>
<td>Stakeholder commenters overall considered the device to have some potential to improve outcomes compared with current treatment options for a small population. However, they generally viewed the WEB device as an incremental technology that would not disrupt the care paradigm, treatment costs, care delivery system, or other aspects of health care.</td>
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**Topic Summaries**

We present below 5 summaries on topics deemed to have high potential for disruption.

**Neovasc Reducer to Treat Refractory Angina**

**Highlights**

The 6 stakeholders commenting on this topic thought that Neovasc Reducer implant could have moderate to large disruptive potential for improving outcomes and QoL in patients with refractory angina, who have few therapeutic options when medical therapy ineffectively controls symptoms. Most commenters expected this intervention to have a small disruption on the care delivery system because of its perceived similarity to coronary stent implantation. However, commenters generally anticipated it could have a much larger disruption to how patients with refractory angina are managed.

**Patient Population**

The Neovasc Reducer device is intended to treat adults aged 18 years or older with Canadian Cardiovascular Society (CCS) grade III or IV chronic angina due to obstructive coronary artery disease that is unsuitable for conventional revascularization and does not respond to optimal medical therapy. (The 4-point CCS scale classifies angina based on severity, from grade I [no
limitation/angina during ordinary physical activity such as walking or climbing stairs] to grade IV [discomfort with any physical activity, angina may be present at rest]).

**Intervention**

The Neovasc Reducer (herein referred as the Reducer) is a stent-like, permanent implant intended to treat refractory angina by improving blood flow to ischemic heart tissue. Physicians implant the Reducer in the coronary sinus, the large vein that drains blood from heart muscle, to create a pressure backflow. This purportedly modulates blood flow through the coronary sinus and redistributes blood to areas of heart muscle that have poor circulation.

To deploy the balloon-expandable, hourglass-shaped device, a physician inserts the delivery catheter at the jugular vein in the neck and advances it to the coronary sinus, located on the external heart wall between the left atrium and left ventricle. Implantation purportedly takes about 20 minutes with patients under local anesthesia.

More information about angina is available from the American Heart Association.

**Evidence Development Summary**

The manufacturer continues to evaluate the Neovasc Reducer in 3 ongoing studies outside the United States.

The 3-arm, prospective-retrospective REDUCER-I observational study (NCT02710435, phase not stated) is assessing improvement in angina symptoms in up to 400 adults aged 18 years or older with refractory angina and limited or no options for revascularization. Primary outcomes are change in CCS grade through 6 months, incidence of major adverse cardiac events (MACE) through 30 days, and rate of device- or procedure-related SAEs, both through 30 days after implantation. Selected secondary outcomes include CCS improvement and MACE incidence through 5 years. The study is scheduled to complete in December 2022.

A prospective, single-arm study (NCT01566175, phase not stated) is assessing safety and efficacy of the Neovasc Reducer implant in up to 100 adults, aged 18 years or older, with CCS grade III or IV refractory angina who are not candidates for surgical or catheter-based revascularization. The primary outcome is a decrease of at least 2 CCS grades through 6 months after implantation. The study is scheduled to complete by December 2021.

The randomized, double-blind CrossRoad trial (NCT04121845, phase not stated) is comparing Reducer implantation with a sham procedure in up to 40 adults, aged 18 to 85 years, with CCS grade II to IV refractory angina who are not candidates for surgical or catheter-based revascularization. The primary outcome is change in exercise capacity measured by maximal oxygen consumption through 6 months after intervention. The RCT is scheduled to complete in December 2021.

In February 2015, Verheye et al reported outcomes data from the only published RCT that compared Reducer implantation with a sham procedure (diagnostic coronary angiography) for treating refractory angina. The phase II COSIRA trial (NCT01205893) assessed the proportion of patients who improved by at least 2 CCS grades after 6 months (primary outcome) among 104 adults aged 18 years or older with CCS grade III or IV refractory angina who were not candidates for revascularization.

CCS grade improved by at least 2 grades in 35% (18 of 52) of the Reducer group compared with 15% (8 of 52) of the control group at 6 months after the procedure ($P = .02$). CCS grade improved by at least one grade in 71% (37 of 52) of the treatment group compared with 42% (22 of 52) of the control group ($P = .003$). Scores on the 100-point Seattle Angina Questionnaire...
(SAQ) QoL survey improved significantly in the Reducer group compared with the control group (17.6 vs 7.6 points; \(P = .03\)). Investigators observed no significant differences in exercise time or the mean change in the left ventricular wall motion index as assessed by dobutamine echocardiography. By 6 months, 1 patient in the treatment group and 3 in the control group had experienced a myocardial infarction, and 1 patient in the control group had died.\(^{185}\)

Verheye and coauthors acknowledged that their trial lacked statistical power to detect an improvement in ischemia using objective measurements such as stress testing or wall-motion index, adding “a larger trial would be necessary to show such a benefit.” Further, they noted that since the COSIRA trial, better techniques for detecting improvement in myocardial ischemia that use magnetic resonance imaging and positron emission tomography “have become more commonplace and would be attractive methods to use in phase III studies of the coronary-sinus reducing device.”\(^{185}\) However, as of November 2019, the manufacturer had not announced any additional large, randomized trials of the Reducer in the United States or elsewhere to evaluate the technology for treating refractory angina.

In July 2018, Königstein et al\(^{186}\) reported single-center experience in 48 adults, mean age 68.8 ± 8.9 years, treated with the Reducer device for CCS grade III or IV refractory angina. CCS grade improved from a mean of 3.4 ± 0.5 at baseline to 2.0 ± 1.0 (\(P < .001\)) at median 12.5-month follow-up (range = 2 to 32 months). All 5 domains on the SAQ survey (ie, physical limitations, angina stability, angina frequency, disease perception, treatment satisfaction) improved significantly after Reducer implantation. Mean exercise duration increased from 03:43 ± 01:30 min:sec at baseline to 04:36 ± 02:18 (\(P = .025\)). Distance on the 6-minute hall walk increased from 299.9 ± 97.9 m at baseline to 352.9 ± 75.3 m (\(P = .002\)). Left ventricular ejection fraction (LVEF) at stress increased from 51.0% ± 10.0% at baseline to 56.5% ± 10.0% (\(P = .004\)), and left ventricular wall motion score index improved from 1.58 ± 0.4 at baseline to 1.37 ± 0.3 (\(P = .004\)). Investigators observed no periprocedural or long-term adverse events.

In October 2018, Giannini et al\(^{190}\) reported outcomes from 141 adults with refractory angina treated with the Reducer device in general clinical practice in the international REDUCE patient registry. Investigators achieved procedural success in 98.6% (139 of 141) of patients, with unfavorable coronary sinus anatomy preventing implantation in 2 patients. No SAEs occurred during a median follow-up of 14 months (range = 6 to 70 months). Mean CCS grade improved from 3.05 ± 0.53 at baseline to 1.63 ± 0.98 at last follow-up (\(P < .001\)). Overall, 81% of patients (113 of 139) reported angina reduction of at least 1 CCS grade, and 45% of patients (63 of 139) achieved angina reduction of at least 2 CCS grades. All 5 domains on the SAQ QoL survey improved significantly (\(P < .001\) for all). Further, the mean number of anti-ischemic drugs prescribed was reduced by last follow-up (2.37 ± 0.97 vs 2.17 ± 0.95; \(P = .003\)).

In October 2019, Ponticelli et al\(^{191}\) reported 2-year outcomes from the first 50 patients treated with the Reducer implant at a single center in Milan, Italy. At 2 years after implantation, 10 patients (20%) had undergone percutaneous coronary intervention (ie, balloon angioplasty with or without stenting), including 3 treated for acute coronary syndrome, and 5 patients had died, including 2 from cardiovascular causes (stroke and cardiac arrest). At 2-year follow-up among 45 surviving patients, CCS grade improved by at least 1 grade in 75.6% of patients (34 of 45) and by at least 2 grades in 35.6% of patients (16 of 45), corresponding to a significant reduction in mean CCS score vs baseline (1.74 ± 0.86 vs 2.98 ± 0.52; \(P < .001\)). Scores on 4 of 5 SAQ domains had improved significantly (\(P < .001\) for all).
Manufacturers and Regulatory Status

Neovasc, Inc (Vancouver, British Columbia, Canada) manufactures the Reducer device. FDA granted Breakthrough Device designation to the Neovasc Reducer for treating refractory angina in October 2018. On November 1, 2019, the company announced it intended to submit a full Premarket Approval application to FDA for the Neovasc Reducer for treating refractory angina by the end of 2019, supported by data from the COSIRA trial, the REDUCER-I European postmarket study, and other independent studies published in peer-reviewed journals.

Results and Discussion of Stakeholder Comments

Six stakeholders, reflecting clinical, nursing, and research perspectives, provided comments and ratings on Neovasc Reducer treatment for refractory angina. We have organized the following discussion of stakeholder comments by the parameters on which they commented.

**Patient outcomes, quality of life, and overall health:** All commenters thought that the Reducer implant has moderate to high potential to improve patient outcomes and QoL. A clinician stated, “Patients that have refractory angina despite optimal medical therapy have very few options,” adding that few US health care facilities offer device-based interventions, such as enhanced external counterpulsation, transmyocardial laser revascularization, or spinal cord stimulation, that had been used in the past for treating resistant angina. This commenter added, “The procedure appears to be safe, effective, and relatively quick, similar to implantation of a coronary stent.” A researcher stated, “A CCS score improvement from ‘severe’ (3-4) to ‘moderate’ (1-2) is significant and may translate into more patients living independently or working.” A clinician suggested it would be prudent for FDA to require an additional randomized trial to substantiate the clinical benefit of this technology, noting the well-demonstrated potential for a large placebo effect in treatments targeting angina.

**Health disparities:** Commenters were divided on whether this intervention would disrupt health disparities. A clinician and a researcher expected that most health plans would reimburse for Reducer implantation for appropriate patient candidates. The clinician stated, “Given that it is a relatively simple procedure that would be done by interventionalist[s] very comfortable with similar procedures already (eg, coronary artery stents), it would likely be available in most hospitals with cath [catheterization] labs.” However, another clinician stated, “Large numbers of patients eligible for this treatment are typically found only at large referral centers. Further, familiarity with coronary sinus access, for the most part, is lacking for most coronary interventionalists; hence it would need to be learned. This implies that at least initially, there would be limited access to this treatment outside of major centers.” Further, a researcher and a clinician anticipated that disparities might increase because uninsured or underinsured patients would be less likely to gain access to this intervention.

**Health care delivery system:** All commenters thought this intervention has small potential to disrupt the health care delivery system. Generally, commenters expected this intervention would be limited to a relatively small patient population and would be performed by interventional teams experienced in similar procedures, operating in existing catheterization laboratories or interventional suites without need for additional equipment besides the implants and their proprietary delivery catheters. One clinician stated, “If efficacious, this device could prevent emergency department visits or hospital admissions for angina, as well as unnecessary catheterizations in patients with known severe disease not amenable to further interventions.”
Current paradigm of patient care: Most commenters thought Reducer implantation would have at least a moderate disruptive effect on the current care paradigm for patients with refractory angina. One researcher stated, “For the small subset that have refractory angina, it could be a great way to get symptom relief without taking more medicines or risking stents, which are more invasive and riskier.” A clinician stated, “Because it involves only a simple procedure, and not protracted treatment (eg, as with enhanced external counterpulsation) or use of daily medications, there may be considerable patient demand.” Four commenters, comprising clinicians and researchers, anticipated that a potential initial barrier to adoption could be physician awareness and need to navigate a learning curve for using the technology in a population typically managed with medical therapy. The 2 clinicians also cited device costs and level of insurance reimbursement as potential barriers to its use.

Health care costs: Although estimated device and procedure costs in the United States are not widely available, most commenters expected only moderate cost disruption, likely comparable to other cardiac catheterization procedures, affecting a relatively small patient population. One clinician stated, “The cost of treatment with this device will certainly supersede that of the usual medications used for such patients, and with controversy over benefit, it is unclear how it will be viewed by insurers. This will certainly create conflict between patients/physicians and insurers.” Another clinician noted this product has the potential to significantly reduce treatment costs for these patients, who often undergo “several cardiac catheterizations a year to see if ‘anything can be fixed,’ because it is challenging for the health care team caring for such a patient not to be able to offer anything.”

Overall disruption potential: Commenters generally thought this intervention could cause a moderate to large overall disruption for patients with medically refractory angina who are not candidates for surgical or catheter-based revascularization procedures. One researcher stated, “Pain and disability in patients with refractory angina are an unmet medical need and a significant driver of health care utilization and costs in the United States. Even without addressing disease progression, emerging treatments that improve physical function and QoL have the potential to be cost effective and become adopted as standard of care.” A clinician anticipated that patient demand might be strong if patients perceive this technology as providing a new and effective therapeutic option. At the same time, most commenters cited gaps in the available evidence and the need for additional data from RCTs to better define the therapeutic effect of Reducer implantation for refractory angina. A clinician and a nurse called for further sham-controlled trials that collected more “hard endpoints,” such as survival and incidence of heart attack, stroke, and cardiovascular-related hospitalizations, in addition to more subjective endpoints, such as QoL measures.

Optimizer to Treat Moderate to Severe Chronic Heart Failure

Highlights

Most of the 9 stakeholders commenting on this topic thought that cardiac contractility modulation (CCM) with the implantable Optimizer device has moderate to large potential to disrupt care for patients with heart failure. This was across several domains, including patient outcomes, treatment costs, health care disparities, patient management, and the health care delivery system. Commenters reflecting patient and nursing perspectives rated this technology as having
large disruptive potential, especially given the existing lack of heart failure treatment options along the clinical pathway between medical management and highly invasive interventions, such as left ventricular assist devices and heart transplantation. The device costs about $19 100 in the United States, although estimated procedural costs have not been widely reported.

Patient Population

This device is intended for adults aged 18 years or older with a diagnosis of New York Heart Association (NYHA) functional class III heart failure. Further, these are patients who remain symptomatic while on guideline-directed medical therapy and are in normal sinus rhythm (ie, not candidates for cardiac resynchronization therapy) with LVEF between 25% and 45%.

Intervention

CCM with the implantable Optimizer device delivers nonexcitatory electrical pulses to the heart during the myocardial absolute refractory period to improve systolic contraction in the weakened heart muscle of patients with moderate to severe heart failure.\textsuperscript{200,201} CCM purportedly normalizes phosphorylation of regulatory proteins to improve calcium handling, thereby interrupting the remodeling cascade to reverse left ventricular enlargement and improve left ventricular contractile strength.\textsuperscript{202,203} More information about heart failure is available from the American Heart Association.

Physicians place the implantable pulse generator (IPG) in a subcutaneous pocket in the patient’s right pectoral region using techniques similar to those used to implant conventional pacemakers and defibrillators.\textsuperscript{204} Clinicians place 2 standard pacemaker leads through the subclavian vein on the right ventricular septum: one lead to sense local electrical activity and the second to deliver CCM therapy. Physicians can also implant a third lead in the right atrium for additional electrical sensing.\textsuperscript{201,204}

Physicians program and interrogate the Optimizer IPG with the Omni II Programmer System, which includes a magnetic induction telemetry wand, a programmer interface box, and a touchscreen tablet or laptop computer with proprietary software.\textsuperscript{201}

The Optimizer IPG delivers pulses at regular intervals during the day, purportedly unnoticed by patients. Patients recharge the IPG’s battery at home for about 60 to 90 minutes once a week, using a noninvasive charging system placed over the implant.\textsuperscript{200,201}

Evidence Development Summary

The manufacturer continues to evaluate the Optimizer device in 3 ongoing studies in the United States.

One nonrandomized study (NCT03339310), scheduled to complete in November 2019, is evaluating the Optimizer with a 2-lead configuration in up to 60 adults with moderate to severe heart failure. This study is assessing change in exercise tolerance and device-related adverse events (primary outcomes) and efficacy of CCM delivery with the Optimizer device using 2 leads vs 3 leads.\textsuperscript{205}

A second prospective, nonrandomized study (NCT03102437), scheduled to complete in January 2020, was designed to allow controlled access to the Optimizer Smart System for up to 350 adults with moderate to severe heart failure until FDA granted the device regulatory approval. The study is assessing serious device-related adverse events (primary outcome) and change in NYHA functional class and QoL.\textsuperscript{206}
As required by FDA’s approval order for the Optimizer, Impulse Dynamics is conducting a single-arm, nonrandomized, observational patient registry (NCT03970343) to measure the rate of procedure-related complications through 30 days and device-related complications through 1 year in patients treated with the Optimizer in general clinical practice. The postmarketing registry is scheduled to enroll up to 620 patients, with an estimated completion date of July 2022.

A nonrandomized European pilot study (NCT03240237), scheduled to complete in March 2021, is evaluating the Optimizer device in a different population: adults who have heart failure with preserved ejection fraction (ie, LVEF ≥ 50%).

In October 2018, Abraham et al reported that CCM with the Optimizer Smart device plus optimal medical therapy improved exercise tolerance and QoL and reduced heart failure–related hospitalizations through 6 months compared with optimal medical therapy alone. The RCT FIX-HF-5C (NCT01381172) compared treatment in 160 adults aged 18 years or older with NYHA functional class III to IV heart failure and LVEF between 25% and 45% enrolled at more than 40 centers across the United States and Germany.

In this trial, exercise tolerance quantified by peak oxygen consumption (VO₂) improved by 0.84 mL O₂/kg/min (95% Bayesian credible interval, 0.123-1.552) in the Optimizer plus optimal medical therapy group compared with the control group, satisfying the primary endpoint. The Optimizer treatment group also showed significant improvement compared with the control group in Minnesota Living With Heart Failure Questionnaire (MLHFQ) scores (−21.3 points vs −10.2 points; P < .001), NYHA functional class (≥1 class change; 81.4% vs 42.7%; P < .001), and 6-minute hall walk distance (43.0 ± 80.7 m vs 9.3 ± 87.4 m; P = .009).

In a 2017 systematic review, Bohannon and Crouch found that a change of 14.0 m to 30.5 m in 6-minute hall walk distance might be clinically important across multiple patient groups. Clinically meaningful changes in MLHFQ scores between 5 and 19 have been reported.

In the FIX-FH-5C trial, the composite rate of cardiovascular death and heart failure–related hospitalizations was significantly lower in the Optimizer group than in the control group: 2.9% vs 10.8% (P = .048). Seven device-related events occurred, yielding a lower bound of 80% of patients free from device-related events, satisfying the primary safety endpoint.

In January 2019, Anker et al reported that Optimizer therapy in real-world practice demonstrated improvement similar to that seen in clinical trials. Investigators measured changes in heart failure–related hospitalization, NYHA functional class, MLHFQ scores, and death among 140 adults with NYHA class III to IV heart failure and LVEF between 25% and 45% treated at 31 centers in a European patient registry. Hospitalizations decreased by 75%, from 1.20 patients per year at baseline to 0.35 patient per year at 2 years after Optimizer implantation (P < .0001) in the entire patient group and similarly in subgroups. After 3 years, the observed death rate was similar to that predicted by the Seattle Heart Failure Model for the entire patient group (82.8% vs 76.7%; P = .16) and the subgroup with LVEF between 25% and 34% (79.4% vs 78.0%; P = .81). However, the 3-year death rate was better than predicted in the subgroup, with LVEF of 35% to 45% (88.0% vs 74.7%; P = .046). NYHA functional class and MLHFQ scores showed progressive improvement over time in the overall group and both subgroups (P < .002).

In a systematic review and meta-analysis of 4 RCTs (total enrollment, n = 801; Optimizer enrollment, n = 394) reported in June 2019, Mando et al found that cardiac contractility modulation with the Optimizer might improve MLHFQ scores without statistically significant changes in 6-minute hall walk distance, arrhythmic events, hospitalizations, or death rate. After 6 months’ mean follow-up, Optimizer therapy was associated with improved MLHFQ scores (standardized mean difference [SMD] = −0.69; P = .0008). However, researchers observed no
significant differences between Optimizer and non-Optimizer groups in heart failure–related hospitalizations (OR = 0.76; \( P = .12 \)), all-cause hospitalizations (OR = 0.73; \( P = .33 \)), 6-minute hall walk distance (SMD = 0.67; \( P = .10 \)), arrhythmias (OR = 1.40; \( P = .14 \)), pacemaker/implantable cardioverter-defibrillator malfunction/sensing defect (OR = 2.23; \( P = .06 \)), or all-cause mortality (OR = 1.04; \( P = .92 \)).

Manufacturers and Regulatory Status

Impulse Dynamics (USA), Inc (Orangeburg, New York) manufactures the Optimizer device. FDA approved the company’s premarket approval (PMA) application for the Optimizer Smart System on March 21, 2019.\(^{216,217}\) The device is indicated to improve 6-minute hall walk distance, NYHA functional class, and QoL in patients with NYHA class III heart failure and LVEF between 25% and 45% who remain symptomatic despite guideline-directed medical therapy and who are in normal sinus rhythm (ie, not candidates for cardiac resynchronization therapy).\(^{216,217}\) FDA had granted the Optimizer device Breakthrough Device designation in July 2015.\(^{201}\) In 2016, the latest model, the Optimizer Smart, replaced (ie, for new device implantations) all earlier Optimizer versions (ie, II, III, IV) used in clinical trials.\(^{201}\)

In May 2019, Impulse Dynamics reported that the first US patient to receive an Optimizer device after FDA approval was treated at the Ohio State University Wexner Medical Center (Columbus, Ohio).\(^{218}\) Device implantation reportedly took about 1 hour, and the patient was sent home uneventfully the next day.\(^{218}\) However, the company has not announced any sales projections or other information about how widely the Optimizer is diffusing among US hospitals since FDA approval.

Cost Information

According to ECRI Institute’s PriceGuide database, member hospitals reported an average price paid of $19,100 for the Optimizer Smart device (as of October 14, 2019).\(^{219}\) Estimated implantation costs at US centers have not been widely reported since the device became commercially available in March 2019.

Results and Discussion of Stakeholder Comments

Nine stakeholders, reflecting clinical, research, nursing, health systems, and patient perspectives, provided comments and ratings on CCM with the Optimizer implant.\(^{220-228}\) We have organized the following discussion of stakeholder comments by the parameters on which they commented.

**Patient outcomes, quality of life, and overall health:** Six commenters—a patient,\(^{223}\) 2 nurses,\(^{222,224}\) 2 researchers,\(^{225,226}\) and a health systems commenter\(^{227}\)—considered Optimizer therapy to be an important new therapeutic option with moderate to large potential to improve outcomes for a large portion of the population with heart failure whose condition continues to deteriorate despite optimal medical therapy. But 3 commenters, with clinical\(^{220}\) and research perspectives,\(^{221,228}\) expressed skepticism about the technology’s ability to durably improve outcomes given the general lack of long-term data demonstrating fewer heart failure–related hospitalizations or reduced mortality.

**Health disparities:** Overall, commenters expressed concern that this technology might increase disparities among the population with heart failure, many of whom are of lower socioeconomic status and might be uninsured or underinsured. Most commenters noted that
patients with more generous private health insurance might be most likely to receive the Optimizer device, whereas patients with public insurance (ie, Medicare or Medicaid) could be less likely to receive it. A patient noted the general lack of data on Optimizer safety and efficacy in populations other than white men and called for more research of the technology in women and underrepresented ethnic groups. A clinician noted that in addition to potential disparities related to insurance coverage, the technology might be accessible or offered only at large tertiary medical centers, creating further disparities, at least initially.

**Health care delivery system:** Three commenters, with clinical and research perspectives, anticipated that the Optimizer would represent a small disruption to the health care delivery system, mostly because they predicted low use of the technology. However, one of the researchers anticipated the disruption would gradually increase if more long-term efficacy data were available and the device were to become a more established technology. The other 6 commenters, reflecting patient, nursing, research, and health systems perspectives, noted that implementing a program to offer Optimizer therapy would represent a moderate to large disruption to the care delivery system, ultimately depending on the number of patients who receive the technology.

Commenters generally expected the same clinicians and centers that implant pacemakers and defibrillators to implant the Optimizer devices, resulting in less disruption to those services unless use and demand were substantial. Three commenters—a patient, a nurse, and a researcher—anticipated that more staff could be needed, initially to screen candidates and train patients on how to recharge and care for the devices at home and over the long term to monitor the implanted devices. A patient and a nurse suggested that more home care nurses would be required to safely monitor patients at home, at least during an introductory period, especially if remote monitoring and management were available and patients had fewer office visits to evaluate the devices and their health status.

One nurse suggested an Optimizer program might be an attractive new revenue stream for some hospitals, potentially creating a risk of overutilization, given how it would shift office-based medical management to an interventional cardiology procedure. Another nurse and a researcher noted that if Optimizer therapy demonstrates clinical benefit in general practice similar to that seen in clinical trials, some hospitals might see fewer heart failure–related hospitalizations and reduced use of more aggressive heart failure interventions (eg, left ventricular assist devices, heart transplantation), which are used because heart failure typically progresses over time (although some patients may select palliative care over more invasive options).

**Current paradigm of patient care:** Most commenters expected that Optimizer therapy would have moderate to large disruptions to the way cases of heart failure are managed, shifting from office-based medical management to an interventional procedure that requires regular follow-up visits to monitor device performance and safety. A patient and 2 nurses expected more disruption than other commenters to current heart failure care models from adding Optimizer therapy. The patient suggested that requiring patients to recharge the device weekly could make care more inclusive and give patients more sense of control and involvement in their own care, potentially improving satisfaction and QoL. However, a clinician and a researcher anticipated low adoption of this technology, resulting in little disruption to how heart failure is managed in most patients with the condition.
**Health care costs:** Commenters generally thought that adding Optimizer therapy could disrupt the costs of heart failure care. Device implantation would increase short-term costs. However, over the long term, Optimizer therapy could help lower total costs if the implants reduce heart failure–related hospitalizations and more aggressive interventions, such as left ventricular assist devices and heart transplantation. One clinician anticipated a substantial increase in treatment costs if Optimizer therapy were to be widely used among the population with heart failure with reduced ejection fraction, adding, “This, especially without any clear survival/mortality benefits, would be highly controversial in an environment where the focus is on reducing health care costs.”

**Overall disruption potential:** Most commenters thought that, for patients with heart failure, the Optimizer device is an important additional therapeutic option that has the potential to improve QoL, slow disease progression, and delay the need for more aggressive interventions. Commenters with patient, nursing, and research backgrounds expressed the strongest support for the Optimizer’s overall disruptive potential, especially given the treatment gap between medical therapy and highly invasive options, such as left ventricular assist devices and heart transplantation. Five commenters—a clinician, a researcher, a patient, a nurse, and a health systems commenter—called for additional clinical trials to better identify or stratify patient subgroups most likely to benefit from Optimizer therapy and to evaluate the technology in a more diverse population of patients with heart failure than the patients in available trials. These commenters also suggested a need for longer-term trials that could more clearly identify a possible benefit in death rates, which in turn could lead to wider use and more disruptive potential.

**Organ Care System Heart to Treat End-stage Heart Failure Requiring Transplantation**

**Highlights**

The 7 stakeholders commenting on this topic generally expected Organ Care System (OCS) Heart preservation for donor hearts to represent a moderate to large disruption to current heart transplantation practices, potentially becoming a new standard of care for this indication. Although the underlying transplantation surgery would likely remain the same, most commenters anticipated this intervention could increase the number of donor hearts available for transplant. This change could allow more patients awaiting heart transplantation to receive a donor heart sooner, potentially improving outcomes and QoL for this group.

**Patient Population**

OCS Heart is intended to preserve and allow outside-the-body assessment of donor hearts intended for transplantation into adults aged 18 years or older who are candidates for heart transplantation.

**Intervention**

Recent studies indicate that only about 40% of donor hearts are used, because of their condition after donation and transport. At the current levels of donor heart availability, a substantial number of patients remain on the waiting list for extended periods, with the annual
death rate approaching 20% for patients on the waiting list. Substantial interest exists in increasing the number of donor hearts that can be used.

The Organ Care System is a portable system intended to maintain a donor organ—heart, lung, or liver grafts—in a warm, functioning state outside the body for an extended period. This purportedly optimizes organ health and allows for continuous clinical evaluation of the donor organ.

OCS Heart is optimized for preserving donor hearts. It is intended to increase the volume of viable donor hearts for transplantation by making longer-distance transport possible. It also purportedly gives clinicians more clinical data to better assess donor organ suitability from a larger pool of donor hearts than are considered suitable for use with conventional cold storage.

Like the other systems, the OCS Heart comprises 2 principal components: a portable battery-powered console and an organ-specific perfusion kit that function together as a system. The system perfuses donor organs with a proprietary blood-based solution to replenish oxygen and essential nutrients.

When physicians harvest the donor heart, they place it in the perfusion module and revive it to a beating state. The self-contained perfusion module maintains the proper temperature and humidity, protects the organ from external contaminants, and allows sterile ultrasound assessment of heart function and sterile blood sampling for laboratory analysis. A wireless monitor allows clinicians to assess the organ’s status and control system functions.

Evidence Development Summary

The manufacturer continues to evaluate the OCS Heart in 3 ongoing studies in the United States.

The single-arm EXPANDHeart pivotal trial (NCT02323321) is assessing the OCS Heart system for preserving and assessing donor hearts that do not meet existing donor heart acceptance criteria for transplantation. The trial’s primary outcome is a composite measure of patient survival at 30 days after transplantation and absence of severe primary donor heart dysfunction in the first 24 hours after transplantation. The trial is scheduled to complete in December 2019 with an enrollment of up to 75 adults aged 18 years or older who are heart transplant candidates.

The single-arm Heart EXPAND Continued Access Protocol (NCT03835754) is intended to provide transplant candidates expanded access to the OCS Heart system to preserve and assess donor hearts that do not meet current donor heart acceptance criteria, while the FDA regulatory review process of the OCS Heart is pending. The study’s primary outcome is patient survival after transplantation and absence of severe, primary right or left ventricular dysfunction of the donor heart within the first 24 hours after transplantation. The study is scheduled for completion by January 2020 with an enrollment of up to 48 adults aged 18 years or older who are heart transplant candidates.

The nonblinded, randomized controlled Donors After Circulatory Death Heart Trial (NCT03831048) is comparing the safety and efficacy of the OCS Heart for preserving and assessing hearts from donors after circulatory death with that of standard static cold storage. The primary outcome is patient survival at 6 months after heart transplantation. The trial is scheduled to enroll up to 212 adults aged 18 years or older who are heart transplant candidates. The estimated completion date is August 2021.

A 2-center observational study (NCT03687723) in Hannover, Germany, is assessing short- and long-term effectiveness of the OCS Heart system for preserving donor hearts in 60 or more
children and adults (no ages specified) who are candidates for heart transplantation. The primary outcome is patient survival at 1 year, and the secondary outcomes are patient and donor heart survival at 30 days after transplantation. The study is scheduled for completion by December 2021.235

In April 2019, Rojas et al236 reported comparative 1-year outcomes from 126 adults with end-stage heart failure who underwent heart transplantation involving standard cold storage donor heart preservation (n = 82) or OCS Heart preservation (n = 44). Total outside-the-body preservation time was significantly longer in the OCS Heart group than in the standard storage group (402 ± 67 minutes vs 225 ± 49 minutes, \(P < .001\)).

In this trial, no significant differences were observed between the OCS Heart group and standard storage groups across several additional measures, including the following: patient survival at 30 days (99.6% vs 91.2%; \(P = .26\)) and 1 year (88.6% vs 78.2%; \(P = .22\)); early graft rejection (9.3% vs 20.0%; \(P = .20\)); total transplant surgery time (488 ± 96.3 minutes vs 451 ± 133 minutes; \(P = .07\)); total mechanical ventilation time (7.1 ± 15.4 days vs 17.6 ± 36.9 days; \(P = .12\)); intensive care unit stay (14.2 ± 21 days vs 24.7 ± 36.9 days; \(P = .32\)); postoperative usage of extracorporeal membrane oxygenation (18.2% vs 28.4%; \(P = .28\)); and incidence of bleeding requiring repeat or repair surgery (20.5% vs 20.7%; \(P = .20\)).236

Also in April 2019, Schroder et al237 reported preliminary results from the EXPANDHeart trial (NCT02323321) evaluating the OCS Heart system to preserve expanded criteria donor hearts among adults aged 18 years or older who were candidates for heart transplantation. Of 93 eligible donor hearts evaluated on the OCS Heart system, 75 were successfully transplanted into registered transplant candidates, resulting in an 81% utilization rate. The average (mean) donor heart perfusion time with the OCS Heart was 6.35 hours. Severe left- or right-ventricular primary heart graft dysfunction occurred in 10.7% of patients. Patient survival at 30 days and 1 year was 94.7% and 88.0%, respectively.

Manufacturers and Regulatory Status

TransMedics, Inc (Andover, Massachusetts) manufactures the OCS Heart system. The OCS Heart is under clinical evaluation for preserving donor hearts that meet both current donor graft acceptance criteria and expanded acceptance criteria, in 1 pivotal trial232 and 3 additional trial protocols (no phase stated).233-235 In June 2019, TransMedics reported that FDA granted the company an investigational device exemption (IDE) to begin a clinical trial evaluating the OCS Heart for preserving hearts obtained from donors after circulatory death for the first time in the United States.234,238

TransMedics submitted a PMA application to FDA for the OCS Heart system in April 2014 based on results of the PROCEED-II trial designed to demonstrate noninferiority of the OCS heart system to standard-of-care storage of donor hearts.239,240 The FDA review was ongoing as of October 2019, with no further details announced from TransMedics or FDA.

In April 2018, FDA approved TransMedics’ PMA for similar technology, the OCS Lung system, for preserving donor lungs selected using standard lung graft acceptance criteria.241 The company is also evaluating the OCS Lung for use in preserving donor lungs selected under expanded acceptance criteria.229

Cost Information

According to ECRI Institute’s SELECTPlus database, member hospitals reported an average price paid of $250 000 for the OCS Heart console unit plus about $58 100 for the single-use
perfusion kit (as of October 28, 2019).242 Estimated implantation costs at US centers have not been widely reported since the device became commercially available in March 2019.

Results and Discussion of Stakeholder Comments

Seven stakeholders, reflecting clinical, nursing, research, health systems, and caregiver perspectives, provided comments and ratings on OCS Heart preservation of donor hearts for transplantation.243-249 We have organized the following discussion of stakeholder comments by the parameters on which they commented.

Patient outcomes, quality of life, and overall health: Commenters generally thought that the OCS Heart has moderate to large disruptive potential for patient outcomes and QoL, primarily by increasing the number of patients who could successfully receive a donor heart. A clinician stated, “It is a much more physiologic way to transport and maintain an organ than the current cold storage method. If newer data hold up, [it] could become the standard of care for organ transplant transportation and could increase the number of organs available, and to what group.”244 One commenter with a health systems perspective stated, “Should results of studies not yet completed affirm the early results, the intervention may substantially increase the usability of donor hearts.”246 A caregiver stated, “It is implicitly inferred that an organ transported in this way would be healthier for donation and therefore create better outcomes for the patient.”243 Most commenters also wanted to see future clinical data that confirm the promising results demonstrated in the initial trials.

Health disparities: Commenters expected that this technology could moderately disrupt disparities, potentially increasing the available donor heart supply by extending the time and distance over which donor hearts could be transported to transplant candidates. A health systems commenter stated, “Donation after circulatory death would make more hearts available for transplant. Since hearts are in short supply, even a moderate change in utilization could have a disproportionately large effect.”248 A researcher stated, “Because increasing the number of successfully transported and transplanted hearts can increase access, it could reduce the rate of death for [patients on] the waiting list.”245

Health care delivery system: Commenters generally expected this intervention to have a moderate to large disruption to the health care delivery system. A caregiver243 and a clinician244 gave it the highest ratings. Overall, commenters thought the biggest disruption would be in increasing the number of patients who ultimately receive a donor heart and leave the waiting list. A commenter with a health systems perspective stated, “OCS Heart will require additional equipment, recurring supplies, additional training, and potentially more staff and time to monitor the organ. If the system results in a greater number of transplants, that could have a significant effect on staffing and bed needs.”248 A nurse stated, “Managing the patient shouldn’t change much on the unit. Changes in the OR [operating room] will need to be implemented by how the organ is delivered to the sterile field.”247 This commenter further noted that hospitals will need to develop and implement new protocols that address how to use the OCS Heart, how to assign costs to the patient and hospital, how to ensure adequate staffing to operate the preservation system while waiting for the donor organ to be transplanted, and how to manage available resources.247 But the potential for a greater supply of donor hearts would not substantially alter standard care for patients awaiting transplant or for the surgical techniques to transplant donor hearts, commenters concurred.
Current paradigm of patient care: Overall, commenters thought this intervention would have a moderate to large disruption on the current paradigm of care for patients who undergo heart transplantation. A nurse stated, “I think problems will arise in the OR [operating room] with staff until they are used to using the OCS,” citing specific aspects of disruption that might include clinician ease of acquisition; clinician convenience and ease of use; clinician learning curve; and anticipated side effects, risks, and adverse events. A health systems commenter suggested, “There may also be some potential bioethical issues surrounding the concept of donation after circulatory death.” A clinician stated that this device’s use “would be a huge disruption in the way organs are kept and transplanted. I do not see any potential controversy as long as future data are good.”

