Priority Area 13: Pulmonary Disease, Including Asthma

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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. HHSA290201000006C). 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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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.

Carolyn M. Clancy, M.D.  
Director  
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H. 
Director, Center for Outcomes and Evidence 
Agency for Healthcare Research and Quality

Elise Berliner, Ph.D. 
Task Order Officer 
Center for Outcomes and Evidence 
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 identifying 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 4 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 16,000 leads about potential topics has resulted in identification and tracking of about 1,800 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 600 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 annually. Topics eligible for inclusion are those interventions expected to be within 0–4 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 350 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.
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 seven or 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 three topics in the system for which (1) preliminary phase III or later data were available; (2) information was compiled by May 16, 2013, in this priority area; and (3) we received five to nine sets of comments from experts between October 25, 2011, and May 18, 2013. (Nineteen topics in this priority area were being tracked in the system as of May 18, 2013.) We present summaries on two topics (indicated below by an asterisk) that emerged as having high-impact potential on the basis of experts’ comments; one of which was in the previous Potential High-Impact Interventions report and one of which is newly added. 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.

Priority Area 13: Pulmonary Disease, Including Asthma

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<th>Topic</th>
<th>High-Impact Potential</th>
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<td>1. *Ivacaftor (Kalydeco) for treatment of cystic fibrosis in patients with G551D-CFTR mutation</td>
<td>Moderately high</td>
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<tr>
<td>2. *Off-label azithromycin for prevention of chronic obstructive pulmonary disease exacerbations</td>
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<tr>
<td>3. School-based preventive asthma care technology (SB-PACT) program for management of asthma in school children</td>
<td>No high-impact potential at this time</td>
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Discussion

Pulmonary disease is a priority area in which relatively few interventions have been identified as meeting criteria for tracking in the AHRQ Healthcare Horizon Scanning System. The experts deemed two topics as having potential for high impact: a new disease-modifying drug targeted at one of the genetic mutations seen in patients with cystic fibrosis (CF) and off-label daily use of the antibiotic azithromycin to prevent chronic obstructive pulmonary disease (COPD) exacerbations.
Ivacaftor (Kalydeco) for Treatment of Cystic Fibrosis in Patients with G551D-CFTR Mutation

- **Key Facts:** Before the approval of ivacaftor, therapies for CF had improved median survival times, but patients still had a shorter-than-normal life expectancy and required extensive treatment over a lifetime to maintain their health as well as possible. Thus, an unmet need has existed for novel, effective therapies to improve outcomes in this patient population. One new therapy has emerged to address a very small proportion of the CF population, but the remainder of the CF population still has only suboptimal therapy choices. The oral tablet ivacaftor (Kalydeco™, Vertex Pharmaceuticals, Inc., Cambridge, MA) targets the defective CF transmembrane conductance regulator (CFTR) protein that causes CF. The drug is intended as a first-line treatment for patients with the G551D-CFTR mutation—about 4% of patients with CF. Ivacaftor tablets are indicated for oral administration, one 150 mg dose every 12 hours for patients 6 years of age or older. Several phase III trials have been cosponsored by the Cystic Fibrosis Foundation, of Bethesda, MD. In trials, effects on pulmonary function were reported as early as 2 weeks, and a statistically significant treatment effect was reported to be maintained through week 48. Also through week 48, investigators reported, patients given ivacaftor were 55% less likely to have a pulmonary exacerbation than were patients given placebo. Ivacaftor in combination with an experimental CF drug, lumacaftor, has also been shown to improve lung function in patients with CF who have two copies of the CFTR-F508del mutation, according to recent phase II trial results. About 90% of North American patients with CF are purported to be heterozygous for the F508del mutation and about 50% of North American patients with CF are homozygous for that mutation, giving ivacaftor the potential for a much broader indication in the future. Additionally, ivacaftor is being evaluated in 10 other CFTR gene mutations known to cause CF, which could also expand the indicated patient population.

In January 2012, the U.S. Food and Drug Administration (FDA) granted marketing approval for ivacaftor for treating patients aged 6 years or older who have a G551D mutation in the CFTR gene. According to GoodRx, an online aggregator of pharmacy prescription-drug prices, ivacaftor costs about $27,053–$28,806 for 60, 150 mg tablets, which is about $329,145–$350,473 per patient per year. Third-party payers (Aetna for example) are starting to cover the drug with precertification requirements to qualify the patient as appropriate for treatment and to impose quantity limits for each prescription. Copayments vary according to the terms of a patient’s insurance benefits.

