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

Priority Area 09: Infectious Disease Including HIV/AIDS

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U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
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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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.

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

Yen-pin Chiang, Ph.D.
Acting 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

Contents

Figures

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 eight 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 May 15, 2014, in this priority area; and (3) we received five to eight sets of comments from experts between July 1, 2013, and May 23, 2014. (Forty-two topics in this priority area were being tracked in the system as of May 15, 2014.) All eligible topics were deemed through expert comment processes to have potential for high impact; seven of these topics were in the December 2013 report; 3D oral regimen for treating hepatitis C is a new topic added to this report. One topic in the December 2013 Potential High Impact Interventions report is not included in this report because it has been archived from the system after being tracked through development to U.S. Food and Drug Administration (FDA) approval, and followed post-approval: "Emtricitabine/tenofovir (Truvada) for prevention of HIV infection." This drug has not diffused widely, having received third-party coverage for the prevention indication from only a few payers and intended for use in a relatively small population. For this report, we aggregated related topics for summary and discussion (i.e., individual drugs into a class). We present seven summaries of eight topics (indicated below with an asterisk) that emerged as having higher impact potential on the basis of experts' comments and their assessment of potential impact. The material on interventions in this Executive Summary and report is organized alphabetically by disease state and then by intervention. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary.

Priority Area 09: Infectious Disease Including HIV/AIDS

Topic	High-Impact Potential
1. * 3D oral regimen (ABT-450/r, dasabuvir, ombitasvir) for treatment of chronic hepatitis C virus infection	High
2. * Antimicrobial copper surfaces in the intensive care unit for prevention of hospital-acquired infections	High
3. * Fecal microbiota transplantation for treatment of recurrent *Clostridium difficile* infection	High
4. * OraQuick in-home rapid test for detection of HIV infection	Moderately high
5. * Retrofitted private intensive care rooms to reduce hospital-acquired infections	High

Topic	High-Impact Potential
6. * RTS,S/AS01 (Mosquirix) for prevention of malaria caused by *Plasmodium falciparum*	Lower end of the high-impact-potential range
7. * Sofosbuvir (Sovaldi) for treatment of chronic hepatitis C infection	High
8. * Xpert MTB/RIF Test for simultaneous detection and drug-sensitivity testing of *Mycobacterium tuberculosis*	Moderately high

Discussion

Health Care–Acquired and Bacterial Infections

Experts identified four interventions involving health care-acquired and bacterial infections as having potential for high impact: antimicrobial copper surfaces in hospitals, especially intensive care units (ICU), to reduce hospital-acquired infections; renovation of multi-patient ICUs to single-patient units to prevent health care–acquired infections; a treatment for recurrent *Clostridium difficile* infection (CDI); and a rapid test to determine whether a patient has a drug-resistant form of tuberculosis (TB).

About 2 million health care–acquired infections (HAIs) are documented in the United States annually and result in 100,000 deaths. The U.S. Centers for Disease Control and Prevention (CDC) has estimated that HAIs burden the U.S. health care system with additional costs of $28 billion to $45 billion annually. On average, HAIs add an estimated 19.2 hospital days per patient contracting an HAI, at a per-patient cost of $43,000. Patients contracting an HAI have a 1-in-20 chance of dying in the hospital and a 1-in-4 chance of dying if the infection was contracted in the ICU.

Antimicrobial Copper Surfaces in the Intensive Care Unit for Prevention of Hospital-Acquired Infections

- **Key Facts:** About 20% to 40% of HAIs of exogenous origin are attributed to cross infection from the hands of health care personnel, and despite common infection-control practices (hand-washing and frequent surface disinfection) the number of HAIs each year continues to rise. Surfaces in patient rooms, including the ICU, typically consist of stainless steel and plastics that possess no antibacterial properties and serve as fomites for disease transmission between disinfection procedures.

  The intrinsic antimicrobial properties of copper and copper alloys (brasses and bronzes) for touch surfaces on hospital hardware and equipment might add another safeguard against disease transmission between cleanings. Antimicrobial Copper (CuVerro®, Global Brass and Copper Holdings, Inc., Schaumburg, IL) touch surfaces can be incorporated into a wide variety of components, including bedrails, handrails, door handles, grab bars, intravenous (IV) poles, food trays and carts, sinks, faucets, shower and lavatory components, work surfaces, computer keyboards, equipment adjustment knobs, and face plates. Copper's antimicrobial properties purportedly remain effective for the product's lifetime. These surfaces purportedly continuously reduce bacterial contamination and achieve a 99.9% reduction of gram-negative and gram-positive bacteria within 2 hours of exposure. As many as 479 alloys, such as brass and bronze, have been registered to be antimicrobial, providing options to fit various clinical and aesthetic demands. Copper surfaces purportedly exert their antibacterial activity in two sequential steps: (1) by disrupting the integrity of bacterial cell membranes through oxidation and disrupting physiologic functions such as electrostatic potential and (2) by interacting with numerous enzymes crucial for normal metabolic activity as antimicrobial copper ions penetrate compromised cells to alter cell metabolism.

Copper surfaces are intended to be used in combination with standard infection-control procedures. Published studies have shown that antimicrobial copper surfaces have reduced the microbial burden found on surfaces in the ICU and may lead to lower infection rates in patients staying in copper-fitted rooms. In one RCT (n=650), Salgado et al. (2013) reported that patients presenting for admission to three ICUs in the United States were randomly assigned to placement in rooms fitted with six copper alloy surfaces or standard surfaces. Patients admitted to copper-fitted rooms had a significant reduction in HAI or colonization with methicillin-resistant *Staphylococcus aureus* (MRSA) or vancomycin-resistant enterococci infections compared with such infection rates in patients placed in standard rooms.

The Copper Development Association purports that the cost to convert primary touch points to copper surfaces on room components—bed rails, cabinet hardware, chairs, countertops, door levers, grab bars, hand rails, IV poles, keyboards, light switches, linen hampers, computer mouse devices and other data-input devices, tables, sinks, and faucets—is about $7,700 to $15,000 per room. According to the association, making these conversions could reduce total infection rates by 20% and the reduction in HAIs could make the renovations cost-effective within 1 year, although independent cost-effectiveness studies have not been published yet. An important research question, however, centers on the optimal number and placement of copper surfaces required to achieve the desired benefits.

In July 2012, the Agency for Healthcare Research and Quality awarded a $2.5 million interdisciplinary research collaboration grant to the University of California, Los Angeles, to conduct a 4-year RCT to determine whether reducing surface bacteria through use of copper surfaces decreases HAI rates, improves treatment outcomes, and reduces costs. The study is evaluating copper, plastic, or sham stainless steel surfaces to better understand their role as fomites.

- **Key Expert Comments:** Overall, experts commenting on this intervention stated that antimicrobial copper touch surfaces could significantly reduce HAIs and associated morbidity, mortality, and costs. Although a significant capital investment may be required to retrofit frequently touched surfaces in ICUs, the intervention is expected to quickly accrue savings. Except for a one-time disruption in patient management, antimicrobial copper is not expected to alter hospital operations. Although antimicrobial copper surfaces may reduce surface pathogens, experts warn that infection rates may not decline as much as expected because HAIs can be contracted from bacteria already colonizing the patient's body and that copper surfaces would not protect against the direct contact of health care workers practicing poor hand hygiene. Finally, because it is not possible to run truly blinded studies in rooms fitted with copper surfaces, experts suggested that more and larger unblinded RCTs should be performed before initiating large-scale retrofitting projects.
- **Potential for High Impact:** High

Fecal Microbiota Transplantation for Treatment of Recurrent *Clostridium Difficile* Infection

- **Key Facts:** In 2010 in the United States, an estimated 500,000 individuals experienced CDIs at an estimated cost of at least $1 billion. Recurrent CDI is increasingly common and challenging to treat effectively. About 15% to 30% of patients have a recurrence after treatment with metronidazole (Flagyl®) or vancomycin (Vancocin®). Vancomycin is commonly used after a second CDI recurrence, but when vancomycin therapy is stopped, up to 65% of patients develop recurrence. A relatively new antibiotic, fidaxomicin (Dificid®), is

a third-line antibiotic therapy, but other therapeutic options are needed that do not involve antibiotic therapy.

Fecal microbiota transplantation (FMT) is a nonantibiotic option. Fecal microbiota from a healthy donor is intended to recolonize a patient's intestinal flora with beneficial bacteria that will "crowd out" or otherwise make the environment in the bowel unfavorable for *C. difficile* colonization. Shortly before the procedure, which can be delivered by any of several methods (e.g., capsules, colonoscopy, nasogastric tube, enema), healthy donors who have completed screening for other diseases (e.g., syphilis, HIV, hepatitis A, B, and C) submit fresh stool, which is mixed with saline into a solution and administered to the patient. Typically, this procedure is required only once in most patients to achieve a persistent resolution, although data have shown that a second administration for patients in whom CDI recurred after an initial FMT results in resolution in most of those patients. In the only RCT comparing FMT to a standard treatment of patients with recurrent CDI (n=43), Van Nood et al. (2013) reported that 81% of patients treated with oral vancomycin followed by FMT administered through a nasoduodenal tube resolved *C. difficile*–associated diarrhea compared with 31% of patients treated with oral vancomycin alone and 23% of patients treated with vancomycin and bowel lavage ($p<0.001$ for both comparisons with the infusion group). Results were so compelling that the trial's Data and Safety Monitoring Board halted the trial early after an interim analysis. In a case series (before-and-after study), Agrawal and colleagues (2014) analyzed data on more than 146 patients with recurrent CDI who received FMT at nine U.S. treatment centers. They reported that after one treatment, CDI was cured in 86% of patients and improved in 14%. Other, smaller trials have reported similar success rates, some as high as a 100% cure rate.

The U.S. Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER) sponsored a public workshop in May 2013 on FMT and standards for the procedure. FDA announced that FMT falls within the agency's definition of a biological product and drug. Because CBER has not approved FMT for any therapeutic purpose, the agency has stated that it would require an investigational new drug (IND) application from any center intending to treat a patient with FMT for any condition. Several weeks later, FDA reconsidered this policy as a result of "subsequent communications, [in which] physicians and scientists have expressed concern to FDA that FMT is not appropriate for study under FDA's investigational new drug application (IND) regulations (21 CFR Part 312). Some health care providers have stated that applying IND requirements will make FMT unavailable…." FDA indicated that it "intends to exercise enforcement discretion regarding the IND requirements for the use of FMT to treat *C. difficile* infection not responding to standard therapies provided the treating physician obtains adequate informed consent from the patient or his or her legally authorized representative for the use of FMT products."

Shortly thereafter, in June 2013, FDA granted Rebiotix, Inc., of Roseville, MN, fast-track designation for its proprietary off-the-shelf microbiota suspension (RBX2660) for treating recurrent CDI.

In March 2014, FDA modified its draft guidance adding that the agency plans to continue exercising enforcement discretion as long as (1) the stool donor is known to either the health care provider or the patient and (2) the physician performing the FMT procedure directs the donor and stool screening and testing. OpenBiome (Medford, MA), a nonprofit, public stool bank operated by the Microbiome Health Research Institute, proposed to FDA that institutions providing FMT procedures exceeding a set number of FMT procedures annually be required to participate in a trial under an IND. OpenBiome asserts such a policy would balance the need for collecting meaningful data on FMT with the need to treat

patients in a timely manner. OpenBiome also intends to sponsor an IND that would allow physicians to continue using universal donor stool if the guidance is enforced as currently proposed.

About 540 cases of FMT treatment have been reported in the clinical literature, and more than 75 clinicians now perform the procedure in the United States. Additionally, some researchers are investigating the feasibility of patients banking their own fecal material upon admission to eliminate the need for donor feces. Reported costs associated with screening donor blood and stool for contagious agents, preparing the donor fecal sample, and placing a retention enema tube are estimated to be $1,500. According to Smith et al. (2014), the cost of testing donors can be reduced to $250 per treatment by using a centralized stool bank with multiple collections from universal donors. If the procedure is done by colonoscopy, the average cost of colonoscopy could add about $3,710 to the total cost of the procedure ($1,060 for patients with Medicare). However, costs of multiple regimens of antibiotic therapy for recurrent CDI, physician office visits, and hospitalizations from complications of recurrent CDI easily exceed the reported costs of one FMT. Third-party payers (e.g., Aetna, Humana, HealthPartners) have started to cover the procedure for patients with recurrent CDI who do not respond to a specified number of antibiotic courses.

- **Key Expert Comments:** Overall, experts concluded that results from the small number of FMT studies completed thus far are compelling, although most studies are case series. Experts are eager to see larger, controlled comparative studies (comparing to antibiotic therapies) to better determine the appropriate role of FMT in clinical practice and the best processes and standards to ensure safety in screening and processing donor material. Experts noted several potential societal barriers to acceptance of the procedure and a lack of standardized protocols; however, they also noted that the severity of recurrent CDI and its adverse impact on patient quality of life is prompting patients to seek out the procedure.
- **Potential for High Impact:** High

Retrofitted Private Intensive Care Rooms to Reduce Hospital-Acquired Infections

- **Key Facts:** Despite infection-control efforts, about one-third of patients admitted to an ICU contract an infection, which may increase length of stay, cost of care, and morbidity. HAIs can be transmitted between ICU patients by direct contact (principally via caregivers' hands), respiratory droplets, and via fomites (medical/computer equipment, sink faucets, beds, and chairs). Although many facilities building new ICUs are building single-patient ICU rooms, most existing ICUs have multiple patient beds in one room. Renovating traditional multiple-patient ICU settings to create single-patient room designs may help to prevent and contain infections, thereby improving patient outcomes. Several design elements in private ICU rooms (e.g., increased patient area and an increased sink-per-patient ratio) can purportedly reduce HAI transmission. Additionally, single-room ICU design purportedly improves hand hygiene among health care workers. Private rooms also can help to improve patient comfort and satisfaction on HCAHPS (the Hospital Consumer Assessment of Healthcare Providers and Systems). Higher satisfaction scores could help hospitals obtain higher reimbursement and remain competitive with other hospitals. Retrofitting ICUs to a single-patient room design represents a significant investment in infrastructure and equipment, which theoretically can provide long-term cost savings. However, investigating the effects of ICU design on HAI rates for research purposes has been cost prohibitive. Thus, available evidence typically consists of before-and-after studies

or has been gathered during outbreaks of resistant organisms during which multiple infection-control measures are used, complicating interpretation of the results.

In a prospective, parallel-assignment trial, patients treated in a unit renovated with private ICU rooms in Jerusalem, Israel, acquired fewer antibiotic-resistant infections and had more antibiotic-free days compared with patients treated in the ICU before the renovation to private rooms and patients treated in an ICU with room dividers. Proper hand hygiene was observed more frequently for patents in private rooms than for patients treated in a unit with room dividers.

In a comparative study at a teaching hospital in Montreal, Quebec, Canada, Teltsch et al. (2011) reported that ICU rooms renovated to a single-patient design reduced the acquisition of *C. difficile* by 43%, MRSA by 47%, and yeast by 51%. Patients (n=5,468) in renovated, private ICU rooms had a 10% reduction in the adjusted length of stay compared with patients (n=2,732) treated in rooms before the renovation.

In a retrospective study, Bonizzoli et al. (2011) reported that patients (n=818) admitted to an ICU in Florence, Italy, had fewer pathogenic microbiologic cultures from both bronchial aspirate and blood culture after rooms were renovated from a bay-room design to a single-patient room design. A significant decrease in antibiotic use was also observed after the renovation.

The American Institute of Architects recommended in 2006 that private rooms become the standard for new hospitals. The recommendations were developed by a panel of hospital administrators, doctors, architects, engineers, and infection-control experts. Private ICU rooms are being implemented in hospitals across the United States, particularly in newly constructed units. Building single-patient ICU rooms can cost millions of dollars; however, according to one benefit-cost analysis, the estimated net social-benefit cost of a bed in a private room is about $70,000 more than a bed in a semiprivate room. Third-party payers are not expected to provide additional reimbursement for private rooms. Instead, additional costs for private rooms are expected to be absorbed by the facility and could potentially lead to additional out-of-pocket expense for patients.

