Priority Area 13: Pulmonary Disease, Including Asthma

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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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Financial Disclosure Statement
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 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, 540 Gaither Road, Rockville, MD 20850, or by email to: effectivehealthcare@ahrq.hhs.gov.

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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 18,000 leads about potential topics has resulted in identification and tracking of about 2,000 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 550 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 150 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 four topics for which (1) preliminary phase III data on drugs, phase II or III data on devices and procedures were available, or programs were being piloted; (2) information was compiled before November 4, 2014, in this priority area; and (3) we received five to seven sets of comments from experts between January 1, 2014, and November 13, 2014. (Eighteen topics in this priority area were being tracked in the system as of November 4, 2014.) We present three summaries on four topics (indicated below by an asterisk) that emerged as having high-impact potential on the basis of experts’ comments. One of these, portable warm blood perfusion system (Organ Care System) for lung transplantation, was in the June 2014 Potential High-Impact Interventions report. Another topic that was in the June 2014 report, the oral tablet azithromycin for prevention of chronic obstructive pulmonary disease exacerbations, was archived and thus removed from this iteration of the high impact report. This drug was tracked in the Healthcare Horizon Scanning System since September 28, 2011 and it has diffused as an off-label use of a drug; thus, it no longer meets criteria for tracking in the horizon scanning system. The material in this Executive Summary and report is organized alphabetically by intervention. Readers are encouraged to read the detailed information on these interventions that follows the Executive Summary.

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Discussion

Pulmonary disease is a priority area in which a moderate number of interventions have been identified as meeting criteria for tracking in the Healthcare Horizon Scanning System. Experts deemed four topics as having high-impact potential: An oral drug for treating patients with cystic
fibrosis (CF), two oral drugs for treating idiopathic pulmonary fibrosis (IPF), and a novel, portable, warm-blood perfusion system for lung transplantation.

**Cystic Fibrosis**

About 30,000 people in the United States have CF, and no cure is available. The disease is caused by mutations in the CF transmembrane conductance regulator (CFTR), an ion channel involved in facilitating the movement of chloride ions and other charged particles across cellular membranes. CF affects the cells that produce mucus, sweat, and digestive fluids, causing severe damage to the lungs and gastrointestinal tract. Patients are treated with agents to ease symptoms and reduce complications from infections, excessive thick mucus in the lungs, and gastrointestinal symptoms. Common treatments consist of routine use of antibiotics (oral, injected, or inhaled), anti-inflammatory medicines (oral or inhaled), bronchodilators (inhaled), or mucus-thinning medicines. Ventilators, chest physiotherapy, and exercise are also used to help release the thick mucus that accumulates in the lungs. A limited number of lung transplants are available for patients with severe disease. Patients with CF have a shortened life expectancy (40–50 years). A person needs mutated copies of the gene from both parents to develop CF. Researchers have identified more than 1,800 mutations associated with the disease. Therapies targeting CFTR mutations have been proposed to treat CF; however, therapies targeting molecular defects are not available for the majority of patients with CF, although two new drugs have come onto the market in the past two years. CTRF mutations that have been targeted in new drug therapies are the G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, and G1349D mutations. However, these nine mutations represent only about 4.5% of patients with CF. Another mutation, the F508del mutation, is more widespread. 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 and another 39% of CF patients have one copy of the mutation. 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, the G551D mutation. Subsequently, the drug has been under study as part of a combination therapy described below.

**Combination Lumacaftor and Ivacaftor for Treatment of Cystic Fibrosis**

- **Key Facts:** Lumacaftor (Vertex Pharmaceuticals, Inc., Boston, MA) is a small-molecule corrector that targets the F508del CFTR mutation, which causes defects in both CFTR trafficking to the surface of cells and ion gating/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 phase III TRAFFIC and TRANSPORT trials, patients treated with lumacaftor and ivacaftor orally, twice daily, had significant improvements in lung function and fewer exacerbations after 24 weeks of therapy than did patients treated with placebo.

