



The burden of hepatitis C virus disease in commercial and managed Medicaid populations

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TABLE OF CONTENTS

EXECUTIVE SUMMARY	1
BACKGROUND	3
RESULTS	6
Diagnosis and Stage of disease	6
Costs and Utilization	8
Comorbidity Analysis	12
Commercial Disease Stage Transition	14
CONSIDERATIONS FOR PAYERS	15
CAVEATS AND LIMITATIONS	18
APPENDIX A: METHODOLOGY	19
APPENDIX B: KEY DATA SOURCES	22
REFERENCES	24

EXECUTIVE SUMMARY

The prevalence of hepatitis C virus (HCV) infection in the United States is approximately 1%, based on analysis of the National Health and Nutrition Examination Survey (NHANES), from 2003 to 2010, which estimated that there were approximately 2.7 million chronically infected individuals in the noninstitutionalized civilian population.¹ Because NHANES does not survey homeless, incarcerated, or active military populations, these numbers are likely an underestimate of total cases and prevalence. The Centers for Disease Control and Prevention (CDC) estimates that there were approximately 29,700 new cases of HCV in 2013.²

The U.S. Preventive Services Task Force (USPSTF) updated its screening recommendations for people at high risk for HCV infection in 2013. As in the past, risks were identified as past or current injection drug use, intranasal drug use, chronic hemodialysis, being born to an HCV-infected mother, incarceration, receiving tattoo(s) under unregulated circumstances, and other percutaneous exposure to HCV. Additionally, the USPSTF recommended a one-time screening of people who received blood or blood products prior to 1992 and of adults born between 1945 and 1965.³ Because risk factors for HCV infection and HIV infection are similar, the CDC recommends yearly screening for HCV in patients infected with HIV.⁴

Our study was performed to analyze the burden of HCV for a typical adult population in the United States, emphasizing actual costs and utilization for commercial insurers and managed Medicaid payers.

Our findings showed, in part, that the portion of members diagnosed with HCV by sex and stage of disease for a commercially insured adult population in 2013 showed a higher prevalence of HCV among males than females. The average age of HCV-infected adults is 51.3 years, and males with HCV are slightly older than females. The majority of individuals with HCV have “Chronic HCV” (83.1% of total). Chronic HCV includes patients who have HCV infection causing liver disease and those who are HCV carriers. More advanced liver disease, combining “Cirrhosis” and “End-Stage Liver Disease,” comprises about 15% of the HCV population. On average, the allowed per patient per month (PPPM) cost for HCV to a commercial insurer is about four times the cost for a demographically similar average patient who does not have HCV—\$2,432, compared with \$608. The allowed PPPM cost for HCV patients is higher for the more advanced stages of liver disease. The highest PPPM cost is for HCV patients who received a liver transplant in 2013, the year of the analysis.

We also examined a portion of members diagnosed with HCV by stage of disease and sex for a managed Medicaid population, across the two-year period 2012 to 2013. We note several differences in the HCV prevalence rates for the Medicaid population compared with the commercial one. The overall prevalence rate of HCV is 7.5 times higher, and the average age is lower. There are more females diagnosed with HCV than males in the Medicaid population; this is because about two-thirds of the population covered by Medicaid during the years of the study is female, compared with about half of a commercial population.

In both commercial and Medicaid populations, very few HCV-diagnosed members have had a liver transplant. In addition, we analyzed a select group of comorbid conditions because they are known from previous research to adversely affect liver health, and to be associated with poor adherence to treatment, or with poor outcomes.^{5,6} Diabetes and hyperlipidemia are associated with liver disease; mental health disorders are associated with poor treatment adherence; and alcohol dependence and/or alcoholic liver disease are associated with both liver disease and treatment adherence issues. Injection drug use is associated with both HCV and with HIV/AIDS and is also associated with liver disease and poor treatment adherence. These diagnoses have much higher prevalence in the HCV-infected population compared with the HCV-free population adjusted for age and sex. Diagnosed diabetes and/or alcohol dependence and/or alcoholic liver disease are associated with more advanced stages of liver disease.

Progression of liver disease in individuals infected with HCV has been studied in clinical cohorts and projected to large populations through modeling.⁷ By contrast, we performed a longitudinal study of claims data to derive empirical population-level disease stage transition probabilities. For patients with chronic HCV, 3.2% had progressed to cirrhosis, 1.4% progressed to end-stage liver disease, and 0.2% had undergone a liver transplant. The remaining 95.2% of chronic HCV patients had not progressed to more advanced liver disease during the 24-month period. For those having cirrhosis, the progression to a more advanced level of liver disease was more pronounced, with 16.9% having end-stage liver disease, and 1.6% having undergone liver transplant by the end of the 24-month period. For those with end-stage liver disease, 8.6% had a liver transplant.

It is well documented that the HCV population has a high prevalence of associated comorbid conditions.⁵ The results of our analysis confirmed this, and we also found that the diagnosed prevalence of comorbid conditions was generally higher in the subset of the HCV population with more advanced liver disease. In fact, a poster presentation to the International Liver Conference in April 2015 suggested that chronic HCV infection had a limited effect on mortality, unless severe comorbidities were also present.⁸ Providers and payers alike have already recognized the contribution of comorbid conditions to the severity and speed of progression of liver disease, and the issue of adherence to treatment. Our analysis underscores the need to treat the whole HCV patient, not just the HCV infection. This involves maximizing the patient's liver health and caring for comorbid conditions that affect overall physical and behavioral health status.

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BACKGROUND

The recent approval of curative and well-tolerated pharmaceutical treatments to eradicate the hepatitis C virus (HCV) has focused attention on the health burden and costs of the HCV-infected population.

The prevalence of hepatitis C virus (HCV) infection in the United States is approximately 1%, based on analysis of the National Health and Nutrition Examination Survey (NHANES), from 2003 to 2010, which estimated that there were approximately 2.7 million chronically infected individuals in the noninstitutionalized civilian population.¹ Because NHANES does not survey homeless, incarcerated, or active military populations, its numbers are likely an underestimate of total cases and prevalence. The Centers for Disease Control and Prevention (CDC) estimates that there were approximately 29,700 new cases of HCV in 2013.²

HCV is a virus that is transmitted from person to person by exposure to blood and other secretions through the skin (percutaneously). New HCV infections in the United States result most commonly from needle sharing among injection drug users, and, to a lesser extent, in healthcare settings (e.g., needlestick injuries) or by neonatal infection from an HCV-infected mother. Sexual transmission and sharing personal items such as razors or toothbrushes are inefficient means of transmission. Prevalent disease has resulted from transfusion of blood and blood products, and from transplanted organs, prior to being screened for HCV, which began in 1992. It has also been a result of persistence of infection from this cause and the others enumerated above.² In the NHANES survey, factors that were associated with chronic HCV infection were current or prior use of illicit drugs other than marijuana, having received a blood transfusion before 1992, and having at least 10 lifetime sexual partners. About half of the population aged 20 to 59 had one of those risk factors (NHANES does not assess drug use or sexual behavior in people aged 60 or older).¹