- **Key Expert Comments:** Overall, experts concluded that results from the available studies of retrofitting ICUs with private rooms are promising. They thought that the intervention has significant potential to address the unmet need of reducing HAIs when combined with other best practices for infection control. Significant capital investment would be required for infrastructure and equipment for private rooms, the experts agreed; however they concluded that reductions in HAIs and associated liability would eventually be cost-saving. Patients and clinicians would appreciate the improved privacy and communication provided by single-patient room designs, the experts thought.
- **Potential for High Impact:** High

Xpert MTB/RIF Test for Simultaneous Detection and Drug-Sensitivity Testing of *Mycobacterium Tuberculosis*

- **Key Facts:** According to the World Health Organization, *Mycobacterium tuberculosis* infection is highly underdiagnosed because current TB testing methods require weeks to deliver a definitive result. During that time, infected patients go untreated or may be placed on ineffective therapies, thereby continuing to spread TB and creating a significant public health hazard. Thus, the need for effective, rapid diagnostics and new treatments to address resistant strains that are emergent globally is significant. The Xpert MTB/RIF (*M. tuberculosis*/rifampicin) test (Cepheid, Sunnyvale, CA) is a nucleic acid–based test that is

run on Cepheid's GeneXpert® real-time polymerase chain reaction (PCR) system. The test is intended to simultaneously detect *M. tuberculosis* complex species and determine whether the identified bacterium is susceptible to rifampicin, a first-line therapy for TB. The assay is intended to yield results in about 2 hours, which would enable relatively rapid initiation of treatment. In July 2013, FDA granted Cepheid marketing clearance for the Xpert MTB/RIF test through the 510(k) de novo clearance process, a regulatory pathway for medical devices considered to be of low-to-moderate risk but which have no comparable predicate device already cleared for marketing. Xpert MTB/RIF is indicated for the rapid molecular detection of *M. tuberculosis*-complex DNA, as well as the detection of rifampin resistance associated with mutations of the *rpoB* gene in specimens positive for *M. tuberculosis*. The GeneXpert GX4-4 system costs about $78,200 and an Xpert MTB/RIF test cartridge costs about $72. Standard basic testing for TB costs about $20–$40, and testing for rifampicin resistance can add another $20–$30. An analysis by Choi et al. (2013) of the impact of incorporating Xpert MTB/RIF into a TB diagnostic algorithm found that TB testing without molecular testing was most costly ($2,728 per patient) compared with intensive and selective Xpert MTB/RIF testing algorithms ($2,673 and $2,482, respectively), when all health system costs were considered. Additionally, intensive Xpert MTB/RIF testing was expected to improve health outcomes and be highly cost-effective compared with other molecular testing methods. In August 2013, FDA categorized the Xpert MTB/RIF test as "moderate complexity" under the Clinical Laboratory Improvement Amendments (CLIA), which could facilitate diffusion.

- **Key Expert Comments:** Overall, experts thought that this test has potential as a rapid, sensitive, and specific diagnostic test to address the unmet need for more rapid diagnosis and better initial management of suspected TB. This, in turn, could improve patient health outcomes and reduce disease spread, thought experts. By knowing a patient's TB status before the patient leaves the physician's office, appropriate treatment could be given sooner and proper infection control measures could begin to be implemented, the experts noted. The Xpert MTB/RIF test detects resistance only to rifampin, which is a common first-line antibacterial agent. Susceptibility to other agents would still need to be guided by traditional testing methods. Nevertheless, the Xpert MTB/RIF test could replace other PCR methods of detection and provide an improved approach to diagnosis and treatment. This could improve outcomes for patients, especially those with limited access to care.
- **Potential for High Impact:** Moderately high

Hepatitis C Virus Infection

Hepatitis C virus (HCV) is the primary cause of death from liver disease and the leading cause for liver transplantation in the United States. According to a CDC report (August 2012), "Recommendations for the Identification of Chronic Hepatitis C Virus Infection Among Persons Born During 1945–1965," an estimated 3.2 million Americans have chronic HCV infection and 75% of those infected are in this age range. From 50% to 80% of infected people are unaware they are infected. Additionally, HCV is seen in patients with HIV. Of the 1 million people with chronic HIV infection in the United States, about 50,000 also have chronic HCV infection. Some calculations suggest that HCV-related mortality will continue to increase over the next two decades without effective new treatment. Also, total U.S. annual medical costs for HCV-infected people are expected to almost triple, from $30 billion in 2009 to about $85 billion by 2029. Chronic HCV infection is considered clinically "curable"—that is, the virus can be suppressed to undetectable levels with antiviral therapy. Intensive ongoing research has led to many drugs in development in new drug classes. The relatively recent explosion in HCV drug development has come about

because of effective and efficient in vitro methods that enable developers to quickly screen and evaluate potential candidates. The HCV community is particularly interested in simple, all-oral, interferon alfa (IFN)-free regimens that can be completed within 8–12 weeks—a shorter time frame than previous treatments. Two new, oral anti-HCV drugs, simeprevir (Olysio™; Janssen Research & Development, LLC, a unit of Johnson & Johnson, New Brunswick, NJ) and sofosbuvir (Sovaldi™; Gilead Sciences, Inc., Foster City, CA), were approved by FDA on November 22, 2013, and December 6, 2013, respectively, for treating chronic HCV genotype 1 in combination with IFN and ribavirin (RBV). Sofosbuvir was also approved for treating patients infected with HCV genotype 4 in combination with IFN/RBV, and even more importantly, as the first IFN-free treatment option with RBV in patients infected with HCV genotypes 2 or 3. Sofosbuvir was also the first direct-acting antiviral agent approved for treating patients co-infected with HIV or awaiting liver transplantation. Physician surveys have reported that many hepatologists have been "warehousing" their patients, waiting for effective, better tolerated, all-oral therapies to be available before prescribing treatment. Some clinicians are treating patients off-label using only the two antivirals sofosbuvir and simeprevir taken together, basing their decision on results from a phase II trial demonstrating high sustained virologic response at 12 weeks (SVR12) and following guidance from the American Association for the Study of Liver Diseases and the Infectious Disease Society of America. A number of other manufacturers also have all-oral HCV regimens in phase II or phase III development. Manufacturers with the most advanced candidates include AbbVie, Bristol-Myers Squibb, and Merck & Co., Inc. Regimens b**y** Bristol-Myers and Merck were too early in development to obtain expert opinion. However, two topics for which data were available and for which we sought expert comment emerged as having potential for high impact: sofosbuvir (Sovaldi) for treating chronic HCV infection and the 3D regimen (ABT-450/ritonavir, ombitasvir, and dasabuvir) for treating chronic HCV genotype 1 infection.

Interferon-free Treatment of Chronic Hepatitis C Infection

- **Key Facts:** The landscape of HCV treatment changed in May 2011 when the first NS3/4a protease inhibitors boceprevir and telaprevir were FDA approved for use in combination with IFN and RBV for treating chronic HCV genotype 1 infection. Protease inhibitors were shown to improve cure rates for HCV, genotype 1, compared with IFN and RBV alone, but up to half of patients are unable to tolerate any IFN-containing treatment regimen, so developing an IFN-free regimen—and one that can treat other genotypes— has continued to be paramount to improving treatment options. Also, protease inhibitors have been associated with significant side effects, including anemia and severe rash.

  We present two novel IFN-free options: Sofosbuvir (Sovaldi) for treating chronic HCV genotype 1, 2, and 3, and the 3D regimen (ABT-450/ritonavir, ombitasvir, and dasabuvir) for treating chronic HCV genotype 1 infection. Sofosbuvir is a uridine nucleotide analog HCV NS5B polymerase inhibitor purported to target the active site of the HCV RNA polymerase to inhibit elongation of the growing HCV RNA genomic transcript. It purportedly has broad efficacy against multiple HCV genotypes and is being evaluated as part of multiple therapeutic regimens. In phase III clinical trials, sofosbuvir has been administered orally, once daily for 12 or 24 weeks in combination with RBV for patients infected with HCV genotype 2 or 3, and with RBV and IFN for treatment-naive patients infected with genotypes 1, 4, 5, or 6. Sofosbuvir is also being investigated in combination with other direct-acting antiviral agents, including a once-daily, fixed-dose combination with the NS5A inhibitor ledipasvir and a once-daily regimen with the protease inhibitor simeprevir. The intention is to create a convenient, all-oral treatment that would eliminate

the need for IFN and/or RBV in patients with chronic HCV genotype 1 infection. In phase III trials, sofosbuvir and RBV in combination were reported to be noninferior to IFN/RBV treatment in patients with chronic HCV genotype 2 or 3 infection who had no prior treatment. Treatment-naïve patients with chronic HCV genotype 1 infection achieved high (>90%) SVR12 rates with fixed-dose sofosbuvir/ledipasvir with or without RBV. Eight weeks of sofosbuvir/ledipasvir therapy was noninferior to 12 weeks of sofosbuvir/ledipasvir therapy. Furthermore patients with chronic HCV genotype 1 infection who were previously treated with IFN-based therapy achieved higher than 90% SVR12 rates after receiving sofosbuvir/ledipasvir with or without RBV for 12 or 24 weeks. Combination sofosbuvir/RBV also achieved high SVR12 rates in patients co-infected with HIV and HCV genotype 1 after 24 weeks of therapy and genotype 2 or 3 after 12 weeks of therapy. Preliminary data also suggest sofosbuvir could be effective in preventing HCV reinfection in liver transplant patients. The most common side effects reported in patients given sofosbuvir and RBV or sofosbuvir/ledipasvir, include dizziness, fatigue, headache, insomnia, and nausea.

In December 2013, FDA approved sofosbuvir in combination with RBV for treating chronic HCV genotype 2 or 3 infection as well as sofosbuvir in combination with IFN/RBV for treating patients infected with chronic HCV genotype 1 or 4. Sofosbuvir was also approved for treating patients with HIV co-infection or hepatocellular carcinoma who are awaiting a liver transplant.

FDA granted breakthrough therapy designation to the once-daily fixed-dose combination of sofosbuvir and ledipasvir in July 2013. In February 2014, Gilead filed a new drug application with FDA for sofosbuvir/ledipasvir, for treating adults with chronic HCV genotype 1 infection. In May 2014, Janssen Research & Development submitted a supplemental new drug application to FDA for sofosbuvir in combination with its NS3/4A protease inhibitor simeprevir (Olysio™) for treating chronic HCV genotype 1 infection in adults naïve to treatment with advanced fibrosis and null responders with all stages of liver fibrosis.

According to a U.S.-based, online aggregator of prescription-drug prices, the retail cost of sofosbuvir ranges from about $84,000 to $92,000 for a 12-week treatment course, depending on the pharmacy and geographic location. If approved for marketing, the cost of 12 weeks of the fixed-dose combination sofosbuvir/ledipasvir could approach $100,000 by some estimates. The cost of a 4-week supply of generic RBV (1,000 mg) is about $300. The cost of a 4-week supply of IFN is about $3,300.

Our searches of 11 representative, private, third-party payers that publish their coverage policies online found 6 payers that have specific policies providing coverage of sofosbuvir, typically as a specialty tier drug requiring prior authorization and quantity limits. If the combination sofosbuvir/ledipasvir is approved for marketing, many market analysts think that third-party payers will cover the combination as an IFN-free option for treating HCV genotype 1. However, third-party payers have started to demonstrate resistance against potentially unsustainable pricing for HCV treatment.

First-quarter sales of sofosbuvir (2014) grossed $2.27 billion, far surpassing the launch of telaprevir (Incivek), which grossed $1.56 billion in the first year. In April 2014, UnitedHealth Group, Inc., announced the company paid more than $100 million for sofosbuvir during the drug's first quarter of availability, far exceeding what the payer expected to spend on the drug. In June 2014, Oregon Health Plan announced plans to exercise a special waver limiting member access to sofosbuvir and simeprevir based an analysis of cost and efficacy.

The 3D oral regimen (AbbVie, North Chicago, IL, and Enanta Pharmaceuticals, Inc., Watertown, MA) consists of boosted protease inhibitor ABT-450/ritonavir, NS5A inhibitor ombitasvir (ABT-267), and non-nucleoside polymerase inhibitor dasabuvir (ABT-333). The 3D regimen was designed to induce high SVR12 rates in patients with chronic HCV genotype 1 infection by targeting three distinct processes that are essential for HCV replication. In clinical trials, dasabuvir (250 mg) and RBV (weight-based) were both dosed twice daily, and a fixed dose combination of ABT-450/ritonavir (150 mg/100 mg) co-formulated with ombitasvir (25 mg) was dosed once daily. The 3D regimen, with or without RBV, has also been studied in a number of clinical trials evaluating treatment of HCV genotype 1 infection. In the PEARL-III and PEARL-IV randomized trials, treatment-naïve patients with HCV genotype 1a and 1b infections with no evidence of cirrhosis achieved SVR12 rates of more than 90% when given the 3D regimen in combination with RBV or the 3D regimen with placebo. Patients with HCV genotype 1 infection and Child-Pugh class A cirrhosis achieved 90% SVR rates of more than 90% whether given 12 or 24 weeks of the 3D regimen and RBV. These rates were superior to an estimated historical control rate achieved with a telaprevir-based regimen. The 3D regimen also resulted in high SVR12 rates that were noninferior and superior to a historical control rate assumed with telaprevir in patients with chronic HCV genotype 1 infection who were previously treated with IFN/RBV and had a relapse, a partial response, or a null response, but no cirrhosis. The most common adverse events reported with the 3D regimen were fatigue, headache, and nausea.

In May 2013, FDA granted the 3D regimen with or without RBV breakthrough therapy status for treating chronic HCV genotype 1 infection and in April 2014, AbbVie filed a new drug application. If approved, the regimen is estimated to cost about $60,000 for 12 weeks of treatment, including rebates and discounts, according to one financial analyst. If outcomes are satisfactory and the cost is lower than that of other regimens, this 3D regimen is expected to be covered by third-party payers and also may force manufacturers of other regimens to lower the cost.

- **Key Expert Comments:** Overall, experts commenting on sofosbuvir and the 3D regimen considered these interventions as having very high potential to address significant unmet needs for HCV treatment. Both interventions used for all-oral HCV treatment have been reported in trials to show high efficacy and be well tolerated by patients who cannot tolerate IFN or do not want to use it. Both interventions also provide a shorter and simpler dosing regimen than dosing for current treatment options, which is expected to improve patient adherence to treatment and outcomes. The high efficacy of sofosbuvir observed thus far in HCV genotypes other than genotype 1 is also perceived to be a significant advantage that will increase the drug's potential impact. Additional research comparing emerging IFN-free treatment options would be particularly useful to prescribing physicians and patients, the experts noted. The high cost of sofosbuvir, the 3D regimen, and other emerging HCV therapies combined with the large population of patients requiring treatment could be unsustainable to the health care system, thought several experts. The financial strain on the system could require payers to implement controversial coverage policies, such as treating only patients who have established liver disease.
- **Potential for High Impact:** High

HIV/AIDS

HIV infection continues to be a major public health concern, continuously challenging physicians, researchers, and public health officials to find the best practices to contain the epidemic.

HIV prevention measures remain crucial in controlling the disease. CDC estimates that as many as 50,000 people are newly infected with HIV in the United States annually; 78% of new infections occur in men who have sex with men (MSM) and 20% of new infections arise in women. Women are twice as likely to be infected with HIV through heterosexual contact. According to a CDC study, about half of all new HIV infections occur from the approximate 16% of people living with HIV who are unaware of their infection. Experts identified one intervention as having potential high impact: OraQuick In-Home Rapid Test for detection of HIV infection.

OraQuick In-Home Rapid Test for Detection of HIV Infection

- **Key Facts:** Although an over-the-counter HIV test has been available since 1996, it requires that a blood sample be mailed to a laboratory for analysis; results are available the next business day at the earliest. A simple, rapid in-home test that patients can interpret might improve HIV screening rates by increasing the privacy and confidentiality of testing. It might also empower individuals about their health decisions and provide a more rapid assessment of HIV status without the need for followup testing to confirm negative results. Increased screening could reduce HIV transmission rates and improve disease management through earlier treatment.

  The OraQuick In-Home HIV Test (OraSure Technologies, Inc., Bethlehem, PA) is a rapid, home-based HIV test that became available over the counter in October 2012. OraQuick is designed to detect HIV-specific antibodies found in a patient's saliva. The test provides easy access to first-line testing that is affordable, safe, simple, rapid, painless, and anonymous. The test kit includes a single-use testing device and a test tube containing testing reagent. The testing device is a lateral flow immunoassay with an integrated oral swab. The test is predicated on an oral swab–based test that has been available to health care professionals since 2004. Changes were made only to the packaging and instructions to create the home version of the test. To conduct the test, an individual collects his or her saliva sample from along the gum line using the oral swab, then places the swab end of the testing device in the test tube with reagent for 20 minutes. The testing device contains colloidal gold particles bound to protein A, which will bind antibodies from the saliva sample in solution and migrate along the device. The tube has two indicator lines toward the distal end that are viewed by the user to determine the result—one line indicates the test result and the other that the test was valid. The kit includes resources on HIV and HIV testing, including a hotline with 24-hour customer support to answer questions regarding testing and interpretation as well as referral to care if needed. A negative test result 3 months after the last risk event is likely to be a HIV-negative result. An HIV-positive test result requires followup testing by Western blot analysis to confirm infection. In a large clinical trial (n=5,662) used to support regulatory filing, the sensitivity of this in-home HIV test was 91.67% and specificity was 99.98%.