Health care costs: Commenters generally expected the OCS Heart system to moderately disrupt heart transplantation costs. All commenters expected higher upfront costs for health care providers to obtain the technology and higher procedural costs for organ storage and transport compared with static cold storage. Further, most commenters expected higher short-term treatment costs overall if more candidates awaiting heart transplantation received a donor heart sooner. However, commenters generally acknowledged that management and care of patients awaiting transplant, as well as surgical and related costs for heart transplantation for patients who receive a donor heart, are already considerable, so the additional cost for OCS Heart preservation would likely be only moderately disruptive. A clinician stated, “Expect a small cost increase, but compared to the overall cost of transplant care plus the cost of caring for patients while awaiting transplant, this would likely result in a cost savings for all if more people get hearts sooner.”

Overall disruption potential: Commenters anticipated this technology could represent a moderate to large overall disruption on heart transplantations, potentially becoming a new standard of care. A clinician stated, “[It] could increase available donor hearts per year, increase the [geographic] range [of transport] to provide better access and immunologic matching, and could improve posttransplant outcomes since organs are better preserved.” A commenter with a health systems perspective stated, “By addressing a core limitation of heart transplantation (ie, viability of donor hearts), the intervention has the potential to substantially disrupt the current standard of care.”

Paradise Renal Denervation System to Treat Resistant Hypertension

Highlights

The 9 stakeholders commenting on this topic generally agreed that renal denervation might cause moderate, and potentially large, disruption to the case management of patients with treatment-resistant hypertension, considering that this is a subset of the overall large patient population with high blood pressure. Some commenters suggested that if renal denervation were to gain FDA approval, medical device companies and some early adopting providers could push for broad use of renal denervation, potentially outside of labeled indications, while pharmaceutical firms would pressure against renal denervation use because it might threaten their large market for antihypertensive drugs. Some commenters cautioned against potential overuse of renal denervation if it is viewed by patients and some providers as a one-time “quick
fix” that is easier to recommend and comply with than adherence to a continued multidrug regimen of antihypertensive medications and diet and lifestyle changes.

**Patient Population**

This intervention is intended for adults aged 18 to 75 years with average blood pressure (taken in a physician’s office) of 140/90 to 180/110 mm Hg (ie, stage 2 hypertension) who have previously tried antihypertensive medication and are currently taking 0 to 2 antihypertensive medications.

**Intervention**

The Paradise Renal Denervation System is a catheter-based device intended to treat difficult-to-manage hypertension. The American Heart Association defines treatment-resistant hypertension as elevated blood pressure (ie, above treatment goals) despite the concurrent use of 3 or more antihypertensive drug classes, or blood pressure that reaches treatment targets with concurrent use of 4 or more antihypertensive medications. About 15% of individuals with hypertension have treatment-resistant disease, which is associated with greater risk of cardiovascular disease and/or side effects associated with simultaneous use of multiple medications. More information about hypertension is available from the American Heart Association.

The Paradise system offers a device-based approach to treating hypertension. Known as renal denervation, use of the device ablates (ie, destroys) the renal sympathetic nerves that line the main renal arteries connecting the kidneys to the aorta. Research has suggested that overstimulation of the renal sympathetic nerves can contribute to resistant hypertension by increasing renin release, which leads to an increase in renal sodium reabsorption and a reduction of renal blood flow.

To perform renal denervation, the patient typically is placed under conscious sedation with local anesthesia. The physician inserts a proprietary balloon catheter into the femoral artery in the groin and advances it into the left and right renal arteries, alternately. Each artery receives 2 to 4 applications of circumferentially delivered ultrasound energy, about 7 seconds each. The liquid-cooled balloon purportedly protects the artery walls from heat damage while the sympathetic nerves are ablated. The physician removes the catheter using standard interventional techniques after treating both renal arteries. The Paradise system purportedly provides more complete ablation to more of the vessel by delivering energy circumferentially (ie, in a 360-degree circular pattern) from the balloon; earlier-generation systems (that failed in development) typically delivered ablation focally (ie, point by point at the catheter tip), which could increase the chance of incompletely ablating the target nerves, depending on device placement.

**Evidence Development Summary**

The manufacturer continues to evaluate the Paradise Renal Denervation System in 2 ongoing studies that include centers in the United States and 1 ongoing study in Japan.

The RCT RADIANCE-HTN (NCT02649426), scheduled to complete in March 2020, is comparing renal denervation with the Paradise system with a sham procedure (renal angiogram) in up to 292 adults with hypertension. One patient subgroup (TRIO cohort) has average blood pressure of 140/90 mm Hg or higher despite taking 3 or more blood pressure medications. Another subgroup (SOLO cohort) has average blood pressure between 140/90 and 180/110 mm Hg.
Hg while taking 0 to 2 antihypertensive medications. The primary outcome for the trial is the average reduction in daytime systolic (ie, the top number) blood pressure.258

The RCT RADIANCE-II (NCT03614260), scheduled to complete in December 2020, is comparing renal denervation with the Paradise system with a sham procedure in up to 225 adults with average blood pressure between 140/90 and 180/120 mm Hg who are taking 0 to 2 classes of currently or previously prescribed blood pressure medications. The trial is assessing change in average daytime systolic blood pressure and the occurrence of major adverse events (primary outcomes).259

The phase III RCT REQUIRE (NCT02918305) in Japan is comparing renal denervation with the Paradise system with a sham procedure in up to 225 adults with 24-hour average systolic pressure above 140 mm Hg or average office-measured blood pressure of 150/90 mm Hg or higher. The trial is measuring decrease in average 24-hour systolic blood pressure through 3 months after intervention.260

In June 2018, Azizi et al254 reported that renal denervation with the Paradise system significantly reduced average daytime systolic blood pressure compared with a sham procedure through 2 months after intervention in the absence of blood pressure medications. The interim results from the RADIANCE-HTN (NCT02649426) trial included 146 adults across 53 US and European centers in the SOLO cohort who had baseline average daytime blood pressure between 135/85 and 170/105 mm Hg if they had a 4-week cessation of up to 2 antihypertensive medications.

In this trial, renal denervation showed a greater reduction in daytime ambulatory systolic blood pressure (−8.5 mm Hg; standard deviation [SD] = 9.3) than the sham procedure did (−2.2 mm Hg; SD = 10.0; baseline-adjusted difference between groups: −6.3 mm Hg; 95% CI, −9.4 to −3.1; \(P= .0001\)). Investigators observed no major adverse events in either group.

In March 2019, Azizi et al261 reported results from 140 of these 146 SOLO cohort patients for whom 6-month follow-up had been completed. Patients whose at-home blood pressure between months 2 and 5 was 135/85 mm Hg or higher were started on standardized stepped-care antihypertensive drug therapy. At 6 months after intervention, 65.2% of the renal denervation group vs 84.5% of the sham group were receiving standardized stepped-care antihypertensive therapy (\(P = .008\)). The renal denervation group had a lower average number of antihypertensive medications than did the sham procedure group (0.9 ± 0.9 vs 1.3 ± 0.9; \(P = .01\)). The renal denervation group also had lower average defined daily doses than did the sham procedure group (1.4 ± 1.5 vs 2.0 ± 1.8; \(P = .02\)). Further, the renal denervation group had greater reductions in average daytime systolic blood pressure than the sham treatment group despite less intensive, stepped-care antihypertensive drug therapy (−18.1 ± 12.2 vs −15.6 ± 13.2 mm Hg; difference adjusted for baseline blood pressure and number of medications: −4.3 mm Hg; 95% CI, −7.9 to −0.6; \(P = .02\)). Investigators observed no major adverse events in either group through 6 months.261

**Manufacturers and Regulatory Status**

ReCor Medical, Inc (Palo Alto, California) manufactures the Paradise system. In July 2018, FDA granted ReCor Medical’s request to begin the RADIANCE II pivotal trial (phase not stated) to support a regulatory submission. The company expects to complete the 225-patient pivotal trial by December 2020 but has not announced an anticipated timeline for submitting a PMA application to FDA for the Paradise system.259,262
Results and Discussion of Stakeholder Comments

Nine stakeholders, reflecting clinical, nursing, research, patient, and health systems perspectives, provided comments and ratings on renal denervation with the Paradise system to treat resistant hypertension. We have organized the following discussion of stakeholder comments by the parameters on which they commented.

Patient outcomes, quality of life, and overall health: Overall, most commenters anticipated that renal denervation with the Paradise system would have moderate to high potential to improve patient outcomes and QoL if it reduces or eliminates the need to take blood pressure medications. A clinician, a nurse, and a researcher rated this technology’s potential to improve outcomes the highest among commenters, citing treatment-resistant hypertension as a major health problem affecting a large patient population for whom effective new treatments are needed. At the same time, all commenters noted a need for additional clinical trial data to monitor outcomes beyond 6 months after the intervention to assess the technology’s long-term safety and effectiveness at reducing resistant hypertension.

Health disparities: Most commenters expressed concern that renal denervation could increase disparities if public and private third-party payers were to not provide insurance coverage for the procedure. A researcher suggested that insurance coverage for renal denervation would not necessarily ensure access if ever-increasing high deductibles and copayments put the intervention financially out of reach of some health plan beneficiaries. A patient speculated that older patients, who are more likely to have hypertension and require multiple antihypertensive drugs, could potentially benefit most from the procedure but might be considered at high procedural risk and, thus, deemed ineligible to receive renal denervation. Six commenters, with research, clinical, nursing, and health systems perspectives, also suggested that geographic disparities could develop if renal denervation were implemented mostly or exclusively at regional centers with high-volume interventional cardiology or interventional radiology programs.

Health care delivery system: Commenters generally anticipated that implementing a renal denervation program would likely only moderately disrupt the health care delivery system. The commenters concurred that the interventional cardiology or interventional radiology teams most likely to perform renal denervation would require modest additional training and would perform these procedures in existing interventional suites. However, some commenters thought the potential disruption could increase if additional long-term studies demonstrate that renal denervation provides a clinically important and long-lasting reduction in high blood pressure. A clinician, a researcher, and a health systems commenter anticipated that future high demand for renal denervation would increase workloads on interventional radiology or interventional cardiology teams and increase use of interventional suites. The clinician suggested that widespread use of renal denervation could reduce the need for other procedures and hospitalizations to address complications from uncontrolled high blood pressure. Further, this commenter suggested that if renal denervation becomes widely accepted, it would probably shift from being performed initially only in hospitals to being performed in a physician office setting. A researcher anticipated that, ultimately, the large potential population of patients with resistant hypertension could encourage medical device manufacturers and some medical facilities to heavily promote renal denervation to encourage high demand and use, which might prompt...
some health care providers to expand staffing and capacity of interventional facilities to accommodate increased demand for the procedure.270

**Current paradigm of patient care:** Commenters generally expected renal denervation to have a somewhat larger disruption on individual patient management than on the health care delivery system. If future studies show a larger and long-lasting blood pressure reduction, commenters suggested, renal denervation could largely disrupt care by shifting it from mostly office-based antihypertensive drug therapy to a (most likely) one-time interventional procedure. A patient believed that renal denervation would likely be recommended more often in younger patients than in older patients, who might have higher procedural risk due to more coexisting health conditions.269 A health systems commenter,263 a researcher,270 and a patient269 anticipated that pharmaceutical companies that make hypertension medications might mount efforts to resist renal denervation’s use because it would reduce use of medication management for hypertension in a large patient population.

Another commenter with a health systems perspective cautioned that, if effective, renal denervation might be overused because a one-time procedure might be easier for physicians to recommend.267 This commenter stated, “In much the same way that stents are used as a catch-all for vascular occlusions, to the point that they may be overused instead of encouraging lifestyle changes, I worry that this medical procedure would allow for a permanent destruction of nerves for patients with resistant hypertension, instead of broaching the more difficult discussion of lifestyle change, which may have more long-lasting health benefits.”267 A researcher expressed a similar concern, stating, “Due to the high cost of [blood pressure] pharmaceuticals, the lifetime need for them, and their potential side-effects, concerned patients will envision [renal denervation] as a ‘quick fix.’”270 This commenter also suggested that “If significant ‘new’ revenue is to be realized by clinical facilities, . . . facility-employed clinicians will be induced by management to increase the volume of procedures, which may include performing [renal denervation] on patients [in whom the procedure is] unwarranted or a clinical risk.”270

**Health care costs:** Commenters generally expected renal denervation to have at most a moderate disruption to health care costs, largely because reliable cost estimates for the technology and procedure are not yet available. Most commenters expected hospitals to face some increased costs to implement a renal denervation program, although experienced interventional teams would perform the procedures in existing interventional suites. However, most commenters cited the theoretical effect of higher upfront costs for the renal denervation procedure mitigating the long-term treatment costs by potentially reducing or eliminating the need for lifetime blood pressure medications and avoiding costs for treating complications from uncontrolled hypertension. A researcher anticipated that renal denervation could become a new revenue source for facilities performing outpatient or overnight-stay procedures.270 This commenter also predicted that potential reimbursement for renal denervation from private insurers would likely be positive for hospitals, be cost-neutral if covered by Medicare, and represent a financial loss from Medicaid payers.270

A patient anticipated that the potential disruption to treatment costs would affect patients the most.269 This commenter proposed that if renal denervation successfully helps many patients reduce or eliminate their need for continued blood pressure medications, pharmaceutical companies would, in turn, raise prices for patients who continued to use their products, to compensate for losses incurred from renal denervation.269
**Overall disruption potential:** Commenters generally thought that renal denervation would likely have more moderate disruptive potential to the substantial population with hypertension but could have higher disruptive potential for the still considerable subset of patients with true drug-resistant hypertension. The failure of some earlier-generation renal denervation devices in past clinical trials made commenters hesitant to speculate strongly about the future of the Paradise system. All commenters called for further clinical trials to measure the long-term safety and efficacy of this technology and to more clearly identify the patients most likely to benefit from the procedure. A patient exemplified these sentiments, stating, “If more information regarding the potential risks and side effects becomes available, and the procedure benefits outweigh the risks for the patient with resistant hypertension, this could be a game changer in how these patients are treated, as well as with changes in drug and insurance coverage. The standard of care may take a huge shift from long-term medication management to cure; however, the risks associated with eradicating the sympathetic nervous system still need to be explored.”

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**Tafamidis (Vyndaqel, Vyndamax) to Treat Amyloid Transthyretin-mediated Cardiomyopathy**

**Highlights**

Most of the 6 stakeholders commenting on this topic thought that tafamidis could become a “game-changing” standard of care for transthyretin-mediated cardiomyopathy, a rare heart condition with a very poor prognosis. Although use of the oral medication is unlikely to cause major disruptions at health care facilities, it could substantially change how these cases are managed and have large downstream effects, such as postponing or avoiding the need for eventual heart transplantation. Commenters anticipated that the drug’s $225,000 annual list price could create controversy and disrupt patient access, depending on how and whether public and private payers provide insurance coverage for the treatment.

**Patient Population**

Tafamidis is intended for adults aged 18 years or older with hereditary (ie, caused by a genetic variant in the transthyretin gene, TTR) or wild-type (ie, not caused by any known genetic variant) amyloid transthyretin–mediated cardiomyopathy (ATTR-CM).

**Intervention**

A life-threatening disease, ATTR-CM occurs as transthyretin-based amyloid fibrils accumulate in the heart and leads to heart failure. Few treatments exist, and they typically involve supportive measures to manage heart failure symptoms. Life expectancy for patients with ATTR-CM is about 2.5 years after diagnosis for the hereditary form of the disease and 3.6 years after diagnosis of the wild-type form. Therefore, an unmet need exists for disease-modifying treatments with the potential to improve outcomes for these patients.

Tafamidis is a first-in-class oral drug intended to stabilize transthyretin tetramers (4-unit molecules) and interfere with the process of amyloid creation that underlies ATTR-CM. In patients with ATTR-CM, transthyretin tetramers dissociate into monomer (single-unit) intermediates that misassemble into amyloid aggregates. Amyloid is a protein, and amyloid aggregates gradually stiffen heart muscle, leading to heart failure. By stabilizing transthyretin...
tetramers, tafamidis purportedly reduces levels of amyloidogenic transthyretin monomers, potentially modifying the course of ATTR-CM.

Tafamidis is available in 2 nonsubstitutable formulations (ie, patients take one formulation or the other at a time but cannot mix), Vyndaqel and Vyndamax. The recommended dosages are as follows: tafamidis meglumine (Vyndaqel) taken as four 20-mg capsules daily; and tafamidis (Vyndamax) taken as one 61-mg capsule daily (intended for patient convenience).

More information about ATTR-CM is available from the American Heart Association.

Evidence Development Summary

The manufacturer continues to evaluate tafamidis in 2 ongoing studies in the United States. A single-arm, unblinded phase III study (NCT00935012) is assessing the long-term safety and efficacy of oral tafamidis 20 mg daily for treating ATTR-CM in adults (ie, aged 18 years or older) for up to 10 years (primary outcome). The study is scheduled to enroll up to 31 patients and has an estimated completion date of December 2021.

Another phase III single-arm, unblinded study (NCT02791230) is assessing all-cause mortality and incidence of treatment-related adverse events of oral tafamidis meglumine 80 mg daily or oral tafamidis 61 mg daily for treating ATTR-CM in adults (ie, aged 18 years or older) for up to 5 years (primary outcomes). The study is scheduled to enroll up to 2000 patients and has an estimated completion date of December 2024.

A single-arm, observational postmarketing study in Japan (NCT04108091) is evaluating the incidence of adverse drug reactions (primary outcome) and survival rate (secondary outcome), both through 30 months, in children and adults of any age treated with tafamidis for ATTR-CM. The study is scheduled to enroll up to 360 patients and has a scheduled completion date of April 2024.

In September 2018, Maurer et al reported that tafamidis reduced the hierarchical combination of all-cause mortality and frequency of cardiovascular-related hospitalizations (primary outcome) compared with placebo ($P < .001$) among 441 patients with ATTR-CM through 30 months. The all-cause mortality was 29.5% (78 of 264) in the tafamidis group compared with 42.9% (76 of 177) in the placebo group (HR = 0.70; 95% CI, 0.51-0.96). The rate of cardiovascular-related hospitalizations was lower in the tafamidis group, which had a relative risk ratio of 0.68 (0.48 per year vs 0.70 per year; 95% CI, 0.56-0.81). Tafamidis treatment reduced the rate of decline in distance on the 6-minute walk test by 75.68 m (standard error = ± 9.24; $P < .001$). Tafamidis also reduced the rate of decline in Kansas City Cardiomyopathy Questionnaire–Overall Summary score by 13.65 points (standard error = ± 2.13; $P < .001$). Investigators observed similar rates and types of adverse events in both groups.

Manufacturers and Regulatory Status

Pfizer, Inc (New York, New York) manufactures tafamidis meglumine and tafamidis. On May 3, 2019, FDA approved tafamidis meglumine 20-mg capsules under the trade name Vyndaqel, and tafamidis 61-mg capsules under the trade name Vyndamax, for treating ATTR-CM. FDA had previously granted tafamidis Orphan Drug, Breakthrough Therapy, Fast Track, and Priority Review designations for treating ATTR-CM. It is the first drug approved specifically to treat ATTR-CM.
Cost Information

Pfizer reportedly established a $225,000 per-year list price for tafamidis meglumine and tafamidis. The company has announced a patient assistance program to help eligible patients gain access to tafamidis therapy for ATTR-CM.

Results and Discussion of Stakeholder Comments

Six stakeholders, reflecting clinical, research, and health systems perspectives, provided comments and ratings on tafamidis for treating ATTR-CM. We have organized the following discussion of stakeholder comments by the parameters on which they commented.

**Patient outcomes, quality of life, and overall health:** All commenters thought this intervention has moderate to high potential to disrupt patient outcomes. Commenters with clinical and research perspectives rated it the highest. “This is really a true treatment for this condition, rather than a palliative therapy, such as a diuretic,” one clinician stated. Another clinician stated, “There is no other available medication to specifically treat cardiac amyloidosis, and the current standard of care for either HFpEF [heart failure with preserved ejection fraction] or HFrEF [heart failure with reduced ejection fraction] does not fully treat these patients.”

**Health disparities:** Commenters expected tafamidis to create a small to moderate disruption to health disparities, largely due to the rare incidence of ATTR-CM. However, most commenters anticipated disparities could increase based on how and whether public and private third-party payers reimburse tafamidis treatment for ATTR-CM. Some genetic variants strongly associated with ATTR-CM are believed to be more common in persons of African descent (estimated to be present in 3% to 3.5% of this group). Since ATTR-CM can often be mistaken for hypertensive damage, ATTR-CM is likely a widely underdiagnosed form of heart failure in the African American population. One clinician expected variation in how insurers cover the treatment and obstacles for providers and patients to obtain coverage. This commenter also noted that although still rare, ATTR-CM diagnoses have increased in recent years due to greater awareness of the disease and better diagnostic imaging techniques. A researcher suggested that broad access to tafamidis by appropriate patient candidates could reduce the number of patients with ATTR-CM who eventually would require heart transplantation.

**Health care delivery system:** Most commenters expected tafamidis to have a small disruption to the health care delivery system. Although costly, the drug is administered orally. However, 2 clinicians and a researcher suggested wide use of tafamidis could potentially reduce cardiovascular-related hospitalizations and heart transplantations in this small patient group. One clinician anticipated some shift of patients to tertiary care centers because tafamidis therapy would most likely be prescribed and managed by specialist physicians at large heart failure care programs.

**Current paradigm of patient care:** Most commenters expected availability of tafamidis to have a larger disruption on the care paradigm than on the care delivery system. A researcher stated, “This would be a new paradigm of therapy with the goal changing from managing symptoms to preventing them by slowing disease progression.” A clinician stated, “If there is indeed mortality benefit in real-world data, tafamidis will be a ‘game changer.’” The biggest controversies will be price and insurance company approval. There could be controversy if the real-world data and subsequent trials do not find the same results as the 2018 trial.
et al.”281 Another clinician also called tafamidis a potential “game changer,” stating, “It is really the only medication that seems to decrease the progression; it may save some patients from getting a heart transplantation” or extend the time to an eventual heart transplantation.282

Health care costs: Most commenters suggested the drug’s high cost could create a large potential disruption, especially if combined with uncertainty or varying levels of coverage by public and private third-party payers. One clinician stated, “I could see the expense of this drug making its way into the media, causing all kinds of issues for the pharmaceutical industry.”282 However, commenters also noted that this is a relatively rare condition and standard care for these patients can also be expensive, including repeat hospitalizations or heart transplantation.

Overall disruption potential: Most commenters suggested tafamidis has high overall disruptive potential, especially given the poor prognosis for patients with ATTR-CM receiving standard therapies. One clinician stated, “The current guideline-directed medications for congestive heart failure do not adequately treat amyloid patients. Tafamidis will have a monopoly on this market, and as the disease is more readily recognized and diagnosed, tafamidis will establish itself as the new standard.”281 Another clinician stated, “Device therapy, such as pacemakers and defibrillators, both expensive technologies, may be required less frequently if the [tafamidis] medication really stems the tide of the disease, but actually may be more frequently used as patients will likely live longer and may be better candidates for ICD [implantable cardioverter-defibrillator] therapy, if they have a longer life expectancy.”282 However, 2 commenters, with research285 and health systems280 perspectives, expected a small overall disruption due in part to oral administration in a very small patient population.
Chapter 4. Mental and Behavioral Health Conditions

Chapter Summary

For the Mental and Behavioral Health Conditions priority area, we considered for inclusion 10 topics for which (1) preliminary phase III data for drugs, phase II (or equivalent) data for devices and procedures, or some human data for off-label uses or programs were available; (2) information was compiled and sent for stakeholder comment before October 1, 2019; and (3) we received at least 5 sets of comments and ratings from stakeholder commenters between April 1, 2019, and October 10, 2019.

As of October 1, 2019, we were monitoring 20 topics in this priority area, including the 10 considered for inclusion in this report. The topics encompass pharmaceuticals and devices intended to treat 10 mental and behavioral health conditions. One topic, Ketamine (NRX-100)/Cyclurad (NRX-101) to Treat Severe Bipolar Depression With Acute Suicidal Ideation, is currently undergoing stakeholder comment; however, fewer than 5 sets of stakeholder comments were received for the topic before October 1, so it was not considered for inclusion in this report. The remaining 9 topics are still too early in development to meet criteria (as outlined above) for eligibility for this report. The 20 topics we are monitoring in this priority area will be listed in the December 2019 PCORI Health Care Horizon Scanning System: Horizon Scanning Status Report.

Topics Considered for Inclusion in This Report

Table 4.1 lists 3 topics selected for inclusion during the High Potential Disruption Report decision meeting. A majority of the horizon scanning team voted that these topics had high potential for disruption, based on stakeholder ratings and comments and available data. Topics are listed and discussed alphabetically by title.

Table 4.1 Included Topics for Priority Area: Mental and Behavioral Health Conditions

<table>
<thead>
<tr>
<th>Topic Title</th>
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<tr>
<td>Esketamine (Spravato) for Treatment-Resistant Major Depressive Disorder</td>
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<tr>
<td>MDMA-assisted Psychotherapy to Treat Severe Posttraumatic Stress Disorder</td>
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<tr>
<td>SEP-363856 to Treat Schizophrenia</td>
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</tbody>
</table>
Table 4.2 lists 7 topics considered, but not selected, for inclusion during the High Potential Disruption Report decision meeting. A majority of the voting team agreed that these topics lacked high potential for disruption, based on stakeholder ratings and comments and available data. Each record contains a note explaining the reasons for exclusion.

Table 4.2 Topics Considered but Not Included for Priority Area: Mental and Behavioral Health Conditions

<table>
<thead>
<tr>
<th>Topic Title</th>
<th>Exclusion Reason(s) and Notes</th>
</tr>
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<tbody>
<tr>
<td>Brexanolone (Zulresso) to Treat Postpartum Depression</td>
<td>Stakeholder commenters thought that potential for disruption depends heavily on its clinical uptake and that clinical uptake would likely be small. Commenters also had safety concerns and thought that more data are needed to compare brexanolone with current standard of care therapies.</td>
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<tr>
<td>Cranial Electrotherapy Stimulator (Cervella) to Treat Generalized Anxiety Disorder</td>
<td>Stakeholder commenters thought that the lack of safety and efficacy data for Cervella (cleared through the 510[k] pathway) would limit the clinical uptake of this intervention. In addition, the device is unlikely to provide more than an incremental benefit, if any, relative to other, more widely used devices.</td>
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<tr>
<td>Dasotraline to Treat Moderate to Severe Binge Eating Disorder (BED)</td>
<td>Stakeholder commenters thought that additional information was needed about overall efficacy and adverse events of dasotraline and could not speculate on its potential disruption at this time. Results from an ongoing phase III trial need to be reviewed to determine whether this drug used for treating BED has potential for disruption.</td>
</tr>
<tr>
<td>External Trigeminal Nerve Stimulation (eTNS; Monarch) to Treat Attention-deficit/Hyperactivity Disorder (ADHD)</td>
<td>Stakeholder commenters thought that this intervention is likely to be costly, difficult to implement, and incrementally beneficial, if at all, and will not likely displace current medical therapy. In addition, they noted that additional studies are needed to compare Monarch eTNS with current standard-of-care therapies and to assess long-term efficacy and outcomes.</td>
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<tr>
<td>Ketamine to Treat Posttraumatic Stress Disorder</td>
<td>Stakeholder commenters thought that ketamine is unlikely to be widely used or to replace cognitive behavioral therapy as the standard of care, citing barriers to patient acceptance, side effects of prolonged use, and the risk of dependence. They also thought that additional information was needed about overall efficacy and long-term effects of ketamine in this population, disagreeing about whether efficacy data from depression treatment were applicable.</td>
</tr>
<tr>
<td>Molindone HCl Extended-release (SPN-810) to Treat ADHD and Impulsive Aggression</td>
<td>Overall, stakeholder commenters agreed that there was insufficient evidence to determine whether the benefit of reduced aggression purported by this drug would outweigh the demonstrated potential for serious short- and long-term side effects of antipsychotic use, and they concluded that approval for the drug was unlikely.</td>
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Table:

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<tr>
<th>Topic Title</th>
<th>Exclusion Reason(s) and Notes</th>
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<tbody>
<tr>
<td>Viloxazine HCl (SPN-812) to Treat ADHD</td>
<td>Although stakeholder commenters agreed that preliminary data show potential for viloxazine to be a safe and effective nonstimulant treatment with a low risk of dependence, they thought there would be very little disruption to the health care system because of the availability of similar, approved treatments.</td>
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**Topic Summaries**

We present below 3 summaries on topics deemed to have high potential for disruption.

**Esketamine (Spravato) for Treatment-Resistant Major Depressive Disorder**

**Highlights**

Esketamine HCL is the only FDA-approved formulation of the anesthetic ketamine available for treating major depressive disorder (MDD); IV and intranasal ketamine were studied and used off-label for treatment-resistant MDD for about 10 years before esketamine approval. Esketamine’s cost is substantially higher than that of IV or intranasal ketamine—$36,500 vs an estimated $3,600 per treatment. Five stakeholders commenting on this topic were cautiously optimistic that the noninvasive, rapid delivery of esketamine might lead to a net improvement in patient outcomes. But they also thought that the FDA requirement for certified facilities, physician-supervised administration, posttreatment monitoring, and patient vehicle-driving restrictions might limit patient acceptance and diffusion or negatively disrupt some aspects of health care delivery. For example, esketamine’s cost relative to off-label ketamine and limited access to certified facilities might increase health disparities unless the drug receives widespread reimbursement.

**Patient Population**

Esketamine is intended for adults with treatment-resistant MDD (ie, inadequate response to 2 or more oral antidepressants of adequate dose and duration in the current episode of depression).

**Intervention**

Esketamine nasal spray is the (S+)-enantiomer of ketamine, delivered through a single-use intranasal device. The drug is indicated for use in combination with an oral antidepressant for treatment-resistant depression in adults. Esketamine is absorbed by the lining of the nasal passages and into the bloodstream, purportedly leading to rapid (within hours) improvement in depression symptom severity in patients with MDD. The Mayo Clinic website offers more information about treatment-resistant MDD.

Esketamine’s mechanism of action is noncompetitive antagonism to the N-methyl-D-aspartate (NMDA) receptor. Blocking activation of the NMDA receptor facilitates sensory input, moderates emotional responses, and might increase dopamine, norepinephrine, and serotonin levels in the brain.
The single-use nasal spray device contains 28 mg of esketamine and delivers two 14-mg sprays per device. Treatment is initiated in the induction phase at weeks 1 to 4 at a dose of 56 mg on day 1 and 56 or 84 mg subsequently, twice weekly. During the maintenance phase, from weeks 5 to 8, esketamine is administered once weekly at a dose of 56 or 84 mg, and at week 9 and subsequently it is given every 1 or 2 weeks at a dose of 56 or 84 mg. A 5-minute rest is indicated between the use of each 28-mg device to allow the body to absorb the medication.313

Patients take the intranasal spray themselves but in a health care setting certified to provide the treatment under the supervision of a health care professional. Its use requires patient monitoring in that health care setting for 2 hours after administration. Patients are also advised to not drive or operate machinery until the next day, after sleep.313 Esketamine is quickly metabolized and the majority is eliminated from the body within 24 hours.314

Esketamine was approved with a boxed warning about the risk of suicidal thoughts and behaviors in young adults and that it carries the potential for misuse and abuse.313 Therefore, it is not dispensed directly to patients and is available only through enrollment in the Spravato REMS program.

Evidence Development Summary

The manufacturer has reported data from 5 completed phase III clinical trials that evaluated esketamine in combination with an oral antidepressant to treat adults with treatment-resistant MDD.

In the phase III active control, double-blind TRANSFORM-1 trial (n = 346), adults aged 18 to 64 years with treatment-resistant MDD received fixed-dose intranasal esketamine twice weekly for 4 weeks (56 or 84 mg) or placebo, and all arms initiated a new oral antidepressant.315

Although the results numerically favored esketamine over placebo for both dosages, the change in Montgomery-Åsberg Depression Rating Scale (MADRS) total score from baseline to day 28 was not statistically significant (P = .09) for the 84-mg esketamine group based on a mixed-effects MMRM analysis. The 56-mg esketamine group and secondary endpoints could not be formally evaluated.315

Overall response rates (≥50% improvement from baseline) and remission rates (MADRS total score ≥ 12) at day 28 were higher for both esketamine groups than for the placebo group. Response rates at day 28 were 54.1% and 53.1% in patients treated with 56 and 84 mg of esketamine HCL, respectively, compared with 38.9% for placebo. Remission rates at day 28 were 36.0% and 38.8% in patients treated with 56 and 84 mg of esketamine HCL, respectively, compared with 30.6% of patients receiving placebo. The most common adverse events reported were altered taste, nausea, vertigo, and dizziness (incidence = 20.9% to 26.1%).315

In the phase III randomized, double-blind TRANSFORM-2 trial (n = 197), adults aged 18 to 64 years who had moderate to severe, recurrent or persistent MDD and a history of no response to 2 or more antidepressants in the current episode of depression similarly received fixed-dose intranasal esketamine twice weekly for 4 weeks (56 or 84 mg) or placebo, and all arms initiated a new oral antidepressant.

The mean change (least squares mean [SE] difference) in MADRS total score for intranasal esketamine was numerically superior to placebo at day 28 (−4.0 [1.69]; 95% CI, −7.31 to −0.64; 1-sided P = .01) and was statistically significant 24 hours after the dose (1-sided P = .01).316

In the phase III active control, double-blind TRANSFORM-3 trial (n = 138), patients aged 65 years or older with treatment-resistant MDD received flexible-dose intranasal esketamine twice
weekly for 4 weeks (28, 56, or 84 mg) or placebo, and all arms initiated a new oral antidepressant.

Patients treated with esketamine did not achieve statistically significant improvement in the primary outcome of depression severity at 28 days based on change from baseline in MADRS total scores. The mean (SD) change in MADRS total scores from baseline to day 28 was –10.0 (12.74) for esketamine and –6.3 (8.86) for placebo. Based on MMRM analysis, the median-unbiased estimate of the difference between esketamine and placebo was –3.6 (95% CI, –7.20-0.07; 1-sided \( P = .03 \)).\(^{317}\)

In the phase III randomized, double-blind SUSTAIN-1 trial (n = 703), adults aged 18 to 64 years with treatment-resistant MDD received flexible-dose intranasal esketamine twice weekly for 4 weeks (56 or 84 mg) and then once weekly or every other week or placebo, and all arms initiated an oral antidepressant.

Relapse was reported for 26.7% of patients in the esketamine group and 45.3% of patients in the placebo group (2-sided \( P = .003 \), weighted-combination test). The weighted estimate of HR showed that treatment with esketamine decreased the risk of relapse by 51% compared with placebo among patients with stable remission (HR, 0.49; 95% CI, 0.29-0.84). The most common adverse events reported were altered taste, vertigo, dissociation, somnolence, and dizziness (incidence 20.4% to 27.0%).\(^ {318}\)

In the phase III long-term safety and efficacy trial, SUSTAIN-2 (n = 802), adults aged 65 years or older with MDD and a history of nonresponse to 2 or more antidepressants in the current episode of depression received flexible-dose intranasal esketamine twice weekly for 4 weeks (28, 56, or 84 mg) and then once weekly or every other week for 48 weeks in conjunction with an oral antidepressant. Participants who entered the study directly received a newly initiated oral antidepressant, and those entering from the TRANSFORM-3 trial continued the same antidepressant.

The mean (SD) change in MADRS total score from the induction phase to the endpoint was –16.4 (8.76) and from the optimization/maintenance phase to the endpoint was 0.3 (8.12). At the end of the induction phase, the response rate was 78.4% and the remission rate was 47.2%. Of responders proceeding to the optimization/maintenance phase, the response rate was 76.5% and the remission rate was 58.2% at the endpoint.

Discontinuation rates due to adverse events were 6.7% during induction phase and 4.1% during maintenance phases; 6.9% of patients experienced serious treatment-related adverse events. The most common treatment-related adverse events were dizziness (33.0%), nausea (25.1%), headache (24.9%), dissociation (22.4%), somnolence (16.7%), altered taste (11.8%), hypoaesthesia (11.8%), vertigo (10.8%), vomiting (10.8%), and viral upper respiratory tract infection (10.2%).\(^ {319}\)

An ongoing phase III trial (NCT03434041) intends to assess the effectiveness of flexibly dosed intranasal esketamine (56 or 84 mg) in addition to a newly initiated oral antidepressant compared with placebo, also in addition to a newly initiated oral antidepressant.\(^ {320}\) Researchers plan to enroll 234 adults aged 18 to 64 years with treatment-resistant depression. The primary outcome measure is change in depression symptom severity from baseline. Secondary outcome measures include percentage of participants with onset of clinical response and percentage of participants whose disease is in remission. The primary completion date is April 2021.

