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

Priority Area 09: Infectious Disease Including HIV/AIDS

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
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Contract No. HHSA290-2010-00006-C

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December 2014

Statement of Funding and Purpose

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

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

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

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Financial Disclosure Statement

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

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Suggested citation: ECRI Institute. AHRQ Healthcare Horizon Scanning System Potential High-Impact Interventions: Priority Area 09: Infectious Disease Including HIV/AIDS. (Prepared by ECRI Institute under Contract No. HHSA290-2010-00006-C.) Rockville, MD: Agency for Healthcare Research and Quality. December 2014. http://effectivehealthcare.ahrq.gov/index.cfm/

Preface

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

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the Institute of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

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

We welcome comments on this Potential High-Impact Interventions report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to: effectivehealthcare@ahrq.hhs.gov.

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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 November 4, 2014, in this priority area; and (3) we received five to seven sets of comments from experts between January 1, 2014, and November 13, 2014. (Fifty-three topics in this priority area were being tracked in the system as of November 4, 2014.) Five topics were deemed through expert comment processes to have potential for high impact. Three of these topics were in the June 2014 report; two new topics added to this report are daclatasvir (Daklinza®) for treating chronic hepatitis C virus (HCV) infection, and the combination pill ledipasvir/sofosbuvir (Harvoni™), also for treating chronic HCV infection. The following five topics in the June 2014 Potential High-Impact Interventions report are not included in this report because they were archived from the system:

- The topic "Antimicrobial copper surfaces in the intensive care unit for preventing hospital-acquired infections" was archived after being tracked in the Healthcare Horizon Scanning System since July 2011. We consider this intervention to be diffused; it is not subject to U.S. Food and Drug Administration (FDA) approval.
- The topic "Fecal microbiota transplantation for treating recurrent *Clostridium difficile* infection" was archived after being tracked in the system since April 2012. We consider this intervention to be diffused; FDA has chosen to exercise enforcement discretion for the procedure, allowing it to diffuse.
- The topic "OraQuick in-home rapid test for detection of HIV infection" was archived after being track in the system for 2 years after the October 2012 FDA approval.
- The topic "Retrofitted private intensive care rooms to reduce hospital-acquired infections" was archived after being tracked in the system since December 2011; we believe it has diffused.
- The topic "RTS,S/AS01 (Mosquirix) for prevention of malaria caused by *Plasmodium falciparum*" was archived based on expert comments stating the malaria vaccine has low relevance for patients in the United States who are not traveling to endemic areas. Waning efficacy, safety concerns, and poor risk-to-reward ratio for patients in the United States were cited by experts as limiting impact of the intervention.

Additionally, two new topics were excluded based on expert comments. The topic "Vaccine (PXVX0200) for prevention of cholera" was deemed low impact based on a limited unmet need in the United States (expected to be used only by some international travelers and aid workers). The topic "Computer-tablet-based kiosks to facilitate HIV self-testing of patients in emergency departments" was deemed by experts to not be high impact because of poor expected utilization by emergency departments and privacy concerns (i.e., the kiosks are used only to screen for HIV; oral screening would occur in a public place based on responses to a questionnaire regarding HIV risk factors), and lack of linkage to followup care.

For this report, we aggregated related topics for summary and discussion (i.e., individual drugs into a class). We present two summaries of five 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. *Daclatasvir (Daklinza) for treatment of chronic hepatitis C virus infection	High
2. *Ledipasvir and sofosbuvir (Harvoni) for treatment of chronic hepatitis C virus infection	High
3. * Ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets (Viekira Pak) for treatment of chronic hepatitis C virus infection	High
4. RTS,S/AS01 (Mosquirix) for prevention of malaria caused by *Plasmodium falciparum*	Prior high impact (June 2014) topic; archived on basis of new expert comments finding no potential for high impact
5. * Sofosbuvir (Sovaldi) for treatment of chronic hepatitis C virus infection	High
6. Tablet-based kiosks to facilitate HIV self-testing of patients in emergency departments	No high-impact potential; archived on basis of expert comments
7. Vaccine (PXVX0200) for prevention of cholera	No high-impact potential; archived on basis of expert comments
8. * Xpert MTB/RIF Test for simultaneous detection and drug-sensitivity testing of *Mycobacterium tuberculosis*	Moderately high

Discussion

Hepatitis C Virus Infection

HCV is the primary cause of death from liver disease and the leading cause for liver transplantation in the United States. According to a Centers for Disease Control and Prevention (CDC) report issued in June 2014, "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 baby boomers. From 45% to 85% of infected people are unaware they are infected and can potentially transmit the disease. Additionally, HCV is common to patients with HIV, complicating treatment for these medically vulnerable patients. Of the 1 million people with chronic HIV infection in the United States, about 50,000 also have chronic HCV infection. Some calculations suggested that HCV-related mortality would 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 research has led to many HCV drugs in development and to new HCV 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 simply administered, all-oral, once-daily interferon alfa (IFN)-free regimens that can be completed within 8–12 weeks—a shorter time frame than previous treatments and one that does not require injections. 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 within the past year for treating one of six HCV genotypes—genotype 1. The drugs are to be used in combination with IFN and ribavirin (RBV). Sofosbuvir was also approved for treating genotype 4 in combination with IFN/RBV, and even more importantly, as the first IFN-free treatment option with RBV for treating genotypes 2 or 3.

