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October 2014

Hepatitis C Workshop: Meeting Summary

About PCORI

PCORI is committed to transparency and a rigorous stakeholder-driven process that emphasizes patient engagement. PCORI uses a variety of forums and public comment periods to obtain public input to enhance its work. PCORI helps people make informed healthcare decisions and improves healthcare delivery and outcomes by producing and promoting high-integrity, evidence-based information that comes from research guided by patients, caregivers, and the broader healthcare community.

PCORI was authorized by the Patient Protection and Affordable Care Act of 2010 as a nonprofit, nongovernmental organization. PCORI's purpose, as defined by the law, is to help patients, clinicians, purchasers, and policy makers make better-informed health decisions by "advancing the quality and relevance of evidence about how to prevent, diagnose, treat, monitor, and manage diseases, disorders, and other health conditions."

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Executive Summary

On October 17, 2014, PCORI held the Hepatitis C Workshop in Arlington, Virginia. Participants in this multi-stakeholder workshop discussed whether comparative clinical effectiveness research (CER) can help to answer questions about hepatitis C screening, diagnosis, and treatment. More than 40 invited stakeholders attended in person. The meeting was open to the public via teleconference and webinar.

Before the workshop, invited participants proposed some CER questions about hepatitis C. PCORI staff grouped the questions into four categories: care delivery, screening and diagnostic tests, head-to-head trials, and patient populations and timing of treatment. PCORI staff refined the stakeholders' inputs and drafted four representative questions in each category. These questions were discussed, revised, and ranked by the participants during breakout sessions at the workshop.

Related Information

- Blog: Bringing Stakeholders Together to Talk About Hepatitis C
- Advisory Panel on Assessment of Prevention, Diagnosis, and Treatment Options
- September 2014 Advisory Panel meeting on Assessment of Prevention, Diagnosis, and Treatment Options

In the plenary session that followed, breakout leaders presented the ranked questions to all the participants. After review and discussion, the participants identified the following questions as top priorities:

- What is the comparative effectiveness of available healthcare delivery approaches for reaching, screening, assessing disease, treating, and preventing new infections and reinfections of Hepatitis C?
- What approaches for linking primary-care physicians with specialty teams are most effective in accurately diagnosing and effectively treating patient with hepatitis C, particularly individuals in rural or medically underserved areas?
- Which screening methods have the highest linkage to care? Which methods work best in which settings?
- Which of two all-oral interferon-free strategies for the treatment of chronic genotype 1 hepatitis C infection, including sofosbuvir/ledipasvir and paritaprevir/ritonavir/ombitasvir/dasabuvir +/- ribavirin, will maximize sustained virologic response and minimize adverse effects and harm?
- Is there a benefit to treating early-stage patients versus delaying therapy? / What are the comparative benefits and harms of treating all patients with Hepatitis C virus infection versus waiting to treat only those patients who show signs of liver disease?

Contents

Background

More than 3 million Americans are infected with hepatitis C virus (HCV), a potentially deadly chronic disease that can damage the liver and cause liver cancer. Hepatitis C is a problem that poses a significant burden for patients, their families, and our healthcare system.

Although the recent approval of new medications offers the promise of transforming treatment of HCV infection, only limited post-marketing data are available to date. As a result, a substantial number of questions remain about how best to screen, diagnose, and treat hepatitis C. These questions focus on disease symptoms, drug side effects, treatment adherence, quality of life, population differences, and other issues related to patient preferences and outcomes.

Given the range of opinions about how to best use the new HCV drugs, PCORI was well-positioned—as an independent, nonprofit research funder—to convene a broad range of healthcare stakeholders to explore potential avenues for further research. The goal of these discussions was to identify patient-centered comparative clinical effectiveness research (CER) questions that might be the focus of a PCORI Funding Announcement.

Interest in HCV treatment as a subject for one or more PCORI-funded studies arose out of PCORI's process for prioritizing CER topics for potential funding. The process starts with solicitation of potential research topics from patients, clinicians, researchers, purchasers, payers, industry, and other healthcare stakeholders. PCORI's multi-stakeholder advisory panels then rank those topics for potential recommendation to PCORI's Board of Governors for approval.

Many stakeholders asked PCORI to consider funding research on hepatitis C treatment, which PCORI's Advisory Panel on Assessment of Prevention, Diagnosis, and Treatment Options then ranked as a high-priority topic when it met on September 12. PCORI next convened a large stakeholder workshop on October 17 to provide further input on whether specific CER questions might be the subject of PCORI-funded research. More than 40 invited stakeholders attended in person, with up to 150 other members of the public tuning in via teleconference and webinar.

Before the workshop, the invited stakeholders were asked to propose hepatitis C–related CER questions for discussion during the meeting. PCORI staff grouped the questions into four categories: care delivery, screening and diagnostic tests, head-to-head trials, patient populations and timing of treatment.

Topic	Number of Questions Submitted
Care delivery	24
Patient subpopulations and timing of treatment	21
Head-to-head trials comparing new therapies	15
Screening and diagnostic tests	5

PCORI staff refined the stakeholders' inputs and drafted four representative questions in each category for the breakout sessions. These questions were discussed, revised, and ranked by the participants at the breakout sessions.

Introductory Remarks

Dr. Joe Selby, PCORI's Executive Director, welcomed the meeting participants. He noted that the workshop is an assembly representing the US healthcare community, particularly those who have had a long interest in screening, diagnosing, and treating hepatitis C. In addition to the in-person attendees, more than 130 people participated via webinar and teleconference.

Dr. Selby explained that this workshop was one of a series designed to help PCORI focus its research agenda, and to help the institute decide whether comparative clinical effectiveness research (CER) can be useful in answering questions that matter to patients, clinicians, and other decision makers in particular areas. He noted that multiple stakeholders had previously indicated that hepatitis C treatment is an area in which CER could make a difference and that in its September 2014 meeting, PCORI's Advisory Panel on Assessment of Prevention, Diagnosis, and Treatment Options considered screening, diagnosing, and treating hepatitis C as the highest priority topic. Dr. Selby reminded the participants that PCORI does not study cost or cost-effectiveness, and therefore such topics would not be discussed in this workshop.

The charge for the workshop attendees was to address two questions:

- Are there patient-centered CER questions in the area of hepatitis C screening, diagnosis, and treatment that the group advises PCORI to support?
- If so, which questions are highest priority in terms of importance to patients?