Three phase III trials on lumacaftor have been completed, and one phase III extension trial is ongoing. In November 2014, the company submitted a new drug application (NDA) to FDA for a fixed-dose combination of lumacaftor (400 mg) and ivacaftor (250 mg) administered orally, twice daily, for treating patients with CF aged 12 years and older who have two copies of the F508del mutation. FDA granted orphan drug and breakthrough therapy statuses for the combination regimen.
The manufacturer has not released cost information for lumacaftor. Ivacaftor alone costs more than $300,000 annually and is among a number of recently approved orphan drugs considered harbingers of skyrocketing pharmaceutical treatment costs. Financial analysts predict the fixed-dose combination lumacaftor and ivacaftor could have a reduced cost of $150,000 to $200,000 annually, because of a larger eligible patient population. If approved for marketing, payers are expected to cover the fixed-dose combination lumacaftor and ivacaftor, because payers have generally covered ivacaftor.

- **Key Expert Comments:** Overall, experts stated that as a targeted therapy for CF, lumacaftor has potential for addressing a significant unmet need in CF management. Treatment with lumacaftor and ivacaftor demonstrated benefit in patients with CF who have two copies of the F508del mutation, but not in patients with only one copy of the mutation. This suggests that combination therapy could be appropriate for about half of patients with CF, if approved, as 47 percent of CF patients in the United States are homozygous for F508del. High costs could limit patient access to the drug if third-party payers do not cover the majority of the drug cost. However, payers have reimbursed for use of the predecessor ivacaftor, and thus reimbursement of the combination therapy is anticipated. Lumacaftor demonstrated its ability to improve outcomes, quality of life, and longevity by reducing pulmonary exacerbations, hospitalization, and 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:** High

**Idiopathic Pulmonary Fibrosis**

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. 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, IPF 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.

**Oral treatment options for idiopathic pulmonary fibrosis**

**Pirfenidone**

- **Key Facts:** Pirfenidone (Esbriet®; InterMune, Inc., Brisbane, CA, and F. Hoffmann-La Roche, Ltd., Basel, Switzerland) is a synthetic pyridone analog purported to inhibit the synthesis of transforming growth factor (TGF)-beta and TGF-alpha, two cytokines thought to play a role in the fibrosis and inflammation associated with IPF pathogenesis. Pirfenidone is administered orally as three capsules, three times daily (for a total of 801 mg). Patients are
titrated to the full dose by the third week of therapy. In the phase III ASCEND trial, patients (n=555) with IPF treated with pirfenidone had a significant relative reduction in the proportion of patients with declining lung function or who died compared with patients given placebo after 52 weeks. Patients given pirfenidone were also more likely to have no decline in lung function compared with patients given placebo. Pirfenidone treatment also reduced the decline in the 6-minute walk distance and improved progression-free survival compared with placebo. The most common adverse reactions occurring in patients treated with pirfenidone compared with placebo include abdominal pain, diarrhea, fatigue, headache, nausea, rash, and upper respiratory tract infection.

In October 2014, FDA approved pirfenidone for treating IPF. Based on a December 2014 query of U.S.-based, online aggregator of prescription drug prices, a 30-day supply of pirfenidone (267 mg) costs between $8,000 and $8,240. Our searches of 11 representative, private, third-party payers that publish their coverage policies online found 1 payer that has a policy providing coverage for pirfenidone with prior authorization required. The drug’s manufacturer has stated it would implement a patient support program to facilitate diffusion; it will provide educational and financial support services.

### Nintedanib

- **Key Facts:** Nintedanib (Ofev®; Boehringer Ingelheim GmbH, Ingelheim, Germany) 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 lung repair that lead to lung fibrosis in IPF. Nintedanib is administered 150 mg orally, twice daily, with food. Some patients may require a dose reduction to 100 mg, twice daily, or treatment interruption to manage adverse events. In two replicate phase III trials (INPULSIS-1 and INPULSIS-2), patients (n=1,066) with IPF who were given nintedanib (150 mg) twice daily had a significantly smaller decline in lung function compared with lung function in patients given placebo, after 52 weeks of therapy. In the INPULSIS-2 trial, patients treated with nintedanib had a significant increase in time to the first acute exacerbation compared with patients treated with placebo. The most common adverse reactions occurring in patients treated with nintedanib compared with placebo include abdominal pain, decreased appetite, diarrhea, elevated liver enzymes, headache, nausea, and vomiting.