In 2013, the U.S. Preventive Services Task Force (USPSTF) recommended screening people who are at high risk of HCV infection. Those ongoing risks were identified as past or current injection drug use, intranasal drug use, chronic hemodialysis, being born to an HCV-infected mother, incarceration, receiving tattoo(s) under unregulated circumstances, and other percutaneous exposure to HCV. Additionally, the USPSTF recommended a one-time screening of people who received blood or blood products prior to 1992 and of adults born between 1945 and 1965.³ Because risk factors for HCV infection and HIV infection are similar, the CDC recommends yearly screening for HCV in patients infected with HIV.⁴

Acute infection with HCV is generally asymptomatic, though some people may have symptoms such as fatigue, nausea, generalized aching, or abdominal pain. Most people who are infected (74% to 86%) do not spontaneously clear the virus from their bodies and develop chronic HCV. HCV targets the liver, where it may lead to inflammation and then to scarring (fibrosis). Over time, some people develop cirrhosis and, eventually, liver failure, or end-stage liver disease (ESLD). Because of the liver's ability to continue to function despite HCV infection, chronic infection may be asymptomatic, and many chronic HCV infections are discovered only when routine liver function tests are found to be abnormal, while others are discovered through screening programs. Cirrhosis eventually develops in about 15% to 20% of patients with chronic HCV infection. Additionally, patients with HCV-related liver disease have an increased risk of developing hepatocellular carcinoma (primary cancer of the liver). Liver disease that is due to chronic HCV infection is the most common reason for liver transplantation in the United States. The chance of progression of liver disease is related to the genetic strain of HCV, and the timing of progression from initial infection to advanced liver disease varies greatly among individuals.⁹

The landscape of HCV is constantly changing. The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA), in collaboration with the International Antiviral Society-USA (IAS-USA), has produced online guidance and recommendations for hepatitis C management. They are continuously updated, as new information and new treatments become available.¹⁰ According to these expert recommendations, “Evidence clearly supports treatment in all HCV-infected persons, except those with limited life expectancy (less than 12 months) due to non–liver-related comorbid conditions.”¹⁰ Successful treatment results in sustained virologic response (SVR), which is the absence of detectable HCV. SVR is durable in more than 99% of patients, and patients who have achieved SVR have evidence of improvement in liver disease, non-liver manifestations of liver disease, and both liver-related and all-cause mortality. Additionally, patients who have achieved SVR no longer transmit HCV to others.¹⁰

Prior to 2011, standard pharmaceutical treatment for HCV was based on regimens that included interferon and ribavirin. SVR rates did not exceed 50% for patients with genotype 1 and were approximately 80% for genotypes 2 and 3. Because these regimens required self-injection over the course of several months and also caused unpleasant side effects, treatment nonadherence and discontinuation were common. Direct-acting antiviral drugs were first marketed in 2011, and standard treatment became triple therapy with interferon, ribavirin, and a protease inhibitor. By 2014, sofosbuvir, ledipasvir-sofosbuvir in fixed dose combination, and ombitasvir-paritaprevir-ritonavir plus dasabuvir were approved as all-oral regimens for the treatment of HCV. The side effect profile for these new therapies is more favorable than for previous regimens, and SVR rates approach 90% to 95% in clinical trials of patients with genotype 1 disease, previously considered relatively refractory. Treatment duration is 12 to 24 weeks, depending on the drug regimen, the viral genotype, and the stage of liver disease.¹¹

U.S. patients infected with HCV have a high prevalence of other chronic conditions. A study of 7,411 HCV-infected patients, based on a multipayer U.S. database of commercial claims, found that almost all of them had a comorbid condition during a two-year study period. Drug use occurred in 12.9% and alcohol use in 4.8% of HCV patients who received treatment during the study period. The two most frequent comorbid conditions were liver disease (37.5%) and connective tissue disease (37.5 %), both of which were more common in HCV patients compared with those who were free of HCV. Substance-related mental disorders and depressive disorder were 1.39 times and 3.72 times more common in treated HCV patients compared with those who were free of HCV.⁵

Comorbid conditions have an important effect on mortality in patients infected with HCV. A study presented at the International Liver Conference in April 2015 analyzed a national database of hospital patients in France. The purpose of the study was to compare HCV infection with alcohol use disorders. It showed that chronic HCV infection had a limited effect on mortality, unless comorbid conditions were present. In contrast, patients with alcohol dependence experienced higher mortality rates, regardless of the presence of other conditions. In patients with alcohol use disorders, withdrawal or abstinence was associated with lowered mortality risk, including in patients with HCV infection.⁸

Commercial insurer costs associated with chronic HCV virus infection and liver complications were assessed in a retrospective matched cohort study using paid claims from 2002 to 2010. Definitions for stages of HCV disease were based on International Classification of Diseases, Clinical Modification (ICD-9-CM), diagnosis coding. In this population, the mean age was 49.5 years, and 61.7% of the HCV patients were male. The population was highly comorbid, with diabetes, at 15.1%, and chronic obstructive pulmonary disease (COPD), at 9.0%, being the most common comorbid conditions. Other comorbid conditions related to liver disease included AIDS/HIV (2.0% of the population), alcoholism (3.85%), and substance abuse (3.0%). The average incremental annual cost for HCV patients compared with patients without HCV (in 2009 dollars) was reported to average \$9,681, for all stages of liver disease. Incremental annual costs by stage of liver disease, compared with patients without HCV, were reported to be:

- No liver disease: \$5,879
- Compensated cirrhosis: \$5,330
- Decompensated cirrhosis: \$27,845
- Hepatocellular carcinoma: \$43,671
- Liver transplant: \$93,609

Incremental annual prescription drug costs (including but not limited to antiviral drugs) averaged \$2,739; they were \$2,659 for those without liver involvement, and \$3,102 for those with compensated cirrhosis.¹² These estimates are reported in 2009 dollars based on the data period 2002 to 2010 and therefore do not take account of regimens that include direct-acting antiviral drugs.

In an analysis of paid claims (2002 to 2010) for the commercially insured population with HCV, total and HCV-related cost and utilization were presented by stage of liver disease. Cost and utilization were considered to be related to HCV if diagnosis codes or procedure codes for HCV, liver disease, or HCV treatment were listed as primary or secondary diagnoses on the claim. Using this methodology, 56% of costs were considered to be HCV-related, and this proportion increased with the severity of the liver disease (46% for non-cirrhotic liver disease; 57% for cirrhosis; and 71% for end-stage liver disease).¹³

A poster presentation to the April 2015 World Liver Congress assessed healthcare costs from 2000 to 2013 by stage of liver disease, based on a database of commercial claims from multiple payers. Each of the HCV cohorts was statistically significantly older and with a higher percentage of male patients compared with the HCV-free population. Rather than using actual costs, the differences in per patient per month (PPPM), healthcare costs were estimated using a bin bootstrapping method adjusted by propensity score, with age, sex, Charlson Comorbidity Index, and previous HCV treatment experience as covariates in the model. PPPM costs were higher for each of the HCV cohorts, and this was statistically significant. The adjusted monthly incremental costs (in 2013 dollars) for each stage of liver disease were:

- Non-cirrhotic: \$1,633
- Compensated cirrhosis: \$1,885
- Decompensated cirrhosis: \$3,360
- Hepatocellular carcinoma: \$7,904
- Liver transplant: \$21,589

The analysis excluded patients with concomitant HIV disease, and the HCV patient index date was defined by the diagnosis date of most severe liver disease.¹⁴

Our study was performed to analyze the burden of HCV for a typical adult population in the United States, emphasizing actual costs and utilization for commercial insurers and managed Medicaid payers.

