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THE HEPATITIS C EPIDEMIC: LOOKING AT THE TIP OF THE ICEBERG

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FOREWORD

Despite the forest of actuarial and clinical details that we assemble in this report, the authors are struck by the emerging human tragedy of the Hepatitis C epidemic. People are not mortality rates and patients are not the sum of the office visits and operations they suffer. We believe that better information leads to better decisions, and we hope that this paper will contribute to ameliorating the human aspects of this emerging epidemic.

The authors would like to thank the following individuals for their advice, contributions, disagreements and insights: John Wong, MD, New England Medical Center; David Sugano, Ph.D., Sr. Director, Pharmoeconomics, Schering-Plough Corporation; Charles Scammell of Schering-Plough, and Mary Pat Pauley, MD, Kaiser-Permanente. Any omissions or errors are solely the responsibility of the authors and are in no way attributable to any of these other individuals. In addition, several colleagues at Milliman & Robertson, Inc. made invaluable contributions, including David Mirkin, MD, and Peter Lopatka, ASA.

In developing cost estimates, the authors have sought to provide estimates that are consistent with the approaches that payers such as insurers, HMOs or government programs use to think about costs. These organizations often tend to think about the total cost of care for individuals rather than the cost of care for a particular condition. Other researchers have produced excellent cost estimates based on models that attempt the difficult task of quantifying the cost of Hepatitis C as a disease—separate and distinct from other conditions that an infected individual may have. Not surprisingly, our estimates differ from those other estimates. Our work in no way diminishes the value or accuracy of the results of researchers using other approaches.

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EXECUTIVE SUMMARY

Background

The purpose of this report is to present a financial and healthcare management view of the unfolding Hepatitis C epidemic, with an eye toward encouraging high quality, efficient care. The National Health and Nutrition Examination Survey indicates that about 4 million Americans (1.8% of the population) have Hepatitis C antibodies,[1] of which about 2.7 million have active Hepatitis C virus (HCV) infection.[2] This compares with an estimate of about 750,000 Americans infected with HIV.[3] Most cases are believed to have been contracted before 1990,[4] and about 30,000 new cases occur annually.[5] There are several other hepatitis viruses that can produce diseases of varying severities, but Hepatitis C is believed to have caused the most chronic infections in the US[6] and no vaccine is currently available.

People currently infected with HCV will incur tens of billions of dollars of medical costs and lost productivity over the next two decades. The burden that this will impose on insurers, HMOs, employers and governments will depend on the distribution of the infected patients, their health status, the treatments available and the coordination of care.

Our projections show the estimated total costs of people with HCV infections and the expected savings due to curative treatment of HCV. The approach used in this report is consistent with the usual medical cost basis used by HMOs and with risk-adjusted capitation rates, for example, the amounts paid to Special Needs Plans for people with HIV/AIDS.[7] We believe our approach is particularly useful for HMOs, reinsurers, employers and others responsible for assuming total costs for HCV-infected people. Not surprisingly, our estimates differ from the figures of researchers who attempt the difficult task of isolating the costs of HCV from other costs incurred by an HCV patient. Our work in no way diminishes the value or accuracy of the results of researchers using those other approaches.

This report presents our estimates of the scope of HCV's coming financial crisis. We estimate a return on investment for aggressive, curative HCV treatment, considering total healthcare costs for the healthcare system and for certain private or public payers. We also identify ways that healthcare payers, institutions and professionals can best provide treatment for patients—for those who can be cured of HCV and for those who cannot. The leading treatment for HCV is a combination of two medicines, Interferon-Alfa and ribavirin.[8] We follow standard convention in calling this "combination therapy."

Findings

In summary, we estimate that:

- Our cost-benefit analysis shows that every $1 spent on combination therapy can result in about $4 of medical cost savings. The return includes present value considerations and considers total payments for medical care.
- People with HCV currently consume at least $15 billion per year for all their medical care.
- Without effective curative treatment, total healthcare costs for patients infected with Hepatitis C will peak at an estimated $26 billion (in current dollars) per year in about 2021.
- For a typical patient, curative treatment (combination therapy) pays for itself within 10 years—before considering avoided disability costs and lost productivity costs. This considers the total healthcare costs of both patients who respond and patients who don't respond to treatment as well as the present value of future healthcare spending.
- The disability losses associated with HCV will cost employers billions of dollars. If all of the eligible population were working and were treated with combination therapy, employers would save at least $4-5 billion (present values) in lost work-time costs over the course of the epidemic.

Limitations

Although HCV has infected Americans for at least 50 years,[9] the virus was not fully identified until 1989.[10] Because knowledge of the HCV epidemic is now in its early stages, the projections and clinical guidelines presented here necessarily involve assumptions and reliance on incomplete information. Consequently, projections of the epidemic made several years from now will probably look different in some ways than the ones we present here. Information on how the epidemic will emerge in particular US populations is sparse. Furthermore, HCV clinical practice is in its early stages. We expect that future improvements in knowledge, technology and pharmaceutical therapy will render some aspects of this study obsolete.

This report reflects the methodology and findings of its authors and does not represent an endorsement of any product or policy by Milliman & Robertson, Inc. If this report is copied, it must be distributed in its entirety. The clinical and therapeutic descriptions presented here must not replace sound clinical judgment. We urge the reader to review the report in its entirety and carefully examine the assumptions we have made.

