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The Costs and Benefits of Expanding Hepatitis C Screening in the Indian Health Service

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ABOUT THIS BRIEF

The Indian Health Service (IHS) provides medical services to approximately 2.2 million American Indian and Alaska Native (AI/AN) people in the United States. According to surveillance data from the Centers for Disease Control and Prevention (CDC), AI/AN populations have the highest incidence of acute hepatitis C virus (HCV) and the highest rate of HCV-related mortality relative to other racial and ethnic groups (CDC 2018). Given its disproportionate effect on the AI/AN community, understanding the seroprevalence of HCV and its associated costs can assist in determining whether and by how much to expand screening in the population served by IHS.

CDC and the U.S. Preventive Services Task Force (USPSTF) currently recommend one-time screening for all adults born between 1945 and 1965—a recommendation that IHS has been working to implement within its own service population. In addition, recent evidence from other health agencies suggests that adhering to these recommendations and expanding screening may further reduce HCV burden and costs over time (Moon et al. 2017).

Results provided in this brief indicate that expanding HCV screening in the IHS service population to include all women of reproductive age or universal screening for all individuals ages 15–64 would be cost-beneficial in the long term at a seroprevalence of 0.20 percent or above, although this depends on the utilization of certain higher- and lower-cost medications. Studies estimate seroprevalence in AI/AN populations to be higher than 0.20 percent, ranging from 0.82 percent to 11.5 percent (McMahon et al. 2004; Mera et al. 2016; Neumeister et al. 2007).

Our model to estimate the seroprevalence threshold at which expanded screening becomes cost-beneficial is highly sensitive to the cost of the drugs used to treat HCV. If more expensive drugs are used, the seroprevalence at which screening becomes cost-beneficial rises to as much as 10.0 percent. Given the range of seroprevalence estimates for AI/AN populations, it is likely that expanded screening would be cost-beneficial even if more expensive drugs are used, but expanded screening is unlikely to be cost-beneficial if the majority of HCV-positive patients receive the most expensive drug regimens currently available.

The remainder of this brief further details the motivation of and findings from our study. A technical appendix provides information about the methods used.

INTRODUCTION

Hepatitis C (HCV) affects approximately 3.5 million Americans and is a key driver of rising rates of liver cancer in the United States (Reilly and Leston 2017). Chronic HCV infection may be asymptomatic for decades and still cause liver disease, and it is the leading cause of end-stage liver disease, hepatocellular carcinoma (HCC), and liver-related death in the Western world (Westbrook and Dusheiko 2014). These and other HCV-associated sequelae are long lasting, costly, and complex to manage. Advanced liver disease can escalate to require a liver transplant or lead to early mortality.

HCV screening, which involves a relatively simple blood test followed by a confirmatory test if the screening result is positive, can help detect HCV cases early and thereby improve people's quality of life and avoid costly HCV-associated sequelae. In addition, new and more effective treatment regimens have emerged since 2012 (when CDC last updated its HCV screening recommendations). Specifically, the U.S. Food & Drug Administration (FDA) has approved new direct-acting antiviral (DAA) therapies for HCV that can help achieve sustained virologic response (SVR, essentially a cure) in about 90 percent of patients with chronic HCV. These oral medications are also very well tolerated, meaning that a high proportion of patients who start treatment complete it. Widespread access to these treatments, however, has been limited by their high cost and restrictive policies for obtaining Medicaid and other third-party payer coverage of high-cost drugs.

CURRENT RECOMMENDATIONS FOR HEPATITIS C SCREENING:

- Screening process: Anti-HCV antibody testing followed by confirmatory test for HCV RNA (CDC 2013)
- Populations recommended for screening:
 - High-risk groups, including those with past or current injection drug use, receipt of a blood transfusion before 1992, born to a mother with HCV, and other medical exposures (CDC 1998)
 - One-time screening for all adults born between 1945-1965, regardless of risk (CDC 2012)



Despite these barriers to DAA use, recent studies have demonstrated how beneficial these therapies are to a population with high HCV seroprevalence (Moon et al. 2017; Westbrook and Dusheiko 2014; U.S. Department of Veterans Affairs 2018a). For example, the Department of Veterans Affairs (VA) has secured funds to treat almost all people living with HCV in its service population and is on the verge of eradicating HCV in the veteran population (Moon et al. 2017). The introduction of DAAs and their use in the VA system resulted in a 21-fold increase in the number of affected veterans achieving SVR between 2010 and 2015; also, the proportion of treated patients achieving SVR rose from 36.0 percent to 90.5 percent during that time. Estimates suggest that the VA will be able to successfully treat the majority of remaining veterans with HCV in the coming years (Moon et al. 2017).

Similar to the VA, the Indian Health Service (IHS) serves a population disproportionately affected by HCV—the American Indian/Alaska Native (AI/AN) population has more than twice the rate of HCV incidence and nearly three times the

rate of HCV-related mortality as the general U.S. population (CDC 2018). However, unlike the VA, IHS has not received additional funding to obtain advanced HCV therapies for those who need it. In general, resources are a key consideration in any agency's decision on whether to expand screening and associated treatment. For IHS in particular, a clearer understanding of the costs and benefits associated with different approaches to HCV screening and treatment can help in its decision making around use of HCV-related resources.

To assist IHS in determining the conditions under which expanding screening and treatment could be cost-beneficial to the Indian health care system, this study seeks to identify the specific population seroprevalence at which the net costs of expanding screening, including any savings from averting costly HCV-related sequelae, balance the net costs of the current screening approach. It also describes how recommendations for screening expansion might change for different IHS subpopulations.

Key study questions

-  At what HCV seroprevalence does expanded HCV screening and treatment become cost-beneficial for IHS, relative to the current (baseline) level of screening and treatment?
-  How does the net benefit of expanding screening and treatment vary in different IHS subpopulations (all people born between 1945 and 1965, women of reproductive age, or people ages 15–64)?

DEVELOPING THE COST-BENEFIT MODEL

To address the study's key objectives and questions, we developed an overarching cost-benefit model for assessing various scenarios of expanded screening and treatment in the population served by IHS.¹ The model takes into account HCV seroprevalence, the ability of a dedicated program to retain patients through the various stages of screening and treatment, costs of HCV screening and treatment, current understanding of HCV disease progression, and costs of HCV-associated sequelae.