In October 2014, FDA approved nintedanib for treating IPF. Based on a December 2014 query of a U.S.-based, online aggregator of prescription drug prices, a 30-day supply of nintedanib (150 mg) can cost between $8,200 and $8,760. Our searches of 11 representative, private, third-party payers that publish their coverage policies online found 1 payer that has a policy providing coverage nintedanib for treating IPF, with prior authorization required. In October 2014, the manufacturer announced the company had implemented a patient support program to facilitate nintedanib diffusion; it features nurse-support access 24 hours a day, 7 days a week, financial support resources, and educational resources.

### Pirfenidone and Nintedanib

- **Key Expert Comments:** Overall, experts commenting on these interventions thought pirfenidone and nintedanib have potential to address a significant unmet need in IPF treatment by delaying deterioration in lung function and mortality. However, these drugs are expected to have only a moderate impact on health outcomes because of their inability to
halt or reverse disease progression. Additionally, the drug has been ineffectual in some patients or has had waning efficacy. Limited clinical data, difficulty in accurately diagnosing IPF, cost and reimbursement issues, and increased physician visits to monitor adverse events could pose barriers to pirfenidone and nintedanib diffusion. However, these drugs are expected to be widely used for IPF patients, because of a lack of other treatment options.

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

**Lung Transplantation**

In 2012, 1,754 lung transplants were performed in the United States, with 1,616 patients awaiting transplants 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 transplants 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 supportive therapies (i.e., ventilation, pharmacologic interventions) when the lungs are transplanted. In an effort to increase the suitable donor lung supply, new alternatives such as the use of lungs from older donors, lungs donated after cardiac death, and other suboptimal or marginal donor lungs have been pursued. To improve their condition to purportedly acceptable functional levels, 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 below one technology, the Organ Care System (OCS) Lung for lung transplantation. Another normothermic ex vivo lung perfusion system, the XVIVO Perfusion System (XPS™), was recently FDA approved and is also being tracked in the horizon scanning system. However, expert comments had not been received on XVIVO in time for this report.

**Portable Warm Blood Perfusion System (Organ Care System) for Lung Transplantation**

- **Key Facts**: Only about 10% to 30% of donated lungs are considered to be suitable for transplantation, according to lung transplant and organ donor experts. Developing new strategies to better preserve or improve donor-lung quality could affect the number of lungs available for transplantation. Standard methods of donor organ preservation expose the organ to sustained periods of ischemia and hypothermia, which can result in organ damage that can make an organ unsuitable for transplantation. The Organ Care System for lung preservation (OCS Lung) is in development by TransMedics, Inc. (Andover, MA) as a portable, ex-vivo, warm blood perfusion, 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 is expected to be completed in October 2015. Interim data being reported from this trial (n=264) indicates 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; however another system, the XPS and Steen solution, purportedly works in a similar fashion and received FDA approval in August 2014 under the humanitarian device exemption program. The indication is for warm EVLP of organs outside the body pending transplantation. According to an 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 cost per patient for organ procurement (OCS is available outside the U.S.) 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.

- **Key Expert Comments:** Experts commented that the unmet need is great for more transplantable donor lungs of better quality. The experts generally agreed that this intervention has high potential to increase the quantity and quality of viable donor lungs. Experts were optimistic about both provider and patient acceptance of this technology. For the OCS Lung to deliver on the intervention’s 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
Pulmonary Disease Interventions
Lumacaftor and Ivacaftor for Treatment of Cystic Fibrosis

Unmet need: About 30,000 people in the United States have cystic fibrosis (CF). The disease is caused by mutations in the CF transmembrane conductance regulator (CFTR). The most common CFTR allele present in patients with CF is CFTR-F508del, which causes a deficiency in trafficking CFTR to the cell membrane. 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. No cure exists for CF; patients are treated with agents to ease symptoms and reduce complications from infections, excessive thick mucus in the lungs, and gastrointestinal manifestations. Therapies targeting CFTR mutations have been proposed to improve CF management; however, therapies targeting the appropriate molecular defect are not available for the majority of patients with CF.

Intervention: Lumacaftor is a small-molecule corrector targeting the F508del CFTR protein, a CFTR isoform with defects in both trafficking and gating/flow. Lumacaftor is intended to correct faulty protein processing so CFTR can be transported to the cell surface. 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. The manufacturer is pursuing a fixed-dose combination of lumacaftor (400 mg) and ivacaftor (250 mg) administered orally, twice daily, for treating patients with CF aged 12 years and older who have two copies of the F508del mutation. Lumacaftor is intended for patients with two copies of the F508del mutation and not for patients with other mutations that cause CF.

