

Estimating the Prognosis of Canadians Infected With the Hepatitis C Virus Through the Blood Supply, 1986-1990

Second Revision of HCV Prognostic Model Incorporating
Data From the Compensation Claimant Cohort

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Table of Contents

Table of Contents.....	2
Executive Summary.....	5
1. Background.....	9
2. Model Structure and Assumptions.....	12
2.1 Model Structure	12
2.2 Model Assumptions	14
2.3 Analytic Method	15
3. Model Parameters- General Approach to Data Synthesis.....	16
3.1 Data Sources	16
3.2 Synthesizing Published Data	17
3.3 Estimating Transition Probabilities.....	18
3.4 Estimating Stage-specific Transition Probabilities: The Markov Maximum Likelihood Method	21
3.5 Using the Markov Maximum Likelihood Method To Estimate Transition Probabilities From Retrospective Data.....	25
4. Estimating Model Parameters from the Literature (Tables 4.1-4.9).....	26
4.1 Seroconversion from HCV RNA+ to HCV RNA- Status.....	26
4.2 Development and Progression of Liver Fibrosis.....	28
4.2.1 Non-Cohort Studies - Chronic Liver Disease and Retrospective Analyses of Historically Defined Transfusion-Associated Hepatitis	29
4.2.2 True Cohort Studies.....	30
4.3 Factors Affecting Fibrosis Progression.....	31
4.3.1 Treatment Efficacy	31
4.3.2 Patterns of Treatment by Disease Stage, Age, and Co-Morbidity	34
4.3.3 Age, Sex and Alcohol- (Table 4.3-3).....	34
4.3.4 HIV Co-Infection.....	35
4.3.5 ALT level and Genotype.....	36
4.3.6 Hemophilia (Tables 4.3-6-1, 4.3-6-2).....	37
4.3.7 Obesity.....	40
4.3.8 Acquiring HCV Infection Through Transfusion.....	40
4.4 Development of Hepatocellular Carcinoma (HCC).....	41
4.4.1 Risk of HCC in Cirrhotics (Table 4.4-1).....	41
4.4.2 Risk of HCC in HCV-Infected Individuals Without Cirrhosis	42
4.5 Excess Mortality	43
4.6 Transition Rates Post-cirrhosis	44
5. Analysis of Clinical and Demographic Data Characterizing Claimants for Compensation	45
5.1 Data sources.....	45
5.2 Data management	47
5.3 Descriptive analysis of claimants for compensation in 2004.....	47
5.3.1 Patient characteristics	47
5.3.2 Hemophilia and other underlying conditions for blood transfusion (Table 5.3-2).....	49
5.4 Estimating the True Fibrosis Stage Distribution from Claims Data	49
5.5 Using the Estimated Stage Distribution to Calculate Progression Rates Between Fibrosis Stages	52
6. Final Parameters for the New Model: Combining Data From the Literature and From the Compensation Cohort.....	53
6.1 Choosing Fibrosis Transition Rates	54
6.2 Modeling the Prognosis of Hemophilics.....	57
7. Validating the Revised Stage-based Prognostic Model.....	58
8. Prognosis of Post-transfusion hepatitis C Patients Based on Projections of the Markov Model.....	61
8.1 Sixty year projection based on pooled transition rates derived from literature.....	61
8.2 Sensitivity analysis	63
9. Estimating the Stage Distribution of Post-transfusion HCV-infected Individuals Who Have Not Yet Presented to Claim Compensation	64
9.1 Approach 1: Regression method.....	65
9.2 Approach 2: True target population distribution method.....	66

9.3 Comment	68
10. Discussion.....	69
11. Tables	76
Table 4.1 Seroconversion From HCV RNA+ to RNA-: Literature Review	77
Table 4.2-1 Fibrosis Stage Transition Probabilities, Published Non-Cohort Studies	78
Table 4.2-2 Fibrosis Stage Transition Probabilities, Non-Cohort Studies, “Markov Maximum Likelihood” Technique	79
Table 4.2-3 Fibrosis Stage Transition Probabilities, Prospective Cohort Studies, “Markov Maximum Likelihood Technique”	81
Table 4.2-4 Summary Transition Probabilities, Literature and Post-transfusion Cohort for 2004 Model	82
Table 4.3-1-1 Effectiveness of Pegylated Interferon Therapy	83
Table 4.3-1-2 Effectiveness of Peginterferon therapy – seven studies used for Meta analysis	85
Table 4.3-2 Hepatologists reported proportion of patients with hepatitis C receiving interferon/ ribavirin combination in their clinical practice.....	86
Table 4.3-3 Risk Factors for Progression of Liver Fibrosis.....	87
Table 4.3-4-1 Hemophilia and HIV: Effects on Progression of Liver Disease in HCV Infected Patients.....	88
Table 4.3-4-2. Relative Risk of Death in Hemophilic Patients With and Without HIV Infection.....	89
Table 4.4-1 Development of HCC in HCV Patients With Cirrhosis	90
Table 4.5-1 Excess Mortality Post- transfusion: Rate Ratios Comparing Post-transfusion All-cause Mortality to General Population Mortality, by Age Group and Years Elapsed Since Transfusion	91
Table 4.5-2 Other Parameters Used in the Prediction Model	92
Table 5.3-1 Baseline Clinical and Serological Features of Hepatitis C Claimants, 2004*	94
Table 5.3-2 Baseline Clinical and Serological Features in Hepatitis C Claimants: Comparisons between Hemophilics and Non-hemophilics	96
Table 5.3-3 Propensity Score Method for Estimating True Stage Distribution	97
Tables 5.4-1 – 5.4-3 Observed and Estimated Stage Distribution of Living Claimants, August 2004	98
Table 5.4-2 (Non-hemophilic).....	99
Table 5.4-3 (hemophilic)	100
Table 5.4-4 Adjusted HCV Stage Distribution (N & %) by Age Group for Alive Non-Hemophilic Patients. At the Time of Claim (Males and Females).....	101
Table 5.4-5 Adjusted HCV Stage Distribution (N & %) by Age Group for Alive Hemophilic Patients At the Time of Claim (Males and Females)	102
Table 5.4-7 Adjusted HCV Stage Distribution (N & %) by Age Group for Alive Female Patients.....	104
Table 6 Summary of Transition Probabilities used in the 2004 HCV Markov Prediction Model	105
Table 7.1 Model Validation: Observed Disease Severity Distribution in Compensation Claimants (August 2004), and Predicted Distribution, Based on Age and Sex of Blood Transfusion Recipients and Literature- Derived Fibrosis Transition Rates	106
Table 7.2 Validation Study	107
Table 8.1-1 Prognosis by Calendar Year. All HCV Patients (stage specific rates).....	108
Table 8.1-2 Prognosis by Calendar Year. Non-hemophilic HCV Patients.	109
Table 8.1-3 Prognosis by Calendar Year. Hemophilic HCV Patients.	110
Table 8.1-4 Prognosis by Calendar Year-- -- Non-hemophilics, Age 10-19	110
Table 8.1-5 Prognosis by Calendar Year-- -- Hemophilics, Age 10-19.....	112
Table 8.1-6 Prognosis by Calendar Year-- -- Non-hemophilics, Age 20-29	113
Table 8.1-7 Prognosis by Calendar Year-- -- Hemophilics, Age 20-29.....	114
Table 8.1-8 Prognosis by Calendar Year-- -- Non-hemophilics, Age 30-39	115
Table 8.1-9 Prognosis by Calendar Year-- -- Hemophilics, Age 30-39.....	116
Table 8.1-10 Prognosis by Calendar Year-- -- Non-hemophilics, Age 40-49	117
Table 8.1-11 Prognosis by Calendar Year-- -- Hemophilics, Age 40-49.....	118
Table 8.1-12 Prognosis by Calendar Year-- -- Non-hemophilics, Age 50-59	119
Table 8.1-13 Prognosis by Calendar Year-- -- Hemophilics, Age 50-59.....	120
Table 8.1-14 Prognosis by Calendar Year-- -- Non-Hemophilics, Age 60-69.....	121
Table 8.1-15 Prognosis by Calendar Year-- -- Hemophilics, Age 60-69.....	122
Table 8.1-16 Prognosis by Calendar Year-- -- Non-Hemophilics, Age 70-79.....	123
Table 8.1-17 Prognosis by Calendar Year-- -- Hemophilics, Age 70-79.....	124
Table 8.1-18 Prognosis by Calendar Year-- -- Non-Hemophilics, Age 80-89.....	125

Table 8.1-19 Prognosis by Calendar Year-- -- Hemophilics, Age 80-89.....	126
Table 8.2-1 Sensitivity Analysis: Source of Transition Rates Between Fibrosis Stages	127
Table 8.2-3 Monte Carlo Simulation Describing Overall Uncertainty in the Prediction Model-- Predicted Rates of Major Events and their 95% Confidence Interval	128
Table 9.1-1 Estimated Disease Severity Distributions for Prospective Claimants Based on Current Claimant Data.....	129
Table 9.1-2 Estimated Stage Distribution of Potential Future Claimants Using the Linear Regression Method (Non-hemophilics only).....	130
Table 9.1-3 Estimated Stage Distribution of Potential Future Claimants Using the Linear Regression Method (Hemophilics)	131
Table 9.1-4. Estimated Current Distribution (%) of Alive, Non-hemophilic HCV patients Who Were Infected During 1986-1990, and Have Not Claimed for Compensation Prior to 2004.....	133
12. Figures	134
Figure 2.1 Structure of Decision Model As Programmed in DATA Pro.....	135
Figure 5.1 Age at Time of Infection Among HCV Compensation Claimants.....	136
Figure 5.3 Compensation level and Mortality	138
Figure 5.4 Distribution of Disease Severity by Fibrosis Stage	139
Figure 5.6 Distribution of Projected and Observed HCV Stage Distribution, HCV Compensation Claimants.....	140
Figure 7.1 Model Validation: Cumulative Proportion with Cirrhosis, 2004 Model (stage specific transition rates) vs. Salomon (age and gender specific transition rates).....	141
Appendix A. Publications derived from this study:.....	142
Appendix B. SAS Code Used in the Markov-Maximum Likelihood Method.....	143
Appendix C. Survey.....	145
References.....	148

Executive Summary

Hepatitis C virus (HCV) is one of the most common causes of liver disease in Canada. Before serologic testing for the presence of hepatitis C became available in 1990, blood transfusion and blood product use were a major source of HCV infection. Between 1986 and 1990, surrogate marker testing was employed to screen blood donors in the United States to reduce the risk of HCV infection in general population. In Canada, no surrogate marker testing was ever employed. As a result, many individuals in Canada became infected by HCV through blood transfusion and blood products during this time window.

On March 27, 1998 federal, provincial, and territorial governments announced an offer of financial assistance to individuals who were infected with HCV through the blood system between January 1, 1986 and July 1, 1990. In 1999, court orders in British Columbia, Ontario and Québec were obtained approving a settlement agreement which made approximately \$1.2 billion available to compensate claimants, who included individuals with transfusion-acquired hepatitis C infection (including hemophiliacs), those with HIV who became co-infected with HCV, and secondarily infected individuals.

The compensation agreement linked compensation levels to the severity of clinical illness. However, the long-term prognosis of HCV infection is uncertain and variable, and experts disagree. In order to assist in ensuring the long-term sufficiency of the fund, a working group was struck in November of 1998 to assemble the available evidence and construct the best possible estimates of the prognosis of the HCV infected cohort. This “medical model”, a Markov

state-transition model, (1), served as the basis of the actuarial model which estimated future payments from the compensation fund.

The compensation agreement between governments and plaintiffs calls for an estimate of the sufficiency of the compensation fund every three years. In order to assist in the process of assuring the sufficiency of the fund, the original prognostic model has undergone two subsequent revisions. This document describes the second revision of the original model. Serial revision is required because new information regarding both the characteristics of compensation claimants (e.g. HCV stage distribution and size of claimant cohort) and HCV outcome data (e.g. natural history prognostic data, treatment patterns and treatment intensity) continues to become available. Older projections become less accurate as time passes.

The first revision took place in 2002 by a working group which included some members of the original group (M.K., J.H, L.S.) and two new members (P.W. and Q.Y.). Two major differences in the 2002 prognostic model, in comparison to the original model, were present. The first was that the prognosis of the post-transfusion cohort was explicitly linked to liver fibrosis stage. This made it considerably easier to use the “medical model” to estimate future payments, as compensation levels were closely linked with fibrosis stage. The second major difference was that we had detailed clinical and demographic data from 2,466 compensation claimants.

This second revision includes one new member (M.S.), and differs from the first revision in several aspects. First, the number of compensation claimants has increased from 2446 to 4530 or by 85%. Thus, the results reflected in this report are more representative of the target cohort.

Second, we have revised the stage transition probabilities by incorporating data from newly published prognostic studies and transition rates derived directly from the post-transfusion cohort. Third, antiviral therapy has continued to evolve, with combination pegylated interferon and ribavirin proving to be progressively more effective, and becoming the mainstay of antiviral therapy in the past few years. We have therefore performed a new meta-analysis to estimate sustained virologic response rates in patients treated with pegylated interferon and ribavirin. Fourth, a revised survey of hepatologists to evaluate practice patterns with respect to antiviral therapy has been incorporated into the current report.

The model predicts that 26% of non-hemophilic patients alive in 2004 will ultimately develop cirrhosis, and 17% will ultimately die of liver disease. Because hemophilic patients are younger, and are frequently co-infected with HIV, they will have higher cumulative rates of cirrhosis and HCV death (36% and 27% respectively).

Predictions of the current model relative to those of the earlier two models are reported in Table 7.2. Prognostic projections of the current model, in general, fall between those of the first two models. (1, 2). The differences between the second and first revisions are attributable to several factors. First, there are now more claimants in early HCV stages (F0-F1) than when the last simulation was performed (77.8% vs. 64.8%). Second, the stage transition probabilities used in current projections were adjusted downward after incorporating several newly published studies and data from the compensation cohort. Finally, more effective treatment (combination pegylated-interferon/ ribavirin) is now available.

This document reports specific projections for 10-year age strata for individuals with transfusion acquired hepatitis C infection who are hemophilics as well as those who are non-hemophilics. We also report sensitivity analyses that estimate the degree of uncertainty associated with these projections.

The prognostic model's limitations include the fact that incomplete biopsy data were available. This means that the true extent of liver damage at the time of claim is unknown in 80% of claimants. In addition, limited data are currently available estimating the number and stage distribution of future compensation claimants, though the number of outstanding claims is believed to be small. However, this model likely represents the state of the art in estimation of HCV prognosis. Future revisions that include additional data from the compensation cohort, particularly longitudinal clinical data, will be invaluable in refining our estimates of the long term prognosis of this group.

This work represents a multidisciplinary effort between experts in hepatitis C clinical care, epidemiology, biostatistics, and decision modeling. It represents a unique application of decision modeling methods to a public policy question of great import to Canadians. It allows estimates of the sufficiency of the compensation fund to rest on the best current evidence, incomplete though it presently is. Finally, this work provides uniquely detailed prognostic estimates that will be of value to HCV patients and their physicians who want to know what the future holds for them.

1. Background

Hepatitis C virus (HCV) is one of the most common causes of liver disease in Canada. Recent studies suggest that the prevalence of HCV infection in the Canadian population is about 1.0 % and the estimated number of people with HCV is about 300,000 (3, 4). Before serologic testing for the presence of hepatitis C became available in 1990, blood transfusion and blood product use were a major source of HCV infection. Between 1986 and 1990, surrogate marker testing was employed to screen blood donors in the United States to reduce the risk of HCV infection in general population. In Canada, no surrogate marker testing was ever employed. As a result, individuals in Canada continued to become infected by HCV through blood transfusion and blood products during this time window. On March 27, 1998 federal, provincial, and territorial governments announced an offer of financial assistance to individuals who were infected with HCV, directly or indirectly through the blood system between January 1, 1986 and July 1, 1990. Up to \$1.1 billion was to be made available to compensate claimants, who included hemophiliacs, secondarily infected HCV claimants, those with HIV who became co-infected with HCV, as well as all others with HCV infection acquired through blood transfusion during the period in question.

In order to settle on an appropriate compensation scheme, the federal and provincial governments as well as the claimants reviewed a number of models of the natural history of hepatitis C. Because of disagreement regarding the natural history of this disease, the Canadian Association for the study of the Liver (CASL), an impartial body with no stake in the outcome of compensation negotiations, was approached by both stakeholders to produce the best available model of the natural history of HCV. In November of 1998, CASL approached individuals with

expertise in hepatitis C epidemiology, hepatitis C clinical care and decision modeling to assist in the construction of a model. As a result, an ad-hoc working group was formed. Drs. Murray Krahn, Jenny Heathcote, Linda Scully, Leonard Seeff and John Wong, were the key members of the working group.

This working group evaluated and accepted the validity of the structure of the Bennet/Wong Markov chain model (5, 6), but subsequently simplified it. Each parameter in the model was reviewed. Key parameters, such as the excess mortality rate, the incidence rates of cirrhosis, hepatocellular carcinoma (HCC) and decompensated cirrhosis, were updated by systematically reviewing and synthesizing the literature. Confidence limits and/or plausible ranges were identified for key model parameters. With this revised model, the cumulative probability of acquiring cirrhosis, decompensated liver disease, and liver death were predicted using baseline characteristics. For the transfusion cohort as a whole, the 20 year and lifetime cumulative probability of developing liver cirrhosis was 13.4% and 24.9% respectively. Similarly, the 20 year and cumulative lifetime probability of dying of HCV-related liver disease was 2.5% and 12.3%, respectively.

However, the original model had two major limitations. First, it used clinical staging for HCV progression rather than serological and pathological staging, on which the compensation agreement was based. Second, the previous model was developed before any clinical or demographic information was available regarding actual claimants. The model was therefore based only on estimates derived from the literature.

The compensation agreement between governments and plaintiffs calls for an estimate of the sufficiency of the compensation fund every three years. In order to assist in the process of assuring the sufficiency of the fund, the first revision of the original prognostic model was completed in 2002. by a working group consisting of several members of the original research team (Drs. Jenny Heathcote, Linda Scully, and Murray Krahn) and two new members Dr. Peter Wang (Epidemiology) and Dr. Qi-Long Yi (Biostatistics).

The specific objectives for the first revision of the prognostic model were:

- i) Create a fibrosis-stage based Markov prognostic model (fibrosis stage 1 (F1), fibrosis stage 2 (F2), fibrosis stage 3 (F3) , fibrosis stage 4 (F4, cirrhosis)
- ii) Review and synthesize the existing literature to derive the transition probabilities between these health states and document the impact of the baseline characteristics on these transition probabilities.
- iii) Use the available Canadian compensation data to provide independent estimates of transition probabilities, and other key probabilities for the model.
- iv) Project the prognosis (expressed in cumulative probabilities of adverse events) of claimants over their remaining lifetimes in accordance with HCV severity levels stipulated in compensation package.

This second revision of the prognostic model retains the objectives of the first revision. Our intent remains to use a fibrosis based Markov model (i), update our literature review regarding transition probabilities (ii), use the most current data from the compensation claimants (iii), and

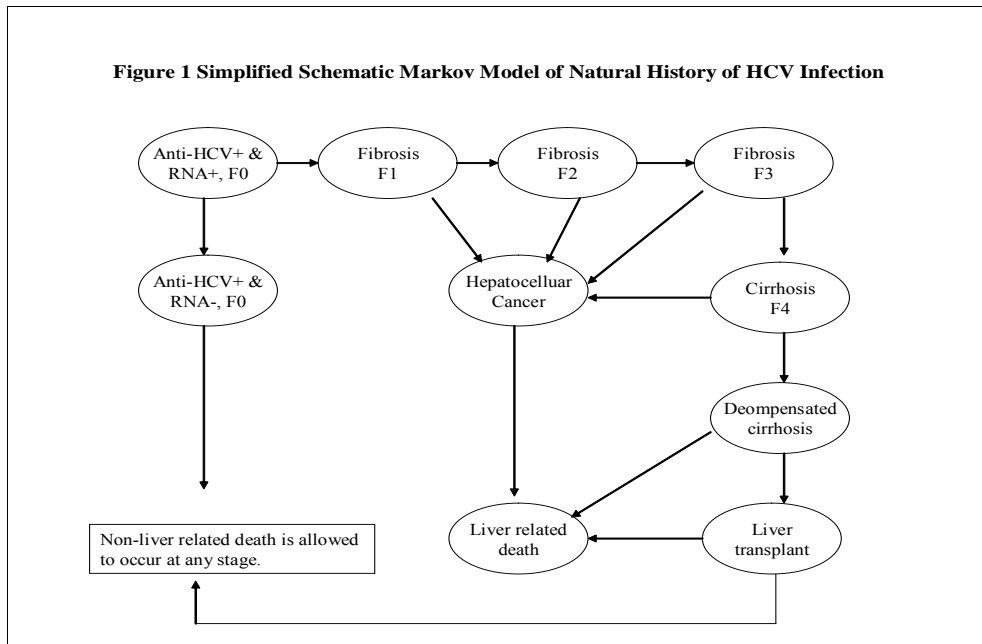
project future outcomes. Efforts to update our projections for this revision have focused mainly on objectives ii and iii. In addition, Dr. Morris Sherman joined the team as an additional content expert and reviewer.

2. Model Structure and Assumptions

2.1 Model Structure

The proposed model, which was revised from the previous Markov model (1, 2), is comprised of two major components: model structure and model parameters. Structure refers to the health states that are represented within the model and the allowable transitions between those health states. Model parameters include the numerical values assigned to transitions between health states, i.e. the transition probability from one stage to another.

Figure 1 Simplified Schematic Markov Model of Natural History of HCV Infection



Each circle represents a health state for the individuals infected due to blood transfusion in Canada between 1986 and 1990. Each solid arrow represents possible transitions between health states that may occur each year. (A detailed representation of the tree as programmed in DATA PRO is shown in Appendix B, Figure 2.1). This model is largely consistent with the one used in the first revision except for the new path from liver transplant to non-liver related death. In the previous models, death post transplant was modeled using a cumulative mortality rate for all individuals post transplant. In this revision we disaggregate mortality rates into disease-specific and general population mortality rates. This modification is particularly important in the elderly as deaths from competing causes rise with increasing age. The current version of the model adheres closely to the contemporary understanding of the biology of HCV disease by

representing fibrosis as the key to defining prognosis. In so doing, it also represents health states that more closely reflect compensation levels defined in the compensation agreement.

Transitions between fibrosis stages (F0 to F4) are explicitly represented in the current version of the model (both first and second revisions). For patients with F0 disease, a distinction is made between those who are RNA+ and those who are not (a subclassification of a *pathological* category according to *serology*). Patients with F4 disease are separately considered according to whether they have compensated or decompensated cirrhosis (a *clinical* distinction).

2.2 Model Assumptions

This model structure involves a number of specific assumptions, which are described below.

2.2.1. There is no excess HCV-related mortality in patients whose liver disease has not yet progressed to F4. Thus, the excess mortality attributable to rare HCV-related events such as B-cell lymphoma, renal failure, and symptomatic mixed cryoglobulinemia are not explicitly represented in the model. The sole exception to this is hepatocellular carcinoma. Patients are allowed to develop and die from HCC at earlier stages, although this is very uncommon.

2.2.2 The probability of progressing to HCC for an HCV-RNA negative person is extremely low. We assume that it is zero and do not explicitly model this transition.

2.2.3 The only difference between RNA+ and RNA- patients is the transition rate from F0→F1. We assume that transition rate from F0 to F1 for a RNA- patient is “0”. After the F0 stage, serologic status (i.e. RNA- and RNA+) is not explicitly represented. We assume that future prognosis is determined by fibrosis stage alone.

2.2.4. Our model is unidirectional. Thus, regression from a later to an earlier stage (e.g. F1 to F0, F2 to F1, F3 to F2) is not permitted, although there is recent evidence to suggest that this may occur in some individuals. Also, the disease progresses one stage a time. Thus, skipping stages within a single cycle (one year) is not allowed (e.g. F1 directly to F3).

2.2.5. The effect of treatment on disease progression is not explicitly represented in the model diagram, but is incorporated within the model structure in the form of an efficacy parameter modifying the annual probability of disease progression in patients who are treated. The effects of other covariates, such as sex, and age are also incorporated into the model, although they also are not explicitly represented in the diagram.

2.2.6 We assume that hemophilic status does not affect HCV disease progression (see section 4.3.6). However, hemophiliacs account for 27.3% of HCV patients in our cohort (as of 2004), and had very different age and sex distributions (younger, more males), and a high rate of co-infection with HIV (40.5% vs. 0.33% in non-hemophiliacs). Thus, non-hemophilic patients and hemophilic patients were modeled separately.

2.3 Analytic Method

Prognostic results were generated using first order Monte Carlo simulation, as implemented in DATA PRO (7). This allows the model to be much more compact, because it allows a large number of prognostic variables to be represented as tracker variables (i.e. variables that are modified for each individual as they progress through the model) rather than having to be explicitly represented in the model as Markov health states.

For each combination of age, hemophilic status, and starting distribution, 10,000 simulated patients were run through the prognostic model one at a time. The cumulative proportion in any stage (e.g. cirrhosis, liver death) thus represents the number, out of 10,000, who at any time within the specified interval, entered that health state.

3. Model Parameters- General Approach to Data Synthesis.

3.1 Data Sources

Three sources of data were reviewed: the previous models, published data, and data directly collected from the HCV compensation agreement claimants.

1) Data From the Previous Models- Some model parameters as well as most aspects of model structure were carried over from the previous modeling efforts. These included transition probabilities for late stage HCV infection, defined as stages of HCV infection after cirrhosis (e.g. transition probabilities from cirrhosis to HCC). After reviewing studies published in the last few years, we were convinced that these transition probabilities derived in our last reports remain valid. Thus, they were incorporated without amendment in the current model. Similarly, the excess mortality ratios attributable to transfusion itself were derived from Vamvakas (8, 9). As in the previous model, information describing the initial distribution at time of infection, for model simulations that began at the time of infection (not the baseline model) including age, sex and year of exposure were derived from the report by Remis et. al (8, 9). The simulations used for the 2004 (baseline) model, that begin on August 31, 2004, used the actual stage distributions derived from the compensation cohort.

2) Transition probabilities for stages earlier than cirrhosis, i.e. from F0 to F4, were derived from a comprehensive literature review in 2002 and updated in 2004. Since some studies on the progression of fibrosis do not present the information exactly as the model requires, transformation of the data was performed to derive the transition probabilities between HCV RNA+ and F1, F1 and F2, ..., F3 and F4. The method used to derive stage-specific transition probabilities was based on a simplified Markov Chain model using an iteration technique (see section 3.4) (10).

3) Data compiled from compensation claim files were also used to calculate transition probabilities, which were compared with literature based transition probabilities.

3.2 Synthesizing Published Data

In order to identify references pertaining to the natural history of hepatitis C, especially transition probabilities between stages, we reviewed three data sources: 1) Medline references describing publications in the medical, public health, and biological literature from 1980 through 2004; 2) Conference proceedings; 3) Reports from previous studies (Remis et al (11). and Krahn et al (1, 2)). The reference lists of relevant articles were also obtained and reviewed in order to locate additional references.

Selected members of the panel (P.W. and Q.Y.) reviewed all of the published reports. The entire panel reviewed the aggregated data and provided a consensus judgment on which studies should be included in the data synthesis.

When several studies were available to estimate a single stage transition probability, a mean probability was estimated using weighted average approach (12) using the following equation.

$$\text{The summary (mean) transition rate} = \frac{\sum P_i * W_i}{\sum W_i}$$

where P_i and W_i are the individual transition probability derived from a single study and the individual study weight, respectively. The weight for each study is the inverse of the variance for the transition probability (12). When the variance was not available (e.g. studies that reported median progression rates, and those derived using the “Markov maximum likelihood” approach described below), the number of patients in the sample was used as the weight. Since many of the studies reported a rate of developing an event, rather than a probability, rates were transformed into probabilities using the following formula: $\text{probability} = 1 - \exp(-\text{rate})$. For a small number, $\text{probability} \cong \text{rate}$ (13).

When published papers did not report transition rates directly, but basic information was available, secondary calculations were performed to derive those rates. This is particularly true for transition probabilities between fibrosis stages (10). These derived transition probabilities were pooled with the reported rates to find the weighted average transition rate.