Sofosbuvir was also the first direct-acting antiviral (DAA) agent approved for treating patients co-infected with HIV or awaiting liver transplantation. In October 2014, a new sofosbuvir drug combination drug was approved (Harvoni; Gilead Sciences) that does not require IFN or RBV as part of the regimen. It is a fixed-dose combination of ledipasvir and sofosbuvir for treating genotype 1 infection and is the first IFN/RBV-free regimen on the market. Also in December 2014, Viekira Pak™ (AbbVie Inc., North Chicago, IL) was approved for treating genotype 1 infection.

Physician surveys reported that many hepatologists had been "warehousing" patients, waiting for effective, better tolerated, all-oral therapies to be available before initiating treatment. Some clinicians were also treating patients off-label with sofosbuvir and simeprevir before the November 2014 approval of their combined use. Clinicians based their off-label decisions 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.

These new drugs are all costly, and although payers have signaled resistance to the high prices, and particularly off-label use, our searches revealed that payers are covering these novel regimens (including sofosbuvir and simeprevir) as specialty-tier drugs requiring prior authorization and quantity limits. Some payers limit treatment to patients with advanced liver fibrosis (stage 3 and 4) or compensated liver disease. 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 Bristol-Myers Squibb, and Merck & Co., Inc. The Merck regimen is too early in development to obtain expert opinion. However, four topics for which data were available and for which we sought expert comment emerged as having potential for high impact: sofosbuvir (Sovaldi), ledipasvir/sofosbuvir (Harvoni), daclatasvir (Daklinza), and ombitasvir/paritaprevir/ritonavir and dasabuvir (Viekira Pak).

Interferon-free Regimens for Treating Chronic Hepatitis C Infection

- **Key Facts:** The HCV treatment landscape changed in May 2011 when FDA approved the first NS3/4a protease inhibitors boceprevir and telaprevir for use in combination with IFN and RBV for treating chronic HCV genotype 1 infection. Protease inhibitors were shown to improve cure rates for genotype 1 infection, compared with IFN and RBV alone, but up to half of patients are unable to tolerate any IFN-containing treatment regimen. Thus, 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 four novel IFN-free options: Sofosbuvir for treating chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection; ledipasvir/sofosbuvir for treating HCV genotype 1 infection, daclatasvir for treating genotype 1, 2, 3, 4, 5, or 6 infection, and ombitasvir/paritaprevir/ritonavir and dasabuvir (Viekira Pak) for treating chronic genotype 1 infection.

Sofosbuvir: This 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 trials, sofosbuvir has been administered orally, once daily for 12 or 24 weeks in combination with RBV for treating HCV genotype 2 or 3, and with RBV and IFN for treating genotypes 1, 4, 5, or 6 in patients who have had no prior treatment. Sofosbuvir has also been studied in combination with other DAA agents and against multiple genotypes. Combined with the drug ledipasvir, which inhibits activity of the HCV NS5A protein, this regimen offers the first all-oral IFN- and RBV-free treatment option for chronic HCV genotype 1 infection. The fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) can be administered for 8, 12, or 24 weeks depending on HCV RNA level, treatment history, and cirrhosis status.

Sofosbuvir and RBV regimens: In phase III trials, patients infected with HCV genotypes 2 and 3 who had no prior treatment and were given sofosbuvir and RBV achieved SVR12 rates of 93% and 85%, respectively. Treatment-naïve patients with chronic HCV genotype 1 infection receiving 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. The most common side effects reported for sofosbuvir and RBV are diarrhea, 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.

Sofosbuvir in combination with IFN/RBV: Preliminary data also suggest sofosbuvir could be effective in preventing HCV reinfection in liver transplant patients. In December 2013, FDA approved sofosbuvir in combination with IFN/RBV for treating 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.

Ledipasvir/sofosbuvir with or without RBV regimens: Treatment-naïve patients with chronic HCV genotype 1 infection achieved more than 90% SVR12 rates with fixed-dose ledipasvir/sofosbuvir with or without RBV. Eight weeks of ledipasvir/sofosbuvir therapy was noninferior to 12 weeks of ledipasvir/sofosbuvir 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 ledipasvir/sofosbuvir with or without RBV for 12 or 24 weeks. The most common side effects reported for ledipasvir/sofosbuvir are diarrhea, dizziness, fatigue, headache, insomnia, and nausea.

In October 2014, FDA approved ledipasvir/sofosbuvir for treating patients infected with HCV genotype 1. Additionally the drug's prescribing information states that 8 weeks of ledipasvir/sofosbuvir therapy could be considered for patients with HCV RNA of less than 6 million IU/mL who have received no prior treatment and do not have cirrhosis.

Sofosbuvir in combination with simeprevir: In November 2014, FDA granted Janssen Research & Development marketing approval for its NS3/4A protease inhibitor simeprevir

(Olysio) in combination with sofosbuvir for treating chronic HCV genotype 1 infection in adults who have had no prior treatment or who have had treatment but do not have cirrhosis.

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. The cost of the fixed-dose combination ledipasvir/sofosbuvir ranges from about $103,000 to $111,000 for 12 weeks or $68,000 to $74,000 for 8 weeks, depending on the pharmacy and geographic location. 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 9 payers that have policies providing coverage of sofosbuvir and 5 payers that have policies providing coverage of ledipasvir/sofosbuvir, typically as a specialty tier drug requiring prior authorization and quantity limits.

