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## Overview of Cost, Reimbursement, and Cost-Effectiveness Considerations for Hepatitis C Treatment Regimens

This section summarizes the US payer system, explains the concepts of cost, price, cost-effectiveness, value, and affordability, and addresses the cost-effectiveness of HCV treatment. This section aims to be informational. As described, actual costs are rarely known. Accordingly, the HCV guidance does not currently utilize cost-effectiveness analysis to guide recommendations.

### Drug Cost and Reimbursement

Many organizations are involved with hepatitis C drug distribution and each can impact costs as well as decisions about which regimens are reimbursed ([US GAO, 2015](#)); ([US CBO, 2015](#)). The roles these organizations have in determining the actual price paid for drugs and who has access to treatment include the following:

- Pharmaceutical companies determine the wholesale acquisition cost (WAC) of a drug (analogous to a sticker price). The company negotiates contracts with other organizations within the pharmaceutical supply chain that allow for rebates or discounts to decrease the actual price paid.
- Pharmacy benefit managers (PBMs) act as intermediaries between pharmaceutical companies and health insurance companies. They negotiate contracts that may include restrictions on the types of providers or patients who can be reimbursed for treatment. They might also offer exclusivity (restrictions on which medications can be prescribed) in exchange for lower negotiated prices, often provided in the form of WAC discounts.
- Private insurance companies often have separate pharmacy and medical budgets, and use PBMs or directly negotiate drug pricing with pharmaceutical companies. Insurance companies determine formulary placement, which impacts the choice of regimens and out-of-pocket expenses for patients. An insurance company can cover private, managed care Medicaid, and Medicare plans and have different formularies for each line of business.
- Medicaid is a heterogeneous consortium of insurance plans that includes fee-for-service and managed care options. Most plans negotiate rebates with pharmaceutical manufacturers (through PBMs or individually). For single-source drugs such as all-oral HCV treatments, Medicaid plans receive the lowest price offered to any other payer (outside of certain government agencies), and the minimum Medicaid drug rebate is 23.1% of the average manufacturer price (AMP). Differences in negotiated contracts between plans have led to Medicaid patients in different states having widely varied access to HCV therapy ([Lo Re, 2016](#)); ([Barua, 2015](#)); ([Canary, 2015](#)). State Medicaid programs have benefited from the Patient Protection and Affordable Care Act (ACA), although such benefits are mitigated in states that have opted out of expanding Medicaid coverage under the ACA. As the price of HCV therapies has decreased, states have loosened their Medicaid treatment restrictions with a growing number providing treatment to all infected persons. Many states, however, continue to restrict access to HCV treatment based on stage of liver fibrosis or history of recent drug use. Proposed rollbacks of Medicaid expansion implemented under the ACA threaten to reduce insurance coverage among HCV-infected people and could lead to new treatment restrictions.
- Medicare covers HCV drugs through part D benefits and is prohibited by law from directly negotiating drug prices. These drug plans are offered through PBMs or commercial health plans, which may negotiate discounts or rebates with pharmaceutical companies.
- The Veterans Health Administration receives mandated rebates through the Federal Supply Schedule program, which sets drug prices for several government agencies (including the Department of Veterans Affairs, federal prisons, and the Department of Defense) and typically receives substantial discounts over average wholesale price (AWP).
- State prisons and jails are usually excluded from Medicaid-related rebates and often do not have the negotiating

- leverage of larger organizations and, therefore, may pay higher prices than most other organizations.
- Specialty pharmacies receive dispensing fees and may receive additional payments from contracted insurance companies, PBMs, or pharmaceutical companies to provide services such as adherence support and/or management of adverse effects, and outcome measurements, such as early discontinuation rates and sustained virologic response rates.
  - Patients incur costs (eg, copayment or coinsurance) determined by their pharmacy plan. Patient assistance programs offered by pharmaceutical companies or foundations can cover many of these out-of-pocket expenses or provide drugs at no cost to qualified patients who are unable to pay.

Except for mandated rebates, negotiated drug prices are considered confidential business contracts. Therefore, there is almost no transparency regarding the actual prices paid for hepatitis C drugs ([Saag, 2015](#)). However, the average negotiated discount of 22% in 2014 increased to 46% less than the WAC in 2015, implying that many payers are paying well below the WAC for HCV medications ([Committee on Finance US Senate, 2016](#)).

## Cost-Effectiveness

Cost-effectiveness analysis (CEA) compares the relative costs and outcomes of 2 or more interventions. CEA explicitly recognizes budget limitations for healthcare spending and seeks to maximize public health benefits within those budgetary constraints. The core question that CEA addresses is whether to invest limited healthcare dollars in a new treatment/therapy or use that money to invest in another healthcare intervention that would provide better outcomes for the same monetary investment. The focus of CEA is, therefore, not simply cost or saving money but health benefits. It assumes that all available resources will be spent and provides a framework for prioritizing among available treatment options by formally assessing the comparative costs and health benefits accrued from a new treatment relative to current treatment.