  A behavioral study was conducted of a cohort of ethnically diverse MSM (n=27) who engaged in risky behaviors for contracting HIV (i.e., never or rarely used condoms, multiple partners) to determine whether they would use the test to screen potential sexual partners. The authors reported 10 of 100 screened individuals received a positive test result. Six of the 10 who screened positive were unaware of their HIV status. No sexual intercourse occurred after positive tests results were received. Most study participants purportedly expressed a strong desire to continue using the home test and would buy it. The manufacturer warns that the test should not be used to make decisions on behavior that may put one at increased risk of contracting HIV.

FDA approved the test in July 2012 for sale directly to consumers. The test can detect antibodies to both HIV-1 and HIV-2 and is the first, and so far the only, rapid over-the-counter test approved for detecting any infectious disease.

The test costs about $40 when purchased directly from the manufacturer. Our searches of 11 representative, private, third-party payers that publish their coverage policies online found that only Aetna lists a coverage policy about the HIV home test kit stating that it does not cover home HIV test kits that can be obtained without a physician's prescription.

- **Key Expert Comments:** Overall, experts commenting on this intervention thought that the OraQuick rapid in-home HIV test has potential to meet a significant unmet need by increasing HIV screening rates in people who engage in high-risk behaviors but are reluctant to undergo HIV screening in clinics. In-home testing was thought to have potential to improve screening rates because of its relatively modest $40 cost to purchase and perform testing. Experts commented that patients who know their HIV status are more likely to seek treatment and avoid high-risk behaviors, which could positively affect public health outcomes and reduce costs to the system. However, for individuals with positive results, more would likely seek treatment, thereby increasing demands on the health system. Experts theorized OraQuick's use could also affect patient management when patients with a positive home test present at health clinics for additional testing and counseling.
- **Potential for High Impact:** Moderately high

Malaria

Globally in 2010, an estimated 219 million people were infected with malaria and 660,000 people died from the disease, despite disseminated use of vector control with insecticide-treated bed nets and indoor residual spraying combined with intermittent prophylactic pharmacotherapy. Malaria places a significant economic burden on developing nations, accounting for an estimated 40% of medical costs, 60% of visits to health clinics, and up to half of all hospitalizations in endemic countries. Malaria is the second leading cause of death in Africa and the leading cause of death in Africa in children younger than 5 years. People traveling to endemic areas (e.g., vacation, expatriation, military service) are also at risk of contact with infected mosquitoes. Although malaria has largely been eliminated from the United States, CDC reported 1,925 cases of malaria in 2011, a 14% increase from 2010. All but five cases were contracted when patients traveled to endemic areas. *Plasmodium falciparum* was identified in 49% of these malaria cases. Between 1957 and 2011, 63 outbreaks of locally transmitted malaria were documented in the United States. The outbreaks occurred from local mosquitoes that were infected from biting people carrying malaria parasites that were acquired in endemic areas. The infected mosquitoes then transmitted malaria to local residents; thus, the potential risk of reemergence still exists. Children, pregnant women, the elderly, and immunosuppressed individuals have the highest risk of mortality. Vaccination against malaria parasites such as *P. falciparum*, the most deadly species of malaria parasite, could reduce the incidence of malarial disease in people living in or traveling to endemic areas. One intervention for preventing malaria was identified for this report as having high-impact potential.

RTS,S/AS01 (Mosquirix) for Prevention of Malaria Caused by *Plasmodium Falciparum*

- **Key Facts**: Malaria represents a significant burden to the health care systems of countries endemic for the disease as well as a significant health concern for people planning to travel to endemic areas. No licensed vaccines exist for preventing malarial disease. Prevention methods include vector control in the form of insecticide-treated bed nets, residual spraying,

and personal mosquito repellant, as well as prophylactic use of antimalarial drugs. RTS,S/AS01 is a prophylactic vaccine in clinical development designed to prevent malarial disease caused by the parasite *P. falciparum*. RTS,S/AS01 is a recombinant protein consisting of the central repeat and C terminal portions of the *P. falciparum* circumsporozoite protein fused to hepatitis B virus surface antigen, expressed in *Saccharomyces cerevisiae*. In addition, excess hepatitis B virus surface antigen is expressed to form the vaccine construct into virus-like particles. RTS,S/AS01 also contains the novel proprietary AS01 adjuvant. The vaccine is purported to be a "pre-erythrocytic vaccine" that induces protective antibody responses that prevent sporozoites from invading hepatocytes during the short window of time in which sporozoites are in circulation or by attacking liver schizonts. RTS,S/AS01 also purportedly induces strong interferon gamma–producing CD4+ T-cell responses, which could contribute to killing liver schizonts.

In a phase III RCT (n=6,537), children aged 6–12 weeks vaccinated with RTS,S/AS01 had a 31.3% reduction in the first or only episode of clinical malaria up to 14 months after the first dose of vaccine compared with children given a control vaccine. In another phase III RCT, children (n=6,000) aged 5–15 months or 6–12 weeks were given RTS,S/AS01 or a nonmalaria control vaccine. RTS,S/AS01 was 55.8% effective against clinical malaria in the 14 months after the first dose of vaccine in children aged 5–15 months. The vaccine was 47.3% effective against severe malaria in children aged 5–15 months. Serious adverse event frequency did not differ between groups. Researchers report that patients aged 5–15 months who received RTS,S/AS01 experienced generalized convulsive seizures at a rate of 1.04 per 1,000 doses administered.

Some investigators theorize that RTS,S/AS01 may reduce the risk of infection from each malaria exposure, rather than conferring "all or nothing" protection to those taking the vaccine. Thus, vaccinated individuals could eventually experience malaria if the transmission rate is high enough. Investigators expect the vaccine to have a greater impact on the incidence of the first or total episodes of clinical malaria instead of on the overall population experiencing disease.

RTS,S/AS01 is in phase III development with longer-term results of protective efficacy 30 months after the third vaccination expected to be available by the end of 2014. These results are expected to be the basis of filings that could lead to regulatory approval by 2015. Although vaccines typically gain marketing approval only when they demonstrate efficacy greater than 90%, the World Health Organization has called for a first-generation malaria vaccine with 50% efficacy against serious disease by 2015, with second-generation vaccines providing at least 80% efficacy by 2025.

- **Key Expert Comments:** Overall, experts stated that the high burden of disease and suboptimal methods of malaria prevention present a significant unmet need for new interventions to prevent malarial disease for people living in or traveling to areas endemic for *P. falciparum*. The efficacy seen in children aged 6–12 weeks and children aged 5–17 months could provide a significant improvement in health outcomes, the experts stated. However, they noted that suboptimal efficacy and waning protection provide a need for further development of second-generation vaccines. RTS,S/AS01 is expected to reduce demands on malaria treatment facilities in endemic areas but could require additional infrastructure investment for cold-chain management (controlling the temperature at which the vaccine is shipped and stored) and patient followup for subsequent booster immunizations.
- **Potential for High Impact:** Lower end of the high-impact-potential range

Health Care-Acquired and Bacterial Infection Interventions

Antimicrobial Copper Surfaces in the Intensive Care Unit for Prevention of Hospital-Acquired Infections

Unmet need: Health care–associated infections (HAIs) are a significant cause of mortality, morbidity, and costs in the U.S. health care system.[1] Of HAIs arising from exogenous origin, about 20% to 40% are attributed to cross infection from the hands of health care personnel.[2] About 2 million HAIs are documented in the United States annually and result in 100,000 deaths.[3] Additionally, the U.S. Centers for Disease Control and Prevention (CDC) estimates that HAIs add between $28 billion and $45 billion to annual U.S. health care costs.[4] On average, HAIs add an estimated 19.2 hospital days and $43,000 in additional costs for each patient who contracts an HAI.[5] Further, patients contracting an HAI have a 1-in-20 chance of dying if the infection is acquired while hospitalized and a 1-in-4 chance of mortality if the infection is contracted in the intensive care unit (ICU).[6]

Hospital surfaces in patient rooms, including the ICU, typically consist of stainless steel and plastics that purportedly possess no antibacterial properties and serve as fomites for disease transmission between disinfection procedures in many health care settings. In some cases, these surfaces can be colonized with live microbes for days or weeks, providing a contamination source to the hands and equipment of health care workers, professionals, visitors, and patients. The intrinsic antimicrobial properties of copper and copper alloys (brasses and bronzes) for touch surfaces on hospital hardware and equipment could add another safeguard against disease transmission between cleanings.[7]

Intervention: Antimicrobial copper touch surfaces (CuVerro®, Global Brass and Copper Holdings, Inc., Schaumburg, IL) can be incorporated into a wide variety of components, including bedrails, handrails, door handles, grab bars, intravenous (IV) poles, food trays and carts, sinks, faucets, shower and lavatory components, work surfaces, computer keyboards, equipment adjustment knobs, and face plates. Copper's antimicrobial properties purportedly remain effective for the product's lifetime, and they do not rely on coatings or impregnated surfaces that may wear off or wash away.[7] The International Copper Association, a manufacturer association, claims that copper touch surfaces continuously reduce bacterial contamination, achieving 99.9% reduction of gram-negative and gram-positive bacteria within 2 hours of exposure and that the surface delivers continuous antibacterial activity between routine cleaning and sanitizing steps.[8,9]

Antimicrobial copper consists of copper alloys such as brass and bronze, copper nickels, and copper with nickel and zinc.[1,10] Manufacturers intend these alloys to have strength comparable to stainless steel. Copper alloys are reported to be durable. Natural tarnishing does not impair the surface's efficacy, and copper touch surfaces have been deemed to not be harmful to people or the environment.[1,11]

The manufacturer association purports that copper surfaces exert their antibacterial activity in two sequential steps. First, antimicrobial copper purportedly disrupts the integrity of bacterial cell membranes through oxidation and disrupts physiologic functions such as electrostatic potential. Second, copper ions purportedly penetrate compromised cells and alter cell metabolism by interacting with numerous enzymes crucial for normal metabolic activity.[12] The use of antimicrobial copper is intended to supplement and not substitute for standard infection control practices, and users are advised to continue to follow all current infection control practices.[8] Thirteen companies are manufacturing products containing the Antimicrobial Copper mark for use in health care settings.[13,14]

Clinical trials: In an RCT (n=650), patients admitted to three ICUs in the United States were randomly assigned to placement in rooms fitted with six copper alloy surfaces (bed rails, overbed tables, IV poles, arms of the visitor's chair, and any two of the following items: nurses' call button,

computer mouse, bezel of the touchscreen monitor, or palm rest of a laptop computer) or standard surfaces.[15] Patients admitted to copper rooms had a 45% reduction in HAI or colonization with methicillin-resistant *Staphylococcus aureus* (MRSA) or vancomycin-resistant enterococci (VRE) compared with those infection rates in patients placed in standard rooms (p=0.020).[15] Additionally, patients assigned to rooms with copper surfaces had a 58% reduction in contracting an HAI alone (no VRE or MRSA colonization) compared with patients placed in standard rooms (p=0.013).[15]

In another analysis, investigators sampled copper-containing objects (n=282) in 32 ICU rooms and noncopper-containing objects (n=288) in 27 ICU rooms to examine the ability of antimicrobial copper to lower the microbial burden (MRSA and VRE) on commonly touched objects and to mitigate the acquisition of HAIs. The copper content of the objects was as follows:

- Bed rails, 99.99% copper alloy
- Tray tables, 90% copper alloy
- Chair arms, 90% copper alloy
- Monitors, 90% copper alloy
- IV poles 75% to 95% copper alloy
- Call buttons, 70% to 95% copper alloy

Using copper significantly reduced the total mean microbial burden in the ICU room by 87.4% (p=0.003). Copper was also effective in reducing the mean microbial burden on four of the six objects (bedrails [reduced by 99%, p=0.0003], call buttons [by 90%, p=0.003], IV poles [by 67%, p=0.11], and chair arms [by 38%, p=0.11]). Using copper showed no reduction in the mean microbial burden on tray tables or monitors.

Staphylococcus was the predominant organism isolated from each object regardless of the surface composition and comprised 78.7% of the mean microbial burden of copper-containing rooms and 55.5% of rooms that were not copperized. According to investigators, MRSA and VRE were frequently isolated from noncopper-containing objects but were not isolated from copper-containing objects.[16]

Manufacturer and regulatory status: The International Copper Association, Ltd., New York, NY, advocates for Antimicrobial Copper. It is the only hospital touch surface with a U.S. Environmental Protection Agency (EPA) public health registration, allowing manufacturers to claim that copper surfaces can kill specific bacteria (*S. aureus*, MRSA, VRE, *Enterobacter aerogenes*, *Pseudomonas aeruginosa*, and *Escherichia coli* O157:H7) that cause infections and pose a threat to human health.[8] Although the manufacturer association makes no claims of efficacy against other organisms, the literature has shown that the copper might also be effective against viruses, other bacteria, and fungal pathogens.[7,17] More than 479 antimicrobial copper alloys are EPA-registered public health antimicrobial products intended to address both practical and aesthetic demands.[18]

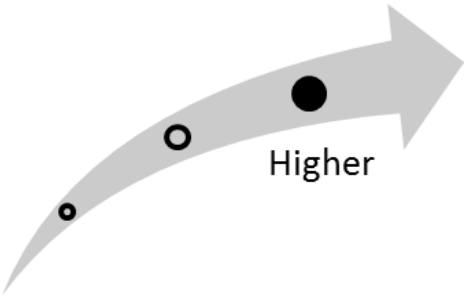
Diffusion and costs: The additional cost of manufacturing a copper sink for a hospital room is estimated at $40–$60 each,[19] which might be considered marginal because drop-in sinks and wall-hung sinks made from antimicrobial copper can cost about $500–$900 and $1,300, respectively.[20] According to the Copper Development Association, the cost to convert primary touch points to copper surfaces—on bed rails, cabinet hardware, chairs, countertops, door levers, grab bars, hand rails, IV poles, keyboards, light switches, linen hampers, computer mouse devices and other data input devices, tables, sinks, and faucets—is about $7,700 to $15,000 per room.[21] Thus, the total cost to outfit a 420-bed hospital with copper surfaces would be between $3 million and $6 million.[21] The Copper Development Association estimates that converting all of the previously mentioned items will reduce total infection rates by 20%, which would translate to an annual cost savings of $7.2 million, making the renovation cost effective within 1 year.[21]

In July 2012, a research collaboration involving teams from the David Geffen School of Medicine at University of California, Los Angeles (UCLA), the UCLA Fielding School of Public Health, and the Henry Samueli School of Engineering and Applied Science at UCLA announced that the U.S. Agency for Healthcare Research and Quality (Rockville, MD) had awarded them $2.5 million to conduct a 4-year, randomized study to determine whether reductions of surface bacteria due to the use of copper surfaces lead to decreased HAI rates, improve treatment outcomes, and reduce costs. The study is evaluating copper, plastic, or sham stainless steel surfaces to determine their role in HAI transmission.[22]

Clinical Pathway at Point of This Intervention

ICUs typically contain stainless steel and plastic surfaces that are disinfected with standardized terminal cleaning procedures when patients are discharged from a room. Antimicrobial copper touch surfaces might help prevent the accumulation of pathogens between cleanings.[23]

Figure 1. Overall high-impact potential: antimicrobial copper surfaces in the intensive care unit for prevention of hospital-acquired infections



Overall, experts commenting on this intervention stated that antimicrobial copper touch surfaces might significantly reduce HAIs and associated morbidity, mortality, and costs. Although a significant capital investment may be required to retrofit frequently touched surfaces in ICUs, the intervention is expected to quickly provide durable cost savings and improved patient outcomes. Except for a one-time disruption in patient management to retrofit rooms, using antimicrobial copper is not expected to alter hospital operations. Because it is not possible to run truly blinded studies in rooms fitted with copper surfaces, additional and larger unblinded RCTs should be performed before initiating large-scale retrofitting projects, thought experts. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion of Comments

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

Unmet need and health outcomes: Overall, the unmet need of reducing HAIs is quite significant, the experts agreed, noting current infection-control practices and education have not lowered these rates adequately in many cases. Also, new Medicare rules declining to reimburse for hospital readmissions arising from a HAIs have contributed to the unmet need, the experts noted. Overall, these experts stated that copper surfaces might help address the unmet need by reducing HAIs. However, copper surfaces would not affect the number of HAIs caused by the patient's endogenous flora or infections spread by health care workers who touch a sick patients and do not observe proper infection control practices, one clinical expert noted.[28]

Acceptance and adoption: The practice of using antimicrobial copper surfaces in ICUs would be widely accepted by both patients and physicians, the experts thought. They indicated this intervention might be a simple, nontoxic way help to solve a complex and burdensome problem in health care. Patients will likely accept an intervention that is expected to improve their health outcomes, the experts speculated. One expert representing a research perspective stated that physicians are more likely to accept this intervention if they will not personally bear the cost of fitting facilities with antimicrobial copper.[24] A one-time capital investment for new copper fixtures (which are slightly more expensive than current fixtures) is required, the experts noted; however, they opined that the fixtures are likely to be cost-saving eventually because extended ICU admissions can be among the most expensive occurrences in health care.