The cost of sofosbuvir remains an issue. Sofosbuvir sales in the third quarter of 2014 grossed $7.3 billion, far surpassing the launch of telaprevir (Incivek), which grossed $1.56 billion in the first year. Telaprevir's manufacturer, Vertex Pharmaceuticals, withdrew the drug from the market in September 2014 because of low sales. In April 2014, the insurance company UnitedHealth Group, Inc., announced it had paid more than $100 million for sofosbuvir during the drug's first quarter of availability, far exceeding what the payer expected to spend. In June 2014, another insurer, Oregon Health Plan, announced plans to exercise a special waver limiting member access to sofosbuvir and simeprevir based an analysis of cost and efficacy.

Daclatasvir: Daclatasvir is an HCV NS5A inhibitor under study in multiple treatment settings in combination with both FDA-approved and investigational DAAs. For example, daclatasvir is being evaluated with the protease inhibitor asunaprevir and nonnucleoside polymerase inhibitor BMS-791325 as part of an oral, fixed-dose, three-DAA regimen for treating patients with HCV genotype 1 infection. Additionally, daclatasvir is being studied in combination with sofosbuvir for treating patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection.

Daclatasvir/asunaprevir regimen: In a phase III trial, previously untreated patients given a combination of daclatasvir/asunaprevir for 24 weeks achieved an SVR12 rate of 90%. Patients who did not achieve an SVR with previous IFN-based therapy and patients unable to tolerate IFN-based therapy achieved SVR12 rates of 82% after 24 weeks of daclatasvir/asunaprevir. SVR12 rates for patients with cirrhosis who were treated with daclatasvir/asunaprevir were 84%. This combination is not yet FDA approved. Although the manufacturer is not pursuing marketing approval for a dual regimen containing asunaprevir, studies of the dual regimen suggest daclatasvir could be used in combination with a second-generation protease inhibitor, such as simeprevir.

Daclatasvir/sofosbuvir: In a phase II, open-label randomized controlled trial, patients with chronic HCV genotype 1, 2, or 3 infection were treated with daclatasvir and sofosbuvir orally, once daily, with or without RBV for 12 or 24 weeks. The SVR12 rate for patients with genotype 1 or 2 infection given daclatasvir/sofosbuvir for 24 weeks was higher than 90%. Patients with genotype 3 infection treated with daclatasvir/sofosbuvir for 24 weeks achieved SVR12 rates of 89%. High SRV12 rates were observed among patients who received RBV and patients who did not. The most common adverse events observed in patients given daclatasvir and sofosbuvir were fatigue, headache, and nausea. This combination is not yet FDA approved.

As the HCV treatment landscape continues to evolve rapidly, daclatasvir is being developed for use in multiple settings. In February 2014, FDA granted daclatasvir/asunaprevir breakthrough therapy status for treating chronic HCV genotype 1b infection. In April 2014, the drug's manufacturer, Bristol-Myers Squibb, New York, NY, submitted a new drug application (NDA) to FDA for this combination and indication and for daclatasvir in combination with other DAAs for treating other HCV genotypes. However, in October 2014, the company retracted the submission for daclatasvir/asunaprevir because an indication for treating only HCV genotype 1b would place the combination poorly in the U.S. market for HCV treatments. The NDA submission for daclatasvir in combination with other DAAs (including sofosbuvir) for treating various HCV genotypes is still pending with FDA. The company anticipates submitting an NDA for the fixed-dose three DAA regimen in the first quarter of 2015. No cost information is available for daclatasvir at this time. If shown to be safe and effective and priced competitively, the drug is expected to be covered by third-party payers and also may force manufacturers of other regimens to lower the cost.

Viekira Pak: The Viekira Pak (AbbVie, North Chicago, IL, and Enanta Pharmaceuticals, Inc., Watertown, MA) consists of co-formulated NS5A inhibitor ombitasvir (ABT-267), boosted protease inhibitor paritaprevir (ABT-450) and ritonavir, and the nonnucleoside polymerase inhibitor dasabuvir (ABT-333), which is administered separately. The 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. Two ombitasvir/paritaprevir/ritonavir (12.5/75/50 mg) tablets are taken once daily (in the morning) and one dasabuvir (250 mg) tablet is taken twice daily (morning and evening) for 12 weeks with RBV. Patients with HCV genotype 1a infection with cirrhosis require 24 weeks of therapy. Patients with HCV genotype 1b infection without cirrhosis do not require RBV.

The Viekira Pak, 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 and no evidence of cirrhosis achieved SVR12 rates of more than 90% when given the Viekira Pak in combination with RBV or the Viekira Pak with placebo. Patients with HCV genotype 1 infection and Child-Pugh class A cirrhosis achieved SVR rates of more than 90% whether given 12 or 24 weeks of the Viekira Pak and RBV. These rates were superior to an estimated historical control rate achieved with a telaprevir-based regimen. Treatment with the Viekira Pak 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. In the SAPPHIRE-I trial, the most common adverse reactions reported in 10% or more of patients taking the Viekira Pak were asthenia, diarrhea, insomnia, nausea, and pruritus.

On December 19, 2014, FDA granted the Viekira Pak marketing approval for treating patients with chronic HCV genotype 1 infection, including those with compensated cirrhosis. According to the manufacturer the drug will cost about $83,319 for 12-weeks of treatment. The Viekira Pak is expected to be covered by third-party payers and also may force manufacturers of other regimens to lower their prices. At least one pharmacy benefit manager, Express Scripts, has agreed to make the Viekira Pak the required treatment regimen, for its members with chronic HCV genotype 1 infection in exchange for a steep discount from the manufacturer. Express Scripts' national preferred formulary is used by many employers and covers about 25 million people.