Clinical trial: In the phase III, randomized, double-blind, placebo-controlled TRAFFIC trial, patients (n=549) homozygous for the F508del mutation aged 12 years and 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. Patients treated with lumacaftor (600 mg) once daily and ivacaftor or lumacaftor (400 mg) twice daily and ivacaftor achieved a mean absolute change from baseline in percent predicted forced expiratory volume in 1 second (FEV₁) of 4.0% and 2.6%, respectively, compared with patients treated with placebo (p<0.0001 for both). Patients treated with lumacaftor (400 mg) twice daily and ivacaftor also had significantly fewer pulmonary exacerbations than did patients treated with placebo (73 vs. 112; p=0.0169).

In the phase III, randomized, double-blind, placebo-controlled TRANSPORT trial, patients (n=559) homozygous for the F508del mutation aged 12 years and older were treated with the same drug dosage as in the TRAFFIC trial. Patients treated with lumacaftor (600 mg), once daily, and ivacaftor achieved a 2.6% mean absolute change from baseline in predicted FEV₁ compared with patients treated with placebo (p<0.0004). Patients treated with lumacaftor (400 mg), twice daily, and ivacaftor achieved a 3.0% mean absolute change from baseline in predicted FEV₁ compared with patients treated with placebo (p<0.0001). Patients treated with lumacaftor (600 mg), once daily, and ivacaftor had significantly fewer pulmonary exacerbations than did patients treated with placebo (94 vs. 139; p=0.0116). Patients treated with lumacaftor (400 mg), twice daily, and ivacaftor also had significantly fewer pulmonary exacerbations than did patients treated with placebo (79 vs. 139; p=0.0002).

Adverse events that occurred more frequently in patients who received lumacaftor and ivacaftor compared with placebo 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.

Manufacturer and regulatory status: Vertex Pharmaceuticals, Inc. (Boston, MA), is developing lumacaftor (and developed ivacaftor). In November 2014, the company submitted a new drug application to the U.S. Food and Drug Administration (FDA) for a fixed-dose combination of lumacaftor (400 mg) and ivacaftor (250 mg) administered orally, twice daily, for treating patients...
with CF aged 12 years and older who have two copies of the F508del mutation.\textsuperscript{10} FDA has granted orphan drug and breakthrough therapy statuses for the combination regimen.\textsuperscript{11,12}

**Diffusion and cost:** Vertex has not released cost information for lumacaftor. According to a U.S.-based, online aggregator of prescription-drug prices, GoodRx, a monthly supply of ivacaftor costs about $27,000 for 60 tablets of 150 mg each, which is more than $300,000 a year.\textsuperscript{13} Analysts reportedly predict the combined cost for lumacaftor and ivacaftor would be reduced to $150,000 to $200,000 a year, due to a larger eligible patient population and differences in efficacy compared with ivacaftor alone.\textsuperscript{14}

### Clinical Pathway at Point of This Intervention

Patients with CF 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.\textsuperscript{6}

Lumacaftor in combination with ivacaftor has been proposed as a daily therapy to reduce the decline of lung function and the frequency of pulmonary exacerbations, which may slow disease progression.

**Figure 1. Overall high-impact potential: lumacaftor and ivacaftor for treatment of cystic fibrosis**

Overall, experts stated that as a targeted therapy for CF, lumacaftor has potential for addressing a significant unmet need in CF management. Treatment with lumacaftor and ivacaftor demonstrated benefit in patients with CF who have two copies of the F508del mutation, but not in patients with only one copy of the mutation. Consequently, combination therapy, if approved, would be appropriate for about half of patients with CF (47% of CF patients in the United States are homozygous for F508del). High cost could limit patient access to the drug if third-party payers do not cover the majority of treatment costs. Lumacaftor demonstrated its ability to improve outcomes, quality of life, and longevity by reducing pulmonary exacerbations, hospitalizations, and antibiotic use, as well as increasing weight (body mass index [BMI]), compared with placebo. Wide acceptance by clinicians and patients is expected for use of the drug in patients homozygous for F508del mutation. Based on this input, our overall assessment is that this intervention is in the high end of the high-impact-potential range.