The cost-effectiveness of a treatment is typically expressed as an incremental cost-effectiveness ratio (ICER).

$$\frac{\text{cost new treatment} - \text{cost current treatment}}{\text{benefit new treatment} - \text{benefit current treatment}}$$

## Estimating and Interpreting the ICER

Estimating and interpreting the ICER requires answering 3 questions:

1. *How much more money will be spent with the new treatment versus the old treatment?*

The additional cost of new treatment includes that of new medications as well as the costs that will be avoided by preventing disease complications. Prevention of long-term complications is especially important when considering the cost-effectiveness of HCV treatments because the costs of the therapy are immediate, while those avoided by preventing advanced liver disease and other complications of chronic infection often accrue years in the future.

2. *How much more benefit will occur with the new versus the old treatment?*

Life expectancy is a valuable measure of benefit but considering only mortality benefits fails to recognize the value of treatments that improve quality of life. The quality-adjusted life-year (QALY) provides a measure that integrates both longevity and quality of life and is the preferred outcome for CEA.

3. *How is the ICER to be interpreted?*

The ideal CEA would list every possible healthcare intervention, its lifetime medical cost, and QALYs lived. Such a list would allow for perfect theoretical prioritization of spending to maximize QALY across the population. In reality, CEA compares the ICER for a specific treatment to a threshold value and rejects treatments with an ICER exceeding a particular threshold as not being cost-effective. The threshold value is referred to as the societal willingness-to-pay threshold. It is not meant to be a valuation of how much society is willing to pay to save a life.

Rather, it is meant to reflect the average return in QALY expected if the available budget was not used to provide a new treatment but instead invested into the current healthcare system. In the United States, the willingness-to-pay threshold is typically considered to be \$50,000 or \$100,000 per QALY gained.

## Affordability

An intervention that is cost-effective is not necessarily affordable. Affordability refers to whether a payer has sufficient resources in its annual budget to pay for a new therapy for all who might need or want it within that year. Several characteristics of CEA limit its ability to speak to the budgetary impact of interventions being implemented in the real world.

### 1. *Perspective on cost*

CEA seeks to inform decisions about how society should prioritize healthcare spending. As such, it typically assumes a societal perspective on costs and includes all costs from all payers, including out-of-pocket expenses for the patient. When making coverage decisions for therapy, however, an insurer considers only its own revenues and expenses.

### 2. *Time horizon*

From a societal perspective, CEA uses a lifetime time horizon, meaning it considers lifetime costs and benefits, including those that occur in the distant future. Business budget planning, however, typically assumes a 1-year to 5-year perspective. Savings that may accrue 30 years from now have no impact on spending decisions today because they have little bearing on the solvency of the current budget.

### 3. *Weak association between willingness-to-pay and the real-world bottom line*

Societal willingness-to-pay thresholds in CEAs are not based on actual budget calculations and have little relationship to a payer's bottom line. Willingness-to-pay is meant to be an estimate of the opportunity cost of investing in a new therapy. In economics, opportunity cost refers to how else that money could have been spent and the benefits lost from not investing in that alternative ([Wong, 2017a](#)). When payers make a decision about coverage, the calculation is more straightforward and relates to the short-term cost of medications and the budgetary impact. Given the rapid development of new technologies and therapies, funding all of them (even if they all fell below the societal willingness-to-pay threshold) would likely lead to uncontrolled growth in demand and exceed the limited healthcare budget.

There is no formula that provides a good means of integrating the concerns of value and affordability. When new HCV therapies are deemed cost-effective, it indicates that these therapies provide good benefit for the resources invested and providing such therapy to more people would be a good long-term investment. Determining the total resources that can be spent on HCV treatment, however, depends on political and economic factors that are not captured by cost-effectiveness determinations.

## Cost-Effectiveness of Current Direct-Acting Antiviral Regimens for Hepatitis C Treatment

Since the first direct-acting antivirals (DAAs) received US Food and Drug Administration approval in 2011, several cost-effectiveness investigations have compared DAA-based regimens to previous standard-of-care regimens to calculate ICERs. They have also investigated the cost-effectiveness of eliminating HCV treatment restrictions. Compared to interferon-based regimens, the ICER for DAAs has consistently been estimated at <\$100,000 per QALY for all genotypes and fibrosis stages.

Several studies have compared DAA regimens against one another. In general, when given a choice between recommended HCV DAA regimens, the less costly regimen is preferred as a more efficient use of resources (even if it requires multiple tablet dosing). Because of the similar efficacy of most DAA regimens, cost becomes the critical factor driving relative cost-effectiveness. Studies have also estimated the cost-effectiveness of HCV treatment in special populations, including patients awaiting liver transplantation, HIV/HCV-coinfected patients, those with chronic kidney disease, persons who inject drugs, and adolescents—all with favorable ICERs. At this time, it is reasonable to conclude that DAA regimens provide good value for the resources invested.