The ongoing, open-label, phase III SUSTAIN-3 trial (NCT02782104) intends to assess the long-term safety of intranasal esketamine in 2 open-label phases: a 4-week flexible-dose induction phase (if applicable) and a flexible-dose optimization/maintenance phase.\(^ {321}\)
Researchers plan to enroll 1150 adults aged 18 years or older with treatment-resistant depression who had previously participated in one of several clinical trials (NCT02417064, NCT02418585, NCT02493868, NCT02422186). Primary outcome measures include incidence of treatment-emergent adverse events (TEAEs) and various biophysiologic and neuropsychologic measures. Secondary outcome measures include change in baseline of depressive symptoms and severity and quality-of-life measures. The primary completion date is August 2021.

Manufacturers and Regulatory Status

Esketamine HCL is manufactured by Janssen Research & Development, LLC, a unit of Johnson & Johnson (New Brunswick, New Jersey). FDA approved esketamine HCL on March 5, 2019, for treatment-resistant depression in adults. The approval required a REMS that specifies that esketamine be administered in a “certified doctor’s office or clinic,” that patients’ blood pressure be monitored, and guidance be given on food and liquid intake. Clinicians must also provide guidance for patients who might also be using other nasally administered medications for other conditions, such as corticosteroids or decongestants, on the day of esketamine administration. FDA had granted esketamine Breakthrough Therapy designation in November 2013 for treatment-resistant depression.

In August 2016, FDA granted Breakthrough Therapy designation for Spravato for MDD with imminent risk for suicide. The manufacturer plans to seek an expanded indication based on data from 2 completed phase III trials, ASPIRE I (NCT03039192) and ASPIRE II (NCT03097133). In June 2019, the Department of Veterans Affairs (VA) formulary committee voted against including Spravato on the VA’s formulary, restricting access to preapproved, case-by-case treatment.

Cost Information

Johnson & Johnson set esketamine’s wholesale acquisition cost (WAC) at $295 per 28-mg device. The Institute for Clinical and Economic Review’s draft evidence report evaluated the cost-effectiveness of esketamine plus a new oral antidepressant compared with the cost-effectiveness of a new oral antidepressant alone (no additional therapy). For esketamine, the lifetime incremental cost-effectiveness ratio was about $198 000 per quality-adjusted life year (QALY) gained, compared with no additional treatment, falling above the oft-cited cost-effectiveness threshold of $150 000 per QALY. Cost per life year gained was $2.6 million for esketamine compared with no additional therapy, and cost per depression-free day was about $330. The average 5-year annualized potential budgetary impact of using esketamine plus a new oral antidepressant at esketamine’s WAC was an additional per-patient cost of about $12 700.

The report also evaluated the 1-year treatment costs associated with esketamine compared with the cost of IV ketamine, including administration costs, and found the costs of esketamine are substantially higher than those of IV ketamine. The annual direct cost of esketamine treatment for year 1 is $36 500, compared with $3600 for ketamine treatment. For year 2 and future years, the annual direct cost is about $30 800 and $2500 for esketamine and IV ketamine, respectively.

Janssen offers copayment assistance up to $7150 annually for commercially or privately insured patients, including those insured through state and federal health exchanges, who pay $10 per treatment for esketamine medication. The savings program does not cover the cost of
administration. The program is unavailable to individuals who use any state or federal government-funded health care program to cover medication costs.325

Results and Discussion of Stakeholder Comments

Five stakeholders, reflecting clinical, health systems, and research perspectives, provided comments and ratings on esketamine.326-330 We have organized the following discussion of stakeholder comments by the parameters on which they commented.

**Patient outcomes, quality of life, and overall health:** Commenters offered mixed opinions on the potential for esketamine to improve patient outcomes. Several commenters thought that, based on the study results, esketamine might improve patient outcomes,326-328 particularly regarding the rapid delivery mechanism.330 However, one researcher expressed concern about the mixed results across studies,330 and several commenters wanted to see more clinical studies that directly compare esketamine with other treatments such as IV ketamine, repetitive transcranial magnetic stimulation, electroconvulsive therapy (ECT), and augmentation with second-generation antipsychotics or lithium. One clinician, who runs a ketamine clinic, noted from experience that ketamine continues to work for years as a maintenance therapy and reduces hospitalization rates and suicidal ideation.328 A researcher was concerned that the adverse effects of esketamine, including dizziness and dissociation, could have a negative impact on QoL outcomes.330

Three commenters, with research327,330 and clinical329 perspectives, thought that stringent regulatory requirements, including administration in a certified facility, the 2-hour posttreatment monitoring period, and driving restrictions, might discourage patients from trying this treatment and thus limit its uptake. These commenters also cited the cost of the drug and lifetime cost-effectiveness ratio as potential limiters to widespread diffusion, thereby reducing potential impact on long-term effectiveness and patient outcomes.

**Health disparities:** Most commenters thought that esketamine would have minimal positive effects and potential negative effects on health disparities because of the method of supervised administration at certified health care facilities, lack of access to local certified facilities, length of posttreatment monitoring and restrictions, high cost, and limited willingness of providers to prescribe nontraditional treatments.326,327,329 However, one clinician noted that obtaining insurance coverage would greatly improve access to the treatment and the approval of this intervention might contribute to reducing the stigma surrounding depression treatment.328

**Health care delivery system:** Overall, commenters thought that esketamine would have a moderate impact on the health care delivery system. Three commenters—a health systems comment and 2 clinicians—remarked that the requirements for certified facilities, medically supervised administration, and posttreatment monitoring might require additional medical facilities or specialty clinics, additional space at existing facilities, and an increase in staff to monitor patients.326,328,329 The other 2 commenters, with research perspectives, thought that the requirements, along with the cost, could limit access in rural areas, lead to poor compliance, and potentially reduce the overall impact of this intervention.327,330

**Current paradigm of patient care:** Commenters generally agreed that esketamine would have a low to moderate impact on the current care paradigm. Three commenters—a clinician, a researcher, and a health systems commenter—noted that the intranasal device is easy to use and less invasive than IV ketamine and ECT.326,328,330 However, all commenters thought that the current administration and monitoring requirements are inconvenient for the physician and the
patient, specifically regarding the need for additional physician training and time, higher resource expenses, and the burden on the patient in terms of the weekly or biweekly dosing schedule, time off work, postadministration monitoring, and driving restrictions.

A researcher wanted more information about coverage, copayments, and the need for preauthorization, as well as treatment duration, tolerance risk, dependence, and long-term side effects, to effectively assess the drug’s potential to shift the current care paradigm.330 Another researcher thought that this treatment would lead to high disruption only if efficacy were proved for patients with MDD who have not improved using other treatment regimens.327

**Health care costs:** Most commenters thought that esketamine has moderate potential to disrupt costs; however, some views conflicted. Three commenters—2 clinicians and 1 researcher—thought that the treatment is expensive compared with the cost of other options for treatment-resistant MDD, including off-label IV ketamine.328-330 One of the clinicians wanted more information about insurance coverage and noted that the patients’ costs include weekly loss of work time.328 One commenter with a health systems perspective thought the treatment inexpensive, considering the potential to decrease visits to crisis centers and admissions to mental health facilities.326 The clinician thought that a generic formulation could be administered and covered by payers for a fraction of the cost.328

**Overall disruption potential:** Most commenters thought esketamine has low potential overall to disrupt the health care system. Some thought it might cause a negative disruption. For example, most commenters remarked that esketamine is less cost effective, is more intrusive to patients, and would likely impose a higher burden on clinicians than off-label IV ketamine.326,327,329,330 A health systems commenter and researcher thought that the need to provide certified facilities for administration, the 2-hour postadministration monitoring period, and restrictions on driving and operating machinery would likely limit physicians’ willingness to prescribe and patients’ willingness to accept this treatment.326,327 Two researchers stressed the need for additional controlled studies to further assess the efficacy and safety of intranasal esketamine.327,330 However, one clinician noted that esketamine use represents a novel paradigm to treat depression; has a rapid, positive effect in an emergency; and might help patients who are not helped by currently approved treatments.328 The same commenter strongly advocated for insurers to pay for IV ketamine.328

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**MDMA-assisted Psychotherapy to Treat Severe Posttraumatic Stress Disorder**

**Highlights**

MDMA (3,4-methylenedioxymethamphetamine; also known by the street names Ecstasy and Molly) is a psychoactive drug given during psychotherapy to purportedly enable the therapist and patient to more efficiently communicate and for the patient to access and reprocess traumatic events. The 8 stakeholders commenting on this topic agreed that MDMA-assisted psychotherapy represents a significant departure from the standard of care and has the potential to be a quicker and more effective treatment for severe posttraumatic stress disorder (PTSD) than treatment with standard psychotherapy and selective serotonin reuptake inhibitor drugs. Commenters rated the overall disruption potential of MDMA-assisted psychotherapy as moderate to high, citing the
long duration of each therapy session, required clinical training, infrastructure changes, cost, and
issues with patient selection. Commenters thought that MDMA’s Schedule I classification and
substance abuse potential might be a barrier to widespread implementation.

**Patient Population**
This treatment is intended for adults aged 18 years or older who meet diagnostic criteria in
the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5) for severe
PTSD and have had at least one unsuccessful attempt with either talk therapy or drug treatment.

**Intervention**
MDMA (also known by the street names Ecstasy and Molly) is a psychoactive drug under
study for use during psychotherapy sessions led by specially trained therapists to improve
symptoms of severe PTSD. MDMA works by activating the trace amine-associated receptor 1
(TAAR1) and inhibiting vesicular monoamine transporter 2, thereby increasing concentrations of
these neurotransmitters, which are involved in the regulation of emotion, arousal, and
memory.

MDMA is thought to produce a sense of euphoria, well-being, and “positive mood
state.” It is also thought to produce prosocial feelings, such as a sense of closeness to others,
greater sociability, greater sensory perception, extraversion, and an increased tolerance of others’
views and feelings. MDMA use is believed to lead to “an expanded mental perspective”
and “improved self-examination.” The “openness” that MDMA-assisted psychotherapy
purportedly produces is intended to improve negative behaviors and feelings associated with
PTSD, such as hostility, mistrust, withdrawal, emptiness, hopelessness, and estrangement.

MDMA taken by the patient purportedly enables the therapist to more efficiently establish a
therapeutic relationship with the patient and increase 2-way communication during a prolonged
psychotherapy session. Patients given MDMA have reported gaining greater access to their
memories and helpful insights when revisiting traumatic events during therapy sessions.
MDMA use is also thought to energize patients. It produces its psychological and physical
effects by increasing levels of neurotransmitters in the brain, including dopamine,
norepinephrine, serotonin, oxytocin, prolactin, and cortisol.

In the most recent clinical trials, MDMA has been given to patients before an 8-hour
psychotherapy session. The initial dose is 80 or 120 mg followed by a supplemental half-dose of
40 or 60 mg given 1.5 to 2 hours later, if necessary, totaling 80 to 180 mg per session. The
treatment period consists of 3 sessions—1 per month for 3 months. Study participants are also
required to remain overnight after the session and be driven home the following day.

During the 8-hour MDMA-assisted psychotherapy session, specially trained therapists
encourage patients to revisit traumatic experiences with the goal of reprocessing intense thoughts
and feelings that arise. The psychotherapy session alternates between periods of patient
introspection and engagement with the therapist. Patients are monitored overnight at the site and
meet with their therapists for a 90-minute, follow-up therapy session the next day for further
emotional reprocessing.

The National Institute of Mental Health website offers more information on PTSD.

**Evidence Development Summary**
MDMA-assisted psychotherapy is being evaluated in an ongoing multisite, phase III double-blind
RCT (NCT03537014) comparing it with psychotherapy and placebo. The trial is scheduled
to complete in June 2020. Adults (n = 100) aged 18 or older with current severe PTSD are randomly assigned to treatment with MDMA-assisted psychotherapy or manual psychotherapy and placebo for 3 monthly psychotherapy sessions. The primary endpoint is PTSD symptoms assessed by the Clinician-administered PTSD Scale for DSM-5 (CAPS-5); the secondary endpoint is functional impairment assessed by the Sheehan Disability Scale.

Investigators reported a pooled analysis of 6 phase II double-blind RCTs conducted from April 2004 to February 2017 (NCT00090064, NCT00353938, NCT01958593, NCT01211405, NCT01689740, NCT01793610). In these studies, adults (n = 103) aged 18 years or older with chronic, moderate to severe PTSD, who had had at least one unsuccessful attempt at treatment or who were unable to tolerate talk or drug therapy, were given doses of MDMA (75 to 125 mg, n = 72) or placebo or controlled doses (0 to 40 mg, n = 31) during manual psychotherapy sessions. The sessions consisted of two to three 8-hour sessions spaced 1 month apart. Three nondrug 90-minute therapy sessions preceded the first MDMA exposure, and 3 to 4 followed each experimental session. The primary endpoint was PTSD symptoms assessed using the CAPS-5 instrument, and secondary endpoints were depression symptoms and severity, psychological distress, and QoL.

In a pooled analysis of these trials, patients who received 2 sessions of MDMA-assisted psychotherapy achieved the primary endpoint of reduced CAPS-5 total scores from baseline based on a mixed model for repeated measures (MMRM) analysis (estimated mean difference [SE] between groups = −22.0 [5.17]; P < .001). The between-group Cohen’s d effect size indicated a large treatment effect (Cohen’s d = 0.8). After 2 experimental sessions, more participants in the active group no longer met CAPS-5 PTSD diagnostic criteria compared with the control group (active 54.2%, control 22.6%). Depression symptom improvement on the Beck Depression Inventory-II was numerically greater for the active group than for the control group (MMRM analysis estimated mean difference [SE] between groups = −6.0 [3.03]; P = .05). All doses of MDMA were well tolerated; however, some expected reactions occurred at greater frequency in the active group during experimental sessions and within the 7 days after treatment.

Manufacturers and Regulatory Status

MDMA-assisted psychotherapy is being investigated by the Multidisciplinary Association for Psychedelic Studies (MAPS; Santa Cruz, California) in phase III trials for treating severe PTSD in adults. FDA granted Breakthrough Therapy designation to MDMA-assisted psychotherapy for severe PTSD in August 2017.

After MDMA was designated a Schedule 1 controlled substance in 1985, the developer, MAPS, filed a Drug Master File application in 1986, followed by an Investigational New Drug application in 2001 for the use of MDMA in combination with psychotherapy.

Results and Discussion of Stakeholder Comments

Eight stakeholders, reflecting clinical, therapist, health systems, and research perspectives, provided comments and ratings on MDMA-assisted psychotherapy. We have organized the following discussion of stakeholder comments by the parameters on which they commented.

Patient outcomes, quality of life, and overall health: Overall, commenters agreed that MDMA-assisted psychotherapy shows promise as a rapid and highly effective treatment for severe PTSD, compared with standard psychotherapy, which can take months or years. A clinician thought that the underlying concept of combining MDMA with psychotherapy is sound. This commenter thought that the rapid release of serotonin creates a euphoria that
might make it easier for patients to access and reprocess painful memories associated with their traumas, a core element of PTSD psychotherapy. In addition, this clinician thought that the treatment has significant potential to expand options for patients with PTSD.\textsuperscript{308} A researcher noted that a recently published systematic review found moderate-quality evidence supporting a large beneficial effect of MDMA.\textsuperscript{310,312} However, a health systems commenter noted that more frequent psychotherapy combined with antidepressants might still be the most effective option over the long term.\textsuperscript{309} A therapist thought that greater improvement during the acute treatment phase might improve patient compliance with treatment,\textsuperscript{306} while the commenter with a health systems perspective thought that standard psychotherapy might have a higher compliance rate.\textsuperscript{309} The health systems commenter\textsuperscript{309} and 2 researchers\textsuperscript{310,311} expressed concern about the treatment’s substance abuse potential, due to high rates of comorbid substance use disorder in this population. A therapist\textsuperscript{306} and 2 researchers\textsuperscript{310,311} noted that larger follow-up studies are needed to assess long-term outcomes, as well as additional outcomes, including anxiety symptoms, depression symptoms, QoL, and adverse events.

**Health disparities:** Commenters saw potential for MDMA-assisted psychotherapy to disrupt health disparities both positively and negatively. Four commenters, a health systems commenter,\textsuperscript{304} a clinician,\textsuperscript{307} a therapist,\textsuperscript{306} and a researcher,\textsuperscript{310} expressed concern that MDMA-assisted psychotherapy would increase disparities because of its potential costs and resource-intensive nature. The researcher noted that insurance does not currently cover the therapy, and patient out-of-pocket costs would be substantial.\textsuperscript{310} However, 2 commenters—a clinician\textsuperscript{306} and a researcher\textsuperscript{311}—noted that obtaining insurance coverage would potentially reduce disparities. The same 4 commenters, reflecting health systems,\textsuperscript{304} clinical,\textsuperscript{307} therapeutic,\textsuperscript{306} and research\textsuperscript{310} perspectives, noted that the length of the therapy session (8 hours), the required overnight stay, additional multiweek training required for therapists, and potentially limited number of facilities with resources for this treatment might pose barriers to widespread implementation. However, the therapist and 2 clinicians commenting on this intervention agreed that this treatment might ultimately reduce disparities and be more cost effective over the long term by decreasing the number of sessions needed to achieve meaningful trauma processing and symptom relief.\textsuperscript{306-308} Three commenters, with research\textsuperscript{305,311} and health systems\textsuperscript{309} perspectives, noted the importance of appropriate patient selection and consideration of individual factors that might influence response to this treatment.

**Health care delivery system:** Overall, commenters anticipated that MDMA-assisted psychotherapy would have a moderate to large disruption to the health care delivery system, in particular the mental health system. Three commenters, comprising a clinician,\textsuperscript{307} a therapist,\textsuperscript{306} and a researcher,\textsuperscript{310} anticipated that infrastructure changes would be needed to accommodate the 8-hour therapy sessions, overnight stays, and posttreatment follow-up. The therapist also noted the importance of securing the medication in the facility.\textsuperscript{306} These 2 clinicians\textsuperscript{306,307} and a researcher\textsuperscript{311} noted that specialized training is required for therapists to administer MDMA-assisted psychotherapy. A health systems commenter, a therapist, and a clinician\textsuperscript{304,306,308} noted that this treatment could increase the number of patients who could be treated and decrease the amount of long-term care delivered. One clinician thought that MDMA-assisted psychotherapy might significantly shorten all steps of the psychotherapy process compared with standard psychotherapy for PTSD, which can take months or years.\textsuperscript{308} This commenter also thought that MDMA-assisted psychotherapy might reduce inpatient admissions. However, a commenter with a research perspective questioned whether treatment effects would be sustained over the long
term and whether patients would require ongoing therapy or medication. This commenter also expressed concern about the potential for patients to develop dependence on MDMA. Additionally, a clinician thought that MDMA’s status as a Schedule I drug would limit more significant disruption.

**Current paradigm of patient care:** Commenters generally expected MDMA-assisted psychotherapy to cause moderate to large disruption to the standard of care for PTSD, shifting from standard psychotherapy to a resource-intensive but shorter and potentially more effective treatment. Most commenters thought this treatment would be more inconvenient for patients and clinicians, citing the length of session and required overnight stay, the need for specially trained mental health professionals, and appropriately resourced facilities. A therapist and a researcher noted that prescribing physicians would need to understand how MDMA works and interacts with other medications. The therapist pointed out that patients would need to be educated about what to expect while on MDMA, including potential adverse events, to carefully weigh the risk and benefits with their clinician. Four commenters—a therapist, a clinician, a researcher, and a health systems commenter—expressed concern that MDMA, as a Schedule I drug, carries the potential for misuse and abuse, a particular risk for this patient population because of the rate of comorbid substance use disorders. Depending on the regulations for dispensing the controlled substance, it could place a considerable burden on physicians to prescribe and administer MDMA. Three commenters with therapeutic and research perspectives thought that access might be limited in rural areas because of a lack of appropriately resourced facilities, and the treatment might be cost prohibitive to those with no insurance or high copayments.

**Health care costs:** Most commenters agreed that MDMA-assisted psychotherapy would moderately disrupt costs. Although short-term costs would likely increase, long-term costs could decrease. Three commenters, with clinical, research, and health systems perspectives, suggested that costs would increase because of the need for additional facilities that can accommodate overnight stays, specialized therapist training, delivery of long therapy sessions, and increased security. A therapist and 2 clinicians thought that if the treatment were effective, fewer sessions would be required for symptom reduction and potential remission, leading to reduced inpatient and emergency department (ED) admissions, faster return to work, and fewer associated morbidities, thereby decreasing long-term costs. One of these clinicians noted that insurers might be reluctant to cover this treatment because of MDMA’s Schedule I status. Additionally, another researcher thought controversy would arise around using “recreational drugs” in a clinical setting, potentially limiting uptake of the intervention. Two commenters, with health systems and research perspectives, noted that the treatment might be too expensive for some patients. One researcher suggested that disruption to cost would depend on who qualifies for this treatment.

**Overall disruption potential:** Overall, commenters thought that MDMA-assisted psychotherapy has the potential to be a highly effective treatment and cause substantial disruption to the health care system. Two researchers noted that it would be a novel treatment modality and significant departure from the current standard of care. One therapist thought MDMA-assisted psychotherapy could become a standard of care for treatment-refractory PTSD. Conversely, 2 clinicians noted that the resource-intensiveness of the therapy and required specialized training pose barriers to implementation. These 2 clinical commenters believed controversy would surround the abuse liability for individuals at risk for comorbid
substance use disorders. These commenters also noted the need for appropriate patient selection, with criteria addressing comorbid substance abuse disorders and disease severity. One of these clinicians thought that FDA approval would require a comprehensive REMS. The therapist suggested that this treatment might “usher in a greater awareness of and openness to medical treatment with psychedelics.” One of the clinicians wondered about the “potential for ‘pain pill mill’–style operations that will accept insurer reimbursement and administer this drug indiscriminately with substandard therapy,” and cited “ketamine clinics as an emerging health issue and warning of what may come.” Three commenters with therapeutic, research, and health systems perspectives suggested further research on long-term effects, adverse reactions, and use in patients with comorbid substance use disorders.

SEP-363856 to Treat Schizophrenia

Highlights

SEP-363856 is a novel antipsychotic drug to treat schizophrenia that works without blocking dopamine receptors in the brain. The 9 stakeholders commenting on this topic agreed that SEP-363856 has shown a significantly better side effect profile than dopamine-blocking antipsychotics and has the potential to become a first-line therapy. Commenters thought that reduced side effects might improve adherence to the medication regimen, QoL, and overall health. Fewer side effects might also reduce ED visits, hospitalizations, and the burden of care to treat side effects of obesity and diabetes caused by long-term use of dopamine-blocking medications. Commenters were eager to see whether additional studies would confirm these early findings of efficacy and reduced side effects.

Patient Population

SEP-363856 treatment is intended for adults aged 18 to 40 years with schizophrenia.

Intervention

Patients with schizophrenia report that undesirable effects—such as tremor, restlessness, difficulty sleeping, dizziness, sexual side effects, and weight gain—from available antipsychotic medications negatively affect their daily activities and QoL. These negative side effects are one of the main reasons patients stop taking their medication, and nonadherence with recommended antipsychotic medication dosing reportedly occurs in 50% to 75% of patients.

SEP-363856 is an oral medication that purportedly treats both positive and negative schizophrenia symptoms, as well as depression symptoms, with fewer side effects than dopamine-blocking medications. It works differently from available antipsychotics because it does not block the D2 dopamine or serotonin 2A (5-HT2A) receptors. The exact way SEP-363856 produces its antipsychotic effect is unknown, but it is believed to activate TAAR1 and serotonin 1A (5-HT1A) receptors. SEP-363856 has not been found to cause tremors, involuntary muscle contractions, restlessness, or weight gain.

In clinical trials, SEP-363856 (25, 50, or 75 mg) has been given orally, once daily, for up to 26 weeks.

More information about schizophrenia is available from the National Institute of Mental Health.
Evidence Development Summary

A phase II multicenter, double-blind RCT (NCT02969382) investigated the efficacy and safety of flexibly dosed SEP-363856 (50 or 75 mg/day) vs placebo in hospitalized adults aged 18 to 40 years (n = 245) who met DSM-5 criteria for schizophrenia and experienced acute exacerbation of psychotic symptoms. The primary endpoint was change in positive and negative schizophrenia symptom severity as assessed by the Positive and Negative Syndrome Scale (PANSS). Secondary endpoints included change in depression symptom severity and incidence of adverse events.

Koblan et al³³⁴ reported in 2019 that the PANSS total score reduction at week 4 was significantly greater for SEP-363856 than placebo (−17.2 vs −9.7; P = .001; effect size = 0.45). The reduction was also greater than the effect with placebo in the following: PANSS negative subscale score (−3.1 vs −1.6; P = .008; effect size = 0.37), the PANSS general psychopathology subscale score (−9.0 vs −4.7; P < .001; effect size = 0.51), the Clinical Global Impressions (CGI)-Severity score (−1.0 vs −0.5; P < .001; effect size = 0.52), and the Brief Negative Symptom Scale total score (−7.1 vs −2.7; P < .001; effect size = 0.48). The reduction in the PANSS positive subscale score was also greater for SEP-363856 than for placebo (−5.5 vs −3.9; P = .02; effect size = 0.32). Overall, discontinuation rates were similar for SEP-363856 and placebo (21.7% vs 20.8%), including those due to an adverse event. Changes in weight, lipids, glucose, and prolactin were comparable between SEP-363856 and placebo. The incidence of adverse events was higher for SEP-363856 than for placebo for the following events (incidence of ≥ 2%): somnolence (6.7% vs 4.8%), agitation (5.0% vs 4.8%), nausea (5.0% vs 3.2%), diarrhea (2.5% vs 0.8%), and indigestion (2.5% vs 0%). The percentage of patients who reported any extrapyramidal (ie, movement) symptom was similar between SEP-363856 and placebo (3.3% vs 3.2%).

Results have not yet been reported for the completed phase II SEP361-202 trial (NCT02970929). SEP361-202 is a multiregional, open-label extension trial of the safety and tolerability of once-daily SEP-363856 (20, 50, or 75 mg) for 26 weeks in adults aged 18 to 40 years (n = 157) meeting DSM-5 criteria for schizophrenia who completed the 4-week double-blind treatment phase of study SEP361-201. The primary endpoint was adverse events and secondary endpoints included change in positive and negative symptom severity, change in depression symptom severity, and time to relapse.

Manufacturers and Regulatory Status

SEP-363856 is manufactured by Sunovion (Marlborough, Massachusetts), a subsidiary of Sumitomo Dainippon Pharma (Osaka, Japan), in collaboration with PsychoGenics (Paramus, New Jersey). Sunovion evaluated SEP-363856 to treat schizophrenia in the 2 phase II trials reported above: NCT02969382, completed July 2018, and NCT02970929, completed January 2019. In May 2019, FDA granted Breakthrough Therapy designation for SEP-363856 to treat patients with schizophrenia.³³⁸

Results and Discussion of Stakeholder Comments

Nine stakeholders, reflecting clinical, nursing, health systems, and research perspectives, provided comments and ratings on SEP-363856.³³⁹-³⁴⁷ We have organized the following discussion of stakeholder comments by the parameters on which they commented.
**Patient outcomes, quality of life, and overall health:** Overall, commenters agreed that an effective antipsychotic with an improved side effect profile, compared with dopamine-blocking antipsychotics, would significantly improve health outcomes for patients. Most commenters noted that medication adherence is a significant barrier to treating schizophrenia and nonadherence is often directly related to medication side effects. Therefore, they thought that a medication with reduced side effects would lead to improved adherence and ultimately improved outcomes. One nurse thought adherence would lead to well-managed symptoms, thereby reducing ED visits and hospitalizations. Two commenters—a clinician and a researcher—thought that overall health would be improved by avoiding long-term consequences associated with dopamine-blocking antipsychotics, including cardiovascular risk factors, drug-induced movement disorders, and metabolic issues. However, one commenter with a health systems perspective thought that without additional support, patients might be less compliant with the once-daily pill than with competing long-acting drugs. Five commenters—4 researchers and a health systems commenter— noted that although this drug has shown preliminary efficacy, evidence is limited and longer-term and comparative effectiveness studies are needed. These commenters noted that schizophrenia requires lifelong treatment, the study population is not generalizable to the entire population of patients with schizophrenia, and outcomes were assessed at only 4-week follow-up. One researcher doubted SEP-363856’s effect on positive symptoms because the data were not statistically significant. One clinician speculated that SEP-363856 might have efficacy in patients who do not respond to other treatments, due to its novel mechanism of action.

**Health disparities:** Generally, commenters thought that SEP-363856 was similar to other available treatments and would have a minimal impact on health disparities. Four commenters, with research and health systems perspectives, agreed that the most disruptive factor would be improved adherence because of the favorable side effect profile and low incidence of adverse events. Three commenters—a clinician and 2 researchers—thought that the decreased risk of comorbidities, such as obesity and diabetes, would reduce disparities. Most commenters did not think SEP-363856 would affect access to care. A clinician expected that the drug would initially be more expensive than available generic antipsychotics. A nurse noted that the higher cost might increase disparities for uninsured and underinsured patients, although a researcher thought that disparities would not be affected for insured patients. A researcher and a nurse wanted to see additional studies that include a broader population, including nonhospitalized and female patients.

**Health care delivery system:** Most commenters agreed that SEP-363856, as another oral antipsychotic, would have minimal disruption on care processes, staffing, and infrastructure. However, most commenters agreed that if SEP-363856 were proven to have similar efficacy and improved tolerability compared with available treatments, medication adherence would increase, the condition would be better managed, and overall health would improve. A clinician thought that, based on the data, SEP-363856 would be unlikely to be more efficacious than available antipsychotics. A clinician, a nurse, and a researcher thought that improved tolerability and adherence would reduce acute exacerbations of psychosis and hospitalizations. The researcher noted that this treatment might reduce the burden of care for obesity and diabetes, both of which are side effects of long-term use of available antipsychotics. Another researcher noted that care might shift from the inpatient to outpatient setting because of the convenient once-daily dosing.
Current paradigm of patient care: Commenters offered mixed opinions about whether SEP-363856 has the potential to disrupt the current paradigm of patient care. Five commenters, with clinical and research perspectives, agreed that the main disruption would be due to the potential reduction in long-term side effects, including weight gain, metabolic effects, and movement disorders, leading to improved medication adherence and disease management. However, a nurse and a health systems commenter noted that nonadherence might be due to other factors, such as cognitive impairment or poor insight. The nurse expressed concern that access and ease of acquisition might be affected if treatment is available only to inpatients. Several commenters noted that data are very limited thus far and larger, longer-term studies are needed. Two commenters, from health systems and research, thought that if additional trials were successful, this drug might become the new standard of care.

Health care costs: In general, commenters thought there would be minimal disruption to health care costs. A clinician, a researcher, and a nurse thought that the long-term costs of schizophrenia treatment might decrease because improved tolerability would lead to improved medication adherence, thereby improving overall health and reducing ED visits and hospitalizations. Another researcher thought that if SEP-363856 proves to be effective and safe, it would likely be cost effective. Three commenters, with clinical, research, and health systems perspectives, expected that SEP-363856 would be more costly when released than available generic drugs.

Overall disruption potential: Despite limited data, most commenters thought that SEP-363856 has moderate potential to disrupt the health care system, most notably regarding patient outcomes and overall health. They cited improved tolerability, increased medication adherence, and reduced long-term consequences (ie, those associated with dopamine-blocking antipsychotics, including cardiovascular risk factors, drug-induced movement disorders, and metabolic issues). Several clinicians and a researcher were optimistic about this new treatment and noted that the novel, nondopamine mechanism of action is the first advance in schizophrenia treatment in decades. A health systems commenter and a nurse saw potential for this medication to become the standard of care. Four commenters—a clinician, a health systems commenter, and 2 researchers—advocated for additional data from larger, long-term studies. Another health systems commenter thought that this drug would have minimal disruption on the health care delivery system because of its similarity to available treatments.
Chapter 5. Rare Diseases

Chapter Summary

For the Rare Diseases priority area, we considered for inclusion 23 topics for which (1) preliminary phase III data for drugs, phase II (or equivalent) data for devices and procedures, or some human data for off-label uses or programs were available; (2) information was compiled and sent for stakeholder comment before October 1, 2019; and (3) we received at least 5 sets of comments and ratings from stakeholder commenters between April 1, 2019, and October 10, 2019.

As of October 1, 2019, we were monitoring 99 topics in this priority area, including those considered for inclusion in this report. These 99 topics encompass pharmaceuticals, gene and cellular therapies, surgical procedures, and implantable devices intended to treat or prevent 64 rare diseases and/or related conditions. Five topics in this priority area are undergoing or have been queued for stakeholder comment; however, fewer than 5 sets of stakeholder comments were received for those topics before October 10, and they were not considered for inclusion in this report. The remaining 71 topics are too early in development to meet criteria (as outlined above) for eligibility for this report.

The 99 topics monitored in this priority area will be listed in the December 2019 PCORI Health Care Horizon Scanning System: Horizon Scanning Status Report.

Topics Considered for Inclusion in This Report

Table 5.1 lists 16 topics selected for inclusion during the High Potential Disruption Report decision meeting. A majority of the horizon scanning team voted that these topics had high potential for disruption, based on stakeholder ratings and comments and available data. Topics are listed and discussed alphabetically by title.

<table>
<thead>
<tr>
<th>Topic Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apremilast (Otezla) to Treat Behçet’s Disease</td>
</tr>
<tr>
<td>Caplacizumab-yhdp (Cablivi) to Treat Acquired Thrombotic Thrombocytopenic Purpura</td>
</tr>
<tr>
<td>Casimersen to Treat Duchenne Muscular Dystrophy</td>
</tr>
<tr>
<td>Crizanlizumab-tmca (Adakveo) to Prevent Recurrent Vaso-Occlusive Crises From Sickle Cell Disease</td>
</tr>
<tr>
<td>Fenfluramine Hydrochloride Low-dose (Fintepla) to Treat Dravet Syndrome</td>
</tr>
<tr>
<td>Galcanezumab-gnlm (Emgality) to Treat Episodic Cluster Headache</td>
</tr>
<tr>
<td>Givosiran (ALN-AS1) to Prevent and Treat Acute Hepatic Porphyrias</td>
</tr>
<tr>
<td>GT-AADC to Treat Aromatic L-Amino Acid Decarboxylase Deficiency</td>
</tr>
<tr>
<td>Idebenone (Puldysa) to Treat Duchenne Muscular Dystrophy</td>
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<tr>
<td>LentiGlobin to Treat Transfusion-Dependent β-Thalassemia</td>
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<tr>
<td>Luspatercept-aamt (Reblozyl) to Treat Transfusion-Dependent β-Thalassemia</td>
</tr>
<tr>
<td>Onasemnogene Abeparvovec-xioi (Zolgensma) to Treat Spinal Muscular Atrophy</td>
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</tbody>
</table>
Table 5.2 lists 7 topics considered but not selected for inclusion during the High Potential Disruption Report decision meeting. A majority of the voting team agreed that these topics lacked high potential for disruption, based on stakeholder ratings and comments and available data. Each record contains a note explaining the reasons for exclusion.

Table 5.2 Topics Considered but Not Included for Priority Area: Rare Diseases

<table>
<thead>
<tr>
<th>Topic Title</th>
<th>Exclusion Reason(s) and Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaboxadol (OV101) to Treat Angelman Syndrome</td>
<td>Stakeholder commenters agreed that available data, which were limited, showed no improvements in behavior, sleep, or gait, which are important patient-oriented outcomes.</td>
</tr>
<tr>
<td>Nintedanib (Ofev) to Treat Interstitial Lung Disease in Systemic Sclerosis</td>
<td>Stakeholder commenters noted this intervention was not compared with the standard of care, which is much cheaper and has shown more overall improvement than just one functional measure: forced vital capacity. Commenters also were concerned it did not improve other patient-oriented outcomes and had a high rate of side effects. Further, commenters doubted wide diffusion, given the limited availability through specialty pharmacies and the high costs.</td>
</tr>
<tr>
<td>NT-501 (Renexus) to Treat Macular Telangiectasia Type 2</td>
<td>Stakeholder commenters agreed that the phase II clinical trial results for NT-501 (Renexus) showed some clinical effect for short-term health outcomes. More data from longer trials are needed to assess the potential for disruption. We continue to actively monitor this topic.</td>
</tr>
<tr>
<td>PXT3003 to Treat Charcot-Marie-Tooth Disease Type 1A</td>
<td>Stakeholder commenters thought the potential for disruption was small, citing the drug’s questionable mechanism of action, small clinical effect, and dosing-related issues. More data are needed.</td>
</tr>
<tr>
<td>Solriamfetol (Sunosi) to Treat Excessive Daytime Sleepiness in Narcolepsy</td>
<td>Stakeholder commenters thought solriamfetol to treat excessive daytime sleepiness in narcolepsy was not a significant enough departure from the mechanism of action, side effect profile, and health care paradigm of current standard of care to be considered as having high potential for disruption. This topic has been archived.</td>
</tr>
<tr>
<td>Tasimelteon (Hetlioz) to Treat Sleep Disturbances of Smith-Magenis Syndrome</td>
<td>Stakeholder commenters generally thought the data were not clinically significant enough to justify the high cost of the drug as compared with current standard-of-care therapies. This topic has been archived.</td>
</tr>
<tr>
<td>Trofinetide (NNZ-2566) to Treat Rett Syndrome</td>
<td>Stakeholder commenters thought the current data were limited and the intervention might be cost prohibitive. We continue to actively monitor this topic.</td>
</tr>
</tbody>
</table>
We present below 16 summaries on topics deemed to have high potential for disruption.