Dr. Bryan Luce, PCORI's Chief Science Officer, described the workshop structure and reviewed the agenda. The in-person attendees then introduced themselves. The attendees represented a wide range of stakeholders, including researchers, patients, caregivers, clinicians, industry, payers, and the public health and policy communities.

Dr. David Hickam, PCORI's Program Director for Clinical Effectiveness Research, gave a brief history of hepatitis C and reviewed the changing landscape of antiviral therapy, the clinical impact of hepatitis C, and the disease's variable clinical course.

Breakout Sessions

The participants divided into four breakout sessions, each spending about two hours discussing and revising the four potential CER questions in one category. Using an approach similar to the Pareto principle, the breakout groups spent about 30 minutes ranking the final questions.

Dr. Harold Sox, PCORI's Director of Research Portfolio Development, asked each breakout group to consider the following elements when discussing the CER questions:

- Target condition
- Target population
- Compared interventions
- Proposed outcome measures (including patient-centered outcomes)
- Study design
- Feasibility of doing the study as outlined and potential problems
- Possible results and how they might alter practice or policy
- Feasibility of scaling up the intervention to national-level adoption

Care Delivery

Breakout leader: Dr. Gillian Sanders, Duke University and Clinical Research Institute
PCORI staff moderator: Ms. Penny Mohr, Program Officer, Improving Healthcare Systems Program

Stakeholder participants:

- Dr. Sanjeev Arora, Project ECHO
- Dr. Eliav Barr, Merck & Co.
- Dr. Brian Edlin, Hepatitis Education Project
- Ms. Ronni Marks, Hepatitis C Mentor and Support Group
- Dr. Dianne Padden, American Association of Nurse Practitioners
- Mrs. Pamela Rich, Institute on Healthcare Costs, National Business Group on Health
- Dr. Ada Stewart, American Academy of Family Physicians
- Dr. Neeta Tandon, Health Economics and Outcomes Research, Janssen
- Dr. Vikrant Vats, Blue Cross and Blue Shield Association

PCORI staff participants:

- Ms. Kim Bailey, Engagement Officer
- Ms. Ashton Burton, Contracts Specialist
- Dr. Anne Trontell, Program Officer, Clinical Effectiveness Research
- Dr. Kara Odom Walker, Deputy Chief Science Officer

Question 1. What approaches for linking primary care physicians with specialty teams are most effective in accurately diagnosing and effectively treating patients with hepatitis C, particularly people in rural or medically underserved areas?

The group discussed Project ECHO in New Mexico, where specialists (using telecommunication techniques) train primary care doctors and community health providers in rural areas and underserved

communities. It was noted that, in New Mexico, there are no primary care doctors who are treating hepatitis C. For Project ECHO, giving the medicine does not require a lot of support, but overall effectiveness of the program requires supporting healthcare practitioners and knowing what individual patients need to support them in treatment adherence. The ECHO project could be scaled up to include broader population representation and disease severity. Primary care doctors can treat hepatitis C as well as specialists do, if the primary care doctors are educated in how to do it and can make use of healthcare extenders to support treatment adherence and other important aspects of treatment.

Comments included:

- One urban program is diagnosing hepatitis C but does not have support from specialists. Specialists sometimes say that they do not want to treat those with co-occurring HIV infection and other comorbidities. A study is needed to adapt the ECHO model to individual circumstances and provide care for all patients. New oral treatment regimens will make treatment in the primary care setting easier.
- Linking primary care providers with specialists via technology (e.g., telemedicine) could help to increase access to care.
- There is a huge gap in translating studies' results into actual patient support.
- Do specialists have more time and ancillary support resources than primary care doctors?

A participant said that it would be good to have a large clinical trial in a community setting to produce real-world research to ensure that patients get effective treatment. With regard to the primary outcome of such a trial, such an approach would make trials patient-centered. A useful trial might be one that proved the overall effectiveness of a given course of treatment. It would involve quality-of-life issues and relationships—whatever is important to the patients themselves, not just what is important to the healthcare providers. Research needs to be patient-centered and assess the impact on patients' quality of life, functional capacity, sleep, and other factors of treating hepatitis C before cirrhosis develops. In practice, treatment is usually reserved for patients who have already developed cirrhosis.

It was pointed out that programs based on this comprehensive approach, on an international scale, had to take into consideration the importance of adapting to the individual cultural and psychological factors of each different community.

The target population would be a broad population using inclusion criteria from Project ECHO. With regard to interventions, the Project ECHO model could be compared with usual care; other interventions could also be evaluated. The proposed outcome measures would include cure of hepatitis C, functional capacity, quality of life, and sleep. Conducting the study as outlined would address problems that are important to patients.

Question 2. What is the comparative effectiveness of various team-based approaches versus individual physician treatment to improve medication adherence and cure rates for patients diagnosed with hepatitis C? These may include intensive case management, intermediate case management, multidisciplinary clinical management approaches, pharmacy management models, comprehensive medication therapy management, cognitive behavioral therapy, and patient navigation.

Some questions that arose during the discussion:

- Is there a disconnect between team-based approaches and management approaches?
- What will best support the treatment of hepatitis C by primary care physicians?
- How do we better target treatment approaches to patient populations? How do we determine which approaches work best by subpopulation (e.g., What works in the prison system? What works among IV drug users? What works for baby boomers?)
- There are different ways to manage medications. Which is the way to go?
- What interventions will give the richest results?
- How do you assess whether a patient is "high-risk" or "non-adherent"?

It was noted that people need support to do the right thing. Project ECHO added a community health worker to the team to address individual patient barriers to treatment and help ensure that the knowledge of the team gets translated effectively.

One participant observed that community health workers are not used enough and are often undervalued, even though they contribute hugely to issues such as adherence.

Discussion points included:

- It is important to have a multidisciplinary treatment team, but the existing infrastructure for multi-disciplinary teams is weak where the patients are (e.g., in rural areas, urban areas).
- It is important to treat patients in a culturally appropriate setting that does not require traveling long distances.
- Treatment that takes into consideration psychological, social, and cultural factors will be more effective.
- The ECHO approach is to be commended, but its transferability and scalability are unknown. It is likely that other approaches will be necessary. It is important to address systematically what can be done within the limitations in which many work—where and how is it possible to "get the biggest bang for our buck"?