The cost-benefit model compares the net costs associated with a baseline level of screening to those associated with an expanded level of screening. We calculated the difference in these net costs at different seroprevalence levels to generate an estimate of the *net benefit*, or savings, associated with each seroprevalence level. Expanded screening is considered cost-beneficial at a particular seroprevalence if, at that seroprevalence, the net benefit is positive (meaning that the net cost of expanded screening is less than the net cost of the baseline screening approach). The calculation can be expressed in the equation with variable components below.

Equation for estimating net benefit at a specific seroprevalence (i)

$$B_i = C_b - C_e, \text{ where}$$

B_i = Net benefit at seroprevalence i

C_b = Net cost of baseline screening approach

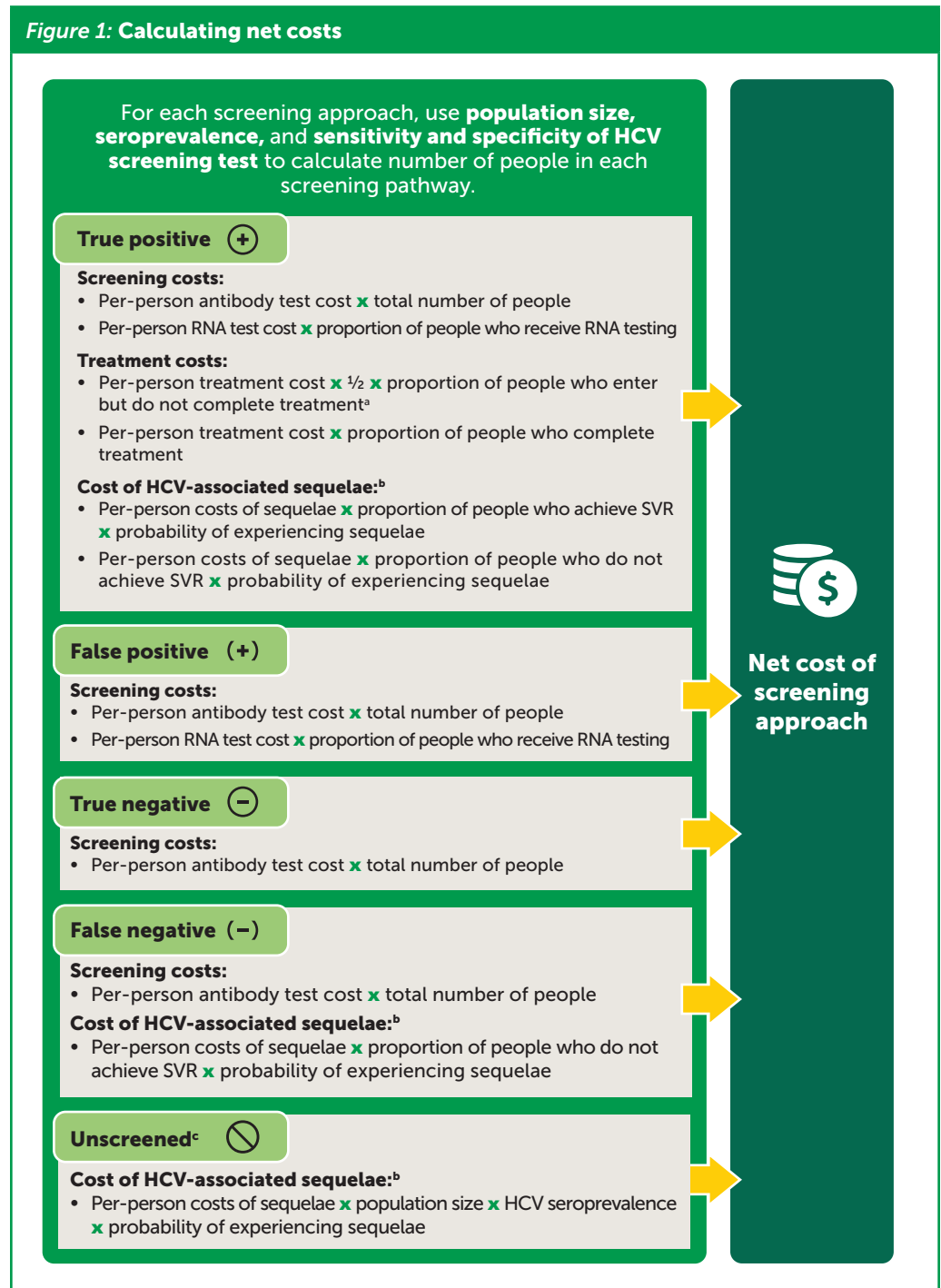
C_e = Net cost of expanded screening approach

The net benefit was calculated at several different hypothetical seroprevalence levels. We used the range of calculated net benefit values to determine the seroprevalence level at which the net benefit was equal to zero. We considered this point to be the seroprevalence threshold; if the true population seroprevalence is greater than this threshold, the net benefit would be positive and expanded screening could be considered cost-beneficial.

To calculate each net cost variable, we considered costs and savings that would apply to the IHS system under either the baseline or expanded screening approach. Calculating the net cost includes three categories of inputs, described below (Figure 1; Table 1).

1. **Inputs for estimating the number of people in five key screening pathways:** (a) those with HCV who correctly receive a positive screening test (true positive); (b) those with HCV who incorrectly receive a negative test (false negative); (c) those without HCV who incorrectly receive a positive test (false positive); (d) those without HCV who correctly receive a negative test (true negative); and (e) those who do not get screened (unscreened). Inputs for this calculation include the size of the target population, range of hypothetical HCV seroprevalence values in the target population, and sensitivity and specificity of the HCV screening test.
2. **Inputs for estimating the costs of screening and treatment under each pathway.** This category includes per-person costs of HCV screening, confirmatory testing, and treatment, as well as the number of people in each pathway from inputs under (1) incurring each cost and the expected number of patients retained through each stage of the screening and treatment process.
3. **Inputs for estimating the probability of developing HCV-associated sequelae under each pathway and the costs associated with them.** These inputs include assumptions about the expected retention of patients in each pathway through each stage of the screening and treatment process from inputs under (2), estimates of the probability of people developing HCV-associated sequelae, and costs associated with having these sequelae.

Figure 1: Calculating net costs



^a We assumed that those who do not complete treatment complete half of their prescribed treatment course, on average.

^b See the Technical Appendix for details on how these costs were calculated.

^c Refers to the population screened under the expanded but not the baseline screening approach.

ESTIMATING NET BENEFIT

For each key input into the cost-benefit model, we identified values through a targeted literature search and review of publicly available data (Table 1). We estimated the net benefit under one primary and three secondary screening scenarios to understand how it might differ for various subpopulations. The key difference between these scenarios is the population size screened and compared under the baseline and expanded screening approaches (Table 2)—all other input values are the same across these scenarios.