### Results and Discussion of Comments

Six experts, with clinical, research, or health systems backgrounds, offered perspectives on this intervention.\textsuperscript{15-20} 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. Successful
treatment has doubled the life expectancy of patients with CF over the past 35 years, one clinical expert noted. This expert cautioned that although ivacaftor has improved health outcomes in patients with CF, the drug can be used in only a small population of patients. Treatment with lumacaftor has significant potential to improve the lives and live expectancy of a far greater proportion of patients. Lumacaftor has demonstrated an ability to increase lung function and BMI and reduce exacerbations, hospitalizations, and antibiotic use, in clinical trials, the experts noted. However, lumacaftor demonstrated less benefit than ivacaftor in their respective homozygous patient populations (i.e., patients with G551D benefit more from ivacaftor treatment than patients with F508del benefit with lumacaftor treatment), one clinical expert noted.

**Acceptance and adoption:** The experts generally thought lumacaftor acceptance among clinicians and patients would be high. Clinician acceptance and adoption of lumacaftor is expected to be similar to ivacaftor uptake, which was greater than 80% in the first year the therapy became available, one clinical expert noted. However this expert also noted as more targeted therapies with high treatment costs emerge, payers will push back on drug manufactures with less inclusive coverage policies for orphan drugs, which could affect third-party coverage and patient adoption.

Patients have also expressed strong interest in new targeted therapies. Additionally, patients are expected to favor pills, because current supportive CF therapies often require nebulizers and chest therapy, which are time consuming, noted one clinical expert. However, one health systems expert noted treatment costs could deter some patients from using lumacaftor.

**Health care delivery infrastructure and patient management:** Lumacaftor could reduce demands on health care staff and facilities by reducing pulmonary exacerbations, leading to fewer hospitalizations, physician visits, and less need for intravenous antibiotics at home or in a health care setting, experts noted. As an oral therapy, lumacaftor would not significantly change how patients are managed, the experts thought.

**Health disparities:** The high cost of lumacaftor could create health disparities, the experts opined. One clinical expert noted that Medicaid in Alabama has decided not to cover ivacaftor, which led to a lawsuit and could create a treatment disparity.
Oral Treatment Options for 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.\(^{21,22}\) 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, IPF 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.\(^{22,23}\)

**Intervention:** Pirfenidone (Esbriet®) is a synthetic pyridone analog that purportedly inhibits synthesis of transforming growth factor (TGF)-beta and TGF-alpha, although the exact mechanisms are unclear.\(^{24,25}\) TGF-beta has roles in fibrosis and proliferation and differentiation of fibroblasts. TGF-alpha is involved in inflammation. By inhibiting these two cytokines, pirfenidone purportedly inhibits inflammation and fibrosis in the lungs, delaying IPF progression.\(^{24,25}\) Pirfenidone is administered orally as three capsules (801 mg), three times daily; patients begin with one capsule (267 mg) three times daily, and titrate to the full dosage after 2 weeks of therapy.\(^{26}\)

Pirfenidone treatment also had a relative increase of 132.5% in the proportion of patients with no decline in FVC (p<0.001). Pirfenidone treatment also reduced the decline in the 6-minute walk distance (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 two previous phase III trials, the between-group difference favoring pirfenidone was significant for death from any cause (p=0.01) or from IPF (p=0.006).\(^{27}\) The most common adverse reactions occurring in patients treated with pirfenidone compared with placebo include nausea (36% vs. 16%), rash (30% vs. 10%), upper
respiratory tract infection (27% vs. 25%), diarrhea (26% vs. 20%), fatigue (26% vs. 19%), abdominal pain (24% vs. 15%), and headache (22% vs. 19%).

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), twice daily, or placebo. In INPULSIS-1, patients treated with nintedanib had an adjusted annual rate of change in FVC of -114.7 mL versus -239.9 mL with placebo (difference, 125.3 mL; 95% confidence interval [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). 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). The most common adverse reactions occurring in patients treated with nintedanib compared with placebo included diarrhea (62% vs. 18%), nausea (24% vs. 7%), abdominal pain (15% vs. 6%), elevated liver enzymes (14% vs. 3%), vomiting (12% vs. 3%), decreased appetite (11% vs. 5%), and headache (8% vs. 5%).

