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

Priority Area 09: Infectious Disease Including HIV/AIDS

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www.ahrq.gov

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

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Statement of Funding and Purpose

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

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

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

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Financial Disclosure Statement

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

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Preface

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

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

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

We welcome comments on this Potential High-Impact Interventions report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 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

David Meyers, M.D.
Acting Director
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

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

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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 21,000 leads about potential topics has resulted in identification and tracking of about 2,250 topics across the 14 AHRQ priority areas and 1 cross-cutting area; more than 600 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice 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 170 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 five topics for which (1) preliminary phase III data for drugs were available; (2) information was compiled and sent for expert comment before May 8, 2015, in this priority area; and (3) we received five to seven sets of comments from experts between July 1, 2014, and May 18, 2015. (Fifty-four topics in this priority area were being tracked in the system as of May 8, 2015.) All five topics were deemed through expert comment processes to have potential for high impact, and all of these topics were in the December 2014 Potential High-Impact Interventions report.

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. 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. * Sofosbuvir (Sovaldi) for treatment of chronic hepatitis C virus infection	High
5. * Xpert MTB/RIF Test for simultaneous detection and drug-sensitivity testing of *Mycobacterium tuberculosis*	Moderately high

Discussion

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. HCV has six genotypes, with genotype 1 accounting for about 70% of HCV infections in the United States. According to a U.S. Centers for Disease Control and Prevention (CDC) report issued in June 2014, titled "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 that they are infected and can potentially transmit the disease. Additionally, HIV/HCV coinfection is common, complicating treatment options for these medically vulnerable patients. Of the 1 million people with 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 treatments. 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. In general, patients with HCV infection are considered to be cured if they achieve a sustained virological response (SVR), which is defined as undetectable HCV RNA levels 12 or 24 weeks after treatment (SVR12 or SVR24, respectively). Until 2011, the only approved treatment for chronic HCV infection was interferon (IFN) and ribavirin (RBV) for 24–48 weeks; about 40% to 50% of patients with HCV genotype 1 infection who completed treatment achieved SVR with IFN/RBV. These two drugs' low treatment success rate, coupled with their high toxicity, presented a significant unmet need for new antiviral drugs for treating chronic HCV infection.

In 2011, the U.S. Food and Drug Administration (FDA) approved the first direct-acting antivirals (DAAs) for treating chronic HCV infection, the protease inhibitors boceprevir (Victrelis®) and telaprevir (Incivek™). Incorporating protease inhibitors into HCV treatment regimens shortened the duration of treatment and improved cure rates for some patients with chronic HCV infection; however, these drugs were effective only against HCV genotype 1 and still required co-administration of IFN and RBV. Because of the rapidly changing landscape of HCV drug development in the past half-decade, telaprevir sales were discontinued in October 2014, and boceprevir will be discontinued as of December 2015, according to a statement by its manufacturer, Merck & Co., Inc., because of declining market demand.

The HCV drug pipeline is rapidly evolving, and the HCV community is particularly interested in oral, once-daily, IFN-free DAA regimens that can be completed within 6–12 weeks—a shorter time frame than previous treatments and one that does not require injections. Because the generic names of these HCV drugs and drug combinations are long and complex, for the reader's ease, we will refer to their recognized brand names in this executive summary.

In 2013, two oral anti-HCV DAA drugs, simeprevir (Olysio®) and sofosbuvir (Sovaldi®), were approved for treating HCV genotype 1 infection for 12 weeks, in combination with IFN/RBV. Sofosbuvir was also approved for treating HCV genotype 4 infection in combination with IFN/RBV for 12 weeks. Additionally, Sovaldi provided the first IFN-free DAA treatment option indicated for treating HCV genotypes 2 or 3 in combination with RBV for 12 and 24 weeks, respectively.

Sovaldi was also the first DAA agent approved for treating patients coinfected with HIV or awaiting liver transplantation. In October 2014, a new oral single pill combination therapy that included Sovaldi was approved as Harvoni®. It does not require IFN or RBV as part of the regimen.

It is a fixed-dose combination of ledipasvir and Sovaldi for treating HCV genotype 1 infection and was the first IFN/RBV-free regimen on the market. In December 2014, ombitasvir/paritaprevir/ritonavir tablets plus dasabuvir tablets (Viekira Pak™; AbbVie, North Chicago, IL), a multi-pill IFN/RBV-free regimen was also approved for treating genotype 1.

Physician surveys have 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 Sovaldi and Olysio before the November 2014 approval of their combined use. Clinicians based their off-label decisions on results from a phase II trial demonstrating high SVR12 rates and following guidance from the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America.