- **Key Expert Comments:** Overall, experts commenting on this topic thought that this drug could meet the need for a novel, effective, oral treatment for appropriate CF patients, although this view was tempered by the fact that the drug is intended for only the 4% or so of patients with CF who have the mutation. Experts thought that this drug would affect current care processes and patient management by offering patients a convenient oral therapy to directly treat CF’s cause, which could reduce the need for intravenous treatments, ventilation therapy, and chest physiotherapy, if the drug halts disease progression. At the time of review, the annual estimated cost of ivacaftor was $294,000, and that price has come down significantly since then. Nonetheless, cost was identified as a significant and potentially controversial issue. Even for patients with prescription drug coverage, copayments were expected to be significant.

- **Potential for High Impact:** Moderately high
Off-Label Azithromycin for Prevention of Chronic Obstructive Pulmonary Disease Exacerbations

- **Key Facts:** COPD is the third most common cause of death and chronic complications in the United States. Acute COPD exacerbations dramatically change the disease course and are associated with a rapid decline in lung function and worsening quality of life. Better treatments to prevent COPD exacerbations are needed. Azithromycin (Zithromax®, Pfizer, Inc., New York, NY), is a macrolide antibiotic with broad-spectrum activity that binds to the 50S ribosomal subunit of susceptible bacteria, interfering with microbial protein synthesis. Macrolide antibiotics are also purported to have anti-inflammatory properties, which could play a role in preventing COPD exacerbations. Azithromycin is being evaluated for off-label use to prevent COPD exacerbations and slow disease progression in patients who continue to have acute exacerbations despite receiving standard care. The drug is administered orally, at a dosage of 250 mg, once daily.

   In a randomized controlled trial, patients with COPD (n=1,577) who were at increased risk of exacerbations received azithromycin 250 mg daily or placebo for 1 year besides standard care to determine if daily azithromycin could reduce the frequency of COPD exacerbations. Patients treated with azithromycin were reported to have a longer median time to the first exacerbation and less-frequent exacerbations than patients treated with placebo. But hearing decrements were more common in the azithromycin group than in the placebo group.

   Adverse events associated with azithromycin that could dissuade a physician from prescribing it for prophylaxis in patients with COPD include hearing loss and cardiac arrhythmias. Additionally, investigators noted concern about antibiotic-resistant bacteria in patients treated with daily azithromycin.

   In May 2002, FDA granted marketing approval for azithromycin for treating acute bacterial COPD exacerbations due to *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae* infection. Azithromycin is currently not FDA approved for prophylaxis of COPD exacerbations in patients at elevated risk, but the drug could be used off label in this patient population. The wholesale cost of azithromycin (generic) can be as low as $1.20 per 250 mg dose. We were unable to identify any third-party payers that list formulary determinations concerning use of azithromycin for preventing COPD exacerbations.

- **Key Expert Comments:** Overall, experts commenting on this intervention stated that daily prophylactic azithromycin has the potential to reduce the rate of exacerbations in patients with COPD. Slowing disease progression could lead to improved quality of life in patients and reduced costs. However, a number of triggers for COPD exacerbations exist, and the patient subpopulations in which azithromycin could be most effective remain poorly understood. Azithromycin is not expected to replace treatment but to be additive to COPD treatment options. Experts thought it would minimally disrupt patient management while potentially reducing the incidence of serious complications.

- **Potential for High Impact:** Lower end of the high-impact-potential range
Pulmonary Disease, Including Asthma, Interventions
Ivacaftor (Kalydeco) for Treatment of Cystic Fibrosis in Patients with G551D-CFTR Mutation

Unmet need: Current therapies for cystic fibrosis (CF) have improved predicted median survival, but patients with CF still have a shorter-than-normal life expectancy and require extensive treatment over a lifetime to maintain good health as much as possible. Thus, an unmet need has existed for novel, effective medications to improve outcomes in this patient population.

