AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 13: Pulmonary Disease, Including Asthma

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U.S. Department of Health and Human Services
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www.ahrq.gov

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Prepared by:
ECRI Institute
5200 Butler Pike
Plymouth Meeting, PA 19462

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290-2010-00006-C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or 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 (formerly the Institute of Medicine) and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High-Impact Interventions report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to: effectivehealthcare@ahrq.hhs.gov.

Richard Kronick, Ph.D.
Director
Agency for Healthcare Research and Quality

Arlene S. Bierman, M.D., M.S.
Director
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director, Evidence-based Practice Center Program
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Elise Berliner, Ph.D.
Task Order Officer
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

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Executive Summary

Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 3 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 24,500 leads about potential topics has resulted in identification and tracking of about 2,400 topics across the 14 AHRQ priority areas and 1 cross-cutting area; more than 750 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice a year. Topics eligible for inclusion are those interventions expected to be within 0–3 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 195 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the five to eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts' rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of "lower," "moderate," or "higher" within the high-impact-potential range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ's Effective Health Care Web site.

Results

The table below lists the seven topics for which (1) preliminary phase III data for drugs were available; (2) information was compiled and sent for expert comment before November 6, 2015, in this priority area; and (3) we received six to eight sets of comments from experts between January 1, 2015, and November 16, 2015. (Twenty-eight topics in this priority area were being tracked in the system as of November 6, 2015.) For this report, we aggregated related topics for summary and discussion (i.e., individual drugs into a class). We present four summaries on six topics that emerged as having high-impact potential on the basis of experts' comments. They are noted with an asterisk below. Five of these topics were in the June 2015 report; one new topic added to this report is mepolizumab for treating eosinophilic asthma. The material in this Executive Summary and report is organized alphabetically by disease state and then by intervention. Readers are encouraged to read the detailed information on these interventions that follows the Executive Summary.

Priority Area 13: Pulmonary Disease, Including Asthma

Topic	High-Impact Potential
1. * Lumacaftor and ivacaftor (Orkambi) for treatment of cystic fibrosis	Moderately high
2. * Mepolizumab (Nucala) for treatment of eosinophilic asthma	Moderately high
3. * Nintedanib (Ofev) for treatment of idiopathic pulmonary fibrosis	Moderately high
4. * Pirfenidone (Esbriet) for treatment of idiopathic pulmonary fibrosis	Moderately high
5. * Portable warm blood perfusion system (Organ Care System; OCS) for normothermic lung transplantation	Moderately high
6. * Portable warm blood perfusion system (Xvivo Perfusion System; XPS) for normothermic lung transplantation	Moderately high
7. Reslizumab (Cinquil) for treatment of eosinophilic asthma	No high-impact potential at this time

Discussion

Eligible Topics Not Deemed High Impact

We briefly discuss a single topic that was deemed to have no high-impact potential at this time based on experts' comments.

- **Reslizumab (Cinquil) for treatment of eosinophilic asthma:** Reslizumab is in phase III clinical trials for treating eosinophilic asthma; this investigational drug is administered intravenously. Experts thought that reslizumab's route of administration may limit its impact and diffusion, given that potential competitors have subcutaneous dosing and may be self-administered by patients. We continue to track this intervention in the AHRQ Healthcare Horizon Scanning System to monitor reporting of additional new data.

Eligible Topics Deemed High Impact

Pulmonary disease is a priority area in which several interventions have been identified as meeting criteria for tracking in the Healthcare Horizon Scanning System. Experts deemed six topics as having high-impact potential: An oral drug for treating patients who have cystic fibrosis (CF), an injectable drug for treating eosinophilic asthma, two oral drugs for treating idiopathic pulmonary fibrosis (IPF), and two portable warm blood perfusion systems for normothermic lung transplantation.

Cystic Fibrosis

Lumacaftor/Ivacaftor (Orkambi) for Treatment of Cystic Fibrosis

- **Key Facts:** About 30,000 people in the United States have CF; no cure is available. The disease is caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that encodes the CFTR membrane protein, which facilitates the movement of chloride ions and other negatively charged particles across cell membranes. CF affects the cells that produce mucus, sweat, and digestive fluids, causing severe damage to the lungs and gastrointestinal tract. A person needs two mutated copies of the gene to develop CF; researchers have identified more than 1,800 mutations associated with the disease. In January 2012, the U.S. Food and Drug Administration (FDA) approved the first oral therapy, ivacaftor (Kalydeco™), as the first treatment directly addressing a *CFTR* mutation, G551D. Subsequently, the drug was under study as part of a combination therapy with lumacaftor. Lumacaftor is a small-molecule corrector that targets the F508del *CFTR* mutation. According to the Cystic Fibrosis Foundation's 2014 patient registry, almost 47% of CF patients in the United States have two copies of the F508del mutation and another 39% of CF patients have one copy. The F508del mutation causes defects in both CFTR trafficking to the surface of cells and ion gating and flow at the surface of cells. Lumacaftor is intended to correct faulty protein processing so CFTR can be transported to the cell surface. Once trafficking is corrected with lumacaftor, CFTR activity can be enhanced with combination therapy using ivacaftor, which further improves ion gating and water flow and increases hydration and clearing of the mucus in the lungs. In the completed phase III TRAFFIC and TRANSPORT trials, patients treated with lumacaftor/ivacaftor had significant improvements in lung function and fewer exacerbations than did patients treated with placebo.

In July 2015, FDA approved fixed-dose combination lumacaftor 400 mg/ivacaftor 250 mg (Orkambi™) for treating patients with CF aged 12 years or older who have two copies of the F508del mutation. Four phase III trials are ongoing.

Lumacaftor/ivacaftor reportedly costs about $20,000 for a 4-week supply, or $260,000 per year. The manufacturer has established a patient support program to facilitate access to the combination drug. Our searches of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found 7 payers that have policies regarding lumacaftor/ivacaftor coverage; the drug is a specialty pharmaceutical requiring prior authorization and having quantity limits.

- **Key Expert Comments:** Overall, experts stated that as a targeted therapy for CF, lumacaftor/ivacaftor has potential to address a significant unmet need. They noted that treatment demonstrated benefit in patients with CF who have two copies of the F508del mutation, but not in patients with only one copy—47% percent of U.S. patients with CF are homozygous for F508del. High costs could limit patient access to the drug because even with insurance coverage, copayments could be high. Lumacaftor/ivacaftor demonstrated the ability to improve outcomes, quality of life, and longevity by reducing pulmonary exacerbations, frequency and length of hospitalizations, antibiotic use, as well as increasing weight, compared with placebo. Wide acceptance by clinicians and patients is expected for use of the drug in these patients.
- **High-Impact Potential:** Moderately high

Eosinophilic Asthma

Mepolizumab (Nucala) for Treatment of Eosinophilic Asthma

- **Key Facts:** Asthma is a chronic, inflammatory, respiratory system disorder characterized by airway-wall inflammation, airway narrowing, and bronchial hyper-responsiveness, which may be severe. Of the roughly 1.4 million patients with severe asthma, an estimated 40% to 60% have elevated eosinophil levels in their airways, which are thought to contribute to disease pathogenesis. Short-acting or long-acting beta-2 agonists, as well as corticosteroids, may be prescribed to control asthma symptoms, but these treatments are not completely effective in about 5% of patients with severe asthma. Uncontrolled severe asthma may lead to hospitalization or death. Interleukin 5 (IL-5) is a hematopoietic cytokine produced by cells such as basophils, eosinophils, mast cells, natural killer T cells, and T helper 2 lymphocytes. IL-5 is thought to be the major promoter of eosinophil growth, activation, degranulation, and survival; the cytokine is also thought to be an essential signal promoting eosinophil chemotaxis from the bone marrow into the lung. Mepolizumab is a humanized monoclonal antibody that selectively binds free IL-5, thereby inhibiting asthma pathogenesis mediated by eosinophilic inflammation. Mepolizumab purportedly reduces eosinophil counts in sputum, blood, and lung tissue, resulting in reduced asthma exacerbations and reduced need for treatment with systemic glucocorticoids. In two completed phase III trials (MENSA, SIRIUS), patients receiving mepolizumab had a decrease in the rate and severity of asthmatic symptom exacerbations, as well as an increased likelihood of controlling symptoms using a lower corticosteroid dose. In these trials, the most common adverse events reported were headache and nasopharyngitis.