RESULTS

Throughout this report, we use the term prevalence to mean the portion of the total population identified as having HCV based on diagnosis codes in claims data. As we have noted previously, many individuals with HCV infection are asymptomatic. Others may not seek healthcare. For these reasons, using claims data as a source of information produces an HCV prevalence rate that is lower than those derived from survey data or from clinical records.

We assigned each person in the HCV-infected population to one of five stages based on specific liver disease ICD-9-CM diagnosis codes. The codes were chosen to be consistent with the risk adjuster model promulgated by the U.S. Department of Health and Human Services for use in insurance plans that are qualified by the Patient Protection and Affordable Care Act. The five stages are hierarchical—that is, a patient is assigned to the single, most advanced stage for which they qualify. The five stages are shown in Figure 1.

Figure 1: Stages of HCV

Stage of Disease	Brief Description
Chronic HCV	Diagnoses for HCV infection, but without cirrhosis or worse; includes those with acute HCV and unspecified HCV with or without hepatic encephalopathy
Cirrhosis	Diagnoses for HCV infection and cirrhosis, but not end-stage liver disease or liver transplant
End-Stage Liver Disease	Diagnoses for HCV infection and end-stage liver disease, but not liver transplant
Liver Transplant (surgery in past)	Diagnoses for HCV infection and a liver transplant prior to 2013 (the year of analysis)
Liver Transplant (surgery in 2013)	Diagnoses for HCV infection and a liver transplant in 2013 (the year of analysis)

Additional details about this model are provided in the Methodology section.

DIAGNOSIS AND STAGE OF DISEASE

The portion of members diagnosed with HCV by sex and stage of disease for a commercially insured adult population in 2013 is shown in the table in Figure 2. We observed a higher prevalence of HCV among males than females. The average age of HCV-infected adults is 51.3 years, and males with HCV are slightly older than females. The majority of individuals with HCV have “Chronic HCV” (83.1% of total). Chronic HCV includes patients who have HCV infection causing liver disease and those who are HCV carriers. More advanced liver disease, combining “Cirrhosis” and “End-Stage Liver Disease,” comprises about 15% of the HCV population.

Figure 2: HCV Prevalence by Sex and Stage of Disease in a Commercially Insured Adult Population (2013)

Stage of Disease	Male		Female		Total				
	HCV Patient Count	HCV Prevalence	HCV Patient Count	HCV Prevalence	HCV Patient Count	% of Total Patients	HCV Prevalence	Average Age	
Chronic HCV	17,611	0.171%	11,459	0.104%	29,070	83.1%	0.136%	50.5	
Cirrhosis	1,902	0.018%	841	0.008%	2,743	7.8%	0.013%	55.1	
End-Stage Liver Disease	1,714	0.017%	673	0.006%	2,387	6.8%	0.011%	55.2	
Liver Transplant (surgery in past)	537	0.005%	114	0.001%	651	1.9%	0.003%	56.3	
Liver Transplant (surgery in 2013)	96	0.001%	23	0.000%	119	0.3%	0.001%	56.1	
Total HCV	21,860	0.212%	13,110	0.119%	34,970	100.0%	0.164%		
Average Age	52.2		49.7						51.3

Source: Milliman analysis of a commercially insured adult population (ages 18-64, n = 21,272,609), 2013 Truven MarketScan Database.

The portion of members diagnosed with HCV by stage of disease and sex for a managed Medicaid population, across the two-year period 2012 to 2013, is shown in the table in Figure 3. We note several differences in the HCV prevalence rates for the Medicaid population compared with the commercial one. The overall prevalence rate of HCV is approximately 7.5 times higher, and the average age is lower. There are more females diagnosed with HCV than males in the Medicaid population; this is because about two-thirds of the population covered by Medicaid is female, compared with about half of a commercial population. In both commercial and Medicaid populations, very few HCV-diagnosed members have had a liver transplant.

Figure 3: HCV Prevalence by Sex and Stage of Disease in a Managed Medicaid Adult Population (2012-2013)

Stage of Disease	Male		Female		Total				
	HCV Patient Count	HCV Prevalence	HCV Patient Count	HCV Prevalence	HCV Patient Count	% of Total Patients	HCV Prevalence	Average Age	
Chronic HCV	3,591	1.410%	4,803	0.922%	8,394	87.5%	1.082%	41.8	
Cirrhosis	327	0.128%	253	0.049%	580	6.0%	0.075%	50.2	
End-Stage Liver Disease	378	0.148%	196	0.038%	574	6.0%	0.074%	51.2	
Liver Transplant	*	*	*	*	42	0.4%	0.005%	54.2	
Total HCV	4,325	1.686%	5,265	1.008%	9,590	100.0%	1.236%		
Average Age	47.4		39.3						43.0

Source: Milliman analysis of a managed Medicaid adult population (ages 18-64, n = 766,248), 2012-2013 Milliman Health Research Database.

COSTS AND UTILIZATION

On average, the allowed PPPM cost for the HCV population is about four times the cost for a population adjusted for age and sex not having HCV—\$2,432 PPPM, compared with \$608 per member per month (PMPM). The allowed PPPM cost for HCV patients is higher for the more advanced stages of liver disease. The highest PPPM cost is for HCV patients who received a liver transplant in 2013, the year of the analysis. The table in Figure 4 shows the 2013 allowed PPPM by sex and stage of disease in a commercially insured adult population.

Throughout this report we compare the HCV population estimates with those of an “HCV-free” population. The HCV-free population is those not having HCV, but adjusted by age and sex for the HCV population. As such, the HCV-free estimates reflect the specific underlying mix of comorbidities, socioeconomic, and other demographic factors.

Figure 4: Allowed PPPM by Sex and Stage of Disease in a Commercially Insured Adult Population (2013)

Stage of Disease	2013 Allowed PPPM		Total	
	Male	Female	2013 Allowed PPPM	HCV Patient Count
Chronic HCV	\$1,905	\$1,620	\$1,793	29,070
Cirrhosis	\$3,357	\$3,231	\$3,318	2,743
End-Stage Liver Disease	\$5,995	\$5,887	\$5,965	2,387
Liver Transplant (surgery in past)	\$7,125	\$7,245	\$7,146	651
Liver Transplant (surgery in 2013)	\$45,149	\$35,748	\$43,337	119
Total HCV	\$2,666	\$2,043	\$2,432	34,970
HCV-free PMPM^a	\$602	\$618	\$608	

Source: Milliman analysis of a commercial adult population (ages 18-64, n = 21,272,609), 2013 Truven MarketScan Database.

