Research Prioritization Topic Brief

Topic 1: "Hepatitis C"

What is the comparative effectiveness of antiviral treatments for Hepatitis C on short- and long-term outcomes? Outcomes of interest include the rate of sustained virologic response (SVR), fibrosis, cirrhosis, hepatocellular carcinoma, and other patient-centered outcomes (e.g., quality of life, functional outcomes, anxiety). Do these findings differ depending on specific patient subgroups such as patients with no/early/advanced liver disease or in specific genomic subgroups? (Note a specific interest in exploring the role of Sovaldi® (sofosbuvir) as compared to other new antivirals vs older drugs.)

PCORI Scientific Program Area: Assessment of Prevention, Diagnosis, and Treatment Options

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October 17, 2014

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Criteria	Brief Description
Introduction	
Overview/definition of topic	DESCRIPTION OF CONDITION[1-3] • Hepatitis C virus (HCV) is a small, enveloped, single-stranded RNA virus • HCV is transmitted primarily through exposure to infected blood via: o Injection drug use (most common means of transmission in the United States) o Receipt of donated blood, blood products, and organs o Needlestick injuries in health care settings o Birth to an HCV-infected mother (4% of pregnancies) o Less commonly, transmission can occur through sex with an infected person • Infection with HCV can cause both acute and chronic hepatitis (liver inflammation): o Acute infection is generally asymptomatic or causes nonspecific symptoms o Approximately 80% of patients with acute HCV infection develop chronic infection (as indicated by persistent HCV RNA in the blood and/or elevated liver enzyme tests reflecting ongoing inflammation in the liver) • Of the 6 known genotypes of HCV, genotypes 1, 2, and 3 are the most common in the United States, causing 97% of all infections o Genotypes 4-6 are more common in other parts of the world (e.g., >90% of cases in Egypt are genotype 4 and genotype 5 is most common in South Africa) • Chronic HCV is the most common cause of cirrhosis and the most common indication for liver transplantation in the United States
Relevance to patient-centered outcomes	SYMPTOMS[1,2] • Acute infection with HCV is often asymptomatic • Among individuals with chronic infection, approximately 20-30% develop cirrhosis over a 20- to 30-year period • Cirrhosis means the patient has developed advanced scarring or fibrosis in the liver, and this scarring develops in response to chronic inflammation; as it progresses, cirrhosis can lead to decompensated liver disease, the symptoms of which include: o Fatigue, weakness, poor appetite o Ascites (large volume fluid collection in the abdomen) o Esophageal varices (dilated blood vessels in the esophagus), which can lead to severe bleeding o Encephalopathy (confusion caused by ammonia and other toxins in the blood) o Jaundice (yellowing of the skin due to buildup of bilirubin) o Gynecomastia (tender enlargement of the breast tissue) o Splenomegaly (spleen enlargement) o Anemia (low red blood cells), thrombocytopenia (low platelets) OUTCOMES[3-5] • Among the 20-30% of patients with chronic HCV developing cirrhosis, several important outcomes occur at higher rates: o Decompensated liver disease: for patients with HCV cirrhosis, the 5-year probability for liver decompensation is 22.2%, with a yearly incidence of 4.4% o Hepatocellular carcinoma (HCC): the 5-year probability of developing HCC is