Table 1: Inputs for cost-benefit model

Inputs	Treatment
Seroprevalence in AI/AN population	0.82–15.5 ^a
IHS service population sizes	
Full 1945–1965 birth cohort	211,014 ^b
Women of reproductive age	384,171 ^c
All people ages 15–64	1,036,125 ^c
Sensitivity and specificity of HCV screening test ^d	
Sensitivity	0.98
Specificity	0.99
Retention through stages of screening and treatment ^e	
Percentage with positive screening who receive RNA test	68.3 ^f
Percentage of confirmed chronic HCV cases who enter treatment	57.5 ^g
Percentage of confirmed chronic HCV cases who complete treatment	90.1
Percentage of those who complete treatment and achieve SVR	90.0
Costs of HCV screening and treatment	
Antibody screening test	\$4.50 ^h
Confirmatory RNA test	\$72.50 ^h
Treatment	\$7,756 ⁱ
Disease progression ^j	
Percentage of those who do not achieve SVR and develop cirrhosis	16.0
Percentage of those who achieve SVR and develop cirrhosis	3.0
Percentage with cirrhosis who develop HCC	4.9
Percentage with cirrhosis who develop decompensation	7.3
30-year costs of HCV-associated sequelae ^k	
Cirrhosis (30-year cost)	\$81,096
Hepatocellular carcinoma (30-year cost)	\$648,147
Decompensation (30-year cost)	\$267,986

^a McMahon et al. 2004; Mera et al. 2016; Neumeister et al. 2007.

^b Reilley et al. 2016.

^c IHS 2015; refers to the AI/AN population eligible to receive IHS services.

^d All values from Tang et al. 2017.

^e All values from Mera et al. 2016, a study of a Cherokee Nation screening and treatment program.

^f Sensitivity analysis 2 (described below) used a value of 85.0 percent.

^g Sensitivity analysis 2 (described below) used a value of 18.0 percent (Hossain et al. 2014).

^h Turner et al. 2015, Slade et al. 2013, and additional expert opinion.

ⁱ Based on the cost of Glecaprevir/Pibrentasvir. Sensitivity analysis 1 (described below) considered the cost of Sofosbuvir/Velpatasvir (\$14,419 per person) and the cost of Ledipasvir/Sofosbuvir (\$52,578 per person) (U.S. Department of Veterans Affairs 2018b). For all analyses, average per-person costs assume that approximately 60 percent of patients will be eligible for an 8-week course of the treatment in question and 40 percent will require a 12-week course.

^j All values from Westbrook et al. 2014.

^k All values based on annual Medicaid costs as reported by Younossi et al. 2017; 30-year costs reflect assumptions about disease course and the average length of time spent in each disease state, described in greater detail in the Technical Appendix.

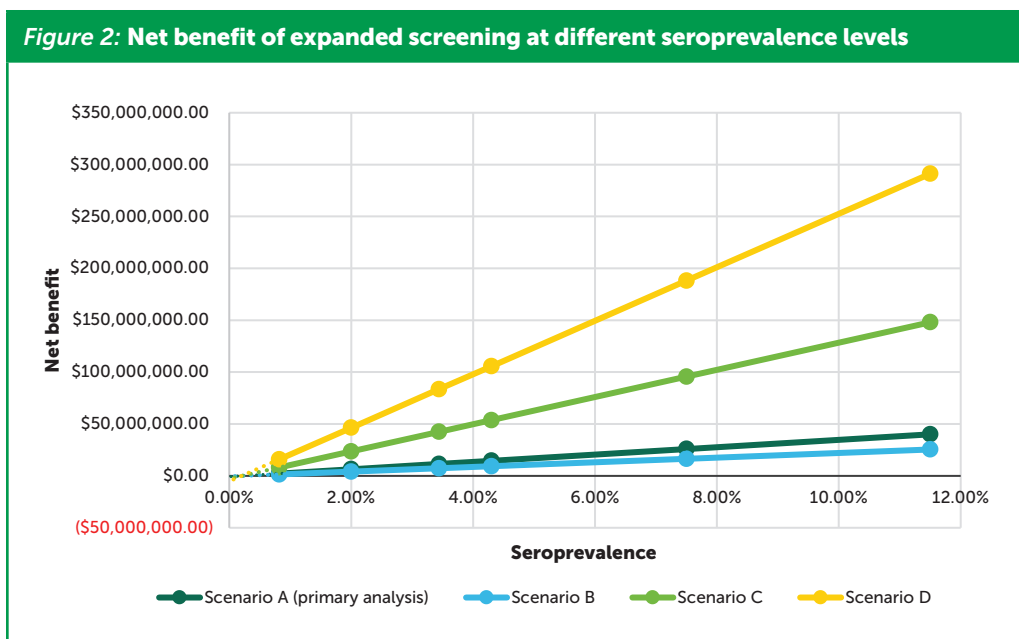
Table 2: Screening scenarios tested

Scenario	Baseline screening approach	Expanded screening approach
A (primary)	Screening 32.5 percent of the 1945–1965 birth cohort ^a (N = 68,514)	Screening the full 1945–1965 birth cohort (N = 211,014)
B	Screening 57.1 percent of the 1945–1965 birth cohort ^b (N = 120,487)	Screening the full 1945–1965 birth cohort (N = 211,014)
C	Screening the full 1945–1965 birth cohort (N = 211,014)	Screening the full birth cohort + women of reproductive age (N = 595,184)
D	Screening the full 1945–1965 birth cohort (N = 211,014)	Screening the full birth cohort + all people 15–64 (N = 1,036,125)

^a Reilley et al. (2016) estimated that this percentage was the proportion of the birth cohort screened in the IHS service population as of 2015, the last year for which such data are available.

^b Based on the fact that Reilley et al. (2016) estimated that 7.9 percent of the birth cohort in the IHS service population had been screened in 2012 and 32.5 percent in 2015, and assuming a constant increase in the rate of screening of 8.2 percentage points per year, we estimated that 57.1 percent of this population would be screened by 2018 in this scenario.

Our primary analysis finds that at a population seroprevalence of 0.20 percent or greater, screening the full 1945–1965 birth cohort is cost-beneficial (Figure 2). The same seroprevalence threshold of 0.20 is found under other scenarios as well, such as when including women of reproductive age (Scenario C) or expanding to universal screening (Scenario D). In larger populations, the net benefit increases more rapidly as the theoretical population seroprevalence increases, indicating that if the true population seroprevalence is relatively high, expanding screening to a large population is highly cost-beneficial.