In November 2015, FDA approved mepolizumab (Nucala®) as an add-on maintenance therapy for patients aged 12 years or older who have severe eosinophilic asthma with a history of exacerbations. Four phase III trials are ongoing. Mepolizumab is also being developed for use in chronic obstructive pulmonary disease.

Because mepolizumab is so recently approved for treating eosinophilic asthma, no cost information is available yet. However, one news source estimated that the drug may cost $10,000 to $15,000 per year. The manufacturer has established a patient support program to facilitate access to mepolizumab. Our searches of 11 representative, private, third-party payers that publish their coverage policies online found one payer that has a policy regarding mepolizumab coverage. The drug is covered, with quantity limits, in patients with severe eosinophilic asthma whose symptoms are not adequately controlled with long-term beta agonists and inhaled corticosteroids.

- **Key Expert Comments:** Overall, experts stated that mepolizumab has potential to address a significant unmet need in managing severe asthma symptoms, decreasing use of corticosteroids (that have significant side effects), reducing exacerbations, and reducing the number of hospital visits, but more long-term safety and efficacy data are needed. Patients and clinicians are likely to accept mepolizumab; however, patients will need to learn to self-administer the drug, which may initially pose a barrier to acceptance. If mepolizumab effectively controls asthma symptoms, its use could reduce emergency room visits and hospitalizations. Reducing these demands on infrastructure could offset the cost of the drug. Patients who are uninsured or underinsured may experience difficulty affording the drug, exacerbating disparities, but manufacturers' patient assistance programs may lessen this exacerbation.
- **High-Impact Potential:** Moderately high

Idiopathic Pulmonary Fibrosis

Oral Options (Nintedanib [Ofev], Pirfenidone [Esbriet]) for Treatment of Idiopathic Pulmonary Fibrosis

- **Key Facts:** IPF is a progressive lung disease in which scarring or thickening of lung tissue occurs with no identifiable cause. Scarring begins at the lung periphery and progresses toward the center, making breathing progressively more difficult. Between 80,000 and 100,000 people in the United States are living with IPF, and about 30,000 new cases are diagnosed in the United States annually. Patients with IPF have a median life expectancy of 2–3 years from initial diagnosis, and no approved medications are available for slowing disease progression. Common signs and symptoms of IPF include shortness of breath and a chronic, dry, hacking cough. Other signs and symptoms may develop over time and include rapid, shallow breathing; gradual, unintended weight loss; fatigue or malaise; aching muscles and joints; and chest pain. Although the cause of IPF is unknown, it occurs more commonly in people who work around dust or fumes, are between 40 and 70 years old, have a history of smoking, or are male. Patients can use portable oxygen to aid breathing and may receive corticosteroids to reduce dyspnea during acute exacerbations. A limited number of patients with IPF receive a lung transplant. However, patients with IPF have the highest waiting-list mortality rate of any indication for lung transplant; thus, a large unmet need exists for effective treatment.

  Nintedanib. Nintedanib (Ofev®) is a tyrosine kinase inhibitor that targets the intracellular signaling of multiple proangiogenic growth factor receptors purportedly

involved in the pathogenesis of IPF, including vascular endothelial growth factor receptor 2 (VEGFR2), fibroblast growth factor receptor (FGFR), and platelet-derived growth factor receptor (PDGFR). Blocking these receptors is thought to inhibit the cycles of inflammation and repair that lead to lung fibrosis in IPF. In two completed, replicate phase III trials (INPULSIS-1 and INPULSIS-2), patients with IPF who were given nintedanib had a significantly smaller decline in lung function than did patients given placebo. In the INPULSIS-2 trial, patients treated with nintedanib were reported to have significantly increased time to the first acute exacerbation compared with patients given placebo. Preliminary data from an extension trial, INPULSIS-ON, suggest that nintedanib's benefit is maintained through 2 years of treatment. The most common adverse reactions reported, including in the long-term safety study, include appetite loss, diarrhea, nausea, and vomiting.

In October 2014, FDA approved nintedanib for treating IPF. Two phase III trials are ongoing.

The retail cost of a 30-day supply of nintedanib ranges from $8,190 to $8,780. Our searches of 11 representative, private, third-party payers that publish their coverage policies online found 10 payers that have policies for nintedanib coverage; the drug is subject to prior authorization. The manufacturer has implemented a patient support program to facilitate access to nintedanib; it features nurse-support access 24 hours a day, 7 days a week and financial support and educational resources.

Pirfenidone. Pirfenidone (Esbriet®) is a synthetic pyridone analogue reported to inhibit the synthesis of transforming growth factor (TGF)-alpha and TGF-beta, two cytokines thought to play a role in the inflammation and fibrosis associated with IPF pathogenesis. In the completed phase III ASCEND trial, patients with IPF who were treated with pirfenidone had a significant relative reduction in the proportion with declining lung function or who died compared with those outcomes in patients given placebo. Patients given pirfenidone were more likely to have no decline in lung function than patients given placebo. Pirfenidone reduced the decline in the 6-minute walk distance and improved progression-free survival compared with placebo. Recent data pooled from the ASCEND trial and another phase III trial suggest that pirfenidone's benefit continued after 2 years of treatment. The most common adverse reactions reported in patients treated with pirfenidone included nausea and rash.

In October 2014, FDA approved pirfenidone for treating IPF. One phase III trial is ongoing, evaluating pirfenidone's long-term safety and efficacy in patients with IPF. A 30-day supply of pirfenidone reportedly costs about $7,800. Our searches of 11 representative, private, third-party payers that publish their coverage policies online found 10 payers that have policies covering pirfenidone; prior authorization is required. The drug's manufacturer has implemented a patient support program to facilitate diffusion; it provides educational, procurement, and financial support services.

- **Key Expert Comments:** Overall, experts commenting on these interventions thought both nintedanib and pirfenidone have potential to address a significant unmet need in IPF treatment by delaying deterioration in lung function and mortality in patients with IPF. However, these drugs are expected to have only a moderate impact on health outcomes because of their inability to halt or reverse disease progression. Further, limited long-term clinical data, difficulty in accurately diagnosing IPF, cost and reimbursement issues, and increased physician visits to monitor adverse events could pose barriers to nintedanib and

pirfenidone use. However, these drugs are expected to be widely used for treating IPF because of a lack of other treatment options.

- **High-Impact Potential:** Moderately high

Lung Transplantation

Portable Warm Blood Perfusion Systems (Organ Care System, Xvivo Perfusion System) for Normothermic Lung Transplantation

- **Key Facts:** In 2012, 1,754 lung transplantations were performed in the United States, with 1,616 patients on the national waiting list. Standard donor lung preservation methods use cold preservation by Perfadex®, which has played a significant role in extending lung preservation times from about 4 hours to more than 25 hours. However, the number of transplantations performed is still limited by the number of suitable donor lungs available, and only about 10% to 30% of donated lungs are considered to be suitable. Additionally, in 10% to 20% of patients who have undergone lung transplantation, donor lungs have been so severely damaged by the time of transplantation that the patient requires additional support (i.e., ventilation, pharmacologic interventions) when the lungs are transplanted. To improve their condition to acceptable functional levels for transplantation, new technology is being developed to better preserve lungs by mimicking the physiologic activity of lungs. The approach is termed normothermic ex vivo lung perfusion (EVLP), which could expand the pool of acceptable donor lungs. We describe two warm blood perfusion technologies that experts thought have high-impact potential: the Organ Care System (OCS Lung) and Xvivo Perfusion System (XPS).