These new drugs are 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 as specialty-tier drugs requiring prior authorization and quantity limits for many patients with HCV (often basing treatment eligibility on disease stage).

Four topics for which data were available and for which we received expert comments emerged as having potential for high impact: Sovaldi, Harvoni, Viekira Pak, and daclatasvir (Daklinza®). A number of other manufacturers also have all-oral HCV DAA regimens in phase II or phase III development. Manufacturers with the most advanced candidates include Bristol-Myers Squibb and Merck & Co., Inc. We are tracking grazoprevir/elbasvir (Merck & Co., Inc.) in the horizon scanning system, but at the time of this report had not yet received expert comments on this intervention. We have also not yet received expert comments on Bristol-Myers Squibb's Daklinza/asunaprevir/beclabuvir (DCV-TRIO), but have briefly discussed this intervention here to offer a full perspective on HCV treatment regimens containing Daklinza.

Direct-Acting Antiviral Regimens for Treating Chronic Hepatitis C Infection

- **Key Facts:** Until recently, treatment for patients with chronic HCV infection required treatment with IFN and RBV, a regimen with significant toxicity and a high rate of treatment failure. A number of DAAs have become available in the past 2 years for treating the various genotypes of HCV to continue addressing the significant unmet need for additional HCV therapies that provide safe, effective, and rapid treatment of chronic HCV infection of any genotype.

  We discuss four novel DAA options: Sovaldi for treating chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection; Harvoni for treating HCV genotype 1 or 4 infection, Viekira Pak for treating chronic genotype 1 or 4 infection, and Daklinza for treating genotype 1, 2, 3, 4, 5, or 6 infection.

  Sovaldi and Sovaldi combination therapies. This is a uridine nucleotide analogue HCV NS5B polymerase inhibitor targets the active site of the HCV RNA polymerase to inhibit elongation of the growing HCV RNA genomic transcript. Phase III trials have shown it to have broad and high efficacy (>85% SVRs) against several HCV genotypes and it has been evaluated as part of multiple-drug regimens. In December 2013, FDA approved Sovaldi in combination with IFN/RBV for treating chronic HCV genotype 1 or 4; Sovaldi was also approved for treating patients with HIV coinfection or hepatocellular carcinoma who are awaiting a liver transplant. In December 2013, FDA also approved Sovaldi in combination with RBV for treating chronic HCV genotype 2 or 3 infection. Sovaldi is 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. Sovaldi has also been studied in combination with other DAA agents and against several genotypes. Combined with the ledipasvir, which inhibits activity of the HCV NS5A protein, this regimen offers the first all-oral, IFN-free treatment option for chronic HCV genotype 1 infection. The fixed-dose combination ledipasvir (90 mg)/Sovaldi (400 mg) can be administered for 8, 12, or 24 weeks depending on HCV RNA level, treatment history, and cirrhosis status. In November 2014, FDA approved the NS3/4A protease inhibitor Olysio for use in combination with Sovaldi 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. In October 2014, FDA approved Harvoni for treating patients infected with HCV genotype 1. Additionally the drug's prescribing information states that 8 weeks of Harvoni 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.

According to a U.S.-based, online aggregator of prescription-drug prices, GoodRx, the retail cost of Sovaldi ranges from about $85,000 to $92,000 for a 12-week treatment course, depending on the pharmacy and geographic location. The cost of the fixed-dose combination Harvoni ranges from about $64,000 to $69,000 for 8 weeks and from $97,000 to $103,000 for 12 weeks. The cost of a 4-week supply of generic RBV (1,000 mg) is about $400. The cost of a 4-week supply of IFN is about $3,500.

Our searches of 11 representative, private, third-party payers that publish their coverage policies online found that all have policies providing coverage of Sovaldi and Harvoni, typically as a specialty tier drug requiring prior authorization and quantity limits. Two third-party payers consider Sovaldi a preferred drug; eight consider Harvoni a preferred drug. Additionally, six third-party payers have indicated that patients must have documented advanced liver disease to be considered for coverage for one or more DAAs.

The cost of HCV DAAs remains controversial. Sales of Sovaldi and Harvoni reached $4.55 billion in the first quarter of 2015, far surpassing the launch of the protease inhibitor telaprevir (Incivek), which grossed $1.56 billion in its first year, making it the largest drug launch ever before Sovaldi came to market. Telaprevir's manufacturer, Vertex Pharmaceuticals, Inc. (Boston, MA), withdrew the drug from the market in September 2014 because of low sales.

Viekira Pak. Viekira Pak 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 and one dasabuvir (250 mg) tablet is taken twice daily 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.