- **Key Expert Comments:** Overall, experts commenting on all the above regimens considered these interventions to have very high potential to address significant unmet needs for HCV treatment. Interventions used for all-oral HCV treatment have been reported in trials to show high efficacy and to be well tolerated by patients who cannot tolerate IFN or do not want to use it. These interventions also provide shorter and simpler dosing regimens than current treatment options, and that is expected to improve patient adherence and outcomes. The high efficacy of sofosbuvir and sofosbuvir in combination with daclatasvir observed thus far in HCV genotypes other than genotype 1 is also perceived to be a significant advantage that will increase the drugs' 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 emerging HCV therapies combined with the large population of patients requiring treatment (i.e., more than $200 billion to treat all patients who are thought to currently have chronic HCV infection in the United States) 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.
- **High-Impact Potential:** High

Tuberculosis

According to CDC, 9,582 cases of tuberculosis (TB) were reported in the United States in 2013, a rate of 3.0 cases per 100,000 people. In 2011, 9.2% of TB cases were resistant to the first-line treatment isoniazid, and 1.3% were resistant to both isoniazid and rifampin, the drug most commonly used in conjunction with isoniazid. Additionally, the proportion of reported primary multidrug-resistant TB cases occurring in foreign-born individuals increased from 30.8% (149 of 484) in 1993 to 89.5% (85 of 95) in 2013. Nucleic acid-based TB testing has been commercially available in the United States for almost two decades and has been shown to have high diagnostic accuracy and provide additional benefit compared with empirical TB treatment. CDC recommends routine use of nucleic acid-based testing to guide initial management of patients suspected of TB. However, results take weeks to obtain and a method that delivers quicker, accurate results is needed.

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 are untreated or may be placed on ineffective therapies (i.e., therapies to which the strain is resistant), 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 detecting 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 $40, and drug susceptibility testing can add another $102. 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. Additionally Davis et al. (2014) concluded Xpert MTB/RIF could greatly reduce the frequency and magnitude of unnecessary empiric treatment, contact investigation, and housing in patients suspected of active pulmonary TB compared with standard sputum culture testing. 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.
- **High-Impact Potential:** Moderately high

Hepatitis C Virus Infection Interventions

Interferon-Free Regimens for Treating Chronic Hepatitis C Virus Infection

Unmet need: The landscape of hepatitis C virus (HCV) infection treatment changed in May 2011 when the U.S. Food and Drug Administration (FDA) approved the first NS3/4a protease inhibitors boceprevir and telaprevir for use in combination with interferon (IFN) and ribavirin (RBV) for treating chronic HCV genotype 1 infection.[1,2] 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,[1,2] but up to half of patients are unable to tolerate any IFN-containing treatment.[3] Also, protease inhibitors are associated with significant side effects including anemia and severe rash.[4] 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.[3]

Intervention: Four novel IFN-free options are presented in this section: ledipasvir/sofosbuvir (Harvoni™), for treating HCV genotype 1 infection; sofosbuvir (Sovaldi®) for treating chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection; daclatasvir (Daklinza®) for treating HCV genotype 1, 2, 3, 4, 5, or 6 infection; and ombitasvir/paritaprevir/ritonavir and dasabuvir (Viekira Pak™) for treating chronic HCV genotype 1 infection.

Sofosbuvir-containing regimens: Sofosbuvir is an FDA-approved uridine nucleotide analog polymerase inhibitor in phase III trials for treating chronic HCV infection.[4,5] 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.[4] Nucleot(s)ide analogs such as sofosbuvir are thought to have broader efficacy against different HCV genotypes and a higher barrier to viral resistance than nonnucleot(s)ide polymerase inhibitors, which function via allosteric inhibition.[4] Sofosbuvir has been investigated in combination with a number of investigational agents. It has also been approved as part of a fixed-dose combination with the drug ledipasvir, a drug that inhibits activity of the HCV NS5A protein, providing the first all-oral treatment that eliminates the need for IFN or RBV in patients with chronic HCV genotype 1 infection.[6] 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.[7,8] 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.[9] Fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) is administered for 12 weeks in patients who have chronic HCV genotype 1 infection with or without cirrhosis who are naïve to treatment or without cirrhosis who are treatment experienced.[10] Treatment-experienced patients with cirrhosis are given ledipasvir/sofosbuvir for 24 weeks.[10] Additionally the drug's prescribing information states that patients who are naïve to treatment, without cirrhosis, and who have pretreatment HCV RNA less than 6 million IU/mL could be considered for 8 weeks of therapy,[10] which could comprise between 35% to 40% of individuals infected with HCV genotype 1, according to the manufacturer.[11]

Daclatasvir-containing regimens: Daclatasvir is an investigational HCV NS5A inhibitor.[12] The drug purportedly has a low drug-drug interaction profile, which could support its use in patients with comorbidities.[12] Daclatasvir (30 or 60 mg) is being investigated in multiple treatment settings in combination with both FDA-approved and investigational DAAs. For example, daclatasvir (30 mg) is being evaluated with asunaprevir (200 mg) and BMS-791325 (75 mg), administered twice daily, as part of an oral, fixed-dose, three-DAA regimen for treating patients with HCV genotype 1 infection.[13] Asunaprevir is a NS3/4a protease inhibitor and BMS-791325 is an investigational

nonnucleoside polymerase inhibitor.[14,15] The HCV NS3 protease and its essential cofactor, NS4A, cleave viral polyproteins, allowing assembly of functional particles.[16] Additionally, daclatasvir (60 mg) is being studied in combination with sofosbuvir (400 mg) for treating patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection.[17]