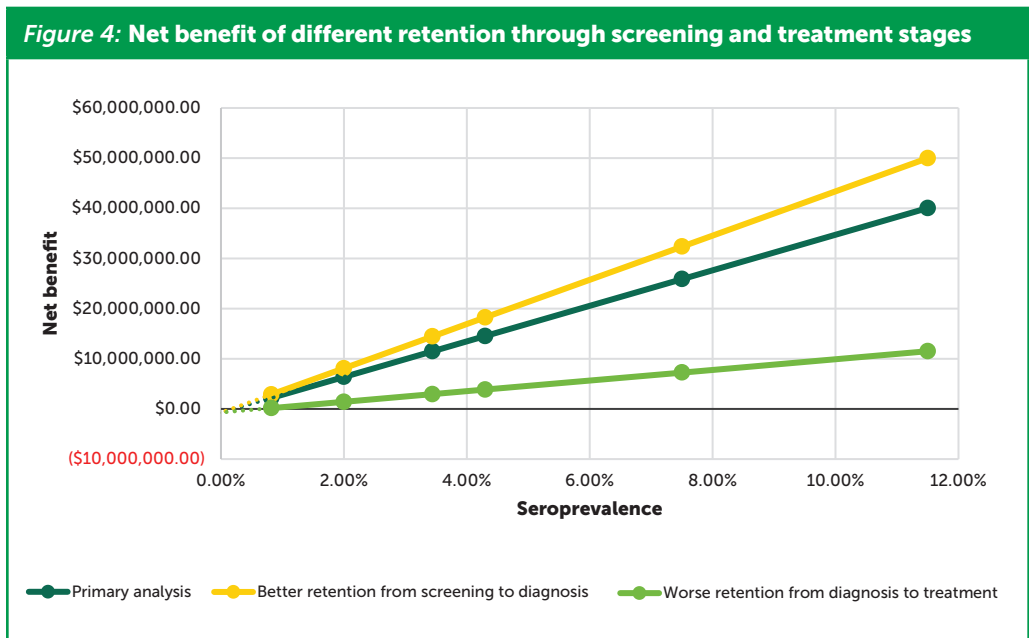
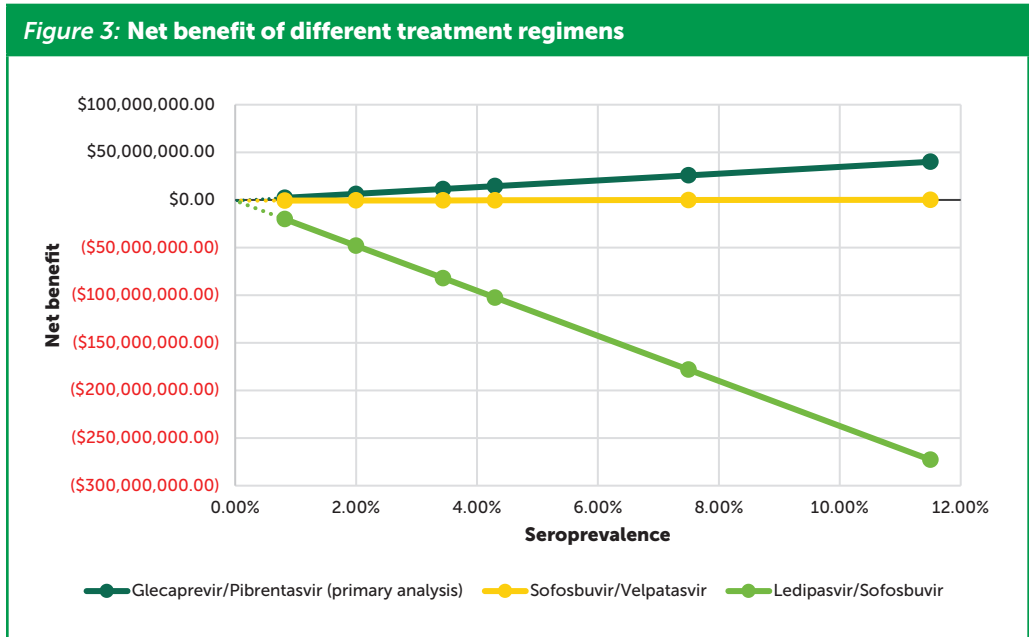


Sensitivity analyses

To test the robustness of our results, we conducted two sensitivity analyses: (1) varying the costs of treatment regimens² and (2) varying the proportion of patients retained at different stages in the screening and treatment process.³ We conducted all sensitivity analyses using the model and parameters from our primary analysis (Scenario A).

The results from the first sensitivity analysis showed that the seroprevalence threshold at which screening expansion becomes cost-beneficial can increase substantially, depending on the cost of treatment. The primary analysis demonstrated that if a relatively inexpensive drug—Glecaprevir/Pibrentasvir—is used to treat all chronic HCV patients, the seroprevalence threshold at which expanded screening is cost-beneficial is quite low. In contrast, if all patients are treated using the most expensive regimen considered—Ledipasvir/Sofosbuvir—expanded screening is never cost-beneficial; that is, the large cost of treating all chronic HCV infections with Ledipasvir/Sofosbuvir never outweighs the potential costs associated with leaving chronic infection untreated (Figure 3). However, for the second most expensive therapy we considered—Sofosbuvir/Velpatasvir—the seroprevalence threshold of cost-benefit is much lower, at 10 percent. Given that all three of the drug regimens considered achieve SVR in a similarly large proportion of patients (around 90 percent), these findings suggest that using a relatively inexpensive regimen such as Glecaprevir/Pibrentasvir for the majority of patients and using more expensive regimens only when clinically necessary would be the approach most likely to be cost-beneficial to IHS.

The second sensitivity analysis found that the seroprevalence threshold at which expanded screening becomes cost-beneficial is less sensitive to a program's ability to retain patients through key stages of screening and treatment. If 85.0 percent of those with a positive HCV antibody test were retained and received confirmatory RNA testing, rather than 68.3 percent, the seroprevalence at which expanded screening becomes beneficial falls from 0.20 percent to 0.16 percent. Similarly, if we assume that only 18.0 percent of patients with a confirmed chronic HCV diagnosis receive treatment, rather than 57.5 percent, the seroprevalence at which expanded screening becomes beneficial increases to 0.67 percent (Figure 4).