3.3 Estimating Transition Probabilities

Two methods have been generally used in literature to derive transition probabilities between health states from published studies: *direct* and *indirect* estimation. In *direct* estimation, the fibrosis progression rate is defined as the ratio of the difference in fibrosis stage expressed in METAVIR units between two biopsies and the interval between the two biopsies in years. Direct

estimation is only possible when serial biopsy information (i.e. at least two biopsies) is available with an accurate estimate of the time interval between biopsies. When only a single biopsy is available (most studies), only *indirect* estimation of fibrosis progression is possible. Using the indirect method, the current fibrosis stage in METAVIR units is divided by the estimated number of years of infection. The date of the first blood transfusion is often used to estimate the time at which the initial infection occurred.

Both direct and indirect methods have drawbacks in estimating disease transition probabilities. When the disease transition probability is estimated indirectly, the rate of fibrosis progression is assumed to be constant between all stages (e.g. $p_{01} = p_{12} = p_{23} = p_{34}$), an assumption which may not be plausible, and which has been questioned in the literature (14). Although the direct method is able to directly estimate the rate of transition between fibrosis stages, and does not require the assumption of constant transition probabilities, it does require paired liver biopsies, which are only available in a few studies. Thus, its application is greatly limited because of small numbers and unrepresentative samples. In addition, transition probabilities derived from either method are likely influenced by the timing of the biopsies performed. Sampling variation in the time of biopsy within fibrosis stages could result in significant variations in estimated transition rates.

For example, suppose a patient remained in pathologic stages F1 and F2 each for 5 years, and that the transition between stages occurs at the end of year 5. If sampling occurs in years 5 and 6, the estimated population transition rate derived from that single estimate is 1.0, whereas if sampling takes place at years 1 and 10, the estimated transition rate is 0.1. The biases related to the timing of biopsy are of little concern in a population based study assuming the timing of

biopsy is random. However, because biopsies are often triggered by clinical events which may correlate with changing fibrosis stages, an upward bias in transition rates attributable to sampling pattern may exist. Some studies, e.g. Poynard et. al. (15) report prognosis in terms of the average (or median) number of *fibrosis units per year*. This is a variable that could potentially apply either to an individual or to a population. However, what is required for our model is the average *transition rate* between stages per year. This value, for an individual, can only take the value of zero or one- either an individual changes stages or he does not. For a cohort, this value represents the proportion of the cohort transitioning between stages within a given cycle. It is important to note that we treat these values (*fibrosis units per year* and *transition rates*) as being interchangeable.

For a cohort the mean number of fibrosis units per year is equal to the mean transition rate between stages. If we are considering transitions between two stages, the number of fibrosis units per year change is equivalent to the percentage of subjects that transit to the next stage. Based on an exponential survival model, the mean progression rate, whether it is expressed as the transition rate between stages or as the number of fibrosis unit changes/ per unit time, is equal to the reciprocal of the mean survival time in one stage (or sojourn time). For example, if the mean rate of fibrosis progression per year was 0.133, then mean survival time is equal to $1/0.133=7.5$ years. In other words, the progression time from entering one stage to leaving this stage is equal to 7.5 years. Therefore, the reported progression rates as calculated in fibrosis units from published studies using either the direct or indirect method have the same meaning as the transition rate we defined and can be used as an estimate of the mean transition rate between stages in our model.

Another concern associated with simple direct or indirect estimation is related to the assumption that HCV patients are homogeneous and have similar fibrosis progression rates. Even within individuals, however, progression rates may vary as a function of fibrosis stage and age (14). Variation across individuals has also been convincingly demonstrated. Poynard (16), for example, suggests that there are at least three populations in terms of disease progression: rapid, intermediate, and slow progressors. To reflect the inter-group differences in disease progression, Poynard has suggested using logistic regression to model disease progression. In this approach, other covariates, such as age and sex can be incorporated. While this modeling approach has some appealing aspects, it still assumes that the within-group transition rate is consistent across different stages. This is potentially problematic, as the population of any group will change with time. As the “rapid progressors” depart, the mean rate of progression for the residual cohort will fall.

Our model uses a single transition rate for each modeled transition between health stages. This rate represents a mean rate that takes into account variation across individuals, although it does not fully represent the prognosis of any single individual. This mean rate also does not explicitly take time dependency into account. If transition rates fall over time, as one would expect with the changing composition of fibrosis health states (fast progressors depart more quickly leaving more slow progressors over time), the model as currently specified may overstate progression rates in the very long term.

3.4 Estimating Stage-specific Transition Probabilities: The Markov Maximum Likelihood Method

According to the Markov chain model, the HCV stage distribution of patients after T years of follow-up, $P_T=(P_0,P_1,P_2,P_3,P_4)$, depends on a transition matrix, M_T , and the initial distribution, $P_0=(p_0,p_1,p_2,p_3,p_4)$.

$$P_T = P_0 * (M_T)^T. \quad (1)$$

$$M_T = \begin{bmatrix} 1-p_{01} & p_{01} & 0 & 0 & 0 \\ 0 & 1-p_{12} & p_{12} & 0 & 0 \\ 0 & 0 & 1-p_{23} & p_{23} & 0 \\ 0 & 0 & 0 & 1-p_{34} & p_{34} \\ 0 & 0 & 0 & 0 & 1 \end{bmatrix}.$$

where p_{ij} , which is unknown but assumed to be fixed, is the transition probability from i th stage to j th stage. Given P_0 , T and observed P_T , the unknown transition probabilities, p_{01} , p_{12} , p_{23} and p_{34} , can be estimated through an iteration process.

At the first step, M_T^0 , an initial set of transition probabilities, (p_{01}^0 , p_{12}^0 , p_{23}^0 and p_{34}^0) are given for p_{01} , p_{12} , p_{23} and p_{34} , to calculate an expected stage distribution, \hat{P}_T^0 . The differences (residual) between the expected and observed distributions are compared against a pre-set convergence criterion, usually a very small value (e.g. 0.0001). After each iteration, the previous transition probabilities are revised in order to minimize the differences between the expected and observed HCV stage distributions. The same process is repeated until a set of transition probabilities are found (converged) which best reproduces the observed HCV disease distribution .

Assuming that we are doing the i 'th iteration and have p_{01}^i , p_{12}^i , p_{23}^i and p_{34}^i

$$\hat{P}_T^i = P_o * \begin{bmatrix} 1-p_{01}^i & p_{01}^i & 0 & 0 & 0 \\ 0 & 1-p_{12}^i & p_{12}^i & 0 & 0 \\ 0 & 0 & 1-p_{23}^i & p_{23}^i & 0 \\ 0 & 0 & 0 & 1-p_{34}^i & p_{34}^i \\ 0 & 0 & 0 & 0 & 1 \end{bmatrix}^T .$$

The differences, Residual (Res), between the expected and the observed stage distribution is

$$Res = \hat{P}_T^i - P_T = \begin{bmatrix} \hat{P}0 - P0 \\ \hat{P}1 - P1 \\ \hat{P}2 - P2 \\ \hat{P}3 - P3 \\ \hat{P}4 - P4 \end{bmatrix}$$

and the squared residual sum is Res`*Res, where Res` is a row vector. In our analysis, 0.000001 was defined as the convergence criterion. If the residual sum is greater than 0.000001, $p_{01}^i, p_{12}^i, p_{23}^i$ and p_{34}^i will be modified to be $p_{01}^{i+1}, p_{12}^{i+1}, p_{23}^{i+1}$ and p_{34}^{i+1} .

The transition probabilities are modified according to the sign of the residual. If the expected proportion for stage S is less than the observed proportion, we will decrease the probability of transition from stage S to stage S+1. Otherwise, we would increase the corresponding transition probability. That is,

$$P_{s,s+1}^{i+1} = P_{s,s+1}^i + \text{sign}(\hat{P}_s - P_s) * \Delta ,$$

where $\text{sign}(\cdot) = -1$ if $\hat{P}_s - P_s$ is negative, and $\text{sign}(\cdot) = 1$ if $\hat{P}_s - P_s$ is positive. Δ is the step width. For this model, 0.0001 was used.

With this approach we are able to estimate the stage-specific transition probabilities from F0 to F1, ..., F3 to F4 based on the stage distribution from one biopsy examination.

For example, Kenny Walsh et. al. reported data with 17 years of follow-up (17). At the end of the study, the stage distribution was 49% in F0, 34% in F1, 10% in F2, 5% in F3 and only 2% in F4. The initial distribution is given as (1, 0,0,0,0), that is, we assume that all subjects had no fibrosis at beginning. The initial transition probabilities are given as (0.10,0.10, 0.10,0.10).

At the first step, we have expected stage distribution,

$$\hat{P}_T^0 = (1,0,0,0,0) * \begin{bmatrix} 0.9 & 0.1 & 0 & 0 & 0 \\ 0 & 0.9 & 0.1 & 0 & 0 \\ 0 & 0 & 0.9 & 0.1 & 0 \\ 0 & 0 & 0 & 0.9 & 0.1 \\ 0 & 0 & 0 & 0 & 1.0 \end{bmatrix}^{17} = (0.1668,0.3150,0.2800,0.1556,0.0826)$$

$$\text{Res} = (0.1668,0.3150,0.2800,0.1556,0.0826) - (0.49, 0.34, 0.10, 0.05, 0.02)$$

Since expected P_0 , P_1 are less than observed P_0 , and P_1 , we need to decrease transition probabilities, p_{01} , p_{12} , but p_{23} and p_{34} need to be increased. We then pursue the next iteration.

Convergence was achieved after 1384 iterations: the expected stage distribution is (0.4899, 0.3402, 0.1000, 0.0498, 0.0200) and the squared residual is 0.0000001. The estimated transition probabilities are (0.0411, 0.0469, 0.1029, 0.0877). The probabilities tell us that disease progression is slow from F_0 to F_1 , and F_1 to F_2 , but faster from F_2 to F_3 and F_3 to F_4 .

In this second revision we have adapted the iteration approach to incorporate maximum likelihood estimation. The maximum likelihood approach can use individual data and produce an approximated variance of the estimated stage specific rates. In addition, this approach results in more rapid convergence. Details for this method and the corresponding SAS codes for the above statistical calculations are provided in the paper by Yi et. Al. (Appendix C) and also in Appendix D.

3.5 Using the Markov Maximum Likelihood Method To Estimate Transition Probabilities From Retrospective Data

The proposed method can be applied to either prospectively gathered data, or to cross-sectional studies. In either case, all that is required is an estimate of the starting distribution and of the final distribution. However, estimating stage specific transition probabilities for non-prospective data is potentially problematic, as followup for most non-prospective cohorts will be incomplete. Various selection pressures may result in certain fibrosis stages being over-represented in the

cases that are ultimately gathered for study. For example, if patients with more advanced disease are more likely to come to clinical attention and be included in a non-prospective study, late-stage transition probabilities will tend to be biased upward. Underrepresentation of patients with stage F0 disease will lead to a higher transition probability from F0 to F1. Missing patients in F2 and F3 will cause higher proportions with cirrhosis relative to F2 and F3, even higher than the patients in F3. This will lead to very high transition probability from F3 to F4, and lower transition probabilities from F1 to F2 and F2 to F3.

4. Estimating Model Parameters from the Literature (Tables 4.1-4.9)

4.1 Seroconversion from HCV RNA+ to HCV RNA- Status

Research has shown that hepatitis C virus infection may be self-limited or persist (18-22) and the transition from HCV RNA+ to HCV RNA-, i.e. clearance of the virus, is a part of natural course of disease during the acute period of hepatitis (23). In a prospective study of 43 hepatitis C patients with a history of illicit drug use, Villano (22) concluded that approximately 85% of people with acute hepatitis C infection develop persistent viremia after a 72-month follow-up. In a review by Hoofnagle (23), the proportion of patients infected by HCV developing chronic hepatitis was estimated to be 85%. Among 41 patients with post-transfusion hepatitis C, 10 (25%) recovered and 31 (75%) progressed to chronic liver disease after 6 years (19). Alter et al. (18) reported a study on community acquired hepatitis C, in which chronic hepatitis developed in 60 (62 percent) of 97 HCV-infected patients at a followup period ranging from 9 to 48 months (18). Wiese (24) reported that 55% of HCV infected patients were RNA+ after 20 years of followup.

Theoretically, all patients should experience the HCV-RNA positive stage, and individuals who are HCV-RNA negative were presumably converted from the RNA positive state sometime following the period of acute infection. However, estimating the rate of seroconversion within the first six months, and estimating the annual rate of seroconversion thereafter is not straightforward. It is not even clear that *any* seroconversion takes place after the acute period. All seroconversion may be taking place after the acute infection.

Most published studies, and our own data describing the 1986-1990 post-transfusion cohort, simply describe serologic status some years after HCV infection was acquired. Our own data describe RNA+ and RNA- status approximately 14-18 years post transfusion. We assumed that 15% of individuals seroconvert within the first 6 months, based on the published estimate of Hoofnagel (23). For each published study, we estimated the subsequent annual rate of seroconversion from RNA+ to RNA- based on the remaining cumulative rate and the mean duration of followup in the study. The weighted transition rate, incorporating the data from all published studies, is estimated as 0.013 (see summary table 4.1 in appendix A).

In our compensation cohort, there are 138 RNA- among 1935 claimants who have both transfusion dates and RNA tests available. With an average duration of 17 years, the estimated transition rate from HCV RNA+ to HCV RNA- is therefore 0.0042 (Table 4.3-1). When published data are pooled with our own data from the compensation cohort, the weighted transition rate is 0.0067 (Table 4.3-1). In the simulation study by Salomon et. Al. the transition rate range used was 0-0.01. In our prediction model, we use a rate of 0.006, identical to that used in the 2002 simulation.

4.2 Development and Progression of Liver Fibrosis

Our primary inclusion criterion for prognostic studies of patients with chronic HCV infection was the presence of liver biopsy data expressed using the METAVIR staging system in which the extent of liver fibrosis is expressed in METAVIR units on a scale of 0 (no fibrosis) to 4 (cirrhosis) system (25). We also included studies in which fibrosis stage was expressed using a staging system (e.g. Ishak) that could readily be converted to the METAVIR system. This excluded most studies published prior to 1996. Thus, the dataset from which the most important prognostic dataset was derived differs quite significantly from that used in our 1998 study, but was quite similar to that used in the 2002 study.

We considered the taxonomy of Seeff (26) which we used in our 1998 study to aggregate individual studies characterizing the prognosis of HCV infection. Seeff identified 4 types of study: post transfusion studies, chronic liver disease studies, retrospective analyses of historically defined transfusion associated hepatitis, and retrospective-prospective non-A non-B and C hepatitis studies. Post transfusion studies are studies in which individuals who develop post transfusion hepatitis are prospectively followed. Chronic liver disease studies are prognostic studies that select individuals for inclusion who present for clinical care, usually at tertiary care centres. Retrospective analyses of historically defined transfusion-associated hepatitis studies are case series in which an attempt is made to ascertain the time elapsed from infection by determining the date of transfusion at which time the infection was presumably acquired.

Retrospective-prospective studies are those in which a post-transfusion or post-infection cohort is identified retrospectively, and then prospectively followed.

4.2.1 Non-Cohort Studies - Chronic Liver Disease and Retrospective Analyses of Historically Defined Transfusion-Associated Hepatitis

We aggregated data from these two study designs because they both suffer from potentially significant biases. Chronic liver disease studies, while often prospective, are usually cases identified in the clinical care, often in the tertiary care setting. Thus selection bias attributable to more severe illness, and referral filter bias, attributable to the clinical care setting, potentially serve to select an unrepresentative stage distribution of HCV liver disease. Moreover, the true date of infection is usually not known with certainty, but is inferred from the transfusion history. Thus, recall bias is also potentially a problem.

The largest and perhaps best known retrospective study (n=2,235) was that of Poynard and colleagues (15). The annual progression rate in this study was estimated by Poynard using a presumptive date of infection, and calculated using the indirect method. It was reported as 0.133 fibrosis units per year (95% CI 0.125-0.143). Similar results were reported by Matsumura et al. (24) in a Japanese retrospective study of 239 clinical patients. In this study the authors also calculated transition rates ranging by stage, which are from 0.11, 0.12, 0.16, and 0.15 for the transition from F0 to F1, F0 to F2, F0 to F3, and F0 to F4, respectively. Several other studies reported annual rates of fibrosis progression similar to that reported by Poynard (15, 27-29). Some of the studies collected patients with two or more biopsies, so reported transition rates were estimated using the direct method. Therefore, these transition rates may not start from F0, but from F1, F2, or a more advanced stage, but are assumed to be constant within the covered range. All the studies with repeated biopsies have a relatively small sample sizes. Table 4.2-1 summarizes these previously published disease transition rates from retrospective studies, using transition rates calculated using the *direct* or *indirect* methods. These transition rates across

fibrosis stages varying from 0.129 to 0.134, are very close to the 0.133 fibrosis units per year calculated from Poynard's data (15).

There were a number of new studies on HCV stage transition probabilities published after our 2002 report. Ryder(30) and colleagues published fibrosis transition probability results based on a prospective repeat liver biopsy study of 214 British HCV infected patients. All patients were untreated. The mean interbiopsy interval was a median of 2.5 years with the rate of progression of 0.17 Ishak fibrosis points per year. Similar studies were also reported by others (31-33).

Table 4.2-2 also reports disease transition rates derived using the *Markov maximum likelihood* technique if the stage distribution was reported in the paper. Studies that used Ishak scores were converted to METAVIR scores before the MML technique was used to derive transition rates. Lower rates of disease progression are observed in intermediate stages, and higher in the early and particularly in the later stages.

4.2.2 True Cohort Studies

In prospective studies, a distinct *inception cohort* is identified by exposure to or infection with HCV. Thus all members of the cohort are identified at the same time, and selection, referral and recall biases, which are potential problems inherent in the use of retrospective data, are mitigated.

In general, there was a paucity of disease transition rates from cohort studies. Findings derived from the available studies suggest the disease transition rates were lower than those reported in non-cohort studies. In two different cohort studies in healthy women infected with contaminated

Anti-D immune globulin, Kenny-Walsh (17) and Wiese et al. (24) reported that only 2% of the initial infected population developed cirrhosis 17-20 years after infection.

Estimation of transition probabilities using the “Markov maximum likelihood” technique shows that the weighted mean transition probabilities are about 0.046, 0.054, 0.096, 0.117 for transition from F0 to F1, F1 to F2, F2 to F3, and F3 to F4, respectively (see table 4.2-3). Thus, there appears to be a clear distinction between transition rates in early fibrosis stages (F0-F2), which are lower, and transition rates between late fibrosis stages (F3-F4), which are relatively higher, a pattern that is also present in the non-cohort studies. Our committee believed that this pattern is most likely reflective of the true pattern of fibrosis transition probabilities, as these data are least affected by bias. This pattern, however, may be at least in part attributable to the effects of increasing age and body mass index as cohorts age. Our method was unable to separately estimate the effects of these variables, but implicitly does capture their effects.

It is instructive to observe that transition rates within true cohort studies are approximately half of those observed in the non-cohort studies, providing a rough guide as to the magnitude of the effects of potential bias on observed transition rates.

4.3 Factors Affecting Fibrosis Progression

4.3.1 Treatment Efficacy

Treatment has been proven to be very effective in delaying or reversing fibrosis progression in patients with either Interferon alone or with interferon in combination with ribavirin in responders. However, not every patient responds to treatment. According to Sobesky et al. (27), the sustained responder rate for interferon therapy alone is about 20%. In patients treated with

combination therapy, the response rate is higher, but varies by stage of disease. Pooled efficacy data from two randomized trials reported in our original report (1) showed that patients with mild chronic hepatitis, moderate chronic hepatitis, and cirrhosis have sustained virological response rates of 36%, 43%, and 21% respectively.

Published reports also suggest that response rates vary by genotype. Combination therapy using non-pegylated interferon yields sustained response rates of approximately 25-28% in genotype 1 patients and 62% in non-1 genotypes.

The newly approved pegylated interferon (or peginterferon) has a much longer half-life than the standard interferon and is more effective, though not all patients can tolerate the side effects associated with therapy. Results from a recent large international randomized clinical trial (34) suggest that the sustained virological response rate in the group treated with peginterferon was approximately double that of the group treated with interferon alfa-2a.

In order to accurately incorporate the effect of combined peginterferon/ ribavirin treatment on HCV progression rates, a meta analysis of peginterferon/ ribavirin therapy and its effects on CHC was performed. After a literature search, 15 clinical trials were identified. Five of the 15 studies used peginterferon monotherapy rather than peginterferon and ribavirin combination therapy, and were therefore excluded from the meta analysis. Four additional studies were also excluded as they either used a 24-week treatment regimen or were included highly selected patients (e.g patients who did not respond to monotherapy or an exclusively African-American population). Six studies were ultimately included to derive the overall effect of Peginterferon on

hepatitis C. As the sample sizes vary from one study to another, the SVR for each individual study was weighted by its sample size in the intervention group. Based on the six studies, the effects are: 54%, 34%, and 61% for overall, genotype I, and non-genotype I, respectively. (Table 4.3-1a and Table 4.3-1b) These response rates are somewhat higher than those used in the previous model. We used the higher response rate estimates reported here in our simulation (Table 6).

Disease progression rates are very low or zero in those who respond to treatment. Sobesky compared patients treated with Interferon to untreated patients and found the median fibrosis progression rate based on paired biopsies to be 0.000 METAVIR Units/yr in 150 treated patients, and 0.1333 in 86 untreated controls. Poynard et al (35) investigated the impact of a combination regimen or interferon alone on the progression of liver fibrosis, and found that after treatment the progression rates become negative or zero for either interferon alone or interferon combined with ribavirin. Both studies above reported that the patients receiving treatment had a zero mean progression rate. However, patients with a sustained response got higher regression rates and lower progression rates, than patients without a response. Since most studies examining progression of liver pathology in treated patients have a short time horizon, we employed a conservative assumption for the current model. We very conservatively assumed that the treatment decreases the progression rate (in responders) of liver fibrosis to 10% of that in untreated patients. Like the previous model, we also assumed that this treatment effect occurs only in patients with sustained response, and there was no fibrosis regression. This assumption results in the net effect of potentially overestimating the rate of progression to late stage disease in the entire post-transfusion cohort.

4.3.2 Patterns of Treatment by Disease Stage, Age, and Co-Morbidity

In 2002, we repeated our 1998 survey of Canadian hepatologists to understand patterns of antiviral therapy for HCV patients in Canada. Forty-four (of approximately 50) hepatologists in Canada were contacted and faxed or e-mailed a survey questionnaire. Thirty-eight of 44 responded, for an overall response rate of 86.4%. Based on the survey data, the treatment rate for patients with and without fibrosis is 80% (median) and 14% respectively. Patients with decompensated cirrhosis are usually not offered treatment (see table 4.3-2).

(see table 4.3-2).

In 2004, we again surveyed Canadian hepatologists to see whether patterns of antiviral therapy had changed using a brief questionnaire. Appendix E provides the survey covering letter, questionnaire as well as the summary results. As the results from the 2004 survey are virtually identical to those in the 2002 survey, the 2002 survey results were used in this report as it has a larger sample size.

4.3.3 Age, Sex and Alcohol- (Table 4.3-3)

The effect of age, sex and alcohol on disease progression has been consistently demonstrated in the literature. It has been suggested that HCV elimination after infection may be faster in females than in males (36). Based on a large retrospective data set, Poynard (15) found that sex, age at first transfusion and alcohol are important prognostic factors. If age at transfusion is >40 , the progression rate will be 1.5 times of that in people with age <40 . The risk ratio (RR) of progression in men as compared to women is approximately 1.39. As compared to patients with no alcohol intake, patients with alcohol intake ≥ 50 g per day and 1-49 g per day have RR of progression of liver fibrosis of about 1.34 and 1.14. Other studies have also found alcohol to be a

very significant risk factor for the progression of liver fibrosis (37-41) irrespective of study design or definition of alcohol abuse. However, most prognostic studies do not report progression rates by risk factors. Therefore, for our revised model, the progression rates from F0 to F4 will still use the pooled progression rates for all studies, without adjustment for age, gender, or alcohol intake, following the method used in our previous (1998 and 2002) prognostic models.

4.3.4 HIV Co-Infection

Studies have shown that co-infection with the HIV virus may accelerate progression of HCV-related liver disease (Tables 4.3.4-1, 4.3.4-2). Some studies have demonstrated that patients with HIV/HCV co-infection have higher serum and liver HCV RNA levels than those with HCV infection alone (42). Studies have also suggested that HCV patients with HIV co-infection are more likely to develop end-stage liver disease. Ragni and co-workers (41) followed 157 hemophiliacs, 54% of whom were infected with HCV, for a period of 24 years. Ragni found that the rate of end-stage liver disease (ESLD) was higher in HIV positive than HIV negative patients (12.9% vs 9.7%). The adjusted RR for HIV infection was 3.72 (95% confidence interval 1.25-11.09). Benhamou et al (37) directly studied the impact of HIV co-infection on the progression rate of HCV infection. He compared a cohort of 122 HIV-HCV co-infected patients with a control group of 122 HIV-negative HCV-infected patients. The median fibrosis progression rate in co-infected patients was 0.153 (95% CI, 0.084-0.125) and in control patients was 0.106 (95%CI 0.084-0.125) fibrosis units per year. This suggested a rate ratio for progression of about 1.5 for HCV patients with HIV co-infection, in comparison to patients infected with HCV alone.

Mortality rates also seem to be strongly affected by HIV/HCV co-infection (Table 4.3.4-2). Yee et al. (42) studied a cohort of 310 hemophilic patients infected with HCV between 1961 and

1985, and found that the progression rate to death related to liver disease is 3% and 21% for those HIV negative and positive, respectively, over a 13.3 year interval, with an HIV relative risk (RR) for mortality of 7.

In considering how to incorporate this information in the model, we had to take account of the fact that prognostic studies often do not report HIV status. Therefore, our overall stage-specific transition rates undoubtedly incorporate information from some individuals who are HIV positive. Separately estimating the prognosis of those with HIV infection might run the risk of double counting. However, for hemophilic patients, HIV status usually is reported. In our own data, 40.5% (Table 5.3-2) of hemophilic patients are HIV positive. Though HIV testing information is not available in non-hemophilics, we assumed that HIV positivity was more common in hemophilics since they received blood products repeatedly and were exposed to blood products much earlier. In our model for hemophilics, therefore, we incorporated the effect of HIV status by assuming that fibrosis transition rates between F0 and F4 were increased, on average by a factor of 1.44 (37). We also used the pooled mortality rate ratio of 4.7 (Table 4.3.4-2) to adjust upward the risk of non-liver death in HIV/HCV co-infected patients

4.3.5 ALT level and Genotype

Liver biopsy is usually recommended for patients who have persistent or intermittent abnormalities in alanine aminotransferase (ALT) levels for > 6 months (43). Published data suggest that patients with normal or near-normal ALT levels have a favorable prognosis. For example, Mathurin et al. (44) compared 102 patients with persistently normal ALT and 102 patients with higher ALT, and found a progression rate of 0.07 fibrosis units per year in patients with near normal ALT levels (ALT <45 units), in comparison with a rate of 0.15 fibrosis units

per year in patients with an elevated ALT level (≥ 50 units). Hui et. al. also found that individuals with an elevated ALT level were more likely to progress (45)

Genotype and its effect on HCV progression has been the subject of a number of reports (15, 46, 47). Although the literature generally does not support the hypothesis that genotype is an independent prognostic factor, conflicting reports exist. For example, in a study of 140 patients with chronic hepatitis C, Kobayashi et al. (48) reported that unfavourable progression was more likely to occur in patients with genotype 1b. By contrast, genotype has been shown to be a powerful predictor of response to antiviral therapy (see section 4.3.1 above).

4.3.6 Hemophilia (Tables 4.3-6-1, 4.3-6-2)

Hemophilia is a group of hereditary bleeding disorders characterized by a deficiency of one of the factors necessary for coagulation of the blood. The two most common forms of the disorder are hemophilia A and hemophilia B. Hemophilia A is the result of a deficiency of antihemophilic factor VIII and hemophilia B represents a deficiency of the plasma thromboplastin component, factor IX. The last half-century has witnessed important advances in the treatment of hemophilia. Studies from Europe show the mortality among persons with hemophilia declined substantially (49, 50). For example, the mean age at death of patients with severe hemophilia increased from less than 10 in the 1930s to around 25 years in the 1970s (49, 50). The primary reason for this decline was the increased wide application of clotting factor replacement products for treating life-threatening bleeding episodes (51).