	10.1% among patients with HCV cirrhosis, with a yearly incidence of 2.0% - most cases occur in patients with advanced cirrhosis o Rare immune system-related complications: cryoglobulinemia, lymphoma o Mortality: the CDC estimates that 15,106 deaths were caused by HCV in 2007, and HCV-related deaths increased significantly between 1999 and 2007 as the population of patients with HCV has aged ▪ Per another report, among 200 patients with compensated cirrhosis at baseline, the probability of survival after diagnosis of decompensated HCV-related liver disease was 51% percent at 5 years
Burden on Society	
Recent incidence and prevalence in populations and subpopulations	INCIDENCE (NEW CASES)[3] • The incidence of HCV infection is difficult to estimate because acute infection is typically asymptomatic and therefore seldom detected or reported • Per adjusted CDC estimates, ~17,000 new HCV infections occurred in 2007 PREVALENCE (PROPORTION OF POPULATION LIVING WITH THE CONDITION)[1,3] • It is estimated that 185 million individuals worldwide are infected with HCV • Approximately 3-4 million individuals in the United States have chronic HCV infection, with higher rates among men and African-Americans • The prevalence of HCV is particularly high among: o Patients born between 1945-1965 o Current or former injection drug users o Incarcerated people o Homeless people o Veterans o Recipients of blood transfusions or organ transplants before July 1992 (before testing became more rigorous) o Chronic hemodialysis patients o Patients with human immunodeficiency virus (HIV)—1/3 of HIV patients also have HCV
Effects on patients' quality of life, productivity, functional capacity, mortality, use of health care services	QUALITY OF LIFE[1,6] • The sequelae of decompensated liver disease (fatigue, ascites, hepatic encephalopathy, variceal bleeding,) have a profound impact on patient quality of life • The extent to which earlier HCV infection stages may affect quality of life is debated o For example, there may be a causative link between HCV infection and depression relating to infection of brain cells • Treatments for HCV, particularly interferon (IFN) have a profound negative impact on quality of life due to both physical (constitutional symptoms, anemia, autoimmune disease) and psychological (severe depression) side effects PRODUCTIVITY[7] • Regardless of whether patients are undergoing active treatment, evidence exists that chronic HCV infection is associated with decreased work productivity and increased absenteeism; this is also the case for liver transplant recipients FUNCTIONAL CAPACITY[8]

	• Non-cirrhotic patients with chronic hepatitis C have lower performance on 6-minute walk testing compared to healthy controls o The explanation for this is not clear, but may relate to the symptoms (e.g., depression) patients with earlier stages of infection can experience • Patients with cirrhosis have worse 6-minute walk performance than non-cirrhotic HCV patients, and 6-minute walk in this population correlates with clinical parameters (albumin, anemia) and survival MORTALITY • If decompensated liver disease develops, mortality is dramatically increased (see "Outcomes" above)

How strongly does this overall societal burden suggest that CER on alternative approaches to this problem should be given high priority?	• For 2013, the total yearly cost of HCV is estimated at $6.5 ($4.3-$8.4) billion[9,10]
	  o It is predicted that this cost will peak in 2024 at $9.1 ($6.4-$13.3) billion
	  o The lifetime cost of an individual infected with HCV in 2011 was estimated at $64,490 in 2011 dollars; the lifetime cost increased to $205,760 when adjusted for medical inflation. It is significantly higher among individuals with a longer life expectancy
	• Given the costs of HCV, along with its impact on mortality, quality of life, and other important parameters, HCV treatment should be considered a high-priority target for comparative effectiveness research (CER) evaluating the impact of available treatments on patient-centered outcomes
	• Its substantial public health impact led the Institute of Medicine (IOM) to designate comparison of treatments for HCV as a priority area for CER[11]

Options for Addressing the Issue	

Based on recent systematic reviews, what is known about the relative benefits and harms of the available management options?	SCREENING/EARLY DIAGNOSIS[12,13]
	• Screening and early diagnosis utilize HCV antibody tests
	• The CDC and USPSTF recommend screening the following populations for HCV:
	  o Born in the United States between 1945 and 1965
	  o History of injecting illegal drugs
	  o Received clotting factors made before 1987
	  o Received blood/organs before July 1992
	  o History of chronic hemodialysis
	  o Have evidence of liver disease (abnormal liver blood tests)
	  o HIV-infected patients
	
