Future Considerations for the Evaluation of Hepatitis C Virus Treatments in Pan-Genotypic Therapy for Noncirrhotic Treatment-Naive Patients

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SUMMARY

Given the recent approval of the first pan-genotypic chronic hepatitis C virus (HCV) therapy, managed care, health systems, and clinicians will need to evaluate current practices related to essential laboratory assessments used to select therapy. Historically, clinicians and payers required a battery of tests to determine HCV genotype, viral load, degree of fibrosis, and organ function. In light of current and forthcoming approvals of pan-genotypic therapy, clinicians and payers can expect a more competitive marketplace and a downward curve in the price of therapy. Ultimately, this development will lead to the cost of screenings and assessments having an increased role in selecting an optimal HCV therapy.

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In the current environment of highly effective and well-tolerated curative agents for chronic hepatitis C virus (HCV), guidelines have recommended the broad use of direct-acting antivirals (DAAs) for the vast majority of individuals with chronic HCV.¹ Until the approval of sofosbuvir/velpatasvir, the first pan-genotypic DAA, all other currently recommended DAA regimens had segmented the market around a patient's HCV genotype, which can include 1(a or b), 2, 3, 4, 5, or 6. In the United States, the vast majority of cases are genotype 1a or 1b.¹⁻³

Before June 2016, approved U.S. guideline-recommended chronic HCV therapies encompassed a variety of options that included elbasvir/grazoprevir, daclatasvir+sofosbuvir ledipasvir/sofosbuvir, paritaprevir/ribavirin/ombitasvir+dasabuvir, paritaprevir/ribavirin/ombitasvir, and simeprevir+sofosbuvir.^{1,4-9} Each of these medications requires genotype testing plus a variety of additional testing and considerations in accordance with labeling approved by the U.S. Food and Drug Administration (FDA), including determining resistance-associated variants (RAVs), drug/drug interactions, prognosis of liver disease assessed by Child-Pugh, and cirrhosis with or without compensation. The results of these assessments may indicate that further therapeutic action should be considered. For example, Child-Pugh class C is indicative of decompensated cirrhosis, which warrants the addition of weight-based ribavirin therapy. After considering drug-drug interactions and other clinical factors in the setting of pan-genotypic sofosbuvir/velpatasvir, genotype testing, along with other commonly used

laboratory and diagnostic assessments, may not be required (Table 1).¹⁰

Given the wide variety of guideline-directed therapies that are equally relatively safe and effective and the likelihood of additional pan-genotypic agents in the future, it is important to be mindful of the minimum required screenings and their costs in order to efficiently use the DAA therapeutic options available to patients. Additional pan-genotypic medication in the pipeline from a number of manufacturers will lead to a downward curve of the medication price. Subsequently, this downward curve would require health systems, clinicians, and payers to be mindful of the laboratory and assessment costs before and during HCV therapy. Considering the complexities involved in the determination of the true price for medications (e.g., manufacturer rebates), the authors intentionally excluded the cost of therapy from cost of laboratory screenings and assessments.

Laboratory screenings and assessments required to properly evaluate the on-label use of current guideline-directed therapies are compiled in Table 1.^{1,4-9} This table is not comprehensive and highlights the laboratory and screening assessment likely required for noncirrhotic treatment-naive patients. Screenings and assessments to verify that a patient is noncirrhotic are included for completeness. In addition, as more pan-genotypic agents come to market, clinicians, health systems, and payers need to be mindful that the screenings and assessments required before and shortly after initiating treatment vary between therapies. The fee-for-service costs per the Centers for Medicaid and Medicare Services are included for reference.^{11,12}

According to FDA-approved prescribing information for various therapies, determination of RAVs only needs to be considered for elbasvir/grazoprevir and daclatasvir + sofosbuvir regimens in patients with genotypes 1a and 3. Although degree of fibrosis/cirrhosis may not be specifically required for some agents, such as elbasvir/grazoprevir and ledipasvir/sofosbuvir, it may be considered best practice to determine the degree of cirrhosis/fibrosis, since it is pertinent to the overall clinical picture. In addition, determination of hepatic prognosis measured by Child-Pugh and need for additional screening for complications of cirrhosis such as esophageal varices and hepatocellular carcinoma may be warranted.