Apremilast (Otezla) to Treat Behçet’s Disease

Highlights

Blood vessel inflammation is a characteristic of Behçet’s disease, a rare disorder that causes canker mouth sores, genital ulcers, and eye inflammation. Treatment options for the ulcers have been associated with toxicity and suboptimal efficacy. Apremilast (Otezla) targets the inflammation process and has been studied as a treatment for the ulcers; FDA approved the drug for this indication in July 2019.

Six stakeholders commented on this topic before the FDA approval. They generally agreed that apremilast is a safe, effective, and convenient oral therapy for treating symptoms, such as oral ulcers, arising from Behçet’s disease. They thought that the drug had comparable efficacy but better tolerability than the current standard-of-care treatment, tumor necrosis factor (TNF) inhibitors. They thought apremilast could reduce the burden on patients and the health system from follow-up appointments with multiple specialists. However, the targeted therapy’s high cost combined with copayment assistance programs for patients with private insurance might lead to health disparities. Commenters thought that apremilast might become standard care for Behçet’s disease, but its overall disruption potential could hinge on whether long-term, comparative data become available to further validate its efficacy for this indication.

Patient Population

Apremilast is intended for adults aged 18 years or older with oral ulcers associated with Behçet’s disease.

Intervention

Apremilast is a small-molecule inhibitor of phosphodiesterase type 4 that promotes increases in intracellular cyclic adenosine monophosphate, leading to decreased expression of proinflammatory mediators such as TNF-α, IL-17, and IL-23. Blood vessel inflammation is a characteristic of Behçet’s disease, which investigators suspect is linked to overactive Th17 cells and increased IL-17 production, suggesting that apremilast might alleviate oral ulcers associated with Behçet’s disease. For more information on the disease, see National Organization for Rare Disorders. Apremilast is taken orally as 30-mg tablets twice daily.

Evidence Development Summary

Preliminary data are available for the phase III randomized, crossover RELIEF trial (NCT02307513). Trial subjects were adults (n = 207) aged 18 years or older with active Behçet’s disease and at least 3 oral ulcers at the time of random assignment or at least 2 oral ulcers at time of screening. Enrolled subjects were given apremilast 30 mg, twice daily, or a placebo, for 12 weeks. Then patients given placebo crossed over to treatment with apremilast through 64 weeks.

Patients given apremilast achieved the primary endpoint of reduced oral ulcer burden over 12 weeks (area under the curve from weeks 0 through 12 [AUCWk0-12], which measures the number
of oral ulcers over time, accounting for their recurring-remitting pattern), compared with patients given placebo ($P < .0001$). Patients taking apremilast also had fewer oral ulcers ($P = .002$) and oral ulcer pain ($P = .004$) from weeks 1 through 12 than patients given placebo. Apremilast patients with oral ulcers achieved a 62% complete response as well as a 70% relative reduction in oral ulcer pain by week 28. Patients initially given placebo, who crossed over to receive apremilast at week 12, gained benefits comparable to those attained by the initial active treatment group.

Adverse event rates were similar between groups during the control period (78.8% for the apremilast group vs 71.8% for the placebo group). The most common adverse events reported by patients taking the drug included diarrhea, headache, nausea, and upper respiratory tract infection.

Manufacturers and Regulatory Status
Apremilast is manufactured by Celgene Corp (Summit, New Jersey), which was acquired by Bristol-Myers Squibb (New York, New York) in January 2019. FDA approved apremilast for oral ulcers associated with Behçet’s disease on July 19, 2019. FDA had approved the drug for treating psoriatic arthritis in March 2014, and in September 2014 expanded the indication to include treating plaque psoriasis.

Cost Information
According to the online retail pharmacy price aggregator GoodRx, a 30-day supply of 60 apremilast 30-mg tablets costs about $3370.

Results and Discussion of Stakeholder Comments
Six stakeholders, reflecting clinical, health systems, and research perspectives, provided comments and ratings on apremilast. Comments were provided before FDA approval in July. We have organized the following discussion of stakeholder comments by the parameters on which they commented.

Patient outcomes, quality of life, and overall health: Overall, commenters considered apremilast to be effective and well tolerated for treating oral ulcers and pain due to Behçet’s disease. This rare disease has limited treatment options and can complicate eating and drinking as well as other health outcomes and QoL parameters. However, a researcher commented that apremilast use resulted in health improvements similar to TNF inhibitors, and another noted that its comparable efficacy to colchicine and azathioprine is unknown.

Health disparities: Most commenters thought that the high cost of apremilast combined with copayment assistance programs for patients with private insurance would likely lead to health disparities in patients with government insurance or those who are uninsured. However, a researcher noted that the oral administration of apremilast might reduce health disparities in patients with low health literacy who would not need to learn to self-inject TNF inhibitors. However, these patients would need to remember to take pills twice daily.

Health care delivery system: Commenters agreed that apremilast would have a minimal impact on the health care delivery system because of the simple oral administration of the drug combined with the small number of patients with Behçet’s disease.
**Current paradigm of patient care:** Overall, commenters thought that apremilast could disrupt care paradigms due to its enhanced convenience and improved tolerability, which might improve adherence, reduce the need for patient monitoring, and reduce complications such as infections and drug toxicity, thereby reducing overall burden to the health care system. A commenter with a clinical perspective noted that current treatment options for Behçet’s disease are limited by poor efficacy and substantial toxicity. This clinician thought that the safety and efficacy would likely make it standard of care. However, a researcher thought that apremilast should be considered only in people who have not responded to other agents first, which might limit its potential to disrupt the current standard of care. This commenter also thought that patient outcomes were similar to those reported for TNF inhibitors, somewhat limiting disruptions to care, and thought that comparative trials are needed to determine apremilast’s role in Behçet’s disease management.

**Health care costs:** Commenters agreed that apremilast would substantially add to treatment costs in patients who have used traditional anti-inflammatory agents such as colchicine. However, costs to the system might be similar to those of TNF inhibitors. Reduced complications from toxicity and infections might reduce costs to the system. Commenters agreed that costs to patients would largely depend on their insurance status.

**Overall disruption potential:** Overall, commenters thought that apremilast has the potential to moderately disrupt treatment paradigms for oral ulcers associated with Behçet’s disease. One commenter with a clinical perspective thought that apremilast could become the first-line standard of care because of its safety and efficacy and the lack of FDA-approved treatments. A commenter with a health systems perspective thought that apremilast could disrupt care by decreasing the number of providers that a single patient requires for care, which currently includes dentists, dermatologists, pulmonologists, and gynecologists. However, another health systems commenter thought cost would be the single biggest factor affecting the adoption and downstream disruption potential of apremilast. A researcher commented on the importance of examining additional disease outcomes, such as visual symptoms, disease progression, and QoL. Another researcher commented that efficacy comparisons are needed between apremilast and the current standard of care. Two researchers agreed that although apremilast seems effective in reducing oral ulcer frequency and pain, longer-term comparative efficacy trials with standard-of-care options (including concomitant steroids) are needed to better understand the role of apremilast in managing Behçet’s disease.

**Caplacizumab-yhdp (Cablivi) to Treat Acquired Thrombotic Thrombocytopenic Purpura**

**Highlights**

In February 2019, caplacizumab-yhdp, an injected therapy, became the first FDA-approved agent indicated for treating acquired thrombotic thrombocytopenic purpura (aTTP). This rare, potentially fatal autoimmune disease is estimated to affect fewer than 2000 US adults each year. Pivotal trial results suggest caplacizumab-yhdp might greatly reduce the composite rate of aTTP-related death, aTTP recurrence, or thromboembolic events. Caplacizumab’s list price is $270,000 for a course of treatment, and the US Centers for Medicare & Medicaid Services has granted caplacizumab-yhdp a New Technology Add-on Payment (NTAP). The 5 stakeholders...
commenting on this topic agreed that caplacizumab-yhdp could have a positive impact on patient outcomes compared with the standard of care for aTTP.

**Patient Population**

Caplacizumab-yhdp (Cablivi) is intended for treating adults aged 18 years or older with a diagnosis of aTTP.

**Intervention**

Caplacizumab-yhdp is a selective, bivalent antibody fragment intended to treat aTTP by targeting von Willebrand factor. Purplish bruises (purpura) on the skin or mucous membranes are a hallmark of aTTP, and other common symptoms include fever, nausea, rapid heart rate, headache, speech changes, confusion, or seizure. This rare autoimmune disease develops when the body produces autoantibodies against the ADAMTS13 enzyme (ie, von Willebrand factor–cleaving protease), which is involved in regulating the blood-clotting protein, von Willebrand factor. Caplacizumab-yhdp purportedly inhibits the interaction between von Willebrand factor and platelets by targeting the von Willebrand factor A1 domain, potentially blocking ultra-large von Willebrand factor–mediated platelet interactions and formation of the string-like blood clots that are characteristic of aTTP.

Caplacizumab-yhdp is intended for use in patients who are also receiving plasma exchange and immunosuppressive therapies (eg, rituximab). The recommended first dose of caplacizumab-yhdp is an 11-mg bolus IV injection at least 15 minutes before initial plasma exchange in a clinic or hospital setting, with an 11-mg subcutaneous caplacizumab-yhdp injection after the first plasma exchange treatment.

After each daily plasma exchange, a subcutaneous caplacizumab-yhdp injection (11 mg) is administered. These injections continue to be administered for another 30 days after the last of the plasma exchange sessions. Patients self-inject under the skin (ie, subcutaneously) at home, or a family caregiver administers the injection, as appropriate. If signs of aTTP persist (eg, suppressed ADAMTS13 activity) after the initial treatment course, physicians may prescribe an additional 28 days of daily caplacizumab-yhdp subcutaneous injections.

The therapy might increase risk of bleeding or bruising. Patients are advised to discontinue caplacizumab-yhdp use if they experience more than 2 aTTP recurrences while taking it.

For more information about aTTP, see the [National Institutes of Health’s Genetic and Rare Diseases Information Center website](https://www.ncbi.nlm.nih.gov).}

**Evidence Development Summary**

The manufacturer continues to evaluate caplacizumab-yhdp in an international trial involving up to 10 US centers.

The ongoing single-arm, phase III Post-HERCULES trial (NCT02878603) is intended to assess the long-term safety and efficacy of caplacizumab-yhdp therapy administered as an initial IV infusion followed by daily subcutaneous injections for 6 months. The trial is designed with multiple primary endpoints through the 36-month follow-up visit or until 7 days after treatment ends (whichever is latest). The endpoints include the following:

- Death rate
- Proportion of patients with aTTP-related events and disease recurrence
- Number of and time to aTTP-related events
• Number of and time to disease recurrences
• Proportion of patients with reported major thromboembolic events
• Number of and time to major thromboembolic events
• Change from baseline in cognitive function and QoL
• Number of patients with antidrug antibodies
• Incidence of adverse events

The trial is enrolling about 104 adults aged 18 years or older with aTTP who completed the HERCULES trial. The follow-up trial’s primary completion date is October 2020.367

Sanofi has initiated a single-arm phase II/III trial of caplacizumab-yhdp in Japan to treat aTTP in up to 18 adults aged 18 years or older. The primary outcome will assess caplacizumab-yhdp effectiveness, defined by the proportion of participants who experience aTTP recurrence during treatment. Secondary outcomes include pharmacokinetics, pharmacodynamics, safety, and immunogenicity of caplacizumab-yhdp. The trial is scheduled to complete in January 2021.368

The phase III randomized controlled HERCULES trial (NCT02553317) compared placebo and caplacizumab-yhdp administered after daily plasma exchange and then for 30 days after completing plasma exchange therapy in 145 adults aged 18 years or older who had aTTP.369 The caplacizumab-yhdp group had a shorter median time to platelet count normalization (primary outcome) than did the placebo group (2.69 days, [95% CI, 1.89-2.83] vs 2.88 days [95% CI, 2.68-3.56] \( P = .01 \)). After 6 months, caplacizumab-yhdp patients were 1.55 times as likely as placebo patients to experience a platelet count normalization.

The composite measure of aTTP-related death, aTTP recurrence, or a thromboembolic event, a key secondary outcome, was significantly lower in the caplacizumab-yhdp group than in the placebo group (12% vs 49%; \( P < .001 \)). Recurrence of aTTP during the trial was significantly lower in the caplacizumab-yhdp group than in the placebo group (12% vs 38%; \( P < .001 \)). Caplacizumab-yhdp group patients needed fewer plasma exchanges and had shorter hospitalizations than placebo group patients. No caplacizumab-yhdp group patients developed refractory disease, compared with 3 patients in the placebo group.

Mucocutaneous bleeding (ie, in the junction between skin and mucous membranes), the most common adverse event, occurred in 65% of the caplacizumab-yhdp group and in 48% of the placebo group. One caplacizumab-yhdp group patient died from cerebral ischemia after the treatment period, and 3 placebo group patients died during the trial treatment period.369

Manufacturers and Regulatory Status

Ablynx NV (Ghent, Belgium), a Sanofi SA (Paris, France) company, manufactures caplacizumab-yhdp. On February 6, 2019, FDA approved Ablynx’s Biologics License Application for caplacizumab-yhdp, under the trade name Cablivi, to treat aTTP in adults in combination with plasma exchange and immunosuppressive therapy.364-366 FDA previously granted caplacizumab-yhdp Orphan Drug, Fast Track, and Priority Review designations.364-366

Cost Information

According to Sanofi, caplacizumab-yhdp has a wholesale acquisition cost of $270 000 for treating a typical aTTP episode. The company reportedly has launched a patient assistance program to provide financial support to eligible patients to access caplacizumab-yhdp therapy.364
On October 10, 2019, Sanofi announced the US Centers for Medicare & Medicaid had granted NTAP status, intended to encourage use of costly new medical technologies in the hospital setting, for caplacizumab-yhdp, as part of the 2020 Inpatient Prospective Payment System (IPPS). Sanofi reported that under the NTAP, acute care hospitals reimbursed under the IPPS might receive up to $32,215 per qualifying case for caplacizumab-yhdp treatment. According to the company, the NTAP for caplacizumab-yhdp became effective October 1, 2019, and will remain in effect for a minimum of 2 years, but will not exceed 3 years.

**Results and Discussion of Stakeholder Comments**

Five stakeholders, reflecting clinical, research, and health systems perspectives, provided comments and ratings on caplacizumab-yhdp for treating aTTP. Comments were received after FDA approval but before the NTAP announcement. We have organized the following discussion of stakeholder comments by the parameters on which they commented.

**Patient outcomes, quality of life, and overall health:** Overall, commenters thought that caplacizumab-yhdp use could have a moderate to large positive disruption on patient outcomes compared with the standard of care for aTTP, especially because it is the first therapy FDA has approved to treat aTTP. Two clinicians noted that the secondary outcomes in the HERCULES trial, including a 74% reduction in the composite of death, major thrombosis, or disease recurrence, appeared more impressive than the primary outcome (shortened time to platelet recovery) and might be more clinically meaningful for patients. One of the clinicians stated, “The difference in early recurrence will be the major benefit of caplacizumab” and should help prevent aTTP exacerbations. One researcher predicted a smaller disruptive potential due to the likely small number of patients who might receive caplacizumab to treat aTTP.

**Health disparities:** Commenters generally agreed that the availability of caplacizumab-yhdp is unlikely to reduce health care disparities but could increase them, based on the drug’s high cost and the quality of patients’ insurance coverage. One clinician suggested that health care administrators would be disinclined to use caplacizumab-yhdp in patients without insurance coverage for the drug, given the small mortality benefit and the general effectiveness of standard therapy in most patients with aTTP. A researcher anticipated that caplacizumab-yhdp would increase disparities because it is an expensive, perishable immunochemical targeting a rare disease and might be stocked only at large tertiary centers, thus limiting rural patients’ access to this treatment.

**Health care delivery system:** Commenters thought that caplacizumab-yhdp therapy would not likely substantially disrupt the health care delivery system because it is additive to plasma exchange therapy for a rare condition. A clinician commented that the addition of caplacizumab-yhdp would reduce the need for inpatient treatment of acute aTTP episodes and shift more of that care to the outpatient setting. This commenter also expected a learning curve for clinicians, especially those with less experience treating aTTP.

**Current paradigm of patient care:** Three commenters with clinical and health systems perspectives expected caplacizumab-yhdp to create moderate to large disruptions to current treatment protocols for aTTP, especially when drug cost and insurance coverage availability are considered. One clinician thought that the most compelling argument for its use would likely be its ability to reduce aTTP exacerbations and refractory disease. This commenter also anticipated controversies surrounding caplacizumab-yhdp use that would likely
affect how widely it is integrated into care for aTTP. One likely controversy involves appropriate patient selection and cost-effectiveness in different subgroups with varying disease severity (eg, severe aTTP with neurologic or cardiac involvement). This commenter also expected a continued debate on how long caplacizumab-yhdp therapy should be continued to achieve maximal clinical benefit, especially in conjunction with intensive immunosuppression (with rituximab). Two commenters with research and health systems perspectives anticipated a small disruption to current treatment protocols for aTTP, given that caplacizumab-yhdp is adjunctive therapy.

Health care costs: Two clinicians and a health systems commenter thought caplacizumab-yhdp’s cost (about $270 000 wholesale acquisition cost per treatment regimen) would cause a large disruption in treatment costs for aTTP, at least initially. One of the clinicians stated, “The increased cost to payers and patients may lead to controversy. Some payers are already reluctant to pay for rituximab, which reduces relapses, and [caplacizumab-yhdp] arguably has more long-term benefit than rituximab.” Another clinician anticipated that cost disruption could be minimized in the long term if additional evidence were to demonstrate that caplacizumab-yhdp could substantially reduce the frequency of plasma exchange, aTTP-related hospitalizations, and lengths of stay. A researcher and health systems commenter did not expect caplacizumab-yhdp use to cause much disruption to health care costs, generally because of the rarity of aTTP.

Overall disruption potential: Commenters were divided on the overall disruptive potential of caplacizumab-yhdp, largely given the expected small number of patients likely to receive it. Three commenters with clinical and health systems perspectives expected caplacizumab-yhdp use to cause at least a moderate disruption overall. One clinician noted, “The interplay among safety, efficacy, and cost will be the final determining factors for the use of Cablivi.” Another clinician noted, “Though there is a considerable reduction in the rate of recurrence, particularly early recurrence, which is the most compelling argument for use, this might be offset by earlier use of rituximab. In summary, [caplacizumab-yhdp] would be nice to have for all patients, but cost may limit use.” One commenter with a health systems perspective noted the lack of existing clinical guidelines for aTTP treatment from US-based guideline developers; this commenter proposed that new guidelines could be developed with the recent availability of caplacizumab-yhdp as the first FDA-approved treatment for aTTP.

Casimersen to Treat Duchenne Muscular Dystrophy

Highlights

No Duchenne muscular dystrophy (DMD) cure is available, and the approved targeted treatments apply to only a small subset of genetic variants known to be involved in DMD. Therapies that target additional DMD-causing variants are needed. Casimersen purportedly promotes exon 45 skipping during dystrophin mRNA processing, which allows synthesis of an internally truncated but functional dystrophin protein in patients with DMD who have exon 45 mutations. According to interim data from an ongoing phase III trial, casimersen appears to increase dystrophin production as intended.

The 8 stakeholders commenting on this topic agreed that casimersen has the potential to positively impact longer-term health outcomes, which will be reported upon completion of the phase III trial. Additionally, casimersen’s expected high cost and weekly IV infusion schedule
are likely to increase health disparities and might limit diffusion. Initial increases in health care resource use associated with treatment administration and monitoring might be offset by decreases in long-term care needs if the drug slows or halts DMD progression.

**Patient Population**

Casimersen is intended for males aged 7 to 23 years who have DMD with an exon 45 rearrangement in the dystrophin gene, DMD, and who are on a stable dose of corticosteroids.

**Intervention**

DMD is an inherited, X chromosome–linked genetic disorder caused by point rearrangements or deletions in the dystrophin gene, DMD. DMD encodes the dystrophin protein, which helps promote muscle function. In patients with DMD, the absence of wild-type dystrophin protein causes progressive muscle death and eventual widespread muscle weakness. No cure for DMD is available, and while FDA has approved a dystrophin-replacement gene therapy for patients who have a specific mutation in DMD (ie, in exon 51), the therapy is not suitable for patients with other mutations.

Casimersen, also known as SRP-4045, is a phosphorodiamidate morpholino oligomer (PMO) that purportedly binds exon 45 of dystrophin pre-mRNA (precursor RNA composed of introns and exons) and promotes skipping of exon 45 during mRNA processing. This allows synthesis of an internally truncated but functional dystrophin protein. Therefore, casimersen treatment might promote skeletal muscle function and prevent or delay disease progression in patients with DMD who have DMD exon 45 variants (about 9% of patients with DMD).

In clinical trials, IV casimersen 30 mg/kg is administered once weekly, for up to 144 weeks.

The Muscular Dystrophy Association provides more information on DMD.

**Evidence Development Summary**

The ongoing phase III ESSENCE trial (NCT02500381) is intended to assess the effectiveness and safety of 30 mg/kg of casimersen or 30 mg/kg of golodirsen vs placebo. The trial plans to enroll 222 males aged 7 to 13 years with DMD who have either exon 45 or exon 53 variants. The primary outcome is the 6-minute walk test distance at baseline and week 96. Secondary outcomes include dystrophin expression at baseline and weeks 48 or 96, and several measures of ambulatory function, loss of ambulation, and lung function, all at week 96. The primary completion date is May 2022.

The manufacturer reported interim data from the casimersen and placebo arms of the ESSENCE study in March 2019. Patients with exon 45 variants received either a once-weekly IV infusion of casimersen dosed at 30 mg/kg (n = 27) or placebo (n = 16) for 96 weeks. The interim analysis was performed on data from biopsies of the biceps muscle at baseline and during treatment at week 48. In the casimersen group, mean dystrophin protein (percentage normal dystrophin, as measured by Western blot assay) increased to 1.736% of normal compared to a mean baseline of 0.925% of normal (P < .001). A statistically significant difference in the mean change from baseline to week 48 in dystrophin protein was observed between the casimersen-treated group and the placebo group (P = .009). Of 22 patients who received casimersen and were tested for increased exon-skipping mRNA using reverse transcription polymerase chain reaction (RT-PCR), all had an increase in skipping exon 45 (P < .001) over their baseline levels. According to the manufacturer, this increase represents a 100% response rate. Also, a statistically
significant positive correlation between exon 45 skipping and dystrophin production was observed (Spearman rank correlation = 0.635; \( P < .001 \)).

A separate phase III open-label extension study (NCT03532542) is enrolling patients who completed the ESSENCE trial or other manufacturer-sponsored trials and includes an expanded patient population aged 7 to 23 years. The primary outcome is the incidence of SAEs measured through week 148 after treatment. The study’s primary completion date is June 2026.

Manufacturers and Regulatory Status

Sarepta Therapeutics, Inc (Cambridge, Massachusetts) is developing casimersen to treat DMD. The drug is in phase III clinical development for this indication. Its manufacturer announced that it plans to submit a New Drug Application to treat DMD in the first half of 2020.\(^3\)\(^8\)\(^0\) FDA granted the drug Orphan Drug designation for this indication in June 2019.\(^3\)\(^8\)\(^1\)

Results and Discussion of Stakeholder Comments

Eight stakeholders, reflecting physical therapy, caregiver, clinical, research, and health systems perspectives, provided comments and ratings on casimersen for treating DMD.\(^3\)\(^8\)\(^2\)-\(^3\)\(^8\)\(^9\) We have organized the following discussion of stakeholder comments by the parameters on which they commented.

**Patient outcomes, quality of life, and overall health:** Most commenters agreed that casimersen increases dystrophin expression as intended, although one researcher\(^3\)\(^8\)\(^8\) questioned whether the increase was clinically meaningful. Despite the lack of longer-term data on muscle and ambulatory function (which is expected to be reported after completion of the ESSENCE trial), commenters thought that the drug has the potential to positively impact these patient health outcomes.

**Health disparities:** Most commenters thought that casimersen’s anticipated high cost might increase health disparities for uninsured and underinsured patients. Additionally, 2 commenters with health systems\(^3\)\(^8\)\(^3\) and caregiver\(^3\)\(^8\)\(^5\) perspectives thought that the drug’s weekly IV delivery method could also increase health disparities.

**Health care delivery system:** Most commenters thought that casimersen’s weekly IV infusion regimen would lead to increased health care use, although one researcher\(^3\)\(^8\)\(^8\) questioned whether patients would be able to adopt an alternate long-term dosing schedule. Two caregivers\(^3\)\(^8\)\(^4\),\(^3\)\(^8\)\(^5\) thought that long-term health care use might decrease if the drug slows disease progression and improves patient health outcomes. However, the researcher\(^3\)\(^8\)\(^8\) thought the evidence was insufficient to determine whether the drug would shift care from an inpatient to outpatient setting.

**Current paradigm of patient care:** Because patients will need to visit infusion centers weekly to receive casimersen and will require regular monitoring and follow-up, most commenters thought that patients would initially have more interaction with their health care providers. Commenters thought that patients receiving casimersen would be likely to have prolonged ambulatory function. However, 2 clinicians\(^3\)\(^8\)\(^6\),\(^3\)\(^8\)\(^7\) and a caregiver\(^3\)\(^8\)\(^4\) noted that casimersen’s cost might limit its diffusion. Additionally, 2 of the 3\(^3\)\(^8\)\(^4\),\(^3\)\(^8\)\(^7\) thought that controversy would likely arise over whether the drug’s effect on dystrophin production and the magnitude of clinical improvement will justify its cost, which could also limit acquisition and insurance
coverage. A researcher\textsuperscript{388} noted that the drug transiently accumulated in the kidneys and that the long-term impact on kidney function is unknown.

**Health care costs:** All commenters thought that casimersen will likely be expensive, and patients and clinicians might find obtaining insurance coverage difficult. One caregiver\textsuperscript{385} noted that continued use of a costly drug might be controversial if the long-term effects become evident only years after treatment.

**Overall disruption potential:** Commenters generally agreed that the drug has large potential for disruption in the 9\% of patients with DMD who have exon 45 mutations, but they thought that longer-term data are needed.

**Crizanlizumab-tmca (Adakveo) to Prevent Vaso-Occlusive Crises From Sickle Cell Disease**

**Highlights**

The only FDA-approved treatment for vaso-occlusive sickle cell crises is ineffective in about one-third of patients, and more effective treatments are needed. Crizanlizumab-tmca (Adakveo) is a humanized monoclonal antibody that blocks P-selectin’s interaction with glycoprotein ligand 1 to inhibit the inflammatory and adhesion processes thought to be involved in vaso-occlusive crises (VOCs).

The 7 stakeholders commenting on this topic were generally optimistic about crizanlizumab-tmca’s potential to improve health outcomes and QoL by reducing the number of and increasing the time between hospitalizations from sickle cell disease (SCD) crises. However, monthly infusions required for administering crizanlizumab-tmca would likely disrupt current treatment paradigms and increase costs, because the standard-of-care treatment, hydroxyurea, is an oral therapy. This could increase disparities. Still, if crizanlizumab-tmca leads to fewer hospitalizations, this could reduce the acute care burden on the system and opioid management, potentially saving costs (contingent on final pricing and reimbursement).

**Patient Population**

Crizanlizumab-tmca is indicated for patients aged 16 years or older to reduce the frequency of VOCs in people with SCD.

**Intervention**

*Inherited SCD-inducing genetic rearrangements* alter the shape of hemoglobin molecules, resulting in sickled red blood cells (RBCs) that are more susceptible to oxidative damage, inappropriate adhesion, and vascular obstruction, which can lead to severely painful VOCs, requiring hospitalization.\textsuperscript{390} For more information on SCD, see the National Heart, Lung, and Blood Institute website.

VOCs are thought to be associated with several processes, including chronic inflammation, erythrocyte microvascular occlusion, impaired oxygen supply, and infarction-reperfusion injury. SCD progresses with age, and with it the frequency of VOCs and complications and an increasing risk of death.\textsuperscript{391} Patients may progress to thromboembolic events, stroke, organ failure, or early death. An FDA-approved treatment for SCD, hydroxyurea, can reduce VOC incidence, but it is ineffective in about one-third of adult patients.\textsuperscript{390,392} Another FDA-approved
treatment for SCD, L-glutamine (Endari), has not been proven to significantly reduce the frequency of sickle cell crises or related hospital visits, according to a negative opinion offered by the European Medicines Agency in May 2019.393

Crizanlizumab-tmca (Adakveo) is a humanized monoclonal antibody against P-selectin, blocking P-selectin’s interaction with glycoprotein ligand 1.391 P-selectin is expressed on the surface of endothelial cells and platelets and is thought to promote the inflammatory and adhesion processes involved in VOC.391,394 Crizanlizumab-tmca is administered by IV infusion at a dosage of 5 mg/kg, over a period of 30 minutes on weeks 0 and 2, and every 4 weeks thereafter.395

Evidence Development Summary

The phase II SUSTAIN trial (NCT01895361) involved patients (n = 198) aged 16 to 65 years with SCD who had had 2 to 10 VOCs in the prior 12 months and may also have been receiving hydroxyurea. Patients were randomly assigned in a 1:1:1 ratio to IV treatment with crizanlizumab-tmca 2.5 mg/kg (n = 66) or 5.0 mg/kg (n = 67), or placebo (n = 65) 4 times over 52 weeks.396

Patients given crizanlizumab-tmca achieved the primary endpoint of a reduced median rate of crises per year in the high-dose crizanlizumab-tmca group vs placebo (1.63 vs 2.98; 45.3% VOC reduction; \( P = .01 \)). High-dose crizanlizumab-tmca also increased the median time to first crisis (4.07 vs 1.38 months; \( P = .001 \)) and second crisis (10.32 vs 5.09 months; \( P = .02 \)) compared with placebo. High-dose crizanlizumab-tmca also lowered the median rate of uncomplicated crises per year by 62.9\% (\( P = 0.02 \)). The most common adverse events in patients taking crizanlizumab-tmca included joint pain, chest pain, diarrhea, itching, and vomiting.396

Manufacturers and Regulatory Status

Crizanlizumab-tmca was developed by Novartis AG (Basel, Switzerland). On November 15, 2019, FDA approved crizanlizumab-tmca for reducing the frequency of VOCs in children aged 16 years or older and adults with SCD.395 In July 2019, FDA had accepted the company’s Biologics License Application and granted crizanlizumab Priority Review.397 FDA had granted crizanlizumab Breakthrough Therapy designation for preventing VOCs in patients with SCD in January 2019.394

Cost Information

Crizanlizumab-tmca is estimated to cost about $84,852 to $113,136 per patient annually. This cost was derived from the wholesale acquisition cost of $2357 per vial and weight-based dosing, which assumes that most patients will require 3 or 4 vials each month for treatment.398

Results and Discussion of Stakeholder Comments

Seven stakeholders, reflecting caregiver, clinical, health systems, nursing, and research perspectives, provided comments and ratings on crizanlizumab.399-405 We have organized the following discussion of stakeholder comments by the parameters on which they commented.

Patient outcomes, quality of life, and overall health: Most commenters considered crizanlizumab effective for preventing VOCs and increasing the time between VOCs in patients in whom hydroxyurea is ineffective or intolerable. Clinical and caregiver commenters also thought that crizanlizumab would have a greater impact on improving health outcomes if effective for various SCD variants (such as HbSS, HbSC, HbSβ⁰-thalassemia, or HbSβ⁺-
thalassemia).400,402 One clinician commented that crizanlizumab might become the first effective drug indicated for patients with the HbSC form of the disease.402 One commenter with a research perspective stated concern for whether the clinical response to crizanlizumab was sustainable and whether long-term adverse events or adherence would become an issue.405

Health disparities: A caregiver noted that if crizanlizumab can effectively treat patients, it could reduce disparities by offering a new treatment option for patients with limited options.400 Also, a nurse noted that, because patients with SCD have few treatment options (including hydroxyurea and opioids), they can sometimes be portrayed as drug seekers because they have no way to manage pain. Reduced crises and pain would reduce demands on the system as well as mitigate opioid abuse in this patient population.404

A researcher, a nurse, and a health systems commenter thought that disparities in rural areas or other areas with transportation barriers might occur because of the requirement for 14 infusion visits annually to administer crizanlizumab.399,403,405 A clinician, nurse, health systems commenter, and caregiver estimated that about 75% of patients with SCD have public insurance (50% Medicaid, 25% Medicare), which might not cover crizanlizumab, and patients with private insurance might have high copayments for infusion visits, potentially creating disparities.399,400,402,403 However, another clinician commented that the increased development of new SCD treatments is a positive trend for decreasing disparities.401

Another clinician noted that people with SCD have difficulty finding providers in the community setting who want to take care of them—this reluctance is due to typically low reimbursement rates combined with high resource use for social work, opioid management, etc. A new IV therapy might gain favorable reimbursement, thereby encouraging providers to accept these patients.402

Health care delivery system: Most commenters agreed that reducing VOCs would reduce the burden on the health system in terms of acute care, but monthly administration of crizanlizumab would increase demands on infusion centers. A caregiver, a clinician, a health systems commenter, and a nurse thought that lack of reimbursement might be a barrier to diffusion, thereby limiting its overall disruption to the health care system.399-401,403

Current paradigm of patient care: One clinician thought hydroxyurea should remain first-line therapy because it increases hemoglobin count and potentially offers a survival benefit, which crizanlizumab has not demonstrated.402 A researcher thought that shifting care from oral hydroxyurea to infused crizanlizumab would also change the treatment paradigm.405 Commenters with health systems and clinical perspectives also agreed that crizanlizumab might be used in a select group of patients with SCD because of financial or clinical reasons, including people with the HbSC variant genotypes who receive limited benefit from hydroxyurea (L-glutamine [Endari, FDA approved for SCD treatment in 2017] is available for HbSS disease).399,402 Another clinician warned that many patients with SCD have poor venous access, although that could be overcome by using ports and catheters.401

Health care costs: Overall, commenters agreed that crizanlizumab use, even if costly, might save money by reducing hospitalizations. However, this is highly contingent on the final price of the biologic, which would also highly influence diffusion because of reimbursement and copayments per infusion. One clinician noted, for benchmarking purposes, that IV-administered
L-glutamine was approved in 2017 for treating SCD and costs about $3000 per month, and crizanlizumab would likely be priced similarly or be more costly.\textsuperscript{402}

**Overall disruption potential:** Commenters generally agreed that crizanlizumab demonstrated potential to decrease the number of SCD hospitalizations and increase the time between hospitalizations due to VOCs, which could change the current standard of care for patients seeking better VOC management. Commenters also agreed that larger, longer-term studies are needed to better understand the full disruptive potential of crizanlizumab and which patients would benefit most from its use.

Fenfluramine Hydrochloride Low-dose (Fintepla) to Treat Dravet Syndrome

**Highlights**

Low-dose fenfluramine (FFA) hydrochloride (Fintepla) purportedly treats Dravet syndrome by both positively modulating sigma 1 receptors (Sig-1Rs) in the patient’s brain and modulating serotonergic neurotransmission to alleviate seizures.\textsuperscript{406} The 5 stakeholders commenting on this topic agreed FFA has moderate to large potential to improve patient outcomes, quality of life, and overall health, and moderate to large overall potential to cause disruption. Many commenters thought FFA might change the current standard of care, and a commenter with a patient advocate perspective thought FFA might become a first- or second-line treatment for Dravet syndrome.\textsuperscript{407} Commenters generally agreed FFA might decrease the costs and burden associated with ED visits and hospitalization by reducing seizure frequency.

**Patient Population**

FFA is intended for children aged 2 to 8 years and adults aged 18 to 35 years with Dravet syndrome who are taking 1 or more antiepileptic drugs.