	TREATMENT[1,2,14]
	• The decision of when/how to treat HCV is complicated and should consider the current stage of liver disease, HCV genotype, extra-hepatic manifestations, anticipated adverse effects, patient preferences, and previous treatments attempted
	• Cure with HCV treatment is defined as a "sustained virologic response" (SVR), which is defined by undetectable levels of HCV RNA 12-24 weeks after therapy completion
	  o Data regarding the comparative effectiveness of different regimens on longer term outcomes is limited, but SVR is known to lead to reduced rates of liver-related mortality, hepatic decompensation, and the development of HCC[15]
	• Rapid changes are occurring in HCV treatment. One of the first direct-acting antivirals (DAAs), telaprevir, was recently withdrawn from the market due to advances with

	other medications. Agents currently available for HCV treatment include: o IFN (pegylated interferon alfa-2a or -2b)—stimulate immune response to HCV o Ribavirin—oral antiviral nucleoside analog o Simeprevir/boceprevir (DAAs)—selective HCV protease inhibitors for genotype 1 o Sofosbuvir (DAA)—nucleotide polymerase inhibitor (brand name Solvaldi®) for genotypes 1-6 o Several more DAAs are currently in development, with the following agents expected to receive U.S. Food and Drug Administration (FDA) approval in 2014 ▪ Ledipasvir (NS5A inhibitor) in combination with sofosbuvir for genotype 1 infection[16,17] ▪ ABT-450 (protease inhibitor boosted by ritonavir), ombitasvir (NS5A inhibitor), dasabuvir (non-nucleoside polymerase inhibitor) for genotype 1 infection[18] ▪ Daclatasvir (NS5A inhibitor) and asunaprevir (protease inhibitor) for genotype 1b infection[19] • Recent systematic reviews have evaluated treatment options for achieving SVR with HCV, and there is mounting evidence that regimens including DAAs (particularly the newer agents, sofosbuvir and simeprevir), with or without IFN, are more effective and better tolerated than traditional IFN/ribavirin-based regimens. For example: o There is strong evidence for sofosbuvir + IFN + ribavirin for treatment-naïve patients with HCV genotype 1, and there is evidence supporting this regimen for treatment-experienced patients. o There is strong evidence for sofosbuvir + ribavirin alone for treatment-naïve or treatment-experienced patients with HCV genotypes 2 and 3 (but not genotype 1). o There is strong evidence for simeprevir + IFN + ribavirin for treatment-naïve or treatment-experienced patients with HCV genotype 1. o Though evidence is limited and the combination is not approved by the FDA, the combination of sofosbuvir + simeprevir holds promise for treatment of patients with HCV genotype 1 due to its apparent effectiveness and tolerability. o There is strong evidence for boceprevir or telaprevir in combination with IFN + ribavirin for genotype 1 patients, but these older DAAs are less well-tolerated and have more drug interactions than sofosbuvir/simeprevir. • The new DAAs currently in development are looking to be very effective and may potentially replace the above treatments. • Liver transplant is an option for patients with advanced HCV liver disease, but re-infection occurs in all patients without treatment.
What could new research contribute to achieving better patient-centered outcomes?	New research could contribute to achieving better patient-centered outcomes: • Newer regimens (e.g., sofosbuvir + simeprevir) are much better tolerated than traditional IFN-based regimens, so if confirmed in real-world practice, could have a dramatic impact on patient-centered outcomes (e.g., quality of life, productivity) • Cost-effectiveness research is needed—the cost of treatment for a patient with HCV genotype 1 may be as high as $150,000, which may impact use of newer agents[1] • CER further exploring longer term patient-centered outcomes (e.g., mortality, liver

	failure, HCC, hospitalization) is needed
Have recent innovations made research on this topic especially compelling?	Recent innovations: • The emergence of sofosbuvir and simeprevir, along with other DAAs in development, have dramatically changed HCV treatment • The potential replacement of even some of these new DAAs with additional agents currently in development/under FDA review • These new treatment options strongly warrant further study both in real world practice and in comparison to each other.
How widely does care now vary?	VARIABILITY IN CARE[1,20] • HCV infection is more common in African-Americans than in Caucasians • African Americans appear to have lower rates of SVR with IFN-based therapy vs. Caucasians o Preliminary evidence suggests that this difference may be reduced with sofosbuvir treatment • Limited data have been published regarding treatment of African American and Hispanic patients using regimens that include sofosbuvir or simeprevir. The scarcity of data is mostly driven by low enrollment of these groups in existing trials.