^a HCV-free is the population that does not have HCV, adjusted by age and sex for the HCV population.

The table in Figure 5 shows the 2013 allowed PPPM costs for HCV patients by geographic region. HCV patients in the western part of the country experienced the highest costs for liver transplant. Nevertheless, the average cost to commercial payers for HCV patients did not vary much across the U.S.

Figure 5: Allowed PPPM by Geographic Region and Stage of Disease in a Commercially Insured Adult Population (2013)

Stage of Disease	2013 Allowed PPPM by Geographic Region, United States			
	Northeast	North Central	South	West
Chronic HCV	\$1,874	\$1,878	\$1,810	\$1,651
Cirrhosis	\$3,427	\$3,215	\$3,443	\$3,099
End-Stage Liver Disease	\$6,240	\$6,371	\$5,848	\$5,691
Liver Transplant (<i>Surgery in Past</i>)	\$7,188	\$9,527	\$5,831	\$7,843
Liver Transplant (<i>Surgery in 2013</i>)	\$41,742	\$44,148	\$30,660	\$66,842
Total HCV	\$2,481	\$2,598	\$2,401	\$2,343
HCV Patient Count	7,640	5,131	13,165	9,034

Source: Milliman analysis of a commercial adult population (ages 18-64, n = 21,272,609), 2013 Truven MarketScan Database.

On average, HCV patients incur higher PPM costs across all types of services than do members of a population of similar age and sex not having HCV. The most significant differences in PPM costs for HCV patients, compared with those who are HCV-free, are for inpatient (IP) admissions. Total pharmacy costs are higher for all stages of liver disease, compared with the HCV-free population. The table in Figure 6 shows the allowed PPM costs for the commercially insured HCV-infected population by major service category. A detailed description of these service categories can be found in Appendix B.

Figure 6: Allowed PPM by Service Category and Stage of Disease in a Commercially Insured Adult Population (2013)

Stage of Disease	2013 Allowed PPM by Service Category							
	IP Facility	Outpatient Facility			Professional	Total Rx (incl. antivirals ^b)	Anti-virals ^b	Total PPM
		ER	Surgery	Other				
Chronic HCV	\$445	\$53	\$109	\$265	\$415	\$506	\$231	\$1,793
Cirrhosis	\$983	\$68	\$286	\$524	\$616	\$842	\$479	\$3,318
End-Stage Liver Disease	\$2,740	\$126	\$494	\$673	\$1,108	\$824	\$277	\$5,965
Liver Transplant (surgery in past)	\$3,177	\$83	\$416	\$925	\$1,088	\$1,457	\$403	\$7,146
Liver Transplant (surgery in 2013)	\$31,811	\$192	\$1,619	\$2,324	\$5,486	\$1,905	\$312	\$43,337
Total HCV	\$799	\$60	\$159	\$332	\$507	\$576	\$257	\$2,432
HCV-free PMPM^a	\$133	\$18	\$63	\$87	\$182	\$125		\$608

Source: Milliman analysis of a commercial adult population (ages 18-64, n = 21,272,609), 2013 Truven MarketScan Database.

^a HCV-free is the population that does not have HCV, adjusted by age and sex for the HCV population.

^b Antivirals available in 2013; does not include recently approved antiviral therapies.

In 2013, the HCV population experienced higher inpatient admission rates and longer lengths of stay, more emergency room (ER) visits, and a higher rate of prescriptions, compared with the HCV-free population adjusted for age and sex. The table in Figure 7 shows utilization statistics for a few key service categories by stage of disease.

Figure 7: Utilization per 1,000 Members by Service Category and Stage of Disease in a Commercially Insured Adult Population (2013)

Stage of Disease	2013 Utilization per 1,000 by Service Category					
	Inpatient Admissions			ER Visits	Total Rx Scripts (incl. antivirals ^b)	Antiviral ^b Scripts
	Admits per 1,000	Days per 1,000	Average Length of Stay			
Chronic HCV	258.1	1,418.7	5.5	470.1	24,780.6	756.4
Cirrhosis	429.3	2,470.2	5.8	537.0	32,008.8	1,594.7
End-Stage Liver Disease	1,263.2	7,771.5	6.2	856.9	40,304.3	836.2
Liver Transplant (surgery in past)	910.4	6,450.3	7.1	615.7	55,181.2	1,424.1
Liver Transplant (surgery in 2013)	3,713.4	44,029.5	11.9	1,426.9	76,422.5	930.6
Total HCV	361.9	2,161.9	6.0	506.8	27,119.1	840.5
HCV-free^a	65.8	300.6	4.6	149.3	15,297.5	

Source: Milliman analysis of a commercial adult population (ages 18-64, n = 21,272,609), 2013 Truven MarketScan Database.

^a HCV-free is the population that does not have HCV, adjusted by age and sex for the HCV population.

^b Antivirals available in 2013; does not include recently approved antiviral therapies.

Compared with the commercial population, total allowed PPPM costs were lower for managed Medicaid. This is expected because Medicaid provider fee schedules tend to be lower than in the commercial market. As with the commercial population, costs were higher for more advanced stages of liver disease, and the costs were nearly three times that of the HCV free population adjusted for age and sex. The table in Figure 8 shows allowed PPPM costs by sex and stage of disease for an adult managed Medicaid population across the two-year period 2012 to 2013.

Figure 8: Allowed PPPM by Sex and Stage of Disease in a Managed Medicaid Adult Population (2012-2013)

Stage of Disease	Allowed PPPM		Total	
	Male	Female	Allowed PPPM	HCV Patient Count
Chronic HCV	\$1,498	\$1,341	\$1,409	8,394
Cirrhosis	\$2,343	\$2,307	\$2,327	580
End-Stage Liver Disease	\$3,794	\$3,485	\$3,685	574
Liver Transplant	*	*	\$6,293	42
Total HCV	\$1,785	\$1,488	\$1,622	9,590
HCV-free PMPM^a	\$582	\$572	\$576	

Source: Milliman analysis of a managed Medicaid adult population (ages 18-64, n = 766,248), 2012-2013 Milliman Health Research Database.

^a HCV-free is the population that does not have HCV, adjusted by age and sex for the HCV population.

As with the commercial population, managed Medicaid HCV patients incur higher costs on average than a similar population not having HCV, across all types of services. Inpatient and pharmacy costs combined contributed on average about two-thirds (64.1%) of a Medicaid HCV patient’s total cost of care. While we combined two years of data (2012 and 2013) for our analysis, we observed a 40% decrease in antiviral drug utilization in the Medicaid HCV population from 2012 to 2013. The table in Figure 9 shows the average allowed PPPM costs by service category for a managed Medicaid population across the two-year period.