Implications for IHS costs borne over time

Findings from the cost-benefit model suggest that expanded screening and treatment is likely to be cost-beneficial for IHS populations, given that the true seroprevalence among those IHS serves is likely well above our estimated seroprevalence threshold of 0.20 percent. Furthermore, experience from the VA suggests that, in a closed population with little or no reinfection or transmission, aggressive screening and treatment over a relatively short period of time can cure most, if not all, infected individuals, which may result in significant long-term cost savings by averting HCV-associated sequelae. These findings suggest that if funds can be made available to pursue aggressive screening and treatment within IHS in the near term, the overall system may benefit from large long-term savings.

To assess the potential level of long-term savings, we used some of the inputs from our cost-benefit model to assess the total costs through 2030 associated with screening, treatment, and management of cirrhosis cases in the 1945–1965 birth cohort of the active IHS user population. To understand how the pace of a screening program can influence longer-term savings, we compared three different screening and treatment scenarios:

1. A “fast” scenario, in which all 142,500 individuals in the birth cohort estimated as not screened by 2018 (100 percent of the eligible population)⁴ are screened immediately and 100 percent of identified HCV-positive cases receive treatment
2. A “medium” scenario, in which 21,375 individuals (approximately 15 percent of the total eligible population) are screened every year and 50 percent of identified HCV-positive cases receive treatment
3. A “slow” scenario, in which 11,400 individuals (approximately 8 percent of the total eligible population) are screened every year and 20 percent of identified HCV-positive cases receive treatment⁵

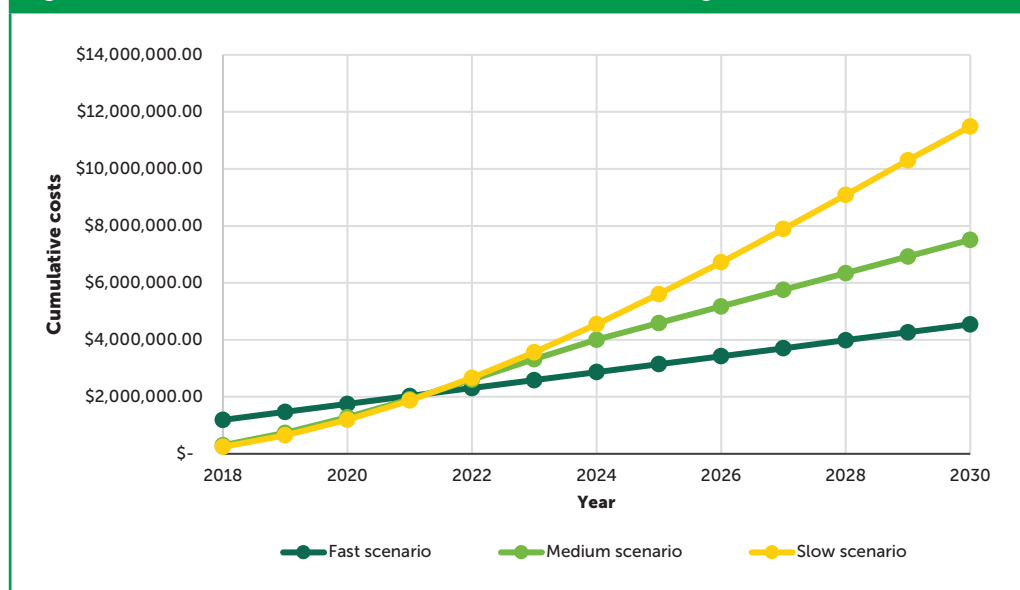
For each scenario, we calculated estimates of the number of AI/AN people screened and treated every year, the number of screened and unscreened people who develop cirrhosis every year, the cumulative number of people with cirrhosis requiring management (including both new cases and cases that developed in previous years), and the costs associated with each of these categories. We then compared total annual and cumulative costs over time for each scenario, assessing costs through 2030.

Over the time period analyzed, the most aggressive screening and treatment scenario resulted in the fewest cirrhosis cases developing over time, as well as the lowest overall costs in the long term (Table 3; Figure 5).

Table 3: Costs accrued over time under different screening and treatment scenarios

Scenario	Year in which screening of full population is achieved	Number of cirrhosis cases that develop (2018–2030)	Total cost of screening, treatment, and cirrhosis management (2018–2030)
Fast	2018	59	\$4,543,430
Medium	2024	126	\$7,058,654
Slow	2030	244	\$11,487,583

Figure 5: Cumulative costs over time under different screening and treatment scenarios



DISCUSSION AND CONCLUSION

The analyses from our study found that expanded screening of AI/AN populations is cost-beneficial at a low hypothetical seroprevalence. The true seroprevalence in the 1945–1965 birth cohort within the IHS service population is likely to be substantially higher than 0.20 percent. Although data on seroprevalence in specific AI/AN populations are limited, there is good evidence to suggest that seroprevalence in these populations is even higher than that for the general U.S. 1945–1965 birth cohort, which is estimated to be 2.6 percent (Denniston et al. 2014). Thus, expanding screening in the AI/AN population could bring a large benefit to IHS and the population it serves.

Magnitude of screening expansion and time horizon for investment

A key factor to consider for possible expansion of screening and treatment is how large the potential expansion should be. Our analysis shows that, at any seroprevalence level above 0.20 percent, expansion to larger populations results in a greater net benefit than smaller-scale expansions. The largest expansion considered—universal screening for all people ages 15–64—yields a greater net benefit than smaller expansion

scenarios. However, our results are sensitive to changes in treatment costs. Treating all HCV cases with a moderately expensive regimen—Sofosbuvir/Velpatasvir rather than Glecaprevir/Pibrentasvir—changes the results considerably; the hypothetical population seroprevalence at which expanded screening becomes cost-beneficial increases from 0.20 percent to 10.0 percent. Further, we used publicly available VA prices to estimate drug costs in our model, but in some cases, the costs reflecting the VA discounts may be lower than what individual patients or facilities pay to obtain the drugs. Any efforts to implement expanded screening programs should consider the likely costs of any treatment regimens that may be used, as these will have a large impact on whether expanded screening will be cost-beneficial. For instance, using the most inexpensive drug regimen when possible, and resorting to more expensive options only when clinically necessary⁶, will likely ensure that expanded screening and treatment would be cost-beneficial to IHS.

Another factor to consider for possible expansion of screening and treatment is how quickly the expansion should roll out. Our findings indicate that, in a closed population with little HCV reinfection or transmission, as in the 1945–1965 birth cohort, aggressive screening and treatment over the next few years will result in fewer cases of cirrhosis overall, minimal screening and treatment costs in subsequent years, and lower total costs over time. Given these substantial long-term gains, an upfront investment by IHS for expanded screening and treatment with DAAs will more likely be cost-beneficial than smaller investments spread over a longer period of time.