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 > 90% when given Viekira Pak in combination with RBV or 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 Viekira Pak and RBV. These rates were superior to an estimated historical control rate achieved with a telaprevir-based regimen. Treatment with 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 Viekira Pak were asthenia, diarrhea, insomnia, nausea, and pruritus.

In December 2014, FDA approved Viekira Pak for marketing for treating patients with chronic HCV genotype 1 infection, including those with compensated cirrhosis. According to GoodRx, the retail cost of Viekira Pak ranges from about $85,000 to $91,000 for a 12-week treatment course, depending on the pharmacy and geographic location.

Our searches of 11 representative, private, third-party payers that publish their coverage policies online found 10 payers that cover Viekira Pak, typically as a specialty tier drug requiring prior authorization and quantity limits. One third-party payer considers Viekira Pak a preferred drug. Additionally, one pharmacy benefits manager, Express Scripts, has made 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. In its first quarter after launch, Viekira Pak generated sales of $231 million, with $138 million in the US alone. However, the company expected Viekira Pak sales to increase in the second quarter because some exclusive payer contracts will take effect in April and May.

Daklinza and Daklinza combination therapies. Daklinza is an HCV NS5A inhibitor under study in multiple treatment settings in combination with both FDA-approved and investigational DAAs. For example, Daklinza is being evaluated with the protease inhibitor asunaprevir and nonnucleoside polymerase inhibitor beclabuvir as part of an oral, fixed-dose, three-DAA regimen (DCV-TRIO) for treating patients with HCV genotype 1 infection. Additionally, Daklinza is being studied in combination with Sovaldi for treating patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection. In the phase III ALLY 1 trial, patients with chronic HCV infection and cirrhosis or liver transplant patients achieved SVR12 rates of 83% and 94%, respectively after 12 weeks of once-daily Daklinza/Sovaldi and RBV treatment. In another phase III trial, patients with chronic HCV genotype 1, 2, 3, or 4 and HIV-1 coinfection who were treated with Daklinza/Sovaldi, once daily, without RBV for 8 to 12 weeks had SVR 12 rates ranging from 76% to 100% depending on variables including treatment duration, prior HCV treatment, and HCV genotype.

In a third phase III trial, patients with chronic HCV genotype 1 infection and compensated cirrhosis who were given the fixed-dose combination tablet DCV-TRIO (Daklinza/asunaprevir/beclabuvir 30/200/75 mg) and RBV or RBV placebo twice daily for 12 weeks had SVR12 rates higher than 90% in patients who were not previously treated. In patients given DCV-TRIO with RBV or RBV placebo who were previously treated, SVR 12 rates of 93% and 87%, respectively, were achieved. The most common adverse events observed in patients given DCV-TRIO were diarrhea, fatigue, headache, insomnia, nausea, and pruritus.

A new drug application (NDA) for Daklinza in combination with other DAAs, including Sovaldi, for treating various HCV genotypes is pending with FDA. In May 2015, FDA granted an amended breakthrough therapy designation for combination Daklinza/Sovaldi for treating genotype 1 in patients with cirrhosis, as well as patients with genotype 1 who experience post-liver-transplant recurrence of HCV. In 2013, DCV-TRIO received a breakthrough therapy designation from FDA. The company had announced plans for submitting an NDA for DCV-TRIO to FDA in the first quarter of 2015, but no new information is available.

No cost information is available for Daklinza 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 may also force manufacturers of other regimens to lower their prices.

- **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 available treatment options, and that is expected to improve patient adherence and outcomes, thought experts. The high efficacy of Sovaldi and Sovaldi in combination with Daklinza 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 have chronic HCV infection in the United States at this time) is likely to be unsustainable in the health care system, thought several experts. The financial strain on the system could require payers to implement controversial coverage policies.
- **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 established 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 is a nucleic acid–based test that is run on the TB test manufacturer'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 cleared 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*.

According to an ECRI Institute PriceGuide analysis, the GeneXpert GX4-4-D system costs about $64,400, and an Xpert MTB/RIF test cartridge costs between $49 and $63 per test when purchasing a set of 10 tests. 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. Finally, 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. In February 2015, FDA cleared Xpert MTB/RIF for use in determining whether patients with suspected TB can be removed from airborne isolation.