Figure 9: Allowed PPPM by Service Category and Stage of Disease in a Managed Medicaid Adult Population (2012-2013)

Stage of Disease	Allowed PPPM by Service Category							
	IP Facility	Outpatient Facility			Professional	Total Rx (incl. antivirals)	Antivirals ^b	Total PPPM
		ER	Surgery	Other				
Chronic HCV	\$460	\$103	\$44	\$126	\$250	\$427	\$179	\$1,409
Cirrhosis	\$776	\$140	\$127	\$183	\$355	\$746	\$388	\$2,327
End-Stage Liver Disease	\$1,894	\$225	\$165	\$201	\$603	\$597	\$151	\$3,685
Liver Transplant	\$4,361	\$119	\$145	\$275	\$686	\$707	\$138	\$6,293
Total HCV	\$582	\$112	\$57	\$135	\$279	\$458	\$190	\$1,622
HCV-free PMPM^a	\$147	\$43	\$33	\$60	\$139	\$154		\$576

Source: Milliman analysis of a managed Medicaid adult population (ages 18-64, n = 766,248), 2012-2013 Milliman Health Research Database.

Note: Liver transplant patient sample size (n = 42).

^a HCV-free is the population that does not have HCV, adjusted by age and sex for the HCV population.

^b Antivirals available in 2012 and 2013; does not include recently approved antiviral therapies.

The managed Medicaid HCV population experienced more than three times higher inpatient admission rates, a longer length of stay, and more than twice as many ER visits, compared with the HCV-free population adjusted for age and sex. The table in Figure 10 shows average utilization statistics across the two-year period for key service categories for an adult managed Medicaid population by stage of disease.

Figure 10: Utilization per 1,000 Members by Service Category and Stage of Disease in a Managed Medicaid Adult Population (2012-2013)

Stage of Disease	Utilization per 1,000 by Service Category					
	Inpatient Admissions			ER Visits	Total Rx Scripts (incl. antivirals ^b)	Antiviral ^b Scripts
	Admits Per 1,000	Days Per 1,000	Average Length of Stay			
Chronic HCV	675.1	3,301.3	4.9	2,585.6	49,801.6	580.1
Cirrhosis	1,101.5	6,360.7	5.8	3,060.5	69,876.9	1,101.5
End-Stage Liver Disease	2,491.3	15,215.2	6.1	3,916.3	69,437.9	520.6
Liver Transplant	2,222.2	20,474.1	9.2	1,955.6	83,466.7	237.0
Total HCV	815.8	4,272.6	5.2	2,690.8	52,363.8	607.5
HCV Free^a	230.1	1,061.0	4.6	1,147.2	36,836.6	

Source: Milliman analysis of a managed Medicaid adult population (ages 18-64, n = 766,248), 2012-2013 Milliman Health Research Database.

Note: Liver transplant patient sample size (n = 42).

^a HCV-free is the population that does not have HCV, adjusted by age and sex for the HCV population.

^b Antivirals available in 2013; does not include recently approved antiviral therapies.

COMORBIDITY ANALYSIS

We analyzed a select group of comorbid conditions because they are known from previous research to adversely affect liver health, to be associated with poor adherence to treatment, or associated with poor outcomes.^{5,6} Diabetes and hyperlipidemia are associated with liver disease; mental health disorders are associated with poor treatment adherence; and alcohol dependence and/or alcoholic liver disease are associated with both liver disease and treatment adherence issues. Injection drug use is associated with both HCV and with HIV/AIDS and is also associated with liver disease and poor treatment adherence.

These diagnoses have much higher prevalence in the HCV-infected population compared with the HCV-free population adjusted for age and sex. Diagnosed diabetes and/or alcohol dependence and/or alcoholic liver disease are associated with more advanced stages of liver disease.

The table in Figure 11 shows the 2013 diagnosed prevalence of certain comorbid conditions for an HCV-infected population, by stage of disease compared with the HCV-free population adjusted for age and sex. As expected, many of these conditions are more common in the HCV-infected population. HIV/AIDS is nearly 15 times more commonly diagnosed in the HCV population (2.9%) than in the HCV-free population (0.2%). Alcohol use disorders are more than 9 times as common in the HCV population (4.7%); drug dependence is nearly 20 times more common (5.7%). Diabetes is present in more than 25% of the population with end-stage liver disease and in more than 30% of HCV patients having had a liver transplant.

Figure 11: Prevalence by Select Comorbidity and Stage of Disease in a Commercially-Insured Adult Population (2013)

Comorbidity	Stage of Disease							HCV Patient Counts
	HCV-free ^c	Chronic HCV	Cirrhosis	ESLD	Liver Trans. (surgery in past)	Liver Trans. (surgery in 2013)	Total HCV	
Alcohol Dependence/ Alcoholic Liver Disease (combined) ^a	0.5%	2.7%	9.7%	22.5%	4.6%	28.6%	4.7%	1,648
Diabetes	8.4%	10.9%	20.1%	24.6%	33.5%	42.0%	13.1%	4,573
Drug Dependence	0.3%	6.2%	3.9%	3.9%	1.4%	2.5%	5.7%	2,005
HIV/AIDS	0.2%	3.1%	1.7%	2.1%	1.2%	0.0%	2.9%	1,010
Hyperlipidemia	12.6%	10.8%	9.9%	8.8%	10.1%	5.9%	10.6%	3,698
Mental Health Disorders (combined) ^b	2.0%	6.2%	6.9%	7.7%	5.7%	12.6%	6.4%	2,231

Source: Milliman analysis of commercial adult population (ages 18-64, n = 21,272,609), 2013 Truven MarketScan Database.

^a "Alcohol Dependence/Alcoholic Liver Disease (combined)" includes members having one or more of: Alcohol Dependence and/or Alcoholic Liver Disease.

^b "Mental Health Disorders (combined)" includes members having one or more of: Depressive and Bipolar Disorders, Personality Disorders, Psychosis and Delusional Disorders, and/or Schizophrenia.

^c HCV-free is the population that does not have HCV, adjusted by age and sex for the HCV population.

The diagnosed prevalence rates of comorbid conditions in a managed Medicaid HCV population were even higher than we observed in the commercial HCV population. HIV/AIDS was diagnosed in 4.4% of the HCV patients compared with just 0.5% of the HCV-free Medicaid population adjusted for age and sex. Alcohol use (13.4%) and drug dependence disorders (25.4%) are also much more commonly diagnosed in the HCV Medicaid population than in the commercial. Diabetes is present in more than 25% of the HCV population with cirrhosis and end-stage liver disease.

Figure 12: Prevalence by Select Comorbidity and Stage of Disease in a Managed Medicaid Adult Population (2012-2013)

Comorbidity	Stage of Disease						
	HCV-free ^c	Chronic HCV	Cirrhosis	ESLD	Liver Trans.	Total HCV	HCV Patient Counts
Alcohol Dependence/ Alcoholic Liver Disease (combined) ^a	2.3%	9.3%	30.0%	54.9%	*	13.4%	1,282
Diabetes	10.1%	11.5%	26.6%	28.9%	*	13.6%	1,300
Drug Dependence	3.0%	26.2%	22.1%	18.3%	*	25.4%	2,438
HIV/AIDS	0.5%	4.5%	3.1%	4.2%	*	4.4%	423
Hyperlipidemia	11.3%	10.4%	14.0%	11.1%	*	10.7%	1,025
Mental Health Disorders (combined) ^b	3.5%	14.2%	12.6%	15.7%	*	14.2%	1,360

Source: Milliman analysis of a managed Medicaid adult population (ages 18-64, n = 766,248), 2012-2013 Milliman Health Research Database.