What is the pace of other research on this topic (as indicated by recent publications and ongoing trials)?	RECENT PUBLICATIONS
	• A MEDLINE search from 8/13/2009 through 8/13/2014 yielded a total of 7,207 citations potentially relevant to the effectiveness of HCV treatment options.
	  o 383 were labeled as randomized controlled trials/therapy
	  o 325 were labeled as meta-analyses or systematic reviews
	  o 12 were labeled as observational studies
	
	ONGOING TRIALS
	• A search of www.clinicaltrials.gov for open studies using the terms “hepatitis C” and “treatment” yielded 125 studies. Of those:
	  o 116 focused exclusively on HCV
	  o 19 listed sofosbuvir as the drug/intervention
	  o 3 focusing on ledipasvir in combination with sofosbuvir (planned completion late 2015) for patients with genotype 1 infection
	  o 3 targeting daclatasvir or asunaprevir for patients with genotype 1b infection (planned completion in 2015)
	  o 1 studying ombitasvir/ABT-450/ritonavir and dasabuvir in patients with genotype 1 infection (planned completion Spring 2015)
	• HCV Target (Hepatitis C Therapeutic Registry and Research Network) is a research consortium (led by University of Florida and University of North Carolina at Chapel Hill) and includes 103 academic and community sites. Investigators have established a common research database and are conducting a longitudinal observational study to answer important questions about HCV therapy with DAAs. More information is available at: http://www.hcvtarget.org/.

How likely is it that new CER on this topic would provide better information to	KEY UNCERTAINTIES IN CLINICAL DECISION MAKING • Impact of newer HCV regimens in racially and economically diverse populations • Cost-effectiveness of newer HCV regimens • Impact of newer HCV regimens on longer term patient-centered outcomes • Comparative effectiveness of the new regimens against each other

guide clinical decision making?	• Whether ribavirin is needed • Duration needed for hard-to-treat patients (e.g., genotype 1a with cirrhosis patients)—do they need 24 weeks? • How short can we make treatment for some patients (i.e., can it be reduced to 8 weeks? 6 weeks?) • Is HIV-HCV really different from HCV mono-infections? • Can we predict which patients with HCV will develop cirrhosis? LIKELIHOOD THAT CER WOULD BE ABLE TO REDUCE THESE UNCERTAINTIES • There is a high likelihood that appropriately designed comparative effectiveness studies would be able to effectively address these and other areas of uncertainty, although longer term outcomes may be challenging to evaluate in randomized trials
Potential for New Information to Improve Care and Patient-Centered Outcomes	
What are the facilitators and barriers that would affect the implementation of new findings in practice?	FACILITATORS • HCV has a reasonably high prevalence (which is increasing), causes substantial morbidity and mortality, and is already considered a high-priority condition • Many treatment options exist for HCV, all of which may affect quality of life and other patient-centered outcomes in different ways • Racial disparities exist in rates of HCV, and likely in response to treatment, but there are gaps in our knowledge about the latter • Given the wide range of available treatment options and remaining areas of clinical uncertainty, CER on treatment for HCV is likely to have an important impact BARRIERS • Cost of newer agents • Difficulty of conducting trials examining longer term patient-centered outcomes
How likely is it that the results of new research on this topic would be implemented in practice right away?	EVIDENCE OF BENEFIT • Findings would be likely to be implemented widely if there is evidence for better patient-centered outcomes. EVIDENCE OF NO BENEFIT OR HARM • It is likely that research demonstrating no evidence for benefit would also impact practice by supporting current practice.
Would new information from CER on this topic remain current for several years, or would it be rendered obsolete quickly by subsequent studies?	Although treatment options continue to evolve, it is likely that new information regarding antiviral treatment and effects on patient-centered outcomes in different populations would remain relevant for years

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