  Organ Care System. The OCS Lung is a portable normothermic EVLP ventilation and monitoring system that purportedly maintains the donor lungs in a "near physiologic state." This potentially optimizes organ health and allows for continuous evaluation during transport. The OCS Lung consists of a portable, battery-operated console with a wireless monitor, a perfusion module described by the manufacturer as a "transparent, sterile chamber designed to protect the organ and maintain the appropriate, warm temperature and humidity," and a solution set to deliver nutrients to the preserved donor lungs. In pilot trials, the OCS Lung console was connected to the donor lung via the pulmonary artery and the trachea. Blood is delivered through the pulmonary artery and drains directly into the perfusion module chamber. A ventilator delivers air to the lungs via the trachea. Donor lungs are perfused with a solution enriched with two red blood cell concentrates that are matched to the intended transplant recipient. With the OCS, clinicians can measure the oxygen concentration in the blood to assess lung function. OCS Lung may also improve donor lung condition so that lungs previously considered marginal in quality are transplantable. Furthermore, by replacing static hypothermic storage with active perfusion, the technology is said to reduce organ-damaging cold ischemic time (particularly during transport from donor to recipient). This potentially increases the time an organ can be maintained outside the body before transplantation. The phase III pivotal INSPIRE trial began recruiting in November 2011 and was completed in October 2015. Interim data reported from this trial (n=264) indicate that patients who were registered primary double-lung transplant candidates and received lungs preserved and transported using either the OCS Lung or cold storage had 30-day survival rates of 98% and 95%, respectively. The OCS is also being investigated for preserving donor hearts.

  The OCS Lung is not yet approved by FDA. According to the ECRI Institute PricePaid database, as of the second quarter of 2013, a disposable perfusion set for the OCS Lung could

add an additional $45,000 per patient for organ procurement (OCS is available outside the United States). The price quoted for the OCS Lung System (monitor) was $225,000. However, the manufacturer has indicated that the OCS Lung preservation equipment could be loaned to the hospital at no cost if the facility agrees to purchase 10 perfusion sets at $45,000 each, for a total cost of $450,000. If FDA approved, use of the system would be part of the bundled payment for organ harvesting and transplantation.

Xvivo Perfusion System. XPS is a normothermic EVLP system that continuously flushes donor lung tissue with Steen™ solution to evaluate, preserve, and recondition initially unacceptable donor lungs. The XPS also ventilates the lungs, providing oxygen to the cells and allowing evaluation of the airways. Donor lungs can stay in the XPS for up to 4 hours, allowing the transplant team to evaluate lung function outside the body, which cannot be accomplished through cold storage. Lungs meeting acceptability criteria and passing the transplant surgeon's examination are transplanted into a suitable recipient. In clinical trials, EVLP with XPS has been successfully used to assess and improve the function of donor lungs initially considered unacceptable for transplantation and then preserve them during transport for subsequent bilateral lung transplantation.

FDA approved XPS in August 2014 under the humanitarian device exemption program; the indication is for "warm EVLP of organs outside the body pending transplantation." Procurement costs of single- and double-lung replacement under cold ischemic storage are about $73,100 and $90,300, respectively. According to the manufacturer, the cost for disposables for the XPS could add $19,024 to the current cost of a lung transplant. According to the ECRI Institute PricePaid database, as of the second quarter of 2011, the capital cost of the XPS system was $250,000. As of August 2015, XPS was available in 18 centers in the United States.

- **Key Expert Comments:** Experts commented that the unmet need is great for more donor lungs of better quality. The experts generally agreed that these two interventions have moderate potential to increase the quantity of viable donor lungs. Experts were optimistic about both provider and patient acceptance of this technology. For OCS and XPS to reach their full impact potential, more data demonstrating reductions in transplantation-associated complications, adverse events, and mortality compared with cold storage are needed, the experts thought.
- **High-Impact Potential:** Moderately high

Cystic Fibrosis Intervention

Lumacaftor/Ivacaftor (Orkambi) for Treatment of Cystic Fibrosis

Unmet need: About 30,000 people in the United States have cystic fibrosis (CF), with an estimated 1,000 new cases arising annually.[1] The disease is caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene.[2] The most common *CFTR* allele present in patients with CF is CFTR-F508del, which causes a deficiency in trafficking the CFTR protein to the cell membrane.[2] According to the Cystic Fibrosis Foundation's patient registry, almost 47% of CF patients in the United States have two copies of the F508del mutation.[3] No cure exists for the disease; patients are treated with agents to ease symptoms and reduce complications from infections, excessive thick mucus in the lungs, and gastrointestinal manifestations.[4,5] Therapies targeting *CFTR* mutations have been proposed to improve CF management (e.g., ivacaftor for patients with CF who have a G551D mutation); however, they do not address all CFTR mutations.[6]

Intervention: Lumacaftor is a small-molecule corrector targeting the F508del CFTR protein, a CFTR isoform with defects in both trafficking and gating and flow. Lumacaftor is intended to correct faulty protein processing so CFTR can be transported to the cell surface.[2] Once there, CFTR activity can purportedly be further improved with combination therapy with ivacaftor, a drug that improves ion gating and water flow in the lungs, resulting in improved hydration and clearing of mucus in the lungs.[7,8] The manufacturer has developed a fixed-dose combination of lumacaftor 400 mg/ivacaftor 250 mg administered orally, twice daily, for treating patients with CF aged 12 years or older who have two copies of the F508del mutation.[9] Lumacaftor/ivacaftor is not intended for patients with other mutations that cause CF.

Clinical trials: In the completed phase III, randomized, double-blind, placebo-controlled TRAFFIC trial, patients (n=549) homozygous for the F508del mutation aged 12 years or older were treated with lumacaftor dosed orally at either 600 mg once daily or 400 mg twice daily in combination with ivacaftor (250 mg) administered orally, twice daily, for 24 weeks.[10] Patients treated with ivacaftor twice daily and lumacaftor (600 mg) once daily or ivacaftor and lumacaftor (400 mg) twice daily achieved a mean absolute change from baseline in percentage of predicted forced expiratory volume in 1 second ($ppFEV_1$) of 4.0% and 2.6%, respectively, compared with patients treated with placebo ($p<0.0001$ for both). Patients treated with ivacaftor and lumacaftor (400 mg) twice daily also had significantly fewer pulmonary exacerbations than did patients treated with placebo (73 vs. 112; $p=0.0169$).[10]

In the completed phase III, randomized, double-blind, placebo-controlled TRANSPORT trial, patients (n=559) homozygous for the F508del mutation aged 12 years or older were treated with the same drug dosage as in the TRAFFIC trial.[10] Patients treated with ivacaftor twice daily and lumacaftor (600 mg) once daily achieved a 2.6% mean absolute change from baseline in $ppFEV_1$ compared with patients treated with placebo ($p<0.0004$). Patients treated with ivacaftor and lumacaftor (400 mg), twice daily achieved a 3.0% mean absolute change from baseline in $ppFEV_1$ compared with patients treated with placebo ($p<0.0001$). Patients treated with ivacaftor twice daily and lumacaftor (600 mg) once daily had significantly fewer pulmonary exacerbations than did patients treated with placebo (94 vs. 139; $p=0.0116$). Patients treated with ivacaftor and lumacaftor (400 mg), twice daily also had significantly fewer pulmonary exacerbations than did patients treated with placebo (79 vs. 139; $p=0.0002$).[10]

In an ongoing phase III PROGRESS rollover study, patients (n=1,029) who completed the TRAFFIC or TRANSPORT trial are receiving lumacaftor/ivacaftor for an additional 72 weeks (for a total of 96 weeks of treatment). In an interim analysis, after 48 total weeks of treatment with lumacaftor/ivacaftor, patients who had previously received lumacaftor/ivacaftor maintained improvement in $ppFEV_1$. Patients who had previously received placebo (who thus had 24 total

weeks of treatment with lumacaftor/ivacaftor at the time of analysis) experienced similar improvements in ppFEV$_1$ as patients who had already received lumacaftor/ivacaftor in the TRAFFIC or TRANSPORT trials ($p < 0.0001$).[11]

Adverse events occurred more frequently in patients who received lumacaftor/ivacaftor than in those who received placebo, and included dyspnea and abnormal respiration. Additionally, 4.2% of patients who received combination therapy discontinued treatment because of adverse events, compared with 1.6% of patients given placebo.[10]

Manufacturer and regulatory status: Vertex Pharmaceuticals, Inc. (Boston, MA), makes lumacaftor/ivacaftor. In July 2015, the U.S. Food and Drug Administration (FDA) approved fixed-dose combination lumacaftor 400 mg/ivacaftor 250 mg (Orkambi™) for treating patients with CF aged 12 years or older who have two copies of the F508del mutation.[12] Four phase III trials are ongoing.