It is important to note that the costs and benefits of expanded screening and treatment accrue at different times, which may also affect decisions about the scale and timing of rolling out any expanded screening or treatment efforts. Costs associated with screening and immediate treatment of chronic HCV infection accrue immediately, whereas the costs of managing HCV-associated sequelae (or the savings associated with averting these sequelae) take longer to develop. Our analyses account for both discounting and rising medical costs over time, but policymakers and program managers will have to further consider other tradeoffs associated with the timing of these costs.

Caveats when reviewing results

Although the study uses the most recent published data to identify key parameters, our review of the literature and available data on HCV in AI/AN populations revealed that there is some uncertainty about the true seroprevalence in AI/AN subpopulations, as well as the natural history of the disease, which poses some challenges and limitations for these analyses. In particular, estimates of the true seroprevalence in key AI/AN communities are wide-ranging and are developed using different populations and methodologies. We are also limited by the relative lack of data on the natural history of HCV for those with key co-morbidities that are frequently found in AI/AN populations, such as diabetes, injection drug use, or alcohol abuse.⁷ Furthermore, our analysis considers only the costs of the most common HCV-associated sequelae, not longer-term or less common issues such as liver transplant.

Concluding remarks

This study demonstrates that expanded HCV screening and treatment is cost-beneficial at a relatively low population seroprevalence, suggesting that efforts to expand screening and treatment for AI/AN populations will likely result in long-term cost savings for IHS. These savings are associated with improved health outcomes for people, including averting HCV-associated sequelae such as cirrhosis, HCC, and hepatic decompensation. Our primary analysis demonstrated that the net benefit associated with screening and treating the full 1945–1965 birth cohort within IHS corresponded to 200–3,000 averted cases of these sequelae (depending on the underlying population seroprevalence).

The economic literature has suggested that expanded HCV screening and treatment is typically cost-effective, given the quality-adjusted life-years (QALYs) saved by treatment. For example, one recent systematic review found that screening the 1945–1965 birth cohort and other high-risk populations costs, on average, about \$39,000 per QALY—a ratio that is typically considered cost-effective in the health economics literature (Coward et al. 2016). Future research could further explore the nonmonetary benefits associated with expanded screening and treatment in AI/AN subpopulations.

The health of those served by IHS also affects stakeholders in other sectors, including health insurers, employers, and other social sector agencies. Understanding the full extent of the potential benefit in expanding HCV requires collecting and analyzing other direct and indirect costs averted, such as those associated with additional HCV-associated sequelae, lost productivity, social service utilization, and out-of-pocket costs.

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ENDNOTES

- ¹ Further details on methods used to conduct the analyses presented in this brief are provided in a technical appendix.
- ² This analysis compared the cost of treating patients with Glecaprevir/Pibrentasvir to the costs of using other common treatment regimens: Sofosbuvir/Velpatasvir and Ledipasvir/Sofosbuvir. Glecaprevir/Pibrentasvir is among the less expensive DAA regimens on the market, whereas Ledipasvir/Sofosbuvir is among the most expensive, and Sofosbuvir/Velpatasvir represents the middle tier of cost. All of these regimens are similarly effective at treating most chronic HCV cases.
- ³ The primary analysis relied on findings from the literature that 68.3 percent of those who receive a positive screening test would go on to receive confirmatory RNA testing, and that 57.5 percent of those with a confirmed HCV diagnosis would enter treatment. However, a dedicated screening and treatment program may perform better at retaining patients from screening to confirmatory testing, and funding constraints may mean that a smaller proportion of patients diagnosed with chronic HCV would enter treatment. This sensitivity analysis considered what might happen if a larger proportion of those with a positive screening test received confirmatory RNA testing, and if a smaller proportion of those with a confirmed HCV diagnosis entered treatment.
- ⁴ Consistent with the primary cost-benefit analysis (Scenario A), this number is the estimated size of the remaining birth cohort that has not yet been screened, based on the estimate from Reilley et al. (2016) that 32.5 percent of this cohort has been screened.
- ⁵ This pace of screening is consistent with results from Reilley et al. (2016), which found that 7.9 percent of the cohort had been screened in 2012 and 32.5 percent in 2015.
- ⁶ We examined how the mix of low- and high-cost drugs would affect the net benefit at a hypothetical seroprevalence of 2.6 percent (data not shown). At this relatively high seroprevalence, if Glecaprevir/Pibrentasvir were to be used in combination with Sofosbuvir/Velpatasvir, a fairly large proportion of patients could be given Sofosbuvir/Velpatasvir – 93 percent – to achieve a net benefit of zero. In contrast, if Glecaprevir/Pibrentasvir were to be used in combination with Ledipasvir/Sofosbuvir, only about 13 percent of patients could be given Ledipasvir/Sofosbuvir to achieve a net benefit of zero.
- ⁷ We relied on estimates of the course of HCV progression in the general population under the assumption that the disease likely progresses in a similar manner in AI/AN populations—an assumption commonly made in the epidemiological and economic literature.

TECHNICAL APPENDIX

This technical appendix provides an in-depth description of our approach to identifying key inputs for the cost-benefit analysis, developing a cost-benefit model and generating estimates of net benefit, and conducting an additional analysis to examine the costs of expanded screening and treatment scenarios over time.

Literature and data review: Costs of HCV and other key model inputs

We conducted a targeted literature review to document key costs associated with HCV screening programs, treatment regimes, and management of sequelae resulting from a failure to detect and treat chronic HCV infection. We searched MEDLINE, Scopus, and Academic Search Premier, and conducted additional reviews of the grey literature for articles published in the past five years and targeting U.S. populations. Using a narrow focus on key terms related to the cost and cost-effectiveness of HCV screening and treatment, we identified and screened 70 relevant articles, and selected 29 for in-depth review. From the references in the reviewed articles, we identified an additional 7 articles. From the total, we selected 9 articles that had specific information on relevant costs and used this information to inform the cost-benefit analysis (described in further detail below).

To identify additional inputs for the model, we conducted a search of available information on levels of prevalence and incidence of HCV, the course of chronic HCV and advanced liver disease, and the ability of existing screening and treatment programs to retain patients through various stages of the screening and treatment process, from initial screening through completion of treatment. To find these estimates, we reviewed recent literature (including articles identified through the literature search that had information on prevalence or incidence regardless of whether cost information was present) and CDC surveillance data. In addition to identifying specific inputs for use in the model (described in greater detail below), we identified a range of seroprevalence estimates from the literature, which informed our analysis and interpretation of results (Table A.1).