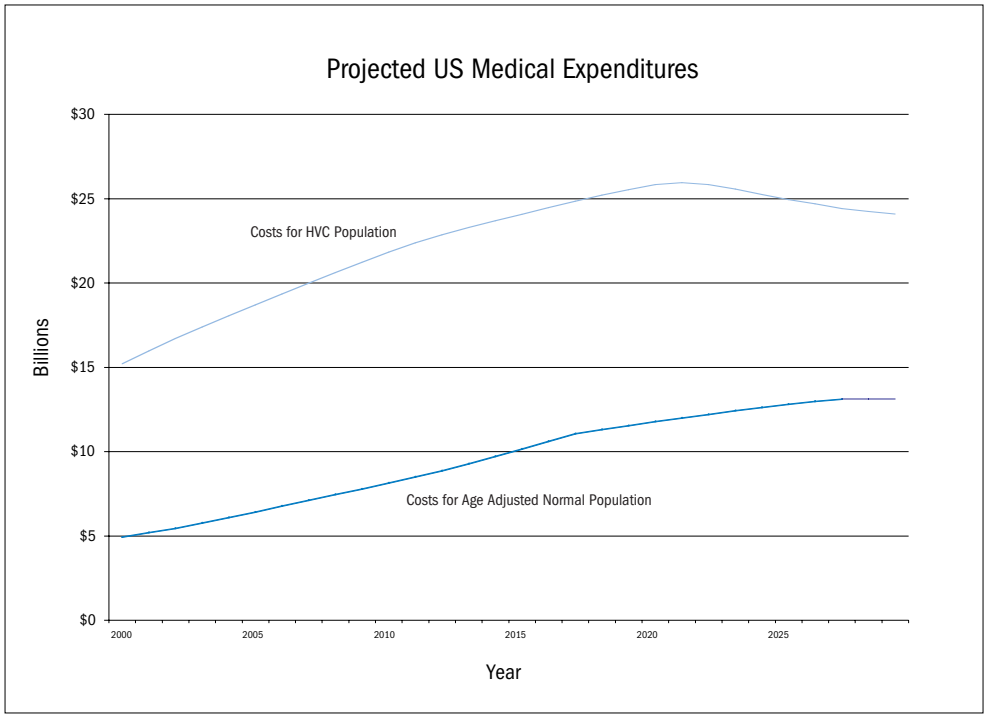
MEASURING THE ICEBERG

Financial Projections

Graph 1 summarizes projected annual US medical claim costs for people with HCV (excluding those with persistently normal liver enzyme tests, as described below)—and compares those costs with the costs with a normal population with the same age mix as the HCV population. The higher line on the graph shows the costs for the HCV population. The lower line represents the costs that the HCV-infected cohort would incur if the cohort had a normal mix of morbidity (were not all infected with HCV). Not all infected individuals are expected to progress to more serious illness. In particular, a test of liver function called ALT is an important indicator of prognosis. We exclude people from the higher line who have persistently normal ALT test results, because these people are less likely to progress to more severe illness.

The costs are for all care, not just care related to HCV. The dollars are the present value of trended medical expenditures.

Graph 1

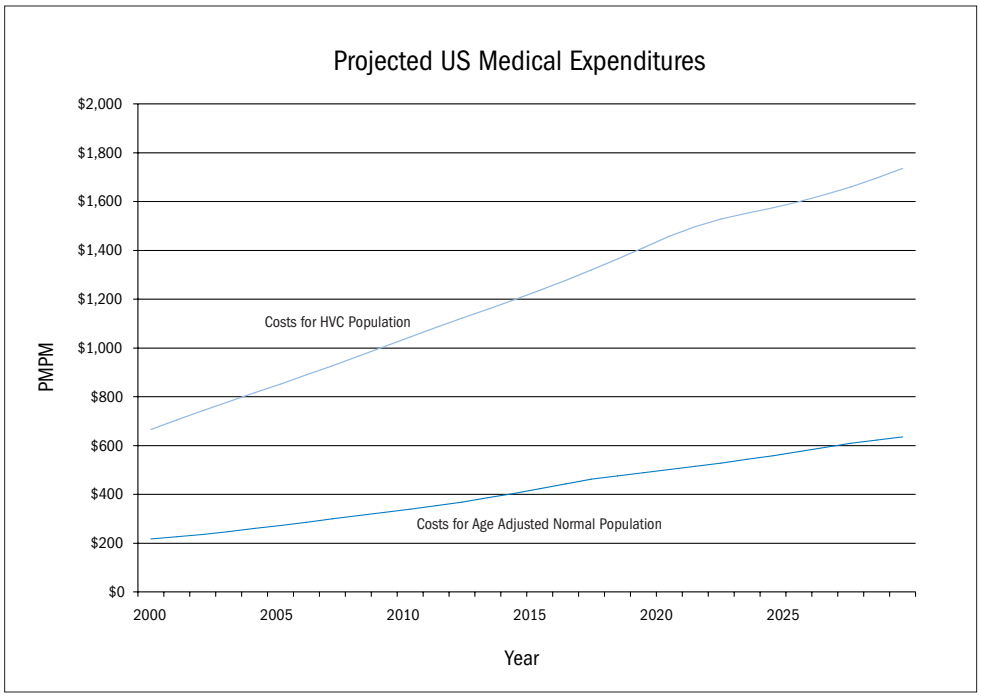


The increase in expenditures reflects the increasing severity of the disease and aging balanced by the accelerating mortality of the affected population.

Graph 2 shows total expenditures on a per member per month (PMPM) basis—for both the HCV population and a normal population with the same age characteristics as the HCV population. Again, we exclude HCV-infected individuals with persistently normal ALT test results from the population considered. The higher line on the graph shows the costs for the HCV population. The lower line represents the costs that the HCV-infected cohort would incur if the cohort had a normal mix of morbidity (were not all infected with HCV).