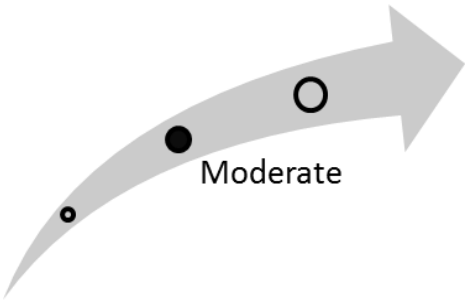
Diffusion and cost: Lumacaftor/ivacaftor reportedly costs about $20,000 for a 4-week supply ($260,000 a year), depending on pharmacy and geographic location.[13] Analysts predict global sales of lumacaftor/ivacaftor could reach $1.6 billion per year in 2016 and $4.2 billion per year by 2020.[14] The State of Vermont anticipates that its Medicaid program will spend $8 million on Orkambi in 2016; this figure exceeds the $5.8 million the State's Medicaid program spent on Harvoni, a costly hepatitis C virus drug, last year.[15] Vertex has established a patient support program to provide financial and third-party payer approval assistance for patients with CF who are taking the drug.[16]

Our searches of 11 representative, private, third-party payers that publish their coverage policies online (e.g., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, Health Partners, Humana, Medica, Regence, United Healthcare, Wellmark) found 7 have policies regarding coverage of lumacaftor/ivacaftor for treating cystic fibrosis; the drug is generally covered with prior authorization and quantity limits for patients who are homozygous for the F508del mutation.[17-23]

Clinical Pathway at Point of This Intervention

A cure for CF does not exist; patients often require chronic use of inhaled, intravenous, or oral antibiotics to prevent or treat acute infections in lungs already weakened by disease. They also use inhaled medications, and chest physiotherapy singly or in combination to help release the thick mucus that damages lung tissue over time. Lung transplantation can reduce the effects of CF for some individuals.[6] Lumacaftor/ivacaftor is intended as a daily therapy to reduce the decline of lung function and the frequency of pulmonary exacerbations by directly correcting the F508del genetic mutation associated with the disease, which may also slow disease progression.

Figure 1. Overall high-impact potential: lumacaftor/ivacaftor (Orkambi) for treatment of cystic fibrosis



Overall, experts stated that as a targeted therapy for CF, lumacaftor/ivacaftor has moderate potential for addressing a significant unmet need in CF management. Treatment with lumacaftor/ivacaftor could benefit patients with CF who have two copies of the F508del mutation (nearly 50% of CF patients in the United States are homozygous for F508del). In clinical trials, lumacaftor/ivacaftor treatment reduced pulmonary exacerbations, frequency and length of hospitalizations, and antibiotic use compared with placebo. However, several experts questioned whether short-term improvements would result in long-term improvements and emphasized the need for long-term studies. One clinical expert noted that clinical trials to date have excluded patients with the most severe lung disease. The same expert noted that side effects not observed in clinical trials are now being reported by patients taking lumacaftor/ivacaftor, and said that the drug is not as well-tolerated or as effective as ivacaftor alone. Acceptance by clinicians may be mixed, due to the drug's modest improvement in symptoms and its high cost. However, experts thought that patients are likely to accept lumacaftor/ivacaftor if long-term safety and efficacy are demonstrated. The drug's high cost could limit patient access if third-party payers do not cover the majority of treatment costs, but this limitation could potentially be overcome by manufacturer patient assistance programs. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts with clinical, research, or health systems backgrounds offered perspectives on this intervention.[24-29] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: A substantial unmet need exists for targeted therapies directly addressing the underlying mutations causing CF pathology, the experts agreed. Lumacaftor/ivacaftor, which corrects CFTR dysfunction, increased lung function and reduced exacerbations, hospitalizations, and antibiotic use in clinical trials, the experts noted. However, some experts questioned whether these short-term improvements would result in an improved quality of life, and they emphasized a need for data from long-term studies.[26,28,29] Lumacaftor/ivacaftor demonstrated less benefit for patients homozygous for the F508del mutation than ivacaftor has in patients homozygous for the G551D mutation, two experts noted.[26,29] Of these two experts, one with a clinical perspective[29] pointed out that patients taking lumacaftor/ivacaftor are now reporting side effects different from those previously observed in clinical trials (e.g., fever, night sweats). The same expert noted that lumacaftor/ivacaftor does not appear to be as well tolerated as ivacaftor alone and was also concerned about interactions between lumacaftor/ivacaftor and other drugs taken by patients with CF.

Acceptance and adoption: The experts offered mixed opinions on lumacaftor/ivacaftor acceptance among clinicians. The drug's modest improvement coupled with its high cost may limit clinician adoption, thought one clinical expert.[29] However, other experts thought that clinicians would be likely to prescribe lumacaftor/ivacaftor if it has long-term efficacy.

Patients have also expressed strong interest in new targeted therapies; they are expected to favor pills, because available supportive CF therapies often require nebulizers and chest therapy, which are time consuming, noted one clinical expert.[29] However, patient acceptance may depend on long-term improvements in quality of life, which have not yet been demonstrated.[24,27]

Health care delivery infrastructure and patient management: As an oral therapy, lumacaftor/ivacaftor would not significantly change how patients are managed, the experts thought. Lumacaftor/ivacaftor use could reduce demands on health care staff and facilities by reducing

pulmonary exacerbations, leading to fewer hospitalizations and physician visits and decreasing the need for other CF therapies, most experts noted.[24-26,28,29]

Health disparities: The high cost of lumacaftor/ivacaftor could increase health disparities if third-party payers do not cover the drug or if patients cannot afford the cost despite insurance, the experts opined.[24,28,29] However, one expert with a research perspective[26] noted that manufacturer patient assistance programs could limit exacerbation of health disparities.

Eosinophilic Asthma Intervention

Mepolizumab (Nucala) for Treatment of Eosinophilic Asthma

Unmet need: Asthma is a chronic, inflammatory, respiratory system disorder characterized by airway-wall inflammation, airway narrowing, and bronchial hyper-responsiveness,[30] which may be severe. Of the roughly 1.4 million patients with severe asthma, an estimated 40% to 60% have elevated eosinophil levels in their airways, which are thought to contribute to disease pathogenesis.[31] Short-acting or long-acting beta-2 agonists, as well as corticosteroids, may be prescribed to control asthma symptoms, but these treatments are not completely effective in about 5% of patients with severe asthma.[30,32] Uncontrolled severe asthma may lead to hospitalization or death. Interleukin 5 (IL-5) is a hematopoietic cytokine produced by cells such as basophils, eosinophils, mast cells, natural killer T cells, and T helper 2 lymphocytes.[33] IL-5 is thought to be the major promoter of eosinophil growth, activation, degranulation, and survival;[33,34] the cytokine is also thought to be an essential signal promoting eosinophil chemotaxis from the bone marrow into the lung.[34]

Intervention: Mepolizumab (Nucala) is a humanized monoclonal antibody that selectively binds free IL-5, thereby inhibiting asthma pathogenesis mediated by eosinophilic inflammation. Mepolizumab purportedly reduces eosinophil counts in sputum, blood, and lung tissue, resulting in reduced asthma exacerbations and reduced need for treatment with systemic glucocorticoids.[35,36] In clinical trials, mepolizumab has been administered as a 100 mg dose, subcutaneously, or a 75 mg dose, intravenously, once every 4 weeks.[35,37] Mepolizumab is intended to be used in combination with standard-of-care treatments, including corticosteroids and beta-2 agonists.