**Intervention**

Low-dose FFA is an amphetamine derivative being developed as adjunctive therapy for treating Dravet syndrome—a rare, severe, infantile-onset form of epilepsy usually caused by a rearrangement in the sodium voltage-gated channel alpha subunit 1 gene, \textit{SCN1A}. Patients with Dravet syndrome have prolonged seizures that are difficult to control with FDA-approved antiepileptic drugs and typically experience cognitive impairment, behavioral problems, muscle weakness, and sleep disorders.\textsuperscript{408}

FFA has been recognized as promoting serotonin release, but this alone is not believed to account for its purported beneficial effects on seizure activity because other serotonin reuptake inhibitors have not shown benefits for managing epilepsy. Recent research found other activity that might account for effects observed in early studies after FFA administration for epilepsy treatment: FFA binds to sigma receptors and acts as a positive allosteric modulator of Sig-1R and alters activity at the Sig-1R when at physiologically relevant concentrations. This activity is thought to block seizure activity and modulate serotonergic neurotransmission.\textsuperscript{406}

In clinical trials, patients themselves take or caregivers give an oral, sugar-free (ie, ketogenic diet–compatible) solution of FFA twice daily in equal doses totaling 0.2, 0.4, or 0.8 mg/kg/day (up to a maximum of 20 or 30 mg/day), for up to 156 weeks.
Evidence Development Summary

Investigators have reported results from 4 trials of FFA to treat Dravet syndrome, ZX008-1503 (NCT02823145), ZX008-1504 (NCT02926898), and ZX008-1501 (NCT02682927) and ZX008-1502 (NCT02826863) pooled together.

In the phase III ZX008-1503 single-arm, open-label extension trial, patients aged 2 to 35 years were eligible to enroll if they had participated in study 1501 or 1502. Patients received a titrated effective dose of FFA beginning with 0.2 mg/kg/day up to a maximum of 30 mg/day as an adjunctive therapy to antiepileptic drugs for up to 156 weeks. The trial was to recruit up to 340 patients. Interim results (median 256 days) presented in December 2018 on 232 patients aged 2 to 19 years indicated that “the median decrease in [monthly] convulsive seizure frequency was –66.8% (range, –100% to 234.9%; \( P < .001 \)).”

Most patients responded to FFA, and 64.4% of patients demonstrated clinically meaningful (more than 50%) reduction in seizure frequency. Profound reductions in seizure frequency (75% or more) were reported in 41.2% of patients. The following adverse events were reported (incidence): fever (21.6%), cold-like symptoms (19.4%), decreased appetite (15.9%), diarrhea (10.8%), and upper respiratory tract infection (10.3%).

In the phase III ZX008-1504 RCT, patients aged 2 to 18 years \((n = 87)\) who were receiving stiripentol were given either FFA 0.5 mg/day \((n = 43)\) or placebo \((n = 44)\) as an adjunctive therapy for 12 weeks. The percentage difference from placebo in mean monthly convulsive seizure frequency for FFA was 54% \((P < .001)\). The median reduction from baseline in monthly convulsive seizure frequency was 1.1% for placebo and 63.1% for Fintepla \((P < .001 vs\) placebo).410

In the 2 phase III ZX008-1501 and ZX008-1502 parallel assignment, placebo-controlled trials, patients aged 2 to 18 years \((n = 130)\) with Dravet syndrome whose seizures were incompletely controlled with antiepileptic drugs were assigned to receive FFA 0.2 or 0.8 mg/kg/day up to a maximum of 30 mg/day as an adjunctive therapy to antiepileptic drugs. The percentage difference from placebo in mean monthly convulsive seizure frequency for FFA 0.2 mg/kg/day was 33.7% \((P = .019)\) and FFA 0.8 mg/kg/day was 63.9% \((P < .001)\). The median percentage reduction from baseline in monthly convulsive seizure frequency for placebo was 17.4%; for FFA 0.2 mg/kg/day, 37.6% \((P = .19 vs\) placebo); and for FFA 0.8 mg/kg/day, 72.4% \((P < .001 vs\) placebo).411

The phase III ZX008-1501, ZX008-1502, and ZX008-1503 trials are ongoing. Primary completion dates for the trials are December 2019 and January 2020.

Manufacturers and Regulatory Status

FFA is being developed by Zogenix, Inc (Emeryville, California). The company initially submitted a New Drug Application to FDA in February 2019.412 FDA issued a refusal to file letter on April 8, 2019, citing missing and incorrect data.413 Zogenix resubmitted a New Drug Application to FDA on September 26, 2019.414

FDA had granted FFA Orphan Drug and Breakthrough Therapy designations in February 2018,415 and Fast Track designation in January 2016416 to treat Dravet syndrome. FFA is also in phase III clinical development for treating Lennox-Gastaut syndrome, a rare, severe form of infantile- or childhood-onset epilepsy.
Results and Discussion of Stakeholder Comments

Five stakeholders, reflecting health systems, caregiver, clinical, patient advocate, and research perspectives, provided comments and ratings on FFA to treat Dravet syndrome.\textsuperscript{407,417-420} We have organized the following discussion of stakeholder comments by the parameters on which they commented.

**Patient outcomes, quality of life, and overall health:** Commenters agreed that FFA has moderate to large potential to improve patient outcomes, QoL, and overall health. All 5 commenters referenced the statistically significant seizure reduction seen in patients taking FFA in the clinical trials as being significant. A patient advocate commented that a reduction in seizure frequency might improve QoL for both the patient and family, citing reasons including fewer trips to the ED, less time the patient would spend in a postictal state, reduced risk for injury during a seizure, and decreased anxiety and fear for patients and caregivers.\textsuperscript{407} A caregiver commented similarly that seizure frequency reduction might improve patient QoL.\textsuperscript{418}

Commenters with clinical\textsuperscript{419} and research\textsuperscript{420} perspectives thought that the trials were of high quality\textsuperscript{419} and well designed,\textsuperscript{420} although the researcher noted that an area of concern might be that the trials lacked consistency in which adjunctive antiepileptic medicines participants were taking. The patient advocate noted that no data were reported regarding the duration of seizures, stating that this would be important to know since status epilepticus is common among patients with Dravet syndrome.\textsuperscript{407}

A patient advocate\textsuperscript{407} and a researcher\textsuperscript{420} had similar thoughts regarding the reported side effects: While the reported side effects were acknowledged as “not insignificant,”\textsuperscript{420} they “are already common side effects of other antiepileptic drugs and/or common issues with Dravet patients”\textsuperscript{407} and “appear to be an acceptable tradeoff if the rates of seizures are brought down that dramatically.”\textsuperscript{420}

**Health disparities:** Commenters generally agreed that FFA treatment does not have significant potential to disrupt health disparities. A caregiver commented that FFA might have small potential to increase disparities in that patients who live in large cities and have access to large institutions might have greater access to this treatment than would patients who live in smaller cities and go to smaller hospitals.\textsuperscript{418} Conversely, a researcher commented that the intervention has the ability to decrease disparities and increase access considering the oral medication might be more accessible than adherence to a ketogenic diet, use of Epidiolex, or vagus nerve stimulation devices.\textsuperscript{420} Commenters with health systems\textsuperscript{417} and clinical\textsuperscript{419} perspectives thought that cost might limit access to FFA but did not comment that this would disrupt health disparities.

**Health care delivery system:** Commenters agreed on average that FFA has moderate potential to disrupt the health care delivery system. The health systems commenter thought the management of this population might change with a seizure frequency reduction of 50\% or more.\textsuperscript{417} A caregiver elaborated that “more patients can be treated, the amount of time patients spend receiving care would be lessened (less time in the hospital), a higher level of care, the process for delivering care would be easier, the care setting would change from inpatient to outpatient, and less staff would be needed to deliver care using this treatment.”\textsuperscript{418} A clinician similarly thought that any effective treatment might provide relief from the societal cost and patient risk to life of frequent hospitalizations, stays in intensive care units, and death from
SUDEP (sudden unexpected death in epilepsy); limit unnecessary trials of ineffective medications; and lessen patients’ need for caregiver support and supervision. A commenter with a patient advocate perspective noted that while the number of ED visits and office visits might decrease, Dravet syndrome is generally drug-resistant and the level of care would still need to be closely managed.

**Current paradigm of patient care:** Commenters differed on the degree to which they thought FFA use has the potential to disrupt the current paradigm of patient care. A researcher noted that the treatment paradigm with FFA is generally the same: Medication will be used to reduce seizure frequency, but seizures will still occur and will need to be treated. A clinician conversely thought that FFA, as a locally accessed and FDA-approved medication, would change the paradigm considerably since many patients travel worldwide for consultations and clinical trials, undergo admission for ketogenic diet initiation, and might undergo surgeries for vagus nerve stimulation or NeuroPace neurostimulator device placement. Several commenters agreed FFA has the potential to improve patient convenience and ease of use. Four of 5 commenters agreed FFA use has the potential to disrupt anticipated side effects, risks, and adverse events.

**Health care costs:** Commenters differed on whether they thought FFA treatment has the potential to disrupt health care costs. A caregiver and a clinician thought that FFA use might reduce costs associated with ED visits, inpatient care, and other medications. But a patient advocate thought the cost of Dravet syndrome to the health care system might remain high even if ED visits and frequency of office visits decreased. A researcher thought that it was unclear whether the reduction in seizure frequency correlates with a reduction in seizure severity that necessitates hospitalization. A commenter with a health systems perspective was unable to comment without cost information.

**Overall disruption potential:** Commenters agreed FFA use has overall moderate to large disruption potential. A patient advocate thought FFA could become a first- or second-line treatment for Dravet syndrome and commenters with caregiver, clinical, and research perspectives similarly thought FFA might change the current standard of care. A health systems commenter thought the 50% or greater seizure reduction seen with FFA might significantly improve quality of life for this patient population.

**Galcanezumab-gnlm (Emgality) to Treat Episodic Cluster Headache**

**Highlights**

Galcanezumab-gnlm, the first FDA-approved drug to treat episodic cluster headache, is believed to work by preventing a neuropeptide thought to contribute to pain signaling of the trigeminal sensory nerve, calcitonin gene–related peptide (CGRP), from binding to its receptor and leading to headache development. Eight stakeholders commented on this topic after its FDA approval in June 2019. They generally thought galcanezumab-gnlm, a self-injected drug, has the potential to significantly improve patient outcomes, QoL, and overall health. Commenters generally thought the intervention is disruptive to the current treatment paradigm,
citing reasons including injections that can be given at home, a patient learning curve for self-administering injections, a potential for decreased need for medical resources to manage symptoms, and the increased convenience of monthly dosing. Commenters generally agreed the medication cost is high, although they differed on whether this might be a significant barrier to access or offset by improved health outcomes that reduce costs elsewhere.

**Patient Population**

Galcanezumab-gnlm injections are intended for adults aged 18 years or older with episodic cluster headache.

**Intervention**

Galcanezumab-gnlm is a humanized monoclonal antibody specific for CGRP and is intended to prevent CGRP from binding to its receptors, which might reduce pain signaling of the trigeminal sensory nerve and prevent cluster headache onset. The recommended dose is 300 mg, which patients self-administer under the skin (ie, subcutaneously) as 3 consecutive injections of 100 mg each at the onset of the cluster headache period and then monthly until the end of the same cluster period.422

**Evidence Development Summary**

Investigators have reported results from one completed trial of galcanezumab-gnlm, CGAL (NCT02397473), to treat patients with episodic cluster headache.

In the phase III CGAL double-arm RCT, adults (n = 106) aged 18 to 65 years with episodic cluster headache attacks were assigned to receive galcanezumab-gnlm at a dose of 300 mg or placebo administered subcutaneously at baseline and at 1 month. Enrolled participants had at least 1 attack every other day, at least 4 attacks total, and no more than 8 attacks per day during a baseline assessment.

Goadsby et al423 reported in 2019:

The primary end point was the mean change from baseline in the weekly frequency of cluster headache attacks across weeks 1 through 3 after receipt of the first dose. The key secondary end point was the percentage of patients who had a reduction from baseline of at least 50% in the weekly frequency of cluster headache attacks at week 3. Safety was also assessed.

The mean (±SD) number of cluster headache attacks per week in the baseline period was 17.8±10.1 in the galcanezumab group and 17.3±10.1 in the placebo group. The mean reduction in the weekly frequency of cluster headache attacks across weeks 1 through 3 was a reduction of 8.7 attacks in the galcanezumab group, compared with 5.2 in the placebo group (difference, 3.5 attacks per week; 95% confidence interval, 0.2 to 6.7; \( P = 0.04 \)). The percentage of patients who had at least a 50% reduction in headache frequency at week 3 was 71% in the galcanezumab group and 53% in the placebo group. No substantial between-group differences were reported in the incidence of adverse events, except that 8% of the patients in the galcanezumab group had injection-site pain.

One phase IIIb trial, CGAR (NCT02797951), is ongoing; it is assessing the long-term safety and tolerability of galcanezumab-gnlm in patients with episodic cluster headache and chronic cluster headache.

In the phase III single-arm, open-label trial, adults (n = 300) aged 18 years or older who completed 1 of the 2 phase III trials (CGAL, NCT02397473, or CGAM, NCT02438826) self-
administer galcanezumab-gnlm at an unspecified dose subcutaneously up to once per month for 4 years. The trial has a primary completion date of November 2021.

Manufacturers and Regulatory Status

Galcanezumab-gnlm is being developed by Eli Lilly and Co (Indianapolis, Indiana). FDA approved it on June 4, 2019, to treat episodic cluster headache. FDA had granted the drug Priority Review for treating episodic cluster headache in March 2019 and Breakthrough Therapy designation for the same indication in September 2018. Galcanezumab-gnlm was also approved by FDA to prevent migraine headache in September 2018. It is in phase III clinical development for preventing chronic cluster headache; an open-label extension study (CGAM, NCT02438826) was scheduled to complete in July 2019.

Cost Information

Upon FDA approval for treating episodic cluster headache, the manufacturer announced that, “The U.S. list price of Emgality . . . is the same per milligram as the migraine indication.” For preventing migraine headache, each 120-mg monthly dose of galcanezumab-gnlm (Emgality) provided in a single-use prefilled pen or syringe costs about $550, or about $6600 per year. Therefore, we estimate that for treating episodic cluster headache, each 300-mg monthly dose of the drug, provided as 3 single-use prefilled syringes containing 100 mg each, will cost about $1375.

Results and Discussion of Stakeholder Comments

Eight stakeholders, reflecting clinical, health systems, patient, and research perspectives, provided comments and ratings on galcanezumab-gnlm. The 2 patients who commented also have advocacy roles regarding support for cluster headache treatment and understanding. We have organized the following discussion of stakeholder comments by the parameters on which they commented.

Patient outcomes, quality of life, and overall health: Commenters generally agreed that galcanezumab-gnlm use has a moderate to large potential to positively disrupt patient outcomes, QoL, and overall health. Two clinicians and a patient rated the potential as large. A clinician stated that cluster headaches are very painful, and this clinician and a health systems commenter noted they are debilitating/disabling. Because CGRP is one of the key neurotransmitters involved in migraine and cluster headache pathogenesis, another clinician noted that targeting CGRP (receptors) is reasonable. Another patient noted that patients with cluster headache often have comorbidities including anxiety, depression, and PTSD, and that reducing the frequency or intensity of episodic cluster headaches might help alleviate symptoms of these conditions. A health systems commenter thought the clinical trial inadequately reported side effects and stated that side effects need to be better reported in future, larger studies.

Health disparities: Most commenters thought the potential for galcanezumab-gnlm use to disrupt health disparities was low. Seven of 8 commenters referenced high cost as a potential limit to patient access. Most commenters also thought that potential to positively disrupt health disparities hinges on insurance coverage of the drug.
**Health care delivery system:** Commenters disagreed on whether galcanezumab-gnlm use has the potential to disrupt the health care delivery system. Ratings ranged from no to large potential for disruption. Two commenters—a health systems commenter and a researcher—who rated the potential for disruption as none commented that the medication is self-injected at home, which is not a departure from how some medications for other medical conditions are taken. Among commenters who rated the potential for disruption as moderate or high, a clinician thought this intervention could reduce ED visits and opioid prescribing for cluster headache pain, and both patients commented that this intervention might offer an at-home solution for patients whose symptoms can make it difficult to leave their homes to seek treatment, which might include IV medications or nerve blocks. Another researcher noted that the monthly dosing regimen is more convenient for both patients and health care providers than current therapies. Of note, both commenters who have a dual patient/patient advocate perspective rated potential to disrupt the health care delivery system as high.

**Current paradigm of patient care:** Commenters generally rated the drug’s potential to disrupt the current paradigm of patient care as moderate. Seven commenters agreed galcanezumab-gnlm has the potential to disrupt patient convenience and ease of use. The patients and researchers noted a learning curve might exist for patients to learn to self-administer injections, and that subcutaneous injections carry a risk of infection. Two commenters with health systems and research perspectives noted the monthly dosing regimen as a positive disruptor. A clinician noted that because of the high cost of galcanezumab-gnlm, comparators might be prescribed first and galcanezumab-gnlm might be covered by insurance only after patients have inadequate responses to those comparators.

**Health care costs:** Commenters generally agreed that the cost of galcanezumab-gnlm is high and a potential barrier to patient access. One researcher thought that this intervention is unlikely to be financially feasible for most patients. Another researcher thought that while the cost of the medication seems expensive from a patient perspective, it does not seem extreme from a health care system perspective. A few commenters with clinical, health systems, and patient perspectives thought the high cost might be offset by a decreased need for other health care resource use, such as outpatient office visits, ED visits, inpatient admission and monitoring, procedures, acute attack medications, and mental health support, as well as patients’ increased ability to seek and maintain employment and health insurance.

**Overall disruption potential:** Commenters generally rated the overall disruption potential of galcanezumab-gnlm to treat episodic cluster headache as moderate. Commenters cited various reasons for positive overall disruption potential, including its being the first medication FDA approved for cluster headache, possible improvements in patient QoL, and convenience. Multiple commenters reiterated that cost is a concern. Both patients stated that this intervention is encouraging to the cluster headache community, with one commenter noting a positive psychological effect that this medication’s availability already seems to have elicited in the community.
Givosiran (ALN-AS1) to Prevent and Treat Acute Hepatic Porphyrias

Highlights

Givosiran (ALN-AS1) is an RNA interference (RNAi) therapeutic that is intended to treat acute hepatic porphyrias (AHPs) in children and adults. In a single clinical trial, treatment with givosiran showed reduction in annual rate of porphyria attacks when compared with placebo through a 6-month period. The 5 stakeholders commenting on this topic generally thought that this intervention would be highly disruptive in terms of patient-oriented health outcomes for individuals who have recurrent attacks, given the ease of administration of givosiran in a home setting. Most commenters also stated that this could reduce overall hospitalizations for AHP attacks, which might save costs overall for both patients and payers. Commenters generally thought that given the lack of effective and less invasive treatments in this rare disease, this intervention might shift the current paradigm of patient care from a hospital to a home setting.

Patient Population

Givosiran is intended for children aged 12 years or older and adults with AHPs, including acute intermittent porphyria, variegate porphyria, and hereditary coproporphyria.

Intervention

AHPs are a group of rare metabolic disorders caused by genetic variants (usually autosomal dominant) in enzymes involved in heme biosynthesis in the liver. They include the manifestations of acute intermittent porphyria, aminolevulinic acid dehydratase-deficiency porphyria, hereditary coproporphyria, and variegate porphyria.436 The disorders are chronic, with no cure, and are associated with serious burden of illness. Acute flares can be life threatening. AHP flares can be precipitated by many triggers that cause a strong induction of aminolevulinic acid synthase 1 (ALAS1), a liver enzyme in the heme biosynthesis pathway, which can lead to accumulation of neurotoxic heme intermediates that manifest in debilitating disease symptoms.436 No treatments are FDA approved to prevent attacks or treat chronic manifestations of these disorders.

Givosiran is an RNAi therapeutic (ESC-GalNAc-siRNA conjugate) intended to treat AHPs by reducing the expression of ALAS1.436 RNAi is a process of gene silencing that naturally occurs in cells, and researchers have adapted the process by developing targeted small interfering RNA (siRNA) molecules that mediate RNAi gene silencing activity in cells expressing messenger RNAs responsible for encoding pathogenic proteins.436 According to the developer, the ESC+GalNAc conjugate RNA improves specificity while maintaining potency and durability.437 Givosiran is intended for preventing or reducing recurrent AHP attacks and is administered as a subcutaneous injection.436 For more information on AHPs, see the Mayo Clinic website.

Evidence Development Summary

The manufacturer continues to evaluate givosiran in an ongoing phase I/II ALN-AS1-002 clinical trial (NCT02949830) on the long-term safety and clinical activity of givosiran in patients with acute intermittent porphyria.

In April 2019, investigators reported results from the ENVISION phase III (NCT03338816) double-blind RCT to evaluate the safety and effectiveness of givosiran in patients with acute
hepatic porphyrias. Patients were assigned to receive either givosiran or placebo in a 1:1 ratio. Patients had active disease, with at least 2 porphyria attacks within the past 6 months, and elevated urinary or plasma porphobilinogen deaminase or delta-aminolevulinic acid values within the past year.\(^{438}\)

The results from the ENVISION trial showed a 74% mean and 90% median reduction in the primary endpoint measure of annualized rate of composite attacks in patients on givosiran relative to placebo during the 6-month double-blind period. Investigators reported statistically significant positive results for 5 of 9 secondary endpoints, with an acceptable overall safety and tolerability profile. Adverse events were reported in 89.6% of givosiran patients vs 80.4% of placebo patients. Additionally, investigators reported that 20.8% of patients experienced SAEs in the givosiran group vs 8.7% in the placebo group. Of the 94 patients enrolled, 93 continued in the open-label extension period of the study.\(^{438}\)

Manufacturers and Regulatory Status

Givosiran is in phase III clinical development by Alnylam Pharmaceuticals, Inc (Cambridge, Massachusetts). In October 2018, Alnylam initiated a rolling submission to FDA for a New Drug Application.\(^{439}\) The company anticipates givosiran might gain approval by the first half of 2020.\(^{440}\) In May 2017, FDA granted givosiran Breakthrough Therapy designation.\(^{441}\) In August 2016, FDA granted the drug Orphan Drug designation.\(^{442}\)

Results and Discussion of Stakeholder Comments

Five stakeholders, reflecting clinical, health systems, and research perspectives, provided comments and ratings on givosiran to treat acute hepatic porphyrias.\(^{443-447}\) We have organized the following discussion of stakeholder comments by the parameters on which they commented.

**Patient outcomes, quality of life, and overall health:** Commenters agreed that givosiran has high potential to improve patient health outcomes and QoL based on results from the phase III ENVISION trial.\(^{438}\) Two researchers expressed concerns that the high adverse SAE rates along with unknown long-term effects of this treatment would negatively affect patient health outcomes.\(^{446,447}\)

**Health disparities:** Commenters with health systems and clinical perspectives shared that patients often give themselves subcutaneous injections at home, which could reduce the barriers to treatment and reduce health disparities and cost of care.\(^{443-445}\) Conversely, one researcher thought that the cost of givosiran as well as its access could increase health disparities.\(^{446}\)

**Health care delivery system:** Commenters generally agreed that this intervention would reduce burden on the health care delivery system due to its administration in a home setting, when compared with the standard of care hemin injection that requires an infusion center or hospital setting. However, a health systems commenter added that a 90% decrease in attacks would not have a large effect on the health care delivery system based on the small population affected by AHP.\(^ {445}\)

**Current paradigm of patient care:** Commenters agreed that this intervention would disrupt current treatment paradigms based on ease of use compared with standard of care. Two researchers thought that the anticipated side effects might be a barrier in shifting the current paradigm of AHP therapy.\(^ {446,447}\) Conversely, a clinician shared that the competing drug Panhematin requires frequent administration and is known to cause side effects such as
secondary iron overload and is associated with complications with venous port access; thus, givosiran would be less invasive and have a better side effect profile.444

**Health care costs:** Most commenters thought that this treatment has moderate potential to disrupt costs for payers and patients because of the expected high cost for givosiran. Conversely, commenters with health systems and research perspectives thought that this intervention could potentially reduce hospital resource use and costs associated with the delivery of givosiran injections.443,445,447

**Overall disruption potential:** Commenters thought that this treatment has moderate to large overall potential to disrupt patient-oriented health outcomes and QoL for some patients with AHP who have recurrent acute attacks. On the contrary, one researcher thought that the occurrence of SAEs, along with the lack of data on long-term benefits, calls into question the overall disruption potential for this treatment.447 A health systems commenter noted that the disruption this treatment could cause would be moderate, because patients who experience recurrent intermittent attacks would still need medical supervision.445

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**GT-AADC to Treat Aromatic L-Amino Acid Decarboxylase Deficiency**

**Highlights**

A gene therapy called GT-AADC is intended to treat aromatic L-amino acid decarboxylase deficiency (AADCD) in children by promoting the production of the enzyme L-amino acid decarboxylase (AADC), which is thought to be critical for the normal conversion of neurotransmitter precursors into dopamine, epinephrine, norepinephrine, or serotonin.448 Current treatments focus on symptoms only and do not significantly alter the course of the disease, which this intervention might be able to do.

The 7 stakeholders commenting on this topic generally agreed GT-AADC to treat AADCD has moderate to high potential for overall disruption. Commenters generally agreed that the intervention demonstrated clinically meaningful efficacy and has the potential to significantly improve patient health outcomes and quality of life compared with current therapies. Commenters noted the potential for disruption to the current paradigm of patient care, citing reasons including travel to treatment centers, health care risks unique to gene therapies, increased or decreased need for follow-up care resources, and clinician learning curve required to use the intervention. Commenters generally agreed the potential to disrupt costs is high, citing the generally high cost of gene therapies and cost of surgery.

**Patient Population**

GT-AADC is intended for children aged 2 to 6 years with genetically confirmed symptomatic AADCD and a head circumference large enough for surgery.

**Intervention**

GT-AADC is an adeno-associated viral vector containing a functional copy of the human dopa decarboxylase gene, *DDC*, and is intended to promote *DDC* expression in patients with AADCD, a childhood onset, progressive, inherited neurometabolic disorder. AADCD is caused by a *DDC* variant that results in the loss of the gene’s encoded enzyme AADC, which is critical
Patients with AADCD experience many symptoms, including severe developmental delays, weak muscle tone, involuntary arm and leg movements, and painful seizures. Treatments only manage symptoms and do not prevent disease progression. Delivery of a functional copy of DDC might enhance neurotransmitter production, restore motor function, and delay or prevent other disease symptoms. In clinical trials, patients received a single intracerebral infusion of GT-AADC ($1.8 \times 10^{11}$ viral genomes [vg] or $2.4 \times 10^{11}$ vg) via stereotactic surgery.

**Evidence Development Summary**

Investigators have reported results from 2 trials of GT-AADC, AADC (NCT01395641) and MIND (NCT02926066).

The phase I/II AADC single-arm trial studied pediatric patients (n = 10) aged 2 years or older with genetically confirmed diagnosis of AADCD and an anti-AAV2 antibody lower than 1.0 optical density. The pediatric patients were treated with a single intracerebral infusion (injected into the bilateral putamen) of the viral vector GT-AADC (AAV2-hAADC) at a dose of $1.8 \times 10^{11}$ vg during stereotactic surgery. Participants were assessed at 3, 6, 9, and 12 months after gene therapy and every 6 months thereafter for 1 further year.

The investigators reported that all patients met the primary endpoint: 12 months after gene therapy, PDMS-2 (Peabody Developmental Motor Scales, second edition) scores were increased by a median of 62 points (interquartile range [IQR] = 39-93; $P = .005$) and homovanillic acid (HVA) concentrations by a median of 25 nmol/L (IQR = 11-48; $P = .01$). However, there was no significant change in 5-hydroxyindoleacetic acid (5-HIAA) concentrations (median difference = 0; IQR = 0-5; $P = .20$).

All patients tolerated the surgeries and vector injections. In total, 101 adverse events were reported (not all were related to treatment), with the most common being fever (16% of the adverse events) and orofacial dyskinesia, or abnormal movement in the face and mouth (10%). Six patients experienced 12 SAEs: 1 death (encephalitis due to influenza B infection not related to treatment), 1 life-threatening pyrexia, and 10 events that led to hospital admission. Transient dyskinesia after gene therapy occurred in all patients but resolved with risperidone treatment. Of 31 treatment-related adverse events, only 1 was severe in intensity, and none led to hospital admission or death.

In the phase II MIND single-arm open-label trial, pediatric patients (n = 10) aged 2 to 6 years with genetically confirmed diagnosis of AADCD were treated with a single intracerebral infusion (injected into the bilateral putamen) of the viral vector GT-AADC (AAV2-hAADC) at a dose of $1.81 \times 10^{11}$ or $2.37 \times 10^{11}$ vg (cohort-dependent) during stereotactic surgery.

The investigators reported pooled data from the phase I/II and phase II trials. Of the 25 participants, 3 were alive more than 7 years after gene therapy, 7 were alive more than 6 years after gene therapy, and 16 were alive more than 2 years after gene therapy. Clinical results from the first 18 patients were compared with results from a natural history cohort.

At baseline, patient ages ranged from 21 months to 8.5 years, and no child had developed full head control, sitting unassisted, or standing capability. Of the 18 patients (receiving the $1.8 \times 10^{11}$ vg dose), 5 of 15 gained full head control ($P < .0001$), 4 of 15 gained sitting unassisted ($P = .0004$), and 1 achieved standing with support at 2 years. At 5 years, 4 out of 7 gained full head control and sitting unassisted ($P < .0001$) and 2 out of 7 standing with support ($P = .005$).

Regarding ambulatory function, 2 patients are using wheeled walkers, 1 additional patient is able to take steps holding an examiner’s hand, and 1 patient is walking independently.
Adverse events in the first year after GT-AADC administration were reported to be generally associated with overall disease state.450

**Manufacturers and Regulatory Status**

GT-AADC is being developed by [PTC Therapeutics, Inc (South Plainfield, New Jersey)](https://www.ptctherapeutics.com). It is in phase II clinical development. PTC Therapeutics plans to submit a Biologics License Application to FDA in late 2019.451 FDA granted Orphan Drug452 and Rare Pediatric Disease453 designations to GT-AADC for treating AADCD.

**Results and Discussion of Stakeholder Comments**

Seven stakeholders, reflecting physical therapy, clinical, health systems, and research perspectives, provided comments and ratings on GT-AADC.454-460 We have organized the following discussion of stakeholder comments by the parameters on which they commented.

**Patient outcomes, quality of life, and overall health:** Commenters agreed that data from the clinical trials demonstrate positive and meaningful outcomes for patients with AADCD treated with GT-AADC. Commenters with research and clinical perspectives noted that current therapies treat symptoms and do not significantly alter the course of the disease.457,458 A physical therapist thought that GT-AADC has the potential to improve patient outcomes, QoL, and overall health, and stated that while QoL measurements are often difficult to collect, it would be helpful to obtain them in this population.454 The same commenter also noted that it would have been informative to have a standardized rehabilitation period after the GT-AADC treatment to maximize that effect of treatment and ensure all subjects would receive the same amount of stimulation. A clinician noted that although the AAV vector can effectively deliver a gene with a good safety record and lasting gene expression, concerns exist about transport barriers, immune response, infection, and duration of the gene effect.456 This commenter also pointed out that while cognitive and language improvements occurred, it is not certain whether this change was due to improved cognition or motor function.456

**Health disparities:** Commenters differed on whether this intervention has the potential to disrupt health disparities. A clinician and a researcher noted that this therapy will likely require administration at highly specialized centers with high technological expertise.457,459 Another researcher had concerns regarding potential high costs as a barrier to patient access.458 A physical therapist noted that this intervention might have the potential to change health disparities for patients with the rare disorder.454

**Health care delivery system:** Commenters generally agreed that this intervention has the potential to disrupt the health care delivery system, for a variety of reasons. A clinician commented that this intervention would likely decrease specialist visits. Another clinician noted potential for increased hospital lengths of stay and potential for increased resource use if the gene effect is altered by transport barriers and immune response.456 A physical therapist thought that GT-AADC might disrupt the health care delivery system in that the acute management process will require increased specialized staff—a multidisciplinary care team prepared for complex cases—and that, because patients might live longer and have residual disability, long-term care will likely include an increased need for rehabilitation including cognitive, speech, occupational, and physical therapy.454
Current paradigm of patient care: All but one commenter agreed this intervention has the potential to disrupt the care paradigm because of the clinician learning curve required to use the therapy.\textsuperscript{454-458,460} Many commenters agreed that this intervention has the potential to impact clinician\textsuperscript{456-458} and patient ease of acquisition.\textsuperscript{456-459} A physical therapist noted a unique challenge of this intervention in that gene therapies, unlike conventional small-molecule drugs or other biologic products, are difficult to stop once initiated and require multidisciplinary care and preparation for adverse effects such as immune responses. Thus, the clinical care team has a learning curve. Additionally, patients will require intense rehabilitation after the intervention, and families will need to learn how to manage the residual disability.\textsuperscript{454} A researcher noted the need for patients to travel to centers that offer the intervention.\textsuperscript{459}

Health care costs: Although cost information was unavailable, commenters generally expected the cost of this intervention to be high and disruptive. Reasons cited included that it is a gene therapy\textsuperscript{454,456,458} and that it requires intracerebral infusion via stereotactic surgery.\textsuperscript{459} A clinician noted that it is unclear whether the therapy cost would be offset by avoiding the costs of less effective therapies and specialist visits and by improved productivity.\textsuperscript{457} A researcher raised concern over how certain costs will be covered and handled, including patient and family travel expenses, Medicaid coverage, insurance payment plan structures, follow-up costs, and caregiver burden.\textsuperscript{458}

Overall disruption potential: Commenters generally agreed that this intervention has overall moderate\textsuperscript{454,456,459} to high\textsuperscript{457,458,460} potential for disruption. A researcher wrote that given the poor QoL these patients now have, this intervention would improve QoL.\textsuperscript{458} A clinician and another researcher thought that this intervention has the potential to greatly help patients.\textsuperscript{457,460} Another clinician noted that this intervention is the only therapy delivered directly to the site of action, although she noted that the standard of care should be something less invasive and more affordable.\textsuperscript{456} A health systems commenter rated the overall potential for disruption as low, but thought that care could be enhanced with its use.\textsuperscript{455}

Idebenone (Puldysa) to Treat Duchenne Muscular Dystrophy

Highlights

No cure for DMD exists, and while FDA approved a dystrophin-replacement gene therapy for patients who have a specific variant in \textit{DMD} (ie, in exon 51), patients with other genetic alterations do not qualify and more treatment options are needed. Idebenone purportedly protects cell viability and function to preserve cellular energy in patients with DMD. The drug appears to improve short-term (1-year) respiratory function in patients with DMD who are not taking corticosteroids, according to data from a phase III trial. The 6 commenters providing input on this topic agreed that idebenone use has the potential to decrease hospitalization rates and ventilator use for respiratory complications, as well as associated costs, but longer-term data are needed. In addition, idebenone’s long-term disruption potential might be limited if its cost is substantially higher than that of corticosteroids, the standard-of-care treatment for managing respiratory symptoms in patients with DMD.
Patient Population

Idebenone is intended for males aged 10 years or older with DMD who are or are not taking corticosteroids.

Intervention

DMD is an inherited, X chromosome–linked genetic disorder caused by point rearrangements or deletions in the dystrophin gene, DMD. DMD encodes the dystrophin protein, which helps promote muscle function. In patients with DMD, the absence of wild-type dystrophin protein causes progressive muscle death and eventual widespread muscle weakness.376

Idebenone is a small-molecule, synthetic, short-chain benzoquinone with similarity to coenzyme Q-10 that purportedly facilitates electron transport within mitochondria. The developer asserts that maintaining correct electron balance is essential for normal energy metabolism—particularly in nerve and muscle cells, which demand more energy, making them more prone to rapid cell damage or death from mitochondrial dysfunction.461 Additionally, idebenone might protect cells from oxidative stress signaling pathways that induce programmed cell death (ie, apoptosis), preserving mitochondrial function and cellular viability.462 These effects could increase energy production within impaired nerve and muscle tissue in patients with DMD.461 Data from the phase II DELPHI trial suggested that idebenone improved respiratory function but not cardiac function (defined as peak systolic radial strain values in the left ventricular inferolateral wall), shaping the selection of phase III respiratory function endpoints.463

In clinical trials, patients take or caregivers give 900 mg of idebenone orally, daily, divided into 3 equal doses of two 150-mg tablets each, taken with meals.

The Muscular Dystrophy Association provides more information on DMD.

Evidence Development Summary

The international phase III DELOS trial investigated the comparative effectiveness of long-term daily idebenone (900 mg) vs placebo across multiple measures of respiratory function in males aged 10 to 18 years with DMD (n = 64) who were not taking corticosteroids during the trial. The trial’s primary endpoint was the percentage change from baseline in predicted peak expiratory flow rate (PEF%p), a respiratory measure known to decline in association with DMD progression.