Question 3. Which healthcare delivery approaches are most effective for screening and treating complex and hard-to-reach people infected with hepatitis C virus (HCV), such as the homeless, prison populations, intravenous (IV) drug abusers, and HIV-infected people?

Discussion points included:

- Determining the best setting in which to treat is critical. Programs must be designed with the population they are attempting to reach in mind, and must reach people where they are. It is more effective to visit prisons for screening and treating HCV-infected people.
- For working with the homeless, one program has a "screening day" on which food coupons are offered to address the hunger needs of this population and thus motivate participation.
- A majority of many programs' cases come from primary care physicians.

- Methadone programs and needle-exchange programs can reach IV-drug-using patients who need treatment.
- Rapid screening tools should be used where appropriate, especially among populations that are not likely to return for follow-up.
- It is highly important to increase education, determine when and where to treat patients, and design outreach and treatment programs that are attentive to the targeted population(s). We need to recommend linking specialist care with primary care, deciding how to prescribe medicine to equip the patient with the right set of tools, and identifying approaches that are the most effective.
- The people who take care of underserved patients are often very idealistic and concentrated on the cure. Their motivation is not always the same as that of the person who has the disease. The patient's interest is often different from that of the care provider.
- Wrap support services (e.g., housing support, food access, energy programs) around interventions and provide incentives to participate in treatment. It was suggested that a strong motivator for participation in a treatment program might be a $5 McDonald's coupon or similar incentive that addresses patient needs and priorities.
- Barriers should be clearly identified. Interventions have to have different structures for different groups.
- A program that offers prevention education as well as treatment is one of the most effective approaches.
- It is important that a strong case can be made to employers. Workers who are healthy are better, stronger, and more productive.

Populations of interest:
- Prison population
- People who inject drugs
- People who use other substances, including alcohol (continuum of substance use)
- Racial/ethnic minorities
- Veterans
- Elderly people

Factors of interest:
- Socioeconomic status: low-income, homeless
- Geography: rural, urban, underserved
- Insurance status: commercially insured, Medicaid, Medicare, underinsured, uninsured
- Disease status/stage of disease
- Comorbidities (e.g., mental illness)
- Co-infection with HIV

The group agreed to combine Questions 1–3 into a new question (Question 5):

Question 5: What is the comparative effectiveness of available healthcare delivery approaches for reaching, screening, assessing disease, treating, and preventing new infections and reinfections of hepatitis C?

The group recommended the following interventions:

- Linking primary care and specialty care
- Telemedicine/telementoring
- Intensive case management
- Community health worker/patient navigator/peer navigator models
- Integrated, multidisciplinary care
- Community mobilization/empowerment
- Pharmacy case management
- Cognitive behavioral therapies
- Prevention of reinfection
- Support groups
- Education
- Adherence support
- Venue-based delivery approaches (e.g., methadone clinics)

They also listed desired outcomes:

- Cure rate
- Functional status
- Treatment completion
- Quality of care, patient satisfaction with care
- Quality of life
- Emotional well-being
- Symptoms, such as fatigue
- Work productivity
- Amelioration of the extrahepatic manifestations
- Healthcare utilization (hospitalization, burden of office visits)
- Reinfection rate
- Transmission rates

Two important deficiencies were noted: lack of capacity and lack of a method to scale up effective programs. Varying needs of patients also must be recognized.

The question was asked: Is a viable multidisciplinary approach to hepatitis C treatment currently available? One participant observed that this kind of approach was not now widely available, but it would be highly cost-effective. Another participant observed that whether an effective program is scalable says more about our present healthcare system than about the intervention itself.

Question 4. How do patient-centered outcomes (e.g., cure rate as measured by sustained virologic response [SVR]) for hepatitis C patients enrolled in Medicaid programs with restrictive formularies for hepatitis C medications (e.g., prior authorization requirements, step therapy requirements, non-coverage of selected medications, restrictions on combination therapy) or targeted eligibility criteria (e.g., biopsy-proven fibrosis) compare with those enrolled in Medicaid programs with fewer restrictions?

Time constraints prevented a discussion of Question 4.

The participants voted on which questions are most important in designing a patient-centered research study.

Rank	Question	Vote Breakdown
1	Question 5: What is the comparative effectiveness of available healthcare delivery approaches for reaching, screening, assessing disease, treating, and preventing new infections and reinfections of Hepatitis C?	**17**
2	Question 1: What approaches for linking primary care physicians with specialty teams are most effective in accurately diagnosing and effectively treating patient with hepatitis C, particularly individuals in rural or medically underserved areas?	**16**
3	Question 3: In hard-to-reach populations, what is the comparative effectiveness and safety of alternative strategies to achieve cure, improve quality of life, prevent reinfection, and reduce transmission? • Target population: medically/socially complex people • Compared interventions: enhanced treatment of hepatitis c versus optimizing treatment of comorbidities	**7**

Screening and Diagnostic Tests

Breakout leader: Dr. John Wong, Tufts Medical Center
PCORI staff moderator: Dr. Harold Sox, Director of Research Portfolio Development

Stakeholder participants:

- Dr. William B. Baine, Agency for Healthcare Research and Quality
- Dr. Thomas J. Berger, Veterans Health Council
- Dr. Bernadette Eichelberger, Academy of Managed Care Pharmacy
- Ms. Linda Gousis, Centers for Medicare and Medicaid Services
- Dr. Jake Liang, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health
- Dr. Andrew J. Muir, Duke University and Clinical Research Institute
- Dr. Nancy Reau, American Association for the Study of Liver Diseases
- Dr. John Ward, Centers for Disease Control and Prevention

PCORI staff participants:

- Dr. Stanley Ip, Program Officer, Clinical Effectiveness Research
- Ms. Katie Lewis, Program Associate, Addressing Disparities
- Ms. Katie Rader, Program Associate

The group discussed the submitted research questions (listed in the next few pages) and modified them (the final version of the questions are listed at the end of the section on screening and diagnosis).

Question 1. What are the comparative benefits and risks of FibroScan and other noninvasive tests for liver fibrosis versus liver biopsy in staging patients with hepatitis C?