Clinical trials: The manufacturer has reported data from two completed phase III trials. In the MENSA trial, patients (n=576) with recurrent asthma exacerbations and evidence of eosinophilic inflammation despite high-dose inhaled glucocorticoid use received mepolizumab 75 mg, intravenously; mepolizumab 100 mg, subcutaneously; or placebo once every 4 weeks for 32 weeks. The rate of exacerbations was reduced by 47% (95% confidence interval [CI], 28 to 60) among patients receiving intravenous mepolizumab and by 53% (95% CI, 36 to 65) among those receiving subcutaneous mepolizumab, as compared with those receiving placebo ($p<0.001$ for both comparisons). Exacerbations necessitating an emergency department visit or hospitalization were reduced by 32% in the group receiving intravenous mepolizumab and by 61% in the group receiving subcutaneous mepolizumab.[35]

In the SIRIUS trial, patients (n=135) with severe eosinophilic asthma who had been taking oral corticosteroids were given mepolizumab 100 mg or placebo, subcutaneously, once every 4 weeks for 20 weeks in addition to their optimized steroid regimen. During the mepolizumab treatment period, corticosteroid dose was systematically reduced, depending on patients' asthma control. Based on symptom improvement, patients who received mepolizumab were 2.39 times more likely to experience a corticosteroid dose reduction than patients given placebo (95% CI, 1.25 to 4.56; $p=0.008$). The median percentage reduction from baseline in the glucocorticoid dose was 50% in the mepolizumab group, as compared to no reduction in the placebo group ($p=0.007$). Despite receiving a reduced glucocorticoid dose, patients in the mepolizumab group as compared to those in the placebo group, had a relative reduction of 32% in the annualized rate of exacerbations (1.44 vs. 2.12, $p=0.04$).[37]

In these trials, the most common adverse events reported in patients receiving mepolizumab were headache and nasopharyngitis.[35,37]

Manufacturer and regulatory status: GlaxoSmithKline, plc (Middlesex, UK), makes mepolizumab. In November 2015, FDA approved mepolizumab as an add-on maintenance therapy for treating patients aged 12 years or older with severe eosinophilic asthma with a history of

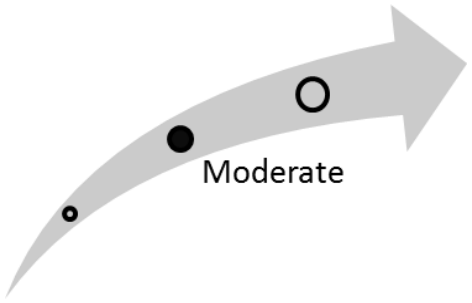
exacerbations.[38] Mepolizumab is also being developed for use in chronic obstructive pulmonary disease.[39]

Diffusion: Because of the recency of mepolizumab's approval, the manufacturer has not released cost information. However, one news source reports that the drug may cost $10,000 to $15,000 per year.[40] For benchmarking purposes, the competing drug omalizumab (Xolair®) costs about $900 for one 150 mg vial.[41] Omalizumab is administered 150–375 mg once every 2–4 weeks,[42] which equates to a cost of between $900 and $4,500 per month ($10,800 to $54,000 per year). In December 2015, GlaxoSmithKline implemented a patient support program to facilitate access to mepolizumab.[43,44] Our searches of 11 representative, private, third-party payers that publish their coverage policies online found 1 payer that has a policy regarding coverage of mepolizumab for treating severe eosinophilic asthma; the drug is covered, with quantity limits, in patients with severe eosinophilic asthma whose symptoms are not adequately controlled with long-term beta-2 agonists and inhaled corticosteroids.[32]

Clinical Pathway at Point of This Intervention

There is no cure for severe asthma, including eosinophilic asthma; treatment consists of controlling symptoms. In about 5% of patients with severe asthma, symptoms are not adequately controlled with standard-of-care treatments such as inhaled corticosteroids and long-acting beta-2 agonists.[32] Mepolizumab is intended to be used in combination with these therapies. Mepolizumab may compete with the approved biologic therapy omalizumab, which targets immunoglobulin E (IgE). Another IL-5 inhibitor, reslizumab (Cinquil™), is being developed for treating severe asthma and is also being tracked in the horizon scanning system. Experts commenting on reslizumab thought that its intravenous route of administration may limit its diffusion as compared to its subcutaneously administered comparators, and is thus not considered to have high-impact potential at the time of this writing.

Figure 2. Overall high-impact potential: mepolizumab (Nucala) for treatment of eosinophilic asthma



Overall, experts stated that mepolizumab has potential to address a significant unmet need in managing severe asthma symptoms, decreasing use of corticosteroids (that have significant side effects), reducing exacerbations, and reducing the number of hospital visits, but more long-term safety and efficacy data are needed. Patients and clinicians are likely to accept mepolizumab; however, patients will need to learn to self-administer the drug subcutaneously, which may initially pose a barrier to acceptance. If mepolizumab effectively controls asthma symptoms, its use could reduce emergency room visits and hospitalizations. Reducing these demands on infrastructure could offset the cost of the drug. Patients who are uninsured or underinsured may experience difficulty affording the drug, exacerbating disparities, but manufacturers' patient assistance programs may lessen this exacerbation. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, or health systems backgrounds, offered perspectives on this intervention.[45-50] We have organized the following discussion of expert comments according to the parameters on which they commented. Please note that we solicited comments on mepolizumab (Nucala) when its intended trade name was Bosatria; additionally, comments were received before the manufacturer released data comparing mepolizumab's safety and efficacy to that of its potential comparators and before FDA approved the drug in November 2015 for treating eosinophilic asthma. Therefore, these recent data and the drug's FDA approval were not considered in this set of expert comments, but may improve experts' future opinions about the drug's potential impact.

Unmet need and health outcomes: Experts generally thought that an unmet need exists for therapies to treat eosinophilic asthma, because patients with severe cases of asthma often have symptoms that are poorly controlled with existing therapies (e.g., corticosteroids). Experts agreed that mepolizumab has potential to reduce asthma exacerbations, reduce the number of hospital visits, and improve patients' quality of life. One expert with a clinical perspective noted that avoiding use of corticosteroids, which have significant side effects, could alone improve patients' quality of life.[49] However, two experts[45,48] with research backgrounds noted that long-term data on the mepolizumab's safety and efficacy are needed.

Acceptance and adoption: Patients and clinicians are likely to adopt the intervention, the majority of experts thought, because of mepolizumab's potential to reduce exacerbations and steroid use, as well as its improved safety profile versus existing therapies. Some experts noted that clinicians may need to train patients on how to subcutaneously self-administer mepolizumab, which could delay adoption.[45,46]

Health care delivery infrastructure and patient management: Most experts thought that if patients self-administer mepolizumab, using the drug would not disrupt health care infrastructure or patient management; however, two experts thought that training patients to inject the drug properly may initially increase demands on infrastructure.[47,50] Like other biologic drugs, mepolizumab's cost could potentially be high, the experts thought,[45-47,49] but if patient use of mepolizumab reduces the costly emergency room visits and hospitalizations due to exacerbation of asthma symptoms, the drug's costs may be offset.[45,48-50]

Health disparities: Two experts with clinical and research backgrounds noted that the incidence of severe asthma is high in patients with low socioeconomic status, and these patients also experience more frequent exacerbation of asthma symptoms.[48,49] These disparities may increase if uninsured or underinsured patients cannot afford the cost of mepolizumab,[45,47] but one research expert thought that the drug would potentially be covered by publicly funded health insurance programs.[50]

Idiopathic Pulmonary Fibrosis Intervention

Oral Options (Nintedanib [Ofev], Pirfenidone [Esbriet]) for Treatment of Idiopathic Pulmonary Fibrosis

Unmet need: Patients with idiopathic pulmonary fibrosis (IPF) have a median life expectancy of 2–3 years from initial diagnosis, and no approved medications are available.[51,52] Between 80,000 and 100,000 people in the United States are living with IPF, and about 30,000 new cases are diagnosed in the United States annually. IPF is a progressive lung disease in which scarring or thickening of lung tissue occurs with no identifiable cause. Scarring begins at the lung periphery and progresses toward the center, making breathing progressively more difficult. Common signs and symptoms of IPF include shortness of breath and a chronic, dry, hacking cough. Other signs and symptoms may develop over time and include rapid, shallow breathing; gradual, unintended weight loss; fatigue or malaise; aching muscles and joints; and chest pain. Although the exact cause of IPF is unknown, it occurs more commonly in people who work around dust or fumes, are between 40 and 70 years old, have a history of smoking, or are male. Patients can use portable oxygen to aid breathing and may receive corticosteroids to reduce dyspnea during acute exacerbations. A limited number of patients with IPF receive a lung transplant. However, patients with IPF have the highest waiting-list mortality rate of any indication for lung transplant; thus, a large unmet need exists for effective treatment.[52,53]

Intervention: In this section we discuss two options for treating IPF: nintedanib and pirfenidone.