PMPM is the unit insurers use to budget premium and expense dollars. Again, the higher line is for the HCV population. The shape of the graph reflects the increasing costs of progression to more severe disease states and the decreasing numbers of infected people due to the effects of mortality. This PMPM represents the costs shown in Graph 1, divided by the surviving population during any year, divided by 12 (months per year).

Graph 2



Graphs 3 and 4 consider the treatment-eligible population only. Graph 3 shows two scenarios for medical expenditures for treatment-eligible patients. In the line that begins with a spike (plunge), we assume that all treatment-eligible patients receive combination therapy in year 1. For the other line, we assume none of the treatment-eligible patients receive combination therapy.

Graph 3 shows that the initial high costs of combination therapy produce reduced costs in subsequent years. While it is unrealistic to expect treatment of all eligible persons in one year, this comparison approximates the cost-savings relationships for medical costs for an "average" individual. These data show that the average discounted payback period for combination therapy is under 10 years.

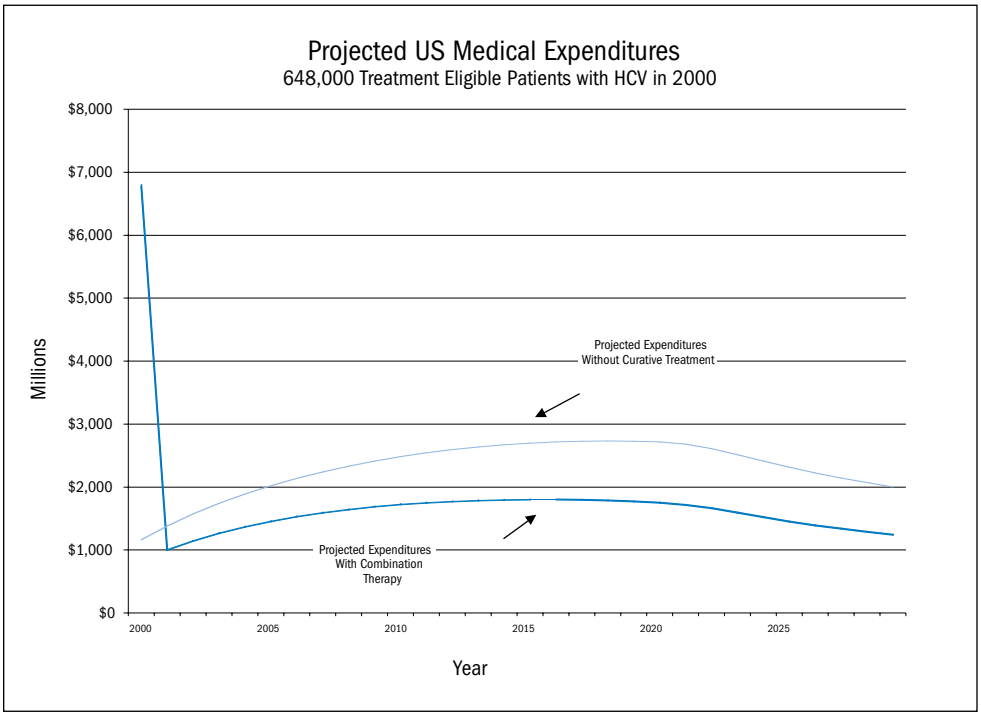
The average course of combination therapy treatment costs about $8,500 per person.[11] While this may appear expensive, the savings over time realized can far exceed the costs. The only other NIH-recommended treatment for HCV, single drug therapy using interferon alone,[12] also has a high cost (but lower than combination therapy) and a lower success rate. Combination therapy is successful at eliminating the Hepatitis C virus in approximately 41% of the treated population with mild to moderate hepatitis and in about 20% of the treated population with cirrhosis. While these success rates may seem too low to justify the high cost of treatment, vigorous analysis of the available data indicates otherwise.

Graph 4 shows how the initial, high cost of combination therapy gets offset by reduced healthcare costs. After about nine years, the initial treatment costs are completely offset (an ROI of 0, by this point). Savings (positive values)

beyond this "breakeven" point contribute to a positive ROI. We estimate that, considering present values, the ROI of curative treatment across a typical treatment-eligible population is about $4 saved for every $1 spent on combination therapy (for an ROI of 4 on Graph 4).

Graphs 3 and 4 show the progression of costs for an "average" treatment-eligible infected person. These results are important for employers, HMOs and other payers, but the results need to be applied cautiously to dynamic populations. These payers would likely see some degree of turnover of members, as current HCV-infected members move to other payers and as infected individuals from outside the payer's organization become new members. To give a sense of the impact, we modeled various turnover assumptions using a "closed block" approach (assuming no new entrants). For the closed block, our modeling suggests that, for each 1% of the HCV population that leaves a payer's program, the ROI reduces by about 15%. The ROI, and the impact of lapses, could be higher or lower for an organization depending on factors such as prevalence rate, disease status and patient compliance.