Overarching comments:

Liver fibrosis marks a patient as at relatively high risk for hepatocellular carcinoma, end-stage liver disease, and death. Such patients have the most to gain from eradication of the hepatitis C virus. Methods to detect fibrosis include liver biopsy and elastography as well as risk scores that take into account clinical features and liver function test results in an individual patient. None of these measures identify all patients at risk (sensitivity) and distinguish them from those that are at low or no risk (specificity).

This research question raises key considerations around delivery, payment, and coverage. It is important to note that payment and coverage fall outside the scope of a potential PCORI initiative. The main question is the sensitivity and specificity of FibroScan and other noninvasive tests versus liver biopsy. The group discussed a key delivery issue—the importance of translating treatment from a specialist to non-specialist setting. Patients would be more satisfied with care if a provider could both test and treat for hepatitis C rather than make a referral.

Other questions centered on policy and practice. Any trial funded should stage patients, using individual tests or a combination, and examine impact on an outcome that has the potential to influence policy and practice. Staging patients with hepatitis C both simplifies and improves care. The group discussed outcomes for this type of study, and participants were largely in favor of designating retention in care as the primary outcome. This a patient-centered, medium-term outcome is an indicator of clinical outcomes.

The group agreed that liver biopsy should not be considered as a comparator. Liver biopsy is considered a "tarnished gold standard"—it carries risk for patients, is not viable for many patients, and more holistic diagnostic options can be used.

Potential study designs:

- Randomized trial:
    - Randomized trial of non-invasive tests to identify fibrosis scores for treatment decisions
    - Noninvasive test versus invasive test versus elastography to determine which testing options are more effective to identify and treat patients
- Retrospective study design
    - Retrospectively identify clinical outcomes that would be helpful to understanding test characteristics

- Decision modeling
    - Prospectively look at agreement among the testing options, either in isolation or in combination.

Question 2.

a. Compare the conventional two-step screening and confirmation protocol (anti-HCB Ab followed by HCV polymerase chain reaction [PCR] if positive) with a "reflex test" (in which anti-HCB Ab is followed by "reflex" HCV PCR if the antibody test is positive).

b. Compare the impact of rapid anti-HCV Ab with "conventional" testing on the outcome of informing the screened people of their HCV status

From a clinical perspective, there are concerns that patients will not return for the second step of a two-step screening or to receive test results and start treatment, so more patients, especially hard-to-reach and vulnerable patients will be easier to cure with rapid testing, a one-visit process in which screening is performed and treatment begun in the same visit . From a patient perspective, increasing diagnosis rates by antibody detection alone may result in false-positives because the immune system of some patients has cleared the infection. Patients want confirmation that they may, in fact, have active infection, which means demonstrating that their blood contains live virus.

2a. Waiting for the patient to come back for second step of testing may decrease the rate of treatment when it is indicated and. In the case of false-positive antibody tests, increase the patient's concerns about an infection that they no longer have.
Diagnosis and linkage to care questions include:

- Does one-stop screening increase uptake into treatment?
- Research design—which populations do and don't make regular healthcare visits?

2b. Questions about the intervention:

- How specific, sensitive, and fast can we make the tests?
- Three possible interventions: reflex antibody test, new core antigen test, and rapid test (need for rapid core antigen test)
- Examine the need for a direct test for the virus (a measure of active infection) versus a two-step process in which antibody-positive patients are tested for the viral genome.

Questions about the study population and practice sites:

- Consider the study population: should it be patients who have regular health visits on an out-patient basis, those who get their care through emergency room visits, those that are entirely outside the health care system, or a combination of these populations.
- Which tests are best for groups that would not necessarily be in medical care.
- Community-based health care centers, emergency rooms, or an academic setting?
- How do you capture the population that will be a continuing source of infections due to needle sharing or other high risk practices?
- Role of risk score in determining which screening test to use.

Based on their discussion, the group revised Question 2 (see below).

Question 3. What are the harms and benefits of different methods to identify people at high risk of contracting hepatitis C?

General comments:

The group primarily discussed two options for identifying people to screen for hepatitis C: *screen everyone and risk-based screening*. The main questions are how effective can a risk-based approach be and are there effective methods for assessing risk? Historically, recommendations for risk-based screening were identified by the Centers on Disease Control and Prevention (CDC) and include screening individuals based on risky behaviors (e.g., drug use), risk of exposure (e.g., individuals with HIV; children born to mothers with hepatitis C), and birth cohort (Individuals born between 1945 and 1965). This last method is considered "stigma free," since patient behaviors and characteristics are not taken into consideration.

There are other risk factors not on CDC's list of recommendations, such as prisoners, the homeless, presence of tattoos, and number of sexual partners. There is also a graduated approach to assessing risk using modeling to develop independent risk factors that can be used to calculate a risk score.

The group noted that one large and important gap in the evidence is understanding the applicability of screening recommendation to groups likely to experience disparities in access to care. To date, most studies have focused predominantly on white populations. There need to be studies to examine the impact of screening interventions on minority communities and others at risk of disparity in treatment and outcomes. There are also problems and needs unique to the veteran population (in particular, Vietnam Veterans).

Harms and benefits of identifying high-risk patients:

Benefits of identifying a person as at high risk of hepatitis C:
- They are more likely to be screened for hepatitis C
- Patients in particular need can be brought into the system for further care and management.
- Integration of hepatitis C treatment and care for other conditions and interventions may reduce the likelihood of progression of liver fibrosis.
- A focus on high-risk patients will maximize the population-level impact of treating hepatitis C infection.

Harms of identifying a person as at high risk of hepatitis C:
- Their at-risk status will be in their medical records, which could affect their access to certain benefits.

- People may experience mental stress after learning of their high risk status.
- People may experience stigma (i.e., public perception of IV drug use)
- After experiencing all these harms, they may still not get treated.

Considerations for research design:
- Surveillance study (periodic testing of high risk individuals who test negative but may later contract hepatitis C)
  - Study populations
    - birth cohort, emergency room [ER] patients, prison population, homeless

- Populations at risk of health care disparities
- Individuals at high risk who are resistant to testing

- Clinical settings in which risk status is assessed
  - Veterans Health Administration [VA]
  - emergency department
  - urban communities

  (PCORI's PCORnet may be leveraged for identifying sites.)
- Compare modes of data collection
  - Patient self-report
  - Physician asks patient
  - Screening through general health questionnaire
- Randomized trials
  - Compare the outcomes of screening everyone vs. screening just those at high risk
  - Subgroup analysis
    - VA versus non-VA populations
    - Different risk score cut-offs for counting a person as at high risk

Question 4. What screening guidelines are likely to identify the largest number of HCV-infected people?