Several studies after the 1980s consistently indicate that bleeding or hemorrhage account for only a small proportion of the increased overall mortality observed among individuals with hemophilia. In a 3-year follow-up of 2,950 hemophiliacs, Soucie et al (51) reported that only 26 (11%) of 236 patients died from hemorrhage (including 6 intracerebral hemorrhage) and the Standardized Mortality Ratio (SMR) was not significantly different from 1. In contrast, 65% of deaths were HIV related, and 8% were caused by liver disease (51). These findings were corroborated by other studies. Based on a survey study of 919 male hemophiliacs, Triemstra and colleagues (52) reported that the overall SMR for the individuals with hemophilia was 2.0. Much of increased SMR could be accounted by HIV infection. They further concluded: *“in the absence of viral infections, the life expectancy of patients with hemophilia would almost equal that of the general male population.”*

As reported above in the section on HIV co-infection, the literature has consistently shown that hemophilic patients with both HCV and HIV were more likely to develop end-stage liver disease (ESLD) in comparison with people with HCV alone. Ragni et al (53) studied ESLD in 157 HCV infected individuals with hemophilia for an average of 24 years. Eighteen developed ESLD, 11 (12.9%) of 85 HIV positive and 7 (9.7%) of 72 HIV-negative. Telfer et al (53-55) followed a cohort of 183 patients with hemophilia and HCV (with/out HIV) and 11 of them developed hepatic decompensation. Kaplan Meier estimates of progression rates are 1.7% at 10 years and 10.8% at 20 years after infection of HCV. A large cohort study of mortality in 4865 hemophilic men and boys by Darby et al in the UK (53-55) showed that the cumulative risks of death from chronic or unspecified liver disease or liver cancer in the 25 years was 1.4 % for all HIV positive patients.

Thus, a review of the published literature suggests that the effect of HIV co-infection on outcomes is at least partially understood, but there are no published reports in which the independent effect of hemophilia on liver-related outcomes or liver-related excess mortality is described. It has been suggested that hemophilia may even play a protective role, as intrahepatic thrombosis, which accounts for “hepatic extinction” may be less common in this group (personal communication, Dr. Ian Wanless). Nonetheless, the independent role of hemophilia itself on HCV progression is unclear. In order to explore potential differences in fibrosis progression rates between patients with and without hemophilia, we compared liver-related outcomes reported in the studies described above with the predictions of the natural history of HCV disease generated by the previous Markov model developed by our group for the entire post-transfusion cohort. A comparison of these data is also provided in Table 4.3-4 (the columns without HIV). HIV negative hemophilics develop end-stage liver disease at a rate between 0.0043-0.0057 in comparison with our 2002 projections for the entire cohort of 0.005 per year. HIV negative hemophilics die from liver-related causes at a rate of 0.0009-0.023 per year, in comparison with our 201 projections of 0.0050 for the entire cohort. These data suggest that hemophilic HCV patients without HIV develop liver related outcomes at a similar rate to that used in our 2002 model. Though this comparison is crude, it suggests that hemophilia does not appear to have a powerful independent prognostic effect on the rate of progression to liver related death or ESLD.

In our model, therefore, we do not assign higher rates of fibrosis progression to hemophilic patients. They are assumed to have the same annual rate of developing fibrosis as non-hemophilic patients. We also assume that there are no independent effects of hemophilia on

mortality, except those mediated through HIV infection. Thus, hemophilics are assumed to have the same prognosis as non-hemophilics, apart from much higher rates of HIV co-infection.

4.3.7 Obesity

It is well known that obesity is a risk factor for hepatic steatosis. Recent studies have shown that visceral obesity may also play a role in accelerating fibrosis in people with hepatitis C. This effect may be mediated by steatosis (56, 57). Obesity is also likely to be associated with poorer response to IFN treatment (58). However, the link between HCV progression and obesity is not consistent. In a study of 148 clinical patients, Fiore and co-workers suggested that the association between hepatitis C and steatosis may be caused by a confounding factor (59). Because body mass index data are infrequently reported in published prognostic studies, this variable was not explicitly represented in our prognostic model. However, each of the prognostic studies from which our progression rates are drawn will include some overweight and obese individuals. Thus, not explicitly representing obesity only introduces bias to the extent to which the distribution of body mass index differs between the studies from which our transition rates are derived, and the population whose prognosis we are estimating (i.e. the post transfusion cohort).

4.3.8 Acquiring HCV Infection Through Transfusion

Some studies in the literature suggest that community acquired hepatitis C tends to be more benign than transfusion acquired infection. In a study of 626 consecutively evaluated nonalcoholic patients with chronic hepatitis C patients, Gordon and colleagues reported that patients with post-transfusion hepatitis C were more likely to develop decompensation than individuals who were not transfusion recipients with a relative risk of 3.92. (60)

Based on stored sera, Rodger et. al. (61) conducted a quasi-cohort study and “followed” 98 patients with community acquired HCV infection for a period of 25 years. They reported that 54% of the anti-HCV positive group had evidence of chronic HCV infection, 69% had elevated ALT levels, but only 8% had progressed to overt cirrhosis. There were no cases of hepatocellular carcinoma. The authors concluded that the natural history of community-acquired HCV may be more benign than previously thought.

In a large cross-sectional study of 6,664 individuals, Roudot-Thoraval (39) examined the association between the onset of cirrhosis and the route of transmission of hepatitis C. The results suggest that the occurrence of cirrhosis was more frequent in blood recipients than in drug users after controlling for duration. However, the role of disease transmission on HCV outcomes is still a matter of debate. In his 1999 editorial published in JGH, Seeff articulated his view of the evidence.

“... while others have suggested that community acquired hepatitis C has a better prognosis than hepatitis C that follows transfusion, I believe it is premature for the authors to reach this conclusion, based on their current data. The numbers of subjects studied thus far are too few, the duration of study is too short and historical comparison is less than ideal. We must await ... the passing of more time before comfortably accepting this conclusion.”

4.4 Development of Hepatocellular Carcinoma (HCC)

4.4.1 Risk of HCC in Cirrhotics (Table 4.4-1)

Published studies have consistently demonstrated a strong association between hepatitis C infection and hepatocellular carcinoma (HCC). Almost all HCV+ patients who develop HCC have had liver disease that has progressed to liver cirrhosis prior to developing cancer. A synthesis of the literature on the HCV and HCC suggests that 0.4-2.5% of people with chronic hepatitis C virus (HCV) eventually develop HCC (62). In our 1998 model, (63-65), the weighted annual probability of progression to HCC given cirrhosis was 1.7% per year. Additional references were included in the 2002 study. In a cohort study of 252 patients with HCV associated cirrhosis, Kato et al (66) found that 151 (90%) of 161 deaths were due to HCC related complications. This fact implies that the incidence rate of HCC among HCV cirrhosis patients is high, perhaps because these were Japanese patients. In a prospective study of 416 patients with HCV related cirrhosis, Degos and his colleagues (62) reported that 13.4% (9.0-17.8%) of the initial cohort developed HCC in 5-years with an annual rate of 2.9%, which is much higher than the earlier reported 5 year risk of 7% (67) and 5% (68). Del Olmo et al (69) performed a longitudinal/retrospective study in which patients with liver cirrhosis were followed for a mean period of 60.3 months. Among 967 cirrhotics, 64 patients developed HCC, for an annual incidence rate of 2.1%. The weighted mean annual rate of all reported studies is 2.1% (see table 4.4-1).

4.4.2 Risk of HCC in HCV-Infected Individuals Without Cirrhosis

Although most HCC patients have cirrhosis, there are some who have no fibrosis or very minimal fibrosis. Bralet et al. (70) retrospectively analyzed 330 HCC biopsy samples, and found 80 cases (approximately ¼) in which the non-tumoral liver showed no or minimal portal fibrosis. If patients with cirrhosis represent 10% of the sample of all patients with hepatitis who are at risk for HCC, then the transition rate to HCC for patients without cirrhosis is approximately 1/40

times the rate of cirrhosis to HCC. Another study from Asia -Pacific region (71) reported results by fibrosis stage. Patients with F0 disease developed HCC at an annual rate of 1.2%, and the patients with more severe fibrosis in F1, F2, and F3 developed HCC with annual rates of 1.3%, 3.4% and 5.7 %, respectively. The pooled annual rate is 2.1%. However, at the time of diagnosis of HCC cirrhosis was found in all the patients except 2 of them, implying that most of patients developed HCC after cirrhosis. Since residents of Japan have the highest incidence rate in HCC on the world, these patients may not be directly comparable to our cohort. We therefore did not use these rates, but adopted the transition rates from the 1998 and 2002 models¹. In the previous models, the annual rate to HCC is 0.0001 in moderate chronic hepatitis C, and zero in mild chronic hepatitis C. We assumed that F0 is similar to the mild chronic hepatitis and that the transition probability was 0. We believed that F1 and F2 stages were more similar to moderate chronic hepatitis and were assigned to be 0.0001. We believed that the risk in F3 patients was higher. We therefore chose a value (0.001) between the values for F1/F2 (0.0001) and the value for F4 (0.021).

4.5 Excess Mortality

Patients who acquire hepatitis C infection through blood transfusion may be at higher risk of death from non–liver causes than the patients who are infected through other routes, and also much higher than the general population. The excess mortality risk in this group is most likely attributable to the diseases for which transfusion is indicated. Indications for transfusions are often recent trauma or severe medical illness.

The BC lookback program (57, 72) evaluated the mortality experience of all individuals transfused within BC between the periods of January 1985 and June 1990. This study reported an

overall mortality rate of 39.8% at 9.75 years among 106,401 individuals who received a transfusion during this period. As indicated in Remis et al. (11), approximately 5% of short term deaths may not have been captured in the lookback program, so the actual mortality rate may be as high as 45% at 10 years.

To account for excess mortality in our cohort, we followed the strategy used in the 1998 and 2002 models, and utilized the survival experience of the cohort reported by Vamvakas⁸. By comparing the survival rates after transfusion for each age group to the survival rate in Canadian population, we estimated the excess mortality ratio according to years elapsed from transfusion. Since the highest likelihood of death occurs within the first 2 years after transfusion, we divided the post transfusion period into four time periods, 0-1, 1-2, 2-10, >10 years (see table 4.6-1). As we can see, for the groups of age <40, rate ratios for the first two years are similar, but the rate ratio drops sharply thereafter. Table 4.6-2 provides age and sex-specific mortality (reported by Statistics Canada in 1997) as well as the estimated baseline distributions for age, sex, and year of first infection, which are only utilized for the simulations that begin at the time of infection (e.g. Table 6.1). For the baseline analyses¹ (Tables 8.1-1 to 8.1-19), observed age, gender, and stage distributions in the compensation cohort are utilized (5.4-1 through 5.4-7). In our baseline analyses we assumed that there was no excess mortality attributable to transfusion, as all patients received blood transfusion more than 10 years ago, and rate ratios after this time period decrease to 1.0.

4.6 Transition Rates Post-cirrhosis

¹ “baseline analysis” is defined as future projections using our best estimate for each model variable

A comprehensive literature review of outcomes for late stage liver disease (post-cirrhosis) was performed in constructing the 1998 and 2002 models.¹ Because little has been published in the last two years describing the prognosis of late stage patients, we adopted transition probabilities from the 2002 model.

5. Analysis of Clinical and Demographic Data Characterizing Claimants for Compensation

5.1 Data sources

In order to be compensated, a claimant or his/her immediate kin is obliged to provide information to validate the claim. All patients included in this study were required to show that they had received blood transfusion or other blood products between January 1, 1986 and July 1, 1990 and to demonstrate that they had one or more of the following serological or clinical manifestations stipulated in the **Hepatitis C January 1, 1986 – July 1, 1990 Class Actions Settlement** agreement:

- Level 1: HCV antibody positivity
- Level 2: HCV-RNA positivity
- Level 3: Non-bridging fibrosis
- Level 4: Bridging fibrosis
- Level 5: Cirrhosis of liver, unresponsive porphyria cutanea tarda, unresponsive thrombocytopenia
- Level 6: liver transplant, decompensation of the liver, hepatocellular cancer (HCC), B-cell lymphoma, symptomatic mixed cryoglobulinemia, glomerulonephritis, renal failure.

Individuals with any known HCV infection or consequences were included. By August 2004, Crawford Adjusters, the administrators of the compensation agreement, had provided the research team with all claim records that had been processed by that date and were deemed to be legitimate (i.e. met the criteria for compensation). At that time 4,530 individuals (2,827 males and 1,703 females) had been accepted as legitimate claimants for compensation, and had been assigned to one of the compensation classes. According to the claims received up to August 31, 2004, 971 (21.4%) of the 4,530 legitimate claimants were deceased.

All data describing the clinical and demographic characteristics of the successful claimants were forwarded to our research team. Information in the database provided by individual claimants or their proxies was cross-checked against the physician reports, and compiled into several data files, which were fully accessible by the research team. The relevant information contained in these files includes:

- Demographic variables: year of birth, sex, place of residence, date of death for deceased people
- Hemophilic history and/or the underlying medical condition necessitating blood transfusion
- Blood transfusion history (for non-hemophilic patients only): date of first transfusion, number of transfusions.
- Serological testing results and dates for HCV-antibody and HCV-RNA status at time of claim being made:

- Severity of HCV infection and supporting diagnostic information. Disease severity was based on a 6 level compensation scale which can be (almost directly) converted into the corresponding METAVIR stages
- Co-infection with HIV for hemophilic patients
- Treatment information: starting time, type of drug, serological testing information:

5.2 Data management

Considerable efforts were expended to check and manage the original data files, in order to address problems of missing data and data entry errors. Each data file was separately reviewed to identify missing data for each variable. The range of values for each variable was reviewed to identify outliers, especially date variables. Logical checks were performed within data files to identify conflicting information. Logical checks were performed between data files to ensure consistency. For example, we reviewed the transfusion file and the claim file to ensure that the dates of reported transfusion were identical. A permanent data set was created for the study, based on the revised and corrected data submitted to the investigators by Crawford Adjusters. The quality of the data had improved considerably since the past revision. No data entry errors were identified.

5.3 Descriptive analysis of claimants for compensation in 2004

5.3.1 Patient characteristics

All 4,530 patients with valid claims for compensation were included in this study. Tables 5.3-1 and 5.3-2 and figures 5.1 to 5.2 provide baseline demographic, clinical, and serological characteristics of the study cohort. There were 2,827 men and 1,703 women. Men were older,

on average, and were more likely to be in a higher compensation category. The observed differences between men and women in terms of age and stage distributions can be largely explained by hemophilia that occurs predominantly (as defined in the compensation agreement) in men. At the time the study started, 971 claimants were deceased. The number of patients from each province is roughly proportional to its population size, with the exception of British Columbia, which was the home of a disproportionate number of claimants

All except 248 individuals (with 958 missing) were positive for serum antibody to HCV based on the last available testing results. Among 2,694 with RNA testing records, 93% were HCV-RNA positive, although those with negative HCV-RNA results may not have submitted them. The blood transfusion history was available for 3,255 non-hemophilic patients, of whom 491 (15.1%) indicated that they received a blood transfusion before 1986. Among those with blood transfusion records, 68% were multiple blood transfusion recipients. A total of 2,027 (62.3%) patients received their first transfusion before the age 50.

Distributions of disease severity (METAVIR stage as well as compensation level) are reported in Table 5.4-1 and Figures 5.3-5.4. Perhaps the most important fact about the observed stage distribution is that biopsy information is missing for 78% of patients. Although most of these patients will probably have early stage disease, this fact is not known with certainty. Cirrhosis was present in 7.1% of claimants, and decompensated cirrhosis, HCC, and previous transplant in 1.7%, 0.6%, and 0.7% respectively. The proportion of patients with more advanced stages of disease are much higher among those with a liver biopsy. For example, 25.5% of those with

biopsy records had cirrhosis (compensated or decompensated) whereas only 4.1% of those without biopsy records were identified as having cirrhosis.

5.3.2 Hemophilia and other underlying conditions for blood transfusion (Table 5.3-2)

In total, 1,236 (27.3% of all claimants) hemophilic patients were included in this study; 1,096 (85.9%) of whom were male. A few female patients are included in this cohort, as “hemophilia” for the purposes of the compensation agreement includes Von Willebrand’s Disease, in addition to inherited Factor 8 and 9 deficiencies. In comparison with other claimants, hemophilic patients were younger (40.1 years vs. 57.6 years), but had similar distributions of serologic status (anti-HCV, HCV-RNA), compensation stages, and previous treatment. A higher proportion of hemophilic claims came from estates of deceased patients. Four hundred ninety (40.5%) of hemophilic patients were HIV positive; only 10 (0.33%) of non-hemophilic individuals were HIV positive.

5.4 Estimating the True Fibrosis Stage Distribution from Claims Data

We initially used the claim data to estimate fibrosis stage distribution using the following system:

- Level 1: HCV antibody positive: unknown fibrosis stage
- Level 2: HCV-RNA positive: unknown fibrosis stage
- Level 3: Non-bridging fibrosis: F1
- Level 4: Bridging fibrosis: F2-F3
- Level 5: Cirrhosis : F4

However, the claim data, as reported, are difficult to use directly for the purposes of estimating the true stage distribution among claimants. As indicated above, nearly 80% of cases (Tables 5.4.1, 5.4.2 and 5.4.3) do not have liver biopsy data. These cases could represent benign liver

disease with minimal or no fibrosis, as one of the indications for liver biopsy is elevated liver enzymes. Patients with normal or minimally elevated liver enzymes are often not candidates for therapy, and therefore may not be offered a biopsy. On the other hand, patients may not be biopsied for a variety of other reasons: I) ineligibility for treatment due to advanced age or comorbidity; ii) refusal; iii) never being offered a biopsy. Thus, some patients without a liver biopsy almost certainly have more advanced liver disease. Relying exclusively on claim information therefore runs the risk of underestimating true severity of stage distribution in those without biopsy information.

We approached this problem in the following way. The Markov states in our natural history model include both pathologic (e.g. fibrosis stage) and clinical (e.g. decompensation, transplant) stages. Thus, we have clinical information regarding end stage disease (decompensated cirrhosis) for the non-biopsy group as well as for the biopsy group. We believed that the completeness and validity of the clinical information was likely to be similar in both (biopsy and no-biopsy) groups. If we assume that progression rates from mild fibrosis to cirrhosis among those without a biopsy are the same as for those with a biopsy, it is possible to retrospectively allocate those without a biopsy to a variety of intermediate stages (F0 to F4).

In the 2002 revision, patients' characteristics (e.g. age, gender, treatment, hemophilic status, stage), which are associated with biopsy, were not taken into account in the stage adjustment for those without biopsy information. To address this limitation, in this report the working group utilized a propensity score approach (73, 74) to estimate true stage distribution. The propensity approach is a means of adjusting for differences in multiple prognostic covariates by collapsing

all covariates into a single variable, which in this case is the “propensity” or probability of having received a liver biopsy. Biopsy and non-biopsy patients with similar propensity scores should have a similar distribution of all covariates, including stage distribution. We accomplished this using the following steps:

- A propensity score for biopsy was derived by fitting a logistic model with biopsy status as dependent variable, and age, gender, compensation level (stage), hemophilic status (yes/no), previous treatment (yes/no), and survival status (alive/dead at 2004) as independent variables (table 5.3.3).
- Based on the propensity score (predicted probability of having biopsy), patients were then classified into three groups: propensity score <0.4 , $0.4-0.6$, and ≥ 0.6 .
- We assumed that patients at late stages (such as decompensated cirrhosis and liver cancer) could be diagnosed using clinical information only, and that there were no “subclinical” or occult cases of decompensated disease in either group. Thus, no further adjustments were made for these stages. We further assumed that RNA negative hepatitis patients did not have liver fibrosis, and therefore no adjustments were made for this group.
- In each group, the stage distributions were compared between patients with and without biopsy records. The patients without biopsy but with the same propensity score were adjusted according to the distribution of patients with biopsy records, for individuals in the following stages: RNA+, F1, F2, F3 and F4.

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Tables 5.4-1 – 5.4-3 show the reported and adjusted stage distribution for all patients alive, hemophilic and non-hemophilic patients. We believe that the adjusted stage distribution is necessary for the purpose of estimating fibrosis transition probabilities directly from the reported compensation data.

The propensity score model was used to generate tables of estimated true (as opposed to reported) stage distributions, stratified by age and sex, as of August 31, 2004. See Tables 5.4-4 through 5.4-7.

5.5 Using the Estimated Stage Distribution to Calculate Progression Rates Between Fibrosis Stages

Given the fact that we know the approximate time at which HCV infection was acquired and have estimated the stage distribution at the time of the claim, it is possible to use data from the compensation cohort to estimate transition rates between fibrosis stages. We used adjusted stage distribution data from the non-hemophilic patients to derive these rates. We chose this group because the time of infection for hemophilic patients is uncertain, and therefore calculation of stage transition rates is also uncertain. We used adjusted data because, as argued above, the unadjusted data assigns all patients without liver biopsy to the F0 stage (i.e. RNA+), an assumption that is certainly incorrect.

Using the “Markov maximum likelihood” approach (10), we derived the fibrosis progression rates from stage distributions in our adjusted claims data. The derived rates are 0.041, 0.088, 0.327 and 0.384 for transitions from F0 to F1, F1 to F2, F2 to F3, and F3 to F4 (cirrhosis), respectively (Table 4.2-4). Note that these rates are lower for F0-F1, and much higher for F2-F4 than any of the literature derived rates (Tables 4.2-1 to 4.2-4). In addition, the estimated number

of years ($41.5 \text{ years} = 1/0.041 + 1/0.88 + 1/0.327 + 1/0.384$) required to progress from infection (F0) to cirrhosis are somewhat longer than the 30 years ($=4/0.133$) reported by Poynard (11). In comparison with the rates derived from the compensation cohort data available in 2002, these transition rates are somewhat lower. The corresponding rates used in the 2002 revision are F0-F1: 0.061 (2002) vs. 0.041 (2004); F1-F2: 0.146 (vs. 0.088); F2-F3: 0.407 (vs. 0.327); and F3-F4: 0.501 (vs. 0.384). Transition rates are lower for the 2004 model largely because the adjusted stage distribution was different. Using the larger, more complete patient sample and better estimation methods (propensity score method), fewer patients appear to have advanced disease, and derived transition rates are correspondingly lower.

It is instructive to compare these transition rates with those derived from the literature using the same methods (i.e. “Markov maximum likelihood” method) in Table 4.2-4. Both cohort and the compensation data show the same pattern: a slower transition from F0-F2, and a more rapid transition from F2-F4. This differs quite dramatically from the single fibrosis progression rate between all stages reported in the literature by many studies, and suggests that the assumption that transition rates are constant across stages is probably incorrect.

6. Final Parameters for the New Model: Combining Data From the Literature and From the Compensation Cohort

We incorporated data from a wide variety of sources into the final prognostic model (see Table 4.6-2 and Table 6 for a summary of all prognostic variables). Data from the compensation cohort were used to estimate the age, gender, and clinical stage distribution (e.g. HCV RNA+, RNA-, fibrosis stages 0-4) at the beginning of the simulation. We also used data from the compensation

cohort to estimate the proportion of claimants with hemophilia and HIV infection. Data from the literature were used to describe treatment efficacy, general population and post-transfusion mortality rates, and the effect of HCV and hemophilia on long-term prognosis. Our clinician survey provided data regarding current treatment patterns among Canadian liver specialists. Finally, we used our previous models as the source of transition probabilities for health states more advanced than liver cirrhosis.

However, a number of key judgments were required in order to integrate the available information in the most valid, defensible, and evidence-based manner possible. These are described below.

6.1 Choosing Fibrosis Transition Rates

Choosing the best transition probabilities between fibrosis stages is both the single most important, as well as methodologically the most challenging aspect of estimating prognosis accurately. We had three sets of data to choose from: 1) non-cohort studies reported in the literature; 2) true cohort studies; and 3) estimates derived from the 1986-1990 transfusion cohort. In addition, we had several methods of deriving transition probabilities: the Markov maximum likelihood method, and the direct and indirect estimation methods.

With respect to the issue of estimation method, our group believed that the Markov maximum likelihood method (10) is able to best represent stage specific transition rates, as it does not require the assumption that transition between stages was constant. The evidence would seem to strongly suggest that transition rates increase with increasing age (Table 4.2-4). We therefore

adopted this approach wherever possible to calculate transition rates, and pooled rates derived from individual studies in order to estimate transition rates.

With respect to the choice of transition probabilities, although we would have preferred to use our own data directly, our group believed that the transition probabilities directly from the claimant cohort, especially for late stage disease (F2-F4) were too dissimilar to those observed in other published studies to be relied upon exclusively, particularly for the transition rates F2-F3 and F3-F4 (see Table 4.2-4). We believed that the observed stage distribution in the post-transfusion data most likely demonstrated some degree of selection bias, as patients with more advanced disease were simply more likely to come to medical attention and/or claim for compensation. Table 6.1 illustrates this point. This table compares the observed stage distribution of compensation claimants to the predicted distribution, using transition rates derived from the literature (This table is described in greater detail in section 6). The observed stage distribution is somewhat different from the predicted stage distribution. There is both more advanced disease and more early stage disease among claimants than one would expect. Because we were concerned about the possibility of selection bias, particularly for disproportionate selection of later stage cases, we were reluctant to rely exclusively on transition probabilities derived from the compensation cohort.

Among prognostic studies reported in the literature, we believed that the prospective cohort studies were the least subject to bias, but probably underestimated the fibrosis transition rates because the population in these studies was much younger and more often female than in other studies, and certainly in comparison to our post-transfusion cohort. Non-prospective studies

usually had a population whose age and gender profile was more similar, but was more subject to bias.

Two approaches were possible. First, we could simply have used the adjusted (for age and gender) prospective cohort data to correct the age and gender problem. However, this would mean building the entire prognostic model on two somewhat unusual studies that described the prognosis of HCV in young women infected in point source outbreaks. This approach would exclude much of the published prognostic data, albeit with the advantage of relying on the least biased data.

Alternatively, we could have pooled all of the literature-derived data, recognizing that demographic factors and selection bias might introduce potentially offsetting errors. Our group discussed the relative advantages of each approach, bearing in mind the considerations outlined in section **7. Validating the Stage-based Prognostic Model**, as described below. We also recognized that if errors were to be made, errors overestimating the rapidity of progression might be preferred, as ensuring the sufficiency of the compensation fund is an important goal of this exercise. Thus, our group ultimately decided to pool all three sources of transition rates. The effects of various transition on our project are explored through sensitivity analyses.

Salomon and colleagues presented a comprehensive epidemiological model of hepatitis C in the United States (75). Salomon's approach was to fit transition rates to their prognostic model empirically. They attempted to derived model parameters that best fit data derived from both a literature survey and epidemiologic data, including seroprevalence data derived from the Third

National Health and Nutrition Examination Survey (NHANES III) to project long-term consequences of HCV.

Salomon's model represents a very high level effort to derive transition probabilities. It differs from ours in the following way: I) Salomon attempts to estimate age and sex-specific transition parameters; II) Salomon does NOT estimate STAGE-SPECIFIC transition parameters; III) Salomon uses epidemiologic data whereas our data are derived only from the literature and from our own prognostic cohort. As a means of checking the validity of our prognostic projections, we used Salomon's published transition rate estimates in our model and compared those projections with our baseline results.

6.2 Modeling the Prognosis of Hemophilics

The compensation data indicate that 27% of claimants are hemophilics, who are about 14 years younger than non-hemophilics and more often male (89% vs. 53%) (Table 5.3-2). The literature also suggests that the general age-related mortality (i.e. non-liver mortality) for hemophilics tends to be lower than non-hemophilics (see section 4.3.6). Thus, we model prognosis for hemophilics and non-hemophilics separately, though we also report projections for the merged cohort.

For the prediction for hemophilics and non-hemophilics, most of parameters are the same except age and sex distributions and excess mortality. The age, sex, and stage distributions were taken from compensation data for hemophilics and non-hemophilics separately. According to Vamvakas (8) the mortality rate >10 years after blood transfusion would be the same as that of the general population. Although hemophilia per se is not associated with a significant increase

of excess mortality, when taking HIV infection into account, the modeled excess mortality for hemophiliacs was approximately twice that of the general population for the entire life span.