Graph 3



Other Impacts

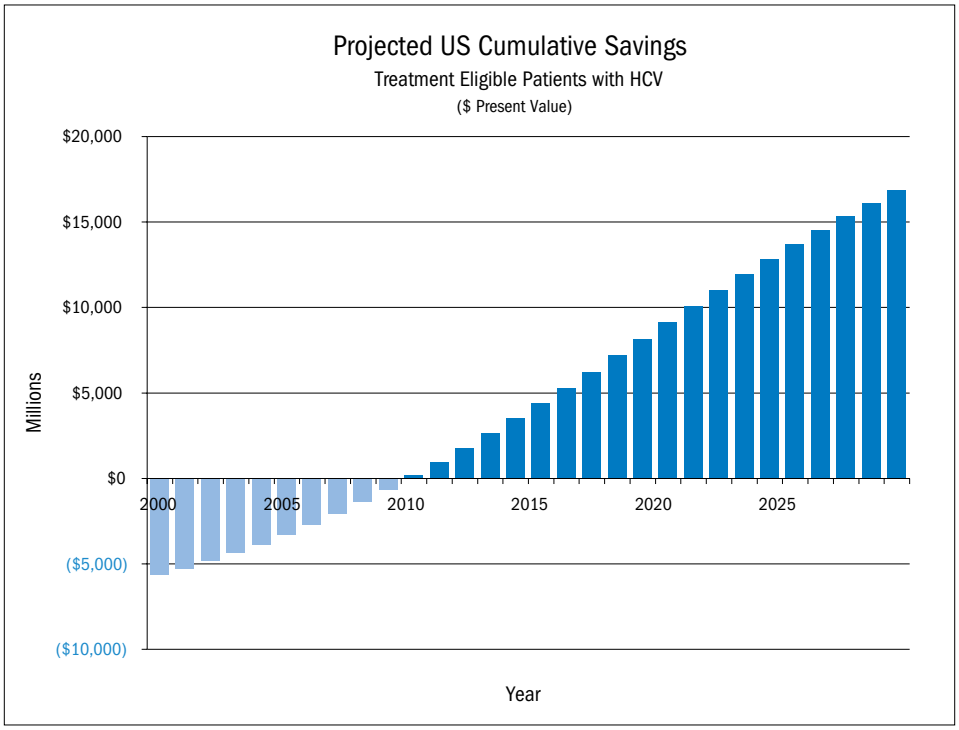
We modeled disability costs for people with mild to moderate hepatitis—whether treatment-eligible or not—by evaluating lost time associated with medical care. We estimate the potential impact to employers due to absenteeism, solely due to physician appointments and hospitalizations. In this estimate, we conclude that employers will lose $4-5 billion in lost work time costs over the course of the epidemic.

HCV has the potential for significant financial loss beyond that which we modeled. The areas of potential indirect costs include:

- Decreased employee productivity
- Workers' compensation costs for occupational exposure
- Malpractice and general liability (new infection via third-party exposure)
- Life years lost (cost to life insurers, lost productivity, lost contributions to society)

These indirect costs add a considerable burden to society and businesses beyond the quantifiable direct medical costs.

Graph 4



The side effects of combination therapy can also lead to lost work time and productivity during the course of treatment. We netted the savings generated by successful curative treatment against the estimated value of lost time due to side effects of the treatment.

Implications and Recommendations for HMOs and Employers

The characteristics of HCV transmission mean that the risks will not be spread evenly across socio-economic groups or across HMOs, employers and other organizations. Some organizations will face more risk than average, and others will face less. The risk will vary with a population's prevalence, distribution of disease state and ability to comply with risk-lowering behaviors. Unfortunately, data on how these factors vary among groups are sparse, so our models assume national averages.

HMOs and Insurers

Some HMOs and insurers will likely have a significant portion of their members infected with HCV. Managers in plans with high turnover rates may believe they can avoid treatment costs by delaying pharmaceutical treatment. However, the consolidation of the insurance industry (which reduces turnover), the higher cure rate for earlier treatment, and standards of care issues counter the arguments for delay. The following are our recommended considerations for HMOs and other insurers:

- Evaluate the HCV risks for the HMO's particular membership and environment
  - Adopt solid, generally accepted criteria for approving non-experimental treatment for HCV
  - Take proactive steps in light of potential membership and public concerns associated with growing awareness of the HCV epidemic
  - Evaluate financial return of aggressive treatment
  - Review claims history to identify currently diagnosed members who have not received curative treatment
  - Consider turnover rates, socio-economic and occupational risk factors

- Develop demand management, disease management, and ambulatory care management
  - Develop policies and procedures to help network providers identify and screen high-risk individuals
    Educate network PCPs about high-risk indicators and clinical signs and symptoms of HCV infection
    Promote PCP attention to patients having HCV symptoms or elevated liver function studies
    - Develop and implement health risk assessment tools for plan use to confidentially identify high-risk members
    - Develop member and provider access to educational materials on HCV risk, screening, prevention, treatment and management (see section below)
  - Establish policies and procedures for member contact, patient monitoring, and patient education
  - Establish triggers for active case management

- Network management, case management, utilization management and concurrent review (see section below)

- Financial
  - Establish appropriate claims policies and procedures regarding coordination of benefits (e.g., with VA beneficiaries, workers' compensation)
  - Ensure appropriate reinsurance for self-insured groups, capitated contracts and for the HMO

Employers

Employee demography will affect an employer's exposure to risk. Employers bear risk for increased medical or workers' compensation claims (if self-insured), premiums or stop-loss costs. Employers also bear the risk for direct and indirect disability costs and lost worker productivity. Because HCV is a blood-borne pathogen, some health workers may have significant workplace risk and employers may face workers' compensation costs.