The group discussed Question 4 in the context of Question 3 and incorporated it into revised Question 3 (see below).

The revised questions and their key elements are:

Question 1. What are the comparative benefits and risks of FibroScan and other noninvasive tests for liver fibrosis versus liver biopsy in staging patients with hepatitis C?

- Target population—High risk (CDC *Morbidity and Mortality Weekly Report* [*MMWR*] definition expanded to include other populations like pregnant women, the incarcerated, homeless, ER, veterans)
- Compared interventions—Invasive tests like liver biopsy, imaging tests, and serum markers (or a combination of methods)
- Study design
  - Possible combined screening and treatment randomized clinical trial (RCT) of long-term clinical outcomes
  - Observational and retrospective
  - Cross-sectional (to measure sensitivity and specificity)

Question 2. What are the effects of doing 1) rapid antibody test versus 2) reflex test versus "conventional" testing on the outcome of linkage to care and patient satisfaction.

- Target population—High risk (CDC *MMWR* expanded to include other populations like pregnant women, the incarcerated, homeless, ER, veterans)
- Compared interventions
  - Rapid antibody, then if positive, draw PCR immediately

- Reflex test (if HCV ab+, automatically check PCR)
  - PCR viral testing
  - Conventional HCV antibody
- Study design—RCT
- Proposed outcome measures (including patient-centered outcomes)
  - Linkage to care
  - Patient-reported outcomes (PROs)
  - Time to viral genome testing

Question 3 (3+4). Which screening methods have the highest linkage to care? Which methods work best in which settings?

- Target population—High risk (CDC *MMWR* expanded to include other populations like pregnant women, the incarcerated, homeless, ER, veterans)
- Compared interventions
  - Screening all
  - Screening high-risk groups
  - Methods for conducting screening (self-report, provider, e-form)
  - Setting (routine healthcare, not receiving routine healthcare)
- Proposed outcome measures (including patient-centered outcomes)
  - Linkage to care
  - Screening performance score
  - PROs (e.g., knowledge, satisfaction)
  - Utilization
- Study design
  - RCT comparing methods for high-risk cohorts (ER population)
  - RCT comparing methods in possible settings (primary care, VA, PCORnet, community health center)
  - RCT: educating providers about managing Hepatitis C treatment

The participants then voted on which screening and diagnostic tests questions are most important in designing a patient-centered research study.

Rank	Question	Vote Breakdown
1	Question 3: Which screening methods have the highest linkage to care? Which methods work best in which settings?	**10**
2	Question 2: Comparison of response rate to rapid antibody test versus reflex test versus “conventional” testing on the outcome of linkage to care and patient satisfaction.	**8**
3	Question 1. What are the comparative benefits and risks of FibroScan and other noninvasive tests for liver fibrosis versus liver biopsy in staging patients with hepatitis C?	**3**

Head-to-Head Trials

Breakout leader: Dr. Camilla Graham
PCORI staff moderator: Dr. Joe V. Selby

Stakeholder participants:
- Dr. Carol L. Brosgart, Forum for Collaborative HIV Research and University of California, San Francisco
- Ms. Karen Chesbrough, Foundation for Physical Therapy
- Ms. Donna Cryer, Global Liver Institute
- Dr. C. Joseph Lim, American Gastroenterological Association
- Dr. Richard Migliori, UnitedHealth Group
- Dr. Poonam Mishra, U.S. Food and Drug Administration
- Dr. David Ross, Veterans Health Administration
- Ms. Lorren Sandt, Caring Ambassadors Program
- Dr. David Lee Thomas, Infectious Diseases Society of America

PCORI staff participants:
- Ms. Emma Djabali, Project Assistant, Office of the Chief Science Officer
- Ms. Kelly Dunham, Program Officer, CER Methods and Infrastructure
- Dr. Mark Helfand, Methodology Committee Member
- Ms. Meheret Shumet, Administrative Assistant, Office of the Chief Science Officer
- Ms. Christine Stencil, Associate Director, Media Relations

Question 1. Which of two all-oral interferon-free strategies for the treatment of chronic genotype 1 hepatitis C infection, including sofosbuvir/ledipasvir and paritaprevir/ritonavir/ombitasvir/dasabuvir +/- ribavirin, will maximize SVR and minimize adverse effects and harm?

- *In patients without cirrhosis*
- *In patients with compensated cirrhosis*
- *In patients with decompensated cirrhosis*
- *In patients who are post-liver-transplant*
- *In patients with HCV-HIV co-infection*
- *In subgroups defined by viral genotype*
- *In patients with end-stage renal disease*
- *In patients who inject drugs*

Discussion points:
- A problem with treatment studies to date is that they have not measured all of the needed patient-centered outcomes.
- An area of concern is that there will be a lot of patients with cirrhosis in the trials (because of good insurance coverage for advanced liver disease), so it will be difficult to enroll people at lesser stages of fibrosis (due to lesser insurance coverage for earlier stages of disease).
- Trials need to be designed to include all treatment-eligible patients.

- An observational real-world study has inherent biases because treatment choice is associated with factors that influence outcomes (confounding by indication).
- PCORI's role is to directly compare active interventions, whereas drug companies will test active treatment against lesser comparators
- A role for PCORI is to identify the populations that drug companies excluded for their efficacy trials—that is, the homeless, drug users, and so on.
- PCORI does not need to spend its energy doing head-to-head trials on populations that would typically be studied already and are widely covered by insurers (e.g., cirrhotic, post-liver-transplant).
- Real-world observational, real-world patient studies are needed, since clinical trials have excluded some important populations; Given the excellent results with all directly-acting antivirals, confounding by indication when comparing them may be a lesser problem than when patient characteristics drive treatment choice.
- It is not PCORI's job to increase drug access, but to find evidence of what drug will work for whom and under what circumstance. In current practice, a narrow section of people are treated, due to costs, generally cirrhotic patients, and this may exclude heavy drinkers, people below the poverty line, and so on. The idea of combining randomized and nonrandomized approaches is useful to expand the evidence base for all subgroups;
- It is important to define populations accurately (e.g., advanced liver disease patients who are currently drinking vs. have already stopped).
- PCORI should look at study outcomes in a period of perhaps less than five years versus longer-term studies, although linkage to claims data sets could provide long-term outcomes (advanced liver disease, transplantation, hepatocellular carcinoma, all-cause mortality).
- There is a lack of evidence aboutelevant patient-centered outcomes (e.g., depression, fatigue) on the populations that are receiving treatment.