Intervention: Ivacaftor (Kalydeco™) is a small-molecule, CF transmembrane conductance regulator (CFTR) modulator that improves the function of the CFTR gene by increasing CFTR activity in transporting negatively charged chloride ions across cell membranes to the cell surface, improving hydration and clearing mucus in patients with CF.\(^1\)\(^2\) Ivacaftor also promotes functional activity for two other CFTR mutations (i.e., F508del, R117H) and has some effect on the wild-type CFTR gene. Ivacaftor targets the defective protein that causes CF and is intended as a first-line treatment for the 4% of patients with CF who have the G551D mutation.\(^3\) Ivacaftor is administered 150 mg twice daily with fat-containing food in patients 6 years of age or older.\(^4\)

Clinical trials: Ivacaftor, already FDA approved, is under study in several phase III trials. In a randomized, double-blind, placebo-controlled, phase III trial, cosponsored by the Cystic Fibrosis Foundation, of Bethesda, MD, and the drug manufacturer, patients (n=161) with at least one copy of CF mutation G551D given ivacaftor had a predicted forced expiratory volume in 1 second measurement that was 10.6 percentage points higher than patients treated with placebo through week 24 (p<0.001).\(^5\) Effects on pulmonary function were observed as early as 2 weeks, and a significant treatment effect was maintained through week 48. Also through week 48, patients given ivacaftor were 55% less likely to have a pulmonary exacerbation than were patients given placebo (p<0.001). Patients treated with ivacaftor also demonstrated a significant improvement in quality of life (p<0.001). By 48 weeks, patients treated with ivacaftor had gained significantly more weight and secreted significantly less chloride in sweat samples, a key indicator for CFTR activity (p<0.001 for both measures). The incidence of adverse events was similar with ivacaftor and placebo, with a lower proportion of serious adverse events with ivacaftor than with placebo (24% vs. 42%).\(^5\)

Manufacturer and regulatory status: Vertex Pharmaceuticals, Inc., of Cambridge, MA, makes ivacaftor. In January 2012, FDA approved ivacaftor for treating patients aged 6 years or older who have a G551D mutation in the CFTR gene.\(^6\)

Diffusion: Ivacaftor in combination with another experimental CF drug, lumacaftor, has also been shown to improve lung function in patients with CF who have two copies of the CFTR-F508del mutation, according to recent, phase II trial results.\(^7\) The F508del mutation is the most common CF mutation; about 90% of patients with CF are heterozygous for F508del in North America, and about 50% of patients are homozygous.\(^7\)

Additionally, the manufacturer is sponsoring a study to evaluate the efficacy of ivacaftor in patients with CF caused by other known mutations including: R117H, G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, and G1349D.\(^8\)\(^9\) Thus, ivacaftor may gain a broader patient indication in the future.

Ivacaftor costs between about $329,145 and $350,473 annually according to a June 2013 query of online pharmacies.\(^10\) The manufacturer has implemented stratified pricing that is based on patient insurance status and income.\(^11\) Although ivacaftor’s price is high, pricing was purportedly derived on the basis of conversations with patients, physicians, and payers.\(^12\) Third-party payers (e.g., Aetna) are starting to cover the drug with precertification requirements and quantity limits.\(^13\) Copayments vary according to the terms of a patient’s benefits.
Clinical Pathway at Point of This Intervention

Routine use of inhaled medications, ventilators, chest physiotherapy singly or in combination helps release the CF-associated, thick mucus that damages lung tissue over time. 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. Lung transplantation can reduce the effects of CF for some individuals. As the disease progresses, some patients require mechanical breathing support, especially while sleeping. Ivacaftor is intended as a first-line treatment for patients with CF who have the G551D-CFTR mutation, and it can be used in conjunction with physiotherapy, mechanical devices, and antibiotics as needed.

Figure 1. Overall high-impact potential: ivacaftor (Kalydeco, VX-770) for treatment of cystic fibrosis in patients with G551D-CFTR mutation

Overall, experts commenting on this intervention expressed some confidence that this drug has potential to meet the need for a novel CF treatment that can improve health outcomes, although this view was tempered by the fact that CF is relatively rare and this drug is intended for only the 4% of patients with the specific mutation. Because the drug is intended to be delivered orally, it could reduce the need for visits to health care facilities for regular oxygen, chest, and intravenous therapies. However, because of the small patient population and the drug’s oral administration, ivacaftor is not expected to have a major impact on health care processes such as staffing or infrastructure requirements; thus, the experts expected it could be easily adopted. The high annual cost of ivacaftor therapy was identified as a potentially controversial issue. Forthcoming information regarding third-party payer coverage, patient copayments, real-world clinical efficacy, and offsets of other health care costs from improved outcomes from the drug will help elucidate and better define these issues. 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. We organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: The unmet need for novel treatments for CF is important, particularly if those treatments are disease-modifying instead of merely palliative, the experts generally agreed. However, they stated that the importance of this unmet need is tempered because CF is a rare condition and that within the small population affected by CF, 96% of patients would be ineligible for this treatment.