- Evaluate potential exposure
  - Consider risks associated with socio-economic characteristics
  - Take risk management action to minimize occupational exposure to HCV
  - Periodically reeducate staff on universal precautions for needle-stick prevention and avoiding contaminated body fluids for all healthcare employees
  - Identify preferred medical care providers for international travelers
  - Educate international travelers of risks of HCV transmission and appropriate precautions

- Develop human resource policies that address return-to-work and productivity issues, Americans with Disabilities Act (ADA) requirements and confidentiality
  - Work with short- and long-term disability carriers to establish disability management guidelines and case management protocols for HCV

- Develop policies and procedures for occupational health physicians and nurses to use for identifying and screening high-risk individuals. Educate occupational health providers about high-risk indicators and clinical signs and symptoms

- Health plan selection
  - Set criteria to consider the quality of HMOs' and insurers' HCV networks and case management programs
  - Choose workers' compensation financial arrangements appropriate to risk
  - Choose stop-loss coverage appropriate to risk
  - Choose pharmaceutical coverage design appropriate to risk

Similar implications would apply to reinsurers, life insurers and disability insurers. Some health systems, such as the Veterans Administration and correctional health systems, would want to take steps similar to those above, but these systems face much higher prevalence than for the general population.

HEPATITIS C CLINICAL MANAGEMENT: MANAGING THE ICEBERG

Introduction

This section addresses a system's approach to healthcare delivery for an HCV population. While treatment techniques will likely change dramatically over the next decade as new therapies and knowledge emerge, organizations that develop and implement sound healthcare management systems will probably find it easier to adopt treatment improvements as they occur.

Goals of Medical Management

Unfortunately, a minority of HCV-infected patients are clinically eligible for curative treatment, and a minority of those will respond completely. Therefore, we also address ways to improve the medical management efficiency and effectiveness for patients who may be candidates for mono therapy with interferon or who are not clinically eligible for pharmacological treatment. A comprehensive payer concerned about healthcare quality—such as an employer, HMO, insurer, Medicaid program, or Veterans Administration program—would want to adopt the following goals for HCV medical management:

- Eradicating the virus in a patient when possible
- Stemming the progression of liver disease
- Maximizing the health status of the patient
- Maximizing functional abilities and preventing disability
- Maintaining or improving the quality of life
- Preventing the spread of the HCV virus to non-infected individuals
- Reducing costs to the system, including medical and disability costs

Identifying and Implementing Best Practices for Screening

Because infected individuals may not develop symptoms of HCV for decades after exposure, high-risk individuals should be referred for screening so they can seek treatment and possible cure or disease management. Individuals may self select for screening or be identified as at risk by astute medical providers. Individuals at high risk for HCV infection include those with histories of blood transfusion before 1990, injection drug use, multiple sexual partners or intranasal cocaine use.[13] Employees with frequent or unprotected exposure to blood or blood products may also be at higher risk.

There are several HCV screening tests. These include testing for the antibody (exposure) to the virus and for the infection with the virus.[14]

- The enzyme immunoassay (EIA) is the most common and inexpensive of HCV antibody tests. Individuals with elevated ALTs should be tested using the EIA, regardless of their risk status. A negative test is usually sufficient for a low-risk individual. The more specific recombinant immunoblot assay (RIBA) is recommended for individuals with a positive EIA or those in the high-risk category. A positive RIBA should be repeated to help protect against treatment based on false positive results.

- An HCV RNA polymerase chain reaction (PCR) directly tests for the presence of the HCV virus and measures the viral load. A positive HCV RNA (by PCR) confirms infection; however, a single negative test does not rule out viremia.

Patients with positive HCV RNA require further clinical assessment to determine if they have liver damage or are candidates for pharmacological treatment. We discuss methods of further clinical assessment later in this report.

Network Management

The demand for HCV-related medical services will continue to rise with the progression of the disease over the next decade. Given the expected increased need and the time needed to develop a provider network, payers should develop a network management strategy that will:

- identify HCV-experienced primary care physicians and consultants,
- insure adequate numbers of HCV-knowledgeable hepatologists, gastroenterologists, internists, infectious disease specialists, and invasive radiologists, and
- contract with hospitals efficient at treating HCV-related admissions.

To approach ideal efficiency, payers will also need contracts and quality services from providers such as commercial laboratories, ambulatory surgical centers, sub-acute and skilled facilities, home health agencies, transplant centers of excellence, hospices and ancillary service providers.

Disease Stages, Progression and Case Management

HCV, like HIV, is a "silent epidemic," in that the infected person may remain asymptomatic for years. The clinical symptoms of the disease often present themselves several decades after an acute infection. Those who develop chronic HCV are often not aware they have the virus.[15]

In its natural history, chronic HCV infection can progress from mild chronic hepatitis to moderate chronic hepatitis to cirrhosis and, finally, to various forms of advanced liver disease,[16] including hepatocarcinoma.

The degree of liver damage caused by chronic HCV infection and disease progression varies with factors including duration of infection, lifestyle (alcohol or drug abuse) and amount of active virus in the blood and genotype of the virus.[17] HCV-caused liver disease may not always progress to more severe forms; however, liver damage does not naturally reverse itself. Given current technology, the only current hope for a "cure" for HCV-caused liver disease is to eradicate the virus before irreversible liver damage occurs or to obtain a liver transplant.

Patients with HCV may also have other difficult-to-manage morbidities, such as HIV, end-stage renal disease or diabetes. Case management of HCV-infected patients should include the following:

- Telephonic clinical support available 24 hours daily
- Coordination of care among multiple professionals including treatments not related specifically to HCV
- Directing patient to preferred facilities and physicians (centers of excellence) for treatment

In our actuarial models, we stratified costs and populations among three groups. The clinical presentation, treatment, prognosis, medical and disability costs vary among these groups. The description of this clinical and treatment stratification is:

- *Mild/Moderate.* These patients may be asymptomatic or have vague, nonspecific symptoms, including fatigue and malaise. The patient may have some degree of liver inflammation or scarring appearing in a liver biopsy. Blood ALT (alanine transferease) levels may or may not be elevated and, if elevated, may not be elevated consistently. Patients with consistently normal ALT levels fall into the group of "watchful waiting," to be monitored for disease progression (if any), and are not indicated for treatment with Interferon Alfa alone or combination therapy.