The Viekira Pak: This consists of the NS5A inhibitor ombitasvir (ABT-267), the boosted protease inhibitor paritaprevir (ABT-450)/ritonavir, and the nonnucleoside polymerase inhibitor dasabuvir (ABT-333). The Viekira Pak was designed to optimize sustained viral response (SVR) rates across different patient populations by targeting three processes that are essential for HCV replication.[16,18] Two ombitasvir/paritaprevir/ritonavir (12.5/75/50 mg) tablets are taken once daily (in the morning) and one dasabuvir (250 mg) tablet is taken twice daily (morning and evening) for 12 weeks with RBV.[19] Patients with HCV genotype 1a infection with cirrhosis require 24 weeks of therapy. Patients with HCV genotype 1b infection without cirrhosis do not require RBV.[19]

Sofosbuvir 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% had 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 or 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.[20]

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 ledipasvir/sofosbuvir, once daily, for 8 weeks with or without RBV, or ledipasvir/sofosbuvir without RBV for 12 weeks. Patients treated with ledipasvir/sofosbuvir with or without RBV for 8 weeks had SVR12 rates of 94% and 93%, respectively. Patients treated with ledipasvir/sofosbuvir for 12 weeks had an SVR12 of 95%. Eight weeks of ledipasvir/sofosbuvir therapy was noninferior to 12 weeks of ledipasvir/sofosbuvir therapy.[21]

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 ledipasvir/sofosbuvir, once daily, with or without RBV or 24 weeks of ledipasvir/sofosbuvir with or without RBV. Twenty percent of patients in the study had liver cirrhosis. The SVR12 rate for patients treated with ledipasvir/sofosbuvir for 12 weeks with or without RBV was 94% and 96%, respectively. Patients treated with ledipasvir/sofosbuvir for 24 weeks with or without RBV achieved an SVR of 99% in both groups.[22]

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.[23]

In studies in which patients were given sofosbuvir and RBV, the most common side effects reported were dizziness, fatigue, headache, insomnia, and nausea.[24]

The most common adverse reactions reported in 5% or more of patients taking ledipasvir/sofosbuvir for 8, 12, or 24 weeks were diarrhea, fatigue, headache, insomnia, and nausea.[10]

Fewer than 1% of patients in the ION trials discontinued treatment due to treatment-emergent adverse events.[10]

Daclatasvir clinical trials: Daclatasvir has been studied in clinical trials in patients infected with various HCV genotypes and in varied treatment regimens. Here we provide some recent data from daclatasvir demonstrating the emerging potential of the drug in HCV care.

In the phase III, double-blind, randomized controlled HALLMARK-Dual trial, patients (n=747) with chronic HCV genotype 1b infection who were treatment-naïve (n=205) received daclatasvir (60 mg) once daily and asunaprevir (100 mg) twice daily or placebo (n=102) for 12 weeks. Patients receiving daclatasvir/asunaprevir continued treatment for 24 weeks, while patients receiving placebo entered another trial evaluating the drug combination. Patients ineligible or unable to take IFN/RBV (n=235), and patients who did not achieve an SVR with previous IFN-based therapy (n=205) also received the same dosages of daclatasvir/asunaprevir for 24 weeks. The SVR12 rate for previously untreated patients given daclatasvir/asunaprevir for 24 weeks was 90%. Patients who did not achieve an SVR with previous IFN-based therapy who were treated with daclatasvir/asunaprevir for 24 weeks achieved an SVR12 rate of 82%. Patients who were ineligible or intolerant to IFN/RBV who were treated with daclatasvir/asunaprevir for 24 weeks achieved an SVR of 82%.[25] SVR12 rates for patients with and without cirrhosis who were treated with daclatasvir/asunaprevir were 84% and 85%, respectively.[25]

In a phase II, open-label, randomized trial, patients (n=211) with chronic HCV genotype 1, 2, or 3 infection were treated with daclatasvir (60 mg) and sofosbuvir (400 mg) orally, once daily, with or without RBV for 12 or 24 weeks.[26] Patients with HCV genotype 1 infection who were not previously treated were given daclatasvir/sofosbuvir with or without RBV for 12 or 24 weeks. Patients infected with HCV genotype 1 who had previous virologic failure with telaprevir or boceprevir in combination with IFN/RBV were given daclatasvir/sofosbuvir with or without RBV for 24 weeks. Patients infected with HCV genotype 2 or 3 were given daclatasvir/sofosbuvir with or without RBV for 24 weeks. The SVR12 rate for previously untreated patients given daclatasvir/sofosbuvir for 24 weeks was 98%. Patients who did not achieve an SVR with previous protease inhibitor therapy who were treated with daclatasvir/sofosbuvir for 24 weeks achieved an SVR12 rate of 98%. Patients with genotype 2 or 3 infection who were treated with daclatasvir/sofosbuvir for 24 weeks achieved SVR12 rates of 92% and 89%, respectively. High SRV12 rates were observed among patients who received RBV and patients who did not receive RBV (94% and 98%, respectively).[26]

In the HALLMARK-Dual study, headache was the most common adverse event reported (24% to 25%) in patients taking daclatasvir and asunaprevir. Discontinuation rates due to adverse events were 1% to 3%. Serious adverse events rates were reported to be 5% to 7%. No clinically meaningful differences were observed in the frequencies of serious adverse events, adverse events leading to discontinuation, or grade 3/4 elevations in liver enzymes in patients with or without cirrhosis. All grade 3/4 liver enzyme elevations observed were resolved after discontinuing treatment, and no deaths occurred.[25] The most common adverse events observed in patients given daclatasvir and sofosbuvir were fatigue, headache, and nausea.[26]