Table 6 is a summary of the final parameters used in the model

7. Validating the Revised Stage-based Prognostic Model

How is it possible to know whether the predictions of our prognostic model are accurate?

One obvious answer might be to compare the predictions of the model with published studies, but this is clearly a circular argument, since it is published prognostic studies that serve as the source of transition probabilities for the model. Hence, the model will predict whatever the studies from which transition probabilities are drawn predict.

Another approach might be to compare the observed stage distribution in our post transfusion cohort to that predicted by the model. If the prognostic features of the model are correctly specified, we should be able to run the model starting at the time at which infection was acquired (time of transfusion) and predict the stage distribution at the present time. The extent to which the predicted distribution matches the observed distribution is one check on the validity of the predictive model.

Table 6.1 compares the adjusted observed stage distribution in the post-transfusion cohort to the stage distribution predicted by the model. The model predicts the present stage distribution by assuming that the age and gender distribution of those infected with HCV at the start of the

simulation is predicted by the demographic characteristics of transfusion recipients, as reported in Remis et. al. ³. The transition probabilities for the model are our best estimates, as described above, hereafter referred to as our *baseline* estimates. We compare stage distributions only for non-hemophilics, as hemophilics for the most part acquired their infections much earlier.

As shown in Table 7.1, our current model predicts the observed-adjusted distribution in non-hemophilics with a moderate degree of fidelity. The observed distribution has slightly more patients in the early stages (eg. 53.8% of the observed and 44.4% of the predicted cohorts are in stage F0); 78.2% of the observed are in F0-F1 observed compared to 76.4% predicted. There are also more patients in the later stages in the observed cohort (e.g. cirrhosis has 6.6% observed vs. 6.2% predicted, decompensated liver disease has 1.5% observed vs. 0.7% predicted). The 2004 model fits the data considerably better than the 2002 model. For the purpose of comparison, the results from the first revision are also provided in Table 6.1. It is evident that the observed and predicted are much closer for the second revision than those in the first revision.

However, this method of establishing the validity of the predictive model has limitations. The observed and predicted stage distributions will match only under certain assumptions: i) all members of the transfusion-acquired HCV cohort did in fact acquire their HCV infections between 1986-1990, and not before; ii) the observed stage distribution at present among those claiming compensation is representative of the post-transfusion cohort as a whole (i.e. no selection biases are operating); iii) our method of predicting true stage distribution among transfusion recipients who did not receive a liver biopsy is approximately correct; iv) our

prediction of the age and gender distribution of HCV infection patients from 1986-90 is approximately correct.

In comparison to the 2002 report, there have been no changes for assumptions 1 and 4. The significantly improved agreement between the observed and retrospectively predicted stage distribution may be due to changes in factors 2 and 3. The stage distribution in our more complete 2004 compensation cohort may be a more accurate reflection of the stage distribution among all patients with transfusion acquired HCV, and/or our method of predicting true stage distribution may be more accurate for those without liver biopsy data.

Another approach to validation is to compare the predictions of our current model to the predictions of other models. Our 1998 model used mainly studies of post-transfusion hepatitis. Although many of these studies were older and did not confirm that the source of hepatitis was HCV, all of these studies were prospective studies with a true inception cohort. We believe that the previous model is a reliable reference in attempting to ascertain the predictive accuracy of the current model. Our 2002 model used a wider selection of studies. Table 7.2 documents differences between the projections of all three models. The 2004 model projections fall between those of the 1999 model and the 2002 model. The 2004 predictions are lower for several reasons: i) the proportion of hemophiliacs that are HIV positive has fallen (24.6% vs. 38.8%); ii) transition rates between fibrosis stages are lower; iii) the starting distribution of patients with advanced disease is considerably lower (F4=12.2% vs 23.5%); iv) life table mortality rates have fallen slightly; v) treatment is now more effective.

Figure 7.1 compares the cumulative probabilities of cirrhosis based on the stage-specific fibrosis transition rates used in the current projection and the stage-constant fibrosis transition rates reported by Salomon (75). For both approaches, cohorts with the same starting age and gender distribution (given by the distribution of transfusion recipients) were used. Both models assume that all patients begin in the RNA+ health state (for comparability with the old model). As shown in this figure, both approaches produced very similar results for the first twenty years. However, the results from the two approaches begin to diverge after years 2020. By 2060 the differences are greatest, with the cumulative proportion of cirrhosis reaching 38% in our model, relative to 45% in Salomon's model. Given the overall level of uncertainty associated with predicting prognosis in the very long term, and the fact that both modeling efforts used different data, methods of synthesizing data, and projecting long term outcomes, we believe that these predictions are sufficiently similar to lend support to the validity of both models.

8. Prognosis of Post-transfusion hepatitis C Patients Based on Projections of the Markov Model

The following section consists of 2 parts: i) our baseline projections for all patients, hemophilics, and non-hemophilics using our best estimates for all model parameters; ii) sensitivity analyses exploring the effects of different transition probabilities, starting distributions, and all other variables. All projections were based on Markov models programmed in DATA PRO (7). The anchor date for the simulation is August 31, 2004.

8.1 Sixty year projection based on pooled transition rates derived from literature

Tables 8.1-1, 8.1-2, and 8.1-3 display the results of projections for the entire transfusion cohort, the entire hemophilic cohort, and the entire non-hemophilic cohort, respectively. Tables 8.1- 4 through 8.1-19 report age-stratified outputs for hemophilic and non-hemophilic patients.

Each table displays the cumulative incidence rate of cirrhosis, death, HCC, transplantation, and liver death, and also lists the sex, age distribution and stage distribution of the patients alive in future years. The predicted results for non-hemophilics and hemophilics differ in death rates and sex distribution.

For the overall population, our model predicts that the cumulative lifetime incidence of cirrhosis in living patients is 38%, starting from a point prevalence rate of 10.6% in August 2004. Thus, about 27% of this cohort who are currently living but do not yet have cirrhosis, are predicted to develop it over the course of their lifetime. About one in 11 (8.6%) will develop liver cancer., and more than 1 in 5 (21.8%) will ultimately die of their liver disease.

Comparison between hemophilics and non-hemophilics shows that more non-hemophilics will die in the next 10, 20, and 30 years, even though cumulative mortality will be similar by the year 2060. Hemophilics are more commonly co-infected with HIV, but the non-hemophilic population is older. In the medium term, the effect of age on mortality is greater than the effect of HIV infection. However the relative proportion of patients who die from liver-related disease is higher in hemophilics, and all other cirrhosis related events are relatively higher than non-hemophilics. Hemophilics are younger with more years to develop liver disease, and HIV-HCV co-infection increases the rate of fibrosis progression.

8.2 Sensitivity analysis

The effects of uncertainty in our prognostic model were explored using a number of scenarios. As in the 2002 report, we have performed a variety of sensitivity analyses. First, we explored the effects of using transition probabilities directly from the compensation cohort. Use of compensation cohort data results in a 20% higher estimate for the lifetime risk of cirrhosis, and a 21% increase in the risk of liver death. In contrast, using the estimated starting distribution at the time of infection, rather than that observed in the compensation cohort, results in a 13% increase in the risk of cirrhosis, but virtually no change in the lifetime risk of liver death.

Finally, we ran analyses using second order Monte Carlo simulation in order to take account of all sources of uncertainty in the model. This includes variables such as treatment efficacy, as well as choosing the source of fibrosis transition parameters. In this approach, probability estimates for the model are represented by probability distributions rather than by fixed point estimates. For each simulation, a set of parameters is randomly drawn from each distribution. This set is used to run a series of simulations using a large number of patients.

Table 6 lists the plausible range for each transition probability and other prediction parameters. Most of the probabilities were assumed to follow a beta distribution, though some of them were modeled using triangle distribution. The "baseline" value was assumed to represent the mean of the distribution. For each randomly sampled set of transition probabilities, 2500 repeated patients with different age, gender, or treatment were simulated. Overall, 500 sets of transition rates were sampled, with 2500 simulations per set. The mean and 95% confidence interval of the predicted event rates at the years 2010 and 2060 year are reported in Tables 8.2-3

Table 8.2-3 suggests that the error in lifetime cirrhosis incidence rate is about +/- 10% in absolute terms (29.1-46.9% and about +/- 25% in relative terms. Similar errors (+/- ~7% in absolute terms, ~30% in relative terms) were present in the lifetime risk estimates for liver death (21.8%). These values reflect the overall uncertainty in our prediction model. This estimate excludes uncertainty attributable to the size and stage distribution among HCV-infected transfusion recipients who have not yet come forward to claim compensation.

9. Estimating the Stage Distribution of Post-transfusion HCV-infected Individuals Who Have Not Yet Presented to Claim Compensation

The compensation agreement is intended to be sufficient to compensate all individuals who claim for compensation within a specified time period. Because the number who have claimed to date is short of the estimated total of potential claimants (up to 9,000), it is useful to estimate the number of future claimants, a topic which is beyond the scope of this report. Equally, important, however, is estimating the stage distribution of the unknown cohort. The prognosis of these individuals, and the total potential claims upon the fund are likely to differ quite substantially depending on whether they all have advanced liver disease at the present time, or whether they have, in general, mild, asymptomatic liver disease.

Hereafter, the group of individuals who were infected with HCV through the blood supply, and who may eventually come forward to claim for compensation, are described as the “unknown” cohort.

Despite the significance of the HCV stage distribution information for the unknown cohort, we have limited direct data upon which to base a reliable estimate of current stage distribution.

Following the method used in the first model revision (2002), we have used two complementary approaches to derive a plausible estimate.

9.1 Approach 1: Regression method

In this approach, we estimate future stage distribution by analyzing temporal trends of those who have claimed already, and projecting these trends forward into the future. We have assumed that the time sequence of a claim is influenced by a person's age, sex, hemophilic status, and HCV disease severity. Thus, we are able to estimate the HCV stage distributions for the "unknown cohort" from the "known cohort". Specifically, we assigned all 4,530 patients in known cohort into 10 groups, and hemophilic individuals into 8 groups (waves) according to their time sequence of claims. The distributions of age (less than 40 and 40+), sex, hemophilic status, and compensation levels were calculated. Six level-specific regression models were fitted using the proportion of claimants within a given level as a dependent variable and the proportions of age, sex, and hemophilia as independent variables. These models were further weighted by the numbers of patients in each wave. We subsequently estimate that all remaining patients would come forward in a seventh wave. Table 9.1-1 displays the estimated level distributions using this approach. Using a similar method, adjusted fibrosis distributions were also calculated for non-hemophilic and hemophilic groups respectively (tables 9.1-2 and 9.1-3).

The results show that most prospective claimants would be in compensation levels 1 to 3, and that 2/3 of patients would be in stages prior to F2 as of August 2004. Different HCV stage

distributions are expected between people with and without hemophilia. In general, hemophilic patients are more likely to have advanced fibrosis, though, paradoxically, decompensated liver disease, HCC, and transplant are slightly less common among hemophilics. Since the current projection was based on a much larger sample size than that in 2002, the results are expected to be somewhat more accurate.

9.2 Approach 2: True target population distribution method

This method assumes that the *predicted* HCV stage distributions (text section 7 and table 7.1) reflect the true distributions for the overall infected cohort (known + unknown). The *predicted* stage distributions, as indicated in section 7, are the distributions, as of August 2004, that our prognostic model predicts under the following assumptions: a) The number and timing of HCV infections between 1986-1990 are correctly predicted using the estimates of Remis et. al., which were based on the number of transfusions during that period, and the estimated per-unit risk of transfusion; b) our stage-transition probabilities, derived from the literature, are approximately correct.

The discrepancies between the *predicted* distribution and the *observed* distribution among compensation claimants for the known cohort are assumed to be entirely accounted for by the fact that the known cohort is a biased sample of the overall cohort. Thus, theoretically, the true HCV stage distributions could be restored when the “known cohort” and “unknown cohort” are combined. Similarly, given the distributions for the overall HCV victims and known cohort, the HCV stage distributions for the unknown cohort can be derived.

Using this method, the following steps are used to estimate the HCV stage distributions for the unknown cohort.

- (1) Estimate the total number of patients (known + unknown) in each stage as of August 2004 by multiplying the predicted stage distribution by the total number of HCV infected patients who are currently alive. This yields the total number of patients within each stage.
- (2) Calculate the difference between the predicted numbers of the alive patients and the observed numbers of the alive patients by stage. The residual for each stage is the number of unknown patients in that stage. The sum of the differences over the stages is the total number of patients in the unknown cohort.
- (3) Repeat these calculations for a variety of estimates of the total number of unknown patients.

As the observed number of patients with HCC and transplant are much higher than predicted, we adjusted the observed number downward to the predicted level. Based on the natural history of HCV, we believe this adjustment is necessary to reflect the fact that some patients became infected by HCV before 1986.

Table 9.1-4 was adapted from the 2002 report of Remis et. al. According to Remis's report, approximately 9,000 HCV patients who were infected by HCV through blood products during 1986-1990 were still alive in 2002. Table 9.1-4 also provides our estimates for the unknown cohort in terms of HCV stage distribution. In comparison with approach 1, these results suggest

that many more individuals would be in stages F1-F3, and fewer in both earlier (eg. RNA+) and later (eg. F4, decompensation) stages.

9.3 Comment

Which of these approaches is more likely to yield a reliable estimate? First, it should be noted that the second approach cannot be used to estimate the stage distribution of hemophilics who are yet to come forward. We do not know when hemophilic patients became initially infected, but for most, infection likely predated the 1986-1990 period during which non-hemophilics were infected. Thus, predictions based on transfusion practice during that period (approach 2) are not useful as a guide to hemophilic patients. The first approach generates our only usable estimate for hemophilics.

With respect to non-hemophilic patients, the situation is less straightforward. On the one hand, we strongly suspect that patients who have presented for compensation to date are an unrepresentative sample of the entire post-transfusion cohort. Thus, simply extrapolating from current trends may lead us astray in attempting to discern the true disease status of those who have come not yet come forward.

On the other hand, approach 1 is based on *real* data from compensation claimants, whereas the estimates of total numbers of patients infected and their current stage distribution (approach 2) are somewhat more *speculative*, based on theoretical numbers of infected patients and literature-derived estimates of the rate of disease progression. Further, estimates of stage distribution appear to be quite stable across waves (Tables 9.1-2 to 9.1-3).

In general, we would suggest using the most conservative approach, i.e. the approach which is most likely to ensure the sufficiency of the compensation fund. In this case, it is not clear which is the more conservative option. Approach 1 has more individuals in the very early (RNA+) and very late (F4, decompensation etc.) stages, whereas approach 2 has more individuals in intermediate stages (F1-F3). Thus, a decision must be made on grounds other than conservatism.

It is our belief that the stage distribution of claimants who have already presented (approach 1) is likely to be quite similar to those who will present in the future. We also believe that it is quite likely that not all claimants will come forward. Thus, the most realistic estimate of the stage distribution of those who will ultimately come forward is probably given by approach 1.

However, a “conservative” approach would be to run the actuarial model using both sets of estimates for stage distribution and use the estimate that results in the greatest fund liability.

10. Discussion

This study reports updated and revised estimates of the natural history of transfusion acquired HCV infection. Building on our previous work, this revision incorporates a more contemporary biological understanding of HCV prognosis. Fibrosis stage and transition rates between fibrosis stages are the key elements of the prognostic Markov model, as implemented in the Markov health states that represent fibrosis stages (F0, F1, F2, F3, F4). The literature expressing HCV prognosis by fibrosis stage, both longitudinal and cross-sectional, was systematically reviewed

and the data abstracted in order to estimate revised and updated transition probabilities between fibrosis stages.

Another key element of this second revision of the post-transfusion HCV prognostic model is the incorporation of virtually complete clinical and demographic data describing characteristics and outcomes of claimants for compensation. In this report, we describe characteristics of 4530 individuals whose claims for compensation had been approved as of August 2004. Close to two thirds (62.4%) of claimants were male, and 21.4% of claims were from the estates of deceased individuals. More than a quarter of claimants (1236/4530) were hemophiliacs, of whom 40.5% were HIV positive. Eighty percent of claimants were compensated at level III or below. Only 17% had received prior drug therapy. Only 21% (no change from last time) of living patients had received a liver biopsy, which made the estimation of true clinical stage distribution very difficult.

Data from the new literature review and from the previous models were used to estimate most prognostic variables, including fibrosis transition rates, treatment efficacy, and the effect of hemophilia and HIV status on prognosis. Fibrosis state-transition probabilities were also developed from the compensation data, and were incorporated into the pooled data from which the baseline model's state transition probabilities were estimated. Data from the compensation cohort was used to estimate age, gender, and stage distribution of claimants, as well as the proportions of individuals with hemophilia and HIV.

Although this model offers a variety of projections, we believe that the most reliable predictions of long-term prognosis are represented in Tables 8.1-1 through 8.1-19. The model predicts that 33% of non-hemophilic patients alive in 2004 will ultimately develop cirrhosis, and 17% will ultimately die of liver disease. Because hemophilic patients are younger, and are frequently co-infected with HIV, they will have higher cumulative rates of cirrhosis and HCV death (46% and 27% respectively). Compared with the results in the 2002 revision, the long term projections for cumulative proportions of cirrhosis and liver related deaths presented in this report are substantially lower for both non-hemophilic and hemophilic patients. Since the current projections were based a more complete claim cohort and updated parameters, the more projections are likely to be somewhat more valid than previous projections.

Why do the projections of the 2004, 2002, and 1998 models differ? Although both the structure and many of the parameters have changed with each iteration of the model, the major differences have to do with the transition probabilities estimating the rate of developing liver cirrhosis. In our first model, we decided to exclude all non-cohort studies, i.e. all studies in which an inception cohort was not identified. In addition, we could not use any studies in which outcomes were represented as fibrosis stages. The first revision of the model (2002) included these studies. Also, by consensus of the members of the study team, all HCV prognostic studies were pooled. This resulted in a substantial worsening of the predicted prognosis of HCV-infected individuals. This judgment was reached because of the concern that the very small number of true prognostic studies were unrepresentative by age and gender, and we were unable to easily adjust for those factors in estimation of stage-specific transition probabilities using the Markov maximum likelihood method. In addition, we reasoned that an error in the direction of overestimating

progression rates was likely to have less serious consequences for the purpose of this project, as ensuring the viability of the compensation fund was a high priority. Finally, the third iteration of the model maintains the same rationale and pooled all cohort and non-cohort data. In addition, we pooled the data from the compensation cohort, as we believed that the sample now included a more complete representation of the entire compensation cohort, and the derived transition rates between stages were more similar to those derived from published studies, decreasing our concern about the possibility of serious selection bias.

This version of the model has unique strengths, and may represent the state of art in estimating HCV prognosis. Key strengths are incorporation of actual data to estimate stage distribution, separate estimates for hemophilic and non-hemophilic patients, estimates of overall model uncertainty generated by Monte Carlo simulation, the direct estimation of current practice patterns among Canadian hepatologists, and the use of complementary prognostic data to qualitatively estimate the overall model uncertainty attributable to study selection.

However, this model also has a number of potential biases and limitations.

Bias 1: We include non-cohort studies in estimation of stage-specific transition rates.

Net Effect: Potential (small-moderate) upward bias in fibrosis transition rates, and possible overestimation of the rate at which cirrhosis develops.

Bias 2: We include compensation cohort data in estimation of stage-specific transition rates.

Net Effect: Potential (small) upward bias in fibrosis transition rates, and possible overestimation of the rate at which cirrhosis develops.

Bias 3: We use a single transition rate between fibrosis stages. Because more rapidly progressing individuals exit disease states at a more rapid rate, state transition rates may fall in the very long term.

Net Effect: Potential (very small) upward bias in fibrosis transition rates, and possible overestimation of the rate at which cirrhosis develops.

Bias 4: We assume that no regression between stages occurs, and that progression continues at 10% of the baseline rate in treated individuals who achieve a sustained virological response.

Net Effect: Potential (small) upward bias in fibrosis transition rates, and possible overestimation of the rate at which cirrhosis develops.

Limitation 1: One key limitation, probably the very most significant limitation, is that the size of the compensation cohort remains unknown. We believe that, as of 2004/2005 most claimants have come forward, but some uncertainty remains regarding the final size of the claimant cohort.

Limitation 2: Another key limitation is the lack of liver biopsy data for many compensation recipients. A number of fairly strong assumptions were required in order to derive reasonably plausible estimates of the true stage distribution. We assumed, for example, that the stage distribution among biopsied and non-biopsied patients is the same, even though this is unlikely

to be true, as patients who were biopsied are more likely to have advanced liver disease. However, we believe that incorporating this assumption to estimate the “adjusted” stage distribution results in less bias than using the unadjusted data, which would incorporate the implicit assumption that all patients without a liver biopsy have no liver fibrosis.

Limitation 3: A third potential limitation is the assumption that transfusion-acquired hepatitis C has the same prognosis as community-acquired hepatitis C. Some current evidence suggests that transfusion-acquired hepatitis C has a less favorable prognosis overall. However, the current state of evidence does not allow us to know whether the prognosis of these two groups differ (see section 4.3-8 above).

Limitation 4: Finally, we were not able to fully adjust for prognostic factors such as alcohol intake and age at which HCV infection was acquired. Most studies did not include detailed clinical information about these prognostic factors. Our inability to adjust does not imply that these factors are not taken into account in our prognostic model. Rather, there is the possibility of prognostic error only to the extent to which prognostic factors differ between the studies and the compensation cohort. For example, if the compensation cohort drinks significantly more alcohol than individuals in the natural history studies (on which the prognostic model is based), we may underestimate the rate at which fibrosis progression occurs. In our view, however, the error attributable to inability to adjust for differences in prognostic factors is relatively small in comparison to the overall prognostic error in the model.

Future studies will be useful in updating and revising model projections. Analysis of the full dataset will make it possible to more accurately estimate the stage distribution of compensation claimants, and potentially, to estimate patient-derived transition probabilities. Comparison of accepted and rejected claims will be useful in estimating the clinical and demographic characteristics of transfusion-acquired and non-transfusion-acquired HCV infection, and provide some information on the generalizability of our model's projections to HCV infected patients as a whole. Finally, this cohort provides an invaluable resource to study the natural history and resource utilization of HCV infected patients in future studies.

11. Tables

Table 4.1 Seroconversion From HCV RNA+ to RNA-: Literature Review

Author	Cohort	Sample size	Years of follow-up	Viral clearance	Chronic-ally infected*	Cleared	Rate in chronic period	Estimated person- yrs	Annual rate
Villano(22)	acute	34	6	6 (18%)	29	1	0.0300	174	0.006
Vogt(4)	acute	67	19.8	30 (45%)	57	20	0.3500	1129	0.018
Mattsson(3)	acute	24	13	8 (33%)	20	4	0.2000	260	0.015
Kenny-Walsh(17)	acute	704	17	314 (45%)	563	173		9571	0.018
Wiese(24)	acute	917	20	412 (45%)	734	229	0.3120	14680	0.016
Barrera(19)	acute	41	6	5 at 6 wks 5 at 6 yrs (24%)	36	5	0.1400	216	0.023
Alter MJ(18)	Chronic		3.75		25	1		94	0.011
Thomas DL(21)	Chronic		8.8		919	90		8087	0.011
Seeff LB(26)	Chronic		25		129		0.23	3225	0.01
Krahn M (76) **	Chronic		17		1935	138		32895	0.0042

Weighted annual rate=0.0067

Rate range used by Salomon JA :0-0.01

*Assuming that virus was cleared in 15% of patients during the acute period and the further clearance will happen during the chronic period.

**Based on 1935 claims with both transfusion date and RNA test available.

Table 4.2-1 Fibrosis Stage Transition Probabilities, Published Non-Cohort Studies

Authors	Fibrosis progression info:	Staging /year				Sample size (with biopsy)	Method Of estimation
		F0→F1	F1→F2	F2→F3	F3→F4		
Poynard et al.(15)	median rate =0.133	0.133	0.133	0.133	0.133	2235	Indirect
Matsumura et al.(47)	F0→F1: 0.11	0.11				118	Indirect
	F0→F2: 0.12	0.12	0.12			84	
	F0→F3: 0.16	0.16	0.16	0.16		18	
	F0→F4: 0.15	0.15	0.15	0.15	0.15	19	
Mathurin et al.(44)	mean rate=0.07 (Norm. ALT)	0.07	0.07	0.07	0.07	102	
	mean rate= 0.15 (High ALT)	0.15	0.15	0.15	0.15	102	
Sobesky et al.(27)	mean rate =0.133			0.133	0.133	86	Direct
Wali M. Et al.(28)	mean rate=0.15		0.15	0.15	0.15	46	Direct
Yano M. et al.(29)	F1→F4: 29.6% in 13 yrs.		0.147	0.147	0.147	27	Derived †
	F2→F4: 42.9% in 10 yrs			0.145	0.145	28	
	F3→F4: 100% in 10yrs				0.195	15	
Weighted mean rate*		0.129	0.131	0.132	0.134		
Probability (1-exp(-rate))		0.121	0.123	0.124	0.125		

* weight=n (77)/ sum(n (77))

† see section 3.3 of the report for details.

Table 4.2-2 Fibrosis Stage Transition Probabilities, Non-Cohort Studies, “Markov Maximum Likelihood” Technique

Author	Selected features of the study	Sample size	Reported Mean Probability	Derived transition probability			
				F0 to F1	F1 to F2	F2 to F3	F3 to F4
Poynard (15)	OBSVIRC	1138 (11yr)		0.155	0.121	0.249	0.252
	DOSVIRC	607 (14yr)		0.183	0.099	0.150	0.258
	Pooled	1745	0.12.5	0.161	0.114	0.207	0.255
Matsumura (47)		239 (23yr)	0.10-0.15	0.095	0.049	0.042	0.139
Mathurin (44)	ALT normal	65 (15yr)	0.07	0.076	0.030	0.076	0.430
	ALT elevated	101 (14yr)	0.14	0.183	0.099	0.086	0.238
	Pooled	166		0.124	0.079	0.092	0.268
Zarski (32) (F4 excluded)*	French: F0=41.9;F1=36.4; F2=14.0;F3=7.8%	129 (11.5ys)	0.036	0.076	0.087	0.164	0.164
	American F0=25.5;F1=33.3; F2=26.6;F3=15.7%	51 (20.4ys)	0.067	0.074	0.086	0.097	0.095
Ryder (30)	Approx. rates** (F0, F1,F2,F3,F4) = 60.7,29.4,6.1,1.4, and 2.3%	214 (18.9ys)	Approximate: 0.027	0.026	0.029	0.079	0.255
Ghany (31)	Stage Rates** (F0, F1,F2,F3,F4)= 17.1,35.0,22.8,13.8,8.9%	123 (14ys)	0.44*4/6=0.29 approximate: 0.113	0.126	0.106	0.143	0.154
Weighted mean				0.127	0.091	0.154	0.226

*: To estimate the transition rates, assumed there are 5% and 10% of patients with F4 have been excluded from the cohort.

** : The reported Ishak stage score was converted into METAVIR scale: Ishak 0 Metavir 0; Ishak 1,2 Metavir 1;Ishak 3 Metavir 2; Ishak 4 Metavir 3; Ishak 5,6 Metavir 4.

Table 4.2-3 Fibrosis Stage Transition Probabilities, Prospective Cohort Studies, “Markov Maximum Likelihood Technique”

Authors	Study Population	Duration of follow-up	Sample size (n)	Fibrosis Stage Distribution	Stage specific transition probabilities derived from Markov Maximum Likelihood [¶]			
					Staging /year F0→F1	F1→F2	F2→F3	F3→F4
Kenny-Walsh (17)	Healthy Women	17 years	363	Proportions: F0: 49%, F1: 34% F2: 10%, F3: 5% F4: 2	0.050 [†] (0.041)	0.058 (0.047)	0.130 (0.103)	0.113 (0.09)
Wiese et al. (24)	Healthy Women	20 years	264	Proportions: F0: 49.6%, F1: 34.8%, F2: 12.5% , F3: 1.3%, F4: 1.8%	0.042 (0.034)	0.051 (0.042)	0.062 (0.05)	0.14 (0.11)
Weighted mean rate*					0.047	0.055	0.101	0.124
Weighted mean transition probability (=1-exp(-rate))					0.046	0.054	0.096	0.117

* Weight= $\frac{n \{I\}}{\sum(n \{I\})}$

[†] Adjusted for gender and age using data from Poynard, Table 4.3-2)

[¶] See section 3.3 for details

Table 4.2-4 Summary Transition Probabilities, Literature and Post-transfusion Cohort for 2004 Model

Data source	Staging /year F0→F1	F1→F2	F2→F3	F3→F4
Retrospective (Clinical patients)	0.127	0.091	0.154	0.226
Cohort (healthy people)	0.046	0.054	0.096	0.117
1986-1990 transfusion cohort	0.041	0.088	0.327	0.384
Mean	0.071	0.078	0.192	0.242

Annual progression rates for chronic hepatitis C virus infection by age and gender
(By Salomon et al.)