  Patients with elevated ALTs may be candidates for treatment. A pre-treatment liver biopsy is currently recommended by NIH[12] to assess the degree to liver damage and indications for therapy, although some professionals conclude that performing a routine liver biopsy on all HCV patients may add cost and unnecessary risk without improving health outcomes.[28]

- *Cirrhosis:* Cirrhotic patients will experience more complications and medical utilization than those with mild/moderate HCV will.[18]

- *Advanced Liver Disease (ALD):* We use this term to describe patients with the multiple symptoms and diagnoses caused by severely compromised liver function. This includes diagnoses such as decompensated cirrhosis, ascites, variceal hemorrhage, encephalopathy and hepatocellular carcinoma. The life expectancy for these patients is short. These patients are not eligible for treatment with mono or combination therapy.

Curative Treatment with Mono or Combination Therapy

In this section, we outline current pharmacological treatment issues for either mono therapy with interferon or combination therapy.[19] We emphasize these therapies because they are the only potentially curative therapies currently recommended by the NIH. We assumed that about 40% of the infected population with persistently elevated ALTs is treatment-eligible with either mono or combination therapy.[20] The remaining population is either ineligible due to contraindications or is eligible for precautionary treatment. Precautionary treatment means that therapy should be decided on a case-by-case basis after careful patient assessment and physician-patient discussion.

General treatment considerations include deciding when to begin therapy and determining which first-line agents to use. Among current options, practitioners must weigh the risk and benefits of "watchful waiting," mono therapy and combination therapy and choose the optimal path for each individual patient. One of the predictors of a successful, sustained response is treatment while the patient is still in the mild/moderate (pre-cirrhotic) stage of the disease.[21]

Physicians and formulary managers must decide what to use as a first-line therapy for previously untreated (naive) patients. Both Interferon Alfa alone and combination therapy (interferon with Ribavirin) are indicated for those patients who are treatment-eligible. The course of treatment for Interferon Alfa alone is less costly than that of combination therapy; however, Interferon Alfa alone has a lower sustained response rate.[22] The argument for using mono therapy as a first-line therapy is to evaluate the response and then treat the relapsers with combination therapy. Arguments for using combination therapy for naive (previously untreated) patients include:

- Avoids the duplicate expense of mono and combination therapies

- Potentially obtains a faster sustained response

- Potentially achieves a greater patient compliance with avoidance of subjecting the patient to the significant drug side effects twice. A course of treatment with Interferon Alfa and its probable side effects may discourage relapsers from complying with an additional six months of therapy and the side effects of combination therapy

Decisions of whether to continue or discontinue therapy depend upon various factors including:

- Biological response to therapy (indicated by ALT levels normalizing)

- Virological response to therapy (HCV-RNA levels declining), Genotype and Histological (degree of fibrosis) response

- Adverse side effects

- Compliance

Among naive patients who achieve a sustained response for six months after therapy, about 95% will continue to maintain the response and are considered successfully treated. For those patients, medical management consists predominantly of maintaining their health status and avoiding risky behaviors such as alcohol or drug use that might compromise liver function.

Patient Education and Intervention

The lay public, and many physicians, suffer from a lack of knowledge about HCV. Patients with the virus may feel stigmatized or unsure of their options.

Key content points of patient education include:

- *Compliance issues:* Patients should be aware that the flu-like symptoms, often reported as a side effect of Interferon Alfa, tend to diminish as treatment continues.

- *Avoid hepatotoxic substances:* There is a positive correlation between alcohol consumption of greater than 50 gm/day and progression to cirrhosis.[23] It is extremely important that all patients with HCV minimize the risk of further liver damage. This means avoiding hepatotoxic substances, especially alcohol and intravenous drugs.

- *Transmission:* Patients should be educated about the methods of transmission, primarily blood borne, and precautions they can use to minimize the risk of transmission. HCV does not appear to be as easily transmitted via sexual contact as HIV.[24]

- *Treatment options and progress:* As new information emerges regarding this disease and treatment options, HCV-infected patients need resources for sound medical information so they will not be tempted to rely on partial or inaccurate information. A few of the resources where patients can access printed or Internet information are from the Hepatitis C Foundation, the Hepatitis Foundation International, the American Liver Foundation, the National Institute of Diabetes and Digestive and Kidney Diseases and the United Network for Organ Sharing.

Some organizations regularly send written materials and follow up with telephone calls to answer questions. Kaiser-Permanente of Northern California uses a classroom approach to initial education. Patients meet as a group and receive information on the disease process, the diagnostic and treatment options, their responsibilities, contraindications and other important aspects of care. Kaiser finds this to be an effective method for educating large numbers of patients and for helping assure continuity in the patient education process. A classroom style approach also helps some patients with the disease feel less isolated.[25]

SUMMARY

We recommend that organizations plan now to manage their members or employees with chronic HCV. As with other chronic disease processes, there are significant opportunities to develop well-managed programs that control cost while providing high-quality services. Unlike other chronic diseases, curative treatments exist for HCV, and we have demonstrated the cost-effectiveness of one such treatment.