The group agreed that PCORI should include all the patient populations listed in the question in a head-to-head trial, with the exception of patients with end-stage renal disease.

One participant suggested that PCORI should commission one large study that encompasses all the populations of interest, as opposed to having separate studies looking at each population. There was a group consensus that this approach would achieve answers most quickly. Key elements for this question are:

- Target populations: patients without cirrhosis, patients with compensated cirrhosis, post-liver-transplant patients, HCV-HIV co-infected patients, and patients who inject drugs (need for clear targets)
- Compared interventions: two all-oral interferon-free strategies for the treatment of chronic genotype 1 hepatitis C infection, including sofosbuvir/ledipasvir and paritaprevir/ritonavir/ombitasvir/dasabuvir +/- ribavirin
- Proposed outcome measures (including short- and long-term patient-centered outcomes): adherence, tolerability, first SVR, long-term outcomes (cirrhosis, decompensated cirrhosis, utilization) hospitalizations, quality of life, cognitive changes, long-term relapse, risk of reinfection
- Study design: large pragmatic adaptive study or observational study
- Feasibility of doing the study as outlined, given potential problems, such as coverage of treatments
- Possible results and how they might alter practice or policy: patients/clinicians have more evidence to make decisions
- Feasibility of scaling up the intervention to national-level adoption: cost

Question 2. Which of the available therapies—existing and recently introduced—for treatment of hepatitis C demonstrate(s) the best outcomes with the fewest side effects?

a. Does interferon still have a role in the treatment of hepatitis C?
b. Can interferon shorten the duration of DAA-based regimen—say, from 12 weeks to 4–8 weeks?
c. Is the magnitude of reduction in risk from complications of hepatitis C, particularly hepatocellular carcinoma, the same with SVR achieved by interferon-free regimens as it is for SVR achieved by interferon-based regimens?
d. What is the extended SVR of these regimens; what is the long-range and population-based toxicity of these regimens; how are these regimens directly compared with one another in terms of response rate; in what situation would one regimen be used over the others; and do patients who are traditionally difficult to treat have different outcomes?
e. How do the various available treatments compare on patient adherence?
f. What treatment dosages and durations of therapies have the best long-term results and the fewest side effects?
g. Does antiviral therapy ameliorate the common nonspecific symptoms of chronic hepatitis C?

Question 3. Would those failing one Direct Acting Antiviral drug (DAA)-based combination regimen respond to another regimen?

Question 4. What are the real-world rates of reinfection, particularly among IV drug users? Do any of the antiviral regimens provide long-term protection against reinfection?

General Commentary:

- Head-to-head trials might not be so much about SVR; they might be more about longer-term complications, outcomes related to quality of life. Patients without cirrhosis may represent the patient group that warrants the most study.
- Better data may come from the doctors who currently treat IV drug users, as opposed to enrolling these patients in a trial/study.
- Is there a benefit to treating early-stage patients?

The group drafted two new outcome questions. The participants then voted on which head-to-head trials question are most important in designing a patient-centered research study.

Rank	Question	Vote Breakdown
1	Question 1: Which of two all-oral interferon-free strategies for the treatment of chronic genotype 1 hepatitis C infection, including sofosbuvir/ledipasvir and paritaprevir/ritonavir/ombitasvir/dasabuvir +/- ribavirin, will maximize sustained virologic response (SVR) and minimize adverse effects and harm?	**20**
2	Question 2: Is there a benefit to treating early-stage patients?	**13**

Patient Populations and Timing of Treatment

Breakout leader: Dr. Martha Gerrity, Drug Effectiveness Review Program, Oregon Health and Sciences University
PCORI staff moderator: Dr. David Hickam, Program Director, Clinical Effectiveness Research

The stakeholder participants were:

- Dr. Michael del Aguila, Bristol-Myers Squibb
- Dr. David Gollaher, Gilead Sciences
- Dr. Jenifer Graff, National Pharmaceutical Council
- Ms. Barbara D. Lardy, America's Health Insurance Plans
- Dr. Juan Carlos Lopez-Tatavera, AbbVie
- Ms. Robin Lord Smith, Hepatitis C Association
- Dr. Samar Muzaffer, Medicaid Medical Directors Network (via teleconference)
- Ms. Ivonne Perlaza Fuller, Hepatitis Foundation International
- Dr. Walter Tsou, American Public Health Association
- Ms. Sarah van Geertruyden, Partnership to Improve Patient Care

The PCORI staff participants were:

- Dr. Naomi Aronson, Methodology Committee Member
- Ms. Cathy Gurgol, Program Officer, Addressing Disparities
- Ms. Jana-Lynn Louis, Program Associate, Clinical Effectiveness Research
- Ms. Jean Slutsky, Chief Engagement and Dissemination Officer

Question 1. What are the safety profile and effectiveness of HCV therapy in specific patient populations? These populations include:

- *Patients co-infected with hepatitis C and HIV*
- *Racial and ethnic patient populations*
- *Older age groups*
- *Infection with different genotypes*
- *Asymptomatic patients versus those who have fatigue or reduced vitality*
- *Receive care from safety-net health facilities*
- *Living in poverty/uninsured*
- *Living in correctional facilities or under correctional supervision*
- *People with serious mental illness*
- *People who consume alcohol heavily*
- *Marijuana users*
- *People who use noninjected drugs (e.g., crystal meth, MDMA, ecstasy, cocaine, heroin, pharmaceutical opioids*
- *People who inject illicit drugs while receiving substance use treatment (e.g., opioid substitution therapy)*
- *People who inject illicit drugs and do not receive substance use treatment*
- *People receiving substance use treatment (e.g., opioid substitution therapy) who do not currently use illicit drugs*

Discussion of Question 1 began with a clarification of the definitions of effectiveness versus efficacy. A participant explained that effectiveness refers to results in a clinical trial with highly controlled circumstances and highly selected populations with some control over the delivery of care, whereas efficacy refers to real-world situations with a great deal of heterogeneity, such as different healthcare delivery systems. It was noted that PCORI is interested in comparative real-world effectiveness, and the group should consider patient-centered effectiveness and outcomes that matter to patients.