Viekira Pak clinical trials: The Viekira Pak, 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 Viekira Pak for treating chronic 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 Viekira Pak and RBV or the Viekira Pak with placebo. Patients infected with genotype 1a achieved an SVR12 of 97.0% with RBV and 90.2%

without RBV. Patients infected with HCV genotype 1b achieved an SVR12 of 99.0% without RBV and 99.5% with RBV.[27]

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 Viekira Pak 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.[28]

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 Viekira Pak and RBV or matching placebos for 12 weeks. Patients receiving the Viekira Pak 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%.[29]

In the SAPPHIRE-I trial, the most common adverse reactions reported in 10% or more of patients taking the Viekira Pak were asthenia, diarrhea, insomnia, nausea, and pruritus. No moderate or severe adverse events occurred more frequently in patients taking the Viekira Pak than those taking placebo.[30] The Viekira Pak is also expected have the same contraindications as ritonavir and RBV when these drugs are administered with the three direct-acting antivirals (DAAs).[18]

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.[9,31] In October 2014, FDA approved ledipasvir/sofosbuvir for treating patients infected with HCV genotype 1.[6] In November 2014, FDA granted Janssen Research & Development marketing approval for its NS3/4A protease inhibitor simeprevir (Olysio™) in combination with sofosbuvir for treating chronic HCV genotype 1 infection in adults naïve to treatment or treatment experienced who do not have cirrhosis.[32,33]

Bristol-Myers Squibb, New York, NY, is developing daclatasvir. The HCV treatment landscape is changing rapidly, and daclatasvir is being developed for use in multiple settings. In February 2014, FDA granted the combination of daclatasvir and asunaprevir breakthrough therapy designation for treating patients with chronic HCV genotype 1b infection.[34] In April 2014, the company submitted a new drug application (NDA) to FDA for daclatasvir in combination with asunaprevir for treating patients with chronic HCV genotype 1b infection, as well as for daclatasvir in combination with other DAAs for treating other HCV genotypes.[12] However, in October 2014, the company announced it would no longer seek approval of daclatasvir in combination with asunaprevir because the combination was intended for patients infected with HCV genotype 1b, which placed the combination poorly in the treatment landscape in the United States;[35] the manufacturer continues to pursue an indication for daclatasvir in combination with other DAAs such as sofosbuvir for treating various HCV genotypes.[12,35]However, on November 25, 2014, FDA issued a complete response letter to the company requesting additional data for daclatasvir in combination with other DAAs for treating chronic HCV infections. The company is in discussions with FDA about the scope of the data required.[36] In 2013, the investigational all-oral 3DAA regimen (daclatasvir/asunaprevir/BMS-791325) received a breakthrough therapy status from FDA.[37] The company anticipates submitting an NDA for the fixed-dose 3DAA regimen to FDA in the first quarter of 2015.[12]

AbbVie, North Chicago, IL, in collaboration with Enanta Pharmaceuticals, Inc., Watertown, MA, makes the Viekira Pak.[19] In December 2014, FDA approved the Viekira Pak for treating patients with chronic HCV genotype 1 infection, including those with compensated cirrhosis.[38]

Diffusion and costs: Sofosbuvir: According to a U.S.-based, online aggregator of prescription-drug prices, GoodRx, the retail cost of a 4-week supply of sofosbuvir is roughly $29,500 ($88,500 for a standard 12-week course).[39] The total cost of 12 weeks of sofosbuvir and IFN/RBV, which would be required to treat HCV genotype 1 or 4 infection, is about $99,300.[39-41] The cost of a 12-week regimen (three 30-day prescription fills) of ledipasvir/sofosbuvir is about $103,750.[42] The cost of 8 weeks of ledipasvir/sofosbuvir (two 30-day prescription fills) is about $69,160. For patients infected with HCV genotype 2 or 3 who are naïve to treatment, daily sofosbuvir and weight-based RBV for 12 or 24 weeks costs about $89,400 and $178,800, respectively.[39,40] Patients with HCV genotype 4 infection who are not eligible for IFN therapy can also be treated with daily sofosbuvir and weight-based RBV for 24 weeks, which costs about $178,800 per patient.[39,40,43]

Daclatasvir: Our searches were unable to find information regarding the potential cost of daclatasvir.

Viekira Pak: According to the manufacturer the drug will cost $83,319 for 12 weeks of treatment.[44]

For benchmarking purposes, treating HCV genotype 1 infection with the protease inhibitor simeprevir for 12 weeks and concomitant IFN/RBV followed by IFN/RBV for an additional 12–36 weeks, depending on the patient's response,[45] costs from about $93,700 to $115,300 per treatment course.[40,41,46] Additionally, the total cost of administering a boceprevir-based regimen ranges from about $68,880 to $123,280.[40,41,47]

For benchmarking purposes, patients with HCV genotype 2 or 3 can be treated with 24 weeks of IFN/RBV, costing about $21,600, and patients infected with HCV genotype 4 can be treated with 48 weeks of IFN/RBV, costing about $43,200.[40,41,48]

Our searches of 11 representative, private, third-party payers that publish their coverage policies online found 9 payers that have policies providing coverage of sofosbuvir for treating HCV infections;[49-57] 5 payers have policies providing coverage of ledipasvir/sofosbuvir for treating HCV infections.[49,51,55,58,59]