- **Key Expert Comments:** Overall, experts thought that this test has potential as a rapid, sensitive 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 the 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 will 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

Direct-Acting Antiviral 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 direct-acting antiviral (DAA) 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, DAA treatment options, some of which are pan-genotypic, are approved or under investigation to address the need for treating chronic HCV infection.[3]

Intervention: Four novel DAA options are presented in this section: sofosbuvir (Sovaldi®) for treating chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection; ledipasvir/sofosbuvir (Harvoni®) for treating HCV genotype 1 infection; ombitasvir/paritaprevir/ritonavir and dasabuvir (Viekira Pak™) for treating chronic HCV genotype 1 infection; and daclatasvir (Daklinza®) for treating HCV genotype 1, 2, 3, 4, 5, or 6 infection. Because the generic names of these HCV drugs and drug combinations are long and complex, for the reader's ease, we will refer to their recognized brand names throughout the remainder of this chapter

Sovaldi-containing regimens. Sovaldi is a uridine nucleotide analogue polymerase inhibitor approved for treating chronic HCV genotype 1, 2, 3, or 4 infection.[5] The HCV NS5B polymerase plays an essential role in HCV genome replication. As a nucleotide analogue, Sovaldi is said to target the active site of the enzyme and inhibit elongation of the growing HCV RNA genomic transcript.[4] Nucleot(s)ide analogues such as Sovaldi 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] Sovaldi has been investigated in combination with a number of investigational agents. It has also been approved as part of a fixed-dose combination with ledipasvir, a drug that inhibits activity of the HCV NS5A protein, providing the first all-oral DAA 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] Sovaldi 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]

Harvoni. Fixed-dose combination ledipasvir (90 mg)/Sovaldi (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 Harvoni 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% and 40% of individuals infected with HCV genotype 1, according to the manufacturer.[11]

Viekira Pak. This consists of the NS5A inhibitor ombitasvir, the boosted protease inhibitor paritaprevir/ritonavir—those three drugs are coformulated in one tablet—and the nonnucleoside polymerase inhibitor dasabuvir. The HCV NS3 protease and its essential cofactor, NS4A, cleave viral

polyproteins, allowing assembly of functional particles.[12] 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.[12,13] Two ombitasvir/paritaprevir/ritonavir (12.5/75/50 mg) tablets are taken once daily and one 250 mg dasabuvir tablet is taken twice daily for 12 weeks with RBV.[14] 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.[14]

Daklinza-containing regimens. Daklinza is an investigational HCV NS5A inhibitor.[15] The drug purportedly has a low drug-drug interaction profile, which could support its use in patients with comorbidities.[15] Daklinza (30 or 60 mg) is being investigated in multiple treatment regimens in combination with both investigational and FDA-approved DAAs. For example, DCV-TRIO (Daklinza/asunaprevir/beclabuvir 30/200/75 mg) is an oral, fixed-dose, three-DAA regimen in development for twice-daily treatment of patients with HCV genotype 1 infection.[16] Asunaprevir is a NS3/4a protease inhibitor and beclabuvir is a nonnucleoside polymerase inhibitor.[17,18] Additionally, Daklinza (60 mg) is being studied in combination with Sovaldi (400 mg) for treating patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection.[19]

Clinical trials: *Sovaldi.* Sovaldi has been studied in numerous clinical trials in patients infected with various HCV genotypes and in varied treatment regimens with or without IFN and RBV. Here we provide selected recent data from Sovaldi 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 400 mg Sovaldi and RBV or placebo once daily 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 PHOTON-2 trial, patients (n=275) with chronic HCV genotype 1, 2, 3, or 4 and HIV-1 coinfection, were given 400 mg Sovaldi once daily and RBV twice daily, for 24 weeks, except patients with HCV genotype 2 infection who were naïve to treatment, who received a 12- week regimen. Patients with HCV genotype 1 or 4 infection had SVR12 rates of 85% and 84%, respectively. Patients with HCV genotype 2 and 3 infection had SVR12 rates of 88% and 92%, respectively.[21]

In studies in which patients were given Sovaldi and RBV, the most common side effects reported were dizziness, fatigue, headache, insomnia, and nausea.[22]

Harvoni. In the phase III, open-label, randomized controlled ION-3 trial, patients (n=647) with chronic HCV genotype 1 infection who were naïve to treatment were given either ledipasvir (90 mg)/Sovaldi (400 mg) once daily with or without RBV for 8 weeks or Harvoni at the same dose once daily without RBV for 12 weeks. Patients treated with Harvoni with or without RBV for 8 weeks had SVR12 rates of 94% and 93%, respectively. Patients treated for 12 weeks had an SVR12 of 95%. Eight weeks of Harvoni therapy was noninferior to 12 weeks of therapy.[23]