*Nintedanib***.** Nintedanib (Ofev®) is a tyrosine kinase inhibitor that targets multiple growth factor receptors purportedly involved in the pathogenesis of IPF. Nintedanib is thought to suppresses proangiogenic intracellular signaling by inhibiting the proliferative growth factor receptor kinase activity of vascular endothelial growth factor receptor 2 (VEGFR2), fibroblast growth factor receptor (FGFR), and platelet-derived growth factor receptor (PDGFR). These receptors are thought to be involved in cycles of inflammation and repair that lead to lung fibrosis in IPF. Researchers have hypothesized that blocking the downstream signaling pathways of these receptors could slow the disease's pathogenic processes.[52] Nintedanib 150 mg is administered, orally, twice daily with food. Some patients may require a dose reduction to 100 mg twice daily, or treatment interruption to manage adverse events.[54]

*Pirfenidone***.** Pirfenidone (Esbriet®) is a synthetic pyridone analogue that purportedly inhibits synthesis of transforming growth factor (TGF)-alpha and TGF-beta, although the exact mechanisms are unclear. TGF-alpha is involved in inflammation, and TGF-beta has roles in fibrosis and proliferation and differentiation of fibroblasts. By inhibiting these two cytokines, pirfenidone purportedly inhibits inflammation and fibrosis in the lungs, delaying IPF progression.[55,56] Pirfenidone is administered orally as 3 capsules (267 mg each), 3 times daily, for a daily total of 2,403 mg; patients begin with 1 capsule 3 times daily and titrate to the full dosage after 2 weeks.[57]

Clinical trials: *Nintedanib.* In two replicate, phase III, randomized, double-blind, 52-week trials (INPULSIS-1 and INPULSIS-2), patients (n=1,066) with IPF were given nintedanib 150 mg or placebo twice daily.[58] In INPULSIS-1, patients treated with nintedanib had an adjusted annual rate of change in forced vital capacity (FVC) of -114.7 mL versus -239.9 mL with placebo (difference, 125.2 mL; 95% CI, 77.7 to 172.8; p<0.001). In INPULSIS-2, patients treated with nintedanib had an adjusted annual rate of change in FVC of -113.6 mL versus -207.3 mL with placebo (difference, 93.7 mL; 95% CI, 44.8 to 142.7; p<0.001). In INPULSIS-1, no significant difference was observed between groups in the time to the first acute exacerbation (hazard ratio [HR] with nintedanib, 1.15; 95% CI, 0.54 to 2.42; p=0.67). In INPULSIS-2, a significant benefit was observed with nintedanib compared with placebo (HR, 0.38; 95% CI, 0.19 to 0.77; p=0.005).[58]

In interim data reported from INPULSIS-ON, an ongoing phase III extension trial for patients who completed one of the INPULSIS trials and had received either nintedanib or placebo, the mean change from baseline was -87 mL for all patients; -96.4 mL for patients continuing treatment with nintedanib in the extension trial (100 total weeks of treatment); and -73.1 mL for patients initiating treatment with nintedanib (48 weeks of treatment). No statistical analyses were reported.[59,60]

The most common adverse reactions occurring in patients treated with nintedanib compared with placebo were gastrointestinal in nature, and include decreased appetite, diarrhea, nausea, and vomiting.[54,60,61]

Pirfenidone. In the phase III, randomized, double-blind, controlled ASCEND trial, patients (n=555) with IPF were treated with pirfenidone 3 times daily (for a total of 2,403 mg) or placebo for 52 weeks.[62] Investigators reported that at week 52, the proportion of patients who either died or who had a decline of 10 percentage points or more in predicted FVC was reduced by 47.9% in the pirfenidone group compared with the placebo group. The proportion of patients with no decline in the percentage of the predicted FVC increased by 132.5% in the pirfenidone group ($p<0.001$). Pirfenidone treatment also reduced the decline in the 6-minute walk test ($p=0.04$) and improved progression-free survival ($p<0.001$), compared with placebo. No significant differences in rates of death from any cause ($p=0.10$) or from IPF ($p=0.23$) were observed. However, in a prespecified analysis pooling results from ASCEND and CAPACITY, a second phase III trial, pirfenidone reduced the risk of death at 1 year by 48%, as compared with placebo (HR, 0.52; 95% CI, 0.31 to 0.87; $p=0.01$).[62] In September 2015, the manufacturer reported data from the same pooled trials suggesting that, after 2 years of treatment, pirfenidone reduced the risk of death by 38% versus placebo ($p=0.0515$).[63]

The most common adverse reactions occurring in patients treated with pirfenidone compared with placebo include nausea and rash.[57]

Manufacturer and regulatory status: Boehringer Ingelheim GmbH (Ingelheim, Germany) makes nintedanib.[54] In October 2014, FDA approved nintedanib for treating IPF.[64] Two phase III studies are ongoing, including the INPULSIS-ON extension trial evaluating nintedanib's long-term safety and efficacy. InterMune, Inc., a subsidiary of F. Hoffmann-La Roche, Ltd. (Basel, Switzerland), makes pirfenidone.[57] In October 2014, FDA approved pirfenidone for treating IPF;[65] one ongoing phase III trial is evaluating the drug's long-term safety and efficacy.

Diffusion: In October 2014, Boehringer Ingelheim implemented a patient support program to facilitate access to nintedanib. It features nurse access 24 hours a day, 7 days a week, financial-support resources, and educational resources. The program offers up to $30,000 annually for copayment assistance, and for some patients with insufficient financial resources, the program covers the entire cost of therapy.[66,67] Roche has implemented a similar program for pirfenidone.[66,68]

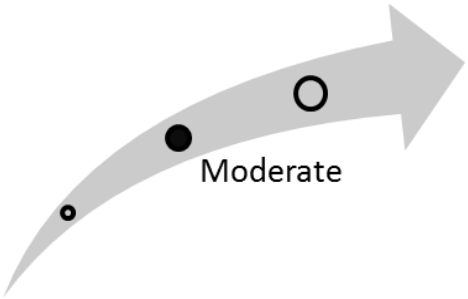
As of June 2015, a 30-day supply of nintedanib (60 capsules) reportedly cost between $8,190 and $8,780;[69] no price information for the drug was available as of December 2015. A 30-day supply of pirfenidone (270 capsules) reportedly costs about $7,800.[70] Our searches of 11 representative, private, third-party payers that publish their coverage policies online found 10 payers that have policies for coverage of pirfenidone and nintedanib for treating IPF.[71-83] The drugs require prior authorization for coverage.

Clinical Pathway at Point of This Intervention

No cure exists for IPF. Treatment focuses on managing stable disease and exacerbations. Symptoms might be managed with corticosteroids. Patients can implement home and lifestyle changes (e.g., reducing exposure to cigarette smoke, increasing physical activity, implementing a healthy diet) to mitigate symptoms as well as using oxygen support to aid breathing. In some cases,

lung transplantation may be considered.[84] Nintedanib and pirfenidone are daily oral antifibrotic treatments intended to slow disease progression in patients with IPF.