Two publications reported results from the DELOS trial. Buyse et al464 reported in 2015 that the PEF%p declined significantly (–9.01% predicted; 95% CI, –13.2 to –4.8; P < .0001) in the placebo group after 52 treatment weeks. But the PEF%p declined less (ie, showed improvement) in patients administered idebenone over the same period (–3.05% predicted; 95% CI, –7.1-0.97; P = .13). A between-group comparison of the PEF%p was statistically significant (5.96% predicted; 95% CI, 0.16-11.8; P = .04). Idebenone administration was associated with a 66% reduction in loss of PEF%p over the trial at week 52; interim measures at 26 treatment weeks (P = .007) and 39 treatment weeks (P = .03) also demonstrated effectiveness. Of note, the investigators based their sample size calculations on a 10.3% between-group difference in PEF%p, which presumably is a clinically important difference. On 4 additional measures of respiratory function, patients receiving daily idebenone showed improvements compared with the placebo group. Fewer respiratory tract infection–related adverse events were noted among patients receiving idebenone than among patients receiving placebo.464
Rummey et al.\textsuperscript{465} authored a 2017 conference abstract also presenting data from the DELOS trial. They indicated that more patients in the placebo group than in the treatment group fell below the thresholds for clinically relevant percentage predicted forced vital capacity (placebo 57\%, idebenone 34\%) or experienced a bronchopulmonary adverse event, resulting in a HR of 0.50 (95\% CI, 0.26-0.97; \(P = .039\)) favoring idebenone.

The ongoing phase III SIDEROS trial (\textbf{NCT02814019}) is assessing the effectiveness and safety of 900 mg of idebenone daily vs placebo. Primary and secondary outcomes include several measures of respiratory function, measured at baseline and week 78. The trial plans to enroll 266 patients with DMD who are receiving corticosteroids, and the primary completion date is August 2021.

SIDEROS-E (\textbf{NCT03603288}) is an open-label extension study enrolling patients who completed the SIDEROS trial; primary and secondary outcomes include adverse event incidence and several measures of respiratory function, also measured at baseline and week 78. The extension study’s primary completion date is December 2023.

\textbf{Manufacturers and Regulatory Status}

Santhera Pharmaceuticals (Pratteln, Switzerland) is developing idebenone for treating DMD. The drug is in phase III clinical development for this indication. In the second half of 2021, Santhera intends to submit to FDA a New Drug Application for idebenone (Puldysa) to treat DMD.\textsuperscript{466} (Note: The manufacturer formerly used the brand name Catena for this indication.\textsuperscript{461}) FDA has granted several designations to idebenone for treating DMD: Orphan Drug designation in August 2016,\textsuperscript{467} Rare Pediatric Disease designation in August 2015,\textsuperscript{468} and Fast Track designation in April 2015.\textsuperscript{461}

Idebenone (Raxone) was approved by the European Medicines Agency in September 2015 for treating Leber’s hereditary optic neuropathy\textsuperscript{469} and is in phase IV clinical development (\textbf{NCT02774005}) in the United States for this indication.

\textbf{Results and Discussion of Stakeholder Comments}

Six stakeholders, reflecting caregiver, clinical, nursing, research, and health systems perspectives, provided comments and ratings on idebenone for treating DMD.\textsuperscript{470-475} We have organized the following discussion of stakeholder comments by the parameters on which they commented.

\textbf{Patient outcomes, quality of life, and overall health:} Commenters generally agreed that idebenone improves respiratory function and QoL without causing severe side effects in patients with DMD who are not taking corticosteroids. But one researcher\textsuperscript{475} questioned the drug’s long-term efficacy, and another researcher\textsuperscript{474} questioned the DELOS study’s small sample size.

\textbf{Health disparities:} Most commenters did not expect idebenone to significantly disrupt health disparities, because patients with DMD often receive oral corticosteroids, and idebenone is also given orally. However, one nurse\textsuperscript{473} and one health systems\textsuperscript{470} commenter noted that the cost of the drug for treating DMD is unknown and might affect disparities.

\textbf{Health care delivery system:} Commenters unanimously agreed that, as an oral drug that patients take themselves, idebenone could potentially reduce hospitalizations due to respiratory complications for patients with DMD.
Current paradigm of patient care: All commenters thought that idebenone has the potential to be easily adopted by patients and caregivers as part of a convenient, less invasive care paradigm because it might improve 1-year respiratory outcomes and prevent the need for ventilator support. However, one clinician was uncertain about whether the drug would affect long-term outcomes and whether patients taking the drug might eventually require additional support. Additionally, a caregiver noted that some patients with DMD might have difficulty adhering to the treatment regimen, which requires taking 2 pills 3 times a day, with food.

Health care costs: Although some commenters noted that idebenone’s cost was unavailable, all thought that the drug would reduce costs associated with respiratory complications, such as hospitalizations and ventilator support. One commenter with a caregiver perspective also noted that idebenone could potentially reduce costs associated with “side effects and secondary illnesses caused by corticosteroid use, such as hypertension, bone weakness, and behavioral changes.”

Overall disruption potential: Commenters generally agreed that idebenone has moderately high potential for disruption because of its positive effect on respiratory function in patients with DMD, although a clinician again questioned its effects on long-term patient health outcomes. A caregiver and a nurse noted that the drug’s adoption might be limited if its cost were significantly higher than that of corticosteroids.

LentiGlobin to Treat Transfusion-Dependent β-Thalassemia

Highlights

LentiGlobin (formerly Zynteglo) is a gene therapy that might permanently enhance a patient’s ability to produce functional hemoglobin B (HBB), enhancing RBC production and relieving transfusion-dependent β-thalassemia (TDT) symptoms. The 7 stakeholders commenting on this topic were generally optimistic about LentiGlobin’s potential to improve short- and long-term health outcomes and QoL by reducing or eliminating the need for RBC transfusions or hematopoietic stem cell transplants (HSCTs). Improved outcomes would also reduce the substantial burden on the health care system and caregivers required for the standard of care. However, commenters were concerned that LentiGlobin’s cost might create disparities if people without insurance or with high copayments have limited access, despite LentiGlobin’s potential cost offsets and the manufacturer’s planned financing options. Commenters also agreed that because LentiGlobin is a novel gene therapy, larger, longer-term studies are needed to better understand its safety, effectiveness, and full disruptive potential.

Patient Population

LentiGlobin is intended for children and adults aged up to 50 years with TDT, also known as β-thalassemia major or Cooley anemia, who have a β0/β0 genotype (no β-globin expression) or a β+/β0 genotype (little β-globin expression).

Intervention

TDT is caused by variants in the hemoglobin B gene, HBB, leading to reduced or absent hemoglobin (Hb). Reduced Hb negatively affects RBC development, causing severe anemia and related complications. Standard supportive care for TDT consists of lifelong, regular blood
transfusions. Iron chelation therapy manages iron overload from transfusions, which can cause serious complications and organ damage. For more information on β-thalassemia, see the National Institutes of Health’s Genetics Home Reference website.

Allogeneic (from a donor) HSCT can address the underlying cause of TDT, but it carries the risk of HSCT-related death, graft failure, and development of GVHD and opportunistic infections, particularly in recipients of HSCT that is not from a matched sibling donor.476

LentiGlobin is a gene therapy that purportedly enhances the patient’s ability to produce functional HBB genes that subsequently improve RBC production. The therapy consists of patient bone marrow–derived CD34+ hematopoietic stem cells that are transduced ex vivo with a lentiviral vector that inserts a functional, modified copy of the βA-T87Q-globin gene, HBB, which purportedly improves effectiveness and allows its expression in patients to be measured. Transduced cells are then expanded ex vivo to facilitate uptake.477

In clinical trials, LentiGlobin is administered as a single IV infusion, at an unspecified dose, after patients are treated with busulfan to destroy the β-thalassemia-causing blood cells. Hb consists of 4 protein subunits, 2 subunits of α-globin (encoded by the HBA1 or HBA2 genes), and 2 subunits of β-globin (encoded by the HBB gene). Patients with β0 thalassemia carry variants in HBB preventing the production of any β-globin. Patients with β+ thalassemia carry HBB variants that allow reduced β-globin production.476 LentiGlobin is under study in patients with both β0 and β+ TDT.

Evidence Development Summary

The phase III Northstar-2 (HGB-207) trial (NCT02906202) involves patients (n = 16) aged up to 50 years with TDT and non-β0/β0 genotypes. Patients were assigned to treatment with myeloablative conditioning with busulfan followed by IV infusion with LentiGlobin. At an average of 9.3 months of follow-up, 10 of 11 patients (with at least 3 months of follow-up) stopped taking RBC transfusions with Hb counts of 11.1 to 13.3 g/dL, which contained 7.7 to 10.6 g/dL of LentiGlobin-derived Hb (HbAT87Q). The investigators reported that 2 patients achieved transfusion independence (TI; weighted average Hb ≥ 9 g/dL without RBC transfusions for ≥ 12 months).478

The phase I/II Northstar (HGB-204) trial (NCT01745120) enrolled patients (n = 10) aged 12 to 35 years with TDT and non-β0/β0 genotypes. Patients were assigned to treatment with myeloablative conditioning with busulfan followed by IV infusion with LentiGlobin. At an average of 36.0 months’ follow-up, 8 of 10 patients with non-β0/β0 genotypes achieved TI. The median duration of TI was 38.0 months and was sustained in the study. Median weighted average Hb during TI was 10.2 g/dL. The liver iron content for patients who achieved TI increased by a median of 67% and 23% from baseline at months 12 and 24, respectively, and then decreased below baseline by a median of 9% and 53% at months 36 and 48, respectively. Patients reinitiated iron chelation therapy at a median 13 months after LentiGlobin treatment.478

The most common nonhematologic grade ≥ 3 adverse events in either study included nosebleed, febrile neutropenia, irregular menstruation, liver veno-occlusive disease, fever, and inflamed mucous membranes in the mouth. No instances of treatment-related death, replication of competent lentivirus, or clonal dominance were observed.478

Manufacturers and Regulatory Status

LentiGlobin is manufactured by bluebird bio, Inc (Cambridge, Massachusetts) and is in phase III development for treating TDT. The company announced that a US regulatory filing for
LentiGlobin is planned for 2020.\textsuperscript{479} FDA had granted LentiGlobin Breakthrough Therapy designation in February 2015 for treating TDT major.\textsuperscript{480}

**Cost Information**

The company has announced plans to price LentiGlobin below the $2.1 million in “intrinsic value” that it estimates the therapy delivers.\textsuperscript{479} Early estimates by a financial firm put LentiGlobin’s price at about $1.2 million in the United States and $900,000 in the European Union.\textsuperscript{479} However, on June 14, 2019, the company announced the EU list price would be €1.58 million ($1.78 million) after winning conditional EU approval.\textsuperscript{481} The company has announced plans to offer payers annuity-based payment agreements that would allow insurers to delay paying about 80\% of LentiGlobin’s costs for up to 5 years after an initial upfront payment. The company also announced plans to offer a value-based payment agreement, accepting payment only if the treatment works.\textsuperscript{479} Finally, the company announced plans for price stability, linking price increases to the Consumer Price Index.\textsuperscript{479}

**Results and Discussion of Stakeholder Comments**

Seven stakeholders, reflecting health systems, caregiver, clinical, patient, and research perspectives, provided comments and ratings on this treatment.\textsuperscript{482-488} We have organized the following discussion of stakeholder comments by the parameters on which they commented.

**Patient outcomes, quality of life, and overall health:** Overall, commenters thought that a single dose of LentiGlobin might substantially improve patients’ short- and long-term health outcomes by reducing or eliminating the need for RBC transfusions and HSCT. A commenter with a caregiver perspective noted that needing fewer transfusions would improve QoL by decreasing the patient’s burden of frequent doctor visits, copayments, and chelation therapy from iron overload, which interfere with patients’ independent living.\textsuperscript{483} However, commenters with health systems\textsuperscript{486} and clinical\textsuperscript{485} perspectives stated concerns regarding the lack of long-term follow-up data for LentiGlobin, and the health systems commenter also noted the small sample sizes of the trials. Another clinician expressed concern that the most recent findings of LentiGlobin are not published in peer-reviewed manuscripts.\textsuperscript{484} A caregiver also expressed concern, wondering whether the adverse events of LentiGlobin have been fully reported.\textsuperscript{483}

**Health disparities:** A caregiver, health systems commenter, and patient stated that, as a potentially curative, one-time infusion for TDT, LentiGlobin might help reduce disparities in patients struggling with care access issues, such as frequent doctor visits and copayments, for blood transfusions and iron chelation treatments, which further undermine patients’ ability to work and maintain insurance coverage.\textsuperscript{483,486,487} A researcher noted that LentiGlobin might also reduce disparities by reducing the need for tissue-matched donors, which delays HSCT treatment for TDT in some populations.\textsuperscript{488} The health systems commenter expressed concern that LentiGlobin’s cost might cause disparities to patient populations lacking sufficient insurance coverage.\textsuperscript{486}

**Health care delivery system:** Commenters generally agreed that if LentiGlobin were to become the standard of care, it might substantially reduce the burden on the system for intensive case management and blood transfusions, chelation therapy, HSCTs, and the complications of these therapies, which must be monitored. The commenters also noted that care for β-thalassemia would shift from acute care hospitals to outpatient treatment at tertiary care facilities that administer and monitor the effectiveness of LentiGlobin.
**Current paradigm of patient care:** Overall, commenters thought that LentiGlobin might change the paradigm of care by providing a one-time treatment for TDT compared with repeated blood transfusions, chelation therapy, and HSCT, which all require more intensive care and monitoring by health care professionals. Commenters with health systems and research perspectives also thought that LentiGlobin could substantially reduce the need for stem cell donors and demands on the donor-matching system.\(^\text{482,488}\)

**Health care costs:** Commenters thought LentiGlobin would be very expensive (estimated $1.8 million), but the one-time treatment costs might be offset by eliminating the long-term costs of blood transfusions, chelation therapy, and HSCT. Commenters with health systems\(^\text{486}\) and caregiver\(^\text{483}\) perspectives noted that the annuity-based payment option offered by the manufacturer might improve access to LentiGlobin. A clinician noted that cost impacts would depend on the patient’s alternatives, HSCT or continuing transfusions.\(^\text{485}\) Giving patients LentiGlobin instead of HSCT might be less controversial because HSCT also has high upfront expenses and carries substantial risk.\(^\text{485}\) A caregiver and a patient noted that many patients with TDT are covered by public insurance or are underinsured or uninsured.\(^\text{483,487}\) A health systems commenter expressed doubt that private or public payers would cover costs for LentiGlobin and wondered whether other means of financing will surface to cover LentiGlobin’s cost.\(^\text{482}\)

**Overall disruption potential:** Commenters generally agreed that LentiGlobin demonstrated potential to provide an effective one-time treatment that could improve health outcomes and quality of life in patients with TDT by eliminating transfusion dependence or the need for HSCT, matching donors, and their related complications, which would change the current standard of care for patients seeking better management. Commenters also agreed that because LentiGlobin is a novel gene therapy, larger, longer-term studies are needed to better understand its safety, effectiveness, and full disruptive potential.

**Luspatercept-aamt (Reblozyl) to Treat Transfusion-Dependent β-Thalassemia**

**Highlights**

Luspatercept-aamt (Reblozyl) is intended to treat TDT by helping RBCs (ie, erythrocytes) mature in affected patients. This treatment is a first-in-class biologic approved by FDA on November 8, 2019. It is administered subcutaneously and could replace the need for regular blood transfusions and iron chelation, which are invasive, costly, and burdensome to the patient and caregiver. Most of the 8 stakeholders commenting on this topic thought luspatercept-aamt use has large overall potential to cause disruption. Clinical trial data were considered to be positive and significant. Commenters thought luspatercept-aamt use might significantly improve patient access to care, improve patient health and QoL, reduce health disparities, change the current treatment paradigm and health care delivery system, and reduce the costs and risks associated with frequent blood transfusion with iron chelation (a highly used current treatment).

**Patient Population**

Luspatercept-aamt is indicated for adults aged 18 years or older with TDT, also known as β-thalassemia major or Cooley anemia. The therapy is not indicated as a substitute for transfusions in anemia that needs to be immediately corrected.
Intervention

Luspatercept-aamt is a first-in-class biologic intended to help RBCs mature as a treatment for TDT.489 This disease is caused by a variant in the beta-globin gene that prevents normal erythrocyte maturation, resulting in severe anemia that requires chronic blood transfusions for survival plus nightly iron chelation to prevent iron overload from repeated blood transfusions.490,491

Luspatercept-aamt purportedly neutralizes certain transforming-growth factor (TGF)-β superfamily ligands to prevent aberrant signaling of Smad2/3, thereby enabling late-stage RBC maturation to restore normal RBC production.489,492,493 The TGF-β ligands signal by way of serine-threonine kinase receptors on the cell surface to proteins known as Smad proteins that accumulate in the cell nucleus to regulate gene expression. TGF-β superfamily signaling has been linked to myriad pathologies, including cancer and cardiovascular diseases.

In clinical trials for treating TDT, luspatercept-aamt is administered as a subcutaneous injection at doses of 0.8 to 1.25 mg/kg, once every 21 days.494

Evidence Development Summary

Investigators have reported results from 3 trials of luspatercept-aamt, A536-04 (NCT01749540) and its open-label extension study A536-06 (NCT02268409) published together, and BELIEVE, or ACE-536-B-THAL-001 (NCT02604433), to treat patients with TDT.

In the phase II A536-04 single-arm, uncontrolled, dose-escalation study and its phase II open-label extension study, A536-06, adults (n = 64; 33 not transfusion dependent; 31 transfusion dependent) aged 18 years or older with TDT participated in a 24-week dose-finding and expansion stage (initial stage) and continue to participate in a 5-year extension stage (primary completion February 2021). Patients received 0.2 to 1.25 mg/kg of luspatercept-aamt (at 7 possible dose levels) subcutaneously every 21 days for ≥ 5 cycles (dose-finding stage) and 0.8 to 1.25 mg/kg (expansion cohort and 5-year extension).

Piga et al495 reported results in 2019:

The primary end point was erythroid response, defined as hemoglobin increase of ≥ 1.5 g/dL from baseline for ≥ 14 consecutive days (without RBC transfusions) for non-transfusion-dependent patients or RBC transfusion burden reduction ≥ 20% over a 12-week period vs the 12 weeks before treatment for transfusion-dependent patients. Eighteen non-transfusion-dependent patients (58%) receiving higher dose levels of luspatercept (0.6 to 1.25 mg/kg) achieved mean hemoglobin increase ≥ 1.5 g/dL over ≥ 14 days vs baseline. Twenty-six (81%) transfusion-dependent patients achieved ≥ 20% reduction in RBC transfusion burden. The most common grade 1 to 2 adverse events were bone pain, headache, and myalgia.

In the phase III BELIEVE, or ACE-536-B-THAL-001, double-arm, randomized controlled trial, adults (n = 336) aged 18 years or older with TDT were randomly assigned in a 2:1 ratio to receive luspatercept-aamt 1 mg/kg with titration up to 1.25 mg/kg (n = 224) or placebo (n = 112) subcutaneously every 21 days in addition to best supportive care for at least 48 weeks, followed by an open-label extension up to 5 years and posttreatment follow-up for up to 3 years (estimated study completion date June 2025).

Cappellini et al492 reported results in 2018:

48 of 224 (21.4%) patients in the luspatercept arm achieved the primary endpoint versus 5 of 112 (4.5%) patients receiving placebo (odds ratio 5.79, \( P < .0001 \)). 44 of 224 (19.6%) patients receiving luspatercept achieved a ≥ 33% reduction in RBC transfusion burden at weeks 37-48 compared with 4 of 112 (3.6%) patients receiving placebo (\( P < .0001 \)). Of 224 patients receiving
Luspatercept, 17 (7.6%) and 23 (10.3%) achieved a ≥ 50% reduction in RBC transfusion burden at weeks 13-24 and 37-48, respectively, compared with 2 (1.8%) and 1 of 112 (0.9%) patients receiving placebo (\( P = .0303 \) and \( P = .0017 \), respectively). The difference of mean change from baseline in transfusion burden from week 13 to week 24 was 1.35 units (\( P < .0001 \)).

158 of 224 (70.5%) patients receiving luspatercept achieved a ≥ 33% RBC transfusion reduction over any consecutive 12 weeks compared with 33 of 112 (29.5%) patients receiving placebo (\( P < .0001 \)); statistically significant differences were also noted for all other transfusion burden reduction endpoints.

Adverse events (AEs) observed in the study were generally consistent with previously reported phase 2 data. Treatment-emergent AEs leading to dose delay or dose reduction were similar between treatment arms. No patient deaths were reported for those treated with luspatercept.

Manufacturers and Regulatory Status

Luspatercept-aamt was developed by Acceleron Pharma, Inc (Cambridge, Massachusetts) in collaboration with Celgene Corp (Summit, New Jersey). Acceleron and Celgene submitted a Biologics License Application to FDA, which was accepted in June 2019. A Prescription Drug User Fee Act (PDUFA) date was set for December 4, 2019, for the \( \beta \)-thalassemia indication, but FDA approved the drug early, on November 8, 2019. The company stated that the indication for use is “for the treatment of anemia in adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions.”

FDA previously granted luspatercept Orphan Drug, Fast Track, and Priority Review designations for the transfusion-dependent \( \beta \)-thalassemia indication.

Results and Discussion of Stakeholder Comments

Eight stakeholders, reflecting caregiver, clinical, health systems, patient, and research perspectives, provided comments and ratings on luspatercept-aamt to treat transfusion-dependent \( \beta \)-thalassemia. Comments were received before the FDA approval. We have organized the following discussion of stakeholder comments by the parameters on which they commented.

**Patient outcomes, quality of life, and overall health:** Commenters agreed that luspatercept-aamt has moderate to large potential to disrupt patient outcomes, QoL, and overall health. A researcher noted that treatment for this patient population is ongoing, costly, and a burden to the health care system, patients, and their families, and thought “this new treatment has the potential to really help the affected patients.” A patient thought the data seem promising, with no major gaps. A health systems commenter stated that the ongoing trials “appear to be well grounded in known theory/concept with potentially promising results.” A researcher noted that most patients had a reduction in number of transfusions. Another researcher thought the change in the care process from requiring up to 4-hour-long infusions every 1 to 2 weeks and nightly iron chelation to a subcutaneous injection every 21 days might “dramatically improve care for patients with difficulty accessing treatment centers.” A caregiver noted the burdens for patients when they depend on transfusions, including experiencing limits on traditional daily living activities, having to rely on others for assistance, making frequent visits for medical care, and traveling for medical care.
Health disparities: Commenters agreed luspatercept-aamt has moderate to large potential to disrupt health disparities. Most thought it might decrease health disparities. A caregiver and 2 researchers thought that it might decrease disparities in access to care. A health systems commenter thought this intervention might improve disparities in care quality by caregivers, as patients will have lower disease burden. A patient stated that luspatercept-aamt has the potential to reduce health disparities in this patient population. However, one clinician thought luspatercept-aamt has moderate potential to increase health disparities, stating that some patients and providers might not choose this drug because patients with SCD (a similar disease) are treated and followed by nonhematologists and that most of those patients depend on medical assistance.

Health care delivery system: Commenters agreed luspatercept-aamt use has moderate to large potential to disrupt the health care delivery system and change the current treatment infrastructure; decrease use of blood transfusions, pretransfusion bloodwork, and iron chelation; decrease hospital admission; reduce needs for specialty visits; overall required treatment resources, and treatment time; alter medical staffing needs; and change the overall care process. A caregiver thought luspatercept-aamt would change the way patients with TDT are managed in the health care system, stating that the current system is “tertiary and designed to treat the problem,” whereas treatment with luspatercept-aamt might prevent the problem.

Current paradigm of patient care: Commenters generally agreed that luspatercept-aamt use has large potential to disrupt the current paradigm of patient care. All commenters thought that the intervention might disrupt clinician and patient ease of acquisition because the treatment is convenient compared with the standard of care, and most commenters noted it is a less invasive treatment. A caregiver thought this intervention might provide an alternative treatment for patients without a matched donor and might reduce side effects associated with transfusions. Three commenters thought this intervention might disrupt anticipated side effects, risks, and adverse events.

Health care costs: Most commenters agreed luspatercept-aamt use might significantly decrease health care costs by avoiding transfusions, although others pointed out that comparisons between any potential decrease in the costs of conventional treatment and the added cost of luspatercept-aamt are unavailable because its cost information has not yet been released and insurance coverage is unknown. A researcher thought the cost of luspatercept-aamt might be lowered in the future if the medication can be used for other conditions as well.

Overall disruption potential: Commenters generally agreed that luspatercept-aamt use has a large overall disruption potential. A health systems commenter thought the intervention might disrupt the standard of care, referencing the significance of the 33% to 50% reduction in blood transfusion burden of patients in the BELIEVE study. A patient stated that “this seems to be a game changer,” reasoning that luspatercept-aamt might increase patient access to care and offer a more convenient treatment option, considering that injections are administered only once every 21 days. A researcher commented that luspatercept-aamt might help patients, who have few options, and the new drug might “reduce the man power, time, and resources needed for the current treatment.”
Onasemnogene Abeparvovec-xioi (Zolgensma) to Treat Spinal Muscular Atrophy

**Highlights**

Zolgensma, approved by FDA in May 2019, purportedly promotes SMN1 expression in patients with spinal muscle atrophy (SMA). This one-time gene therapy provides a treatment option for a condition with few effective options and appears to increase developmental milestone achievement (eg, sitting, standing, walking), improve survival, and decrease the need for ventilator support in patients with SMA type 1, according to interim data from 3 ongoing phase III trials and 1 completed phase I trial.

Comments from the 9 stakeholders commenting on this topic were received before FDA approval and before cost information was available. Commenters agreed that Zolgensma has high potential to improve short-term health outcomes and increase immediate health care costs in patients with SMA, and it might also decrease long-term health care use and costs associated with disease progression. Compared with its competitor nusinersen (Spinraza), which requires quarterly spinal injections, Zolgensma’s one-time dosing regimen is a dramatic shift in the current paradigm of patient care. Several commenters noted that studies enrolling larger numbers of patients with SMA that measure longer-term safety and efficacy outcomes are needed.

**Patient Population**

Zolgensma is intended for infants aged 2 years or younger with SMA (type unspecified).

**Intervention**

SMA is a neuromuscular disorder caused by a genetic defect in the human survival motor neuron 1 gene, SMN1, that results in the loss of the gene’s encoded SMN protein, which is critical for motor neuron function and transmission of signals from the brain to skeletal muscles. Patients with SMA experience motor neuron loss, resulting in progressive muscle weakness and eventual paralysis.508,509

The related SMN2 gene can also produce low levels of SMN protein. The gene’s copy number naturally varies in humans, and SMA disease severity generally correlates with the number of SMN2 copies the patient has (ie, the more copies of SMN2, the less severe the disease). SMA is classified into 1 of 4 types (1, 2, 3, 4), with type 1 being the most severe and having the earliest onset, at about 0 to 6 months.510

Zolgensma is an adeno-associated viral vector containing a functional copy of SMN1 approved for treating SMA (type unspecified).511 Delivery of a functional copy of SMN1 by Zolgensma might delay or halt disease progression in patients with SMA type 1.512 Patients receiving Zolgensma are likely to have SMA types 1 or 2, as onset of these types typically occurs before 2 years of age.510

The FDA-recommended dose of Zolgensma is $1.1 \times 10^{14}$ vg/kg of body weight, delivered by IV via peripheral vein, once. Because patients might experience immune reactions to the viral vector and/or transient changes in liver enzyme function after Zolgensma treatment, patients also receive systemic corticosteroids equivalent to oral prednisolone at 1 mg/kg of body weight per day, starting 1 day before Zolgensma administration and continuing for a total of 30 days. At the end of this 30-day period, clinicians assess patients’ liver function. Patients with normal follow-up results taper the corticosteroid dose over the next 28 days. If liver function abnormalities
Persist, patients continue systemic corticosteroid treatment until laboratory findings are normal and then taper the corticosteroid dose over the next 28 days.513

For additional information on SMA, see the [SMA Foundation website](https://www.smafoundation.org).

**Evidence Development Summary**

Three single-arm phase III studies are ongoing: STR1VE-US (NCT03306277), SPR1NT (NCT03505099), and STR1VE-EU (NCT03461289). These studies are assessing Zolgensma’s effectiveness in patients with SMA type 1. Primary and secondary outcomes include developmental milestone achievement (eg, independent sitting, standing, walking), overall and event-free survival, and ventilator-support independence. The studies’ primary completion dates range from November 2019 to November 2020, but the manufacturer has reported interim data for all (see below). Authors also published data from the completed phase I START trial (NCT02122952; see below). A long-term follow-up extension study of the START trial is also ongoing and is assessing adverse events and SAEs through 15 years after treatment; the study’s primary completion date is December 2033.

In April 2019, the manufacturer reported interim data for the phase III STR1VE-US trial in a news release.514 In September 2019, the manufacturer reported additional STR1VE-US data, as well as interim data for the phase III SPR1NT and STR1VE-EU trials, in a single news release.515 For brevity’s sake, we summarize below the primary and secondary outcomes (as reported in the National Clinical Trials database) as well as adverse event data:

Interim data were reported for 22 of 27 infants with SMA type 1 enrolled in the SPR1NT trial, who had either 2 or 3 copies of SMN2 and had received $1.1 \times 10^{14}$ vg/kg of body weight of Zolgensma at ≤6 weeks of age. As of May 31, 2019 (about 13 months after the study start), all 22 patients (100%) were alive and did not require permanent ventilator support. Of the 10 patients with 2 copies of SMN2, 6 (60%) were able to sit without support for at least 30 seconds at an average age of 7.6 months, and 3 (about 30%) were able to stand with assistance at an average age of 10.1 months. The manufacturer noted that patients with SMA and 2 copies of SMN2 who were not treated with Zolgensma would never be able to sit without support.

In the SPR1NT data, 7 of 18 patients experienced a TEAE related to Zolgensma administration. TEAEs of special interest (ie, related to liver function) were reported in 4 patients; the news release did not note whether patients received additional treatment or whether these events resolved.

Interim data were also reported for 22 infants with SMA type 1 enrolled in the STR1VE-US trial, who had either 1 or 2 copies of SMN2 and had received an unspecified dose of Zolgensma at ≤6 months of age. As of September 27, 2018 (about 11 months after the study start), 21 patients (95%) were alive and did not require permanent ventilator support. Three patients could sit without support for at least 30 seconds; this number had grown to 8 patients as of December 31, 2018 (about 14 months after the study start). As of May 31, 2019 (about 19 months after the study start), 20 patients (91%) were alive and did not require permanent ventilator support. Of 19 patients who had either reached 13.6 months of age or experienced an event (eg, death, ventilator support), 17 patients (90%) survived without requiring permanent ventilation. The manufacturer noted that only 25% of patients with SMA type 1 would be expected to survive without permanent ventilator support at 13.6 months of age. Two patients enrolled in the trial died from respiratory complications, but only one death was attributed to Zolgensma treatment.

Interim data were also reported for 10 of 33 infants with SMA type 1 enrolled in the STR1VE-EU trial, who had either 1 or 2 copies of SMN2 and had received an unspecified dose
of Zolgensma at ≤6 months of age. As of May 31, 2019 (about 9 months after the study start), of
the 10 patients who had reached 10.5 months of age or experienced an event (eg, death,
ventilator support), 9 (90%) survived without requiring permanent ventilation. One patient in the
trial died from respiratory complications and resultant brain damage, which were not attributed
to Zolgensma treatment. But the patient also had abnormal blood test results (ie, liver enzyme
elevation, low blood count) that might have been associated with Zolgensma treatment.

As noted above, Mendell et al in 2017 and Al-Zaidy et al in 2019 published data on the
completed phase I START trial, in which 15 patients with SMA type 1 and 2 copies of SMN2
received either $6.7 \times 10^{13}$ vg/kg (cohort 1; $n = 3$) or $2.0 \times 10^{14}$ vg/kg (cohort 2; $n = 12$) of
Zolgensma at either 6 or 9 months of age. According to Mendell et al, as of August 2017 (4
months before study completion), all 15 patients were alive and event-free at 20 months of age,
as compared with a rate of survival of 8% in a historical cohort. In the high-dose Zolgensma
cohort, a rapid increase from baseline in the score on the Children’s Hospital of Philadelphia
Infant Test of Neuromuscular Disorders (CHOP-INTEND) scale followed gene delivery, with an
increase of 9.8 points at 1 month and 15.4 points at 3 months, as compared with a decline in the
score in a historical cohort. Of the 12 patients who had received high-dose Zolgensma, 11 (92%)
sat unassisted, 9 (75%) rolled over, 11 (92%) fed orally and could speak, and 2 (17%) walked
independently. Four patients experienced abnormal liver function that was resolved with
corticosteroid treatment. Additionally, Al-Zaidy et al reported in 2019 that all 12 patients
receiving high-dose Zolgensma completed the study, and 7 (58%) did not require permanent
ventilation support.

Manufacturers and Regulatory Status

AveXis, Inc (Bannockburn, Illinois), a wholly owned subsidiary of Novartis AG (Basel,
Switzerland), developed Zolgensma for treating SMA type 1. FDA approved the drug for this
indication on May 24, 2019. Its approval was based on data from the ongoing phase III
STR1VE-US trial and the completed phase I START trial. FDA granted Zolgensma Orphan
Drug designation for treating any type of SMA and Breakthrough Therapy and Fast Track
designations for treating SMA type 1.

Cost Information

Zolgensma’s wholesale acquisition cost (WAC) is about $2.1 million. Its manufacturer
established the OneGene Program to provide patients with reimbursement assistance and support
and also created a worldwide expanded-access plan to allow uninsured or underinsured patients
access to the drug.

An April 2019 evidence report from the Institute for Clinical and Economic Review (ICER)
that was published before Zolgensma’s approval evaluated the drug’s cost-effectiveness
compared with that of best supportive care (no additional therapy). Because Zolgensma’s WAC
was not yet available, ICER used a placeholder price of $2 million, which is similar to its actual
WAC. Compared with no additional treatment, Zolgensma’s estimated lifetime incremental cost-
effectiveness ratio was about $243 000 per QALY gained, higher than the generally accepted
cost-effectiveness threshold of $150 000 per QALY. Estimated cost per life year gained was
$182 000. Additionally, ICER estimated total costs of Zolgensma to be $3.7 million compared
with $790 000 for best supportive care. In the same report, ICER also determined that
Zolgensma’s comparator, Spinraza, was not cost effective, with a lifetime incremental cost-
effectiveness ratio of about $1.1 million per QALY gained.
Results and Discussion of Stakeholder Comments

Nine stakeholders, reflecting genetic counseling, caregiver, clinical, research, and systems perspectives, provided comments and ratings on Zolgensma for treating SMA. Readers should note that commenters provided input on this topic before Zolgensma’s FDA approval, and before the manufacturer reported data from the ongoing SPR1NT and STR1VE-EU studies. We have organized the following discussion of stakeholder comments by the parameters on which they commented.

**Patient outcomes, quality of life, and overall health:** Most commenters thought that short-term results were encouraging, but called for longer-term outcomes and studies with larger numbers of enrolled patients. One caregiver noted that the phase I START study did not enroll patients already requiring invasive ventilator support or those requiring tube feeding, and said that, “it would be helpful to include infants who require technical interventions, as there is no way to know if the drug helps slow or halt the progression for them from this point.” One researcher noted that no ongoing or completed studies compared Zolgensma and nusinersen (Spinraza), which might help to determine the drugs’ comparative safety and effectiveness.

**Health disparities:** Most commenters agreed that Zolgensma’s cost is anticipated to increase health disparities, because the drug would likely be expensive and patients who are uninsured or have large copayments will not be able to afford treatment. However, a clinician and 2 researchers also noted that Zolgensma’s single-infusion dosing regimen could decrease health disparities compared with patients who might receive ongoing (quarterly) spinal infusions of Spinraza.

**Health care delivery system:** All commenters agreed that Zolgensma has large potential to reduce long-term health care use (eg, chest physiotherapy, ventilator support, feeding tubes) for patients with SMA. However, one caregiver thought that if Zolgensma “does not decrease the long-term effects of the disease and/or causes liver failure, the level of care may greatly increase for patients and health systems.”

**Current paradigm of patient care:** Most commenters thought that Zolgensma’s single IV dose is a dramatic shift from quarterly spinal infusions of Spinraza. One caregiver pointed out Zolgensma’s potential to cause liver damage, but thought that the drug’s side effects would be less severe and more transient than those observed after Spinraza treatment.

**Health care costs:** All commenters agreed that Zolgensma’s proposed multimillion-dollar price tag has a very large potential to increase immediate health care costs, and they questioned whether third-party payers would cover the drug. Most commenters thought that Zolgensma’s high cost could offset costs associated with long-term care of patients with SMA; one researcher disagreed, stating that patients receiving Zolgensma “will likely need a longer period of costly specialized care due to improved survival.”