In the phase III ION-2, open-label, randomized controlled trial, patients (n=440) with chronic HCV genotype 1 infection who were previously treated with IFN-based therapy were given either ledipasvir (90 mg)/Sovaldi (400 mg) once daily with or without RBV for 12 weeks, or Harvoni at the same dose with or without RBV for 24 weeks. Twenty percent of patients in the study had liver cirrhosis. The SVR12 rate for patients treated with Harvoni with or without RBV for 12 weeks was 94% and 96%, respectively. In patients treated with or without RBV for 24 weeks, 99% in both groups achieved SVR12.[24]

In the phase III, open-label, nonrandomized ION-4 trial, patients (n=335) with chronic HCV genotype 1 or 4 and HIV-1 coinfection were given ledipasvir (90 mg)/Sovaldi (400 mg) once daily with RBV for 12 weeks. SVR12 rates were similar among patients with and without cirrhosis (94% and 96%, respectively) and among patients who were treatment-naïve or treatment-experienced (94% and 97%, respectively).[25]

The most common adverse reactions reported in 5% or more of patients taking Harvoni 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]

Daklinza/Sovaldi. Daklinza 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 Daklinza/Sovaldi demonstrating the emerging potential of the drug in HCV care.

In the phase III, open-label, nonrandomized ALLY 1 trial, patients (n=110) with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection with cirrhosis, or who had received a liver transplant and who were naïve to treatment or treatment-experienced were given Daklinza (60 mg)/Sovaldi (400 mg) once daily with RBV for 12 weeks. Among patients with cirrhosis, 75% were infected with HCV genotype 1; in patients who received a liver transplant, 77% had HCV genotype 1 infection. The overall SVR12 rate was 83% in patients with cirrhosis. In patients who received a liver transplant, SVR12 was 94%. SVR12 rates were comparable regardless of prior treatment experience.[26]

In the phase III, open-label, randomized ALLY 2 trial, patients (n=203) coinfected with HCV genotype 1, 2, 3, 4, 5, or 6 and HIV-1 who were naïve to treatment or treatment-experienced were given Daklinza (30, 60, or 90 mg)/Sovaldi (400 mg) once daily for 8 or 12 weeks. Patients naïve to treatment or who were treatment-experienced with HCV genotype 1 infection had SVR12 rates of 96% and 98%, respectively, after 12 weeks of Daklinza/Sovaldi treatment. SVR12 was 76% in patients naïve to treatment after 8 weeks of therapy. SVR12 rates were 100% in patients infected with HCV genotypes 2 or 3, and 78% in patients infected with HCV genotype 4. SVR12 rates were similar in patients with or without cirrhosis. No HCV virologic breakthroughs were observed, and HIV control was not compromised throughout the study. Post-treatment HCV relapse occurred in 1% to 2% of patients in the 12-week treatment groups and 20% in the 8-week group.[27]

The most common adverse events observed in patients given Daklinza and Sovaldi were anemia, arthralgia, diarrhea, fatigue, headache, and nausea.[26,28]

In the phase III, randomized, double blind, UNITY 2 trial, patients (n=202) with chronic HCV genotype 1 infection and compensated cirrhosis who were naïve to treatment or treatment-experienced were given a fixed-dose combination tablet DCV-TRIO (Daklinza/asunaprevir/ beclabuvir 30/200/75 mg) and RBV (200 mg) tablet or RBV placebo tablet, orally, twice daily for 12 weeks. Patients who were naïve to treatment given DCV-TRIO and RBV or RBV placebo had SVR 12 rates of 98% and 93%, respectively. Patients who were treatment-experienced and were given DCV-TRIO and RBV or RBV placebo had SVR 12 rates of 93% and 87%, respectively.[29] The most common adverse events observed in patients given DCV-TRIO (>10% of patients) were diarrhea, fatigue, headache, insomnia, nausea, and pruritus.[29]

Viekira Pak. This combination drug, 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 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 Viekira Pak and RBV or Viekira Pak with placebo twice daily for 12 weeks. Patients infected with genotype 1a treated with Viekira Pak with or without RBV had

SVR12 rates of 97.0% and 90.2%, respectively. Patients infected with genotype 1b treated with Viekira Pak with or without RBV had SVR12 rates of 99.5% and 99.0%, respectively.[30]

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 Viekira Pak with RBV for either 12 or 24 weeks. In patients treated for 12 weeks, 92% achieved SVR12; in patients treated for 24 weeks, 96% achieved SVR12. These rates were superior to the estimated historical control rate of 47% achieved using telaprevir-based regimens.[31]