Age (years)	Males	Females
<20	0.00-0.05	0.00-0.04
20-29	0.00-0.10	0.00-0.08
30-49	0.03-0.15	0.01-0.12
50-59	0.05-0.20	0.01-0.16
60-69	0.10-0.40	0.02-0.32
>=70	0.20-0.50	0.04-0.40

Table 4.3-1-1 Effectiveness of Pegylated Interferon Therapy

	Authors and Year	Study design and Sample size Patients characteristics	Genotype	Modality	Treatment and follow-up Duration	Sustained response rate (RNA)
Mainly North America based studies	Heathcote,,(78) 2000	RCT N=87 of 271 F3-F4	1=53% 2/3=46%	Peginterferon alfa-2a No ribavirin	180 µg 48 wks	At 72 weeks: 30%
	Lindsay (34), 2001	RCT N=297 of 1,219 F1-F4	1=67% 2/3=28%	Peginterferon alfa-2b No ribavirin	1.0 µg /kg 48 wks	At 48 weeks: 41% At 72 weeks: 25%
	Chung (79), 2004	RCT N=66 of 133 F1-F4	1=68%	Peginterferon alfa-2a plus ribavirin	180 µg 24 wks	At 24 weeks: 44% Geno 1 33% Non-genoype-1 80%
	Reddy (80), 2001	RCT N=159 F1-F4	1=74% Non-I=24%	Peginterferon alfa-2a No ribavirin	180 µg 48 wks	At 72 Weeks 36%
	Torriani (81)	RCT N=868 HIV-HCV co-infection	1=61% Non-1=38%	Peginterferon alfa-2b + ribavirin	180 µg 48 wks	At 72 Weeks 40% Genotype-1=29 Genotype-1 2/3=62
	Fried (82), 2002	RCT N=1121	1=65% Non-I=34%	Peginterferon alfa-2a plus ribavirin	180 µg 48 wks	At 72 Weeks 56% Genoypte-1=41

	Sulkowski(83), 2002	RCT N=20 F1-F4		Peginterferon alfa-2a plus ribavirin	180 µg 24 wks	At 48 weeks 50%
	Jeffers(84), 2004	RCT N=106 (78 blacks) F0-F4	Genotype I only study	Peginterferon alfa-2a plus ribavirin	180 µg	26 in African-Americans 39 in Caucasians
International study	Zeuzem(85)	RCT 223 of 531 F1-F4	1=63 2/3=34	Peginterferon alfa-2a No ribavirin	180 µg 48 wks	At 48 weeks 69% At 72 weeks 39%
	Manns(86), 2001	RCT N=511 of 1530	1=68% 2/3=29%	Peginterferon alfa-2b + ribavirin	1.5 µg/kg for 48 wks	At 48 weeks 65% At 72 weeks 54%
	Pockros(87), 2004	RCT N=210 of 639 F1-F4	1=67% 2/3=32%	Peginterferon alfa-2a No ribavirin	180 µg 48 wks	At 72 weeks 28%
	August-Jorg(88)	RCT N=18 of 37 F1-F4 monotherapy relapsers	1=24% Non-I=76%	Peginterferon alfa-2a plus ribavirin	180 µg 48 wks	At 72 weeks: 72%
	Hadziyannis (89), 2004	RCT N=1311 F1-F4	I=58 Non-I=42	Peginterferon alfa-2a plus ribavirin	180 µg 48 wks	At 48 weeks: Genotype-1=63%
	Bosques-Padilla(90), 2003	RCT N=14 of 32 F1-F4		Peginterferon alfa-2a plus ribavirin	180 µg 48 wks	At 72 weeks 50%
	Shiffman(91), 2004	Non-RCT N=604 F3-F4 non-responder to monotherapy	I=89% Non-I=10%	Peginterferon alfa-2a plus ribavirin	180 µg 48 wks	At 72 weeks 18%

Table 4.3-1-2 Effectiveness of Peginterferon therapy – seven studies used for Meta analysis

Authors and Year	Study design and Sample size Patients characteristics	Modality	Treatment and follow-up Duration	Sustained response rate (RNA)
Torriani(81)	RCT N=289 of 868 HIV-HCV co-infection	Peginterferon alfa-2b + ribavirin	180 µg 48 wks	At 72 Weeks 40% Genotype-1=29 Genotype-1 2/3=62
Fried (82), 2002	RCT N=453 of 1121	Peginterferon alfa-2a plus ribavirin	180 µg 48 wks	At 72 Weeks 56% Genoypte-1=41
Manns(86), 2001	RCT N=511 of 1530	Peginterferon alfa-2b + ribavirin	1.5 µg for 48 wks	At 48 weeks 65% At 72 weeks 54%
August-Jorg(88)	RCT N=18 of 37 F1-F4 monotherapy relapsers	Peginterferon alfa-2a plus ribavirin	180 µg 48 wks	At 72 weeks: 72%
Hadziyannis (89), 2004	RCT N= 400 of 1311 F1-F4	Peginterferon alfa-2a plus ribavirin	180 µg 48 wks	At 48 weeks: Genotype-1=63%
Bosques-Padilla(90), 2003	RCT N=14 of 32 F1-F4	Peginterferon alfa-2a plus ribavirin	180 µg 48 wks	At 72 weeks 50%

Table 4.3-2 Hepatologists reported proportion of patients with hepatitis C receiving interferon/ ribavirin combination in their clinical practice

N=38

Percentage	Median	Mean	Range	
	(95% CI)	(95% CI)	Min.	Max.
1. What % of all patients are not eligible because of co-existing conditions (eg. Depression, heart disease, continuing alcohol and drug abuse).	25.0 (20.0, 32.5)	30.1 (24.3, 35.9)	5	75
2. Overall, what % of all patients with hepatitis C do you treat?	40.0 (33.0, 50.2)	43.6 (37.5, 49.7)	10	85
3. What % of patients with normal enzymes do you treat?	1.5 (0.0, 5.0)	6.0 (2.9, 9.1)	0	45
4. What % of patients with mild hepatitis/nonfibrosis do you treat?	13.8 (10.0, 30.0)	28.7 (19.2, 38.2)	0	100
5. What % of patients with moderate-severe hepatitis with fibrosis do you treat?	80.0 (75.0, 95.0)	76.7 (68.6, 84.8)	12.5	100
6. What % of patients with well compensated cirrhosis do you treat?	75.0 (50.0, 90.0)	62.0 (49.9, 74.1)	0	100
7. What % of patients with decompensated cirrhosis do you treat?	0.0 (0.0, 0.0)	3.8 (0.4, 7.2)	0	50

* from: Wang P, Yi Q, Scully L, Heathcote J, Krahn M. Indications for interferon/ribavirin therapy in hepatitis C patients: findings from a survey of Canadian hepatologists. Can J Gastroenterol 2003;17(3):183-6.

Table 4.3-3 Risk Factors for Progression of Liver Fibrosis

Variable	Category	Relative Risk of Progression	Transition path	Sample size	Source
Age	>=40/<40	1.5	all		Poynard (15)
Sex	Male/Female	1.39	all		Poynard (15)
Alcohol	1-49g/non	1.14			Poynard (15)
	>=50g/non	1.34			
HIV co-infection	Yes/No	3.74	F4 to ESLD	157	Ragni (53)
	Yes/No	1.44	F0 to F4	244	Benhamou (37)
	Yes/No	7.0	F0 to Liver-related Death	310	Yee (92)
ALT	>=50/<=45	2.10	All paths	204	Mathurin (44)

Table 4.3-4-1 Hemophilia and HIV: Effects on Progression of Liver Disease in HCV Infected Patients

Authors	HIV negative hemophilics			HIV positive hemophilics		
	Liver related death (annual rate)	ESLD /Liver Decom. & death (annual rate)	Fibrosis progression rate (METAVIR units/ year)	Liver related death (annual rate)	ESLD /Liver Decom. & death (annual rate)	Progression rate Of Fibrosis (METAVIR units/ year)
Darby et al. (54)	0.0009¶ (25 Years:2.2%)‡			0.007 (25 Years:17.1%)		
Yee et al. (92)	0.0023 (13.3years:3.0%)			0.006 (13.3 year: 8.0%)		
Ragni et al. (53)		0.0043 (24 years: 9.7%)			0.007 (20 year: 12.9%)	
Telfer et al. (55)		0.0057 (20 years:10.8%)*				
Benhamou et al (37)			0.106			0.153
Krahn et al. (1)	0.0021 (20years:4.2%)	0.0050 (20 years:9.6%)				

* May include some patients with HIV.

† Rate Ratio of the progression (HIV+/HIV-)=1.44.

¶ Annual rate

‡ Cumulative rate

Table 4.3-4-2. Relative Risk of Death in Hemophilic Patients With and Without HIV Infection

Author and Year	Sample size	Person years	Event	Death (%)	Mean follow-up (years)	Relative Risk (RR)
Ragni M. (53)	157	3768	All Cause	52.8	24	3.8
Yee T. (92)	310	4123	Non-liver	20.0	13.3	7.1
Soucie J. (51)	2950	7670	All Cause	8.0	2.6	4.7
Darby S. (54)	4865	72975	Non liver	20.6	15+-	4.6
Pooled RR=4.7						

Table 4.4-1 Development of HCC in HCV Patients With Cirrhosis

Author (year)	Sample size	event	Event rate (%)	Mean follow-up (years)	Person years	Annual rate
Fattovich (67)	384	29	7.6	5	1920	0.015
Niederau (64)	141	13	9.2	4	588	0.022
Serfaty (65)	103	11	10.7	3	343	0.032
Degos (93)	416	60	14.7	5	2080	0.029
del Olmo (69)	967	64	6.6	5	3048	0.021
Pooled rate*						0.021

* Weight is the reciprocal of the variance.

Table 4.5-1 Excess Mortality Post- transfusion: Rate Ratios Comparing Post-transfusion All-cause Mortality to General Population Mortality, by Age Group and Years Elapsed Since Transfusion

		Age group specific Mortality ratio					
		Male			Female		
Years after transfusion		<40	40-64	65-	<40	40-64	65-
Proportion		0.0971	0.1372	0.2116	0.1044	0.1891	0.2607
--1		46.178	25.890	5.694	108.267	46.995	9.754
1--2		46.699	3.771	2.464	106.371	6.866	4.138
2--10		1.018	1.920	1.620	2.072	3.481	2.527
10--		1.000	1.000	1.000	1.000	1.000	1.000

* Note: excess mortality estimates derived from Vamvakas et. al. (8, 9)

Table 4.5-2 Other Parameters Used in the Prediction Model

Age and sex-related mortality, 1992 (used only for validation, not projection)

AGE	Female	Male	AGE	Female	Male
0	0.00593	0.00707	50	0.0027	0.00452
1	0.00041	0.00054	51	0.00294	0.00497
2	0.00029	0.00041	52	0.0032	0.00555
3	0.00022	0.00032	53	0.00353	0.00621
4	0.0002	0.00027	54	0.00391	0.00686
5	0.0002	0.00025	55	0.00432	0.00753
6	0.00019	0.00022	56	0.00478	0.00835
7	0.00016	0.00018	57	0.00526	0.0093
8	0.00014	0.00017	58	0.00578	0.01038
9	0.00013	0.00017	59	0.00634	0.01152
10	0.00013	0.00018	60	0.00692	0.01276
11	0.00014	0.0002	61	0.00756	0.01422
12	0.00015	0.00024	62	0.00826	0.01581
13	0.00018	0.0003	63	0.00902	0.01747
14	0.00023	0.00038	64	0.00988	0.0192
15	0.0003	0.00053	65	0.01089	0.02105
16	0.00038	0.00074	66	0.01204	0.023
17	0.00041	0.00098	67	0.01328	0.02511
18	0.00041	0.0012	68	0.01456	0.02735
19	0.00039	0.00135	69	0.01592	0.02975
20	0.00038	0.00139	70	0.01737	0.03225
21	0.00037	0.00132	71	0.01895	0.03514
22	0.00036	0.00125	72	0.02082	0.03876
23	0.00037	0.00121	73	0.02305	0.04307
24	0.00038	0.0012	74	0.0256	0.04776
25	0.0004	0.00122	75	0.02848	0.05248
26	0.00042	0.00126	76	0.03166	0.05723
27	0.00046	0.00128	77	0.03515	0.06224
28	0.0005	0.00128	78	0.03901	0.06756
29	0.00052	0.00129	79	0.04323	0.07343
30	0.00053	0.0013	80	0.04779	0.08016
31	0.00054	0.00132	81	0.05299	0.088
32	0.00054	0.00136	82	0.05908	0.09693
33	0.00055	0.00141	83	0.06608	0.10659
34	0.00061	0.00148	84	0.07383	0.11657
35	0.00069	0.00152	85	0.08224	0.12679
36	0.00074	0.00152	86	0.09134	0.13748
37	0.00078	0.00158	87	0.1014	0.14883
38	0.00086	0.0017	88	0.11285	0.16078
39	0.00098	0.0018	89	0.12603	0.17305
40	0.0011	0.00189	90	0.14078	0.18513
41	0.00119	0.00199	91	0.15625	0.1967
42	0.00126	0.00214	92	0.17164	0.20775
43	0.00136	0.00231	93	0.18639	0.21843
44	0.00147	0.00254	94	0.20015	0.22877
45	0.0016	0.00284	95	0.21287	0.23869
46	0.00179	0.00315	96	0.2246	0.24783
47	0.00204	0.00348	97	0.23545	0.2558
48	0.00229	0.00385	98	0.24561	0.26246
49	0.00251	0.00419	99	0.2551	0.26783

Age distribution of the infected, as estimated from the per-unit transfusion risk

0-	0.0176
5-	0.0107
10-	0.0192
15-	0.0254
20-	0.0322
25-	0.0403
30-	0.0268
35-	0.0292
40-	0.0391
45-	0.0481
50-	0.0644
55-	0.0754
60-	0.0993
65-	0.176
70-	0.1199
75-	0.0924
80-	0.0693
85-	0.0079
90-	0.0068

3) Distribution of year of Exposure

Year	%
1986	0.287
1987	0.247
1988	0.218
1989	0.194
1990	0.054

4) Gender distribution

Sex	%
Male	44.59
Female	55.41

Age and sex-related mortality, 1997 data, used for future projections

AGE	Female	Male	AGE	Female	Male	Age	Female	Male
0	0.00512	0.00620	50	0.00250	0.00408	100	0.32339	0.39215
1	0.00040	0.00043	51	0.00274	0.00453	101	0.34639	0.41712
2	0.00024	0.00032	52	0.00303	0.00503	102	0.37002	0.44281
3	0.00023	0.00026	53	0.00335	0.00555	103	0.3942	0.46916
4	0.00021	0.00021	54	0.00371	0.00610	104	0.41885	0.49612
5	0.00018	0.00017	55	0.00410	0.00670	105	0.44388	0.52362
6	0.00014	0.00014	56	0.00453	0.00739	106	0.4692	0.55159
7	0.00010	0.00012	57	0.00498	0.00818	107	0.49471	0.57996
8	0.00010	0.00010	58	0.00543	0.00906	108	0.52032	0.60865
9	0.00010	0.00010	59	0.00590	0.01001	109	0.54592	0.63757
10	0.00011	0.00012	60	0.00641	0.01105			
11	0.00011	0.00013	61	0.00699	0.01224			
12	0.00015	0.00020	62	0.00767	0.01359			
13	0.00019	0.00029	63	0.00843	0.01508			
14	0.00023	0.00041	64	0.00926	0.01671			
15	0.00027	0.00054	65	0.01018	0.01848			
16	0.00031	0.00067	66	0.01121	0.02044			
17	0.00034	0.00077	67	0.01235	0.02259			
18	0.00035	0.00085	68	0.01356	0.02490			
19	0.00034	0.00091	69	0.01483	0.02735			
20	0.00033	0.00096	70	0.01623	0.03000			
21	0.00032	0.00099	71	0.01785	0.03295			
22	0.00032	0.00102	72	0.01979	0.03626			
23	0.00033	0.00103	73	0.02196	0.03984			
24	0.00034	0.00102	74	0.02429	0.04364			
25	0.00035	0.00100	75	0.02693	0.04781			
26	0.00036	0.00099	76	0.02997	0.05248			
27	0.00038	0.00099	77	0.03354	0.05779			
28	0.00040	0.00102	78	0.03754	0.06370			
29	0.00042	0.00107	79	0.04188	0.07011			
30	0.00044	0.00112	80	0.04672	0.07710			
31	0.00047	0.00118	81	0.05223	0.08474			
32	0.00051	0.00124	82	0.05857	0.09313			
33	0.00054	0.00130	83	0.06560	0.10224			
34	0.00058	0.00135	84	0.07324	0.11203			
35	0.00063	0.00141	85	0.08165	0.12251			
36	0.00068	0.00148	86	0.09102	0.13370			
37	0.00075	0.00156	87	0.10153	0.14562			
38	0.00082	0.00166	88	0.11306	0.15827			
39	0.00091	0.00176	89	0.12548	0.17163			
40	0.00100	0.00187	90	0.13898	0.18572			
41	0.00110	0.00199	91	0.15374	0.20055			
42	0.00122	0.00213	92	0.16993	0.21616			
43	0.00133	0.00227	93	0.18511	0.24109			
44	0.00145	0.00240	94	0.20214	0.25994			
45	0.00158	0.00255	95	0.22012	0.27973			
46	0.00173	0.00274	96	0.23904	0.30045			
47	0.00190	0.00300	97	0.25887	0.32207			
48	0.00208	0.00331	98	0.27957	0.34459			
49	0.00228	0.00367	99	0.30110	0.36796			

Table 5.3-1 Baseline Clinical and Serological Features of Hepatitis C Claimants, 2004*

		Male (N=2827, 62.4%)		Female (N=1703: 37.6)		Total (N=4530)	
		N	%	N	%	N	%
Survival status at 2004	Alive	2090	73.9	1469	86.3	3559	78.6
	Deceased	737	26.1	234	13.7	971	21.4
Biopsy Evidence	Yes	588	20.8	391	23.0	979	21.6
	No	2239	79.2	1312	77.0	3551	78.4
Level of compensation	Level 1	388	15.7	349	21.1	737	17.8
	Level 2	900	36.4	666	40.2	1566	37.9
	Level 3	652	26.4	382	23.0	1034	25.0
	Level 4	118	4.8	88	5.3	206	5.0
	Level 5	191	7.7	91	5.5	282	6.8
	Level 6	225	9.1	82	5.0	307	7.4
	Missing	353		45		398	
HCV-Antibody Test (based on lvl1_fl)	Positive	2031	93.4	1298	92.5	3324	93.1
	Negative	143	6.6	105	7.5	248	6.9
	Unknown	653		305		958	
PCR RNA test (based lvl2_fl)	Positive	1542	93.1	968	93.3	2510	93.2
	Negative	114	6.9	70	6.7	184	6.8
	Unknown	1171		665		1836	
Drug therapy	No	2370	83.8	1411	82.9	3781	83.5
	Yes	457	16.2	292	17.2	749	16.5
HIV Positive, Missing=272	Yes	490	18.3	10	0.6	500	11.7
	No	2183	81.7	1575	99.4	3758	88.3
	missing	154		118		272	
Hemophilics	Yes	1096	38.8	140	8.2	1236	27.3
	No	1731	61.2	1563	91.8	3294	72.7
Blood transfusion	Yes	1713		1541		3255	
	No	1114		161		1275	
Age at first blood transfusion (3255 with transfusion, 1 missing age).	0-9	118	6.9	84	5.5	202	6.2
	10-19	90	6.3	105	6.8	195	6.0
	20-29	216	12.6	312	20.3	528	16.2
	30-39	267	15.6	329	21.4	596	18.3
	40-49	263	15.4	243	15.8	506	15.6
	50-59	325	19.0	196	12.7	521	16.0
	60-69	341	19.9	184	11.9	525	16.1
	70+	93	5.4	88	5.7	181	5.6
Year at first blood transfusion	Missing	1114	39.4	162	9.5	1276	
	<1986	225	13.1	266	17.3	491	15.1
	1986	333	19.4	298	19.3	631	19.4
	1987	346	20.2	300	19.5	646	19.9
	1988	335	19.6	276	17.9	611	18.9
	1989	632	19.9	291	18.9	632	19.4
	1990	244	7.8	111	7.2	244	7.5
	Missing	1114		161		1275	
No. of transfusions 1986-1990	1	543	31.7	487	31.6	1030	31.6
	2	433	25.3	461	29.9	894	27.5
	3	286	16.7	223	14.5	509	15.6
	4	174	10.2	139	9.0	313	9.6
	5	104	6.1	81	5.3	185	5.7
	5+	173	10.1	151	9.8	324	10.0

	Missing	1114	161	1275
Current age, mean(SD) (among alive)		50.7(18.8) (n=2090)	54.0(17.5) (n=1469)	52.0(18.3) (n=3559)

* Percentages were calculated based on available observations excluding missing and unknown categories.

Table 5.3-2 Baseline Clinical and Serological Features in Hepatitis C Claimants: Comparisons between Hemophilics and Non-hemophilics

		Total	Hemophilics N=1,236		non-hemophilics N=3294		Statistical test	
		N	N	%	N	%	Chi	P
Sex	Male	2827	1096	88.7	1731	52.6	499.9	<.0001
	Female	1703	140	11.3	1563	47.4		
Survival status at 2004	Alive	3559	902	73.0	2657	80.7	31.5	<.0001
	Deceased	971	334	27.0	637	19.3		
Biopsy Evidence	Yes	979	195	15.8	784	23.8	34.2	<.0001
	No	3551	1041	84.2	2510	76.2		
Level of compensation	Level 1	737	142	14.4	595	18.9	77.7	<.0001
	Level 2	1566	307	31.1	1259	40.0		
	Level 3	1034	339	34.4	695	22.1		
	Level 4	206	43	4.4	163	5.2		
	Level 5	282	86	8.7	196	6.2		
	Level 6	307	69	7.0	238	7.6		
	Missing	398	250		148			
HCV-Antibody Test (based on lvl1_fl)	Positive	3324	822	93.9	2502	92.8	1.4	0.236
	Negative	248	53	6.1	195	7.2		
	Missing	958	361		597			
PCR RNA test (based lvl2_fl)	Positive	2510	686	94.0	1824	92.9	1.0	0.314
	Negative	184	44	6.0	140	7.1		
	missing	1836	506		1330			
Drug therapy	No	3781	1018	82.4	2763	83.9	1.5	0.221
	Yes	749	218	17.6	531	16.1		
HIV Positive,	Yes	500	490	40.5	10	0.33	1350.4	<.0001
	No	3758	720	59.5	3038	99.67		
	missing	272	26		246			
Age at first blood transfusion	0-9	202			202	6.2		
	10-19	195			195	6.0		
	20-29	528			528	16.2		
	30-39	596			596	18.3		
	40-49	506			506	15.6		
	50-59	521			521	16.0		
	60-69	525			525	16.1		
	70+	181			181	5.6		
Year at first blood transfusion	Missing	1276	1236		40			
	<1986	491			491	15.1		
	1986	631			631	19.4		
	1987	646			646	19.9		
	1988	611			611	18.9		
	1989	632			632	19.4		
	1990	244			244	7.5		
	Missing	1275	1236		39			
No. of transfusions 1986-1990	1	1030			1030	31.6		
	2	894			894	27.5		
	3	509			509	15.6		
	4	313			313	9.6		
	5	185			185	5.7		
	5+	324			324	10.0		
	Missing	1275	1236		39			
HIV Positive (among alive: n=3559)	Yes	222	216	24.6	6	6.6		<.0001
	No	3129	664	75.4	2455	93.4		
	missing	218	22		196			
Sex (among alive: n=3559)	Male	2090	773	85.7	1317	49.6		<.0001
	Female	1469	129	14.3	1340	50.4		
Current age, Mean (SD) (among alive: n=3559)		52.0(18.4) (n=3559)		41.0(13.9) (n=902)		54.8(18.4) (n=2657)		<.0001

Table 5.3-3 Propensity Score Method for Estimating True Stage Distribution

A. Logistic model for propensity score

Parameter	Df	Estimate	SE	Chi-square	P-value
Intercept	1	-2.534	0.231	120.49	<.0001
age	1	-0.014	0.003	17.10	<.0001
gender (female)	1	0.136	0.054	6.28	0.0122
current comp:					
Level -1	1	-2.657	0.348	58.32	<.0001
-2	1	-2.663	0.257	107.43	<.0001
-3	1	1.945	0.149	170.11	<.0001
treat (yes)	1	0.210	0.108	3.80	0.0514
deceased (yes)	1	0.609	0.078	60.44	<.0001
hemo tran (yes)	1	-0.592	0.064	86.42	<.0001

B. Non-hemo patients.

Satge	Propensity 0 < score <0.4		Propensity 0.4<=score<0.6		Propensity 0.6<=score<=1		Adjusted	
	No-bio	With-Bio	No-bio	With-Bio	No-bio	With-Bio	N	%
RNA-	653	1	0	0	0	0	654	24.6
RNA+	829	4	2	0	0	0	776	29.2
F1	134	29	248	274	28	23	649	24.4
F2/3	0	2	0	9	0	140	293	11.0
F4	16		1	5	26	123	175	6.6
De F4	2	3	0	0	24	12	41	1.5
Transplant	2	0	0	0	19	0	21	0.8
HCC	1	0	0	2	4	11	18	0.7
Other liver disease	20	0	0	2	7	1	30	1.1
Total							2657	100

C. Hemo patients

Satge	Propensity 0 < score <0.4		Propensity 0.4<=score<0.6		Propensity 0.6<=score<=1		Adjusted	
	No-bio	With-Bio	No-bio	With-Bio	No-bio	With-Bio	N	%
RNA-	145	0	0	0	0	0	145	16.1
RNA+	249	0	0	0	0	0	225	24.9
F1	296	53	0	0	0	0	320	35.5
F2/3	0	2	0	28	0	15	69	7.6
F4	7	3	13	40	3	14	109	12.1
De F4	1	0	19	0	1	0	21	2.3
Transplant	0	0	3	0	0	0	3	0.3
HCC	0	0	2	1	1	0	4	0.4
Other liver disease	0	0	5	0	1	0	6	0.7
Total							902	100

Tables 5.4-1 – 5.4-3 Observed and Estimated Stage Distribution of Living Claimants, August 2004

Table 5.4.-1 (all patients);

		Observed:						Adjusted	
		Total	%	No Biopsy	%	%		N	%
						biopsy			
Survival status At 2004.6	Alive diseased	3559		2762		797			
		971		789		182			
Total		3559		2762		797		3559	100.0
	RNA-	799	22.5	798	28.9	1	0.1	799	22.5
	RNA+	1084	30.5	1080	39.1	4	0.5	1001	28.1
	F1	1085	30.5	706	25.6	379	47.6	969	27.2
	F2-3	196	5.5			196	24.6	362	10.2
	Cirrhosis	251	7.1	66	2.4	185	23.2	284	8.0
	Dec	62	1.7	47	1.7	15	1.9	62	1.7
	Liver T	24	0.7	24	0.9			24	0.7
	HCC	22	0.6	8	0.3	14	1.8	22	0.6
	Other	36	1.0	33	1.2	3	0.4	36	1.0

The adjustment was made for hemo and non-hemo separately, and overall adjustment was combined from both.