**Overall disruption potential:** All commenters thought that Zolgensma has large overall potential for disruption (eg, improved patient outcomes, less invasive delivery compared with Spinraza, controversial high cost and third-party payer coverage, shift from inpatient to outpatient health care, and decreased long-term resource use). However, 4 commenters with research and caregiver perspectives reiterated the need for longer-term safety and/or efficacy data.
OTL-101 to Treat Adenosine Deaminase–Severe Combined Immunodeficiency

Highlights

OTL-101 is a gene therapy that might improve a patient’s ability to produce adenosine deaminase (ADA), an enzyme that can restore immune function in patients with severe combined immunodeficiency (ADA-SCID). The 6 stakeholders commenting on this topic were generally optimistic about OTL-101’s potential to provide sustained ADA production and restore immune function in patients ineligible for matched family HSCT. They thought this because data showed improved overall survival, event-free survival, reduced patient dependence on immunoglobulin, and cessation of enzyme replacement therapy (ERT), compared with historical control patients treated with standard-of-care HSCT. However, commenters were concerned that OTL-101’s cost might create disparities by limiting access to underserved patients, despite potential cost offsets. Commenters also agreed that longer-term controlled studies are needed to better determine the safety and effectiveness of OTL-101.

Patient Population

OTL-101 is intended for infants and children aged 30 days to 17 years with ADA-SCID who are ineligible for allogeneic bone marrow transplantation from a matched family donor.

Intervention

ADA-SCID is a rare inherited disorder severely effecting the immune system due to genetic variants that inhibit the expression of the adenosine deaminase gene, ADA, which encodes an enzyme crucial for lymphocyte (T cell and B cell) development. Patients with ADA-SCID do not produce functional lymphocytes and thus are perpetually susceptible to severe infections.530 For more information on ADA-SCID, see the National Institutes of Health’s Genetics Home Reference website.

OTL-101 is a cell-based gene therapy made from patient-derived stem cells that have been transfected with a lentiviral vector encoding the human ADA gene ex vivo.531 The therapy is intended for the deficiency in ADA enzyme production, potentially restoring stable lymphocyte development and immunity in patients with ADA-SCID.532

To prepare OTL-101, stem cells from the patient’s bone marrow are harvested and shipped to a manufacturing site, where the cells are purified and transduced with a lentiviral vector that will deliver the ADA gene into the stem cells.533 After preparation, the genetically modified stem cells are frozen and shipped back to the infusion center. The patient then undergoes a pretreatment conditioning regimen with busulfan before the thawing and administration of the cryopreserved OTL-101 product as a single IV infusion.533

Evidence Development Summary

A phase I/II prospective, nonrandomized, single-arm OTL-101-4 trial (NCT02999984) enrolled infants and children (n = 20) aged 30 days to 17 years with ADA-SCID who lacked a medically eligible donor for HSCT, to assess the effectiveness and safety of OTL-101. The overall survival rate was 100% in patients treated with OTL-101 compared with 88% for historical control patients (treated with HSCT; P = .12). Event-free survival was also 100% and compared with 44% for historical control patients (P = .001) at 24 months. OTL-101
demonstrated evidence of immune reconstitution at 24 months after treatment, as 90% of patients receiving the gene therapy were able to stop immunoglobulin replacement therapy compared with 55% of patients given HSCT. No patients given OTL-101 restarted ERT from 30 days to 24 months after treatment, compared with 3 patients who required ERT after HSCT and 7 patients who required additional rescue after HSCT by 24 months.534

OTL-101 was well tolerated, with no deaths or reports of GVHD after treatment, while patients in the HSCT historical control group had 5 acute and 3 chronic GVHD events, including 1 GVHD-related death. The most common SAEs in OTL-101-treated patients were infections and gastrointestinal events.

Manufacturers and Regulatory Status

OTL-101 is manufactured by Orchard Therapeutics, Ltd (London, United Kingdom) and is in phase I/II clinical development for treating ADA-SCID in infants and children aged 30 days to 17 years.535 The manufacturer has announced plans to submit a Biologics License Application to FDA in 2020 with results from its phase I/II registration trial.536 FDA previously granted OTL-101 Orphan Drug, Rare Pediatric Disease, and Breakthrough Therapy designations.537,538

Results and Discussion of Stakeholder Comments

Six stakeholders, reflecting health systems, clinical, physician assistant, and research perspectives, provided comments and ratings on OTL-101.539-544 We have organized the following discussion of stakeholder comments by the parameters on which they commented.

Patient outcomes, quality of life, and overall health: Commenters generally considered OTL-101 effective for sustained treatment of ADA-SCID, which might eliminate the need for standard care consisting of ERT and immunoglobulin therapy or HSCT in patients unable to find suitable donors. Commenters were encouraged by the survival and event-free data and duration of effects compared with historical control patients who also required additional rescue HSCT. However, the commenters cautioned that the use of historical control patients treated with HSCT introduced bias into the study. Two researchers noted variety in outcomes among enrolled patients due to ADA-SCID’s variable penetrance and disease severity as well as variability in donor matching between the HSCT procedures.542,543 Commenters with clinical and physician assistant perspectives noted that effectiveness beyond 24 months (and up to 5 years) is a key endpoint, as that is the expected life span of patients without treatment.540,541 A researcher suggested that large case series will be needed to assess the risk of leukemic transformation in patients treated with OTL-101.543

Health disparities: Commenters with physician assistant and research perspectives noted that OTL-101 use might reduce health disparities by providing a treatment option for children without a biologic matched donor for HSCT.541,542 But the cost of OTL-101 might cause disparities, particularly in vulnerable groups with the highest health disparities.541 A clinician and researcher noted that the low prevalence of ADA-SCID should limit OTL-101’s high cost for most payers, which might limit disparities to access.540,543 One researcher expressed concern that access still might be limited for uninsured, underinsured, or rural patients.543

Health care delivery system: Commenters generally agreed that OTL-101 treatment would simplify the management of patients with ADA-SCID by reducing demands on the system, such as reducing short- and long-term management demands compared with HSCT or long-term ERT and immunoglobulin administration. OTL-101 is manufactured in a single facility that enables
administration to patients at specialized care centers around the country. The small population of patients with ADA-SCID is unlikely to cause health systems to invest in additional resources to deliver the intervention.

**Current paradigm of patient care:** Commenters generally thought that OTL-101 would simplify ADA-SCID management if the treatment’s effects were sustained for at least 2 to 5 years. A physician assistant noted that if OTL-101 becomes standard care for ADA-SCID, it might provide faster access to treatment than HSCT does. A researcher suspected that the biggest impact on treatment paradigms might be the potential elimination of GVHD by replacing HSCT.

**Health care costs:** Commenters suspected that OTL-101 would be expensive, but it might provide long-term cost offsets by reducing the need for subsequent HSCT or ERT and immunoglobulin as well as reducing hospital stays and office visits. Two researchers stated that the competing ADA-SCID treatment Strimvelis costs $650,000 to $700,000 USD per patient in the United Kingdom compared with $100,000 to $250,000 USD per patient for HSCT. They expect OTL-101 to cost more in the United States, and to cost more than HSCT. A physician assistant wondered if patients with public insurance would have the same access to OTL-101 as those with private insurance. But another clinician noted that HSCT is already expensive and OTL-101 might not substantially affect patients’ out-of-pocket costs. Commenters thought that payers would face large upfront cost increases for a limited subset of beneficiaries. Health care providers should require minimal investment to administer OTL-101, assuming that patients are treated at specialized children’s hospitals.

**Overall disruption potential:** Commenters generally agreed that OTL-101 use might provide a long-lasting or sustained cure for ADA-SCID. The gene therapy improved clinical outcomes in terms of overall survival and event-free survival compared with historical controls treated with the standard-of-care HSCT. One main benefit of OTL-101 is that it obviates the need for a matching stem cell donor and eliminates the risk of GVHD, substantially improving tolerability outcomes. OTL-101 might decrease burden on providers and costs to the system by reducing hospital stays and office visits for immunoglobulin and ERT after HSCT. However, long-term studies are needed to determine the effects of OTL-101 beyond 24 months.

### Palovarotene to Treat Fibrodysplasia Ossificans Progressiva

**Highlights**

Palovarotene is an orally administered, selective retinoic acid receptor gamma (RARγ) agonist intended to slow the progression of fibrodysplasia ossificans progressiva (FOP), a rare connective tissue disorder. The disease leads to heterotopic ossification (HO) flares, characterized by abnormal bone growth in muscles, tendons, and ligaments leading to disability and death. The 7 stakeholders commenting on this topic were generally optimistic about palovarotene’s preliminary results, which demonstrated substantial reductions in HO volume and flares. These reductions should improve health outcomes and QoL for patients by slowing disease progression and dependence on supportive care needed for FOP. However, commenters cautioned that the magnitude of palovarotene’s impact would be highly dependent on forthcoming data regarding the drug’s long-term safety and efficacy profile as well as the drug’s expected cost.
Patient Population

Palovarotene is intended for treating FOP in children aged 4 years or older and adults.

Intervention

In patients with FOP, mutant ALK2 overactivates Smad 1/5/8 transcription factors in the bone morphogenetic protein 2 (BMP2) pathway. This leads to HO that manifests as abnormal bone growth in muscles, tendons, and ligaments.\(^{545,546}\) HO flares can occur spontaneously or follow physical trauma (eg, injury, infection).\(^{545,547}\) Once heterotopic bone forms, it cannot be surgically removed because tissue disruption causes additional HO episodes.

HO progressively interferes with normal body functions, including walking, bending, breathing, chewing, and swallowing. Patients typically require a wheelchair by about 20 years of age. Registry data suggest a median life span of about 40 years, with cardiorespiratory failure and pneumonia cited as the leading causes of death.\(^{545,547,548}\) For more information about FOP, see the National Institutes of Health’s Genetic and Rare Diseases Information Center website.

Palovarotene purportedly binds to and activates RARγ to decrease Smad 1/5/8 protein levels and reduce excess BMP signaling to prevent further HO development in patients with FOP.\(^{546,549}\) In an ongoing phase III clinical trial, palovarotene is administered in a 5-mg dose, once daily, to manage chronic FOP. For an FOP disease flare, palovarotene is administered at a dose of 20 mg, once daily for 4 weeks, followed by 10 mg, once daily for 8 weeks.\(^{550}\)

Evidence Development Summary

The phase II single-arm, open-label extension PVO-1A-202 trial (NCT02279095) is assessing the safety and effectiveness of multiple palovarotene dosing regimens for treating chronic FOP and flares in children aged 6 years or older and adults aged up to 65 (n = 53).\(^{551}\) Patients given palovarotene at the chronic or flare dosing achieved a 91% reduction in mean new HO volume in 29 flares compared with 60 untreated flares (719 vs 8001 mm\(^3\); \(P = .01\)).\(^{551}\) Of the 9 patients given palovarotene with no new HO at the flare location at 12 weeks, none had new HO anywhere in the body at 12 months.\(^{551}\) Preliminary results of patients (n = 33) given the chronic or flare dosing reduced new HO (whole body volume) by 28% (21 567 mm\(^3\)) compared with untreated patients (n = 55) from the phase II placebo group and an FOP natural history study (29 731 mm\(^3\)).\(^{551}\)

Manufacturers and Regulatory Status

Palovarotene is manufactured by Clementia Pharmaceuticals, Inc (Montreal, Québec, Canada), an Ipsen Group company (Paris, France), and is in phase III development (MOVE trial, NCT03312634) for preventing FOP flares. The study is scheduled for primary completion in September 2020.\(^{550}\) The company anticipates submitting a New Drug Application to FDA for palovarotene to prevent HO associated with FOP flares in the first quarter of 2020, based on data from a phase II trial.\(^{552}\) Pending favorable results from the MOVE trial, Clementia Pharmaceuticals would likely seek a supplemental New Drug Application for palovarotene to treat chronic FOP.\(^{549}\) FDA granted palovarotene Rare Pediatric Disease designation to treat FOP.
in February 2019. FDA has also granted palovarotene Breakthrough Therapy, Fast Track, and Orphan Drug designations for treating FOP.

Results and Discussion of Stakeholder Comments

Seven stakeholders, reflecting physical therapist, health systems, clinical, nurse practitioner, and research perspectives, provided comments and ratings on palovarotene. We have organized the following discussion of stakeholder comments by the parameters on which they commented.

**Patient outcomes, quality of life, and overall health:** Overall, commenters were generally encouraged by the underlying science and early results of palovarotene, which showed potential to substantially improve patients’ short- and long-term health outcomes by significantly reducing the formation of new HO lesions. But commenters warned that the sample sizes were small, studies were not yet published in peer-reviewed journals, and long-term outcomes were not yet reported. A clinician expressed concern that the benefit of palovarotene might not outweigh the risk. Palovarotene is a retinoic acid derivative and a known teratogen that causes limb malformation in developing fetuses. The same commenter warned that it might negatively affect growth plates, hearing, or vision in growing children, and expressed concern that HO has 4 key stages and that palovarotene acts on the fourth stage, while other experimental agents in development work earlier in the HO pathway.

**Health disparities:** Overall, commenters did not think that palovarotene use would substantially affect health disparities. But a nurse practitioner, a health systems commenter, and 2 researchers noted that access might be limited for underserved patients due to the high costs of new treatments for rare diseases. Two researchers noted that the treatment might improve the life span and probably the QoL for individuals who use the drug and reduce the burden of disease by reducing the need for access to other health care services, which could reduce disparities.

**Health care delivery system:** Commenters generally agreed that the oral administration of palovarotene would not substantially affect the health care delivery system. However, a nurse practitioner noted that reducing the annual volume of HO formation might substantially impact patient QoL as well as decrease the need for supportive care costs. Two researchers added that reducing the frequency and seriousness of HO flares might open the door to additional life-changing interventions for these patients, and having a therapy that acts directly in the disease pathway is a disruptive change to the system.

**Current paradigm of patient care:** Overall, commenters thought that the simple oral administration of palovarotene might disrupt current treatment paradigms by shifting treatment from palliative therapy to directly targeting an underlying mechanism of HO formation. This might substantially slow disease progression, preserve mobility, and alter the natural history of FOP, particularly for patients treated early in life. However, commenters warned that the side effects of palovarotene remain unclear.

**Health care costs:** Commenters generally agreed that palovarotene would likely disrupt health care costs as an expensive therapy intended to serve a small patient population affected by FOP. Two commenters, with nurse practitioner and research perspectives, noted that payers would need to cover the cost of palovarotene to make it accessible. But a health systems commenter noted that if palovarotene slows disease progression, treatment costs might be offset
by improved management of symptoms and mobility.\textsuperscript{555} A commenter with a research perspective noted that despite the expected high cost of the drug, the low prevalence of FOP should limit overall cost on the system.\textsuperscript{559}

**Overall disruption potential:** Commenters were optimistic regarding palovarotene’s early results that demonstrated positive overall disruptive potential as a possible first-in-class treatment for directly slowing FOP progression, which might improve health outcomes and QoL. Reducing HO flares and volume might reduce burden on patients, caregivers, and the health care system by reducing patient dependence on supportive care for FOP. However, commenters expressed reservation that the magnitude of palovarotene’s impact would be highly dependent on forthcoming data regarding the drug’s long-term safety and efficacy profile as well as the drug’s expected cost.

RVT-802 to Treat Pediatric Congenital Athymia

**Highlights**

RVT-802 is a cell-based therapy derived from allogeneic (ie, from a donor) infant thymus tissue and is intended to restore thymus function in pediatric patients born without a thymus (ie, athymia) so they can develop a functional immune system. No FDA-approved treatments are available, and the condition often leads to death by 2 years of age. The 6 stakeholders commenting on this topic were generally optimistic about RVT-802’s potential to improve short- and long-term health outcomes and QoL by reducing or eliminating the need for prophylactic antimicrobial and immunoglobulin therapy in patients with athymia.

However, commenters were concerned that RVT-802’s high projected cost might create disparities by limiting access for uninsured and underinsured patients or patients who cannot afford the copayments. Commenters also warned that patients with congenital athymia often have other complex medical conditions that will not be addressed by RVT-802. Commenters agreed that larger, longer-term controlled studies are needed to better understand RVT-802’s safety (ie, risk of death and autoimmune complications) and effectiveness compared with thymus transplant and HSCT.

**Patient Population**

RVT-802 is intended for infants and children with pediatric congenital athymia, a condition associated with genetic syndromes including complete DiGeorge genetic anomaly (cDGA); coloboma, heart defects, atresia choanae (CHARGE) syndrome; and Forkhead Box N1 (FOXL1) deficiency.

**Intervention**

Pediatric congenital athymia is a very rare disorder associated with several rare, life-threatening genetic diseases (ie, cDGA, CHARGE syndrome, and FOXN1 deficiency) that arise from genetic rearrangements that cause an affected individual to be born without a thymus. About 20 infants are born with congenital athymia each year in the United States. Affected infants cannot produce T cells, which are a critical part of a functioning immune system. Lack of T cells leads to a severe inability to fight infections and eventually results in death, typically by 2 years of age due to infection. No FDA-approved therapies are available for this collection of diseases.\textsuperscript{561} For more information on the disorders caused by athymia, see [Immune Deficiency](#).
RVT-802 is an allogeneic cell-based therapy derived from infant donor thymus tissue and is intended to reconstitute thymus function in patients with athymia so they develop a working immune system. According to the manufacturer, these patients are still capable of producing bone marrow–derived precursor T cells that can migrate from the bone marrow to the implanted RVT-802 tissue product where these precursors can grow into working thymus cells (ie, thymopoiesis). RVT-802 is intended to be a one-time therapy to permanently restore normal immune function in patients. Donor tissue comprising RVT-802 is typically obtained from infants undergoing cardiac surgery, during which thymus tissue is frequently removed to gain access to the heart. After tissue donation, RVT-802 is processed and cultured for 14 to 21 days in a manufacturing facility before implantation at a specialized treatment center.

In clinical trials, RVT-802 is administered by placing a cultured thymus slice into a small incision in the patient’s quadriceps muscle that is then pulled over the slice using an insoluble stitch. Physicians implant between 4 and 18 g of thymus tissue per square meter of body surface area.

Evidence Development Summary

A small, prospective, European pilot trial enrolled patients (n = 12) with cDGA and treated them with allogeneic cultured thymus. The investigators reported that 2 patients died from preexisting viral infections before the thymus cells could become established, and 1 death occurred later from autoimmune thrombocytopenia. One infant required reimplantation after septic shock. Although circulating T-cell counts typically did not reach normal levels in surviving patients, they were able to clear preexisting and subsequent infections. At a median of 49 months, 8 patients no longer needed prophylactic antimicrobials, and 5 no longer needed immunoglobulin replacement. Thymopoiesis was observed in 7 of 11 patients’ biopsies, 5 of whom achieved histologic evidence of full thymocyte maturation. Autoimmune complications were reported in 7 of 12 patients—2 cases of early transient autoimmune hemolysis that resolved and 5 cases of chronic autoimmune complications that included hemolysis, neutropenia, thrombocytopenia, and thyroiditis.

A retrospective review was performed of infants (n = 59; median age at transplantation 5.0 months) with cDGA implanted with cultured thymus slices between January 1, 1993, and July 1, 2010. After transplantation, 20% of patients required 25 emergent pediatric intensive care unit (PICU) admissions, 58% of whom survived to PICU discharge, with 6 patients surviving 6 months after transplantation. Intubation and mechanical ventilation were required in 60% of admissions. The investigators reported that 75% of patients admitted to the PICU had congenital heart disease. But age at transplantation and the presence of congenital heart disease were not associated with risk for PICU admission or PICU death.

Manufacturers and Regulatory Status

RVT-802 is manufactured by Enzyvant Therapeutics GmbH (Basel, Switzerland), a subsidiary of Roivant Sciences GmbH (Basel, Switzerland) in collaboration with Duke University (Durham, North Carolina), and is in phase II clinical development. The company announced that FDA accepted its Biologics License Application for RVT-802 for treating pediatric congenital athymia. FDA is not planning to hold an advisory committee meeting, and the developer anticipates a regulatory decision in December 2019. FDA granted Rare Pediatric
Disease designation to RVT-802 in September 2017 to treat primary immune deficiency resulting from congenital athymia associated with cDGA.\textsuperscript{566} FDA granted RVT-802 Breakthrough Therapy and Regenerative Medicine Advanced Therapy designations in April 2017 to treat cDGA.\textsuperscript{567}

**Cost Information**

Although cost data are not yet available from the manufacturer, the Academy of Managed Care Pharmacy estimates that RVT-802 might have a budget impact of $1.5 million per treated patient.\textsuperscript{568}

**Results and Discussion of Stakeholder Comments**

Six stakeholders, reflecting clinical, health systems, nursing, and research perspectives, provided comments and ratings on RVT-802.\textsuperscript{569-574} We have organized the following discussion of stakeholder comments by the parameters on which they commented.

**Patient outcomes, quality of life, and overall health:** Commenters generally agreed that RVT-802 demonstrated disruptive potential on health outcomes by providing patients with athymia a treatment option for immune reconstitution without needing sibling-matched donor tissue. One clinician noted that RVT-802 might decrease the risk of GVHD compared with the standard-of-care thymus transplantation or HSCT.\textsuperscript{574} This clinician and a researcher were encouraged by the findings that 8 of 9 surviving patients were able to stop taking prophylactic antimicrobials and 5 of 9 ceased immunoglobulin replacement at 49 months.\textsuperscript{573,574} Both of these commenters also noted that more long-term controlled studies are needed to assess the safety and effectiveness of RVT-802 and donor-matched thymus transplantation, HSCT, and supportive care to better understand the therapies’ tradeoff between benefit (immune reconstitution) and risk (death or autoimmune complications).\textsuperscript{573,574}

**Health disparities:** Commenters expressed concern that the expected cost of $1.5 million per patient might limit access to treatment. But commenters noted that athymia is so rare that all patients would likely be referred to highly specialized children’s hospitals, minimizing disparities. A clinician noted that RVT-802 might decrease disparities by obviating the need for sibling-matched donors. But RVT-802’s high cost and current availability at only one US center (Duke University, Durham, North Carolina) and one center in the United Kingdom might cause disparities for families with insufficient financial resources who also cannot travel to one of those locations, or whose insurance coverage would not support treatment out of network in another state or country.\textsuperscript{570}

**Health care delivery system:** One of the clinicians also noted that RVT-802 use might decrease the likelihood of late graft rejections compared with thymus transplants or HSCT.\textsuperscript{574} A nurse noted that, if effective, RVT-802 might substantially reduce demands on hospitals related to serious infections compared with standard care but that additional staff training would be needed regarding preoperative and postoperative management.\textsuperscript{572} Another clinician noted that negative disruptions to the system from RVT-802 might include the 75% survival rate reported in the literature and the PICU stays required for 20% of survivors.\textsuperscript{571} Patients treated with RVT-802 instead of a thymus transplant will still have parathyroid anomaly, which requires either medical attention or a parathyroid transplant.\textsuperscript{571} However, a health systems commenter noted that any disruption to the system would be extremely small due to the small number of patients with athymia.\textsuperscript{569}
**Current paradigm of patient care:** Two commenters with clinical and research perspectives thought that RVT-802 would simplify care because of the minimally invasive one-time implantation procedure (a small incision in the quadriceps muscle) compared with less successful HSCT treatments, which might require additional follow-up. The clinician noted that RVT-802’s benefits seem to outweigh the risks (ie, autoimmunity and respiratory distress) because of successful immune reconstitution and fewer infections. Another clinicians also noted that RVT-802 might make thymic transplantation available to more patients outside of Duke University. But a nurse cautioned that RVT-802 implantation requires highly technical teams during the procedure as well as during follow-up. A clinician noted that RVT-802 might be a high risk–high reward (ie, higher mortality–better immune reconstitution) therapy, but more data are needed to determine whether a significant difference in outcomes exists.

**Health care costs:** Commenters generally agreed that RVT-802 treatment would likely be costly at about $1.5 million. But costs to the system would be limited by the low prevalence of congenital athymia. Clinicians and a nurse noted that patients with congenital athymia have complex medical conditions that require multidisciplinary care and other costly treatments for management. The addition of $1.5 million for RVT-802 for immune reconstitution in this patient population might lead to controversy, as some might think that the resources should be focused on treatments for conditions that will provide a greater overall benefit on outcomes for more patients.

**Overall disruption potential:** Commenters generally agreed that RVT-802 demonstrates potential to provide an effective one-time treatment that might provide immune reconstitution for patients with congenital athymia without requiring matched donor tissue. A clinician noted that RVT-802 use shows potential to increase life span with potentially higher-quality immune reconstitution than HSCT shows in the literature. Commenters generally agreed that the implantation procedure would be easier than a standard thymus transplant but worried that the costs of RVT-802 might limit access to therapy. Two commenters with health systems and clinical perspectives thought that, because of the small numbers of affected patients, the overall disruption to the health system would be small, but if effective in long-term studies, RVT-802 might completely replace the standard of care. Commenters agreed that because RVT-802 is a novel tissue therapy, larger, longer-term studies are needed to better understand its safety, effectiveness, and full disruptive potential, including the cause of long-term autoimmune side effects.

**Viltolarsen to Treat Duchenne Muscular Dystrophy**

**Highlights**

No DMD cure is available, and the approved targeted treatments apply only to a small subset of genetic variations known to be involved in DMD, so therapies that target additional DMD-causing variants are needed. Viltolarsen is intended for patients with DMD who have an exon 53 rearrangement. The drug purportedly promotes exon 53 skipping during dystrophin mRNA processing, which allows synthesis of an internally truncated but functional dystrophin protein. According to data from a completed phase II trial that was announced in a news release, viltolarsen appears to increase dystrophin production as intended.

The 8 stakeholders commenting on this topic generally thought that the drug has the potential to positively impact longer-term health outcomes (eg, muscle strength, ambulatory function),
which are expected to be reported upon completion of an ongoing open-label extension study. Viltolarsen’s weekly infusion schedule is likely to increase health disparities, and its expected high cost might lead to hurdles in obtaining insurance coverage. Some thought that initial increases in health care resource use associated with treatment administration and monitoring might be offset by decreases in long-term care needs. Others questioned whether use of the drug would lead to reduced wheelchair use, fewer hospitalizations, and/or an overall cost savings.

**Patient Population**

Viltolarsen is intended for males aged 4 to 10 years with DMD who have an exon 53 genetic variant and are on a stable dose of corticosteroids.

**Intervention**

DMD is an inherited, X chromosome–linked genetic disorder caused by point rearrangements or deletions in the dystrophin gene, *DMD*. *DMD* encodes the dystrophin protein, which helps promote muscle function. In patients with DMD, the absence of wild-type dystrophin protein causes progressive muscle death and eventual widespread muscle weakness. No cure for DMD exists, and although FDA approved a dystrophin-replacement gene therapy for patients who have a specific mutation in *DMD* (ie, in exon 51), patients with other mutations are not eligible for this therapy. Therefore, additional therapies are needed.

Viltolarsen, also known as NS-065/NCNP-01, is an antisense morpholino oligonucleotide that purportedly binds exon 53 of dystrophin pre-mRNA (precursor RNA composed of introns and exons) and promotes skipping of exon 53 during mRNA processing. This exon skipping allows for synthesis of an internally truncated but functional dystrophin protein. Therefore, viltolarsen treatment might promote skeletal muscle function and prevent or delay disease progression in patients who have mutations in *DMD* exon 53, which represents about 8% of patients with DMD. In clinical trials, low-dose (40 mg/kg) or high-dose (80 mg/kg) viltolarsen is administered by IV, once weekly, for up to 144 weeks.

The Muscular Dystrophy Association provides more information on DMD.

**Evidence Development Summary**

The phase II randomized, double-blind NS-065/NCNP-01-201 study (NCT02740972) evaluated the safety and effectiveness of 1 of 2 doses of viltolarsen (40 or 80 mg/kg) compared with placebo in 16 patients with DMD and exon 53 rearrangements (low-dose n = 6; high-dose n = 6; placebo n = 4). Primary outcomes were adverse event incidence through 24 weeks and muscle dystrophin protein production at 20 through 24 weeks, as measured by Western blot analysis. Secondary outcomes were time to run or walk 10 meters; time to climb 4 stairs; North Star Ambulatory Assessment (NSAA) results; distance traveled in the 6-minute walk test; muscle strength (all vs matched historical controls, at baseline and weeks 20 through 24); muscle dystrophin mRNA production, as measured by RT-PCR, and muscle dystrophin protein production, as measured by mass spectrometry and immunofluorescence (all at 20 through 24 weeks).

Two separate manufacturer news releases from June 2018 and October 2018 reported data from the study. Muscle dystrophin expression increased in all 16 enrolled patients after 20 to 24 weeks of treatment (average = 5.8% of baseline; range = 1.1% to 14.4%). Timed function tests of viltolarsen-treated patients vs age- and treatment-matched natural historical controls
showed improvements for time to run or walk 10 meters velocity, time to stand from supine velocity, and 6-minute walk test distance (values for each of these measures of ambulatory function were not reported). No serious or treatment-related adverse events were observed; all were mild or moderate.

A separate phase II open-label extension study (NCT03167255) is enrolling patients who completed the NS-065/NCNP-01-201 study through week 25 and are receiving a stable corticosteroid dose. Primary outcomes are adverse event incidence and time to stand vs matched historical controls, both measured at baseline and week 144 after treatment. Secondary outcomes include time to run or walk 10 meters, time to climb 4 stairs, NSAA results, distance traveled in the 6-minute walk test, and muscle strength, all vs matched historical controls, at baseline and week 144. The study’s primary completion date is December 2020.

In September 2019, the manufacturer also initiated the phase III double-blind, randomized, placebo-controlled RACER53 trial (NCT04060199) to assess the effectiveness of viltolarsen in males aged 4 to 8 years with DMD who are ambulatory and are receiving a stable corticosteroid dose. The study’s primary outcome is time to stand, measured at baseline and week 48 after treatment. Secondary outcomes include time to run or walk 10 meters, time to climb 4 stairs, NSAA results, distance traveled in the 6-minute walk test, and muscle strength, all measured at baseline and week 48. The study’s primary completion date is November 2024.

Manufacturers and Regulatory Status

NS Pharma, Inc (Paramus, New Jersey), a subsidiary of Nippon Shinyaku Co, Ltd (Kyoto, Japan), in collaboration with the Cooperative International Neuromuscular Research Group (Washington, DC) and TRiNDS (Washington, DC), is developing viltolarsen to treat DMD. The drug is in phase II/III clinical development for this indication. In December 2018, the drug’s manufacturer announced that it had initiated with FDA a rolling New Drug Application,578 which it completed in October 2019.579 For treating DMD, FDA granted viltolarsen Rare Pediatric Disease designation in February 2017,580 Orphan Drug designation in January 2017,581 and Fast Track designation in November 2016.582

Results and Discussion of Stakeholder Comments

Eight stakeholders, reflecting physical therapy, caregiver, clinical, research, and health systems perspectives, provided comments and ratings on viltolarsen for treating DMD.583-590 We have organized the following discussion of stakeholder comments by the parameters on which they commented.

Patient outcomes, quality of life, and overall health: Most commenters agreed that viltolarsen increases dystrophin expression as intended, although a caregiver586 questioned whether the methods used to measure dystrophin expression were standardized or validated. Despite the lack of longer-term published data on muscle strength and ambulatory function (which is expected to be reported upon completion of the 144-week open-label extension trial), commenters generally thought that the drug has the potential to positively impact these patient health outcomes.

Health disparities: Overall, most commenters thought that viltolarsen’s anticipated high cost might increase health disparities for uninsured or underinsured patients. Additionally, 3
commenters with caregiver\textsuperscript{585,586} and research\textsuperscript{590} perspectives thought that the drug’s weekly IV delivery method could also increase health disparities.

**Health care delivery system:** Most commenters thought that viltolarsen’s weekly IV infusion regimen would increase health care resource use. Two caregivers\textsuperscript{585,586} thought that long-term health care use associated with disease progression might decrease if the drug improves patient health outcomes. A clinician\textsuperscript{588} expected that long-term cardiac and respiratory-related care needs would decrease, but that patients would still require use of a wheelchair.

**Current paradigm of patient care:** Because patients would need to visit infusion centers weekly to receive viltolarsen and would require regular monitoring and follow-up, most commenters thought that patients would initially have more interaction with their health care providers. One clinician\textsuperscript{588} was unsure whether patients would be able to reduce or eliminate their use of corticosteroids. A caregiver\textsuperscript{586} and clinician\textsuperscript{587} remarked that patients and clinicians are likely to encounter hurdles to getting insurance coverage for the drug, which could limit its use.

**Health care costs:** Most commenters thought that viltolarsen would likely be expensive, and patients and clinicians might find it difficult to obtain reimbursement from insurance. One caregiver\textsuperscript{585} thought that the drug’s upfront cost could potentially be offset by a reduction in some of the costs associated with long-term care (eg, durable medical equipment, home aides, physical therapy), but a clinician\textsuperscript{587} questioned whether the drug would lead to improved long-term health outcomes (eg, fewer hospitalizations) and overall cost savings.

**Overall disruption potential:** Overall, commenters agreed that the drug has large potential for disruption and is likely to become the standard of care for the 8% of patients with DMD who have exon 53 mutations. One researcher\textsuperscript{590} noted that this assumption depends on the sustainability of the observed short-term improvements in patient health outcomes.
Chapter 6. Potentially Disruptive Trends

Chapter Summary

In addition to the topics included in the previous chapters, the PCORI HCHSS identifies and monitors trends (ie, large, high-level disruptions). These trends can occur across or within clinical areas and arise from a combination of factors that, taken together, create a paradigm shift in health care. Identification of these trends goes beyond the 5 priority areas PCORI initially defined as a focus.

Because of the different nature and focus of trends compared with the topics summarized in the previous chapters, the trend summaries below follow a modified format. Each trend summary begins with a brief paragraph highlighting key takeaways for the reader, followed by a description of the nature and importance of the trend, a listing of clinical areas potentially affected by the trend, and a brief discussion of opportunities and threats (ie, potential positive and negative disruptions) posed by the trend.

As of October 1, 2019, we were monitoring 22 potentially disruptive trends. From among these, the horizon scanning team selected the 15 trends that the team unanimously agreed have high disruption potential. Among the trends presented in this report, 3 major themes have emerged that pertain to 13 of the 15 included trends:

- Artificial intelligence and machine learning: 5 trends
- Proteomics, genomics, and personalized medicine: 5 trends
- Health information technology, apps, and smart devices: 3 trends

The 22 trends we are monitoring will also be briefly described in the December 2019 PCORI Health Care Horizon Scanning System: Horizon Scanning Status Report.

Trend Summaries

We present below 15 summaries on trends deemed to have high potential for disruption. Trends are ordered alphabetically by trend title.

Artificial Intelligence and Machine Learning for Biologically Based Diagnosis of Mental and Behavioral Health Conditions

Highlights

Artificial intelligence (AI) and machine learning (ML) might enable biologically based diagnoses of mental and behavioral health conditions, which currently are diagnosed based on symptoms, family history, and clinical observations. This could lead to earlier, more individualized, and more effective treatment. However, use of this technology might also lead to detection errors and inaccurate diagnoses.
Description

Recent reports show potential for AI and ML to identify biological patterns (e.g., brain waves) that might improve understanding of and assist in detecting or diagnosing mental and behavioral health conditions, including depression, PTSD, schizophrenia, and bipolar disorder.\textsuperscript{591-593} Advances in AI and big data analysis techniques introduce the possibility of using aggregated health care data to produce ML algorithms and models that allow for semiautomated (i.e., requiring minimal human interaction) diagnosis.\textsuperscript{592,594} AI-assisted detection and diagnosis of mental health conditions might promote more timely, targeted, and individualized treatment than current symptom-based methods of diagnosis.\textsuperscript{591,594-596}

Clinical Area(s) Potentially Disrupted

The use of AI and ML for diagnosis might disrupt the field of mental and behavioral health, specifically the diagnosis and treatment of major depressive disorder, PTSD, bipolar disorder, and schizophrenia.

Opportunities

AI might enable more objective, standardized, biologically grounded diagnoses of some mental and behavioral health conditions than traditional methods of diagnosis.\textsuperscript{591,595} Patient outcomes might be improved by providing more accurate and timely diagnoses, leading to earlier and more effective management of the condition, compared with the current symptom-based method of diagnosis.\textsuperscript{591,597} This technology might be more cost effective and reduce long-term treatment costs by appropriately matching patients with the most effective treatments.\textsuperscript{593} Biologically based diagnosis might help reduce the stigma associated with mental illness.\textsuperscript{592,597}

Threats

Due to algorithmic detection errors, the use of AI might lead to inaccurate diagnoses that could have significant implications on patient health outcomes.\textsuperscript{591,597} Additionally, predictive algorithms and models would need to be regularly maintained and validated to ensure accuracy and generalizability.\textsuperscript{591,597} AI might be more costly in the short term than traditional methods of diagnosis. Additionally, the clinician learning curve might be high, and clinicians might view the use of AI as a threat to their autonomy.\textsuperscript{597}

Artificial Intelligence–Enabled Precision Medicine for Cancer Prognosis and Treatment Decisions

Highlights

Using AI to analyze a patient’s personal, family, clinical, genomic, and proteomic information might improve patient care by allowing the clinician to better integrate all of the patient’s information in a way that can help develop an optimal management plan.