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 Viekira Pak and RBV or matching placebos for 12 weeks. Overall, 96% of patients receiving Viekira Pak achieved SVR12 which was noninferior and superior to the historical control rate of 65% assumed with telaprevir-based treatment. Patients with prior relapse had SVR12 rates of 95%; 100% of patients with prior partial response achieved SVR12; and with prior null response had an 95% SVR12 rates.[32]

The most common adverse events reported in patients taking Viekira Pak included insomnia, nausea, and pruritus. In patients taking Viekira Pak in combination with RBV, the most common adverse events reported were asthenia, fatigue, insomnia, nausea, and pruritus and other skin reactions.[33]

Manufacturer and regulatory status: Gilead Sciences, Inc. (Foster City, CA), makes Sovaldi. In December 2013, FDA approved Sovaldi 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. Sovaldi is also approved for treating patients coinfected with HIV or with hepatocellular carcinoma awaiting liver transplantation.[9,34] In October 2014, FDA approved Harvoni for treating patients infected with HCV genotype 1.[6] In November 2014, FDA approved the NS3/4A protease inhibitor simeprevir (Olysio®) in combination with Sovaldi for treating chronic HCV genotype 1 infection in adults naïve to treatment or treatment experienced who do not have cirrhosis. The Janssen Therapeutics unit of Johnson & Johnson, New Brunswick, NJ, makes Olysio.[35,36]

Bristol-Myers Squibb (New York, NY), is developing Daklinza. In February 2014, FDA granted the combination of Daklinza and asunaprevir breakthrough therapy designation for treating patients with chronic HCV genotype 1b infection.[37] In April 2014, the company submitted a new drug application (NDA) to FDA for Daklinza in combination with asunaprevir for treating patients with chronic HCV genotype 1b infection, as well as for Daklinza in combination with other DAAs for treating other HCV genotypes.[15] However, in October 2014, the company announced it would no longer seek approval of Daklinza 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.[38] The manufacturer continues to pursue an indication for Daklinza in combination with other DAAs such as Sovaldi for treating various HCV genotypes.[15,38] However, on November 25, 2014, FDA issued a complete response letter to the company requesting additional data for Daklinza in combination with other DAAs for treating chronic HCV infections. The company is in discussions with FDA about the scope of the data required.[39] In May 2015, FDA granted an amended breakthrough therapy designation to Daklinza/Sovaldi for treating patients infected with HCV genotype 1 who have cirrhosis and for patients infected with HCV genotype 1 who experience post-transplant recurrence of infection.[40] In 2013, the investigational all-oral 3DAA regimen (DCV-TRIO) received a breakthrough therapy designation from FDA.[41] The company had announced plans for submitting an NDA for DCV-TRIO to FDA in the first quarter of 2015,[15] but no new information is available at the time of writing.

AbbVie (North Chicago, IL), in collaboration with Enanta Pharmaceuticals, Inc. (Watertown, MA), makes Viekira Pak.[14] In December 2014, FDA approved Viekira Pak for treating patients with chronic HCV genotype 1 infection, including those with compensated cirrhosis.[42]

Diffusion and costs: *Sovaldi.* According to a U.S.-based, online aggregator of prescription-drug prices, GoodRx, the retail cost of a 4-week supply of Sovaldi is roughly $28,500 ($85,500 for a standard 12-week course).[43] For patients infected with HCV genotype 2 or 3 who are naïve to treatment, daily Sovaldi and weight-based RBV for 12 or 24 weeks costs about $86,000 and $172,00, respectively.[43,44]

Harvoni. The retail cost of a 12-week regimen (three 30-day prescription fills) of Harvoni is about $92,000.[45]

Daklinza. Our searches found no information regarding the potential cost of Daklinza.

Viekira Pak. According to GoodRx, the drug costs $85,000 for 12 weeks of treatment.[46]

Our searches of 11 representative, private, third-party payers that publish their coverage policies online found all 11 have policies providing coverage of Sovaldi for treating HCV infections;[47-57] all 11 have policies providing coverage of Harvoni for treating HCV infections;[47,49-51,55,57-62]and 10 payers have policies providing coverage of Viekira Pak for treating HCV infections.[49-51,57,63-68] Third-party payers generally consider DAAs specialty-tier drugs requiring prior authorization and quantity limits for coverage.