Manufacturer and regulatory status: InterMune, Inc. (Brisbane, CA), in the process of merging with F. Hoffmann-La Roche, Ltd. (Basel, Switzerland), makes pirfenidone. In October 2014, FDA approved pirfenidone for treating IPF.

Boehringer Ingelheim GmbH (Ingelheim, Germany) makes nintedanib. In October 2014, FDA approved nintedanib for treating IPF.

Diffusion: In October 2014, Boehringer Ingelheim announced the company had implemented a patient support program to facilitate nintedanib diffusion. It features nurse-support access 24 hours a day, 7 days a week, financial support resources, and educational resources. The program will offer up to $30,000 annually for copayment assistance, and for some patients with insufficient financial resources, the program will cover the entire cost of therapy. Additionally Roche stated the company would implement a similar program for pirfenidone.

Based on a December 2014 query of GoodRx, a 30-day supply of pirfenidone (267 mg) can cost between $8,000 and $8,240. A 30-day supply of nintedanib (150 mg) can cost between $8,200 and $8,760. Our searches of 11 representative, private, third-party payers that publish their coverage policies online found 1 payer that has a policy providing coverage of pirfenidone and nintedanib for treating IPF. The drugs require prior authorization for coverage.

Clinical Pathway at Point of This Intervention

No known 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, and implementing a healthy diet) to mitigate symptoms as well as oxygen support to aid breathing. In some cases, lung transplantation may be considered. Pirfenidone and nintedanib are daily oral antifibrotic treatments intended to slow disease progression in patients with IPF.
Overall, experts commenting on these interventions thought pirfenidone and nintedanib 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. Additionally, the drug has been ineffectual in some patients or has had waning efficacy. Further, limited clinical data, difficulty in accurately diagnosing IPF, cost and reimbursement issues, and increased physician visits to monitor adverse events could pose barriers to pirfenidone and nintedanib diffusion. However, these drugs are expected to be widely used for IPF patients 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 this pirfenidone and six experts, with similar backgrounds, commented on nintedanib. 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 the ability to moderately slow the decline of lung function and delay mortality. One clinical expert noted great variance in patients’ responses to pirfenidone. One research expert expressed concern regarding the high incidence (>60%) of patients who reported diarrhea while taking nintedanib.

Acceptance and adoption: Clinician acceptance and adoption of both drugs are expected to be high due to a lack of effective treatment options for IPF. However, one concern of clinicians is that IPF is hard to diagnose before prescribing treatment; only 50% of patients in whom IPF is diagnosed actually have the disease, which could complicate prescribing, one clinical expert opined. Difficulties in prescribing the medication could also pose barriers to community physicians, the clinical expert also noted.

Patients are also likely to accept new treatment options for IPF. However, two clinical experts stated that adverse events could reduce patient acceptance. One research expert also identified treatment costs as a barrier to patient acceptance. One health systems expert thought more data would be needed for clinician and patient acceptance. Payers are likely to cover both drugs because IPF has a worse prognosis than some cancers while pirfenidone and nintedanib were estimated to cost about $40,000 annually at the time of expert comment, which is less than many cancer drugs.
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, reductions in hospitalizations and treatment of complications could be observed. However, two clinical experts expect 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.36,42

Health disparities: Experts expected both drugs to be costly and concluded that health disparities could arise if there were differences in coverage among third-party payers and various levels of insurance.
Portable Warm Blood Perfusion System (Organ Care System) for Lung Transplantation

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

**Intervention:** The Organ Care System (OCS) Lung is an integrated and portable ex-vivo lung perfusion 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 methods 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. Furthermore, the system can potentially increase the time an organ is maintained outside the body in good condition before transplantation.

The OCS Lung system 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. Each organ transplant also requires a disposable TransMedics Solution set to provide nutrients and substrates to preserve donor lungs. The portable, battery-operated platform also includes an oxygen supply, ventilator, and a blood pump. The monitor controls the platform and provides donor-organ assessment information.

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 a solution (Steen solution, Vitrolife AB, Göteborg, Sweden) that is enriched with two red blood cell concentrates, matched to the transplant recipient. The enriched solution is also supplemented with other compounds, including cefazolin, ciprofloxacin, voriconazole, methylprednisolone, glucose, multivitamins, and THAM buffer.

While donor lungs are undergoing warm perfusion and ventilation in the OCS system, clinicians can assess the donor lung’s functional capacity 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.