^a "Alcohol Dependence/Alcoholic Liver Disease (combined)" includes members having one or more of: Alcohol Dependence and/or Alcoholic Liver Disease.

^b "Mental Health Disorders (combined)" includes members having one or more of: Depressive and Bipolar Disorders, Personality Disorders, Psychosis and Delusional Disorders, and/or Schizophrenia.

^cHCV-free is the population that does not have HCV, adjusted by age and sex for the HCV population.

COMMERCIAL DISEASE STAGE TRANSITION

Progression of liver disease in individuals infected with HCV has been studied in clinical cohorts and projected to large populations through modeling.⁷ By contrast, we performed a longitudinal study of claims data to derive empirical population-level disease stage transition probabilities. For patients with chronic HCV, 3.2% had progressed to cirrhosis, 1.4% progressed to end-stage liver disease, and 0.2% had undergone a liver transplant. The remaining 95.2% of chronic HCV patients had not progressed to more advanced liver disease during the 24-month period. For those having cirrhosis, the progression to a more advanced level of liver disease was more pronounced, with 16.9% having end-stage liver disease, and 1.6% having undergone liver transplant by the end of the 24-month period. For those with end-stage liver disease, 8.6% had a liver transplant. The table in Figure 13 illustrates the results of our longitudinal study, given 24-month survival in 2012 and 2013.

Figure 13: Probability of Disease Stage Transition in a Commercially Insured Adult HCV Population, Given 24-month Survival

Transition From Disease Stage:	Transition To Disease Stage:					
	Chronic HCV	Cirrhosis	ESLD	Liver Transplant	Total HCV	HCV Patient Count
Chronic HCV	95.2%	3.2%	1.4%	0.2%	100%	16,094
Cirrhosis	n/a	81.6%	16.9%	1.6%	100%	1,353
ESLD	n/a	n/a	91.4%	8.6%	100%	1,009
Liver Transplant	n/a	n/a	n/a	100.0%	100%	417

Source: Milliman analysis of commercial adult population (ages 18-64), 2012-2013 Truven MarketScan Databases.

Note: HCV patients continuously enrolled for 24 months (n = 18,873).

CONSIDERATIONS FOR PAYERS

We have demonstrated that patients infected with HCV incur costs that are far greater than those for patients who are free of HCV infection. Higher costs are associated with advanced stages of liver disease and with the presence of comorbid conditions. These comorbid conditions compound the difficulties of managing HCV disease, as they are associated with medication adherence difficulties and with liver disease complications. Our results are consistent with results of previous clinical and cost studies: the HCV-infected population incurs costs and utilization that are disproportionate to its prevalence.¹²⁻¹⁴

Using the nationwide average statistics derived from our analysis for a commercially insured adult population, we provide an illustration of estimated 2013 chronic HCV population costs (excluding antiviral drugs) in the table in Figure 14. In this illustration, we compare the estimated annual cost (excluding antiviral drugs) of a population having chronic HCV to a population adjusted for age and sex not having HCV (i.e., HCV-free). We note that the cost difference between the chronic HCV and HCV-free populations can be explained by many other demographic factors beyond age and sex, including the number of and complexity of comorbidities and other socioeconomic factors. Quantifying the impact of these other demographic factors is outside the scope of this report.

Figure 14: Illustrative Example: Estimated 2013 Annual Cost (excluding antivirals) of Chronic HCV Patients in a Commercially Insured Adult Population

Population Assumptions		
Health Plan Covered Lives	500,000	A, Assumption
Health Plan Member Months	5,500,000	B, Assumption
% of Members Diagnosed With Chronic HCV	0.00136	C, Milliman analysis: 2013 Truven Marketscan Database
# of Members Having Chronic HCV	680	D = A x C
Chronic HCV Patient Member Months	7,480	E = B x C
Estimated Annual Cost, Medical (Chronic HCV)		
2013 Medical Allowed Cost PPPM	\$1,287	F, Milliman analysis: 2013 Truven Marketscan Database
Estimated Annual HCV Population Cost, Medical	\$9,630,000	G = F x E
Estimated Annual Cost, Rx Other Than Antivirals (Chronic HCV)		
2013 Rx Allowed Cost PPPM (excl. antivirals)	\$275	H, Milliman analysis: 2013 Truven Marketscan Database
Estimated Annual HCV Population Cost, Rx Other	\$2,060,000	J = H x E
Estimated Total Annual Chronic HCV Population Cost (Excluding Antivirals)	\$11,690,000	K = G + J
Estimated Annual Cost, HCV-free		
2013 Allowed Cost PMPM, HCV-free	\$596	L, Milliman analysis: 2013 Truven Marketscan Database
Estimated Total Annual Cost, HCV-free	\$4,460,000	M = L x E
\$ Estimated Population Cost Difference (Excl. Antivirals)	\$7,230,000	N = K - M
% Estimated Population Cost Difference (Excl. Antivirals)	162%	P = N / M

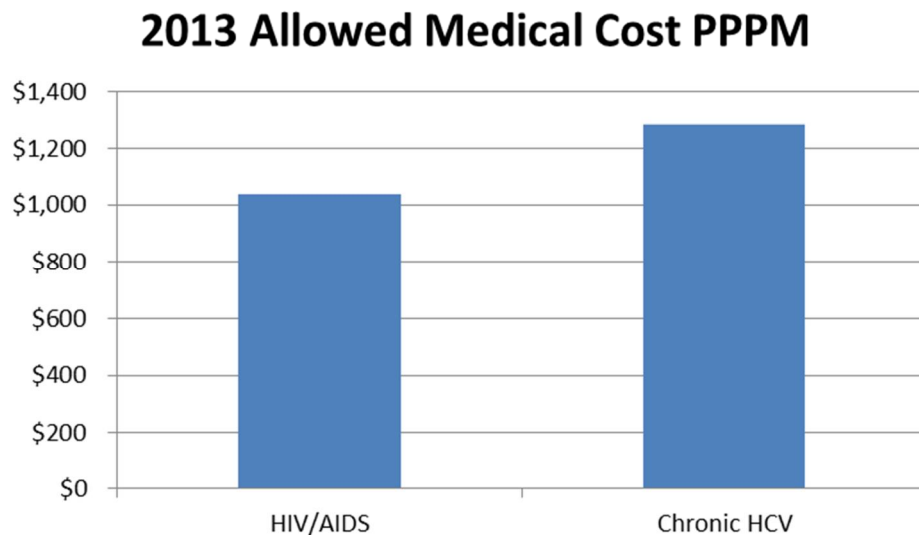
As this example indicates, despite its small size, the chronic HCV population generates a huge cost, beyond the cost of antiviral drugs. While antiviral drug costs have received a great deal of attention, our analysis shows that the cost of care for the liver disease and comorbid conditions in the HCV population means that, despite its low prevalence, HCV disease is a very costly condition.