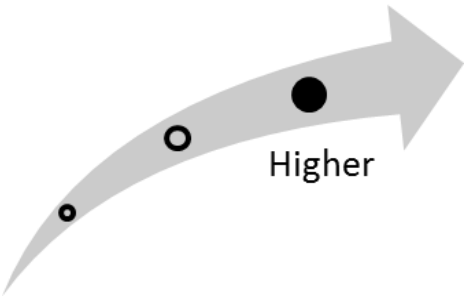
The high cost of HCV DAAs remains controversial. Gilead's sales of Sovaldi and Harvoni reached $4.55 billion in the first quarter of 2015,[69] far surpassing the launch of the protease inhibitor telaprevir (Incivek), which grossed $1.56 billion in the first year.[70] In its first quarter after launch, Viekira Pak generated sales of $231 million, with $138 million in the US alone.[71] However, the company stated it expects Viekira Pak sales to increase in the second quarter because some exclusive payer contracts took effect in April and May.[72] The high cost of the newest HCV DAAs has led third-party payers to choose coverage of either Harvoni or Viekira Pak, based on negotiated costs. The State of Missouri has reportedly received a 30% to 40% discount on Viekira Pak for its Medicaid patients,[73] and discounts upwards of 40% are expected for other third-party payers for both AbbVie and Gilead drugs.[74,75] One pharmacy benefit manager, Express Scripts, has made Viekira Pak the required treatment regimen for its members with chronic HCV genotype 1 infection who use the company's national preferred formulary. Express Scripts' national preferred formulary is used by many employers and covers about 25 million people. This formulary excludes 72 drugs in 2015, including the HCV DAAs Harvoni, Sovaldi, Olysio, and telaprevir. However, its 2015 Preferred Drug Exclusions List states that Sovaldi may be covered in patients who are infected with HCV genotypes 2–6, pending a coverage review.[76] In contrast, other third-party payers such as Aetna, Anthem, Humana, and United Health have decided to cover Harvoni instead of Viekira Pak.[73] However, another third-party payer, Blue Cross Blue Shield Alabama, has indicated that both Viekira Pak and Harvoni are considered preferred drugs for treating HCV genotype 1 infection.[49] Additionally, some third-party payers' coverage policies indicate that HCV DAAs will be considered for coverage only when patients with chronic HCV infection also have advanced liver disease (i.e., fibrosis, cirrhosis, hepatocellular carcinoma), regardless of whether or not the drugs are considered preferred by the payer.[49,51,57,58,61,62] These coverage restrictions, coupled with the high cost of the drugs in the United States, have led some patients with chronic HCV infection to file lawsuits against third-party payers[77] or to seek treatment outside of the United States, where prices for generic versions of HCV DAAs are lower.[78]

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.[79] Subsequent HCV genotype testing is performed to determine the therapy regimen and likelihood of a positive clinical outcome.[79] 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:[80]

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

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



Overall, experts commenting on DAAs 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 the experts. They also thought that oral treatment options provide a shorter and simpler dosing regimen than IFN-based treatment options. The high efficacy of Sovaldi thus far in HCV genotypes 2, 3, and 4 and the potential for treating HCV genotype 4 infections with Daklinza in combination with Sovaldi were also perceived by experts to be a significant advantage that increases the drugs' potential impact. Additional research comparing 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. 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

Experts with clinical, research, and health systems backgrounds provided perspectives on these interventions. Six experts commented on Sovaldi,[81-86] six commented on Harvoni,[87-92] six commented

on the Viekira Pak regimen,[93-98] and seven commented on Daklinza.[99-105] 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 DAA 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. Sovaldi could also improve health outcomes for those with HCV genotypes 2, 3, and 4, some experts concluded.[82,86] Ledipasvir and Daklinza show promise as agents that could be used in combination with Sovaldi to provide an IFN and RBV-free treatment option for patients infected with genotype 1;[91,101] Daklinza in combination with Sovaldi also shows promise for treating genotype 4 infections without IFN or RBV, some experts thought.[103-105] 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 remain high because of their high efficacy, safety, and convenience shown so far. Although the high estimated cost of DAA therapy could pose a barrier to some patients and prescribers, the upfront 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.[85,91] One clinical expert noted that Viekira Pak regimen could compete strongly with Harvoni; however, patient adoption in this competitive space will likely be influenced by prices negotiated for the drugs by both providers and third-party payers.[96]

Health care delivery infrastructure and patient management: All-oral DAA treatment options might entice more patients to seek HCV testing and treatment, some experts thought.[85,89,102] 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 Daklinza stated.[100] The high financial impact of DAAs on health care infrastructure may be mediated, in part, by cost discounts to third-party payers from drug manufacturers, two experts noted.[83,96]

Additionally, experts stated that treatment facilities could spend more time acquiring prior approval from payers than they did previously.[98,99,101]

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.[81,92,105] 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 clinical expert noted.[101] They thought that patients who are poor and uninsured, self-employed, or underinsured could be vulnerable to disparities. However, shorter, all-oral dosing could help patients at risk for health disparities complete the treatment course, some research experts noted.[81,88,104]