Figure 3. Overall high-impact potential: oral options (nintedanib [Ofev], pirfenidone [Esbriet]) for treatment of idiopathic pulmonary fibrosis



Overall, experts commenting on these interventions thought both nintedanib and pirfenidone have the potential to address a significant unmet need in IPF treatment by delaying deterioration in lung function and mortality in patients with IPF. However, these drugs are expected to have only a moderate impact on health outcomes because of their inability to halt or reverse disease progression. Further, limited long-term clinical data, difficulty in accurately diagnosing IPF, cost and reimbursement issues, and increased physician visits to monitor adverse events are issues that could pose barriers to nintedanib and pirfenidone use. However, these drugs are expected to be widely used for treating IPF because of a lack of other treatment options. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, or health systems backgrounds, offered perspectives on nintedanib,[85-90] and six experts, with similar backgrounds, commented on pirfenidone.[91-96] Of these experts, four commented on both interventions.[86,88-90,92,94-96] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: IPF is a progressive and ultimately fatal disease with no effective treatment options. A substantial unmet need exists for treatment options that can halt or delay disease progression, the experts concluded. Experts stated that although pirfenidone and nintedanib do not reverse the course of IPF pathology, both drugs have demonstrated ability to moderately slow the decline of lung function and delay mortality. One research expert noted that clinical trials directly comparing nintedanib to pirfenidone are needed.[93] Two clinical experts and two research experts expressed concern regarding the gastrointestinal adverse events that some patients experienced while taking these drugs.[86,89-91]

Acceptance and adoption: Clinician acceptance and adoption of both drugs are expected to be high because of a lack of effective treatment options for IPF. However, one clinician was concerned that IPF is hard to diagnose before prescribing treatment.[90]

Patients are also likely to accept new treatment options for IPF. One research expert thought that patients and clinicians may prefer pirfenidone due to the drug's improved tolerability versus nintedanib.[86] Two clinical experts also stated that occurrence of adverse events after nintedanib treatment could reduce patient acceptance.[89,90] Experts also identified treatment costs as a barrier to patient acceptance. Some experts thought that payers are likely to cover both drugs because, if left untreated, patients with IPF usually require critical care within several years after diagnosis (e.g., hospitalization, lung transplantation); treating patients with nintedanib or pirfenidone could delay the need for these intensive treatments, as well as related costs.[86,94,95]

Health care delivery infrastructure and patient management: As oral medications, pirfenidone and nintedanib are not expected to have a large impact on health care delivery infrastructure or patient management. If the drugs can slow the decline in lung function in patients with IPF, the number of hospitalizations and the need for treating complications could be reduced. However, a clinical expert expected that increased staffing will be required to handle reimbursement paperwork for both drugs. This expert also opined that additional physician visits will be required to monitor response to the therapy and adverse events.[90]

Health disparities: In terms of health disparities, experts expected both drugs to be costly and concluded that these disparities could arise if there were differences in coverage among third-party payers. However, two experts with clinical and research perspectives noted that manufacturers' patient support programs could limit the occurrence of these disparities.[86,89]

Normothermic Lung Transplantation Intervention

Portable Warm Blood Perfusion Systems (Organ Care System and Xvivo Perfusion System) for Normothermic Lung Transplantation

Unmet need: In 2012, 1,754 lung transplantations were performed in the United States, with 1,616 patients on the national waiting list. The number of transplantations is limited by the number of suitable donor lungs available.[97] Only about 10% to 30% of donated lungs are considered to be acceptable for transplantation, severely limiting the rate of lung transplantations.[98] Developing new strategies to improve donor-lung quality could increase the number of lungs available for transplantation.[98]

Intervention: Two warm blood lung perfusion systems are presented in this section: the Organ Care System (OCS Lung) and Xvivo Perfusion System (XPS).

Organ Care System. The OCS Lung is an integrated and portable ex vivo lung perfusion (EVLP) system intended to assess and improve marginal lungs and potentially preserve or improve the condition of routine donor lungs. The system's potential advantages over conventional organ preservation include immediate and sustained donor lung recruitment at the donor site; reduced time for the organ to be maintained in a cold ischemic state, especially during transport; and continuous organ-quality assessment during transport from donor to recipient.[99] Furthermore, the system can potentially increase the time an organ is maintained outside the body in good condition before transplantation.[100] The OCS Lung consists of a portable, battery-operated platform with a wireless monitor. The central component of the platform is the perfusion module, a transparent, sterile chamber that protects and maintains the lungs with appropriate temperature and humidity.[101] Each organ transplant requires a disposable TransMedics Solution set to provide nutrients and substrates to preserve donor lungs. The platform also includes an oxygen supply, ventilator, and a blood pump.[100,101] The monitor controls the platform and provides donor-organ assessment information.[101] In pilot trials, the harvested lung was connected to the OCS Lung by means of the pulmonary artery and trachea. Blood is delivered through the pulmonary artery and drains directly into the perfusion module chamber. A ventilator delivers air to the lungs via the trachea. Donor lungs are perfused with Steen™ solution that is enriched with two red blood cell concentrates, matched to the transplant recipient. Steen solution provides a buffered extracellular solution for EVLP that consists of human albumin for maintaining optimal colloid osmotic pressure and preventing edema and dextran 40 to coat and protect the endothelium from damage due to leucocyte activity or thrombogenesis.[102,103] Steen solution also contains a low concentration of potassium ions to reduce free-radical generation and avoid vascular spasm under normothermic conditions.[103] The enriched solution is supplemented with other compounds, including cefazolin, ciprofloxacin, voriconazole, methylprednisolone, glucose, multivitamins, and THAM buffer.[100] While donor lungs are undergoing warm perfusion and ventilation in the OCS Lung, clinicians can assess their function by measuring the oxygen concentration in the blood. Once on site for transplantation, warm blood perfusion is stopped, and the lungs are cooled using a heat exchanger or cold flush perfusion. After the lungs are immersed in cold low-potassium solution, transplantation may begin.[100] The manufacturer has not released information regarding average run times on the OCS Lung. In 2014, it was reported that the system had been used for 10.5 hours for a single EVLP procedure; the recipient survived.[104]

Xvivo Perfusion System. The XPS is a normothermic EVLP system that continuously flushes donor lung tissue with Steen solution to evaluate, preserve, and recondition initially unacceptable donor lungs. The XPS also ventilates the lungs, providing oxygen to the cells and allowing evaluation of the airways with a bronchoscope.[105] Donor lungs can stay in the XPS for 4–6 hours, allowing the transplant team to evaluate the lung function outside the body. Lungs meeting

acceptability criteria and passing the transplant surgeon's examination are transplanted into a suitable recipient.[105] The XPS is described as a fully integrated, off-the-shelf cardiac bypass system that includes a centrifugal pump, heater/cooler, ICU-ventilator, gas cylinders, perfusate gas monitor, Steen solution pumps, the Xvivo Organ Chamber™ platform, a touch-screen display, and software to monitor the procedure and system as well as capture data.[106] For evaluation, the lungs are placed in the single-use chamber to maintain humidity and sterility.[107,108] The organ is attached to the XPS through an extracorporeal perfusion circuit that allows continuous flow of nutrients and gas at a rate set by the clinician.[107] The circuit allows fine control of organ temperature, blood pressure, and gas exchange; a leucocyte filter removes white blood cells from the perfusate circuit.[107] A standard ventilator connects to the donor lung via an endotracheal tube.[107] The lungs are ventilated and the surgeon performs a complete evaluation of the lung while it is connected to the XPS before transplantation. Use of the XPS typically runs between 2 and 4 hours.[109]

Clinical trials: *Organ Care System.* In the completed phase III, randomized, controlled, INSPIRE trial, patients (n=264) who were registered primary double-lung transplant candidates were randomly assigned to receive preservation and transport of donor lungs using either OCS Lung or cold storage. Interim data from the study reported, as of September 6, 2013, the first 136 patients had completed the 30-day followup endpoint. Data revealed patient survival on day 30 in patients treated with OCS (n=59) or cold storage (n=77) was 98% and 95%, respectively. Patient survival at 6 months for patients with OCS-treated lungs (n=36) and cold storage treated lungs (n=46) was 97% and 87%, respectively.[110] No adverse reactions regarding the use of the OCS Lung have been reported.