Health care delivery infrastructure and patient management: A one-time disruption in infrastructure and patient management would result from implementing copper touch surfaces in ICUs, the experts stated, noting that rooms would be unavailable during retrofitting with copper surfaces. Reductions in length of stay, hospital costs, and demands on hospital staff could be realized, if copper surfaces reduce HAI incidence, one research expert noted.[29]

Fecal Microbiota Transplantation for Treatment of Recurrent *Clostridium Difficile* Infection

Unmet need: In 2010 in the United States, an estimated 500,000 individuals were infected with *Clostridium difficile* infections (CDIs) at a cost of at least $1 billion.[30] Antibiotic use can disturb the normal bacterial flora of the colon, leading to colonization with *C. difficile* (*C. diff)* and release of toxins that cause mucosal inflammation and damage. Patients infected with *C. diff* typically have watery diarrhea, fever, appetite loss, nausea, and abdominal pain or tenderness.[31] Chronic and relapsing CDIs are increasingly common and a challenge to treat; about 15% to 30% of patients have a recurrence after treatment with metronidazole (Flagyl®) or vancomycin (Vancocin®).[30] Vancomycin is commonly used after a second CDI recurrence. Up to 65% of these patients develop further recurrence after antibiotic therapy is stopped. Fidaxomicin (Dificid®) is a relatively new antibiotic for third-line treatment, but nonantibiotic therapeutic options are needed.[30]

Intervention: Fecal microbiota transplantation (FMT) from the stool of a healthy donor is intended to recolonize a patient's intestinal flora with beneficial bacteria that will "crowd out" or otherwise make the environment in the bowel unfavorable for *C. diff* colonization.[32] The treatment can be delivered by any of several methods—capsules, colonoscopy, nasogastric tube, or enema.[33,34] Method standardization is lacking at this time. For the colonoscopic FMT procedure, healthy donors submit fresh stool on the day of the procedure, and it is mixed with saline into a solution and tested for pathogens, including syphilis, HIV, and hepatitis A, B, and C (the exact pathogens depend on the center). Prospective donors are excluded if they recently used antibiotics or had a bout of diarrhea. The fecal-saline solution is introduced into the patient's right cecum in the intestine by a gastroenterologist, who uses a colonoscope. The remainder of the solution is introduced distally as the colonoscope is withdrawn. Approximately 300–500 mL is infused into the patient; the dose varies by patient weight. For the encapsulated procedure, fecal solution is centrifuged and the fecal pellet is divided by aliquot into 24–34 gelatin pellets, which are ingested over 5–15 minutes on an empty stomach.[34] Typically, FMT is required only once in a patient, although it can be repeated if the infection does not fully resolve.[30,35]

Clinical trials: Only one randomized controlled trial (RCT) has been published that compares FMT to a standard antibiotic therapy, vancomycin. Two other controlled trials have been published, but they do not compare FMT to any antibiotic therapy; they compare stool preparation methods or donor sources. About 15 single-center case series evaluating efficacy have been published using varied methods and donor sources. We report here on the RCT comparing FMT to vancomycin, the RCT on donor sources, and some data from a few case series, including the longest-term data available. The RCT comparing treatments planned to enroll 120 patients who were to be randomly assigned to receive vancomycin (500 mg orally, 4 times daily, for 4 days) followed by bowel lavage and subsequent FMT administered through a nasoduodenal tube; standard vancomycin (500 mg orally, 4 times daily, for 14 days); or standard vancomycin with bowel lavage. The primary endpoint was resolution of diarrhea associated with CDI without relapse after 10 weeks. After 43 patients had been enrolled and treated, an interim analysis was performed. Among FMT-treated patients, 81% had resolution after the first infusion. Two of three patients whose CDI had not resolved after the first infusion had resolution after a second infusion from a different donor. CDI resolution occurred in 31% of patients treated with vancomycin alone and in 23% of patients given vancomycin and bowel lavage ($p<0.001$ for both comparisons with the FMT group). The reported adverse events among the three groups were few and similar, except for mild diarrhea and abdominal cramping in the FMT infusion group on infusion day. After review of these data, the Data and Safety Monitoring Board halted the study because of the high efficacy of FMT, which

confirmed efficacy observed in several earlier case series studies of patients with recurrent CDI who had not achieved success with vancomycin.[36]

Concerns about longer-term efficacy were addressed in part by a long-term follow-up analysis (mean follow-up 11.8 months) of patients with recurrent CDI (n=146) from nine treatment centers. Investigators reported an 86% resolution of diarrhea and 14% improvement of diarrhea after a single FMT. Most patients (81.5%) were treated with colonoscopic FMT; the other patients were treated with FMT by esophagogastroduodenoscopy, push enteroscopy, flexible sigmoidoscopy, or enema. Twenty-four patients developed early CDI recurrence within 90 days of initial FMT; the primary cure rate was reported as 83.5%. Among the 24 patients who developed CDI recurrence, 17 were successfully cured with an additional course of antibiotics, with (n=11) or without (n=6) repeat FMT, resulting in a secondary cure rate of 95.2%. Late recurrence, occurring 90 days after initial FMT occurred in 6 patients. Five of these patients were cured, three with subsequent FMT and two with vancomycin. Serious adverse events were reported in 16 patients within 12 weeks of FMT, which included 10 hospitalizations and 6 deaths, but were not believed to be related to the FMT itself. Recurrent CDI caused five hospitalizations and one death was attributed to complicated CDI. The remaining serious adverse events were unrelated to CDI.[37]

In another case series, patients (n=70) with recurrent CDI were treated with colonoscopic FMT. All patients had CDI diarrhea resolution except those infected with strain type 027 CDI, who had an 89% response rate. Four patients who did not respond to FMT had preexisting serious conditions caused by chronic diarrhea or a comorbidity, and all subsequently died of colitis. Within the first year after FMT, four patients previously treated had a CDI relapse after being treated with antibiotics. Two of these patients were successfully re-treated with FMT, and two were treated with antibiotics for CDI.[38]

In an RCT on donor stool preparations, patients (n=55) with recurrent CDI who were given at least two prior antibiotic courses were treated with colonoscopic FMT. The procedure was administered with either fresh feces (n=27) from related donors or healthy volunteers, or frozen feces (n=17) from healthy volunteers. CDI was cured in 96% (95% confidence interval [CI], 81% to 100%) of patients treated with fresh feces and 95% (95% CI, 71% to 100%) of patients treated with frozen feces. Mild transient fever appeared for two patients receiving frozen stool. No other significant side effects were reported.[39]

In a retrospective study, patients (n=49) with either moderate and recurrent or severe refractory CDI were treated with FMT via nasogastric tube (74%) or colonoscopy (26%).[40] Ninety-four percent of patients exhibited resolved symptoms within 1–4 days. Three patients whose symptoms did not respond to therapy were concurrently taking antibiotics. Four patients had recurrence after FMT and eventually died; however, the deaths were not attributed to recurrent CDI. No adverse events were reported in patients who underwent FMT.[40]

In another prospective study, patients (n=27) with more than three recurrences of CDI were treated with FMT from related donors administered orally, via 24–34 gelatin capsules ingested orally. All patients were successfully treated with CDI resolution up to 6 months after the procedure.[34]

Manufacturer and regulatory status: Until early 2013, FMT was being carried out without regulatory oversight in the United States. Clinician concerns and the lack of clear regulatory guidance for donor screening and donor material processing for FMT led a few specialty societies including the American Gastroenterological Association to contact the U.S. Food and Drug Administration (FDA) in April 2013 to clarify whether FMT was subject to regulation.[41] FDA's Center for Biologics Evaluation and Research determined that FMT falls within the agency's definition of a biological product and a drug.[42] The agency held a public workshop on FMT in May 2013 to exchange information and experience with the scientific and medical communities and to

facilitate clinical development of the procedure.[42] FDA initially announced that use of FMT would require an investigational new drug (IND) application to carry out the procedure for any condition.[42] In clinical situations in which FMT may require urgent action, clinicians were instructed to contact FDA to obtain an "emergency use" IND.[41] Several weeks later, FDA reconsidered this policy as a result of "subsequent communications, [in which] physicians and scientists have expressed concern to FDA that FMT is not appropriate for study under FDA's investigational new drug application (IND) regulations (21 CFR Part 312). Some health care providers have stated that applying IND requirements will make FMT unavailable…."[43] FDA noted the concerns and indicated that it "intends to exercise enforcement discretion regarding the IND requirements for the use of FMT to treat *C. difficile* infection not responding to standard therapies provided the treating physician obtains adequate informed consent from the patient or his or her legally authorized representative for the use of FMT products. Informed consent should include at a minimum, a statement that the use of FMT products to treat *C. difficile* is investigational and a discussion of its potential risks."[43]

In March 2014, FDA modified its draft guidance, adding that the agency plans to continue exercising enforcement discretion as long as (1) the stool donor is known to either the health care provider or the patient and (2) the physician performing the FMT procedure directs the donor and stool screening and testing.[44] OpenBiome (Medford, MA) a nonprofit, public stool bank operated by the Microbiome Health Research Institute proposed to FDA that institutions providing FMT procedures exceeding a set number (e.g., 20 procedures annually) could be required to participate in a trial under an IND.[45] OpenBiome asserts such a policy would balance the need for collecting meaningful data on FMT with the need to treat patients in a timely manner. OpenBiome also intends to sponsor an IND that would allow physicians to continue using universal donor stool if the guidance is enforced as currently proposed.[44]

In June 2013, FDA granted fast-track designation for RBX2660 (Rebiotix, Inc., Roseville, MN) a proprietary microbiota suspension intended for standardized off-the-shelf use for treating recurrent CDI.[46] Additionally, some researchers are investigating the feasibility of patients banking their own fecal material upon admission to eliminate the need for identifying and screening donors.[47]

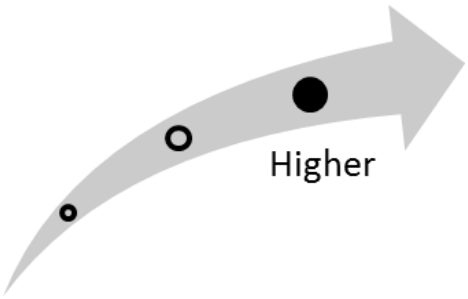
Diffusion and costs: The procedure had been diffusing before the FDA action in early 2013. More than 700 cases of FMT have been reported in the literature[48] and about 50–75 clinicians perform the procedure in the United States.[49] Diffusion could be slowed somewhat because the procedure now can be performed legally only within the context of an FDA-approved IND trial or with an emergency IND. Reported costs associated with screening donor blood and stool for contagious agents, preparing the donor fecal sample, and placing a retention enema tube are estimated to be about $1,500.[50,51] According to Smith et al., OpenBiome can limit the cost of testing donors to about $250 per treatment by providing a centralized stool bank with multiple collections from universal donors.[52] If the procedure is done by colonoscopy, the average cost of colonoscopy could add about $3,710 to the total cost of the procedure ($1,060 for patients with Medicare).[51] However, costs of multiple regimens of antibiotic therapy for recurrent CDI, physician office visits, and hospitalizations from complications of recurrent CDI can easily exceed the reported costs of one FMT.[51] For comparison, a 14-day supply of vancomycin (500 mg, 4 times daily) can cost about $3,500, according to a U.S.-based, online aggregator of prescription-drug prices.[53]

According to one analysis, FMT by colonoscopy is more cost effective than metronidazole, vancomycin, or fidaxomicin therapy for treating the first episode of CDI, and it is more cost effective than administering FMT by enema or nasogastric tube due to improved outcomes.[54] Third-party payers (e.g., Aetna, Humana, HealthPartners) are starting to cover the procedure for patients with CDI whose condition has not responded to a specified number of antibiotic courses.[55-57]

Clinical Pathway at Point of This Intervention

According to CDC, once CDI is confirmed, patients should be taken off the antibiotic that created the environment for the infection to occur. In some patients (20%, within 2–3 days), the infection may resolve without further treatment. If it does not, the patient is typically treated with either oral metronidazole or vancomycin for 10 days.[58] FMT is intended to treat recurrent CDI, although it is also under study as first-line therapy.

Figure 2. Overall high-impact potential: fecal microbiota transplantation for treatment of recurrent *Clostridium difficile* infection



Overall, experts concluded that results from FMT studies completed thus far are promising. They thought that the procedure has significant potential to address the unmet need for effective treatment for CDI recurrence by providing a potentially cost saving, effective treatment that avoids further use of antibiotics, preventing antibacterial resistance, reducing the probability of CDI transmission, and lowering CDI-associated mortality. However, experts were eager to see larger studies to better determine the role of FMT in clinical practice and whether it should be first-line therapy for CDI. Experts noted that several societal barriers to acceptance of the procedure may slow diffusion; however, they also noted that hesitation on the part of patients might be mitigated by poor quality of life and ongoing illness in patients with recurrent CDI. Experts stated that clinicians will have greater acceptance of the procedure once donor screening, testing, and transplant-processing protocols are established or centralized. Experts thought that FMT has high potential to significantly improve health outcomes in patients with difficult-to-treat, recurrent CDI. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this topic.[59-64] We have organized the following discussion of expert comments by the parameters on which experts commented. Please note that the expert comments received predated the very recent FDA action regarding FMT regulation.

Unmet need and health outcomes: Recurrent CDI causes great morbidity, mortality, and costs to patients and the health care system, the experts concurred, and emerging antibacterial resistance associated with these infections represents an important unmet need. FMT has the potential to address the unmet need for recurrent-CDI treatment that does not use antibiotics, according to a general consensus among the experts; meeting this need could significantly affect health outcomes and quality of life. In general, the experts accepted the underlying theory of FMT and were somewhat certain that it could be highly effective, although they thought larger trials are needed to bear this out.

Acceptance and adoption: Clinicians have already began to embrace FMT as adverse events have been reported to be minimal thus far, the experts noted. One clinical expert opined most facilities will eventually have at least one clinician willing to offer FMT.[62] However, some experts thought uncertainty in the regulatory environment could continue to slow acceptance of the procedure among some clinicians. Standardized FMT procedures, such as frozen universal donor specimens and encapsulated FMT, were methods cited by the experts as potentially increasing patient and clinician acceptance. Although many patients with recurrent CDI are already actively seeking this procedure, the experimental nature of FMT (e.g., requiring an IND) could be a barrier to patient acceptance, reserving the procedure for only the sickest patients, one clinical expert noted.[64] Additionally, some experts thought that psychological factors or beliefs may preclude some patients from seeking the treatment.[59,60,64]

Experts generally viewed the procedure as cost neutral or cost saving compared with the cost of multiple failed courses of antibiotics and resultant complications. Encapsulated FMT could reduce costs compared with colposcopic instillation, one clinical expert noted.[64]

Health care delivery infrastructure and patient management: The experts mentioned that health care facilities generally have the staffing and equipment needed to perform the procedure, and they thought minimal disruptions would be seen in infrastructure and patient management. Potential disruptions cited would include shortened duration of inpatient stays. Experts thought FMT could become the standard of care for refractory CDI, displacing antibiotic use, and causing a shift in demands on health care infrastructure and patient management. However, fecal transplants from universal donors, encapsulated FMT, or off-the-shelf microbiota suspension could reduce demands on health care infrastructure and staffing by streamlining patient management for FMT, some experts thought.[60,61,64]

Retrofitted Private Intensive Care Rooms to Reduce Hospital-Acquired Infections

Unmet need: Despite infection-control efforts, about one-third of patients admitted to an ICU contract an infection, which may increase length of stay, cost of care, and morbidity. HAIs can be transmitted between ICU patients by direct contact (principally via caregivers' hands), droplets (from infected airway secretions), and via fomites (inanimate shared objects in patient rooms or ICU environment, including computer equipment, sink faucets, beds, and chairs).[65] Private ICU rooms may help to better isolate patients and contain their infections or prevent them from contracting a new infection, improving patient outcomes.[66] Newly constructed ICUs are often built with private rooms, but the majority of existing ICUs have multiple-patient rooms and may pose increased risk of HAI to patients.