Table 5.4-2 (Non-hemophilic)

		Observed:						Adjusted	
		Total	%	No Biopsy	%	biopsy		N	%
Survival status At 2004.6	Alive diseased	2657 637		2016 494		641 143			
Total		2657	100	2016	100	641	100	2657	100
	RNA-	654	24.6	653	32.4	1	0.2	654	24.6
	RNA+	835	31.4	831	41.2	4	0.6	776	29.2
	F1	736	27.7	410	20.3	326	50.9	649	24.4
	F2-3	151	5.7			151	23.6	293	11.0
	Cirrhosis	171	6.4	43	2.1	128	20.0	175	6.6
	Dec	41	1.5	26	1.3	15	2.3	41	1.5
	Liver T	21	0.8	21	1.0			21	0.8
	HCC	18	0.7	5	0.2	13	2.0	18	0.7
	Other	30	1.1	27	1.3	3	0.5	30	1.1

Table 5.4-3 (hemophilic)

		Observed:						Adjusted		
		Total	%	No Biopsy	%	%		N	%	
						biopsy				
Survival status At 2004.6	Alive diseased	902		746		156				
		334		295		39				
Total		902	100	746	100	156	100	902	100	
	RNA-	145	16.1	145	19.4	.	.	145	16.1	
	RNA+	249	27.6	249	33.4	.	.	225	24.9	
	F1	349	38.7	296	39.7		53	34.0	320	35.5
	F2-3	45	5.0	.	.		45	28.8	69	7.6
	Cirrhosis	80	8.9	23	3.1		57	36.5	109	12.1
	Dec	21	2.3	21	2.8	.	.		21	2.3
	Liver T	3	0.3	3	0.4	.	.		3	0.3
	HCC	4	0.4	3	0.4		1	0.6	4	0.4
	Other	6	0.7	6	0.8	.	.		6	0.7

**Table 5.4-4 Adjusted HCV Stage Distribution (N & %) by Age Group for Alive Non-Hemophilic Patients
At the Time of Claim (Males and Females)**

	Age									
	<20 N=127	20+ N=85	30+ N=283	40+ N=569	50+ N=472	60+ N=421	70+ N=418	80+ N=239	90+ N=43	Total N=2657
RNA- ,N	32.0	16.0	75.0	144.0	92.0	95.0	111.0	70.0	19.0	654
%	25.2	18.8	26.5	25.3	19.5	22.6	26.6	29.3	44.2	
RNA+	51.2	31.1	68.7	146.4	120.5	102.7	137.7	96.7	21.0	776
%	40.3	36.6	24.3	25.7	25.5	24.4	32.9	40.5	48.9	
F1	27.8	25.2	107.7	170.4	125.5	100.2	61.3	31.2	1.0	649
%	21.9	29.7	38.1	29.9	26.6	23.8	14.7	13.0	2.3	
F2/F3	11.8	9.5	20.1	69.4	67.2	54.5	42.3	15.8	2.3	293
%	9.3	11.2	7.1	12.2	14.2	12.9	10.1	6.6	5.3	
Cirrhosis	0.2	3.1	5.4	22.9	44.7	39.6	42.6	15.4	1.1	175
%	0.2	3.7	1.9	4.0	9.5	9.4	10.2	6.4	2.5	
Decom Cirrhosis	1.0	0.0	0.0	2.0	8.0	14.0	12.0	4.0	0.0	41
%.	0.8	0.0	0.0	0.4	1.7	3.3	2.9	1.7	0.0	
Liver Transplant	1.0	0.0	1.0	4.0	6.0	4.0	4.0	1.0	0.0	21
%.	0.8	0.0	0.4	0.7	1.3	1.0	1.0	0.4	0.0	
HCC	0.0	0.0	1.0	1.0	4.0	4.0	3.0	5.0	0.0	18
%.	0.0	0.0	0.4	0.2	0.8	1.0	0.7	2.1	0.0	
other liver disease	2.0	0.0	4.0	9.0	4.0	7.0	4.0	0.0	0.0	30
%.	1.6	0.0	1.4	1.6	0.8	1.7	1.0	0.0	0.0	

Table 5.4-5 Adjusted HCV Stage Distribution (N & %) by Age Group for Alive Hemophilic Patients At the Time of Claim (Males and Females)

	Age									
	<20 N=10	20+ N=168	30+ N=256	40+ N=233	50+ N=131	60+ N=63	70+ N=32	80+ N=7	90+ N=2	Total N=902
RNA- ,N	3.0	47.0	35.0	28.0	13.0	7.0	10.0	1.0	1.0	145
%	30.0	28.0	13.7	12.0	9.9	11.1	31.3	14.3	50.0	
RNA+	2.7	44.5	62.2	55.8	27.5	15.3	13.1	2.8	0.9	224
%	27.3	26.5	24.3	23.9	21.0	24.3	41.1	40.2	47.3	
F1	3.7	51.6	94.8	90.5	52.8	21.0	5.0	0.8	0.0	320
%	36.8	30.7	37.0	38.8	40.3	33.3	15.5	11.1	0.0	
F2/F3	0.3	8.5	23.8	20.2	8.5	5.7	0.9	1.2	0.1	69
%	2.7	5.0	9.3	8.7	6.5	9.0	2.7	16.9	2.7	
Cirrhosis	0.3	14.4	31.2	31.5	19.2	8.0	3.0	1.2	0.1	110
%	3.2	8.6	12.2	13.5	14.7	12.7	9.5	17.5	3.2	
Decom Cirrhosis	0.0	2.0	4.0	5.0	7.0	3.0	0.0	0.0	0.0	21
%.	0.0	1.2	1.6	2.1	5.3	4.8	0.0	0.0	0.0	
Liver Transplant	0.0	0.0	0.0	0.0	2.0	1.0	0.0	0.0	0.0	3
%.	0.0	0.0	0.0	0.0	1.5	1.6	0.0	0.0	0.0	
HCC	0.0	0.0	2.0	0.0	0.0	2.0	0.0	0.0	0.0	4
%.	0.0	0.0	0.8	0.0	0.0	3.2	0.0	0.0	0.0	
other liver disease	0.0	0.0	3.0	2.0	1.0	0.0	0.0	0.0	0.0	6
%.	0.0	0.0	1.2	0.9	0.8	0.0	0.0	0.0	0.0	

The stage distribution for each age group was adjusted to generate the “adjusted” distribution reported in Table 5.4.1-3. The difference between observed and adjusted was distributed into or deducted from each age category proportionally according to the size of that group. For example, the numbers in F1 were deducted proportionally from the observed and distributed into F2/3 and F4. The observed numbers in Decompensated cirrhosis, HCC, Liver transplant and other disease, and RNA- could be diagnosed based solely on clinical evidence were therefore not adjusted.

Table 5.4-6 Adjusted HCV Stage Distribution (N & %) by Age Group for Alive Male Patients

	Age									
	<20 N=86	20+ N=206	30+ N=359	40+ N=425	50+ N=314	60+ N=271	70+ N=269	80+ N=143	90+ N=17	Total N=2090
RNA- ,N	20	50	65	72	56	46	62	39	5	415
%	23.3	24.3	18.1	16.9	17.8	17.0	23.0	27.3	29.4	
RNA+	35	65	91	95	71	70	88	61	9	585
%	40.7	31.6	25.3	22.4	22.6	25.8	32.7	42.7	52.9	
F1	23	64	118	139	95	70	50	14	0	573
%	26.7	31.1	32.9	32.7	30.3	25.8	18.6	9.8	0	
F2/F3	1	10	31	49	41	34	26	5	.	197
%	1.2	4.9	8.6	11.5	13.1	12.5	9.7	3.5	.	
Cirrhosis	.	8	31	51	44	39	35	15	1	224
%	.	3.9	8.6	12.0	14.0	14.4	13	10.5	5.9	
Decom Cirrhosis	1	2	4	6	9	11	8	4	.	45
%	1.2	1	1.1	1.4	2.9	4.1	3.0	2.8	.	
Liver Transplant	.	.	.	1	7	4	2	.	.	14
%	.	.	.	0.2	2.2	1.5	0.7	.	.	
HCC	.	.	2	.	1	5	1	3	.	12
%	.	.	0.6	.	0.3	1.8	0.4	2.1	.	
other liver disease	2	.	5	8	2	5	3	.	.	25
%	2.3	.	1.4	1.9	0.6	1.8	1.1	.	.	

Table 5.4-7 Adjusted HCV Stage Distribution (N & %) by Age Group for Alive Female Patients

	Age									
	<20 N=51	20+ N=47	30+ N=180	40+ N=377	50+ N=289	60+ N=213	70+ N=181	80+ N=103	90+ N=28	Total N=1469
RNA- ,N	15	13	45	100	49	56	59	32	15	384
%	29.4	27.7	25.0	26.5	17.0	26.3	32.6	31.1	53.6	
RNA+	14	12	43	89	70	55	52	33	10	378
%	27.5	25.5	23.9	23.6	24.2	25.8	28.7	32.0	35.7	
F1	13	13	52	107	76	49	32	12	.	354
%	25.5	27.7	28.9	28.4	26.3	23.0	17.7	11.7	.	
F2/F3	9	5	18	51	49	36	18	.	.	186
%	17.6	10.6	10.0	13.5	17.0	16.9	9.9	.	.	
Cirrhosis	.	2	11	27	24	21	20	12	.	117
%	.	4.3	6.1	7.2	8.3	9.9	11.0	11.7	.	
Decom Cirrhosis	.	.	.	1	6	6	4	.	.	17
%	.	.	.	0.3	2.1	2.8	2.2	.	.	
Liver Transplant	1	.	1	3	1	1	2	1	.	10
%	2.0	.	0.6	0.8	0.3	0.5	1.1	1.0	.	
HCC	.	.	1	1	3	1	2	2	.	10
%	.	.	0.6	0.3	1.0	0.5	1.1	1.9	.	
other liver disease	.	.	2	3	3	2	1	.	.	11
%	.	.	1.1	0.8	1.0	0.9	0.6	.	.	

Table 6 Summary of Transition Probabilities used in the 2004 HCV Markov Prediction Model

Type of transition probability	Short Expression	Variable Name in Markov model	Baseline Probability	Low	High	Source
Proportion of whole cohort with RNA- in F0 study population, six months post infection	RNA-	pRNAnegative	0.15			Table 4.1
Proportion of whole cohort with RNA+ in F0 study population, 6 months post infection	RNA+	pRNApositive	0.85			Table 4.1
Proportion of whole cohort with RNA- in F0 study population, year 2004	RNA-	pRNAnegative	0.226			Table 5.3-1 (adjusted from 0.226)
Proportion of whole cohort with RNA+ in F0 study population, year	RNA+	pRNApositive	0.79	0.75	0.85	Table 5.3-1 (adjusted from 0.774)
Transition from RNA+ to RNA- (without treatment)	RNA+→RNA-	PRNApostoRNAneg	0.006	0.003	0.010	Compensation cohort, range: Table 4.1
Transition from RNA- to recover	RNA- to recover	pRNAnegtoRecover	0.002	0.001	0.004	1998 Report
Transition from RNA negative to fibrosis 1	RNA- to F1	pRNAnegtofibrosis1	0.000	0.000	0.000	
Transition from RNA positive to fibrosis 1	RNA+ → F1	pRNApostofibrosis1	0.071	0.041	0.127	Table 4.2-4
Transition from Fibrosis stage 1 to stage 2.	F1→F2	pFibrosis1toFibrosis2	0.078	0.054	0.091	Table 4.2-4
Transition from Fibrosis stage 2 to stage 3.	F2→F3	pFibrosis2toFibrosis3	0.192	0.096	0.327	Table 4.2-4
Transition from Fibrosis stage 3 to stage 4.	F3→Cirr.	pFibrosis3toFibrosis4	0.242	0.117	0.384	Table 4.2-4
Transition from Fibrosis stage 4 (Cirrhosis) to liver decompensation	Cirr.→Dec.	PFibrosis4toDecom.	0.046	0.038	0.054	1998 Report (Table 1)
Transition from Decomp. cirrhosis to Liver transplantation	Dec.→Transp	pDecomCtoTransp	0.033	0.017	0.049	1998 Report (Table 1)
Transition from Fibrosis stage 1 directly to HCC	F1→HCC	pFibrosis1toHCC	0.0001	0.000	0.0020	1998 Report (Table 1)
Transition from Fibrosis stage 2 directly to HCC	F2→HCC	pFibrosis2toHCC	0.0001	0.000	0.0020	1998 Report (Table 1)
Transition from Fibrosis stage 3 directly to HCC	F3→HCC	pFibrosis3toHCC	0.001	0.0001	0.020	1998 Report (Table 1)
Transition from Fibrosis stage 4 directly to HCC	Cirr.→HCC	pFibrosis4toHCC	0.021	0.018	0.024	Table 4.5
HCC to death	HCC →Death	pHCctoDeath	0.860	0.760	0.96	1998 Report (Table 1)
Liver transplantation to Death (first year)	Tran.→Death	pTransptoFail	0.169	0.127	0.210	1998 Report (Table 1)
Liver transplantation to Death (after first year)			0.034	0.024	0.043	1998 Report (Table 1)
Decompensation to liver death	Dec.→Death	PDecomCtoDeath	0.138	0.074	0.202	1998 Report (Table 1)
Treatment:						
Proportion eligible for treatment <65: 0.14*0.42 [#]	RNA+ to F1	Treateffect1	0.058	0.047	0.071	Modified from 2002 report 2002. (Table 6), current report, Table 4.3-1
0.80*0.50	F1 to F2 F2 to F3 F3 to F4	Treateffect2	0.400	0.349	0.454	
0.75*0.25	F4 to Decomp.	Treateffect3	0.188	0.038	0.334	
Excess mortality attributable to transfusion			Table 4.6-1	0.5x	1.5x	Table 4.6-1
Effect of HIV status on fibrosis progression rates			Table 4.3-2	0.5x	1.5x	Table 4.3-2
Excess mortality associated with HIV infection			Table 4.3-4	0.5x	1.5x	Table 4.3-4

† : numbers in the brackets were from retrospective studies while numbers outside were from all the studies.

#: Product of the proportion of patients eligible to treatment and the response rate. Treatment rates were updated based on the completed survey in 2002. The response rate was updated based on the 2004 literature review.

Table 7.1 Model Validation: Observed Disease Severity Distribution in Compensation Claimants (August 2004), and Predicted Distribution, Based on Age and Sex of Blood Transfusion Recipients and Literature- Derived Fibrosis Transition Rates

		Observed-Adjusted		Predicted Non-hemo (%)
		Total (%)	Non hemo (%)	
Survival status at 2004	Alive			42.9
	Deceased			57.1
Hepatitis C stage at 2004 (among alives)	Fibrosis 0	50.6	53.8	44.4
	Fibrosis I	27.2	24.4	32.0
	Fibrosis II-III	10.2	11.0	15.9
	Cirrhosis	8.0	6.6	6.2
	HCC	0.6	0.7	0.5
	Decompensation	1.7	1.5	0.7
	Transplant other	0.7 1.0	0.8 1.1	0.3

*Missing percentages are computed based on all the observations, and the percentages for other categories are based on available observation.

** Adjustment was made by applying observed distribution in patients with biopsy and the observed number of patients with decompensated cirrhosis, and assuming the ratio between the number of patients with decompensated cirrhosis and the number of patients with other level of fibrosis are the same for both with or without biopsy.

Table 7.2 Validation Study

Lifetime Risk of Cirrhosis and Liver Related Death, 1998, 2002, and 2004 Model Projections (Non-hemophilics)

Outcome	Year		
	1998 Model* (30 year risk)	2002 Model (lifetime risk)	2004 Model (lifetime risk)
Overall**			
Cirrhosis	29.4	37.0	33.4
Liver related death	16.9	22.0	17.3
Age Group			
10-19			
Cirrhosis	36.7	53.4	42.5
Liver related death	12.3	39.4	27.7
20-29			
Cirrhosis	35.1	52.3	49.7
Liver related death	11.8	37.2	30.7
30-39			
Cirrhosis	32.7	49.7	44.1
Liver related death	10.9	32.6	25.2
40-49			
Cirrhosis	31.0	49.4	41.3
Liver related death	10.2	30.3	21.8
50-59			
Cirrhosis	21.3	41.9	41.6
Liver related death	6.6	23.9	20.8
60-69			
Cirrhosis	16.8	38.0	33.0
Liver related death	4.2	21.0	14.6
70-79			
Cirrhosis	6.1	24.6	22.5
Liver related death	1.0	12.0	8.0

**Life time prediction by age group in 1999 is not available, so only 30 year prediction post transfusion was listed for reference .*

Table 8.1-1 Prognosis by Calendar Year. All HCV Patients (stage specific rates).

Best Estimates for All Parameters, Starting Distribution: Observed Stage Distribution, August 2004 (revised)*

	2004	2010	2020	2030	2040	2050	2060
Cumulative proportion							
Cirrhosis	10.6	16.4	25.0	31.2	35.1	37.0	38.0
HCC	0.6	2.4	4.6	6.3	7.8	8.5	8.6
Transplant	0.7	1.0	1.6	2.2	2.7	3.0	3.1
Non-liver related death		10.3	27.6	42.6	54.8	65.4	72.4
Liver-related death		3.0	8.2	13.1	17.5	20.4	21.8
All cause death		13.3	35.8	55.7	72.2	85.8	94.2
Changes in Sex distribution							
Female		41.6	42.8	44.1	46.3	48.9	50.6
Changes in age distribution							
25	10.9	4.3
35	15.1	8.0	5.4
45	22.5	17.0	9.8	7.2	.	.	.
55	16.9	24.7	20.7	12.7	10.4	.	.
65	13.5	18.5	29.1	25.7	17.5	17.4	.
75	12.6	13.2	19.6	32.7	32.0	26.7	31.9
85	6.9	10.5	10.7	17.0	31.3	37.4	35.4
95	1.3	3.8	4.6	4.6	8.8	18.5	32.7
Changes in stage distribution In patients alive over time							
RNA+	28.4	20.4	9.8	5.3	2.8	1.5	1.5
RNA-	22.7	24.3	26.7	29.5	32.5	36.3	40.4
Fibrosis1	27.5	28.1	28.8	25.6	22.5	19.8	15.4
Fibrosis2	5.3	7.5	8.6	8.1	7.2	7.5	6.5
Fibrosis3	5.5	5.7	6.7	7.6	7.0	6.8	6.7
Fibrosis4	8.1	11.0	15.1	18.1	20.9	20.4	19.6
Decompensated Cirrhosis	1.8	2.4	3.2	3.7	4.5	4.4	5.6
Transplant	0.7	0.3	0.6	1.4	1.9	2.5	3.4
HCC	0.6	0.2	0.4	0.6	0.6	0.7	0.8

Table 8.1-2 Prognosis by Calendar Year. Non-hemophilic HCV Patients.

Best Estimates for All Parameters*, Starting Distribution: Observed Stage Distribution, August 2004

	2004	2010	2020	2030	2040	2050	2060
Cumulative proportion							
Cirrhosis	8.9	13.1	21.0	27.0	30.9	32.6	33.4
HCC	0.7	2.0	3.9	5.5	6.6	7.2	7.3
Transplant	0.8	1.1	1.5	2.0	2.4	2.6	2.7
Non-liver related death		11.4	31.6	47.9	61.7	71.4	77.2
Liver-related death		2.5	6.4	10.7	14.2	16.4	17.3
All cause death		13.9	38.0	58.6	75.9	87.8	94.5
Changes in Sex distribution							
Female		52.2	54.2	55.5	56.5	59.5	61.8
Changes in age distribution							
25	7.9	5.7
35	10.7	4.0	7.4
45	21.4	11.5	5.3	9.9	.	.	.
55	17.8	23.5	14.9	7.3	15.2	.	.
65	15.8	18.4	29.2	19.7	10.9	26.3	.
75	15.7	17.0	21.1	34.6	26.2	16.7	46.4
85	9.0	14.1	15.2	20.2	36.0	32.5	25.1
95	1.6	5.8	6.9	8.2	11.7	24.5	28.5
Changes in stage distribution In patients alive over time							
RNA+	29.2	20.9	10.1	5.3	3.0	1.3	1.5
RNA-	24.6	25.7	28.1	31.0	33.9	37.8	43.4
Fibrosis1	24.4	28.1	27.7	23.6	21.1	18.6	14.9
Fibrosis2	6.0	8.0	9.1	9.1	8.3	7.9	5.8
Fibrosis3	5.0	5.9	7.1	7.1	6.7	6.3	7.5
Fibrosis4	6.6	9.4	14.3	18.5	19.5	20.4	19.9
Decompensated Cirrhosis	1.5	1.6	2.6	3.7	4.9	5.1	3.3
Transplant	0.8	0.2	0.6	1.2	2.1	2.1	2.9
HCC	0.7	0.2	0.4	0.5	0.7	0.5	0.9

Table 8.1-3 Prognosis by Calendar Year. Hemophilic HCV Patients.

Best Estimates for All Parameters, Starting Distribution: Observed Stage Distribution in Year 2004*

	2004	2010	2020	2030	2040	2050	2060
Cumulative proportion							
Cirrhosis	14.7	18.3	29.3	37.6	42.5	45.2	46.4
HCC	0.4	2.6	5.4	8.0	9.6	10.6	10.9
Transplant	0.3	0.8	1.3	2.2	2.6	2.9	3.1
Non-liver-related death		5.1	16.2	29.8	45.0	57.9	66.9
Liver-related death		3.3	9.7	16.6	21.7	25.1	26.8
Death		8.3	25.9	46.4	66.7	83.0	93.6
Changes in sex distribution							
Female	14.9	13.9	14.2	15.0	16.0	16.7	20.8
Changes in age distribution							
25	18.6	1.2
35	28.4	19.6	1.4
45	25.8	29.8	22.0	1.6	.	.	.
55	14.5	26.2	32.6	25.8	2.2	.	.
65	7.0	14.0	26.7	36.6	32.9	3.5	.
75	3.6	6.2	12.5	24.9	41.1	46.0	6.3
85	0.8	2.6	4.1	9.4	19.9	40.0	65.5
95	0.2	0.3	0.8	1.6	3.9	10.5	28.2
Changes in stage distribution							
In patients alive over time							
RNA+	24.9	17.2	8.6	4.6	3.2	2.1	1.6
RNA -	16.1	17.6	19.8	22.9	26.0	29.5	35.4
Fibrosis1	35.5	34.9	31.4	28.3	23.8	20.6	14.4
Fibrosis2	4.6	9.6	10.3	10.0	8.7	9.1	10.0
Fibrosis3	3.0	5.0	6.7	6.6	7.3	7.6	7.2
Fibrosis4	12.1	12.5	18.2	20.9	22.3	22.6	21.2
Decompensated Cirrhosis	2.3	2.6	3.5	4.2	5.6	4.7	6.4
Transplant	0.3	0.4	0.8	1.9	2.4	2.6	3.0
HCC	0.4	0.3	0.5	0.7	0.7	1.2	0.8

Table 8.1-4 Prognosis by Calendar Year-- -- Non-hemophilics, Age 10-19

Compensation level	Stage	2004 ^A	2010	2020	2030	2040	2050	2060
Cumulative (%)*								
	Cirrhosis	1.9	5.5	15.2	25.4	33.2	38.1	42.5
	Decompensation	0.8	1.3	3.5	7.5	12.0	15.9	19.2
	HCC	0.0	0.7	2.6	5.1	8.3	10.5	11.7
	Liver transplant	0.8	0.9	1.1	1.6	2.4	3.2	3.7
	Non-liver-death		0.3	1.1	2.1	3.8	8.2	17.2
	Liver death		0.9	3.8	8.9	15.7	22.7	27.7
	All Death		1.2	4.9	10.9	19.5	30.8	44.9
	Alive		98.8	95.1	89.1	80.5	69.2	55.1
Distribution among alive:**								
Level 1	F0(RNA-)	25.6	27.2	29.5	31.8	34.8	38.2	41.8
Level 2	F0(RNA+)	40.9	28.0	13.7	7.4	4.7	3.3	1.9
Level 3	F1	22.2	28.3	30.0	28.4	26.2	25.2	20.3
Level 4	F2	5.0	7.5	8.8	8.1	8.0	7.7	8.3
	F3	4.4	4.8	6.2	6.0	5.3	5.2	6.6
Level 5	Cirrhosis	0.3	3.5	9.6	14.6	16.3	15.5	15.5
Level 6	Decompensation	0.8	0.6	1.6	2.6	3.2	2.9	3.1
	Liver transplant	0.8	0.1	0.3	0.6	1.1	1.6	2.0
	HCC	0.0	0.0	0.2	0.3	0.4	0.4	0.5

* Cumulative % is defined as the cumulative percentage of patients who have ever entered the disease stage prior to or during the year in question, among all individuals alive in August 2004.