Ivacaftor appears to have a sound theory underlying its mechanism of action and potential to improve patient outcomes, the experts said, basing their opinions on positive trial results. However,
one health systems expert noted that additional clinical trials evaluating quality of life should be performed to better evaluate the drug’s impact.

The experts stated that the current price of the drug is quite high, but overall, the price may have limited impact because of the small number of patients eligible for this therapy. Additionally, the anticipated reductions in oxygen and chest therapy, hospitalizations, and other complications could significantly offset costs in the long term. However, one expert representing a health systems perspective estimated that treating all eligible patients with ivacaftor would cost the health care system about $400 million annually, which the reviewer regarded as an unsustainable trend for a disease that affects such a small population of patients.

**Acceptance and adoption:** Although one clinical expert stated some patients will always hesitate to accept any new drug, experts thought patient and clinical acceptance would be wide and rapid. Possible barriers to acceptance include issues that could arise from coverage and costs such as high patient copayments. Also, if physicians observe limited efficacy in clinical practice, they could be hesitant to prescribe such an expensive drug.

**Health care delivery infrastructure and patient management:** Because the drug is intended to be administered as an oral treatment and because of CF’s rarity, experts providing comments did not think it would have a major impact on health care operations such as staffing and infrastructure needs. However, some experts suggested that it might reduce frequency of outpatient visits and inpatient care for flares and complications for patients with the affected mutation, requiring significantly less treatment resources.

This drug could affect current care processes and patient management by offering patients a convenient oral therapy to directly treat CF’s cause, the experts thought. A drug that halts disease progression could reduce the need for ventilation therapy, chest physiotherapy, and intravenous fluids, experts noted. However, clinicians would need to spend some time initially to explain to patients the advantages and limitations of the new therapy and how it affects care.

**Health disparities:** The oral administration of ivacaftor could improve health disparities, one expert representing a clinical perspective stated, noting that rural patients and “working families” commonly have barriers to treatment when they must travel frequently to a care facility for intravenous therapy.
Off-Label Azithromycin for Prevention of Chronic Obstructive Pulmonary Disease Exacerbations

**Unmet need:** Chronic obstructive pulmonary disease (COPD) is the third most common cause of death and chronic complications in the United States. Acute exacerbations of COPD dramatically change the disease course and are associated with a rapid decline in lung function and worsening quality of life. Better treatments to prevent COPD exacerbations are needed.

**Intervention:** Azithromycin (Zithromax®) is a azalide, a subclass of macrolide antibiotics. Azithromycin is a broad-spectrum antibiotic that binds to the 50S ribosomal subunit of susceptible bacteria, interfering with microbial protein synthesis. Besides antimicrobial activity, macrolide antibiotics purportedly also have anti-inflammatory properties, which could play a role in preventing COPD exacerbations and position the drug as a useful adjunct to standard of care.

Macrolides are purported to decrease the production of inflammatory cytokines, chemokines, and other mediators, such as leukotriene B4 and matrix metalloproteases. Macrolide antibiotics are also purported to decrease the expression of adhesion molecules that promote neutrophil accumulation in the lungs—neutrophils are a principal mediator of inflammation and tissue destruction. Lastly, azithromycin is also purported to improve airway clearance of apoptotic cells and bacteria, reducing secondary necrosis due to the release of cellular toxins that could contribute to inflammation.

Azithromycin is being evaluated for off-label use to prevent COPD exacerbations and slow disease progression. The drug is given orally, 250 mg, once daily. According to one published report, prophylactic azithromycin would be used in patients who continue to have acute exacerbations despite receiving standard care. Other patient-selection criteria for the treatment include having had at least two acute exacerbations the previous year as a baseline to assess treatment response and to limit overuse of azithromycin.

**Clinical trial:** In a randomized controlled trial, patients with COPD who were at increased risk of exacerbations received azithromycin 250 mg daily (n=570) or placebo (n=572) for 1 year plus standard care to determine if daily azithromycin could reduce COPD exacerbations. The median time to first exacerbation was 266 days (95% confidence interval [CI], 227 to 313) among patients treated with azithromycin, compared with 174 days (95% CI, 143 to 215) among patients receiving placebo (p<0.001). The frequency of exacerbations was 1.48 exacerbations per patient-year in the azithromycin group, compared with 1.83 per patient-year in the placebo group (p=0.01). The hazard ratio for having an acute COPD exacerbation was 0.73 per patient-year (95% CI, 0.63 to 0.84) in the azithromycin group (p<0.001). Hearing decrements were more common in the azithromycin group than in the placebo group (25% vs. 20%, p=0.04).