Intervention: Converting traditional multiple-patient ICU settings to a single-patient room design might reduce HAI transmission to patients who already have serious infirmities. Several design elements in private ICU rooms can purportedly reduce HAI transmission; however, the contribution of each element remains unclear.[65] Increased patient area and an increased sink-per-patient ratio are among the elements thought to reduce HAI transmission. Additionally, some investigators theorize that single-room ICU design improves hand-hygiene adherence among health care workers.[65,67] Separating patients as well as their equipment is thought to provide additional benefit; thus, single-room designs within an open plan could be inadequate because the environment around the single room could provide a reservoir for HAI transmission.[65]

Besides HAI-reduction association, private rooms are more accommodating for family members staying with patients in the ICU, which could decrease the patient's stress and improve privacy.[68] Private rooms are considered the standard for new construction as hospitals position themselves to score high on the government-developed patient satisfaction rating system, HCAHPS (the Hospital Consumer Assessment of Healthcare Providers and Systems) and to remain competitive with other treatment facilities.[68]

Although private ICU rooms represent a significant investment in infrastructure and equipment, they are purportedly part of the greater environment of healing, which can provide cost savings in the long term.[68] However, investigating the effect of ICU design on HAI rates for research purposes alone has been cost prohibitive. Thus, available evidence typically consists of a before-and-after study design or has been gathered during outbreaks of resistant organisms during which multiple infection-control measures are implemented, complicating analysis.[65]

Clinical trials: In a prospective, parallel-assignment trial, patients in Jerusalem, Israel, were treated in ICUs with either seven open-plan beds (ICU-A) or four beds with dividers (ICU-B). In March 2007, patients in ICU-A were moved to a new location consisting of eight beds, each in a private room, while patient-treatment spaces ICU-B were unchanged. Researchers collected data for 62 patients from pre-move ICU-A, 62 patients from post-move ICU-A, 44 patients from pre-move ICU-B and 39 patients from post-move ICU-B. After the move to private rooms the following occurred:[65]

- ICU-A patients acquired fewer antibiotic resistant organisms (3/62, 5%) than patients who remained in ICU-B with room dividers (7/39, 18%; p=0.043, p=0.011 using survival analysis)
- ICU-A patients after the move acquired fewer antibiotic-resistant organisms than patients in ICU-A before moving to private rooms (14/62, 23%; p=0.004, p=0.012 on survival analysis)
- Patients in ICU-A had more antibiotic-free days after moving to private ICU rooms (median=3, interquartile range=0–5) than patients who remained in ICU-B with room

dividers (median=0, interquartile range=0 to 4; p=0.070) or patients in the ICU-A group before moving to private rooms (median=0, interquartile range=0 to 4; p=0.017)

Additionally, proper hand hygiene was observed on 58% of occasions after patients in ICU-A were moved to private rooms compared with 35% of occasions for patients who remained in ICU-B with room dividers (p<0.001).[65]

In another comparative study, patients in a teaching hospital in Montreal, Quebec, Canada, were admitted to an ICU with multiple-bed rooms before a renovation (2,732 admissions) or single-patient ICU rooms after a renovation (5,468 admissions). As a control, new infection rates were collected from patients in an ICU at a nearby teaching hospital with both room designs during the study period. Statistical modeling was used to adjust for background time trends common to both hospitals. Renovating ICU rooms to single-patient design reduced the adjusted combined rate of *C. difficile*, vancomycin-resistant Enterococcus species, and MRSA acquisition by 54% (95% CI, 29% to 70%). Single-room renovations reduced the rates of organism acquisition as follows:[69]

- *C. difficile*, reduced by 43% (95% CI, 7% to 65%)
- MRSA, reduced by 47% (95% CI, 1% to 71%)
- Yeast, reduced by 51% (95% CI, 34% to 64%)

Patients in renovated, private ICU rooms had a 10% reduction (95% CI, 0% to 19%) in the adjusted length of stay compared with patients treated before the intervention.[69]

In a retrospective study of HAI acquisition, investigators reported results from patients (n=818) admitted to an ICU in Florence, Italy. From April 2006 to April 2007, admitted patients were treated in rooms with a bay-room ICU design. From May 2007 to May 2008, patients were treated in a renovated ICU with a single-room design.[70] Reductions in pathogenic microbiologic cultures from both bronchial aspirate and blood culture were observed after rooms were renovated to a single-room design. Respiratory isolates of *E. coli*, *Enterobacter spp*, MRSA, *Proteus mirabilis*, and *Serratia marcescens* were significantly reduced.[70] Renovation to a single-room design also reduced gram-negative bloodstream infections. A significant decrease in antibiotic use, including amoxicillin/clavulanate (p<0.01), ceftriaxone (p<0.01), oxacillin (p<0.05), and vancomycin (p<0.05), was observed after the single-room renovation.[70]

Standards for hospitals: The American Institute of Architects recommended in 2006 that private rooms become the standard for new hospitals. The recommendations were developed by a panel of hospital administrators, doctors, architects, engineers, and infection-control experts.[68] Private ICU rooms are being implemented in hospitals across the United States, particularly in newly constructed units.[68] Studies examining private-room ICU implementation have typically been conducted by investigators in countries outside the United States, including Canada, China, the European Union, and Israel.[65,67,69,70] One physician asserts this is because investigators in these nations have access to information on longevity and other outcomes from their nationalized health care systems, making their findings more informative.[68]

Diffusion and costs: Although patients may prefer private ICU rooms, these rooms are more costly to build and staff than semiprivate rooms. Some researchers stated that building single-patient ICU rooms costs millions of dollars;[65] however, according to one cost-benefit analysis of inpatient private rooms versus semiprivate rooms, the net social benefit of a private room was estimated at about $70,000 relative to a semiprivate room. Investigators believe that considering societal costs is important because hospitals are costly, long-term investments for the community that, once constructed, are extremely expensive to renovate.[71]

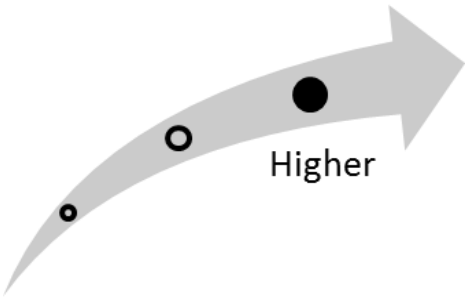
Third-party payers have not typically provided additional reimbursement for private rooms; reimbursement rates have historically been based on semi-private rooms.[68] Thus, additional costs for private rooms are absorbed by the facility and could possibly lead to additional out-of pocket

expense for patients. However, hospitals may see the investment as worthwhile to reduce HAIs, length of stay, and the readmissions that can result and for which Medicare and other payers provide no reimbursement.

Clinical Pathway at Point of This Intervention

Patients are admitted to an ICU for care of serious, life-threatening conditions (i.e., cardiovascular disease, pulmonary disease, renal disease, serious gastrointestinal disorders, stroke or encephalopathy, infections or sepsis, organ failure, severe trauma) that sometimes require lengthy stays of weeks or even months.[72] Severe infections are common in ICUs and risk increases with length of stay.[73] Retrofitting existing multiple-bed ICU room designs with single-patient rooms could reduce the rate of HAIs in this patient population.

Figure 3. Overall high-impact potential: retrofitted private intensive care rooms to reduce hospital-acquired infections



Overall, experts concluded that results from the available studies of retrofitting ICUs with private rooms are promising. Experts thought that this design approach has significant potential to address the unmet need of reducing HAIs when combined with other best practices for infection control. Experts agreed that significant capital investment would be required for infrastructure and equipment for private rooms; however, the experts thought reductions in HAIs and associated liability would eventually be cost-saving. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this topic.[74-79] We have organized the following discussion of expert comments by the parameters on which experts commented.

Unmet need and health outcomes: HAIs cause great morbidity, mortality, and costs to the health care system, noted experts commenting on this intervention. The burden of HAI on patients who are already in critical condition is often life threatening, the experts opined. They also stated that antibiotic resistance is making HAIs tougher to treat, making HAI prevention a high unmet need. Private ICU rooms have been shown to significantly reduce the incidence of HAI and are an important consideration when remodeling or renovating hospital wings, most experts agreed.[74,76-78] However, one expert representing a research perspective stated that the study designs and conduct of the existing data enable only weak conclusions.[75] Additionally, experts stated that private ICUs will not eliminate all HAIs. One health systems expert noted that the intervention should be only one component of a comprehensive HAI-reduction campaign.[79] Another research expert cautioned that many ICU patients have serious comorbid conditions irrespective of the HAI threat, and large improvements in patient health outcomes might not be observed with the intervention.[77] Reductions

in length of stay and complications are expected to be the best endpoints to measure the impact of private rooms, one health systems expert noted.[79]

Acceptance and adoption: Clinicians are expected to appreciate better infection control as well as the ease of communicating freely with patients in private rooms, experts with health systems and research perspectives noted.[76,78,79] Patients are expected to readily accept private ICU rooms as a standard, particularly if having a patient roommate exposes the ICU patient to additional risk, one health systems expert noted.[78] Patients are also expected to welcome being in a more private setting for communication with family and clinicians, one health systems expert opined.[76] However, one barrier to patient acceptance could be additional out-of-pocket costs if third-party reimbursement does not cover additional costs and hospital charges increase, two research experts noted.[75,77]

Health care delivery infrastructure and patient management: Renovations for private rooms would require significant investment in infrastructure, and private ICU rooms could require additional staff to monitor rooms that are farther apart, or the intervention could increase response time, some experts thought.[74,75,77] However, one health systems expert stated that patients need care for their medical conditions, and adjusting to private rooms should not be an issue for facilities that are already focused on quality care.[76] Private ICU rooms are expected to reduce the amount of care needed by reducing HAI incidence and improving health outcomes, one health systems expert stated.[79] Overall, the experts theorized that private ICU renovations would be cost-saving over time.

Health disparities: Private ICU rooms could increase health disparities because rural hospitals and community health centers may not have the resources for ICU renovations.[74,77] Additionally, some experts noted that if a choice exists between private and shared ICU rooms, there may be higher out-of-pocket costs for the patient to have a private room, assuming similar rates of reimbursement, which could create disparities.[76,79]

Xpert MTB/RIF Test for Simultaneous Detection and Drug-Sensitivity Testing of *Mycobacterium Tuberculosis*

Unmet need: According to the World Health Organization, tuberculosis (TB) is highly underdiagnosed. This is a direct result of current TB testing methods, which require weeks to deliver a definitive result; during that time, patients are not treated or placed on ineffective therapies. These patients may also continue to spread TB to others in the community, creating a significant public health concern.[80]

Intervention: The *Mycobacterium tuberculosis*/rifampicin test (Xpert® MTB/RIF) is a nucleic acid–based test run on the GeneXpert® real-time polymerase chain reaction (PCR) system.[80] The test simultaneously detects the presence of *M. tuberculosis* complex species and determines whether the identified bacterium is susceptible to rifampicin, the first-line TB drug.[81]

A real-time hemi-nested PCR reaction is performed to amplify and detect a portion of the *rpoB* gene, a genetic marker that is specific for a subunit of an RNA polymerase essential to TB viability.[80] The antibiotic activity of rifampicin targets the subunit encoded by the *rpoB* gene to inhibit the RNA polymerase, inhibiting bacterial survival.[80] Research has demonstrated that the portion of the *rpoB* gene amplified in the Xpert MTB/RIF assay harbors mutations in the majority of rifampicin-resistant TB strains.[82]

In the assay, TB DNA in the patient sample is detected in the sample by five separate real-time PCR fluorescent probes, which are activated in the presence of amplified *rpoB* DNA and detected by the GeneXpert system.[81] Each of the five probes overlaps a different site known to be mutated in rifampicin-resistant TB if rifampicin resistance can be determined based on the binding signal given from the probes.[81]

To perform the test, a technician first treats a patient sputum sample with a solution containing sodium hydroxide and isopropanol (isopropyl alcohol) to reduce the viability of any *M. tuberculosis,* thereby preventing contamination. Subsequent processing and detection are performed on the GeneXpert system using a single-use, closed Xpert MTB/RIF cartridge that contains all the reagents necessary for testing.[80,81] The procedure's automated nature and the fact that it does not require handling of PCR amplicons are intended to ensure optimal accuracy of the assay by limiting interoperator variability and reducing the potential for false positives caused by amplicon contamination.[81] The assay is intended to yield results in about 2 hours for both the presence of *M. tuberculosis* and antibiotic resistance for positive samples.[80] For a clinician to fully determine an effective treatment regimen, full drug-susceptibility testing would still need to be performed in patients with rifampicin-resistant TB.

Clinical trials: In a diagnostic substudy of a TB prevalence survey conducted in gold mining companies in South Africa, participants' sputum (n=6,893) was tested using liquid culture (reference comparator), Xpert MTB/RIF, and smear microscopy. Sputum samples tested positive for *M. tuberculosis* in 2.7% of samples tested by culture, 2.1% of samples tested by the Xpert MTB/RIF test, and 1.3% of samples tested by microscopy. Sensitivity for the test was 62.6%, specificity was 99.6%, positive predictive value was 81.3%, and negative predictive value was 98.9%. Agreement between Xpert and culture was 98.5%. Sensitivity of microscopy was 17.6%. When individuals with a history of TB treatment were excluded from the analysis, Xpert MTB/RIF specificity was 99.8% and the positive predictive value was 90.6% for detecting *M. tuberculosis*. Costs for testing the 7,000 specimens, with 2.7% of specimen cultures positive for *M. tuberculosis*, were $165,690 for Xpert MTB/RIF and $115,360 for the combination of microscopy and culture.[83]

In a large multicenter trial, patients (18 years of age or older) suspected of having TB or multidrug-resistant TB (n=6,648) presenting with cough lasting at least 2 weeks were tested for TB using Xpert MTB/RIF, culture, and microscopy detection methods. The investigators reported,

"One-off MTB/RIF testing detected 933 (90.3%) of 1033 culture-confirmed cases of tuberculosis, compared with 699 (67.1%) of 1041 for microscopy. MTB/RIF test sensitivity was 76.9% in smear-negative, culture-positive patients (296 of 385 samples), and 99.0% specific (2846 of 2876 non-tuberculosis samples)." The sensitivity and specificity of the MTB/RIF test for rifampicin resistance were 94.4% and 98.3%, respectively. As observed with microscopy, MTB/RIF test sensitivity was not significantly lower in patients co-infected with HIV. Median time to detection of TB was 0 days for the MTB/RIF, 1 day for microscopy, 16 days for liquid culture, and 30 days for solid culture. Using the MTB/RIF test reduced the median time to treatment of patients with smear-negative TB from 56 days to 5 days.[84]

In an international clinical trial, investigators collected three sputum samples from each enrolled patient suspected of having TB or drug-resistant TB (n=1,730). Samples were analyzed by a combination of acid-fast smear, solid culture, liquid culture, and Xpert MTB/RIF tests. Among culture-positive patients, the Xpert MTB/RIF test gave a positive TB result for 551 of 561 smear-positive patients (98.2%) and for 124 of 171 smear-negative patients (72.5%). Additionally, among 609 culture-negative patients, the Xpert MTB/RIF test correctly identified 604 patients as negative for TB infection (99.2%). As for susceptibility testing, compared with conventional culture-based susceptibility testing, the Xpert MTB/RIF test correctly identified 200 of 205 patients with TB as having a rifampicin-resistant infection (97.6%) and 504 of 514 patients with TB as having a rifampicin-sensitive infection (98.1%).[85]

In an additional study, investigators compared Xpert MTB/RIF to culture and microscopy detection methods using samples from pediatric patients with suspected TB (n=164). Xpert MTB/RIF detected 100% of the smear-positive cases and 66.6% of culture-positive cases that were smear negative. In the per-sample analysis, Xpert displayed a similar sensitivity to culture methods and detected threefold more confirmed TB cases than microscopy in a similar amount of time. Four additional culture-negative cases with clinical TB (8.5%) were diagnosed by Xpert MTB/RIF. Xpert MTB/RIF demonstrated 100% specificity when TB was reliably excluded; accuracy was not affected by HIV infection in these patients.[86]