The many confounding variables will make this research challenging. Treatment decisions may depend on the type of healthcare that is available to all patient populations, which in turn may be linked to socioeconomic determinants of long-term treatment outcomes. Two key groups are IV drug users and patients co-infected with hepatitis C and HIV. The group may have to assume that the best treatment for these patient populations will have to be accessible across all HCV genotypes.

Because of the commonalities and important dimensions among the patient populations, a participant proposed that the group consider combining some of the populations.

A participant asked about an evidence gap analysis. The most recent (2012) systematic review included only drugs that were approved by FDA at that time. The major evidence gap is comparative studies of drugs that have come on the market since 2012 and for drugs that will soon be on the market. Few of the studies in the research review were effectiveness studies and still fewer were studies of outcomes in subgroups. Future studies should include subgroup analyses of patients not previously treated, non-responders, and African Americans. It was noted that gaps may occur because of patients who are difficult to treat or have contraindications. Future studies should address evidence gaps that affect

treatment decisions. Mounting real-world, prospective CER of hepatitis C treatment outcomes will be difficult.

A participant commented that the HCV genotype may influence the outcomes of patient-centered treatment more than the specific patient population. Another participant agreed that the different genotypes are present in all subgroups of patients. Reinfection is a concern across all subgroups. Including genotype as a variable may make studies more difficult to perform, if only because it will be hard to enroll enough patients with the less prevalent genotypes.

The group discussed combining substance users, then classifying them according to current or past use. Active drug users are often difficult to recruit into trials and excluded. However, they are an important population to study. PCORI has an opportunity to make a major contribution by studying treatment of marginalized populations such as active drug users.

Key elements of this question:

- Target condition: hepatitis C across all genotypes, previously untreated, and treatment-experienced
- Target population: people with disparities in access to care, people with high-risk behaviors (e.g., active substance use, past substance use, risky sexual behaviors, involvement with criminal justice system)
- Compared interventions: treatment with alternative approaches to enhanced care (e.g., mental health and substance use treatment, public health measures, community outreach)
- Proposed outcome measures (including patient-centered outcomes): prevent reinfection and reduce transmission
- Possible results and how they might alter practice or policy: achieve cure, improve quality of life

Question 2. What are the comparative benefits and harms of treating all HCV-infected patients versus treating only those patients who show signs of liver disease and delaying treatment in those who are at low risk for developing fibrosis of the liver? What stage of liver disease should be a clear indication to start antiviral therapy? How accurate are the methods for staging liver disease due to HCV.

A participant questioned whether it is ethical to withhold treatment from any HCV-infected patient until there is evidence of liver fibrosis. It was noted that two-thirds of people with HCV infection will never develop significant liver disease, which has led to proposals to evaluate newly diagnosed patients for their risk of developing liver disease, which is one of the clinical factors that would inform treatment decisions. However, models to estimate the probability that HCV infection will progress to hepatic cirrhosis do not exist Treating people at very low risk of developing liver disease raises safety concerns (exposing them to the risks of treatment with a relatively low probability of benefiting). Another consideration is treating infected patients to alleviate the extra-hepatic symptoms of HCV infection.

One argument for early treatment of HCV-infected patients, even if asymptomatic, is that it reduces the size of the pool of people who can transmit the disease, which should accelerate progress toward making hepatitis C a rare disease. By this argument, since the early stages of liver damage are often clinically silent, it is important for a patient to know whether he or she can transmit the disease. Both the short-term and the long-term effects of early vs. delayed treatment are important. Patients achieving a SVR with interferon and ribavirin have been far less likely to develop advanced liver disease.

Key elements of this question:

- Target condition: hepatitis C across all genotypes, previously untreated, and treatment-experienced
- Target population: previously untreated, newly diagnosed patients
- Compared interventions: immediate antiviral treatment versus active monitoring and treatment based on disease progression
- Proposed outcome measures (including patient-centered outcomes): quality-of-life measures (short term), development of fibrosis (long-term).
- Study design: randomized trial and/or observational study
- Feasibility of doing the study as outlined: potential problems with patients being willing to be randomized to delayed treatment; confounding by indication in an observational study.
- Possible results and how they might alter practice or policy
- Feasibility of scaling up the intervention to national-level adoption

Question 2 was modified as follows:
What are the comparative benefits and harms of treating HCV-infected patients early versus delaying treatment until the occurrence of early stage liver disease or extra-hepatic manifestations of HCV infection?

a. *What are the predictive factors or models that help determine the risk of progression of liver disease?*

Question 3. Does treating HCV help in the management of identified comorbidities (e.g., diabetes mellitus, cardiovascular disease, chronic kidney disease)?

Comorbidities and symptoms such as fatigue, depression, and anxiety have an impact on an HCV-infected person's quality of life. Comorbidities such as diabetes mellitus, cardiovascular disease, and chronic kidney disease affect treatment of hepatitis. This question applies particularly to Question 1, and the group discussed a proposal to add patients with comorbidities as a sub-population in Question 1.

Question 4. Can antiviral therapy reduce transmission of hepatitis C? Should an attempt be made to eradicate hepatitis C in IV drug users? What interventions can reduce transmission of hepatitis C?

Reinfection rates in the general population after 10 years are very low, about 2%, but these rates may be higher in high-risk groups. A participant was concerned about the reservoir of hepatitis C and suggested that the group focus on IV drug users because of their propensity for reinfection. Early treatment of HCV-infected IV drug users might be unsuccessful if reinfection commonly occurs in this high risk population. According to the discussion, reinfection rates in HCV-infected patients who are treated immediately after diagnosis are lower than expected. A participant posed two questions: (1) What are the real-world reinfection rates? (2) What patient management strategies would be most effective in reducing reinfection rates post-SVR? Since the major factor of reinfection is IV drug use, co-treatment of drug addiction may be necessary to eradicate hepatitis C infection. The highest rates of co-infection are with HIV. . Public health interventions, such as needle-exchange programs, and patient management of hepatitis C may be the most effective strategies to prevent reinfection.

The group voted on which of the three modified questions about patient populations and timing of treatment are most important in designing a patient-centered research study.