Payers generally cover sofosbuvir alone and ledipasvir/sofosbuvir as a specialty-tier drug requiring prior authorization and quantity limits for coverage. However, third-party payers have demonstrated resistance against potentially unsustainable pricing for HCV treatment. Thus, ledipasvir/sofosbuvir coverage could be contingent on the availability and price of other all-oral options such as the Viekira Pak regimen for treating HCV genotype 1 infections.[60]

The third quarter of sofosbuvir sales ending in September 2014 grossed $7.3 billion,[61] far surpassing the second-largest drug launch ever, telaprevir, which grossed $1.56 billion in the first year.[62] In May 2014, one financial analyst estimated sofosbuvir sales in the United States could reach $9.5 billion in 2014.[63] In April 2014, insurer 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.[64] According to an analysis by health care consultant Decision Resources Group, more than half of patients in whom chronic HCV genotype 1 infection had been diagnosed 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.[65] Off-label prescribing of sofosbuvir/simeprevir has risen to 30% of specialists surveyed who reported having patients who were prescribed the combination.[65] In June 2014, insurer Oregon Health Plan announced plans to exercise a special waver limiting member access to sofosbuvir and simeprevir based on an analysis of cost and efficacy.[66] The plan estimates providing sofosbuvir alone for one-third (2,300) of its 7,000 members infected with HCV would cost $196 million, doubling the insurer's system-wide drug spending. In 2013, the plan spent $377 million for pharmaceuticals for all of its 600,000 members.

Oregon Health Plan is particularly sensitive to increases in pharmaceutical spending because of an agreed-upon cap on the payer's costs, beginning in 2012, in exchange for $1.9 billion in federal aid over 5 years.[66]

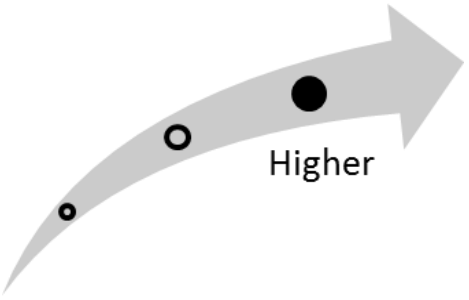
The Viekira Pak is expected to be covered by third-party payers and also may force manufacturers of other regimens to lower their prices. At least one pharmacy benefit manager, Express Scripts, has agreed to make the Viekira Pak the required treatment regimen, for its members with chronic HCV genotype 1 infection who use the company's national preferred formulary, in exchange for a steep discount from the manufacturer. Express Scripts' national preferred formulary is used by many employers and covers about 25 million people; it has announced plans to exclude about 70 drugs in 2015, including ledipasvir/sofosbuvir, sofosbuvir, and simeprevir from its formulary.[44]

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.[67] Subsequent HCV genotype testing is performed to determine the therapy regimen and likelihood of a positive clinical outcome.[67] 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:[68]

- For patients infected with HCV genotype 1, naïve to treatment, daily ledipasvir/sofosbuvir, Viekira Pak, or sofosbuvir plus simeprevir for 12 weeks. For patients with HCV genotype 1a and cirrhosis Viekira Pak, or sofosbuvir/simeprevir require 24 weeks of treatment.
- For patients infected with HCV genotype 2 or 3 naïve to treatment, daily sofosbuvir and weight-based RBV for 12 or 24 weeks, respectively.
- For patients infected with HCV genotype 4, naïve to treatment, daily ledipasvir/sofosbuvir or Viekira Pak for 12 weeks, or sofosbuvir plus weight-based RBV for 24 weeks.
- For patients infected with HCV genotype 5, naïve to treatment, daily sofosbuvir and weight-based RBV plus weekly PEG-IFN for 12 weeks.
- For patients infected with HCV genotype 6, naïve to treatment, daily ledipasvir/sofosbuvir for 12 weeks.

Figure 1. Overall high-impact potential: interferon-free regimens for treating chronic hepatitis C virus infection



Overall, experts commenting on sofosbuvir, ledipasvir/sofosbuvir, daclatasvir, and the ombitasvir/paritaprevir/ritonavir and dasabuvir regimen regarded these interventions as having high potential to address significant unmet needs for HCV infection treatment. All 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 it, noted experts. Experts also thought that oral treatment options 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 2, 3, and 4 and the potential for treating HCV genotype 4 infections with daclatasvir in combination with sofosbuvir were also perceived by experts to be a significant advantage that increases the drugs' 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 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

Experts with clinical, research, and health systems backgrounds provided perspectives on these interventions. Six experts commented on sofosbuvir,[69-74] six commented on ledipasvir/sofosbuvir,[75-80] seven commented on daclatasvir,[81-87] and six commented on the Viekira Pak regimen.[88-93] We have organized the following discussion of expert comments by 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, the 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 the four agents are promising for treating chronic HCV genotype 1 infection. Sofosbuvir could also improve health outcomes for those with HCV genotypes 2, 3, and 4, some experts concluded.[72-74] Ledipasvir and daclatasvir also show promise as agents that could be used in combination with sofosbuvir to provide an IFN and RBV-free treatment option for patients infected with genotype 1;[79,83] daclatasvir in combination with sofosbuvir also shows promise for treating genotype 4 infections without IFN or RBV, some experts thought.[82,83,85,87]

Data have been reported from multiple studies evaluating the Viekira Pak 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 oral HCV drugs 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 some patients and prescribers, limiting diffusion, 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.[69,71,73,79,88,93] 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 Viekira Pak regimen, one clinical expert noted.[90]