In a randomized, multicenter trial, patients suspected of TB presenting at five primary health care facilities in South Africa, Zimbabwe, Zambia, and Tanzania were evaluated at the point-of-care using either Xpert MTB/RIF (n=744) or sputum smear microscopy (n=758). Patients with a negative test result were empirically managed according to local World Health Organization–adherent guidelines. Point-of-care Xpert MTB/RIF had higher sensitivity than smear microscopy (83% vs. 50%; p=0.0001) but similar specificity (95% vs. 96%; p=0.25).[87] Xpert MTB/RIF point-of-care testing had similar sensitivity to laboratory-based Xpert MTB/RIF testing (83%; p=0.99) and higher specificity (92%; p=0.0173). Five percent of point-of-care Xpert MTB/RIF tests failed compared with 6% of laboratory-run Xpert MTB/RIF tests (p=0.22).[87] More patients tested with MTB/RIF had a same-day diagnosis compared with microscopy (24% vs. 13%; p<0.0001) and more patients initiated same-day treatment (23% vs. 15%; p=0.0002). However, by day 56, the proportions of patients receiving therapy were similar for Xpert MTB/RIF and microscopy (43% vs. 42%; p=0.6408).[87]

Manufacturer and regulatory status: Cepheid (Sunnyvale, CA) makes the Xpert MTB/RIF test.[80] In July 2013, FDA granted Cepheid marketing clearance for the Xpert MTB/RIF test through the 510(k) de novo premarket notification process. The de novo classification is a regulatory pathway for medical devices that are considered to pose low-to-moderate risk, but have no comparable predicate device.[88] Xpert MTB/RIF is indicated for the rapid molecular detection of *M. tuberculosis* complex DNA as well as the detection of rifampin resistance associated with mutations of the *rpoB* gene in specimens positive for *M. tuberculosis*.[88]

Diffusion and costs: The price for the GeneXpert GX4-4 system to conduct the testing is $78,200.[89] The Xpert MTB/RIF test costs about $72.[89] For benchmarking purposes, standard basic testing for TB costs about $20–$40, and more advanced testing to determine rifampicin resistance can add another $20–$30.[90]

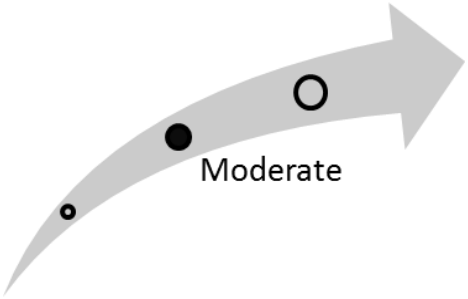
According to one cost analysis of incorporating Xpert MTB/RIF into a TB diagnostic algorithm, TB testing without molecular testing was calculated to cost $158 per patient. Intensive testing in which all samples were evaluated with Xpert MTB/RIF regardless of smear microscopy results was calculated to cost $256 per patient (assuming 3,000 patients tested per year). Selective use of Xpert MTB/RIF for patients with positive smear samples was calculated to cost $162 per patient. When all health-system costs were considered, TB testing without molecular testing was most costly ($2,728 per patient) compared with intensive and selective Xpert MTB/RIF testing algorithms ($2,673 and $2,482, respectively).[91] Additionally, intensive Xpert MTB/RIF testing is expected to improve health outcomes (6.32 quality-adjusted life years [QALY] gained per 1,000 TB patients tested). Intensive Xpert MTB/RIF testing was also considered by the investigators to be highly cost-effective (incremental cost-effectiveness ratio of $39,992 per QALY gained) compared with other molecular testing methods.[91]

This test would likely be billed using current TB codes. In August 2013, FDA categorized the Xpert MTB/RIF test as "moderate complexity" under the Clinical Laboratory Improvement Amendments (CLIA), which likely facilitates diffusion.[92]

Clinical Pathway at Point of This Intervention

A patient initially presents with symptoms that indicate a possible case of pulmonary TB based on his or her medical history, physical examination, symptoms, latent or active TB test results (e.g., tuberculin skin test, QuantiFERON-TB Gold test), and/or chest radiographs.[93,94] The recommended diagnostic procedure for laboratory confirmation of TB is to obtain a respiratory sputum sample from the patient and test the sample simultaneously with a nucleic acid amplification test, an acid-fast bacteria smear test, and liquid or solid media culture.[93] The Xpert MTB/RIF test would be used in place of current nucleic acid amplification tests. Besides identifying the presence of TB, the Xpert MTB/RIF test would also give a preliminary indication of potential antibiotic resistance, which would normally be determined following a positive culture isolate by assaying the isolate's in vitro susceptibility to antibiotics.[80,93]

Figure 4. Overall high-impact potential: Xpert MTB/RIF test for simultaneous detection and drug-sensitivity testing of *Mycobacterium tuberculosis*



Overall, experts commenting on this intervention thought that the Xpert MTB/RIF test has potential to be a rapid, sensitive, and specific diagnostic that could address the unmet need for more rapid diagnosis and better initial management of TB. They thought it has potential to improve patient health outcomes and reduce the spread of TB. By knowing the patient's TB status before he or she leaves the physician's office, experts noted, more appropriate treatment could be given and proper

infection control measures could be implemented. However, the Xpert MTB/RIF test detects resistance only to rifampin, a common first-line antibacterial agent. Susceptibility to other agents would still need to be guided by traditional testing methods. Nevertheless, the Xpert MTB/RIF test could replace other PCR detection methods and provide an improved approach to diagnosis and treatment, the experts thought. That could reduce problems with followup of patients who have limited access to care, experts opined. Based on this input, our overall assessment is that this intervention is in the moderately high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.[95-100] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Current TB diagnostic methods are lengthy, taking days to weeks to confirm or rule out the presence of TB and antibiotic susceptibility, the experts concurred. This, they said, represents a significant unmet need for more rapid diagnostic testing to direct appropriate therapy and implement infection control measures for patients, the community, and health care providers. Experts agreed that the Xpert MTB/RIF test is fast and accurate, which allows health care practitioners to implement infection control procedures almost immediately. Additionally, they noted the advantage that the test provides early detection of rifampicin resistance to guide appropriate antibiotic selection, which could improve health outcomes.

Acceptance and adoption: The experts all generally thought that clinicians would readily embrace Xpert MTB/RIF testing. Xpert MTB/RIF testing has a similar turnaround time and higher accuracy than smear microscopy, which could lead to the elimination of smear microscopy, one clinical expert suggested.[98] Patients were expected to embrace rapid diagnosis, especially if their co-payments remained unchanged, experts opined.

Health care delivery infrastructure and patient management: In general, the experts thought the Xpert MTB/RIF test would not have a large impact on how the disease is treated or diagnosed but that it would allow current treatment strategies to be employed earlier and, therefore, potentially reduce disease transmission; culture and susceptibility testing would still need to be performed. Although experts thought impact on staffing and training would be minimal, they noted that a significant capital investment is required to purchase the GeneXpert system if the facility has not purchased it for other testing. Xpert MTB/RIF testing would add minimal costs or would eventually be cost-saving, experts thought. However, some experts noted, initial costs of the GeneXpert system could to lead to more centralized TB testing centers.[95,99]

Health disparities: The Xpert MTB/RIF assay could improve health disparities by improving access to care, some experts stated.[95,98,99] However, one expert representing a research perspective stated that the GeneXpert system may be too costly in some underserved areas, which could create disparities.[99]

Hepatitis C Virus Infection Intervention

Interferon-Free Treatment of Chronic Hepatitis C Infection

Unmet need: The landscape of hepatitis C virus (HCV) infection treatment changed in May 2011 when the first NS3/4a protease inhibitors boceprevir and telaprevir were FDA approved for use in combination with interferon (IFN) and ribavirin (RBV) for treating chronic HCV genotype 1 infection.[101,102] Protease inhibitors were shown to improve cure rates for HCV genotype 1 in both treatment-naïve and treatment-experienced patients compared with IFN and RBV alone,[101,102] but up to half of patients are unable to tolerate any IFN-containing treatment regimen.[103] Also, protease inhibitors are associated with significant side effects including anemia and severe rash.[104] Lastly, approved protease inhibitors are effective against only HCV genotype 1 infection. Effective, well-tolerated, IFN-free treatment options that are pan-genotypic are needed for treating chronic HCV infection.[103]

Intervention: Two novel IFN-free options are presented in this section: sofosbuvir (Sovaldi™) for treating chronic HCV genotype 1, 2, and 3 infection, and the 3D regimen (ABT-450/ritonavir, ombitasvir, and dasabuvir) for treating chronic HCV genotype 1 infection.

Sofosbuvir is a recently FDA-approved uridine nucleotide analog polymerase inhibitor in phase III trials for treating chronic HCV infection.[104,105] The HCV NS5B polymerase plays an essential role in HCV genome replication. As a nucleotide analog, sofosbuvir is said to target the active site of the enzyme and inhibit elongation of the growing HCV RNA genomic transcript.[104] Nucleos(t)ide analogs such as sofosbuvir are thought to have broader efficacy against different HCV genotypes and a higher barrier to viral resistance than nonnucleos(t)ide polymerase inhibitors, which function via allosteric inhibition.[104] Sofosbuvir has been investigated in combination with a number of investigational agents including ledipasvir, a drug that inhibits activity of the HCV NS5A protein, in an effort to create a convenient, all-oral treatment that would eliminate the need for IFN and/or RBV in patients with chronic HCV genotype 1 infection.[106] Although the functions of NS5A are not fully defined, in vitro studies suggest NS5A plays an essential role in viral replication including the packaging, assembly, and release of infectious particles.[107,108] Sofosbuvir is being evaluated as part of multiple therapeutic regimens. It is administered orally, 400 mg once daily, for 12 weeks in combination with RBV for patients infected with HCV genotype 2, for 24 weeks for patients infected with genotype 3, and for 12 weeks with IFN and RBV for patients chronically infected with HCV genotypes 1 or 4.[109] Fixed-dose combination sofosbuvir (400 mg)/ledipasvir (90 mg) has been administered for 8, 12, or 24 weeks with or without weight-based RBV, depending on a patient's treatment history or liver cirrhosis status, for treating chronic HCV genotype 1 infection.[106,110]

The oral 3D regimen consists of boosted protease inhibitor ABT-450/ritonavir, NS5A inhibitor ombitasvir (ABT-267), and non-nucleoside polymerase inhibitor dasabuvir (ABT-333). The HCV NS3 protease and its essential cofactor, NS4A, cleave viral polyproteins, allowing assembly of functional particles.[111] The 3D regimen was designed to optimize sustained viral response (SVR) rates across different patient populations by targeting three processes that are essential for HCV replication.[111,112] Dasabuvir (250 mg) and RBV (weight-based) are both dosed twice daily, and a fixed-dose combination of ABT-450/ritonavir (150 mg/100 mg) co-formulated with ombitasvir (25 mg) is dosed once daily.[113]

Clinical trials: Sofosbuvir has been studied in a number of clinical trials in patients infected with various HCV genotypes and in varied treatment regimens with or without IFN and RBV. Here we provide some recent data from sofosbuvir trials demonstrating the emerging potential of the drug in HCV care.

In the phase III, randomized controlled VALENCE trial, patients (n=419) with chronic HCV genotype 2 or 3 infection were given sofosbuvir and RBV or placebo for 12 weeks. Among the

patients enrolled, 58% received previous IFN-based treatment and 21% of patients had cirrhosis. Emerging data from phase III trials prompted the investigators to extend treatment in patients infected with HCV genotype 3 to 24 weeks, unblind the study, and terminate the placebo group. Patients infected with HCV genotype 2 and 3 achieved sustained viral responses at 12 weeks after therapy (SVR12) of 93% and 85%, respectively. Patients with HCV genotype 2 and 3 infection and cirrhosis achieved SVR12 rates of 82% and 68%, respectively.[114]

In the phase III, randomized controlled FISSION trial, patients (n=499) with chronic HCV genotype 2 or 3 infection who had not received prior treatment were given either 12 weeks of sofosbuvir (400 mg, once daily) and RBV (1,000 or 1,200 mg/day) or 24 weeks of IFN (180 mcg/week) and RBV (800 mg/day). Researchers reported that sofosbuvir plus RBV met the primary endpoint of noninferiority to IFN/RBV: 67% of patients achieved SVR12 in both groups. The SVR12 rates in patients receiving sofosbuvir plus RBV were 97% and 56% for patients infected with genotype 2 and genotype 3, respectively. The SVR12 rates in patients treated with IFN/RBV were 78% and 63% for patients infected with genotype 2 and genotype 3, respectively. Of patients treated with sofosbuvir and RBV, 20% and 21% of patients treated had compensated cirrhosis, respectively.[115,116]

In the phase III, open-label randomized controlled ION-3 trial, patients (n=647) with chronic HCV genotype 1 infection who were not previously treated were given either sofosbuvir/ledipasvir, once daily, for 8 weeks with or without RBV, or sofosbuvir/ledipasvir without RBV for 12 weeks. Patients treated with sofosbuvir/ledipasvir with or without RBV had SVR 12 rates of 94% and 93%, respectively. Patients treated with sofosbuvir/ledipasvir for 12 weeks had an SVR12 of 95%. Eight weeks of sofosbuvir/ledipasvir therapy was noninferior to 12 weeks of sofosbuvir/ledipasvir therapy.[117]

In the phase III, open-label, randomized controlled ION-2 trial, patients (n=440) with chronic HCV genotype 1 infection who were previously treated with IFN-based therapy were given either 12 weeks of sofosbuvir/ledipasvir, once daily, with or without RBV or 24 weeks of sofosbuvir/ledipasvir with or without RBV. Twenty percent of patients in the study had liver cirrhosis. The SVR12 rate for patients treated with sofosbuvir/ledipasvir for 12 weeks with or without RBV was 94% and 96%, respectively. Patients treated with sofosbuvir/ledipasvir for 24 weeks with or without RBV achieved an SVR of 99% in both groups.[118]

In the phase II, open-label PHOTON-1 trial, patients (n=182) co-infected with HIV and HCV (genotypes 1, 2, or 3) who were not previously treated for HCV were given sofosbuvir (400 mg once daily) and RBV. After 24 weeks of therapy, 78% of patients infected with HCV genotype 1 (n=114) achieved an SVR12. After 12 weeks of therapy, patients infected with HCV genotype 2 (n=26) and genotype 3 (n=42) achieved SVR12 rates of 88% and 67%, respectively.[119]

In studies in which patients were given sofosbuvir and RBV, the most common side effects reported were dizziness, fatigue, headache, insomnia, and nausea.[120] Fewer adverse events were observed in patients treated with sofosbuvir/ledipasvir without RBV compared with patients treated with RBV in all ION studies. The most common adverse events reported in patients taking sofosbuvir/ledipasvir with RBV were fatigue, headache, insomnia, and nausea. Anemia, a common side effect of RBV, was reported in 0.5% of patients taking sofosbuvir/ledipasvir without RBV compared with 9.2% in patients taking sofosbuvir/ledipasvir with RBV.[110] Fewer than 1% of patients in the ION trials discontinued treatment due to treatment-emergent adverse events.[110]

The 3D regimen, with or without RBV, has also been studied in a number of clinical trials in various patient populations infected with HCV genotype 1. Here, we list some recent data from trials demonstrating the emerging potential of the 3D regimen for treating chorionic HCV genotype 1 infection. In two randomized, phase III, trials (PEARL-III and PEARL-IV), patients with chronic HCV genotype 1a (n=305) and HCV genotype 1b (n=419) infection with no evidence of cirrhosis

and who were not previously treated were given 12 weeks of the 3D regimen and RBV or the 3D regimen with placebo. Patients infected with genotype 1a achieved an SVR12 of 90.2% without RBV and 97.0% with RBV. Patients infected with HCV genotype 1b achieved an SVR12 of 99.0% without RBV and 99.5% with RBV.[121]

In the phase III randomized, controlled TURQUOISE-II trial, patients (n=380) with HCV genotype 1 infection and Child-Pugh class A cirrhosis were treated with either 12 or 24 weeks of the 3D regimen with RBV. Patients treated for 12 weeks achieved an SVR12 of 92%. Patients treated for 24 weeks had an SVR12 of 96%. These rates were superior to the estimated historical control rate of 47% achieved using telaprevir-based regimen.[122]

In the double-blind, phase III randomized controlled SAPPHIRE-II trial, patients (n=394) with chronic HCV genotype 1 infection and no cirrhosis, who were previously treated with IFN/RBV and had a relapse, a partial response, or a null response, were treated with the 3D regimen and RBV or matching placebos for 12 weeks. Patients receiving the 3D regimen achieved an SVR12 of 96% which was noninferior and superior to the historical control rate of 65% assumed with telaprevir-based treatment. Patients with prior relapse had an SVR12 of 95%; with prior partial response had an SVR12 of 100%; and with prior null response had an SVR12 of 95%.[123]