Population	Prevalence of positive anti-HCV (%)	Range (%)	Date	Methods
General U.S. population	1.5	1.1–1.9	2003–2010	National Health and Nutrition Examination Survey (NHANES) (Denniston 2014)
AI/AN	11.5	7.5–15.5	2007 (published)	Prospective screening study in an urban AI clinic (Neumeister et al. 2007)
AI/AN	4.3		2012–2015	Cherokee Nation Health Services screening program and HCV registry (Mera et al. 2016)
AI/AN	0.82	0.77–0.87	1992–2002	Alaska Native HCV registry (McMahon et al. 2004)

Developing the cost-benefit model

The cost-benefit model compares the net costs associated with a baseline level of screening to those associated with an expanded level of screening. We calculated the difference in these net costs at different seroprevalence levels to generate an estimate of the *net benefit* associated with each level, as described in the equation below:

Equation for estimating net benefit at a specific seroprevalence (i)

$$B_i = C_b - C_e, \text{ where}$$

B_i = Net benefit at seroprevalence i

C_b = Net cost of baseline screening approach

C_e = Net cost of expanded screening approach

To generate each net cost under each screening approach, we added up the net costs associated with screening, treatment, and management of HCV-associated sequelae, and then compared the total net costs in the baseline and expanded screening approaches to estimate the net benefit at different theoretical seroprevalence levels. We took the specific levels at which we calculated net benefit from the range of estimates of HCV seroprevalence in various AI/AN populations identified in the literature review. The inputs required to conduct these calculations are described below and summarized in Table A.2.

Number of people in each of five screening pathways. We used the sensitivity and specificity of the HCV screening test to calculate the number of people expected to receive each potential test result: true positive, false positive, true negative, and false negative. In the baseline screening approach used in each analysis, we also considered unscreened individuals (that is, people who would not be screened under the baseline screening approach but would be under the expanded screening approach) as a separate pathway.

Costs of screening and treatment under each pathway. We calculated these costs using per-person costs of HCV screening, confirmatory testing, and treatment identified in the literature and data review, and multiplied them by the number of people expected to incur each cost in each screening pathway. This approach required estimates of retention of patients through stages of screening and treatment. Based on the literature and data review, we assumed 68.3 percent of individuals who received a positive screening test would receive confirmatory RNA testing, 57.5 percent of those who received a confirmed chronic HCV diagnosis would enter treatment, 90.1 percent of those who entered treatment would complete it, and 90.0 percent of those who completed treatment would achieve SVR.

Our estimated costs of treatment are based on publicly available data on VA drug prices for common DAA regimens. When estimating the cost of treatment, we considered only the cost of drugs used to treat chronic HCV infection, not personnel or infrastructure costs associated with running a screening and treatment program. We expect these costs would have little or no impact on our analyses, as they are largely fixed and would not vary significantly, depending on the size of the population targeted for screening. Furthermore, we assume the additional activities that providers would need to run a screening and treatment program would fall largely under the current scope of their duties; a dedicated screening and treatment program should not require additional personnel or infrastructure beyond what is already available at IHS facilities.

Probability of developing HCV-associated sequelae. For the people in each of the screening pathways described above, we estimated the probability of developing key HCV-associated sequelae, based on expected retention of patients through stages of screening and treatment (described above) and the following assumptions drawn from the literature and data review (Table A.2):

- **Risk of cirrhosis:** We assumed that HCV-positive individuals who failed to achieve SVR for any reason (whether because of an error in the screening test, failure to receive confirmatory testing, failure to complete treatment, or failure to achieve SVR even with complete treatment) would have a 16.0 percent risk of developing cirrhosis over a 30-year time frame. We assumed 3.0 percent of individuals who did achieve SVR would develop cirrhosis over the same time period.
- **Risk of hepatocellular carcinoma:** We assumed those who develop cirrhosis would have a 3.0 percent annual risk of developing HCC after 10 years of living with cirrhosis (the risk for 0 to 9 years after developing cirrhosis was set to zero). This assumption implies a cumulative 4.9 percent risk of developing HCC over 20 years. Based on the medical literature, we further assumed that those with HCC would live with it for 10 years.
- **Risk of hepatic decompensation:** We assumed those who developed cirrhosis would have a 4.5 percent annual risk of developing hepatic decompensation after 10 years of living with cirrhosis (the risk for 0 to 9 years after developing cirrhosis was set to zero). This assumption implies a cumulative 7.3 percent risk of developing decompensation over 20 years. Based on the medical literature, we further assumed those with the condition would live with it for 10 years.

Costs of HCV-associated sequelae. The costs associated with management of HCV-related disease states are based on Medicaid annual costs from 2014. We applied a 3 percent annual discounting rate (consistent with the literature on discounting health costs in the United States),.. as well as an additional 2.2 percent annual increase in true medical costs (based on Medicaid spending increasing about 5.2 percent annually in recent years and an inflation of 3 percent).

Table A.2: Screening scenarios tested		
Input	Estimate	Notes
Seroprevalence in AI/AN population	0.82–15.5	We sourced specific point estimates from the literature (McMahon et al. 2004; Mera et al. 2016; Neumeister et al. 2007) and calculated net benefit at several seroprevalence levels within this range.
IHS service population sizes		
1945–1965 birth cohort	211,014	Based on Reilley et al. 2016; 32.5% of this population (68,514) has already been screened.
Women of reproductive age (15–44)	384,171	From Indian Health Service 2014; based on 2000 Census categories.
All people ages 15–64	1,036,125	From Indian Health Service 2014; based on 2000 Census categories, and including some members of the 1945–1965 birth cohort.
HCV antibody screening test performance		
Sensitivity	98 percent	From Tang et al. 2017.
Specificity	99 percent	From Tang et al. 2017.
Retention through stages of screening of treatment		
Percentage with positive screen who receive RNA test	68.3 percent	From Cherokee Nation screening program (Mera et al. 2016).
Percentage of confirmed chronic HCV cases who enter treatment	57.5 percent	From Cherokee Nation screening program (Mera et al. 2016).
Percentage of confirmed chronic HCV cases who complete treatment	90.1 percent	From Cherokee Nation screening program (Mera et al. 2016); consistent with reports that DAA treatment is well tolerated and usually completed.
Percentage of those who complete treatment who achieve SVR	90.0 percent	Based on medical literature and findings from Cherokee Nation screening program (Mera et al. 2016).
Costs of HCV screening and treatment		
Antibody screening test	\$4.50	The range identified from the literature was \$3.00–19.44; IHS estimated the cost to be between \$3.00 and \$6.00.
Confirmatory RNA test	\$72.50	The range identified from the literature was \$43.42–\$130.000; IHS estimated the cost to be between \$45.00 and \$130.00.
Treatment	\$7,756	Based on publicly available VA drug price for Glecaprevir/Pibrentasvir. Average per-person costs assumes that approximately 60 percent of patients will be eligible for an 8-week course of treatment and 40 percent will require a 12-week course.
Disease progression		
Percentage of those who do not achieve SVR who develop cirrhosis	16.0 percent	From Westbrook et al. 2014.
Percentage of those who achieve SVR who develop cirrhosis	3.0 percent	From Westbrook et al. 2014 and Younossi et al. 2017.