Rank	Question	Vote Breakdown
1	Question 2: What are the comparative benefits and harms of treating HCV-infected patients early versus waiting to treat only those patients who show progression of liver disease? What are the predictive factors or models that help determine risk of progression of disease? What are the comparative benefits and harms of treating all HCV-infected patients versus treating only those patients who show signs of liver disease or other manifestations of hepatitis C infection?	**23**
2	Question 1: What are safety profile and effectiveness of HCV therapy in specific patient populations?	**18**
3	Question 3: In difficult-to-treat patients, does treating hepatitis C help in the management and treatment of comorbidities such as diabetes mellitus, cardiovascular disease, chronic kidney disease, renal transplant, and HIV infection?	**7**

Plenary session: Review and Discussion of Prioritized CER Questions

The breakout leaders presented their respective final questions and discussed the key elements of each. Other topics included:

- Medicaid evidence-based policies and real budget implications
- Issues of trials sizes and distinction between SVR rates
- Issues of drugs costs/prices, Medicaid budget, and treatment denial
- Feasibility issues of generating a control arm of patients from busy clinical practices
- Capitalizing on first-generation patients treated with DAA drugs
- Methods to synthesize data from multiple ongoing studies
- Use of international cohort studies and large networks
- Headline for the PCORI-funded hepatitis C study
- Impact of hepatitis C treatment on healthcare utilization
- Evidence/data to support changes in treatment policies

Care Delivery

- Appropriateness of observational studies versus RCTs
- Methodological issues of studying individual components versus multi-component approaches; combining interventions
- Feasibility of addressing questions, support/funding by organizations such as the Centers for Disease Control and Prevention, Centers for Medicare and Medicaid Services, and Agency for Healthcare Research and Quality
- Opportunities for collaboration and use comparator groups

Screening and Diagnostic Tests

- VA policy of mandated reflex testing
- Collaboration with the American College of Pathologists

- Regulatory impact of mandated testing
- Issues of clinicians not routinely testing for hepatitis C
- Ways to link people who receive free screening tests to healthcare providers
- Nurse-initiated testing versus physician-initiated testing
- Use of emergency department testing studies

Head-to-Head Trials

- Use of adaptive trial designs
- Taking advantage of existing resources
- Long-term rare side effects
- Systematic exclusion of certain patient populations in pharmaceutical trials
- Problems treating actively using drug addicts due to payment issues
- Drug funding sources in RCTs
- Head-to-head trials that address gaps in ongoing pharmaceutical trials

Patient Populations and Timing of Treatment

- Predictive factors that help determine risk of progression of disease
- Focus on individuals with bipolar disorder and hepatitis B or C; good interventions could be scaled up through help from Centers for Medicare and Medicaid Services and health home state plan amendments
- Ethical issues of early versus late/delayed therapy
- Ethical issues of using RCTs (i.e., withholding treatment)
- Safety and effectiveness of new drugs; balance of risks versus benefits
- Patient priority: What do I need to do to be cured?
- Relationship of comorbidities in hepatitis C disease progression
- Possibility of long-term toxicity and side effects of drugs
- Evidence on risks and benefits of immediate treatment versus risk and benefits of delayed treatment: U.S. Food and Drug Administration evidence supports immediate treatment
- Medicaid and insurance coverage at advanced disease stage and issues of affordability

Ranking of CER questions

The participants then voted on which questions are most important in each area.

Rank	Question	Vote Breakdown
Care Delivery		
1	Question 5: What is the comparative effectiveness of available healthcare delivery approaches for reaching, screening, assessing disease, treating, and preventing new infections and reinfections of hepatitis C?	**11**
2	Question 1: What approaches for linking primary care physicians with specialty teams are most effective in accurately diagnosing and effectively treating patients with hepatitis C, particularly people in rural or medically underserved areas?	**6**
Screening and Diagnostic Tests		
1	Questions 3 and 4 (combined): Which hepatitis C screening methods have the highest linkage to healthcare? Which methods work in which settings?	**13**
2	Question 2: Compare the response rate to rapid antibody test versus reflex test versus "conventional" testing on the outcome of linkage to care and patient satisfaction.	**2**
Head-to-Head Trials		
1	Question 1: Which of two all-oral interferon-free strategies for the treatment of chronic genotype 1 hepatitis C infection, including sofosbuvir/ledipasvir and paritaprevir/ritonavir/ombitasvir/dasabuvir +/- ribavirin, will maximize sustained virologic response (SVR) and minimize adverse effects and harm?	**12**
2	Question 2: Is there a benefit to treating early-stage patients?	**2**
Patient Populations and Timing of Treatment		
1	Question 2: What are the comparative benefits and harms of treating HCV-infected patients early versus waiting to treat only those patients who show progression of liver disease or other manifestations of hepatitis C infection? What are the predictive factors or models that help determine risk of progression of disease?	**20**
2	Question 1: What are safety profile and effectiveness of HCV therapy in specific patient populations?	**8**
3	Question 3: In difficult-to-treat patients, does treating hepatitis C help in the management and treatment of comorbidities such as diabetes mellitus, cardiovascular disease, chronic kidney disease, renal transplant, and HIV infection?	**4**

Next Steps

The input from this workshop is being folded into PCORI's overall process for deciding which CER questions to focus on for future funding. PCORI staff reviewed the workshop proceedings and presented the input to the Science Oversight Committee (SOC) on November 18. The SOC advises PCORI's Board of Governors, which makes final decisions on topics for research funding and the amount of money invested in such studies. The Board considered the SOC recommendation on December 8, 2014 and approved the development of a PCORI Funding Announcement (PFA) providing up to $50 million for up to four comparative clinical effectiveness research (CER) studies on the best ways to diagnose and treat hepatitis C virus infection. With the Board's approval, PCORI will develop a PFA focused on hepatitis C virus (HCV) research questions that emerged as the highest priorities during a multi-stakeholder workshop PCORI hosted on October 17. The four priority topics are:

- Finding out which screening methods and testing strategies in which settings lead to the best detection rates.
- Assessing alternative ways to deliver care to high-risk populations.
- Exploring the trade-offs between long-term virologic response and adverse effects associated with different regimens of new oral antiviral medications.
- Comparing the benefits and harms of starting treatment immediately after a diagnosis versus active surveillance, in which treatment starts once a patient shows progression to liver disease or other manifestations of infection.