In the SAPPHIRE-I and SAPPHIRE-II trials, the most common adverse events reported in both the 3D and placebo arms were fatigue, headache, and nausea.[112] In SAPPHIRE-I, discontinuations due to adverse events were reported in 0.6% of patients given the 3D regimen or placebo.[113] In SAPPHIRE-II, discontinuations due to adverse events were reported in 1% of patients given the 3D regimen and no patients given placebo.[112] The 3D regimen is also expected have the same contraindications as ritonavir and RBV when these drugs are administered with the three direct-acting antivirals.[112]

Manufacturer and regulatory status: Gilead Sciences, Inc. (Foster City, CA), makes sofosbuvir. In December 2013, FDA approved sofosbuvir in combination with RBV for treating patients infected with HCV genotypes 2 or 3 and in combination with IFN/RBV for treating patients infected with HCV genotype 1 or 4. Sofosbuvir is also approved for treating patients co-infected with HIV or with hepatocellular carcinoma awaiting liver transplantation.[109,124] In February 2014, Gilead filed a new drug application with FDA for the once-daily, fixed-dose combination of sofosbuvir and ledipasvir, also made by the company, for treating chronic HCV genotype 1 infection in adults.[125] The fixed-dose combination had been granted breakthrough therapy designation by FDA in July 2013.[126] In May 2014, Janssen Research & Development, LLC, a unit of Johnson & Johnson (New Brunswick, NJ) submitted a supplemental new drug application to FDA for sofosbuvir in combination with its NS3/4A protease inhibitor simeprevir (Olysio™) for treating chronic HCV genotype 1 infection in adult patients naïve to treatment with advanced fibrosis and null responders with all stages of liver fibrosis.[127]

AbbVie (North Chicago, IL), in collaboration with Enanta Pharmaceuticals, Inc. (Watertown, MA), makes the direct-acting antiviral components of the 3D regimen.[128] In May 2013, the 3D regimen with and without RBV received breakthrough therapy designation from FDA for treating chronic HCV genotype 1 infection.[129] In April 2014, AbbVie filed a new drug application with FDA for the 3D regimen.[130] In June 2014, the company announced that the filing had been accepted by FDA and granted priority review.[131]

Diffusion and costs: According to a U.S.-based, online aggregator of prescription-drug prices, the retail cost of a 4-week supply of sofosbuvir is roughly $29,500 ($88,500 for a standard 12-week course).[132] If approved, the cost of a 12-week regimen of the fixed-dose combination sofosbuvir/ledipasvir could be about $100,000, according to one analyst's estimate.[133]

If approved for marketing, the 3D regimen could cost about $60,000 for 12 weeks of treatment, including rebates and discounts, according to another financial analyst's estimate.[134]

For benchmarking purposes, a 12-week treatment course of the protease inhibitor simeprevir is about $72,100.[135] A standard 12-week treatment regimen of the protease inhibitor telaprevir is about $77,100.[136] Boceprevir, also a protease inhibitor, costs about $1,820 per week of treatment with treatment duration ranging from 24 to 44 weeks depending on patient characteristics.[101,137] Thus, the cost of typical boceprevir therapy regimens ranges from about $43,680 to about $80,080. The cost of a 4-week supply of generic RBV (1,000 mg) is about $300.[138] The cost of a 4-week supply of IFN is about $3,300.[139]

Our searches of 11 representative, private, third-party payers that publish their coverage policies online found 6 payers that have policies providing coverage of sofosbuvir for treating HCV infections. Payers generally cover sofosbuvir as a specialty-tier drug requiring prior authorization and quantity limits for coverage.[140-145] If sofosbuvir/ledipasvir is approved for marketing, third-party payers will likely cover the combination as an IFN-free option for treating HCV genotype 1. However, third-party payers have started to demonstrate resistance against potentially unsustainable pricing for HCV treatment. Thus sofosbuvir/ledipasvir coverage could be contingent on the availability and price of other all-oral options such as the 3D regimen for treating HCV genotype 1 infections.[146]

The first quarter of sofosbuvir sales ending in March 2014 grossed $2.27 billion, far surpassing the second-largest drug launch ever, telaprevir, which grossed $1.56 billion in the first year.[147] In April 2014, UnitedHealth Group, Inc., announced that it spent more than $100 million on sofosbuvir during the drug's first quarter of availability. This was reportedly many times more than what the third-party payer expected to spend on the drug.[148] According to an analysis by Decision Resources Group, more than half of patients with chronic HCV genotype 1 infection were prescribed sofosbuvir by 3 months after launch. Also, nearly 20% of patients treated for HCV genotype 1 infection were prescribed simeprevir, the majority of which were prescribed the off-label combination of sofosbuvir and simeprevir with or without RBV, according to surveyed specialists.[149] Off-label prescribing of sofosbuvir/simeprevir has risen to 30% of specialists surveyed who reported having patients who were prescribed the combination.[149] In June 2014, Oregon Health Plan announced plans to exercise a special waver limiting member access to sofosbuvir and simeprevir based an analysis of cost and efficacy.[150] The plan estimates providing sofosbuvir alone for one-third of their 7,000 members with HCV would cost $196 million, doubling the insurer's system-wide drug spending. In 2013 the Plan spent $377M for pharmaceuticals for all of its 600K members. Oregon Health Plan is particularly sensitive to increases in pharmaceutical spending due to an agreed upon cap on the Payer's costs, beginning in 2012, in exchange for $1.9 billion in federal aid over five years.[150]

If the 3D regimen is approved for marketing and priced competitively, third-party payers will likely cover it to improve patient health outcomes and potentially seek more favorable pricing among emerging all-oral HCV therapies.[146]

Clinical Pathway at Point of This Intervention

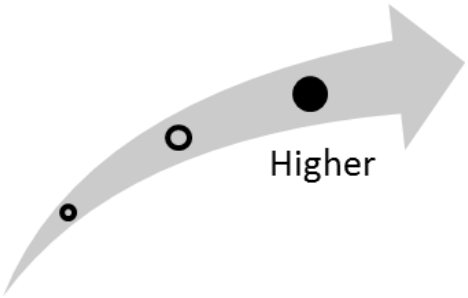
Patients who test positive for HCV and HCV RNA may be considered to have acute or chronic HCV infection, depending on the context. A patient who tests negative for antibodies to HCV and positive for HCV RNA might be chronically infected if immunosuppressed.[151] Subsequent HCV genotype testing is performed to determine the therapy regimen and likelihood of a positive clinical outcome.[151] Rest and hydration are typically prescribed. The American Association for the Study of Liver Diseases and the Infectious Diseases Society of America recommend the following:[152]

- For patients infected with HCV genotype 1, 4, 5, or 6 naive to treatment, who are eligible for IFN, daily sofosbuvir (400 mg) and weight-based RBV plus weekly peg-IFN for 12 weeks

- For patients infected with HCV genotype 1 who are naïve to treatment and who are not eligible to receive IFN, daily sofosbuvir (400 mg) plus simeprevir (150 mg), with or without weight-based RBV, for 12 weeks
- For patients infected with HCV genotype 2 or 3 naïve to treatment, daily sofosbuvir (400 mg) and weight-based RBV for 12 or 24 weeks, respectively, regardless of eligibility for IFN therapy
- For treatment-naïve patients infected with HCV genotype 4 who are not eligible for IFN therapy, daily sofosbuvir (400 mg) and weight-based RBV for 24 weeks

Sofosbuvir is indicated for use in combination with RBV for patients infected with HCV genotypes 2 or 3 and in combination with IFN/RBV for patients infected with genotypes 1 or 4. Sofosbuvir could also be used in combination with simeprevir, or other investigational HCV agents (such as ledipasvir or daclatasvir) for treating patients infected with genotype 1. The 3D regimen is intended for treating patients with chronic HCV genotype 1 infection.

Figure 5. Overall high-impact potential: interferon-free treatment of chronic hepatitis C infection



Overall, experts commenting on sofosbuvir and the 3D regimen regarded these interventions as having high potential to address significant unmet needs for HCV treatment. Both interventions used as part of an all-oral regimen to treat chronic HCV infection have been reported to have high efficacy that is well tolerated by patients who cannot tolerate IFN or do not want to use IFN, noted experts. Experts also thought that both oral treatment options also provide a shorter and simpler dosing regimen than telaprevir or IFN/RBV–based treatment options. The high efficacy of sofosbuvir thus far in HCV genotypes other than genotype 1 is also perceived by experts to be a significant advantage that increases the drug's potential impact. Additional research comparing the safety and efficacy of emerging all-oral treatment regimens would be particularly useful to prescribing physicians and patients, the experts noted. The high cost of sofosbuvir, the 3D regimen, and other emerging HCV therapies combined with the large population of patients requiring treatment could be unsustainable to the health care system. They thought that the financial strain on the health care system could lead payers to implement controversial coverage policies, such as treating only patients with liver disease with the all-oral regimens. 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, and health systems backgrounds commented on sofosbuvir[153-158] and six experts commented on the 3D regimen.[159-164] We have organized the expert comments according to the parameters on which they commented.

Unmet need and health outcomes: A large cohort of aging patients chronically infected with HCV exists in the United States, experts pointed out. Many of these patients have advanced liver disease or are otherwise unable to tolerate IFN-containing regimens and need new IFN-free

treatment options with improved efficacy that are well tolerated, the experts thought. Clinical cure of HCV infection is associated with improved patient health outcomes, the experts stated. Basing their opinion on available evidence, the experts all thought both agents are promising for treating chronic HCV genotype 1 infection. Sofosbuvir could also improve health outcomes for those with HCV genotypes that are not addressed by protease inhibitor therapy, some experts concluded.[156-158]

Data have been reported from multiple studies evaluating the 3D regimen that have consistently demonstrated high efficacy and tolerability in a variety of patient populations (e.g., treatment-naïve, treatment-experienced, cirrhosis, no-cirrhosis) infected with HCV genotype 1, noted experts. Multiple, ongoing studies with large patient populations were also encouraging, the experts noted.

Acceptance and adoption: Experts expect clinician and patient acceptance of sofosbuvir and the 3D regimen to be high because of their high efficacy, safety, and convenience shown so far. Although the high estimated cost of IFN-free therapy could to pose a barrier to diffusion for some patients and prescribers, the up-front cost is expected to be offset by cost savings to the health care system by preventing the need for additional treatment, HCV complications, and health monitoring in the future, some experts commented.[153,155,157,159,164] Treating patients with three oral drugs is already well accepted for HIV treatment, which should lead to increased clinician willingness to initiate HCV treatment with the 3D regimen, one clinical expert noted.[161]

Health care delivery infrastructure and patient management: IFN-free, all-oral treatment options might entice more patients to seek HCV testing and treatment, some experts thought.[156,159,161,164] Improved treatment outcomes could reduce hospitalizations from liver disease and ease the burden on infrastructure and staffing for HCV inpatient treatments, some experts stated, but other experts expected minimal disruptions to infrastructure and management with use of IFN-free treatment options compared with IFN-containing treatment options.

One clinical expert commenting on the 3D regimen anticipated a significant increase in new patients that would ultimately be brought under care for HIV through HCV testing initiatives. Additionally, this expert stated that treatment facilities could spend more time acquiring prior approval from payers than they did previously.[161]

Health disparities: The anticipated high cost of emerging IFN-free HCV therapies could provide possible barriers to treatment for patients such as by requiring preauthorizations or restrictions for coverage, the experts noted.[154,161,164] They thought that patients who are poor and uninsured, self-employed, or underinsured could be vulnerable to disparities. It is becoming increasingly common for middle-income individuals to be priced out of treatment with inadequate insurance and high copayments, making patients avoid or delay treatment, some experts noted.[161,164] However shorter, all-oral dosing could help patients at risk for health disparities complete the treatment course, one research expert noted.[159]

HIV/AIDS Intervention

OraQuick In-Home Rapid Test for Detection of HIV Infection

Unmet need: According to a study from the U.S. Centers for Disease Control and Prevention (CDC), about half of all new HIV infections occur from the approximate 16% of people living with HIV who are unaware of their infection.[165] Additionally, some HIV screening methods can take up to 2 weeks before patients are made aware of their HIV status.[166] Although an over-the-counter HIV test has been available since 1996, it requires that a blood sample be mailed to a laboratory for analysis and results are available the next business day at the earliest. A simple, rapid, in-home test, such as the OraQuick® In-Home HIV Test, that patients can interpret, might improve HIV-screening rates by increasing the privacy and confidentiality of testing, empowering individuals to make health decisions, and providing a more rapid assessment of HIV status without the need for individuals to follow up seronegative test results.[167] Increased screening could reduce HIV transmission rates and improve disease management through earlier treatment.[168,169]

Intervention: The OraQuick In-Home HIV Test is a rapid, home-based HIV test that is available without prescription, over the counter.[167] It is intended to improve HIV-screening rates in people at risk of HIV exposure by removing barriers to screening. The test provides easy access to first-line testing that is affordable, safe, simple, rapid, painless, and anonymous.[167] OraQuick is designed to detect HIV-specific antibodies found in a patient's saliva. The test kit includes a single-use testing device and a test tube containing testing reagent. The testing device is a lateral flow immunoassay with an integrated oral swab.

To initiate the test, people collect a saliva sample from along the gum line using the oral swab; they then place the swab end of the testing device in the test tube with reagent for 20 minutes.[167] For accurate results, people must not eat, drink, or use oral care products for at least 30 minutes before testing themselves.[170]

The testing device contains colloidal gold particles bound to protein A, which will bind antibodies from the saliva sample in solution.[171] The antibody-bound colloidal gold particles migrate along the device, which has two indicator lines towards the distal end. The first indicator line contains HIV antigen that binds the antibody-bound colloidal gold particles only if the saliva sample has antibodies against HIV.[167,171] Presence of HIV antibodies will lead to the generation of a reddish-purple color at the test line, indicating a qualitatively positive result. The second indicator line is an internal control that binds human immunoglobulin G to show that the test has been used properly and that antibodies are present in the sample.

The kit includes resources on HIV and HIV testing, including a hotline with 24-hour customer support to answer questions regarding testing and interpretation as well as referral to care if needed.[172] If a person tests negative for HIV and 3 months have passed since the last risk event, he or she is likely to be HIV negative.[173] If a person tests positive for HIV, followup is required at a health care facility at which infection must be confirmed by Western blot analysis.[166,173]

The OraQuick home test is predicated on an oral swab–based test that has been available to health care professionals since 2004.[174] Changes were made only to the packaging and instructions to create the home test version of the test; the manufacturer made no changes to the test device.[175]

Clinical trials: In a large clinical trial used to support regulatory filing individuals (n=5,662) of unknown HIV status underwent HIV screening in a three-visit process. At the first visit, blood was drawn for HIV laboratory testing. At the second visit, unobserved self-testing with the OraQuick In-Home HIV test was offered; next, testing occurred at a location of the individual's choosing. Finally, at the third visit, the individual provided self-interpreted results of the at-home testing and were provided with laboratory testing results. Ninety-six participants were included in the sensitivity analysis, of which 88 had true-positive results determined by self-test and lab result if

both gave positive results. Eight participants were determined to have false-negative results, reporting a negative self-test result and having a positive laboratory result. Sensitivity of self-testing was 91.67% (95% CI, 84.24% to 96.33%).

A total of 4,903 participants were included in the specificity analysis. Of these, 4,902 participants were determined to be have true-negative results because their self-test results and laboratory results were both negative. One subject was determined to have a false-positive self-test. Specificity was calculated to be 99.98% (95% CI, 99.89% to 100%).[175]

A behavioral study was conducted to determine whether ethnically diverse men who have sex with men (n=27) who engaged in risky behaviors (i.e., never or rarely used condoms, multiple sexual partners) would use the OraQuick In-Home HIV Test to screen potential sexual partners. Participants used home test kits before intercourse with about 100 partners in private and public spaces. Testing purportedly had high acceptability among participants representing ethnic minority populations. Ten individuals who were tested received a positive result; 7 HIV-positive individuals were potential sexual partners and 3 were acquaintances of the participants; 6 of the 10 individuals with a positive result were unaware of their status. No sexual intercourse occurred after positive tests results were received. Most participants expressed a strong desire to continue using the home test and to buy it freely.[176]

The manufacturer warns that the test should not be used to make decisions on behavior that may put one at increased risk for HIV.[177] As with any diagnostic test, the OraQuick In-Home HIV test has the potential to produce false-negative or false-positive results. False-negative HIV test results could have adverse consequences for the individual tested, such as delayed treatment for HIV, which could limit treatment efficacy. Additionally, false-negative results could result in unsuspected HIV transmission in cases in which behavior is altered on the basis of the negative HIV test result. Conversely, false-positive results could result in patient anxiety and wasted health care resources in responding to a positive result for an HIV-negative patient.