Xvivo Perfusion System. In the single-center NOVEL trial, patients (n=308) requiring a lung transplant received lungs preserved with cold storage or XPS (EVLP). Rates of survival and freedom from bronchiolitis obliterans syndrome (BOS) were similar between EVLP and cold storage groups. The ratios between post-transplant forced expiratory volume in 1 second (FEV_1) and predicted FEV_1 were 76±30% and 73±24% (p=nonsignificant) for the EVLP and control groups, respectively. The mean change between pre- and postoperative 6-minute walking tests were also similar (EVLP 181±117 meters vs. cold storage 213±143 meters, p=nonsignificant).[111]

In a three-center trial, donor lungs (n=125) that were initially deemed unsuitable for transplantation underwent EVLP with XPS. Of the 125 perfusions performed, 103 lungs (82.5% utilization after EVLP) were subsequently transplanted. Incidence of primary graft dysfunction at 24 hours and 72 hours after the transplant procedure were 7% and 5%, respectively. Median time to extubation and hospital length of stay were 2 days (range 1–99) and 23 days (range 7–120), respectively.[112]

Patients receiving lungs perfused with XPS could experience the same adverse events that are generally associated with lung transplantation: acute rejection, arrhythmias, BOS, narrowing of air passages, primary graft dysfunction or lung not responding, renal failure or dysfunction, respiratory dysfunction or infection, rupture of the surgical wound, and death.[105] Additionally, in one study, 6% of patients who received lungs treated with XPS required intervention due to airway complications.[112]

Manufacturer and regulatory status: The OCS Lung is undergoing evaluation by TransMedics, Inc. (Andover, MA), for donor organ preservation during lung transplantation;[99] one phase III trial (EXPAND Lung) is ongoing. The OCS is also being investigated for preserving donor hearts. The OCS Lung is an investigational device and is not yet approved by FDA.

XVIVO Perfusion, AB (Göteborg, Sweden), makes the XPS and Steen solution.[113] Three phase II trials are ongoing. In August 2014, FDA approved XPS and Steen solution for normothermic EVLP of organs outside the body pending transplantation under a humanitarian device exemption (HDE).[114]

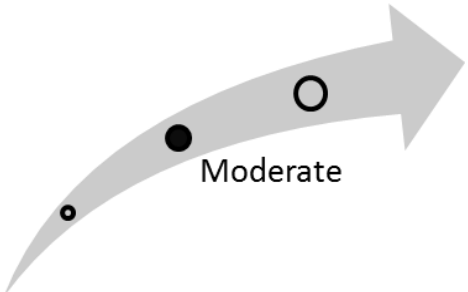
Diffusion and costs: The OCS Lung system is in the innovation stage in the United States. If FDA clears the system, reimbursement for its use would be part of the bundled payment for organ harvesting and transplantation. According to one estimate, using standard methods, single- and double-lung organ procurement costs about $73,100 and $90,300, respectively.[115] According to an ECRI Institute PricePaid analysis, as of the second quarter of 2013, a disposable perfusion set for the OCS Lung could add an additional $45,000 per patient for organ procurement. The price quoted for the OCS Lung System (monitor) was $225,000.[116] The cost of hands-on clinical training for the OCS Lung was $100,000, and clinical field support 24 hours a day, 7 days a week for 1 month costs $120,000. The manufacturer indicated that the OCS Lung preservation equipment could be loaned to the hospital at no cost if the facility agreed to purchase 10 perfusion sets at $45,000 each, for a total cost of $450,000.[117]

According to XVIVO Perfusion, as of August 2015, the XPS system was available in 18 centers in the United States.[118] Additionally, the cost for disposables for the XPS could add $19,024 (3%) to the current cost of a lung transplantation.[119] According to an ECRI Institute PricePaid analysis, as of the second quarter of 2011 (the latest date for which cost data were reported), the capital cost of the XPS system was quoted to be $250,000.[116] In December 2013, the Organ Procurement Organization (OPO) in Michigan reported the purchase of a single XPS that would be shared among the three transplant centers in the State to facilitate EVLP procedures. This is the first reported collaboration in the United States in which an OPO will perform EVLP and transplant centers will perform the lung transplantation. Employees of the three centers reportedly received 2 days of training on the XPS.[120]

Clinical Pathway at Point of This Intervention

The standard method for preserving donor lungs for transplantation is cold flush and static cold storage. This method has traditionally been successful for high-quality donor organs when the ischemia times are not excessive.[100] At the onset of the cold-storage process, the lungs are flushed with a cold solution in an anterograde and retrograde manner to clear the blood from the organ and to ensure proper reperfusion upon transplantation.[121,122] After flushing, the lungs are cooled and stored between 4 and 8°C to reduce the metabolic rate and slow degeneration.[122] Inflated donor lungs are considered to be optimal; collapsed lungs do not tolerate ischemia very well. Lung inflation is done with an inspired oxygen tension of 30% to 50%.[121] The donor lungs are immersed in additional cold preservation solution and placed on ice for transport.[122] The total ischemic time is generally less than 8 hours.[121] The OCS and XPS systems would replace this method.[123]

Figure 4. Overall high-impact potential: portable warm blood perfusion systems (Organ Care System, Xvivo Perfusion System) for normothermic lung transplantation



Experts commenting on the OCS and XPS thought that the unmet need is great for obtaining more transplantable donor lungs that are of higher quality. The experts generally agreed that these interventions have high potential to increase the quantity and, to a lesser extent, the quality of viable

donor lungs. However, for the OCS and XPS systems to deliver on their full impact potential, more data demonstrating reductions in transplantation-associated complications, adverse events, and increased survival rates compared with cold storage or remaining on the wait list are needed, the experts thought. Experts were optimistic about clinicians accepting the EVLP technology, but noted that the cost of the systems and the need for training could be a barrier to acceptance. Based on this input, our overall assessment is that these interventions are in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, or health systems backgrounds, offered perspectives on OCS,[124-129] and six experts, with similar backgrounds, commented on XPS.[130-135] Of these experts, one commented on both interventions.[127,132] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: A substantial unmet need exists for more transplantable lungs. OCS and XPS could address that need, experts agreed, although the number of donor lungs needed is less than the number of organs needed for other types of transplantation (e.g., kidneys, livers, hearts). Patient health outcomes could be improved by the reported increase in lung tissue quality using the EVLP technology; however, procurement costs could limit the systems' use, one clinical expert noted.[128] One health systems expert thought that the increase in the number of available lungs would have the largest impact on patient health outcomes, rather than the condition of the treated lungs.[132] Other experts called for long-term safety and efficacy and survival data to determine the ability of OCS and XPS to improve patient outcomes. Experts with research and clinical backgrounds noted that the OCS Lung and XPS processes would directly compete to fill the unmet need for increasing the pool of transplantable lungs; based on available data, they were unsure about which system would better meet this need.[124,126,129,133]

Acceptance and adoption: Clinician acceptance and adoption of both OCS Lung and XPS are expected to be high if the technologies are shown to increase the pool of donor lungs and improve outcomes, the experts opined. The cost of the systems, the need to train staff on their use, and increased staffing requirements were identified as potential barriers to acceptance.[126,128,132] Patients on the lung transplant waiting list would be eager for new technologies that could improve patient outcomes, one clinical expert stated.[128] However, most experts noted that the method of organ preservation is not decided by the patient.

Health care delivery infrastructure and patient management: Two experts with health systems and research perspectives[125,132] pointed out that the number of lung transplants could double after OCS and XPS adoption, which could result in increased demands on transplant staff and transplant center infrastructure. In terms of patient management, experts thought that the OCS and XPS systems have little potential for disruption because they are used only during organ procurement and have little impact on the rest of the procedure and standard care after the surgery. However, one health systems expert[127] noted that the need for additional treatments after OCS-assisted lung transplantation could be reduced if the device improves lung quality, which could reduce demand on health care infrastructure. Purchasing the OCS or XPS systems, as well as training sessions required for their use, would significantly increase health care costs for lung transplantation, experts concluded. However, one expert anticipated that these costs could eventually be offset by increased revenue from preserving and transplanting more lungs and decreased costs from reduced complications.[130]

Health disparities: Experts offered mixed comments on the impact of OCS and XPS on health disparities. Some experts thought health disparities would not be affected at all.[125,128,129,131] Others

concluded that the high costs associated with using OCS or XPS during lung transplantation, as well as limited access to specialized care and health care coverage in health-disparate populations, could further contribute to disparities.[124,130,132,134]

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