Table A.2: Screening scenarios tested

Input	Estimate	Notes
<i>Disease progression (continued)</i>		
Percentage with cirrhosis who develop HCC	4.9 percent	From Westbrook et al. 2014. Assumes a 3% annual risk of developing HCC among patients with cirrhosis after the first decade of chronic HCV infection; reflects cirrhotic patients' cumulative risk of developing HCC over 20 years (after experiencing zero risk of HCC in the first 10 years of chronic HCV).
Percentage with cirrhosis who develop decompensation	7.3 percent	From Westbrook et al. 2014. Assumes a 4.5% annual risk of developing decompensation among patients with cirrhosis after the first decade of chronic HCV infection; reflects cirrhotic patients' cumulative risk of developing decompensation over 20 years (after experiencing zero risk of decompensation in the first 10 years of chronic HCV).
30-year costs of HCV-associated sequelae		
Cirrhosis	\$81,096	Based on annual Medicaid cost of \$3,850 in 2014 (Younossi et al. 2017). Assumes that people live with cirrhosis for 20 years (over the 30-year time horizon considered). Total per-person cost adjusts for discounting, inflation, and growing Medicaid costs.
Hepatocellular carcinoma	\$648,147	Based on annual Medicaid cost of \$70,224 in 2014 (Younossi et al. 2017). Assumes that people live with HCC for an average of 10 years (over 30-year time horizon considered). Total per-person cost adjusts for discounting, inflation, and growing Medicaid costs.
Decompensation	\$267,986	Based on annual Medicaid cost of \$26,479 in 2014 (Younossi et al. 2017). Assumes that people live with decompensation for an average of 10 years (over the 30-year time horizon considered). Total per-person cost adjusts for discounting, inflation, and growing Medicaid costs.

Sensitivity analyses

We conducted all sensitivity analyses relative to our primary analysis of interest. We replicated the primary analysis, with changes to key parameters, as described below.

Drug costs. Our primary analysis estimated the cost of treatment based on publicly available VA pricing for Glecaprevir/Pibrentasvir, one of the less expensive DAA regimens on the market. In this set of sensitivity analyses, we considered how the costs and benefits of expanded screening would change under two different scenarios: (1) if all individuals receiving treatment were treated with Sofosbuvir/Velpatasvir and (2) if all individuals receiving treatment were treated with Ledipasvir/Sofosbuvir. As with our primary analysis, we assumed that 60 percent of patients receiving treatment would receive an 8-week course of the drug in question, and the remaining 40 percent would receive a 12-week course. Based on these assumptions, we estimated that the average cost of Sofosbuvir/Velpatasvir would be \$14,419 per patient, and the average cost of Ledipasvir/Sofosbuvir would be \$52,578 per person.

Changes in ability to retain patients through screening and treatment. Based on existing studies of HCV screening and treatment programs in AI/AN populations, for our primary analysis we assumed that 68.3 percent of those with a positive HCV antibody screening test would receive confirmatory RNA testing, and 57.5 percent of those with a confirmed chronic HCV diagnosis would enter treatment. Additional findings from the literature and conversations with experts suggested that a targeted IHS screening program may be able to conduct RNA tests for a larger proportion of people but may treat only a relatively small proportion of those with a confirmed chronic HCV diagnosis. We conducted two sensitivity analyses to explore these possibilities: (1) an analysis in which 85 percent of those with a positive screening test received confirmatory RNA testing and (2) an analysis in which only 18 percent of those with a confirmed chronic HCV diagnosis received treatment (consistent with findings from a screening program in North Dakota [Hossein et al. 2014]).

IHS costs borne over time

We assessed the total costs over time associated with screening and treatment of the 1945–1965 birth cohort in the IHS service population to assess how cumulative costs over time might change depending on the approach taken to screening and treatment. We calculated annual and cumulative costs of screening and treatment under the following assumptions:

- The underlying seroprevalence in the population is 2.6 percent (consistent with findings for the general U.S. population born between 1945 and 1965).
- As of 2018, 32.5 percent of the 1945–1965 birth cohort had already been screened, leaving 142,500 individuals eligible for screening (based on the last available estimate of the percentage of this population that has been screened, from 2015 [Reilley et al. 2016], and consistent with the assumptions made in the primary analysis).
- No reinfection or transmission within the population.
- Every year, 1 percent of HCV-positive individuals who do not achieve SVR (meaning those who are not screened, as well as those who are screened but do not receive treatment), develop cirrhosis.
- The annual cost of managing cirrhosis remains constant, at \$4,715 per year (consistent with the input used for the cost-benefit analysis).

We compared three different scenarios:

- A “fast” scenario, in which all 142,500 individuals eligible for screening are screened immediately and 100 percent of identified HCV-positive cases receive treatment. Although this scenario is implausible, it provides an upper bound for what may happen if screening and treatment of all eligible individuals were conducted as fast as possible.

- A “medium” scenario, in which 21,375 individuals are screened every year (approximately 15 percent of the total population remaining to be screened) and 50 percent of identified HCV-positive cases receive treatment.
- A “slow” scenario, in which 11,400 individuals are screened every year (approximately 8 percent of the total population remaining to be screened) and 20 percent of identified HCV-positive cases receive treatment. This scenario is consistent with results from Reilley et al. (2016), which found that 7.9 percent of the population had been screened in 2012 and 32.5 percent in 2015.

Under each scenario, for every year from 2018 to 2030, we calculated the number of AI/AN people screened, the number of screened and unscreened people with HCV, the number treated, the number who achieved SVR, and the cumulative number of both screened and unscreened people with cirrhosis requiring management (including both new cases that developed during the year in question and those that developed in previous years). We summed all annual costs from 2018 to 2030 to arrive at an estimate for the cumulative costs of each screening scenario through 2030.

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