APPENDIX A

Actuarial Modeling Details

We used an actuarial model to project the financial impact of Hepatitis C over the next 30 years. The basic structure of the model, including a description of the methodology we employed, is described in Appendix B. In this section, we highlight many of the key assumptions used in the model. The assumptions come from a number of sources including published articles and insurance claim databases. In addition, we consulted with leading authorities on this disease to check the reasonability of our assumptions.

Assumptions Related to the Prevalence of Hepatitis C

Base population: about 210 million, representing the base population of the US from the NHANES study.

Antibody prevalence rate: 1.8%, or approximately 3.9 million of the base population has antibodies for Hepatitis C.

HCV chronic infection prevalence: 70% of the 3.9 million with the antibodies, or about 2.7 million people. This probably understates the infected population, because it does not consider populations not surveyed (such as the institutionalized population).

Chronic infection but persistently normal serum alanine aminotransferase (ALT) levels: about 30% of the 2.7 million with HCV chronic infection.

Population modeled: 1.9 million people. These people were allocated into three disease states: Mild/Moderate Hepatitis, Cirrhosis and Advanced Liver Disease. Graphs 1 and 2 show costs for these 1.9 million people.

Treatment-eligible rate: 40% of the population under age 60 with mild/moderate hepatitis or cirrhosis. Graphs 3 and 4 show results for this population.

New infections: 30,000 each year.

Population Results

Table 1 shows the result of our model for the treatment-eligible population, assuming that all treatment-eligible infecteds obtain combination therapy in year 1.

Table 1

Treatment-Eligible Population			
		Population after 15 years	
Disease State	Starting Population	Without Curative Treatment	With Combination Therapy
Mild/Moderate Hepatitis	529,000	360,000	210,000
Cirrhosis	119,000	105,000	85,000
Advanced Liver Disease	0	32,000	22,000
Cured	0	0	217,000
Deaths	0	150,000	114,000
Total	648,000	648,000	648,000

We omitted new entrants from Table 1 to simplify the presentation. The changes with treatment primarily reflect people cured of hepatitis and people with cirrhosis who cleared the virus and did not progress to ALD.

Table 2 shows the population results of the "Natural History" model, in which no patients receive curative treatment.

Table 2

Natural History
Treatment Eligible and Non Eligible Population by Disease State

Disease State	Year 0	Year 15
Mild/Moderate Hepatitis	1,423,000	1,189,000
Cirrhosis	429,000	333,000
Advanced Liver Disease	54,000	101,000
New Entrants (added to year 0 as a balancing item)	434,000	0
Deaths	0	717,000
Total	2,340,000	2,340,000

Please note that Table 2 excludes HCV-infected individuals who have persistently normal ALTs.

We note that some experts today believe that a lower portion of infected people will develop cirrhosis. A lower portion of cirrhotics in our model will reduce the cost of the epidemic and will increase the cure rate of combination therapy, because cirrhotics have a lower cure rate.

Table 3

Table 3 shows the figures behind Graph 4. For each year, we show the cumulative net cost or savings of using curative treatment for all 648,000 treatment-eligible infected people in our model. The dollar estimates are all in year 2000 present values.

Projected US Cumulative

Year	Savings (millions)	Year	Savings (millions)
2000	($5,600)	2019	$8,100
2001	($5,300)	2020	$9,100
2002	($4,800)	2021	$10,000
2003	($4,400)	2022	$11,000
2004	($3,800)	2023	$11,900
2005	($3,300)	2024	$12,800
2006	($2,700)	2025	$13,700
2007	($2,000)	2026	$14,500
2008	($1,300)	2027	$15,300
2009	($600)	2028	$16,100
2010	$100	2029	$16,900
2011	$900	2030	$17,600
2012	$1,800		
2013	$2,600		
2014	$3,500		
2015	$4,400		
2016	$5,300		
2017	$6,200		
2018	$7,200		

Cost Assumptions

Tables 4 and 5 show the starting per patient per year (PPPY) claim costs for patients in the three disease states for our two scenarios.

- We derived under-age-65 cost estimates from an internal proprietary database that represents several million managed care group lives from 10 different HMOs across the United States.
- The Medicare cost estimates were generated from HCFA's 1997 5% analytic files. These files represent Medicare fee-for-service claims throughout the country. The cost estimates reflect benefits covered by Medicare before any member cost sharing (e.g., includes copays, deductibles, etc.).
- All estimated costs shown reflect year 2000 cost levels. For the <age-65 figures, we assumed typical HMO allowed charges. For the age-65+ population, we assumed typical Medicare reimbursement plus typical insurer reimbursement for non-Medicare-covered services. We did not reduce these costs for patient cost sharing.
- While eligible patient costs technically represent all medical costs, the conditions on patient eligibility are such that these patients probably had relatively low costs for conditions other than HCV.
- We assume the net direct price (NDP) for combination therapy is about $8,500 per year for an average patient receiving curative treatment. This is a composite price that includes adjustments for 24-week vs. 48-week therapy, regular dose vs. reduced dose, and discontinued therapy due to side effects, genotype and response to treatment. We recognize that pharmacy prices vary dramatically depending upon the payer source and negotiated arrangements. We calculate a full 48-week course of combination therapy at NDP at $13,700. None of these costs are included in Tables 4 or 5.

Table 4

Starting PPPY for Treatment Eligible Patients
Total of All Medical Costs for HCV Patients

Disease State	<Age 65	Age 65+
Mild/Moderate Hepatitis	$700	n/a
Cirrhosis	$2,400	n/a
Advanced Liver Disease	n/a	n/a

Table 5

Starting PPPY for Treatment Non-Eligible Patients (excluded for comorbidities)
Total of All Medical Costs for HCV Patients

Disease State	<Age 65	Age 65+
Mild/Moderate Hepatitis	$2,100	$14,400
Cirrhosis	$6,600	$17,300
Advanced Liver Disease	$34,200	$52,700

Other Assumptions

- *Medical inflation:* 8% per annum, except the cost of combination therapy does not increase, because, in the model, the therapy is given only in year 1.