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.[72,77,84,88,90,93] 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. Additionally, oral HCV treatment could allow more primary care providers to treat patients, one clinical expert commenting on daclatasvir stated.[82]

One clinical expert commenting on the Viekira Pak regimen anticipated a significant increase in new patients who would ultimately be brought under care for HIV through HCV testing initiatives.[90] Additionally, experts stated that treatment facilities could spend more time acquiring prior approval from payers than they did previously.[81,83,90]

Health disparities: The anticipated high cost of emerging IFN-free HCV therapies could provide possible barriers to treatment for patients, who might face the requirements of preauthorization or restrictions for coverage, the experts noted.[70,80,87,90,93] Patients with private insurance are more likely to have difficulty obtaining these new HCV drugs than are patients with Medicaid; however, coverage could also vary greatly by State, one expert noted.[83] 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.[90,93] However shorter, all-oral dosing could help patients at risk for health disparities complete the treatment course, two research experts noted.[76,86,88]

Tuberculosis Intervention

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 are placed on ineffective therapies because the strain they have is resistant to the antibiotic prescribed. These patients may also continue to spread TB to others in the community, creating a significant public health burden.[94]

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.[94] 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.[95]

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.[94] The antibiotic activity of rifampicin targets the subunit encoded by the *rpoB* gene to inhibit the RNA polymerase, inhibiting bacterial survival.[94] 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.[96]

In the assay, TB DNA in the patient sample is detected by five separate real-time PCR fluorescent probes, which are activated in the presence of amplified *rpoB* DNA and detected by the GeneXpert system.[95] Each of the five probes overlaps a different site known to be mutated in rifampicin-resistant TB if rifampicin resistance can be determined by the binding signal given from the probes.[95]

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.[94,95] 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.[95] The assay is intended to yield results in about 2 hours for both the presence of *M. tuberculosis* and antibiotic resistance for positive samples.[94] 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.[97]

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.[98]

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%).[99]

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 three times as many confirmed TB cases as did 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.[100]

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). 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). 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).[101]

In a prospective, cross-sectional study, patients (n=227) presenting to the San Francisco Department of Public Health TB Clinic between May 2010 and June 2011who were suspected of active pulmonary TB were evaluated using either Xpert MTB/RIF or smear microscopy and culture on an outpatient basis. Patients screened with Xpert MTB/RIF (n=156) were given no initial treatment (n=97) or treated empirically (n=59). Thirteen (8%) of the patients screened with Xpert MTB/RIF had culture-positive TB, and only 12 of 59 patients who initiated empiric therapy were positive for TB (positive predictive value, 20%; 95% confidence interval [CI], 11 to 33). Xpert-

guided management could have purportedly decreased overtreatment by 94% and prevented a median of 44 overtreatment days per patient and a total of 2,169 overtreatment days (95% CI; 1,938 to 2,400) annually, without reducing early detection of TB. The investigators projected similar resource savings could be realized from contact investigation by implementing Xpert MTB/RIF testing.[102]

Manufacturer and regulatory status: Cepheid, Sunnyvale, CA, makes the Xpert MTB/RIF test.[94] 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.[103] Xpert MTB/RIF is indicated for the rapid molecular detection of *M. tuberculosis* complex DNA as well as detecting rifampin resistance associated with mutations of the *rpoB* gene in specimens positive for *M. tuberculosis*.[103]

Diffusion and costs: The price for the GeneXpert GX4-4 system to conduct the testing is $78,200. The Xpert MTB/RIF test costs about $72.[104] For benchmarking purposes, standard basic testing for TB (microscopy and culture) costs about $40.[105] Molecular diagnostic testing for TB with the Amplified MTD test (Gen-Probe subsidiary of Hologic, Inc., Bedford, MA) costs about $92. TB drug susceptibility testing costs about $102.[105]

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).[105] 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.[105]

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.[106]

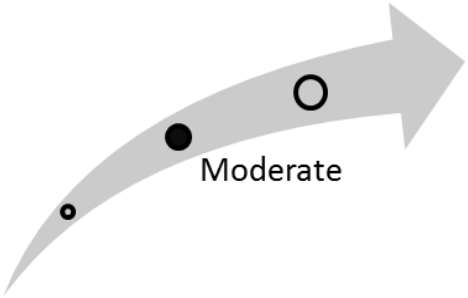
According to data reported by the manufacturer, 173 GeneXpert systems were placed in its commercial clinical business in developed countries during the third quarter of 2014.[107] In the same quarter, a total of 284 GeneXpert systems were placed as part of the manufacturer's High Burden Developing Country program, with a cumulative total of 7,553 GeneXpert systems placed globally as of September 30, 2014.[107] GeneXpert technology will likely diffuse widely to regional hospitals because the GeneXpert platform can also be used to detect common pathogens including *Clostridium difficile*, influenza, and methicillin-resistant *Staphylococcus aureus*.

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.[108,109] The recommended diagnostic procedure for laboratory confirmation of TB is to obtain a 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.[108] 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.[94,108]

Figure 2. 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 moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.[110-115] We have organized the following discussion of expert comments by 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.[113] Patients were expected to embrace rapid diagnosis, especially if their insurance copayments 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.[110,114]

Health disparities: The Xpert MTB/RIF assay could improve health disparities by improving access to care, some experts stated.[110,113,114] However, one expert representing a research perspective stated that the GeneXpert system may be too costly in some underserved areas, which could create disparities.[114]

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