Description

This application of AI uses ML and natural language processing (NLP) to analyze electronic pathology (e-path) records, comprising personal and family history, clinical features, and genetic or protein biomarkers. The intent is to manage patients’ cancer as follows: (1) Predict response to
treatment; (2) evaluate whether subsequent treatment might be beneficial; (3) guide targeted therapy selection (on label or off label) for cancers harboring actionable genomic alterations; and/or (4) help enroll patients in clinical trials of investigational therapies.598-600

The AI algorithms would need to be adapted to understand treatment paradigms for different types of cancers. In addition, the algorithms will also need to learn to recognize and collect information for different e-path records, which may have different formats and content.600 AI’s performance is compared with the gold standard of clinicians manually reviewing e-path records.598 Clinicians then use this information to establish a management plan that is most likely to benefit patients with cancer.

Clinical Area(s) Potentially Disrupted

Many institutions rely on a group of physicians and scientists who make up molecular tumor boards to analyze genomic and proteomic results and make treatment recommendations. However, keeping up with high volumes of newly published clinical knowledge on actionable and/or prognostic biomarkers can be challenging for board members.598,599 Implementation of AI has the potential to disrupt molecular tumor boards by providing faster and more comprehensive data analysis and recommendations for targeted therapies and clinical trials.598,600

Opportunities

AI might improve patient health outcomes by analyzing large amounts of clinical, genomic, and proteomic data that yield recommendations that can help clinicians more quickly identify targeted therapies and/or biomarkers likely to benefit patients.598 If AI can integrate, process, and organize all relevant data, it also might reduce human error rates in cancer detection and diagnosis. In addition, because most prognostic tests evaluate only validated prognostic indicators, AI might help identify novel prognostic markers that can be incorporated in prognosis assessment.599

Threats

Most FDA-approved targeted therapies are intended to treat cancers that harbor specific genetic alterations. If AI-recommended therapies are not yet labeled (ie, FDA approved) for the cancers for which they were recommended, third-party payers might be unlikely to cover either the genomic/proteomic profiling or the targeted therapies.600 Adopting AI-enabled precision medicine might increase disparities by limiting availability of off-label therapies to patients who have the resources to pay for treatments not covered by their insurance.598 Some physicians might be skeptical about using AI-generated treatment recommendations because of prior failed attempts in AI research to yield appropriate and reliable treatment recommendations.601

Artificial Intelligence for Image Triage to Prioritize Emergency Cases

Highlights

AI algorithms applied to diagnostic imaging might help radiologists rapidly identify the most urgent cases from large data volumes. However, the technology could be costly and complicated for health care facilities to implement and maintain.
Description

Several researchers and companies have developed AI software algorithms to screen imaging scans, including conventional X-rays, computed tomography (CT), and ultrasound, in high volumes in hospital EDs or other urgent care settings. These algorithms are designed to provide image triage—that is, to identify the most serious cases that might not be apparent based on traditionally recognized parameters or markers. The intent is to suggest giving these cases priority review by a radiologist. The AI algorithm pushes these cases to the front of the work queue based on identified markers learned by reviewing a multitude of images. Over time, some algorithms purportedly become more accurate at screening for certain indications as they review more images. Some products have already received FDA 510(k) clearance for specific indications using conventional X-rays, CT, and ultrasound, including identification of probable fractures in the cervical spine, intracranial hemorrhage, abdominal aortic tears, and brain aneurysms.

Clinical Area(s) Potentially Disrupted

This AI technology is most likely to disrupt work routines in hospital emergency and radiology departments because it is intended to screen for the most urgent cases and redirect them for priority review by radiologists. These potential disruptions could extend to other units (e.g., surgical, intensive care) based on possible changes in patient acuity identified by AI imaging algorithms.

Opportunities

AI-assisted image triage might improve patient health outcomes if the technology effectively assists radiologists in identifying the most acute cases so these patients can receive appropriate care sooner. From a staffing perspective, AI-assisted image triage might improve workflow by prioritizing higher-acuity cases when radiologist availability is limited. From a medico-legal perspective, implementation of AI-assisted image triage might provide a layer of protection against potential litigation for “missed” events or diagnoses in imaging scans.

Threats

From a resource perspective, the cost and complexity of AI-assisted image triage might limit its adoption to larger, high-volume imaging departments with sufficient resources and experienced staff to implement it. The availability of AI-assisted image triage could raise litigation risk for health care facilities that lack sufficient expertise and resources to implement these systems. Logistically, the availability of multiple AI-assisted image triage products or programs could complicate operations or system maintenance if many software products are required to work together. Such logistical issues might lead to imaging departments restricting use to a limited number of AI-product vendors to minimize system compatibility problems, potentially excluding AI-assisted features offered by competing vendors.
Artificial Intelligence Systems for Early Detection of Acute Kidney Injury Risk in High-risk Patients

Highlights

Many people with advanced chronic kidney disease (CKD) and their clinicians are unaware of their level of organ impairment. AI-enabled diagnostic systems might provide early notification to a clinician that a patient could benefit from more intensive prophylactic management to avert acute kidney injury (AKI). This might shift some aspects of renal management from treatment to prevention and reduce the high morbidity, mortality, and cost associated with AKI.

Description

About 50% of people with advanced (stage IV) CKD are unaware of their level of kidney function impairment.607 This can lead to rapid progression to kidney failure and a need for dialysis, involve immediate consultation with a nephrologist, and have generally poor outcomes. Researchers are developing AI-enabled diagnostics intended to monitor patients at high risk of developing AKI to provide early warning alerts to a clinician about a patient’s deteriorating condition.

For example, DeepMind AI, in collaboration with the Veterans Administration, is developing AI that evaluates data from the electronic medical record (EMR) that purportedly predicts AKI in patients up to 48 hours earlier than current diagnostic approaches.608 They are designing the system to provide clinicians with a warning notification through an app called Streams App. The notification indicates that a patient is a candidate for earlier and more intensive preventive treatment to avoid more invasive procedures like dialysis. In addition, RenalytixAI (KidneyIntelX) is in development for evaluating the long-term risk of AKI in patients with type 2 diabetes mellitus (T2DM).609 KidneyIntelX purportedly identifies patients with T2DM and fast-progressing kidney disease by using ML algorithms that assess a combination of predictive blood-based biomarkers in combination with EMR information to identify patients at high risk of kidney disease progression.

Clinical Area(s) Potentially Disrupted

AI systems capable of detecting subclinical signs of AKI in high-risk patients might shift treatment paradigms to a more effective and meaningful preventive care model for emergency care physicians, nephrologists, and endocrinologists who treat patients with T2DM and advanced CKD.

Opportunities

AI-driven systems might provide an actionable early warning to clinicians of imminent declining kidney function. The alerts could improve disease management and patient outcomes. If these systems can provide early warning of AKI that enables early intervention and averts kidney damage, substantial reductions in clinical and financial burdens to patients and the health care system might occur.
Threats

Some health care professionals might rely too heavily on these systems for patient monitoring and use less of their own clinical faculties. Also, this technology might contribute to alert fatigue experienced by clinicians from all the clinical care tools intended to protect patients and alert clinicians about potential harms.

Artificial Intelligence Voice Assistants for Patient-oriented Health Care Applications

Highlights

AI digital voice assistants using ML and NLP might provide effective home- or hospital-based health care guidance to patients. However, the technology might also pose a threat to patients’ health data privacy.

Description

Digital voice assistants, or conversational agents, have grown into widely used AI software programs designed to respond to natural language and simulate human conversation. These assistants are being positioned to provide patient health care support. Results from the Voice Assistant Consumer Adoption Report for Healthcare 2019 published by Voicebot.ai indicated that there are applications of this in media, communications, and general search, and both the 45- to 60-year-old (54.5%) and 18- to 29-year-old (52.8%) age groups are likely to use voice assistants to meet their health and wellness needs. AI-powered virtual assistants can provide 24-hour support to a wide range of patients who might need access to home care on demand.

For example, LifePod is a voice assistant designed to help people follow a care plan developed by their provider or to contact a caregiver when in need. Another patient voice assistant, Aiva, purportedly reduces the response time needed to connect with the caregiving team by triaging patient requests to the most appropriate caregiver.

Clinical Area(s) Potentially Disrupted

As the adoption of digital voice assistants grows with mounting health care use cases, potential disruption is likely in the health care technology market.

Opportunities

Digital voice assistants might improve patient access to health care by providing convenient, 24-hour medical advice to those in need, in both rural and urban areas. These assistants might also improve patient health outcomes by reducing the burden on health care providers and might decrease costs of care by reducing doctor’s office and clinic visits.

Threats

Inaccuracies in NLP might lead to providing patients with incorrect medical advice, thereby causing subsequent adverse events. In addition, the technology could pose significant threats to patients’ health data privacy and security.
Complete Omics Monitoring: Metabolomics, Proteomics, Genomics, and Transcriptomics for Disease Prevention and Treatment

Highlights

Complete “omics” monitoring is being proposed and marketed as a comprehensive wellness package. New technologies for disease risk prediction and early diagnosis could impact clinical practice by producing more accurate and earlier diagnoses and prognoses to inform patient and clinician decisions about optimal treatment paths. By integrating complete omics monitoring (ie, genomics, transcriptomics, proteomics, and metabolomics), use of these platforms might shift paradigms of screening, diagnosing, and monitoring treatment response. However, this approach could also lead to overdiagnosis or misdiagnosis due to incomplete scientific understanding of what all the omics results signify, lead to inappropriate treatment or follow-up care, and increase disparities due to access to omics testing, interpretation, and counseling about test results and its high cost (both for the testing and interpretation).

Description

Complete omics monitoring is being marketed as a comprehensive wellness package that includes whole genome sequencing, microbiome, metabolome, and proteome analyses. Researchers are exploring complete omics monitoring as a way to screen for disease risk, detect diseases earlier, and identify effective treatment options for patients. The approach is intended to improve early treatment, posttreatment, and progression monitoring of diseases such as cancers, neurodegenerative diseases, and metabolic diseases. For example, Q Bio’s platform uses a 75-minute patient evaluation visit and quarterly omics exams to gather all the necessary data. The company integrates information gained from anatomic, genetic, biochemical, and biometric measurements for early health intervention and disease prevention.

Clinical Area(s) Potentially Disrupted

Integration of omics data might disrupt a wide range of clinical areas, such as primary care, cardiology, allergy and immunology, gastroenterology, neurology, oncology, and infectious disease. Due to its nature, sensitive health information and possible unexpected results shared with patients who underwent testing thinking they were healthy (or had no specific new health-related complaints) could positively or negatively influence their mental and behavioral health, which might need further consideration and attention.

Opportunities

Individual omics technologies have provided insights to advance personalized medicine and identify disease risks earlier to enable intervention; however, the complexity of diseases and the patient management options might be improved by integrating several omics platforms at once. Clinicians might be able to more easily identify patients’ risks or early disease stages to pursue the best treatment options in a shorter time than standard screening and diagnostic processes allow. Additionally, integration of omics data might improve identification of new drug targets and development of effective personalized medicines in the future.
Threats

Complete omics monitoring as a health care “wellness” approach will likely increase costs significantly for participants and also for third-party payers that would need to cover treatment of identified diseases and conditions in their beneficiaries. Omics as a wellness approach might also widen health disparities further because those who could afford to pay for it (i.e., it is unlikely to be covered by insurance) would have health information to inform their course of action that individuals who cannot afford wellness omics testing would not. In addition, those able to afford the testing could pursue care for any unexpected conditions identified by the omics data. Another threat is that the predictive capabilities that omics data offer might lead to overdiagnosis and overtreatment for health issues that might be clinically insignificant or that could resolve on their own. This might negatively impact participants’ mental and behavioral health.

Comprehensive Genomic Profiling in Patients Who Have Cancer to Identify Personalized Targeted Therapy

Highlights

Implementing comprehensive genomic profiling (CGP) into routine cancer care might improve patient health outcomes by detecting actionable genomic alterations (AGAs) that indicate an aggressive cancer or inherited cancer risk that can be treated with targeted therapies. CGP also might improve QoL by helping to identify more effective, targeted therapy that might decrease use of cytotoxic chemotherapy and biologic therapies that are less effective and that can cause SAEs.

Description

CGP involves sequencing a large panel (i.e., thousands) of cancer-associated genes in DNA and/or RNA isolated from a patient’s tumor tissue or blood sample. CGP is intended to detect AGAs known to be therapeutic targets. Clinicians are using CGP (in both germline and somatic testing scenarios) to determine the aggressiveness and inheritable factors of cancers upon initial diagnosis (germline testing) and to select targeted therapies (on label or off label) along the patient’s clinical pathway (somatic testing) to benefit patients with cancers that harbor AGAs600,617,618. CGP also is being used to help identify patients who are eligible for clinical trials of investigational therapies for cancers with specific AGAs617.

Clinical Area(s) Potentially Disrupted

Incorporating CGP into routine care for patients with cancer has the potential to disrupt oncology practice by strengthening collaborations between genetic counselors and clinicians when considering results of germline genetic testing and the expanding number of AGAs that affect the risk and aggressiveness of cancer. CGP used for somatic genetic testing of tumor tissue or circulating tumor cells in the blood to identify AGAs would disrupt clinical practice by providing a much broader view of the kinds and number of gene variants from the tumor that need interpretation. New variants that might drive oncogenesis and resistance to existing therapies are being identified all the time through research. The data provided by CGP can contribute to understanding which gene variants play a role and how they function to drive disease processes, as well as which therapies might target the pathogenic variants identified.
Opportunities

Having sufficient quantity and quality of a tumor sample to conduct multiple single-gene tests over time has been a long-standing problem in oncology. As knowledge about AGAs progresses and more AGAs are identified, repeat genetic testing might be appropriate, but it might be impossible because the tumor sample was used up during initial testing. Next-generation sequencing of hundreds or thousands of genes at once, using a single tissue sample, has made CGP more feasible. Thus, more information is available to clinicians for future decisions about therapeutic targets. Compared with single-gene sequencing approaches, CGP also can identify AGAs quicker without the need for additional testing. In addition to improving patient health outcomes, CGP and related management has the potential to be cost effective. In clinical practice, targeted therapy for treating cancers (eg, breast, lung, kidney) is associated with better outcomes and fewer adverse events for many patients than systemic chemotherapy. In cancers, such as gastric or pancreatic cancer, which lack effective targeted therapies, CGP might aid in identifying gene variants that will be critical to developing effective treatments.

Threats

CGP performed on heterogeneous tumors might not identify all relevant AGAs or not offer information that would benefit patients. Most FDA-approved targeted therapies are indicated for treating cancers that harbor specific genetic alterations, and third-party payers often reimburse for FDA-approved indications. However, third-party payers are reluctant to pay for genetic testing for variants that might lack definitive evidence of being an effective target or that have not been approved by FDA as companion diagnostic tests for a labeled therapy. This might limit access to CGP and therapy options that could target some of the identified variants. Even if CGP is covered by insurance, disparities might increase because only patients with insurance might have access to testing, and when test results identify potential targeted therapies, patients without insurance might be unable to afford the out-of-pocket costs of therapy.

Direct-to-Consumer Genetic Testing Partnerships With Pharmaceutical Companies to Facilitate Drug Development and Treatment

Highlights

Laboratories offering direct-to-consumer (DTC) genetic testing services are establishing collaborations with drug manufacturers to share patient-derived genetic data and volunteered genetic testing questionnaire data. The goal is to drive drug development, enrollment in clinical trials, and, ultimately, patient access to targeted therapies. Effective collaboration might reduce development costs for drug developers, speed development, and lead to additional revenue for drug companies. However, consumers could be unaware of the ways in which companies are profiting from their genetic data. Also, inadequately managed collaborations might pose substantial threats to patient health data privacy.

Description

Laboratories that offer DTC genetic testing services are considering use of patient-derived genetic data and volunteered genetic testing questionnaire data as a way to drive drug
development and treatment. By partnering with pharmaceutical companies, DTC genetic testing companies can provide large data sets that might provide insight into new disease targets worth pursuing by drug companies. The databases from DTC testing might also make it easier for pharmaceutical companies to identify people who have a disease, are asymptomatic, or are carriers for conditions of interest and recruit them for clinical trials in a cost-effective manner. For instance, genetic testing company 23andMe has established collaborations with GlaxoSmithKline, and another genetic testing company, Nebula Genomics, is collaborating with EMD Serono to use consumer data to drive the drug development process.

**Clinical Area(s) Potentially Disrupted**

These collaborations could shift paradigms for drug development, drug target identification, and clinical trial recruitment, and might expedite these processes. Among the clinical areas being affected are medical genetics, neurology, cardiology, oncology, and rare and orphan diseases.

**Opportunities**

Effective collaboration between companies offering DTC genetic tests and drug developers might increase insights into the most promising targets to pursue for drug development, decreasing the cost and time needed to develop new agents. Such collaborations might also enable quicker and more cost-effective recruitment of patients and asymptomatic carriers with rare diseases into appropriate clinical trials. This, in turn, might result in additional new targeted therapies that address unmet needs and improve patient outcomes.

**Threats**

Poorly managed collaboration between DTC genetic test companies and drug developers might pose significant threats to patient health data privacy. Well-managed collaborations might put competing firms at a competitive disadvantage. Consumers who used DTC genetic test services and signed initial consents that their data could be used might not have realized how companies would use or profit from their data: DTC companies can profit by selling the data and drug development companies can profit from the drugs they successfully develop based on those data.

**Fecal Microbiota Transplantation to Treat Diseases Associated With Disturbances in Gut Microbiome (Gut Dysbiosis)**

**Highlights**

Fecal microbiota transplantation (FMT) is being increasingly investigated for treating a variety of gastrointestinal (GI) diseases and a wide range of other conditions suspected of involving or being affected by the gut microbiome—examples are inflammatory bowel disease, obesity, diabetes, autism, major depressive disorder, and multiple sclerosis, to name a few.

Although FDA has not yet approved FMT for any indications, the agency supports its investigational use for some clinical indications, such as treating recurrent *Clostridium difficile* (*C. diff*) infection. The intervention has shown promise in improving patient outcomes and quality of life for treating *C. diff* infection, but many safety concerns exist overall.
Description

FMT is the transfer of donor stool into the GI tract of a patient with the aim of repopulating a healthier GI tract microbiome. FMT might change treatment paradigms and improve health outcomes for patients with various GI diseases and other diseases with GI involvement. FMT can be accomplished directly through colonoscopy or indirectly through a nasal tube, oral feeding tube, enema, or capsule. The stool is sourced from volunteers believed to be healthy who undergo a variety of formal, medical screening processes before donating. The stool is tested for various pathogens before being deemed safe for transplantation. FDA has not approved FMT for any uses, although the agency allows its investigational use. The agency has issued guidance regarding donor screening and stool-testing protections to avoid serious risks of infection transmission. Stool banks such as OpenBiome work with clinicians to make FMT available and safer for use by screening donor stool, preparing the stool for implantation, and freezing it until it is ready for use.

One of the most common uses for FMT currently is in recurrent C. diff infection. FMT has been found, in RCTs, to resolve 80% to 90% of infections caused by recurrent C. diff that did not respond to antibiotics.

Clinical Area(s) Potentially Disrupted

FMT is being investigated in clinical trials (see ClinicalTrials.gov) for numerous diseases and conditions, including inflammatory bowel disease, irritable bowel disease, constipation, primary sclerosing cholangitis, hepatic encephalopathy in cirrhosis, pancreatitis, metabolic syndrome, obesity, T2DM, autism, bipolar disorder, MDD, anxiety, Parkinson’s disease, relapsing-remitting multiple sclerosis, metastatic melanoma, rheumatoid arthritis, and psoriatic arthritis.

Opportunities

FMT might improve patient health outcomes and QoL as a treatment option for many GI, infectious, autoimmune, mental health, and other health conditions. Treatment with and research on FMT might improve our understanding of the microbiome and its association with various diseases and conditions. In addition, use of FMT might reduce use of other treatments, such as antibiotics and biologics. Reduced use of antibiotics could help stem antibiotic resistance. Reduced use of biologics or immunomodulators could avert the risk of serious side effects posed by those therapies.

Threats

FMT poses health risks for patients from transmissible agents that could be contained in the donor stool. FMT’s mechanism of action and health risks are not fully understood and might vary for different conditions and diseases. FMT use might pose legal risks for donor banks if they can be held liable for FMT-related adverse events and health outcomes. FMT use might significantly shift paradigms of care and involve clinician learning curves and changes in treatment models, infrastructure, and care settings, depending on the disease or condition for which it is used. Treatment with FMT might be costly due to the increasing number of tests, processing, and storage required to ensure safety, and disparities in patient access to FMT might occur. Costs also involve recruitment and screening of healthy donors. If donors are paid for their stool samples, the payment could spur some donors to be less than completely honest about their health history.
Gene Editing to Prevent or Treat Disease

**Highlights**

Gene editing technology (called CRISPR in its current form) has the potential to prevent or treat many diseases and be potentially very disruptive to health care. Because of its current experimental nature, this technology poses significant health risks to patients because, in addition to present health risks, the downstream, long-term effects of gene editing are unknown. The technology also raises serious ethical issues because of its potential for editing genetic material in human embryos.

**Description**

Clinical trials using gene editing technology are underway. These technologies hold great promise for preventing and/or treating several diseases and conditions. For example, CRISPR (clustered regularly interspaced short palindromic repeats), the most used and researched editing technique at this time, is a dynamic, versatile tool that can be programmed to target specific stretches of genetic code and edit DNA at precise locations in the human genome. The technology allows researchers to permanently modify genes and has the potential to create therapies with durable effects, including intergenerational effects from human reproduction.

**Clinical Area(s) Potentially Disrupted**

Gene editing technology has the potential to disrupt many clinical areas that involve risks of inheritable diseases, such as macular telangiectasia type 2, SCD, cardiac disorders, and cancers.

**Opportunities**

Gene editing technologies might improve survival and QoL for patients, and it might reduce long-term treatment costs and associated lifestyle adaptation costs for patients and the health care system by providing a one-time, curative treatment option for the condition it targets. Additionally, it might reduce societal burden and health care costs by preventing and/or eliminating certain genetic disorders.

**Threats**

This technology could pose significant health risks to patients and their offspring because much is still unknown about potential short- and long-term (generational) adverse events related to gene editing and its delivery in patients. Its ability to change targeted locations in the genome has potential for misuse, leading to significant ethical and societal threats (eg, unethical alteration of human embryos, “designer” humans).

Integrated Electronic Health Solutions to Improve Cardiovascular Care

**Highlights**

An integrated electronic system that collects multiple physiologic parameters and allows clinical staff to monitor changes in near real time and quickly modify care has the potential to
improve outcomes for patients with cardiovascular disease. However, further research is needed to determine how to implement these systems effectively while not overwhelming clinical staff and creating new patient privacy concerns.

**Description**

Several products are available to collect physiologic data from cardiovascular patients through wearables or smartphones and transfer the data to clinicians. Most products are limited in scope (eg, blood pressure or electrocardiogram alone).\(^6^3^4-^6^3^7\) Product availability and consumer marketing has largely outpaced clinical research on the true clinical utility of these technologies in cardiovascular care.\(^6^3^4\) Limited early data have suggested some integrated digital health interventions introduced during hospitalizations from heart attacks might reduce 30-day readmissions and related health care costs compared with historical controls.\(^6^3^7\)

The American College of Cardiology (ACC) has issued a set of principles intended to guide appropriate integration of eHealth or mobile health technologies into cardiovascular care. ACC calls for more research of digital health applied to cardiovascular care to ensure patient safety, care quality, and positive health outcomes. ACC advises that these technologies should improve the patient experience, care quality, patient safety, and outcomes without hampering clinical workflow.\(^6^3^8\)

**Clinical Area(s) Potentially Disrupted**

The implementation of integrated electronic health solutions for cardiovascular care could disrupt patient management in cardiology and primary care practices, depending on patient needs and coexisting diseases. The availability of more physiologic patient data in near real time might require clinical staff to contact and interact with patients more frequently to address changes in their health conditions and adjust medications or other treatments as needed. Some arrangements or understanding might need to be established between different clinicians to allow for adequate and secure data sharing to ensure optimal disease management while reducing redundancies (eg, duplicate testing, monitoring). The most common cardiovascular conditions monitored with these technologies include hypertension, coronary artery disease, myocardial infarction, and heart failure.

**Opportunities**

Combining several types of collected physiologic data into one integrated platform for cardiovascular patient monitoring in near real time could improve outcomes if clinicians and patients can interact in a timely manner and adjust care as needed. An integrated patient monitoring system that tracks multiple physiologic parameters could also increase technical efficiencies compared with multiple separate systems that track blood pressure, heart rate, weight, and other vital statistics.

**Threats**

The collection and storage of additional clinical patient data might generate further data security risks, as well as questions about who owns or controls the data and where to store the data. The clinical staff’s workload could increase significantly if the additional patient data monitoring requirements are substantial. This additional workload could be controversial depending on whether or how clinicians are compensated for more patient monitoring and data collection and storage. Depending on the technology and standards involved, the use of
competing technologies with multiple components could create system compatibility problems, potentially limiting usefulness for effective patient monitoring. In addition to incompatibility, the use of multiple linked components within a single system might raise quality control concerns regarding device maintenance and data integrity. Cost concerns could emerge about who pays for the technology upfront and for its continued maintenance and quality control. The shift to integrated electronic health solutions could increase disparities if the technology cost or complexity filters out poorer, older, or less tech-minded patients who theoretically would be most likely to benefit.

Psychedelic Drugs to Treat Mental Health Conditions

Highlights

Researchers are investigating the use of psychedelic drugs to treat a variety of mental health conditions. These drugs might improve patient health outcomes and QoL, change the paradigm and infrastructure of mental health care, reduce long-term mental health care costs, and alter our scientific understanding of mental health conditions.

Description

Psychedelic drugs (eg, psilocybin, lysergic acid diethylamide [LSD], N,N-dimethyltryptamine [DMT], 3,4-methylenedioxymethamphetamine [MDMA], ketamine) alter one’s state of consciousness, purportedly by altering certain neurotransmitters in the brain. Their use might provide the user with altered perception, increased introspection, feelings of closeness with others, and positive mood states. These experiences are often reported as deeply profound and life-altering.

Although most psychedelics are designated as Schedule I drugs in the United States, researchers are investigating their potential to treat a variety of mental and behavioral health disorders that have not responded to conventional treatments. The Multidisciplinary Association for Psychedelic Studies was established in 1986 to research and provide education regarding potential therapeutic uses and roles in mental health treatment.639 In September 2019, Johns Hopkins announced the launch of its Center for Psychedelic and Consciousness Research to study various psychedelics to treat certain mental health conditions. The number of clinical trials on the use of psychedelics for mental health conditions is increasing.640

Psilocybin is in clinical trials to investigate treatment for depression, anorexia nervosa, obsessive-compulsive disorder, alcohol use disorder, nicotine dependence, cocaine use disorder, and cancer-related anxiety.641-646 LSD is being explored to treat anxiety associated with life-threatening illness, other anxiety disorders, and depression.647-649 DMT, a drug present in a psychoactive brew called ayahuasca, is being researched as a treatment for depression.650,651 MDMA is in phase III clinical trials for use during psychotherapy to treat PTSD and is being investigated as therapy for social anxiety in adults with autism.652,653 Most of these psychedelics are not intended for frequent or long-term use, and therapeutic effects have been reported with as few as 2 to 3 treatments (eg, MDMA-assisted psychotherapy for PTSD). Ketamine, while not traditionally considered a psychedelic drug, has some psychedelic properties and is being explored off label to treat PTSD.654 A closely related molecule, esketamine (Spravato), has been approved to treat depression.322
Clinical Area(s) Potentially Disrupted

The use of psychedelics for treating mental health conditions could disrupt treatment models for practitioners of psychiatry and other mental health disciplines. The use of these drugs requires a learning curve, different approaches to monitoring their effects, and changes in the duration and setting of treatment sessions.

Opportunities

Psychedelics as a novel drug class used to treat mental health conditions might improve patient health outcomes and QoL. They might also reduce the prevalence of treatment-resistant mental health conditions and reduce costs associated with long-term mental health treatment. Psychedelics might change the paradigm and infrastructure of mental health care. Their use might encourage continued research into additional potential therapeutic uses for psychedelics and might enhance our understanding of mental health conditions.

Threats

Psychedelic use might result in negative health outcomes for some patients. For this reason, they are not recommended for every patient. There may be population health and legal risks to making controlled substances more accessible. There may be increased disparities in access to care if clinicians are hesitant to treat with controlled substances that carry stigma or a significant risk of harm or mental deterioration. Treatment could be costly in the short term if significant costs are associated with building necessary treatment infrastructure.

Smart Device Applications to Improve Mental Health

Highlights

Downloaded smart device applications (apps) are becoming increasingly available to improve a variety of mental health conditions. They show potential to improve outcomes, decrease disparities by improving access to care for some populations, and reduce social stigmas related to mental health conditions. However, more research needs to be conducted regarding their safety, effectiveness, and appropriate clinical context for use.

Description

Mental health apps are intended to relieve symptoms associated with a variety of mental health conditions. They are available as part of curated app libraries or because of consumer online searching. The apps offer features including symptom tracking, self-monitoring, guided meditation, and talk therapy. Authors of a recent study seeking to evaluate quality claims of mental health apps searched Android and iOS app stores and found 1435 apps for anxiety, depression, schizophrenia, self-harm, and substance abuse. Of the apps that met inclusion criteria of purporting to be based on scientific principles (n = 73), about 67% claimed effectiveness at diagnosing a mental health condition or improving symptoms, mood, or self-management. Fourteen percent provided a description that they had been developed based off lived experience, and only one app had a citation to published literature. FDA has not subjected any mental health apps to any regulatory pathway to treat mental health conditions. A recent meta-analysis and qualitative review suggests that mental health apps might be useful adjunctive treatment for depression, noting potential benefits of increased patient access and
decreased costs. More research is needed to determine the safety and efficacy of mental health apps and their appropriate clinical context.

**Clinical Area(s) Potentially Disrupted**

Mental health apps target a variety of mental health conditions, including anxiety, depression, obsessive-compulsive disorder, PTSD, schizophrenia, and substance abuse.

**Opportunities**

Mental health apps might decrease health care disparities by providing more patients with access to mental health resources, especially if regional access to psychiatrists and psychologists is limited. Similarly, the on-demand nature of the apps allows patients to use them wherever and whenever it is convenient. Mental health apps might also improve patient outcomes, augmenting existing treatment plans by providing new and additional support that can be accessed outside of the health care setting. Additionally, these apps might raise awareness of mental health conditions and reduce associated stigma. For patients who are reluctant to reach out for or attend in-person therapy and who therefore forgo any type of help for their condition, apps could enable them to get some help while also preserving some of the discretion they seek.

**Threats**

Mental health apps might decrease the likelihood that a patient seeks a diagnosis and appropriate medical care plan, which is important to receive an accurate psychiatric diagnosis, rule out organic or other causes of mental health conditions, and discuss all treatment options, including pharmacotherapy and psychotherapy. As a result, patient health outcomes might be compromised if patients rely solely on an app and self-diagnose. These apps might also lead to breaches in personal health information, which has a variety of legal and patient-centered ramifications. In addition, mental health apps could be difficult to regulate and might require additional infrastructure for that process.

**Smartphone-guided Medical Examinations and Diagnostics for Use by Patients and Caregivers**

**Highlights**

Smartphone-based apps (ie, mHealth) are expanding care delivery models by providing remote options for diagnosing and identifying optimal treatments. These applications might reduce overall cost of care while reducing disparities. However, device or user errors could lead to misdiagnosis or mistreatment, and significant concerns exist about privacy and security issues involving patient data transmission, storage, and access.

**Description**

An accurate diagnosis, when made in a timely manner, can provide the best insight into treatment options for patients. A recent telehealth and e-health case study highlighted a patient’s case in which acute appendicitis was diagnosed via telehealth that allowed timely surgery to take place. Smartphone apps are now capable of delivering examinations and diagnostic services to patients in remote areas by boosting the use of smartphones as diagnostic devices for multiple age groups. These apps are accompanied by handheld examination kits that
allow patients to perform guided medical examinations and share results with their provider for an appropriate diagnosis and treatment options (eg, TytoCare, MoleScope, RetinaScope).659-661

Clinical Area(s) Potentially Disrupted

The practice of using physician-guided patient self-examinations using smartphones is likely to disrupt telehealth systems and influence the delivery of care to patients in both rural and urban locations. For patients who travel outside their usual care area and wish to be evaluated and receive treatment recommendations from their home clinicians, this technology could provide that option.

Opportunities

Smartphone-based medical self-examinations might decrease the overall cost related to both patient care and care delivery by reducing clinician office visits. These technologies might also reduce disparities in terms of access to care for patients in rural areas. Involving patients and caregivers in the diagnostic process might increase patient autonomy and satisfaction. In addition, mHealth app use might reduce burden on the health system, such as sequela from overlooked symptoms for which patients did not have the time or opportunity to seek in-person evaluation.

Threats

Because of a lack of comprehensive privacy laws for telehealth systems and the fact that patients’ smartphones might not be sufficiently secure, personal health information might be at risk of being hacked, collected, used, or shared for unintended purposes. Additionally, user or device errors could lead to misdiagnosis or mistreatment.

Tissue of Origin–Agnostic, Molecularly Targeted Oncology Drugs

Highlights

FDA has recently approved 3 oncology drugs for use in indications defined solely by a molecular marker irrespective of the cancer’s tissue of origin. This represents a departure from previous FDA oncology drug approvals whose indications pertained to cancers arising from a specific tissue. As additional molecular drivers that are shared across primary cancers are identified, additional tissue-agnostic approvals are likely with the potential to disrupt clinical trial and treatment paradigms for cancer.

Description

Oncology drugs have traditionally been approved by FDA for cancers arising from specific tissues or organs (eg, breast, prostate, lung, blood).662 With the increasing recognition that some of the same genetic changes drive the development of cancers arising in different organs or tissues, investigators began defining patient populations in terms of their molecular subtype irrespective of the organ or tissue in which the cancer arises. These observations were made in so-called basket trials or umbrella trials—the same clinical trial enrolled patients with different cancers, and researchers observed a signal of efficacy for a molecular target of a drug across those cancers. This led to expansion of cohorts or creation of tissue of origin–specific trials with the intent that the
manufacturer seek FDA drug approval for that tissue of origin (eg, ALK inhibitors for non–small cell lung cancer, BRAF inhibitors for melanoma or Erdheim Chester disease).

More recently, however, FDA approved 3 drugs for use in molecularly defined patient populations. That is, the cancer tissue of origin did not matter—eligibility for the drug rested on a molecular target. Examples include pembrolizumab (Keytruda), which received approval to treat unresectable or metastatic, microsatellite instability–high or mismatch repair–deficient solid tumors in adult and pediatric patients. Larotrectinib (Vitrakvi) and entrectinib (Rozlytrek) were approved to treat solid tumors that have a neurotrophic tyrosine receptor kinase gene fusion without a known acquired resistance mutation. This change in approach raises issues regarding clinical trial conduct to provide the supporting evidence for regulatory submissions as well as potential issues with the varied responses to molecularly targeted therapies across different cancer types, particularly for rare cancers or cancers in which a molecular target rarely occurs.

Clinical Area(s) Potentially Disrupted

These drugs have potential to disrupt treatment paradigms for cancer.

Opportunities

Conventional oncology clinical trial designs based on testing a drug only in cancers arising from a specific tissue of origin can be limited by the small number of eligible patients in rare cancers and rare molecularly defined cancer subtypes. Tissue-agnostic clinical trials that enroll cancer patients with a shared molecular subtype could provide a pathway to FDA approval in instances of indications that might not be suited for traditional clinical trial designs. Also, this approach creates new collaboration opportunities for laboratories and companies that offer whole genome and exome sequencing. More health care companies are collaborating with drug development companies, and drug development companies are acquiring genetic testing laboratories to enhance their research and development programs. Drug development companies are also starting to partner with direct-to-consumer genetic test companies to acquire their large data sets and search for molecular targets for cancer therapy development.

Threats

An ever-increasing number of potential molecular targets might increase costs by requiring more widespread testing of tumors using whole genome sequencing or very large gene panels upon initial diagnosis of a patient to identify all potential therapeutic targets. Additionally, evaluating a wider variety of molecular targets not tied to any specific type of cancer might involve a substantial learning curve for providers. Although some targeted therapies have been shown to be therapeutically effective in targeting molecular drivers irrespective of cancer tissue of origin, the efficacy of other drug and molecular driver combinations depends on the tissue of origin. Therefore, drug approvals for tissue-agnostic indications might lead to poor outcomes in certain patients with a molecular driver/tissue-of-origin combination in which the targeted therapy is ineffective.
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