- *Discount rate:* 6%

- *Age Advancement of NHANES Study:* The ages of the populations in the NHANES study are advanced to reflect the time elapsed from the study period to our projection period.

- *Migration Assumptions:* We assumed that, each year, 2% of the HCV-infected population with mild to moderate hepatitis, excluding people with persistently normal ALTs, will develop cirrhosis over the first 20 years.[18] Six percent per year of the people with cirrhosis will develop advanced liver disease. Please note that these migration assumptions apply to the HCV-infected population after excluding individuals who have persistently normal ALTs.

We note that some experts now believe that the migration rates could be about half that level. Reducing these migration rates will reduce the estimated cost of the epidemic. Reducing the number of cirrhotics would increase the number of people who could be cured by combination therapy.

We modeled the migration of the treated population who did not achieve a sustained response (cure) and the not-treated population at the same rate.

- *Disability costs:* We modeled disability costs by evaluating lost time associated with medical care. We valued lost time at $200 per day and assumed one lost day for each physician visit and four lost days for each inpatient hospital day. In addition, we assumed people with advanced liver disease and transplants were totally disabled. We netted the saving generated by successful curative treatment against the estimated lost time due to the side effects of treatment.

- *Mortality rates:* Expressed as a percentage of an adjusted 1975-1980 Society of Actuaries (SOA) mortality table.[27] The adjustment reflects mortality improvements since the table was constructed. The SOA table is commonly used by life insurance companies to calculate premium rates. Multiples of the adjusted table are used to express mortality associated with the Hepatitis C virus. The multiplicative factors used are 1.00 for mild/moderate hepatitis and 4.00 for cirrhosis. The annual mortality rate assumed for advanced liver disease is 20%. These mortality loads were based on discussions with life insurance underwriters.

- *Cure rates:* Therapy with the combination of Interferon Alfa-2b and Ribavirin is successful at eliminating the Hepatitis C virus in approximately 41%[26] of the treated population with mild to moderate hepatitis and in about 20% of the treated population with cirrhosis. Relapse rates are very low.

Table 6 shows the cumulative deaths by year produced by our assumptions of the starting population, mortality and migration. For purposes of contrast, we show the deaths that would occur to the starting population if we had not applied extra loads to people with cirrhosis or advanced liver disease.

Table 6

Year	Cumulative Deaths in Natural History Model	Cumulative Deaths Assuming No Extra Mortality Load
2001	46,000	15,000
2002	90,000	30,000
2003	134,000	47,000
2004	178,000	64,000
2005	222,000	83,000
2006	267,000	103,000
2007	312,000	123,000
2008	359,000	145,000
2009	406,000	169,000
2010	454,000	193,000
2011	504,000	218,000
2012	555,000	245,000
2013	608,000	274,000
2014	662,000	304,000
2015	717,000	336,000
2016	773,000	370,000
2017	830,000	405,000
2018	888,000	442,000
2019	948,000	482,000
2020	1,008,000	523,000

APPENDIX B

Description of the Actuarial Model

We developed an actuarial model to evaluate the economic impact of Hepatitis C on the US population. The model develops the potential cost savings resulting from treating people with combination therapy.

Our model uses a cohort approach to project future costs. We define the affected population as the estimated number of people in the US who have the Hepatitis C virus. The affected population is split into specific cohorts or cells depending on their current disease state and by age. We used eight age bands. Disease-state cells include non-infected or normal ALTs, mild hepatitis to moderate hepatitis, cirrhosis and advanced liver disease. Population movements to other cells or to death is projected annually. Non-infected or normal ALT patients did not migrate among cells.

Our model considers cohorts, but, for explanatory purposes, we illustrate how the model works by considering how an individual could migrate. Consider an individual with mild to moderate hepatitis at the start of the projection period (time equals 0). In year 1, if there is no change in status, the individual remains in the mild to moderate cell. In year 2, assume the disease has progressed to cirrhosis. The person is now moved from the mild to moderate hepatitis cell to the cirrhosis cell. The individual's movement is tracked for at least 30 subsequent years or until death occurs.

Conceptually, we repeated the process for each individual in the initial cohort and tabulated the results by year and by cell. Our models estimate the number of people in each disease state, in each age group, at the end of each year. Movement between cells is defined in transition matrices. The matrices were developed using published studies on the natural history of Hepatitis C, widely accepted actuarial mortality tables and assumptions related to treatment availability.

Next, we develop annual cost estimates for each cell. Cost estimates are based on data from our databases as well as from published sources. Finally, the cost for a cell is multiplied by the number of individuals in the cell. This is done across all cells and the results are then aggregated by calendar year. This provides us with our estimate of annual costs related to the Hepatitis C treatment.

The actuarial model allows us to vary assumptions. If, for example, we assume that the percent of treated patients is zero, we can calculate the costs assuming no one receives curative treatment for Hepatitis C. Changing the percent of eligible treated to zero will produce a natural history model. Without treatment, a larger number of people will progress to the cirrhosis and advanced liver disease states.

We did not model the cost-effectiveness ratios for interferon-only treatment because we believe there is relatively little mono treatment being done today. We did model the cost-effectiveness for combination therapy.

FOOTNOTES

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