Common adverse events associated with azithromycin use include angioedema and cholestatic jaundice, which are potentially serious but were reported rarely. In clinical trials, adverse events associated with patient treatment discontinuation most frequently occurred in the gastrointestinal tracts (e.g., nausea, vomiting, diarrhea, abdominal pain) of patients given azithromycin. Other adverse events associated with azithromycin that could dissuade a physician from prescribing it for prophylaxis in COPD patients include hearing loss and cardiac arrhythmias. Additionally, investigators note concerns about development of antibiotic-resistant bacteria in patients treated with daily azithromycin.

**Manufacturer and regulatory status:** Pfizer, Inc., of New York, NY, makes azithromycin. In May 2002, FDA granted, marketing approval for azithromycin for treating acute bacterial COPD exacerbations due to *Haemophilus influenzae, Moraxella catarrhalis, or Streptococcus pneumoniae*
infection. FDA has not approved azithromycin for prophylaxis of COPD exacerbations in patients at elevated risk, but the drug could potentially be used off label in this patient population.

**Diffusion:** According to GoodRx, an online aggregator of pharmacy prescription-drug prices, the wholesale cost of azithromycin (generic) can be as low as $1.20 per 250 mg dose. Our searches of representative, private, third-party payers that publish their coverage policies online found none that listed coverage determinations concerning azithromycin for preventing COPD exacerbations.

### Clinical Pathway at Point of This Intervention

COPD treatment focuses on managing stable disease and exacerbations. Treatment includes smoking-cessation counseling and nicotine-addiction treatment, medications to address breathing issues (i.e., long-acting bronchodilators, inhaled glucocorticosteroids), and antibiotics for lung infections. Clinicians also recommend that patients with COPD receive annual flu vaccinations and a pneumococcal polysaccharide vaccination. None of these approaches halt disease progression. In cases of advanced disease, supplemental oxygen or surgery (i.e., lung volume reduction, lung transplantation) may be recommended. Azithromycin has been proposed as prophylactic therapy to reduce the frequency of disease exacerbations, which may slow disease progression.

![Figure 2. Overall high-impact potential: off-label azithromycin for prevention of chronic obstructive pulmonary disease exacerbations](image)

Overall, experts commenting on this intervention stated that daily prophylactic azithromycin has potential to reduce the rate of exacerbations in patients with COPD. Slowed disease progression could lead to improved patient quality of life and reduced costs. However, a number of triggers for COPD exacerbations exist, and the patient subpopulations in which azithromycin will be most effective remains poorly understood. Azithromycin is expected to be additive to current COPD treatment options, making minimal disruption to daily patient management while potentially reducing the incidence of serious complications. Based on this input, our overall assessment is that this intervention is in the lower 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. We organized the following discussion of expert comments according to the parameters on which they commented.

**Unmet need and health outcomes:** No cure exists for COPD, the third leading cause of death and a significant source of health care costs, the experts stated. COPD exacerbations can lead to significant declines in lung function and progression towards respiratory failure. Daily prophylactic use of azithromycin seems to be a promising treatment to slow COPD progression, the experts stated. However, one expert cautioned that many COPD exacerbations have no identifiable cause
and many mild to moderate exacerbations may go unreported, complicating analysis of azithromycin’s impact.

**Acceptance and adoption:** Clinicians are expected to readily accept azithromycin as a simple, noninvasive, and affordable treatment to slow COPD progression, with some caveats. Some experts stated risk of hearing loss, cardiac arrhythmias, and antibiotic resistance are factors that would make some physicians reluctant to prescribe the antibiotic. The experts also stated patients would be generally accepting of a simple treatment regimen that could prevent their quality of life from declining.

**Health care delivery infrastructure and patient management:** If azithromycin is effective in preventing COPD exacerbations, reductions in pulmonary, acute, long-term, and intensive care units could be realized, the experts theorized. Although the cost of azithromycin therapy would be additive to current treatment costs, its low cost and its potential to offset costs of complications were seen by some experts as having a neutral or perhaps even cost-saving impact.
References