A similar condition, HIV/AIDS, is already the subject of disease management and focused payer strategies. Both HCV and HIV/AIDS diseases are the result of a chronic viral infection, with similar modes of transmission. However, the overall prevalence of HIV/AIDS is less than one-third of the prevalence of HCV; the CDC estimates that the number of individuals in the United States living with HIV at the end of 2012 is less than 1 million.¹⁵ Additionally, treatment of HCV has the potential for SVR, which is equivalent to viral cure, unlike lifelong treatment of HIV.

In Figure 15, we show the average allowed per patient per month (PPPM) medical costs (excluding drugs) for chronic HCV and HIV/AIDS in 2013. The average PPPM medical costs for chronic HCV are higher than for HIV. These cost estimates are unadjusted and reflect each patient population’s underlying age-sex mix, comorbidities, and other population attributes that may explain some of the difference in medical costs. Nevertheless, the higher prevalence and higher PPPM medical cost for Chronic HCV compared with HIV/AIDS underscores the significant cost contribution of the Chronic HCV population.

All-oral, interferon-free antiviral regimens for HCV became available in 2014. However, we did not include drug costs in the HIV/AIDS versus Chronic HCV comparison, as we did not have 2014 claims data available at the time of this writing. It is important to note that antiviral treatment for HCV consists of one course of medication, while HIV/AIDS antiviral treatment is chronic and lifelong.

Figure 15: 2013 Allowed PPPM Medical Costs of HIV/AIDS and Chronic HCV in a Commercially Insured Adult Population



Source: Milliman analysis of commercial adult population (ages 18-64), 2013 Truven MarketScan Database.

Lastly, it is well documented that the HCV population has a high prevalence of associated comorbid conditions.⁵ The results of our analysis confirmed this, and we also found that the diagnosed prevalence of comorbid conditions was generally higher in the subset of the HCV population with more advanced liver disease. In fact, a poster presentation to the International Liver Conference in April 2015 suggested that chronic HCV infection had a limited effect on mortality, unless severe comorbidities were also present.⁸ Providers and payers alike have already recognized the contribution of comorbid conditions to the severity and speed of progression of liver disease, and the issue of adherence to treatment. Our analysis underscores the need to treat the whole HCV patient, not just the HCV infection. This involves maximizing the patient's liver health and caring for comorbid conditions that affect overall physical and behavioral health status.

CAVEATS AND LIMITATIONS

This report was commissioned by Primrose Healthcare, LLC. The authors are employed by Milliman, Inc. Milliman does not intend to endorse any product or benefit any third party through this report; the report reflects the findings of the authors.

As with any claims analysis, our results and conclusions are based on the underlying data and cannot capture all influences or all real-world conditions. In particular, our analysis is based on recent historical experience but may not reflect present-day experience for many reasons, including new drug therapies and clinical guidelines, as well as the expansion of Medicaid eligibility under the Affordable Care Act (ACA).

Future experience will vary from the estimates presented in this report for reasons including random fluctuation. In addition, we present national average costs for typical populations and benefit designs, but the reader should note that considerable variation from the average results often occur in specific populations. Medicaid entitlement rules, mix of categories (e.g., mix of dual-eligibles), and benefit design may vary by state.

We suggest that this report be distributed in its entirety, as material taken out of context can be misleading.

APPENDIX A: METHODOLOGY

Commercial snapshot analytics

We relied on the 2012 and 2013 Truven MarketScan Commercial Claims Databases. Our starting population reflects a typical adult, employer group population, ages 18 to 64. We only included those having medical and pharmacy coverage and we excluded people associated with capitated plans.

Managed Medicaid snapshot analytics

We relied on Milliman's Health Research Database for 2012 and 2013. Our starting population included all managed Medicaid patients, ages 18 to 64, who had medical and pharmacy coverage. In combining the two years, we assumed 0% cost and utilization trend for the 2012 experience.

Identification of hepatitis C virus (HCV) population

To identify patients with HCV, we required that the individual have at least one inpatient (IP), one emergency room (ER), or one non-laboratory/non-radiology professional claim with one of the following ICD-9 diagnosis codes (in any position on claim):

ICD-9 Diagnosis Code	ICD-9 Code Description
070.41	Acute hepatitis C with hepatic coma
070.44	Chronic hepatitis C with hepatic coma
070.51	Acute hepatitis C without mention of hepatic coma
070.54	Chronic hepatitis C without mention of hepatic coma
070.70	Unspecified viral hepatitis C without hepatic coma
070.71	Unspecified viral hepatitis C with hepatic coma
V02.62	Hepatitis C carrier

HHS-HCC risk adjuster model

We used the U.S. Department of Health and Human Services (HHS)-Hierarchical Condition Categories (HCC) risk adjuster model to assign stage of liver disease to HCV patients.¹⁶

The HHS-HCC risk score model includes four stages of disease progression for liver disease: Chronic HCV, Cirrhosis of the Liver, End-Stage Liver Disease, and Liver Transplant. For individuals staged with Liver Transplant, we assigned them to one of two groups: (1) having the surgery in 2013, or (2) having the surgery prior to 2013. Patients were grouped as having "Surgery in 2013" if they had at least one claim in 2013 with at least one of the following:

Code Type	Code	Code Description
ICD-9-P	50.51	Auxiliary Liver Transplant
ICD-9-P	50.59	Liver Transplant, Not Elsewhere Classified
CPT	47135	Liver Transplant, Orthotopic
CPT	47136	Liver Transplant, Heterotopic
MSDRG	005	Liver transplant w MCC or intestinal transplant
MSDRG	006	Liver transplant w/o MCC

Individuals who were identified as having HCV, but were not assigned to a stage of liver disease by the risk score model are also included in the “Chronic HCV” category. This group includes individuals with acute HCV and unspecified HCV with or without hepatic encephalopathy.

Identification of comorbid conditions

Some of the selected comorbid conditions included in this analysis are also health condition categories within the HHS-HCC risk score model. We used the HHS-HCC risk model’s HCC diagnosis code list to identify the following conditions: diabetes, drug dependence, HIV/AIDS, schizophrenia, depressive and bipolar disorders, psychosis and delusional disorders, and personality disorders.¹⁶ For these conditions, members were identified if they had at least one inpatient, one emergency room, or two or more outpatient (OP) claims with a diagnosis code in any position on the claim.