**Clinical trials:** In the 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.

**Manufacturer and regulatory status:** The OCS Lung is undergoing evaluation by TransMedics, Inc. (Andover, MA), for donor organ preservation during lung transplantation. The phase III INSPIRE trial began recruitment in November 2011 and is expected to be completed in October 2015. The OCS is also being investigated for preserving donor hearts. The OCS Lung is an investigational device and is not yet approved by FDA.
**Diffusion:** The system is in the innovation phase in the United States. If cleared for marketing, reimbursement for use of the system 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. 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. 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. For benchmarking purposes, the manufacturer of another novel donor lung preservation system indicated use of its system could add about $19,000 to the current cost of an organ transplantation. That system is the XPS with Steen solution, which received FDA humanitarian device exemption approval in August 2014. The system maintains donor lungs at normothermic level in a humid chamber, perfused with Steen solution, and provided with gas exchange.

**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. 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. After flushing, the lungs are cooled and stored between 4 and 8 °C to reduce the metabolic rate and slow the degeneration process. 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%. The donor lungs are immersed in additional cold preservation solution and placed on ice for transport. The total ischemic time is generally less than 8 hours. The OCS Lung system would replace this method if approved for marketing and adopted.

**Figure 3. Overall high-impact potential: portable warm blood perfusion system (Organ Care System) for lung transplantation**

Experts commented that the unmet need is great for obtaining more transplantable donor lungs that have higher quality. The experts generally agreed that this intervention has high potential to increase the quantity and quality of viable donor lungs. Experts were optimistic about both provider and patient acceptance of this technology. For the OCS Lung to deliver on the intervention’s full impact potential, more data demonstrating reductions in transplantation-associated complications, adverse events, and mortality compared with cold storage are needed, the experts thought. 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.\textsuperscript{61-66} 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 could address that need, experts agreed, although the number of donor lungs needed is lower than the number of organs needed for other types of organ transplantation (i.e., kidneys, livers, hearts). Patient health outcomes could be improved by the purported increase in lung tissue quality from the OCS process; however the trial that could best support this claim will not be completed until 2015 or 2016, one clinical expert noted.\textsuperscript{66} Other experts called for more safety and efficacy data, as well as long-term efficacy and survival data, to support use of the OCS Lung system.

Acceptance and adoption: Clinician acceptance and adoption of the system is expected to be high if the OCS Lung is shown to increase the pool of donor lungs and improve outcomes, the experts opined. Cost of the OCS Lung and difficulty training staff in use of the system were identified as potential barriers to acceptance.\textsuperscript{62,66}

Patients on the lung transplant waiting list would be eager for new technologies that could help them receive a transplant sooner, one clinical expert stated.\textsuperscript{66} However, most experts noted that the method of organ preservation is not decided by the patient.

Health care delivery infrastructure and patient management: Patient length of stay and staff needed for treating transplant complications could be reduced with widespread use of the OCS Lung if the device is shown to improve lung quality, one clinical expert noted.\textsuperscript{66} Some experts remarked on a possible steep learning curve for widespread use of the OCS Lung, highlighting the training required to properly operate the system. Additionally, some experts thought that an increased pool of donor lungs would lead to more lung transplants resulting in greater demands on transplantation staff and infrastructure.

In terms of patient management, experts thought the OCS Lung system has little potential for disruption because it is used only during the procurement phase of the transplant, having little impact on the rest of the procedure and standard care after the surgery.

The OCS Lung would significantly increase health care costs for lung transplantation, experts concluded. However, experts anticipated the increased cost associated with purchase, disposables and training for the OCS Lung could eventually be offset by increased revenue from preserving and transplanting more lungs and decreased costs from shorter lengths of stay and reduced complications.\textsuperscript{66} Although OCS could add to procurement costs, benefits of the device could still fall within what is considered a reasonable cost-effectiveness range for organ procurement, a clinical expert opined.\textsuperscript{66}

Health disparities: Experts offered mixed comments on the impact of the OCS Lung on health disparities. Some experts thought health disparities would not be affected at all.\textsuperscript{61,63,65,66} Others concluded that the high costs associated with the OCS and lung transplantation and limited access to specialized care or health care coverage in health disparate populations could further contribute to health disparities.\textsuperscript{64,66}
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