Manufacturer and regulatory status: OraSure Technologies, Inc. (Bethlehem, PA), makes the OraQuick In-Home HIV Test. In July 2012, FDA approved the test for over-the-counter sale directly to consumers. The test can detect antibodies to both HIV-1 and HIV-2.[172] The test is the first and so far only rapid over-the-counter test approved by FDA for detecting HIV or any other infectious disease.[172] The test became commercially available in the United States in October 2012.[178]

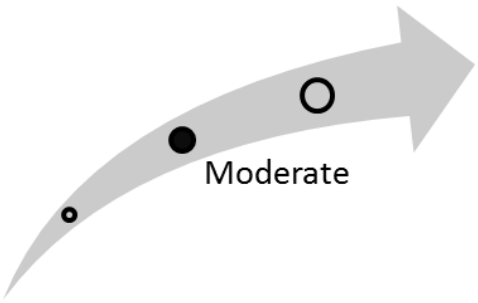
Diffusion and costs: The test costs about $40 when purchased directly from the manufacturer.[179] Our searches of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found that only Aetna lists a coverage policy for the HIV home test kits. Although Aetna covers physician-prescribed HIV testing, it "does not cover home HIV test kits that do not require a physician's prescription under any of its plans."[180] Most health plans do not cover over-the-counter health products.

Clinical Pathway at Point of This Intervention

CDC recommends testing for HIV at least once in individuals 13–64 years of age and annual testing for persons who engage in activities that put them at risk for infection, including sex (vaginal, oral, or anal) with multiple sex partners, sex with someone who is HIV positive or whose HIV status is unknown, sex between a man and another man, sharing needles or syringes (for illegal injected drugs or steroids), exchanging sex for money or drugs, or having a diagnosis of sexually transmitted infections or tuberculosis.[168,169] Testing should occur 3 months after a high-risk event to

ensure accurate detection of antibodies against HIV.[166,169] HIV tests performed in health care facilities can consist of HIV enzyme immunoassays that detect HIV antibodies present in blood, saliva, or urine. All positive HIV-test results must be confirmed with a followup test, such as Western blot, to rule out false-positive results. The OraQuick In-Home HIV Test could compete with the Home Access Express system, a home-based test that detects the presence of HIV antibodies in blood from a finger prick, which is placed on a sample card and mailed to a testing facility. The Home Access Express consumer calls a phone number to receive anonymous test results and counseling.[181]

Figure 6. Overall high-impact potential: OraQuick in-home rapid test for detection of HIV infection



Overall, experts commenting on this intervention thought the OraQuick rapid in-home HIV test has potential to meet a significant unmet need by increasing HIV-screening rates in patients who engage in high-risk behaviors but are reluctant to undergo HIV screening in clinics. In-home testing, thought experts, could improve screening rates in patients who can afford the $40 cost to purchase and perform testing. Experts stated that patients who know their HIV status are more likely to seek treatment and avoid high-risk behaviors, which could positively affect public health outcomes, although an increase in the number of patients seeking treatment from positive test results would be expected to increase demands on the system. Patients presenting to a clinic with a positive at-home result will require confirmatory testing and counseling, noted experts. 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, and health systems backgrounds, offered perspectives on this intervention.[182-187] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: The OraQuick in-home rapid test could fill a significant unmet need, increasing HIV detection rates by providing a private and convenient method of HIV testing and providing rapid results, the experts stated. OraQuick could fill the unmet need to increase HIV testing rates in three main populations: people who do not have access to the health care system, patients uncomfortable asking about HIV testing or who have physicians who do not ask the right questions of their patients, and people who want a high level of privacy, the experts noted. The experts agreed that the OraQuick in-home test appears to be accurate and that earlier HIV detection can bring patients into care earlier, which can improve health outcomes. They noted that patients who test positive are also more likely to modify their behavior, which could lower transmission rates. Some experts also suspect that the kit could be used frequently by some users to screen potential partners, which would be impractical with other screening methods.[182,184]

Acceptance and adoption: Clinicians are expected to accept the test as a simple method to increase HIV testing rates, noted experts. However, experts suspect that clinicians will want to confirm home results with laboratory testing before moving forward with treatment or counseling.

Patients are expected to prefer the privacy and convenience of home testing if the $40 per-test cost is not too high, the experts opined. Some experts thought that patients may use testing to screen partners before planned sexual encounters.[182,184] The test would less likely be used for screening partners before unplanned encounters, one research expert theorized.[182]

Health care delivery infrastructure and patient management: The experts thought diffusion of the OraQuick in-home test could affect patient management in a number of ways. Patients will be presenting to clinics, concerned about a positive HIV result that needs confirmation, the experts noted. These anxious patients could add to demands on facilities providing followup testing and HIV treatment, the experts thought. Some noted that additionally, patients with a positive OraQuick test result could present to clinic in an anxious state, which could have been mitigated with the counseling given before and after testing when the test is performed in a clinic.[185,187] Finally, an increase in the number of patients entering the system for HIV treatment could increase demands on facilities and staff at HIV clinics, experts noted.

Health disparities: The experts were divided on how OraQuick would affect health disparities. Some thought the $40 price could exclude individuals of low socioeconomic status from being tested, while providing a more convenient and anonymous option for patients with some access to health care.[182,186] However, other experts thought for some patients, the $40 test could cost less than having to interact with the health care system.[184,185,187]

Malaria Intervention

RTS,S/AS01 (Mosquirix) for Prevention of Malaria Caused by *Plasmodium falciparum*

Unmet need: Globally in 2010, an estimated 219 million people were infected with malaria and 660,000 people died from the disease, despite disseminated use of vector control with insecticide-treated bed nets and indoor residual spraying combined with intermittent prophylactic pharmacotherapy.[188,189] Travel to endemic areas (e.g., vacation, expatriation, military service) places people at risk of contact with infected mosquitoes.[190] Children, pregnant women, the elderly, and immunosuppressed individuals have the highest risk of mortality.[190,191] Vaccination against malaria parasites such as *Plasmodium falciparum*, the most deadly species of malaria parasite, could reduce the incidence of malarial disease in people living in or traveling to endemic areas.[190,192]

Intervention: RTS,S/AS01 is a vaccine designed to prevent malarial disease caused by the parasite *P. falciparum*.[193] The vaccine is a recombinant protein consisting of the central repeat and C terminal portions of the *P. falciparum* circumsporozoite protein fused to hepatitis B virus surface antigen, which is expressed in the yeast *Saccharomyces cerevisiae*.[188,194] Excess hepatitis B virus surface antigen is also expressed to form the vaccine construct into virus-like particles.[194] RTS,S/AS01 is formulated with the proprietary adjuvant, AS01, to increase immunogenicity. AS01 consists of liposomes with two immunomodulators: 3′-O-desacyl-4′-monophosphoryl lipid A (MPL) and *Quillaja saponaria* 21 (QS21). No licensed vaccines contain AS01.[193]

The *P. falciparum* circumsporozoite protein is thought to aid the parasite in hepatocyte entry.[192] RTS,S/AS01-induced immune responses are thought to provide protection by preventing sporozoites from invading hepatocytes during the short window of time in which sporozoites are in circulation or by attacking liver schizonts.[195] Thus, RTS,S/AS01 belongs to a class of vaccines known as pre-erythrocytic vaccines, which are intended to prevent the parasite from entering the bloodstream.

RTS,S/AS01 purportedly induces levels of anti-circumsporozoite antibodies that are much higher than those produced by repeated natural infection. However, no clear antibody threshold of protection is established.[195,196] RTS,S/AS01 is also purported to induce strong CD4+ T-cell responses characterized by the production of inflammatory cytokines, such as interferon gamma, which could contribute to killing liver schizonts.[195] Preclinical models suggested that protective synergy exists between antibody and cellular responses against malaria infection.[196]

RTS,S/AS01 is theorized by some investigators to reduce the risk of infection from each exposure, rather than conferring "all or nothing" protection to those taking the vaccine. Thus, vaccinated individuals could eventually experience malaria if the transmission rate is high enough. The vaccine is expected by investigators to have a greater impact on the incidence of the first or total episodes of clinical malaria than on the overall population experiencing disease. This hypothesis is supported by the available phase III data.[197] RTS,S/AS01 is administered in three intramuscular injections, monthly.[198]

Clinical trials: In a phase III, randomized controlled, double-blind trial, children (n=6,537) aged 6–12 weeks were given three doses of RTS,S/AS01 or meningococcal serogroup C conjugate vaccine as a control. The coprimary endpoints were vaccine efficacy against the first or only episode of clinical malaria during the 12 months after vaccination.[198] Vaccine efficacy was 30.1% (95% CI, 23.6% to 36.1%) against the first or only episode of clinical malaria in the intention-to-treat population up to 14 months after the first dose of vaccine. Vaccine efficacy was 31.3% (97.5% CI, 23.6% to 38.3%) against clinical malaria in the per-protocol population.[198] RTS,S/AS01 was 26.0% (95% CI, -7.4% to 48.6%) and 36.6% (95% CI, 4.6% to 57.7%) effective against severe malaria in the intention-to treat population and per-protocol populations, respectively.[198]

Children given RTS,S/AS01 had no differences in the frequency of serious adverse events compared with children given control vaccine. Children given RTS,S/AS01 were 99.7% seropositive for anti-circumsporozoite antibodies 1 month after administration of the third dose of vaccine.[198]

In another phase III, randomized, controlled, double-blind trial, children (n=6,000) aged 5–15 months or 6–12 weeks were given RTS,S/AS01 or a nonmalaria control vaccine. The primary endpoint of the analysis was vaccine efficacy against clinical malaria during the 12 months after vaccination.[199] Vaccine efficacy against clinical malaria was 50.4% (95% CI, 45.8% to 54.6%) in the intention-to-treat population and 55.8% (97.5% CI, 50.6% to 60.4%) in the per-protocol population in children aged 5–15 months, in the 14 months following the first dose of vaccine. Additionally, vaccine efficacy against severe malaria was 45.1% (95% CI, 23.8% to 60.5%) and 47.3% (95% CI, 22.4% to 64.2%) in the intention-to-treat and in the per-protocol populations, respectively. When both age groups were combined, vaccine efficacy against severe malaria was 34.8% (95% CI, 16.2% to 49.2%) in the per-protocol population with an average followup of about 11 months.

Children given RTS,S/AS01 had no differences in the frequency of serious adverse events compared with children given control vaccine. Generalized convulsive seizures were reported at a rate of 1.04 per 1,000 doses (95% CI, 0.62 to 1.64) in patients aged 5–15 months who were given RTS,S/AS01.[199]

According to one phase II study, RTS,S/AS01 demonstrated efficacy in the first year that waned over time and with increasing malaria exposure.[200] Additional studies are needed to determine the level of protection conferred by RTS,S and the optimal frequency of booster immunizations required to maximize the protective effects of the vaccine.[198,200]

Manufacturer and regulatory status: The RTS,S construct was created in 1987 by scientists working at GlaxoSmithKline, Middlesex, UK, in collaboration with the U.S. Walter Reed Army Institute of Research, Bethesda. MD.[192] In January 2001, GlaxoSmithKline and the PATH Malaria Vaccine Initiative (MVI), Washington, DC, with funding from the Bill & Melinda Gates Foundation to MVI, entered into a public-private partnership to develop an RTS,S-based vaccine for infants and young children living in regions endemic for malaria in sub-Saharan Africa.[192]

RTS,S/AS01 is in phase III development with longer-term protective efficacy results at 30 months after the third dose of vaccine expected to be available by the end of 2014.[201] These results are expected to be the basis of filings that could lead to regulatory approval by 2015.[202]

Although vaccines typically gain marketing approval only when they demonstrate efficacy greater than 90%, the World Health Organization has called for a first-generation malaria vaccine with 50% efficacy against serious disease by 2015, with second-generation vaccines providing at least 80% efficacy by 2025.[203]

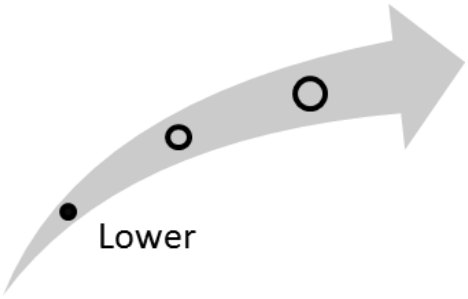
Diffusion: The manufacturer has pledged to sell the vaccine for 5% above the total costs of development. This margin will purportedly be used to fund additional research for tropical diseases.[202] Costs could be significantly higher for people in the developed world who plan to travel to endemic areas.

Countries endemic for malaria such as the African nation of Ghana, have started to develop a walking cold chain (controlling the temperature at which the vaccine is shipped and stored) to disseminate RTS,S/AS01, if approved for marketing, in conjunction with rotavirus and pneumococcal vaccines as part of the Expanded Programme on Immunization.[204]

Clinical Pathway at Point of this intervention

Malaria prevention efforts use insecticide-treated bed nets, residual spraying, personal mosquito repellant, and prophylactic use of antimalarial drugs. Patients with malaria are often treated with antimalarial agents including chloroquine, hydroxychloroquine, mefloquine, quinine sulfate, or a combination of atovaquone and proguanil.[205] RTS,S/AS01 is intended to prevent the incidence of malarial disease caused by infection with *P. falciparum* and would be used in combination with current prophylactic measures.[191]

Figure 7. Overall high-impact potential: RTS,S/AS01 (Mosquirix) for prevention of malaria caused by *Plasmodium falciparum*



Overall, experts commenting on this intervention noted a significant unmet need for protection against malarial disease for people living in or traveling to areas endemic for *P. falciparum*. The experts stated that 30% efficacy in children aged 6–12 weeks and 50% efficacy in children aged 5–17 months could significantly improve health outcomes. However, the experts noted that suboptimal efficacy and waning protection provide a need for further development of second-generation vaccines. RTS,S/AS01 is expected to reduce demands on malaria treatment facilities in endemic areas, the experts noted, but could require additional infrastructure investment for cold-chain management and patient followup for subsequent booster immunizations. 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, and health systems backgrounds, offered perspectives on this intervention.[206-211] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Malaria represents a serious health threat to people traveling to endemic areas for business, leisure, or military service as well as those who reside in endemic areas, the experts noted. Malaria treatment can be costly and lengthy; better preventative options such as vaccination are welcomed, the experts stated. Resistance to current prophylactic and treatment modalities by vector and parasite also increase the need for an effective vaccine, one research expert stated.[211] Additionally, global climate change could present a threat of malaria resurgence in the United States, as research has shown malaria prevalence to be significantly affected by climate, one research expert stated.[211]

A 50% reduction in clinical malaria among children and infants is a welcome advance, because the disease is so widespread in endemic areas, and vaccination could lead to a large reduction in the burden of disease and improved health outcomes, one clinical expert noted.[209] However, the waning vaccine efficacy observed reveals the need for additional studies to determine the frequency of booster immunizations needed to maximize protective efficacy, some experts noted.[206,209-211]

Acceptance and adoption: Clinicians are expected to widely accept a vaccine that can prevent 30% to 50% of clinical malaria caused by *P. falciparum*, thought the experts. They cited the World Health Organization's call for a malaria vaccine with 50% efficacy by 2015 and 80% efficacy by 2025 as contributing to acceptance of a vaccine with less than 90% efficacy, a typical cutoff for vaccine approval and acceptance.

Parents of children in areas endemic to malaria are expected by experts to accept a vaccine that can reduce the risk of malarial disease. However, adult patients at moderate risk of contracting malaria may not widely accept a vaccine that has shown a 30% reduction in disease if the vaccine is not covered by insurance or is perceived as expensive, one expert with a research perspective noted.[210]

Health care delivery infrastructure and patient management: Most experts agreed that vaccination with RTS,S/AS01 would impact health care infrastructure by reducing demands on facilities that treat malaria.[206-208,211] Experts thought that the vaccine will be administered with other childhood immunizations for pediatric patients, requiring minimal changes in patient management and infrastructure. In contrast, they noted, adults might need to make additional visits to a health care facility. Changes to current infrastructure and patient management would be needed for cold-chain management and could pose a barrier to diffusion, one clinical expert noted.[209] Additionally, the clinical expert cited the waning immunity of RTS,S/AS01 could require better management of patient records as well as increased patient visits and followup compared with current management protocols.[209]

Health disparities: Experts agreed that the manufacturer's pledge to sell the vaccine at a cost that is projected to be 5% above the total cost of development would reduce health care disparities globally. However, some experts noted that patients in developed counties are expected to pay more for the cost of developing the vaccine, which could be make the vaccine expensive in developed countries due to the limited patient base in those countries.[206,210,211]

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