## Cost vs Affordability for HCV Treatment

Despite a growing body of evidence that HCV treatment is cost-effective and may even be cost saving over the long term in some cases, many US payers—especially those offering Medicaid insurance products—continue to limit access to HCV treatment. Access has improved as cost has decreased but limitations remain. Proposed reductions in healthcare spending for Medicaid would likely exacerbate the problem as the value of the HCV medications would remain unchanged but the resources available to provide them would shrink.

## Cost-Effectiveness of Screening for HCV

Several cost-effectiveness studies demonstrate that routine, one-time testing for HCV among all adults in the US would likely identify a substantial number of cases of HCV that are currently being missed, and that doing so would be cost-effective. One study employed simulation modeling to compare several versions of routine guidance, including routine testing for adults over the ages of 40 years, 30 years, and 18 years and found that routine testing for all adults aged  $\geq 18$  years was cost-effective compared to risk-based screening, and potentially cost-saving compared to testing only those aged  $\geq 30$  years or aged  $\geq 40$  years ([Barocas, 2018](#)). The study further found that routine testing remained cost-effective unless HCV infection had no impact on healthcare utilization and no impact on quality of life. Another research group similarly found that routine testing of all adults aged  $\geq 18$  years is likely cost-effective compared to risk-based screening, so long as the prevalence of HCV among those born after 1965 exceeds 0.07% ([Eckman, 2019](#)). Notably, these studies reached similar conclusions despite being conducted entirely independently and employing different simulation modeling approaches. Further, a variety of studies have examined the cost-effectiveness of routine HCV testing in specific venues, including correctional settings ([He, 2016](#)), prenatal care settings ([Chaillon, 2019](#)); ([Tasillo, 2019](#)), substance use treatment centers ([Schackman, 2018](#)); ([Schackman, 2015](#)), and federally qualified health centers ([Assoumou, 2018](#)). All of them found that routine testing and treatment for HCV was cost-effective, even when linkage to HCV treatment after testing was poor, and even when the rate of HCV reinfection among injection drug users is common.

Generally, routine HCV testing is cost-effective because the incidence and prevalence of HCV remain high in people who inject drugs with a notable rising prevalence in young adults who may not readily report their stigmatized risk behaviors. Studies conducted in urban emergency departments in the US, for example, reveal that 15% to 25% of patients with previously unidentified HCV infection were born after 1965 and/or have no reported history of injection drug use and are, therefore, missed by even perfect implementation of risk-based screening ([Schechter-Perkins, 2018](#)); ([Hsieh, 2016](#)); ([Lyons, 2016](#)). Reinfection among those actively using drugs is common but because screening is a low-cost intervention, and therapy is both highly effective and cost-effective, routine testing provides good economic value (ie, cost-effective) even when many people need to be tested and treated more than once during their lifetime.

## Conclusions

Many studies have demonstrated the economic value of HCV screening ([Chaillon, 2019](#)); ([Eckman, 2019](#)); ([Tasillo, 2019](#)); ([Assoumou, 2018](#)); ([Barocas, 2018](#)); ([Schackman, 2018](#)); ([Schechter-Perkins, 2018](#)); ([Lyons, 2016](#)); ([Hsieh, 2016](#)); ([Schackman, 2015](#)) and treatment ([Goel, 2018](#)); ([Chhatwal, 2017](#)); ([He, 2017](#)); ([Chahal, 2016](#)); ([Chhatwal, 2015](#)); ([Chidi, 2016](#)); ([Martin, 2016a](#)); ([Lin, 2015](#)); ([Najafzadeh, 2015](#)); ([Rein, 2015](#)); ([Tice, 2015](#)); ([Younossi, 2015a](#)) and made it clear that HCV screening and therapy are cost-effective. In response, in 2020, both the US Centers for Disease Control (CDC) and Prevention and the US Preventive Service Task Force (USPSTF) recommended routine, one-time HCV testing for all US asymptomatic adults aged 18 to 79 without known liver disease ([Owens, 2020](#)); ([Schillie, 2020](#)). A US study found reductions in measures of health care utilization (i.e. liver-related emergency department visits, liver-related hospitalizations, and all-cause hospitalizations) among cases who achieved SVR after DAA therapy compared to matched controls ([Gordon, 2022](#)). The high cost of HCV medications and the high prevalence of disease have led to limited access for some patients. The issue is complex. Although the wholesale acquisition costs of HCV drugs often make treatment appear unaffordable, the reality is that insurers, PBMs, and government agencies negotiate pricing, and few actually pay this much-publicized price. Negotiated pricing and cost structure for pharmaceutical products in the US, however, are not transparent. Thus, it is difficult to estimate the true budgetary impact of providing HCV drugs. Competition and negotiated pricing have reduced prices substantially but cost continues to limit the public health impact of DAA therapies. Insurers,

government, and pharmaceutical companies should work together to bring medication prices to the point where all persons in need of treatment are able to afford and readily access it. Only 3 US states and only 24% of high-income countries are on target to meet the WHO 2030 hepatitis C elimination targets ([Gamkrelidze, 2021](#)); ([Sulkowski 2021](#)).

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