**Distribution % is defined as the stage distribution at a single point in time, the year in question (e.g. 2004, 2010).

Table 8.1-5 Prognosis by Calendar Year-- -- Hemophilics, Age 10-19

Compensation level	Stage	2004	2010	2020	2030	2040	2050	2060
Cumulative (%)*								
	Cirrhosis	3.2	4.6	15.4	25.7	32.5	36.3	40.2
	Decompensation	0.0	0.6	3.2	7.7	12.3	15.9	18.7
	HCC	0.0	0.8	2.7	5.7	8.4	10.4	11.5
	Liver transplant	0.0	0.0	0.3	0.9	1.7	2.3	2.8
	Non-liver-death		0.5	1.9	3.6	6.2	12.4	24.2
	Liver death		0.4	3.0	8.5	15.3	21.6	26.4
	All Death		0.9	4.9	12.1	21.5	34.0	50.7
	Alive		99.1	95.1	87.9	78.5	66.0	49.3
Distribution among alive:**								
Level 1	F0(RNA-)	30.0	30.4	32.1	34.4	37.9	41.3	45.2
Level 2	F0(RNA+)	27.3	18.4	8.7	5.0	3.0	2.0	1.3
Level 3	F1	36.8	36.6	32.7	28.8	26.3	24.8	19.6
Level 4	F2	1.7	7.2	8.4	7.6	7.7	8.3	8.8
	F3	1.0	3.2	5.2	5.0	4.3	4.4	6.1
Level 5	Cirrhosis	3.2	3.7	10.9	15.2	15.5	13.9	13.9
Level 6	Decompensation	0.0	0.5	1.7	2.8	3.4	3.4	3.0
	Liver transplant	0.0	0.0	0.2	0.7	1.4	1.6	1.8
	HCC	0.0	0.1	0.2	0.4	0.4	0.3	0.3

Table 8.1-6 Prognosis by Calendar Year-- -- Non-hemophilics, Age 20-29

Compensation level	Stage	2004	2010	2020	2030	2040	2050	2060
Cumulative (%)*								
	Cirrhosis	3.7	7.6	18.8	29.8	37.5	43.6	49.7
	Decompensation	0.0	0.9	4.0	8.9	13.8	18.2	22.1
	HCC	0.0	1.2	3.6	7.0	9.9	12.3	13.4
	Liver transplant	0.0	0.0	0.3	1.1	1.8	2.6	3.3
	Non-liver-death		0.3	1.3	3.0	7.4	16.7	34.5
	Liver death		0.6	4.1	10.4	18.3	24.7	30.7
	All Death		1.0	5.4	13.4	25.7	41.4	65.2
	Alive		99.1	94.6	86.6	74.3	58.7	34.8
Distribution among alive:**								
Level 1	F0(RNA-)	18.8	20.5	22.2	24.6	27.3	30.5	34.7
Level 2	F0(RNA+)	36.6	24.8	12.4	7.1	4.5	2.6	1.3
Level 3	F1	29.7	32.5	32.6	29.9	28.5	23.0	17.8
Level 4	F2	6.2	9.1	9.6	9.4	8.8	9.8	8.2
	F3	5.0	6.1	7.5	6.7	6.4	7.4	7.2
Level 5	Cirrhosis	3.7	6.3	13.1	17.7	19.0	19.7	23.0
Level 6	Decompensation	0.0	0.6	2.1	3.1	3.7	4.7	4.6
	Liver transplant	0.0	0.0	0.2	0.8	1.4	1.9	2.6
	HCC	0.0	0.1	0.3	0.5	0.4	0.4	0.5

Table 8.1-7 Prognosis by Calendar Year-- -- Hemophilics, Age 20-29

Compensation level	Stage	2004	2010	2020	2030	2040	2050	2060
<hr/>								
Cumulative (%)*								
	Cirrhosis	9.8	12.0	22.2	31.6	37.3	41.3	45.0
	Decompensation	1.2	2.8	6.9	11.8	16.0	19.4	21.6
	HCC	0.0	1.7	3.9	6.7	9.1	10.8	11.4
	Liver transplant	0.0	0.2	0.7	1.4	2.1	2.6	3.1
	Non-liver-death		0.9	2.9	6.9	14.9	28.9	47.7
	Liver death		1.7	6.6	13.2	19.7	25.2	28.5
	All Death		2.6	9.5	20.1	34.6	54.1	76.2
	Alive		97.4	90.5	79.9	65.4	45.9	23.8
Distribution among alive:**								
Level 1	F0(RNA-)	28.0	30.1	32.6	35.8	39.5	43.5	47.3
Level 2	F0(RNA+)	26.5	17.5	8.7	4.8	2.9	1.7	1.4
Level 3	F1	30.7	30.8	28.2	25.4	24.2	19.9	13.4
Level 4	F2	3.0	7.3	8.1	7.3	6.9	8.0	6.9
	F3	2.0	3.8	5.5	5.0	4.3	5.4	5.7
Level 5	Cirrhosis	8.6	8.4	13.2	16.9	16.6	15.9	18.3
Level 6	Decompensation	1.2	1.8	2.8	3.6	3.7	3.7	4.3
	Liver transplant	0.0	0.1	0.6	0.9	1.4	1.6	2.3
	HCC	0.0	0.2	0.3	0.4	0.5	0.4	0.4

Table 8.1-8 Prognosis by Calendar Year-- -- Non-hemophilics, Age 30-39

Compensation level	Stage	2004	2010	2020	2030	2040	2050	2060
Cumulative (%)*								
	Cirrhosis	2.3	5.5	17.0	27.1	34.7	41.4	44.1
	Decompensation	0.0	0.5	3.1	7.2	12.1	16.0	17.9
	HCC	0.4	1.4	3.5	6.3	8.9	10.9	11.5
	Liver transplant	0.4	0.4	0.6	1.3	2.1	2.8	3.2
	Non-liver-death		0.7	2.8	7.6	17.6	36.3	60.5
	Liver death		0.9	3.8	9.3	15.9	22.1	25.2
	All Death		1.6	6.6	17.0	33.5	58.3	85.7
	Alive		98.4	93.4	83.1	66.5	41.7	14.3
Distribution among alive:**								
Level 1	F0(RNA-)	26.8	27.9	29.4	31.6	34.7	39.4	44.2
Level 2	F0(RNA+)	24.6	17.0	8.7	4.9	2.5	1.0	0.7
Level 3	F1	38.6	36.6	32.1	28.7	22.8	17.0	13.0
Level 4	F2	4.2	8.4	9.0	8.1	9.6	8.7	6.6
	F3	3.1	5.2	6.5	6.0	6.2	6.2	5.4
Level 5	Cirrhosis	1.9	4.3	12.2	16.9	18.5	21.1	22.5
Level 6	Decompensation	0.0	0.4	1.7	2.7	3.9	4.4	5.0
	Liver transplant	0.4	0.0	0.2	0.8	1.3	1.7	2.4
	HCC	0.4	0.1	0.3	0.4	0.4	0.6	0.3

Table 8.1-9 Prognosis by Calendar Year-- -- Hemophilics, Age 30-39

Compensation level	Stage	2004	2010	2020	2030	2040	2050	2060
Cumulative (%)*								
	Cirrhosis	13.9	17.5	31.0	41.1	47.5	52.1	53.5
	Decompensation	1.6	4.2	9.9	15.4	20.4	23.4	24.4
	HCC	0.8	3.2	6.4	9.8	12.1	13.3	13.6
	Liver transplant	0.0	0.3	1.3	2.3	3.0	3.4	3.5
	Non-liver-death		1.6	6.2	15.2	29.6	47.4	62.3
	Liver death		3.3	10.2	18.3	25.4	30.2	32.1
	All Death		4.9	16.3	33.4	55.0	77.6	94.4
	Alive		95.1	83.7	66.6	45.0	22.4	5.6
Distribution among alive:**								
Level 1	F0(RNA-)	13.9	15.3	17.4	19.7	22.6	26.2	32.5
Level 2	F0(RNA+)	24.6	16.8	8.0	4.7	2.8	1.5	0.5
Level 3	F1	37.4	35.9	32.6	29.6	25.0	20.1	19.5
Level 4	F2	5.4	10.3	10.2	9.4	10.5	8.7	7.6
	F3	4.0	6.0	7.3	6.5	7.1	7.5	4.6
	Cirrhosis	12.3	12.6	18.9	22.9	23.1	26.1	25.9
Level 6	Decompensation	1.6	2.6	4.0	4.8	5.9	5.9	5.5
	Liver transplant	0.0	0.3	1.0	1.8	2.4	3.3	2.8
	HCC	0.8	0.2	0.5	0.6	0.6	0.8	0.9

Table 8.1-10 Prognosis by Calendar Year-- -- Non-hemophilics, Age 40-49

Compensation level	Stage	2004	2010	2020	2030	2040	2050	2060
Cumulative (%)*								
	Cirrhosis	4.7	9.8	20.9	30.4	38.0	40.9	41.3
	Decompensation	0.4	1.6	5.0	9.5	13.7	15.8	16.1
	HCC	0.2	1.4	3.9	6.6	8.7	9.5	9.7
	Liver transplant	0.7	0.8	1.2	2.0	2.6	3.0	3.1
	Non-liver-death		1.2	5.7	16.2	36.9	63.4	77.0
	Liver death		1.4	5.3	11.4	17.8	21.1	21.8
	All Death		2.6	11.0	27.6	54.7	84.4	98.8
	Alive		97.4	89.0	72.4	45.3	15.6	1.2
Distribution among alive:**								
Level 1	F0(RNA-)	25.7	26.8	28.9	31.8	36.2	40.4	39.0
Level 2	F0(RNA+)	26.1	18.3	8.9	4.5	2.3	1.7	.
Level 3	F1	30.4	31.1	29.6	23.6	18.5	16.1	16.1
Level 4	F2	6.8	9.2	8.9	9.9	8.4	6.4	3.4
	F3	5.6	6.2	7.0	7.6	7.2	6.8	8.5
Level 5	Cirrhosis	4.1	7.1	13.7	17.6	21.1	20.8	20.3
Level 6	Decompensation	0.4	1.0	2.3	3.5	4.1	4.4	7.6
	Liver transplant	0.2	0.1	0.4	1.1	1.6	2.5	5.1
	HCC	0.7	0.1	0.3	0.5	0.6	0.8	.

Table 8.1-11 Prognosis by Calendar Year-- -- Hemophilics, Age 40-49

Compensation level	Stage	2004	2010	2020	2030	2040	2050	2060
Cumulative (%)*								
	Cirrhosis	15.7	19.6	32.2	41.2	47.0	48.7	48.9
	Decompensation	2.1	4.7	10.2	15.7	19.2	20.7	20.9
	HCC	0.0	2.8	6.0	8.5	9.8	10.3	10.3
	Liver transplant	0.0	0.3	1.1	2.0	2.5	2.6	2.7
	Non-liver-death		3.2	14.0	32.4	53.4	68.9	74.0
	Liver death		3.0	10.1	17.6	23.0	25.3	25.7
	All Death		6.2	24.1	50.0	76.4	94.2	99.7
	Alive		93.9	75.9	50.0	23.6	5.8	0.3
Distribution Among alive:**								
Level 1	F0(RNA-)	12.3	13.0	14.7	16.9	19.1	23.3	29.6
Level 2	F0(RNA+)	24.1	16.5	8.1	4.6	2.7	2.1	3.7
Level 3	F1	39.2	37.6	33.9	27.2	21.8	18.3	7.4
Level 4	F2	4.7	9.8	10.3	11.3	10.6	8.5	11.1
	F3	4.0	5.8	7.5	8.5	8.3	6.6	11.1
Level 5	Cirrhosis	13.6	13.8	20.1	23.7	28.4	30.9	22.2
Level 6	Decompensation	2.1	2.9	3.9	5.2	6.0	6.9	14.8
	Liver transplant	0.0	0.4	0.9	1.9	2.2	2.9	.
	HCC	0.0	0.3	0.5	0.7	0.9	0.5	.

Table 8.1-12 Prognosis by Calendar Year-- -- Non-hemophilics, Age 50-59

Compensation level	Stage	2004	2010	2020	2030	2040	2050	2060
Cumulative (%)*								
	Cirrhosis	9.6	18.0	28.5	37.6	41.0	41.6	41.6
	Decompensation	1.7	3.6	8.2	12.8	15.0	15.3	15.4
	HCC	0.8	3.0	5.9	8.2	9.1	9.2	9.2
	Liver transplant	1.3	1.6	2.3	3.0	3.4	3.5	3.5
	Non-liver-death		3.5	14.5	36.4	64.7	78.4	79.2
	Liver death		3.6	9.6	16.1	19.8	20.7	20.8
	All Death		7.1	24.1	52.5	84.5	99.1	100.0
	Alive		92.9	75.9	47.5	15.5	0.9	.
Distribution among alive:**								
Level 1	F0(RNA-)	19.7	21.0	23.3	25.7	29.1	31.5	.
Level 2	F0(RNA+)	25.7	17.9	9.2	4.8	3.0	4.5	.
Level 3	F1	26.8	29.4	26.3	23.0	21.0	16.9	.
Level 4	F2	7.8	9.4	10.7	9.2	8.5	11.2	.
	F3	6.6	7.1	8.4	8.1	6.9	5.6	.
Level 5	Cirrhosis	9.6	12.4	17.4	22.1	23.2	21.3	.
Level 6	Decompensation	1.7	2.1	3.2	4.8	5.0	6.7	.
	Liver transplant	1.3	0.2	0.9	1.6	2.5	1.1	.
	HCC	0.8	0.3	0.4	0.7	0.8	1.1	.

Table 8.1-13 Prognosis by Calendar Year-- -- Hemophilics, Age 50-59

Compensation level	Stage	2004	2010	2020	2030	2040	2050	2060
Cumulative (%)*								
	Cirrhosis	14.8	24.2	34.2	42.9	45.8	46.2	46.2
	Decompensation	5.3	7.7	12.4	16.4	18.5	18.8	18.8
	HCC	0.0	2.5	5.0	6.9	7.5	7.5	7.5
	Liver transplant	1.5	2.3	3.2	3.8	4.2	4.2	4.2
	Non-liver-death		5.8	23.4	46.6	69.4	78.1	78.5
	Liver death		4.6	11.9	17.9	21.0	21.5	21.5
	All Death		10.4	35.3	64.5	90.4	99.5	100.0
	Alive		89.6	64.7	35.5	9.7	0.5	.
Distribution Among alive:**								
Level 1	F0(RNA-)	10.0	11.0	12.8	15.0	16.5	27.7	.
Level 2	F0(RNA+)	21.2	15.3	7.7	4.4	3.2	.	.
Level 3	F1	40.6	39.7	32.2	26.0	24.7	21.3	.
Level 4	F2	3.6	9.6	13.2	10.5	9.6	2.1	.
	F3	3.0	5.0	9.3	9.6	7.1	4.3	.
Level 5	Cirrhosis	14.8	14.1	18.8	26.5	29.0	29.8	.
Level 6	Decompensation	5.3	4.3	4.2	5.1	5.4	8.5	.
	Liver transplant	1.5	0.6	1.3	2.1	3.9	4.3	.
	HCC	0.0	0.4	0.5	0.7	0.4	2.1	.

Table 8.1-14 Prognosis by Calendar Year-- -- Non-Hemophilics, Age 60-69

Compensation level	Stage	2004	2010	2020	2030	2040	2050	2060
Cumulative (%)*								
	Cirrhosis	9.6	19.1	28.0	32.3	33.0	33.0	33.0
	Decompensation	3.4	5.4	9.5	11.7	12.2	12.2	12.2
	HCC	1.0	3.0	5.3	6.1	6.2	6.2	6.2
	Liver transplant	1.0	1.4	2.0	2.4	2.5	2.5	2.5
	Non-liver-death		8.8	34.9	68.8	84.3	85.4	85.4
	Liver death		4.1	9.9	13.6	14.6	14.6	14.6
	All Death		12.9	44.8	82.4	98.8	100.0	100.0
	Alive		87.1	55.2	17.6	1.2	0.0	.
Distribution among alive:**								
Level 1	F0(RNA-)	23.0	24.8	27.8	32.7	35.0	.	.
Level 2	F0(RNA+)	24.7	17.7	9.3	5.7	2.6	.	.
Level 3	F1	24.2	26.3	24.6	22.4	16.2	.	.
Level 4	F2	7.1	8.5	8.2	7.4	6.8	.	.
	F3	6.0	6.5	7.2	5.4	8.5	.	.
Level 5	Cirrhosis	9.6	12.8	17.6	19.6	24.8	.	.
Level 6	Decompensation	3.4	2.8	3.8	4.2	3.4	.	.
	Liver transplant	1.0	0.5	1.1	2.0	1.7	.	.
	HCC	1.0	0.3	0.4	0.6	0.9	.	.

Table 8.1-15 Prognosis by Calendar Year-- -- Hemophilics, Age 60-69

Compensation level	Stage	2004	2010	2020	2030	2040	2050	2060
Cumulative (%)*								
	Cirrhosis	12.7	22.8	31.5	35.2	35.5	35.5	35.5
	Decompensation	4.8	7.7	11.5	13.8	14.1	14.1	14.1
	HCC	3.2	5.2	7.0	7.7	7.8	7.8	7.8
	Liver transplant	1.6	2.1	2.9	3.3	3.3	3.3	3.3
	Non-liver-death		10.8	39.4	70.4	81.6	82.3	82.3
	Liver death		7.6	13.8	17.0	17.7	17.7	17.7
	All Death		18.4	53.2	87.5	99.4	100.0	100.0
	Alive		81.6	46.8	12.6	0.7	.	.
Distribution								
Among alive:**								
Level 1	F0(RNA-)	11.1	12.9	15.3	17.8	20.0	.	.
Level 2	F0(RNA+)	24.3	18.5	9.2	4.7	3.1	.	.
Level 3	F1	33.3	34.4	32.3	31.3	35.4	.	.
Level 4	F2	5.0	10.0	10.1	10.0	4.6	.	.
	F3	4.0	5.4	7.6	6.1	6.2	.	.
Level 5	Cirrhosis	12.7	13.5	20.2	22.1	24.6	.	.
Level 6	Decompensation	4.8	4.3	3.6	5.1	4.6	.	.
	Liver transplant	1.6	0.6	1.3	2.2	1.5	.	.
	HCC	3.2	0.3	0.3	0.7	.	.	.

Table 8.1-16 Prognosis by Calendar Year-- -- Non-Hemophilics, Age 70-79

Compensation level	Stage	2004	2010	2020	2030	2040	2050	2060
Cumulative (%)*								
	Cirrhosis	8.5	17.3	21.6	22.5	22.5	22.5	22.5
	Decompensation	2.3	4.8	7.0	7.4	7.4	7.4	7.4
	HCC	1.1	2.4	3.3	3.4	3.4	3.4	3.4
	Liver transplant	0.7	1.3	1.6	1.7	1.7	1.7	1.7
	Non-liver-death		20.8	69.0	90.5	92.0	92.0	92.0
	Liver death		3.6	7.1	8.0	8.0	8.0	8.0
	All Death		24.4	76.0	98.4	100.0	100.0	100.0
	Alive		75.6	24.0	1.6	.	.	.
Distribution among alive:**								
Level 1	F0(RNA-)	28.7	29.0	31.7	34.8	.	.	.
Level 2	F0(RNA+)	36.6	24.0	12.0	7.1	.	.	.
Level 3	F1	13.4	20.7	21.9	25.2	.	.	.
Level 4	F2	4.7	6.7	8.9	9.0	.	.	.
	F3	4.0	4.9	6.4	3.9	.	.	.
Level 5	Cirrhosis	8.5	11.4	14.7	15.5	.	.	.
Level 6	Decompensation	2.3	2.7	3.1	2.6	.	.	.
	Liver transplant	0.7	0.3	0.8	1.9	.	.	.
	HCC	1.1	0.2	0.6

Table 8.1-17 Prognosis by Calendar Year-- -- Hemophilics, Age 70-79

Compensation level	Stage	2004	2010	2020	2030	2040	2050	2060
Cumulative (%)*								
	Cirrhosis	10.5	12.6	15.8	16.6	16.6	16.6	16.6
	Decompensation	0.0	1.7	3.7	4.0	4.0	4.0	4.0
	HCC	0.0	1.4	2.0	2.1	2.1	2.1	2.1
	Liver transplant	0.0	0.1	0.4	0.4	0.4	0.4	0.4
	Non-liver-death		23.7	74.1	94.9	95.9	95.9	95.9
	Liver death		1.1	3.4	4.0	4.1	4.1	4.1
	All Death		24.8	77.5	98.9	100.0	100.0	100.0
	Alive		75.2	22.5	1.1	.	.	.
Distribution								
Among alive:**								
Level 1	F0(RNA-)	29.1	31.4	37.2	38.4	.	.	.
Level 2	F0(RNA+)	40.9	27.8	12.8	5.4	.	.	.
Level 3	F1	14.1	20.9	23.1	21.4	.	.	.
Level 4	F2	3.0	5.1	7.1	8.0	.	.	.
	F3	2.4	2.8	4.6	7.1	.	.	.
Level 5	Cirrhosis	10.5	10.3	12.1	18.8	.	.	.
Level 6	Decompensation	0.0	1.3	2.5
	Liver transplant	0.0	0.1	0.5
	HCC	0.0	0.3	0.1	0.9	.	.	.

Table 8.1-18 Prognosis by Calendar Year-- -- Non-Hemophilics, Age 80-89

Compensation level	Stage	2004	2010	2020	2030	2040	2050	2060
Cumulative (%)*								
	Cirrhosis	8.5	10.2	11.5	11.6	11.6	11.6	11.6
	Decompensation	2.3	2.4	2.9	2.9	2.9	2.9	2.9
	HCC	1.1	2.9	3.0	3.0	3.0	3.0	3.0
	Liver transplant	0.7	0.5	0.7	0.7	0.7	0.7	0.7
	Non-liver-death		47.9	92.7	95.7	95.7	95.7	95.7
	Liver death		3.4	4.3	4.3	4.3	4.3	4.3
	All Death		51.3	96.9	100.0	100.0	100.0	100.0
	Alive		48.7	3.1
Distribution among alive:**								
Level 1	F0(RNA-)	28.7	32.1	33.7
Level 2	F0(RNA+)	36.6	28.0	15.0
Level 3	F1	13.4	21.5	23.2
Level 4	F2	4.7	5.3	7.5
	F3	4.0	3.5	3.9
Level 5	Cirrhosis	8.5	7.4	12.4
Level 6	Decompensation	2.3	1.8	2.3
	Liver transplant	0.7	0.2	1.3
	HCC	1.1	0.2	0.7

Table 8.1-19 Prognosis by Calendar Year-- -- Hemophilics, Age 80-89

Compensation level	Stage	2004	2010	2020	2030	2040	2050	2060
Cumulative (%)*								
	Cirrhosis	10.5	12.1	13.2	13.3	13.3	13.3	13.3
	Decompensation	0.0	1.3	1.9	1.9	1.9	1.9	1.9
	HCC	0.0	1.0	1.2	1.2	1.2	1.2	1.2
	Liver transplant	0.0	0.0	0.1	0.1	0.1	0.1	0.1
	Non-liver-death		52.1	95.8	98.2	98.2	98.2	98.2
	Liver death		1.0	1.7	1.8	1.8	1.8	1.8
	All Death		53.1	97.5	100.0	100.0	100.0	100.0
	Alive		46.9	2.5	0.0	.	.	.
Distribution								
Among alive:**								
Level 1	F0(RNA-)	29.1	31.1	30.7
Level 2	F0(RNA+)	40.9	27.2	14.2
Level 3	F1	14.1	21.9	25.2
Level 4	F2	3.0	5.4	7.1
	F3	2.4	2.9	7.9
Level 5	Cirrhosis	10.5	9.9	10.6
Level 6	Decompensation	0.0	1.2	2.4
	Liver transplant	0.0	0.0	0.8
	HCC	0.0	0.3	1.2

Table 8.2-1 Sensitivity Analysis: Source of Transition Rates Between Fibrosis Stages

Cumulative Event rate (among alive in 2004)	Source of transition rates	2010	2020	2030	2040	2050	2060
Cirrhosis (%)	2004 model, pooled stage-specific transition rates	16.4	25.0	31.2	35.1	37.0	38.0
	Salomon, age and gender specific transition rates	15.4	25.1	34.4	40.8	43.6	44.9
	Transition rates derived solely from compensation cohort (n=4230)	18.2	28.3	34.2	37.4	39.2	39.9
Liver-related death (%)	2004 model, pooled stage-specific transition rates	3.0	8.2	13.1	17.5	20.4	21.8
	Salomon, age and gender specific transition rates	2.8	7.7	12.9	17.4	20.2	21.9
	Transition rates derived solely from compensation cohort (n=4230)	2.9	9.1	14.4	18.6	20.8	21.8

* From Table 4.2-4

Table 8.2-3 Monte Carlo Simulation Describing Overall Uncertainty in the Prediction Model-- Predicted Rates of Major Events and their 95% Confidence Interval

Event		Predicted Mean rate (%)	95% CI (%) Lower-upper
2010 year	Cirrhosis	16.4	13.9-18.9
	HCC	2.4	1.8-3.0
	Liver death	3.0	2.2-3.8
2020 year	Cirrhosis	25.0	18.2-31.8
	HCC	4.6	3.4-5.8
	Liver death	8.2	5.8-10.6
2030 year	Cirrhosis	31.2	21.8-40.6
	HCC	6.3	4.5-8.1
	Liver death	13.1	8.8-17.3
2040 year	Cirrhosis	35.1	24.6-45.6
	HCC	7.8	5.3-10.3
	Liver death	17.5	10.5-24.5
2050year	Cirrhosis	37.0	26.7-47.3
	HCC	8.5	6.1-11.0
	Liver death	20.4	13.2-27.6
2060year	Cirrhosis	38.0	29.1-46.9
	HCC	8.6	6.0-11.2
	Liver death	21.8	15.2-28.4

Table 9.1-1 Estimated Disease Severity Distributions for Prospective Claimants Based on Current Claimant Data

Wave	Number and proportion in each level					
	Level 1	Level 2	Level 3	Level 4	Level 5	Level 6
Wave 1 1 st 500 N	91 18.5	114 23.2	141 28.7	34 6.9	59 12.0	53 10.8
%						
Wave 2 2 nd 500	117 23.7	116 23.5	145 29.4	28 5.7	38 7.7	49 9.9
Wave 3 3 rd 500	110 22.1	140 28.1	122 24.5	28 5.6	41 8.2	57 11.5
Wave 4 4 th 500	113 23.1	146 29.8	137 28.0	20 4.1	47 9.6	27 5.5
Wave 5 5 th 500	117 25.7	144 31.6	109 23.9	10 2.2	39 8.6	37 8.1
Wave 6 6 rd 500	86 19.1	175 38.9	110 24.4	19 4.2	32 7.1	28 6.2
Wave 7 7 th 500	100 22.1	180 39.7	103 22.7	19 4.2	32 5.1	28 6.2
Wave 8 8 th 500	115 25.2	178 39.0	105 23.0	21 4.6	19 4.2	18 4.0
Wave 9 9 th 500	100 22.8	189 43.2	85 19.4	25 5.7	21 4.8	18 4.1
Wave 10 10 th 134	33 26.8	37 30.0	28 22.8	7 5.7	12 9.8	6 4.9
Unknown	25.0	42.3	19.7	4.3	5.1	3.5

* Note: numbers in each row may not sum to 500 due to missing disease level data.

Table 9.1-2 Estimated Stage Distribution of Potential Future Claimants Using the Linear Regression Method (Non-hemophilics only)

Stage	Observed								Estimated
	Wave 1# N=449	Wave 2 N=444	Wave 3 N=422	Wave 4 N=419	Wave 5 N=421	Wave 6 N=429	Wave 7 N=472	Wave 8 323	
RNA-	18.0	21.3	20.4	23.9	25.8	32.6	32.7	33.2	36.9
RNA+	23.9	24.8	29.8	32.5	31.2	26.5	29.0	26.6	28.9
F1	28.8	28.3	24.1	23.5	23.4	20.8	24.4	19.7	18.9
F2/F3	7.4	6.6	4.4	4.2	3.7	4.3	5.2	7.2	4.7
F4	9.7	7.0	9.0	9.1	8.1	7.2	5.2	7.5	6.0
Decompensated HCC	8.3	8.1	8.8	3.9	6.3	6.1	2.7	3.8	2.9
	2.0	2.0	2.1	2.7	2.1	1.6	1.1	1.6	1.4
Transplant	1.8	1.6	1.4	0.7	0.7	0.9	0.0	0.3	0.3
Total	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100%

Table 9.1-3 Estimated Stage Distribution of Potential Future Claimants Using the Linear Regression Method (Hemophilics)

Stage	Observed								Estimated
	Wave 1# N=151	Wave 2 N=156	Wave 3 N=178	Wave 4 N=181	Wave 5 N=179	Wave 6 N=171	Wave 7 N=128	Wave 8 N=108	
RNA-	11.9	20.0	17.7	18.7	19.9	28.2	26.3	42.6	38.2
RNA+	18.9	17.3	26.9	24.4	23.3	26.4	27.2	20.7	25.6
F1	32.9	38.0	30.2	38.6	35.1	30.0	29.8	24.1	25.7
F2/F3	6.3	6.0	5.2	2.8	3.5	2.4	1.7	3.4	1.7
F4	18.9	11.3	8.6	9.7	9.4	5.6	7.9	8.0	5.5
Decompensated HCC	7.7	6.0	8.6	4.0	8.2	6.8	6.1	1.1	2.5
	3.5	0.7	1.7	1.1	0.0	0.6	0.9	0.0	0.5
Transplant	0.0	0.7	1.1	0.6	0.6	0.0	0.0	0.0	0.4
Total	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100%

Table 9.1-4. Estimated Current Distribution (%) of Alive, Non-hemophilic HCV patients Who Were Infected During 1986-1990, and Have Not Claimed for Compensation Prior to 2004.

	Predicted Stage distribution, 2004	Observed Claimants (adjusted stage)	Assumed total number of patients infected during 1986 and 1990 and alive now																	
			9239			8104			7000			6000			5000			4000		
			Pred.#	Un-known	Un-known	Pred.#	Un-known	Un-known	Pred.#	Un-known	Unknow	Pred.#	Un-known	Un-known	Pred.#	Un-known	Un-known	Pred.#	Un-known	Un-known
RNA-	22.4%	654	2070	1416	21.4%	1815	1161	21.2%	1568	914	20.9%	1344	690	20.2%	1120	466	19.6%	896	242	17.6%
RNA+	22.0%	776	2033	1257	19.0%	1783	1007	18.4%	1540	764	17.5%	1320	544	15.9%	1100	324	13.7%	880	104	7.6%
F1	32.0%	649	2956	2307	34.9%	2593	1944	35.5%	2240	1591	36.4%	1920	1271	37.2%	1600	951	40.1%	1280	631	46.0%
F2	9.9%	182	915	733	11.1%	802	620	11.3%	693	511	11.7%	594	412	12.1%	495	313	13.2%	396	214	15.6%
F3	6.0%	111	554	443	6.7%	486	375	6.9%	420	309	7.1%	360	249	7.3%	300	189	8.0%	240	129	9.4%
F4	6.2%	175	573	398	6.0%	502	327	6.0%	434	259	5.9%	372	194	5.7%	310	123	5.2%	248	51	3.7%
Decomp	0.7%	41	65	24	0.4%	57	16	0.3%	49	8	0.2%	42	1	0.0%	35	0	0.0%	28	0	0.0%
HCC	0.5%	18	46	28	0.4%	41	23	0.4%	35	17	0.4%	30	12	0.4%	25	7	0.3%	20	2	0.1%
Transplant	0.3%	21	28	7	0.1%	24	3	0.1%	21	0	0.0%	18	0	0.0%	15	0	0.0%	12	0	0.0%
Total	100%	2627	9239	6612	100%	8104	5477	100%	7000	4373	100.0%	6000	3373	98.8%	5000	2373	100%	4000	1373	100%

Note: The estimation is approached through following steps. 1. Predict the total number of patients in each stage by multiplying the predicted distribution by the assumed total number of patients infected and still alive. 2. Find the difference, by stage, between the predicted numbers of patients and the number who have come forward for compensation. 3. Calculate the estimated stage distribution using the derived number of patients in each stage. 4. The observed number of patients with HCC and transplant are much higher than predicted. We assume that the claimant data may have been contaminated by infections before 1986, and ignore these patients. 5. The current survival rate of this cohort is about 41.6% according to model prediction.