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 available 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.[106]

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.[106] 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.[107]

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.[106] The antibiotic activity of rifampicin targets the subunit encoded by the *rpoB* gene to inhibit the RNA polymerase, inhibiting bacterial survival.[106] 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.[108]

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.[107] 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.[107]

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.[106,107] 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 reducing interoperator variability and the potential for false positives caused by amplicon contamination.[107] The assay is intended to yield results in about 2 hours for both the presence of *M. tuberculosis* and antibiotic resistance for positive samples.[106] For a clinician to fully determine an effective treatment regimen, full drug-susceptibility testing will still need to be performed in patients with rifampicin-resistant TB.

Clinical trials: In a diagnostic sub-study 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.[109]

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 a cough that had lasted 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 coinfected with HIV. Median time to detecting 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 treating patients with smear-negative TB from 56 days to 5 days.[110]

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%).[111]

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.[112]

In a multicenter, randomized controlled trial, patients suspected of TB who presented at five primary health care facilities in South Africa, Zimbabwe, Zambia, and Tanzania were evaluated 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 than did microscopy-tested patients (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).[113]

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 2011 who 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 that similar resource savings could be realized from contact investigation by implementing Xpert MTB/RIF testing.[114]

Manufacturer and regulatory status: Cepheid (Sunnyvale, CA), makes the Xpert MTB/RIF test.[106] In July 2013, FDA cleared Cepheid's Xpert MTB/RIF test through the 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.[115] 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*.[115] In February 2015, FDA cleared the use of Xpert MTB/RIF for determining whether patients with suspected TB can be removed from airborne isolation.[116]

Diffusion and costs: According to an ECRI Institute PriceGuide analysis, the list price for the GeneXpert GX4-4-D system was about $64,400 as of the first quarter of 2014.[117] According to a similar PriceGuide analysis, the Xpert MTB/RIF test cost between about $49 to $63 per test when purchasing a set of 10 tests.[118] For benchmarking purposes, standard basic testing for TB (microscopy and culture) costs about $40.[119] 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.[119]

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).[119] 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.[119]

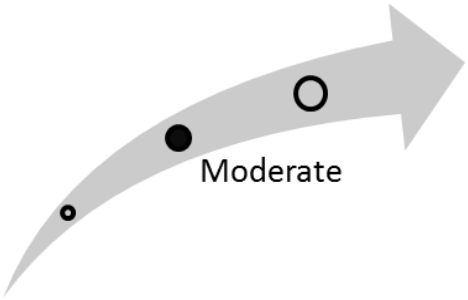
This test would likely be billed using current TB diagnostic procedure codes. In August 2013, FDA categorized the Xpert MTB/RIF test as "moderate complexity" under the Clinical Laboratory Improvement Amendments (CLIA), which likely facilitates diffusion.[120]

According to data reported by the manufacturer, 163 GeneXpert systems were placed in its commercial clinical business in developed countries during the first quarter of 2015.[121] In the same quarter, a total of 133 GeneXpert systems were placed as part of the manufacturer's High Burden Developing Country program, with a cumulative total of 8,321 GeneXpert systems placed globally as of March 31, 2015.[121] 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 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.[122,123] 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.[122] The Xpert MTB/RIF test would be used in place of available nucleic acid amplification tests. Besides identifying the presence of TB, the Xpert MTB/RIF test also gives a preliminary indication of potential antibiotic resistance, which would normally be determined after a positive culture isolate by assaying the isolate's in vitro susceptibility to antibiotics.[106,122]

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 and sensitive 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 can be given and proper infection control measures can be implemented. However, the Xpert MTB/RIF test detects resistance only to rifampin, a common first-line antibacterial agent. Susceptibility to other agents will 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.[124-129] We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: Available 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. However, two experts with clinical and research backgrounds noted that the Xpert MTB/RIF test is an add-on to existing diagnostic technologies, and additional tests would still be required.[125,126] Also one expert representing a research perspective noted that although Xpert MTB/RIF has shown good sensitivity and specificity to date, utility of the test could be limited if mutations of the *rpoB* gene outside of the amplified target DNA sequence were to be more common.[126]

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 reduce inappropriate treatment and improve treatment outcomes.[127,128] Patients were expected to embrace rapid diagnosis, if they were aware that a choice exists for more rapid TB detection, 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.

Health disparities: The Xpert MTB/RIF assay could improve health disparities by improving access to care, one clinical expert stated.[124] However, two experts stated that the GeneXpert system may be too costly in some underserved areas, which could create disparities.[127,128]

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