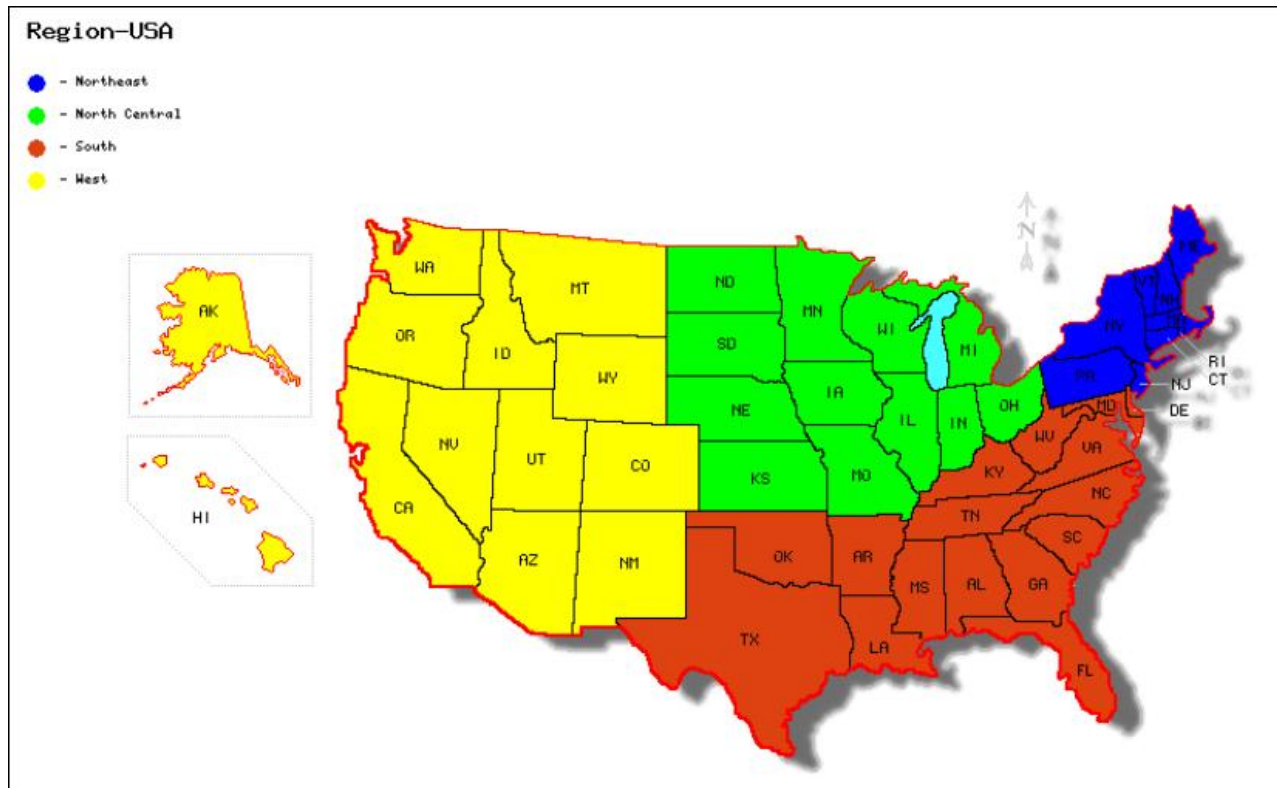
For the remaining comorbid diseases of interest, we developed diagnosis code algorithms. Individuals who had at least one inpatient, one emergency room, or two or more outpatient claims with the disease-identifying diagnosis codes, in any position on the claim, were identified. We can provide a comprehensive list of diagnosis codes used to identify the comorbidities included in this analysis upon request.

Longitudinal analysis: Disease stage transition

For the longitudinal stage transition analysis, we required 24 months continuous enrollment in the period 2012 to 2013 for the HCV population. For the HCV population continuously enrolled, we assigned each patient to a disease stage in both years. In staging the disease for 2013, we selected the most advanced stage reached for each patient. The probability was calculated, within each stage of disease, as the number of people who reach a more advanced stage in 2013 divided by the total number of people assigned to the stage in 2012.

Geographic regions

For the summaries by geographic region, each state (based on residence) was assigned a region as illustrated in the following map:



Mapping image software: diymaps.net.

APPENDIX B: KEY DATA SOURCES

Truven MarketScan® Commercial Claims Databases, 2012-2013. This is an annual medical database that includes private sector health data from approximately 100 payers. The data set contains more than 35 million commercially insured lives. It represents the medical experience of insured employers and their dependents for active employees, early retirees, COBRA continues, and Medicare-eligible retirees with employer-provided Medicare supplemental plans. The data set consists of person-specific clinical utilization, expenditures, and enrollment across inpatient, outpatient, prescription drug, and carve-out services from a selection of large employers, health plans, and government and public organizations. The MarketScan databases link paid claims and encounter data to detailed patient information across sites and types of providers, and over time.

Milliman Health Research Database, 2012-2013. This database is a body of proprietary historical claims experience consisting of data collected from several of Milliman's Health Cost Guidelines™ (HCG) data contributors. The data set represents over 7 million lives and is comprised of medical and prescription drug claims on a line-item level of detail, along with a complete history of per-individual eligibility for all covered lives. Approximately 96% of the lives covered are actively employed commercial lives. Other groups represented include COBRA, Medicare supplemental, and Medicaid.

Health Cost Guidelines categories

The following material is confidential to Milliman, Inc. It describes the assignment of claims into the service categories shown in the sections on healthcare costs and service categories. Note that database analysts would need substantially more detail to completely categorize typical medical claims.

Inpatient facility

This benefit provides for daily semiprivate room and board and ancillary services in short-term community hospitals. Ancillary services include use of surgical and intensive care facilities, inpatient nursing care, pathology and radiology procedures, drugs, and supplies. Costs include facility charges only and do not include professional charges unless performed by staff of the facility and billed on a UB-04 (hospital) claim form. Inpatient facility costs include those for medical, surgical, psychiatric, and alcohol/drug abuse confinements.

Outpatient facility

This benefit provides for services in an outpatient facility setting. Costs include facility charges only and do not include professional charges unless performed by staff of the facility and billed on a UB-04 (hospital) claim form. For all outpatient facility categories, the utilization represents the number of outpatient facility cases.

1. **Emergency room:** This benefit provides for services for emergency accident and medical care performed in the emergency area of a hospital outpatient facility for cases that do not result in an inpatient admission. The average charge includes the cost of emergency room services as well as other services (e.g., radiology, pathology, etc.) provided during an emergency room case.
2. **Surgery:** This benefit provides for outpatient services for surgery, including surgery performed in a hospital outpatient facility or a freestanding surgical facility. The average charge includes facility charges for surgical services as well as other services (e.g., radiology, pathology, etc.) provided during an outpatient surgery case.

3. **Other:** This includes other services, such as cardiovascular testing, physical therapy (PT)/occupational therapy (OT)/speech-language therapy (ST), behavioral health, alcohol and drug abuse, preventive, and pharmacy services, when provided in a hospital outpatient department or a freestanding facility.

Professional

These benefits provide for services performed by a physician or other qualified professional. For consistency, standard utilization labels have been defined for the three types of non-facility utilization: visits, procedures, and units. Visits are synonymous with cases. Procedures represent the number of administration and supply Current Procedural Terminology (CPT)-4 and Healthcare Common Procedure Coding System (HCPCS) codes. Units can capture minutes, number of minute increments, number of tests, etc. Professional services and supplies are counted separately when billed separately.

Pharmacy

This benefit provides for all outpatient prescriptions ordered by an attending physician and dispensed by a pharmacist, and includes the dispensing fee.

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