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TABLE 1 Suggested Laboratory Screenings and Assessments Before and During HCV Therapy for Treatment-Naïve Noncirrhotic Patients

Laboratory Screenings and Assessments	Cost ^a U.S. \$	Treatments					
		Elbasvir/ grazoprevir	Daclatasvir + sofosbuvir	Ledipasvir/ sofosbuvir	PrOD or PrO	Simeprevir + sofosbuvir	Sofosbuvir/ velpatasvir
Genotype	473.91	X	X	X	X	X	
RAV	177.56	X ^b	X ^c				
Degree of fibrosis							
FibroSure	80.62	X	X	X	X	X	X
Ultrasound	124.24	X	X	X	X	X	X
Child-Pugh							
Total bilirubin	6.83	X	X	X	X	X	X
Serum albumin	6.74	X	X	X	X	X	X
Prothrombin time	5.37	X	X	X	X	X	X
ALT	7.22	X			X		
SCr	12.88		X	X		X	X
CBC	11.91	X ^d			X ^e		
Costs compared with sofosbuvir/velpatasvir, U.S. \$							
If RAV required		894.40	888.15	710.59	716.84	888.15	236.68
All other genotypes ^f		704.93	710.59	710.59	704.93	888.15	236.68

Note: X=indicated/recommended. This table highlights laboratory screenings and assessments that are needed for the use of guideline DAA HCV treatment. Additional screenings such as for HIV or HBV coinfection, pregnancy, and drug-drug interactions should be considered for all therapies.

^aDefined by Centers for Medicare & Medicaid Services 2016 laboratory and physician fee schedules.^{11,12}

^bGenotype 1a–nonstructural protein 5A (NS5A) variant.

^cOnly required for genotype 3.

^dOnly required in combination with ribavirin (genotype 1a with NS5A RAVs).

^eMay not be required if ribavirin is not used in patients with genotype 1b.

^fIf genotype is an indication for given treatment.

ALT = alanine aminotransferase; CBC = complete blood count; DAA = direct-acting antivirals; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; PrO = paritaprevir/ribavirin/ombitasvir; PrOD = paritaprevir/ribavirin/ombitasvir + dasabuvir; RAV = resistance-associated variance; SCr = serum creatinine.

As outlined in Table 1, sofosbuvir/velpatasvir requires the least amount of laboratory screenings and assessments. Costs for screenings and assessments in excess of sofosbuvir/velpatasvir are calculated in the last row of Table 1 for each guideline-recommended therapy.

Upon confirmation of a chronic HCV diagnosis, clinicians should be mindful of therapeutic options before ordering further laboratory screenings and assessments. Given current availability, likelihood of additional pan-genotypic agents, and the presence of multiple equally relatively effective therapeutic options, it may be prudent to exercise caution in implementing a one-size-fits-all “pan-assessment” when evaluating therapies. This consideration becomes particularly meaningful in situations where therapeutic choices are limited to institutional or insurance formularies and with future approvals of additional pan-genotypic HCV therapies.

In a scenario with at least 2 therapeutic options, it is reasonable for clinicians and health systems to obtain the following laboratory screenings and assessments regardless of which genotype-specific DAA therapy is under consideration: genotype, cirrhosis/fibrosis, and assessments required to determine

the Child-Pugh score. All other screenings and assessments are dependent on subsequent genotype determination and available therapeutic options for clinicians after weighing factors of a patient’s insurance and health system formularies. Unless pan-genotypic therapies are the only therapeutic option, HCV genotype should always be determined in order to identify and evaluate other therapeutic options in treatment-naïve noncirrhotic patients.

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All authors contributed to study concept and design. Calabrese took the lead in data collection, along with Shaya. Data interpretation was performed by Calabrese and Hynicka, along with Rodriguez de Bittner and Shaya. The manuscript was written and revised by Calabrese and Hynicka, along with Rodriguez de Bittner and Shaya.

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