12. Figures

Figure 2.1 Structure of Decision Model As Programmed in DATA Pro.

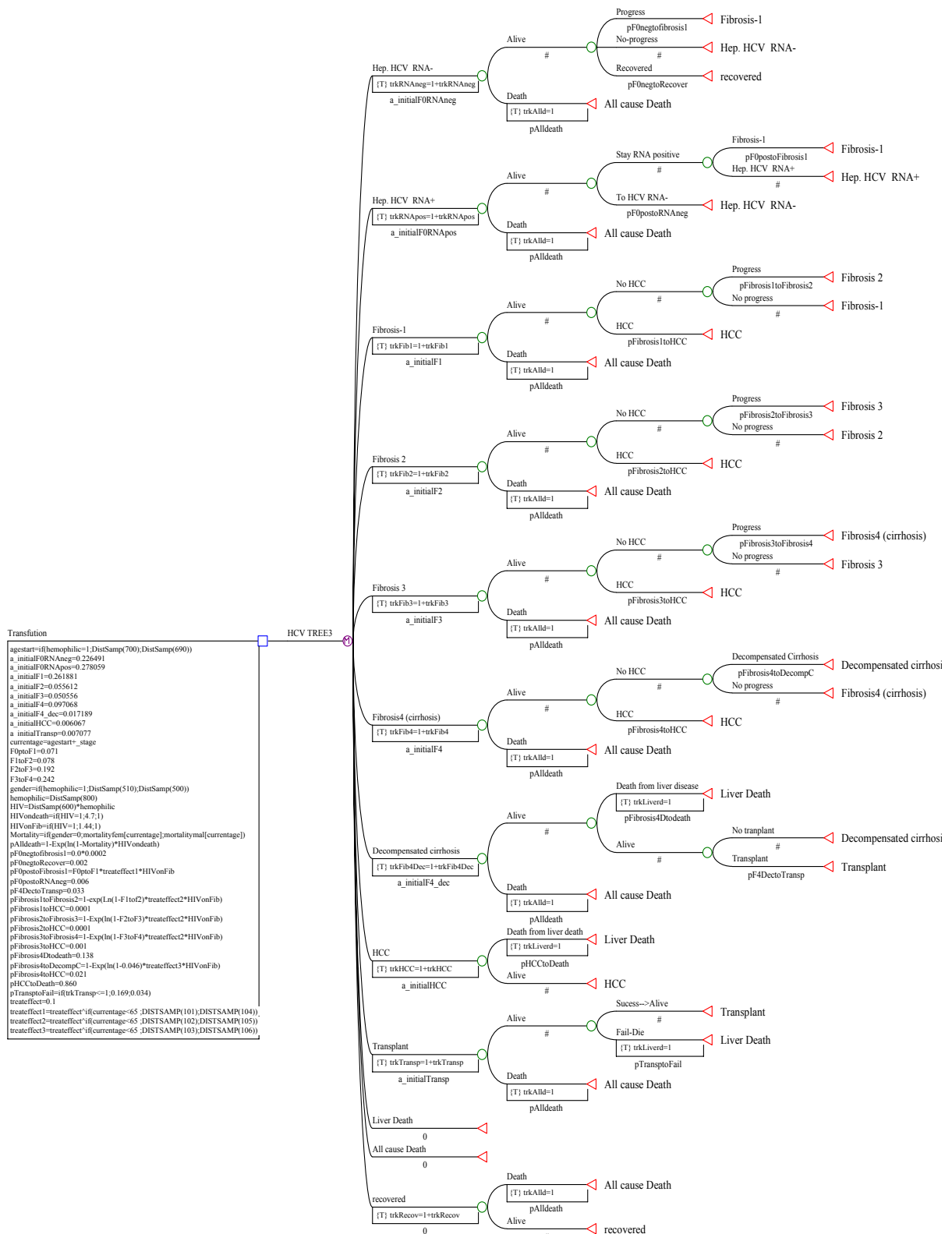


Figure 5.1 Age at Time of Infection Among HCV Compensation Claimants

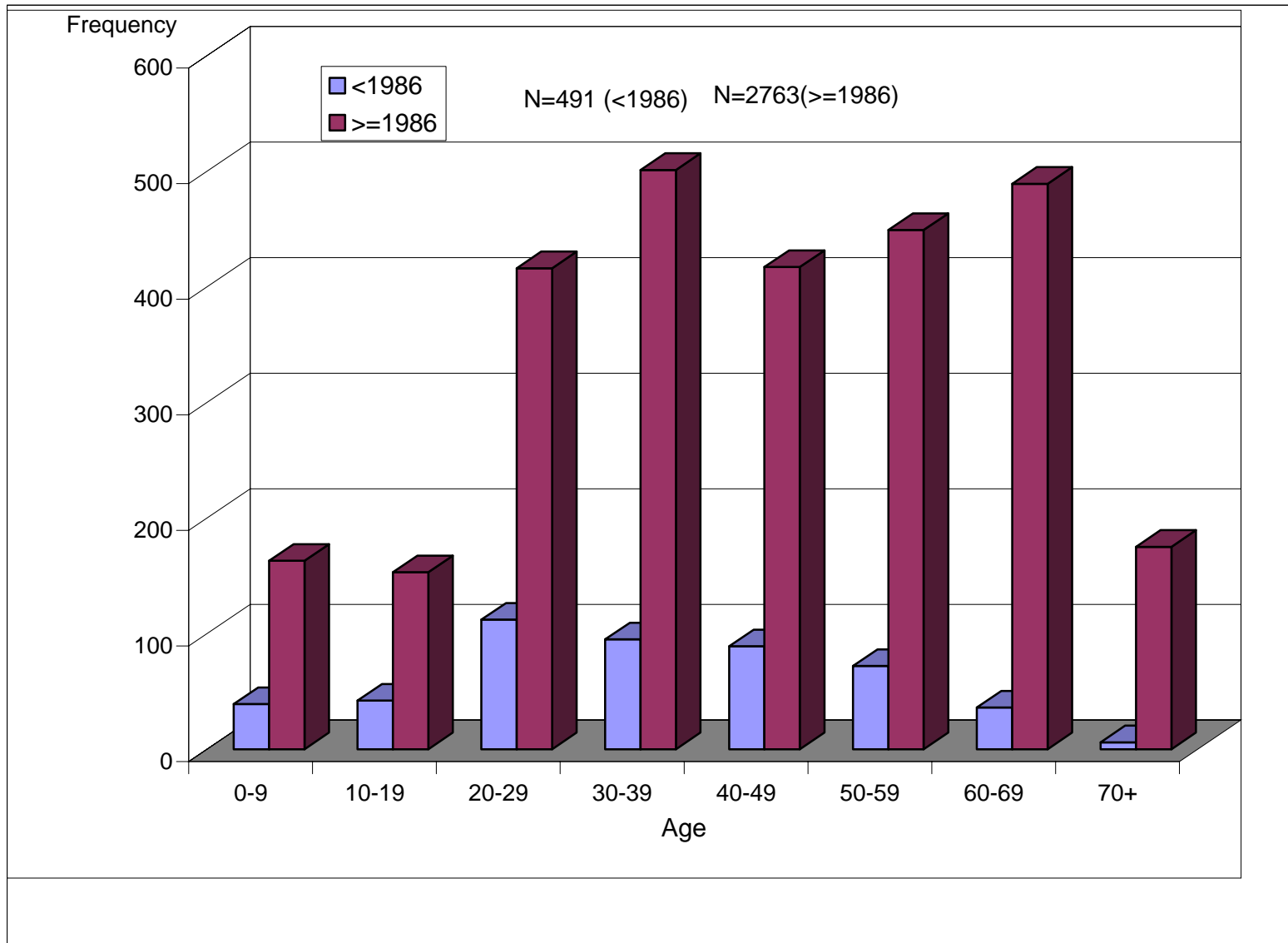


Figure 5.2 Province of Residence, HCV Compensation Claimants

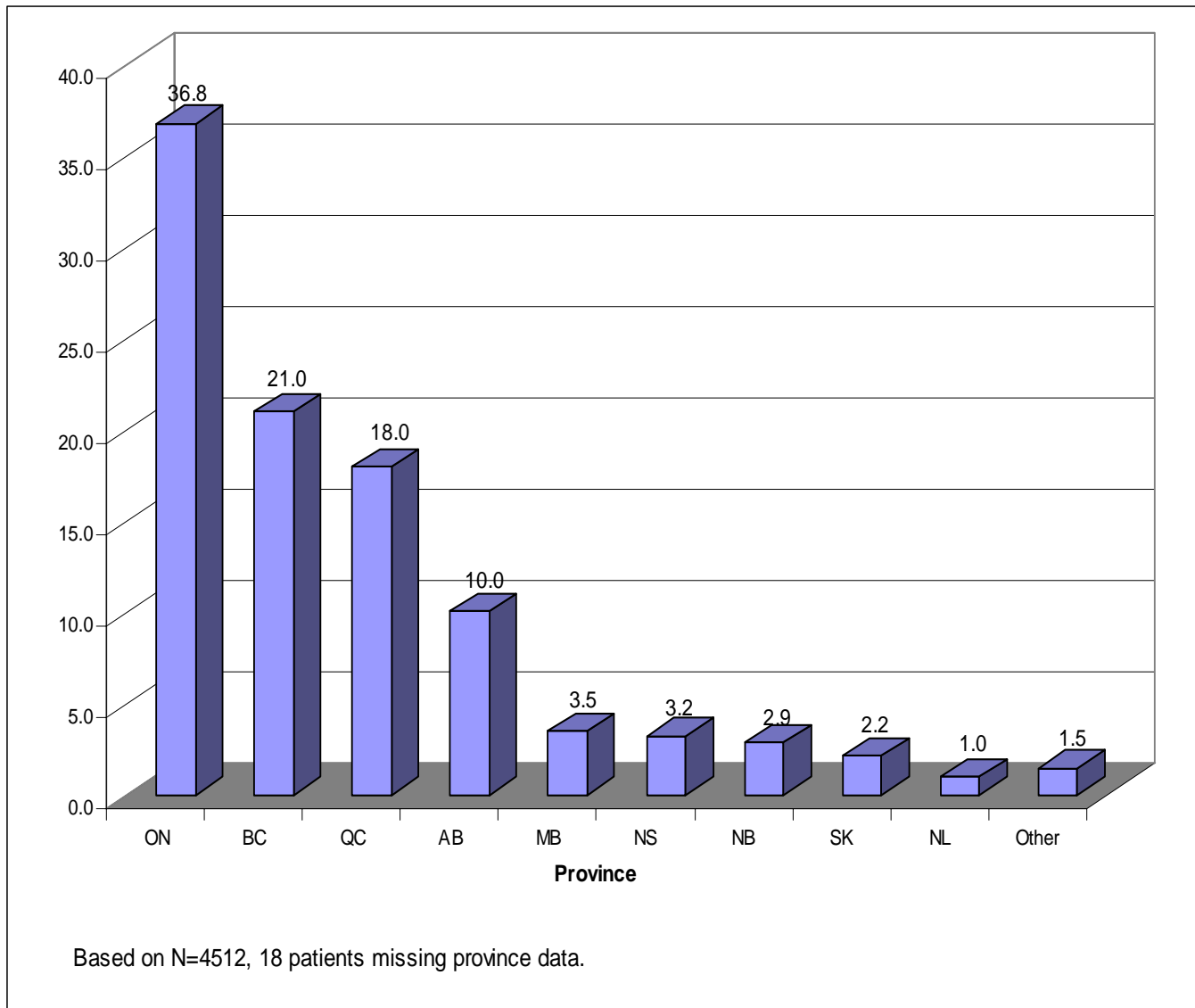


Figure 5.3 Compensation level and Mortality

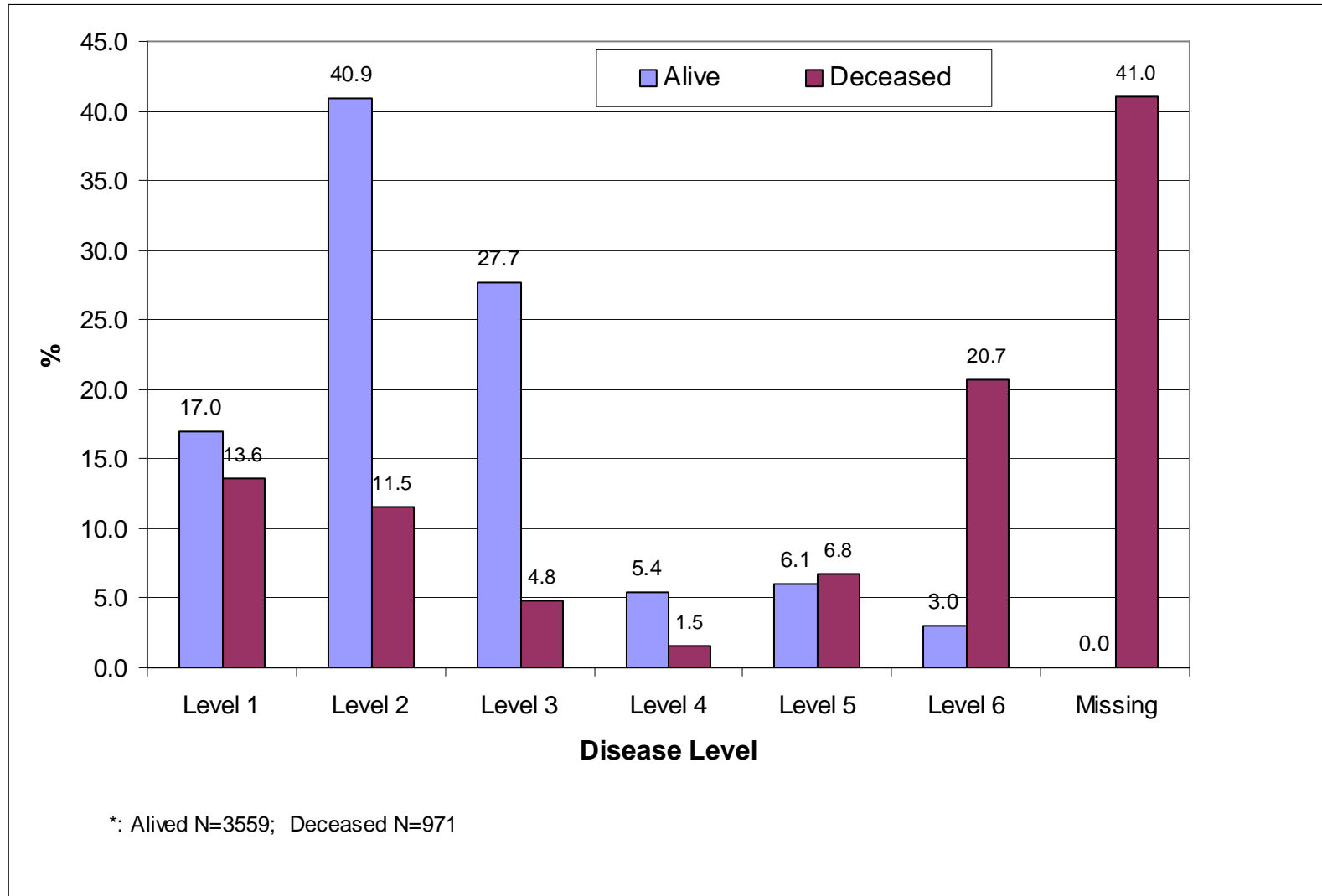


Figure 5.4 Distribution of Disease Severity by Fibrosis Stage

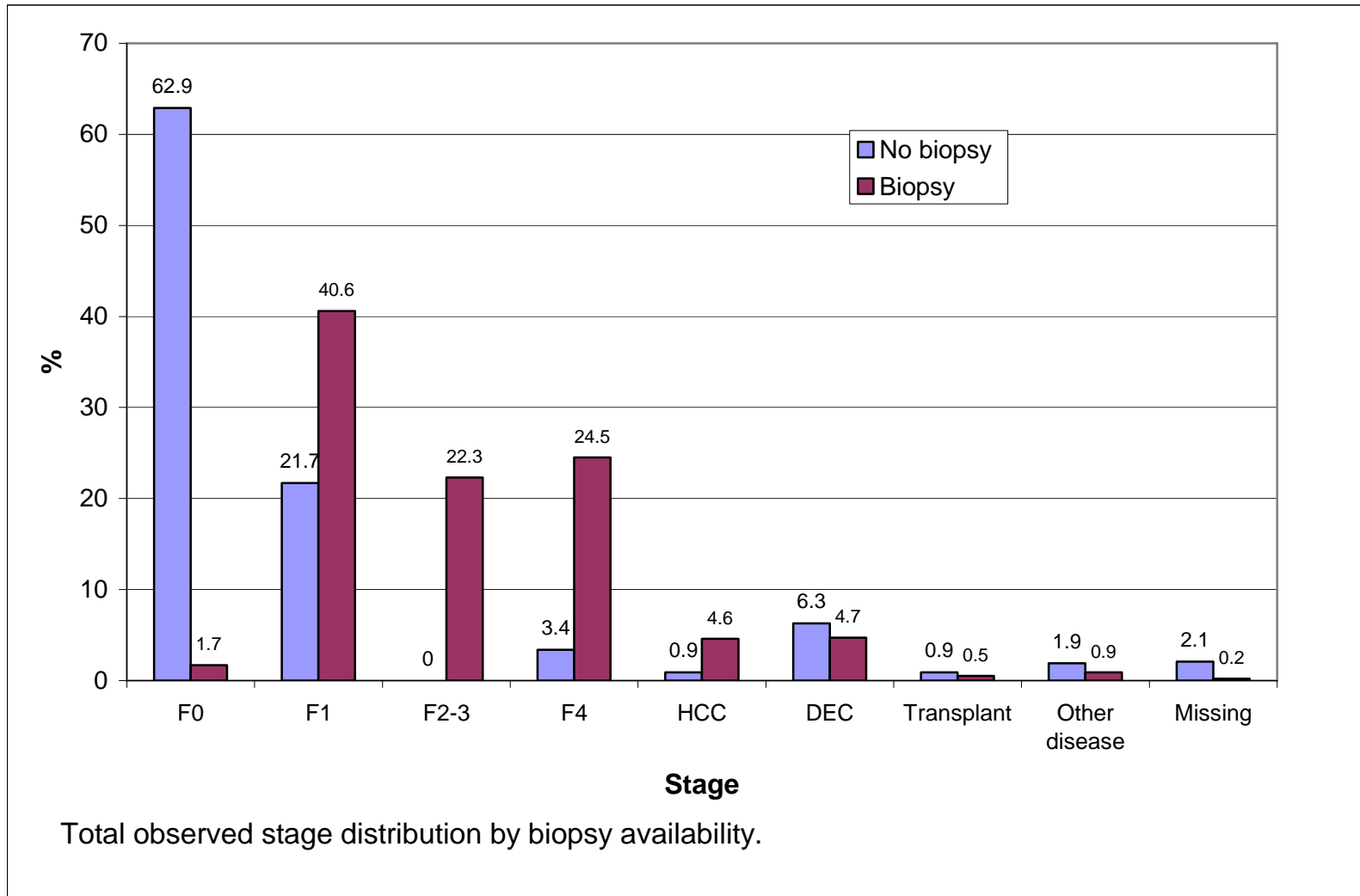


Figure 5.6 Distribution of Projected and Observed HCV Stage Distribution, HCV Compensation Claimants

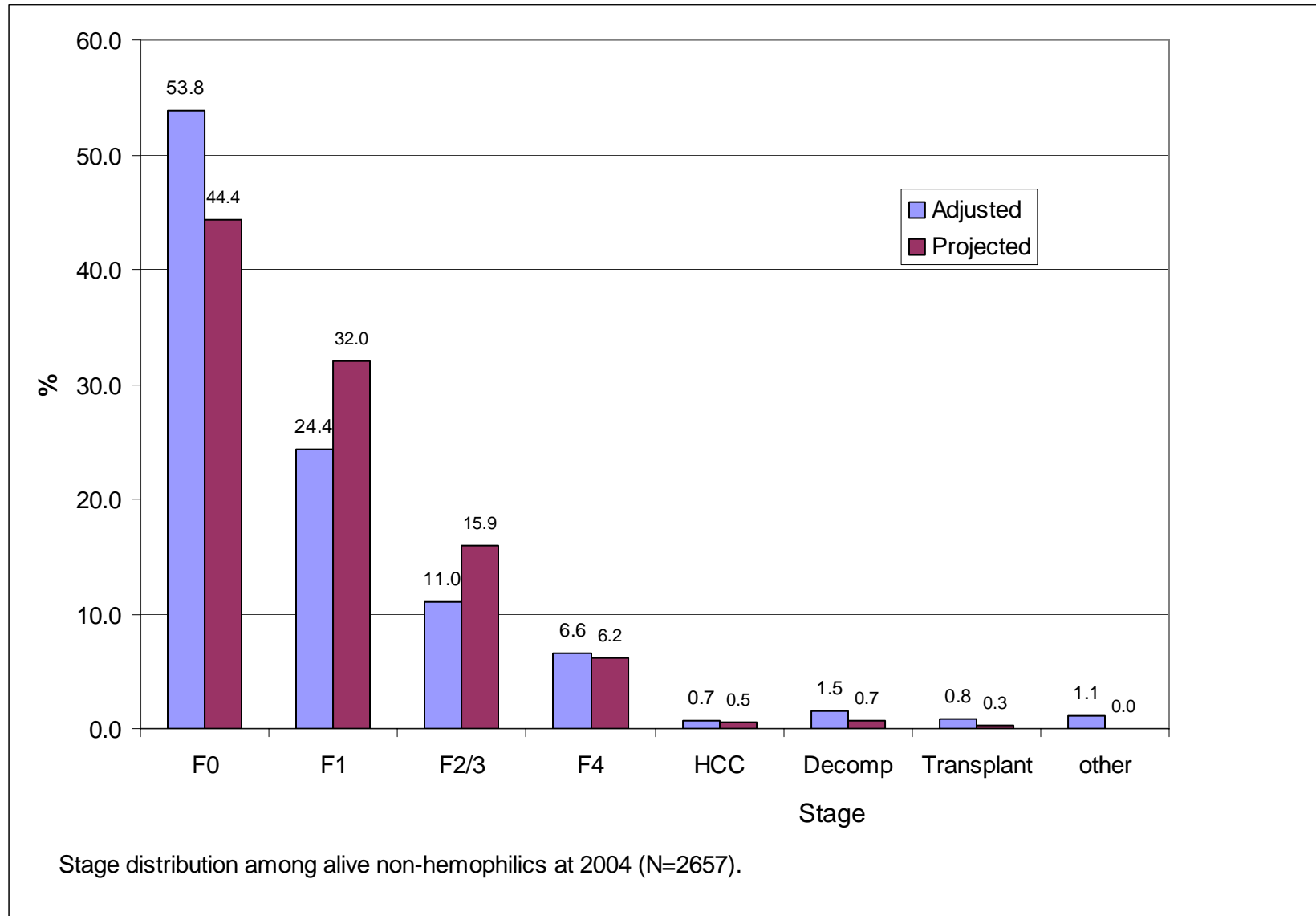
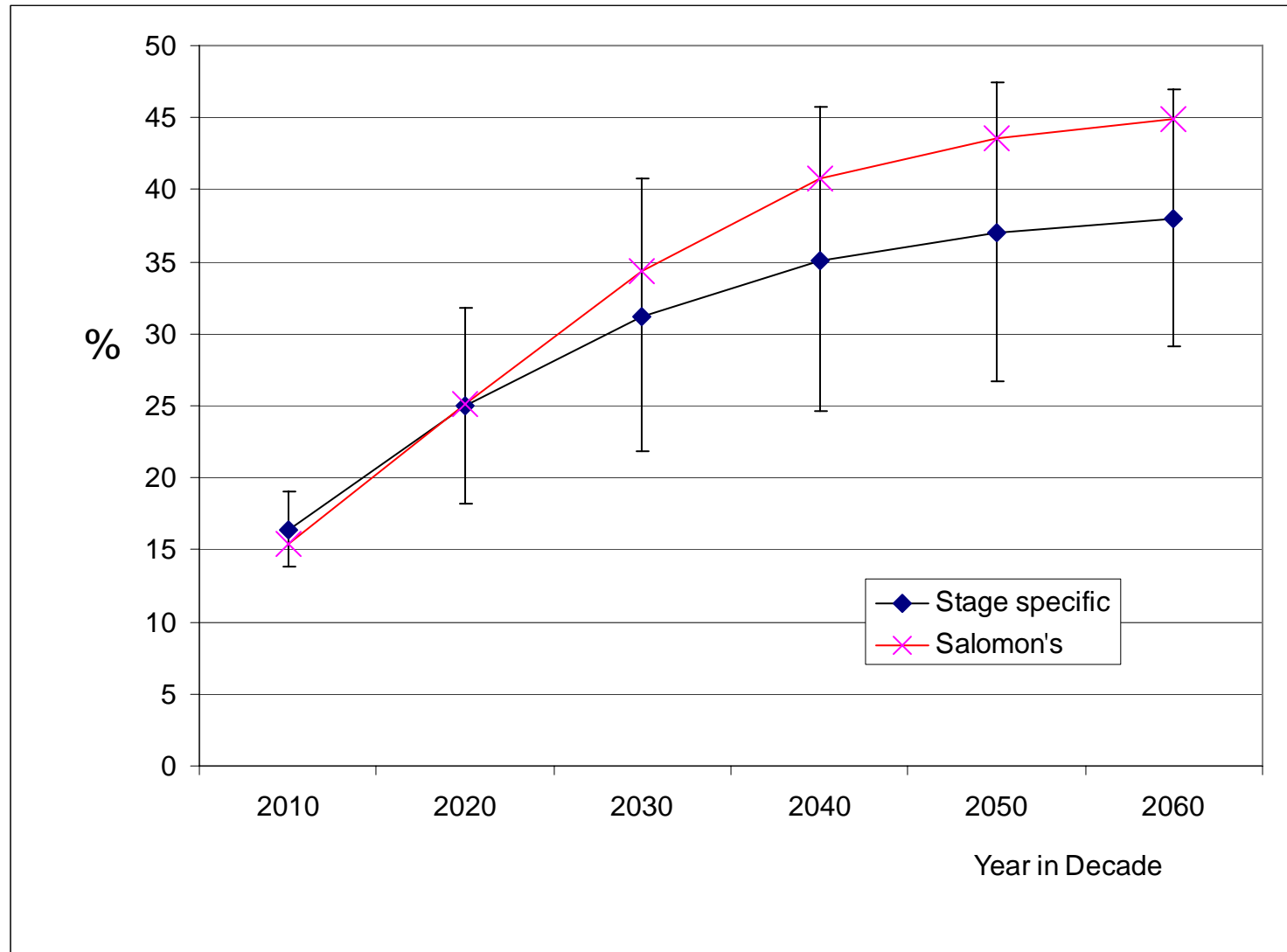


Figure 7.1 Model Validation: Cumulative Proportion with Cirrhosis, 2004 Model (stage specific transition rates) vs. Salomon (age and gender specific transition rates)



Appendix A. Publications derived from this study:

1. Krahn M, Wong JB, Heathcote J, Scully L, Seeff L. Estimating the prognosis of hepatitis C patients infected by transfusion in Canada between 1986 and 1990. *Med Decis Making*. 2004 Jan-Feb;24(1):20-9.
2. Wang P, Yi Q, Scully L, Heathcote J, Krahn M. Indications for interferon/ribavirin therapy in hepatitis C patients: findings from a survey of Canadian hepatologists. *Can J Gastroenterol* 2003;17(3):183-6.
3. Yi Q, Wang PP, Krahn M. Improving the accuracy of long-term prognostic estimates in hepatitis C virus infection. *J Viral Hepat* 2004;11(2):166-74.

Appendix B. SAS Code Used in the Markov-Maximum Likelihood Method

```
options ls=75;

%macro transition(pdis,year);
proc iml;
  use &pdis;
  read all into p;
  year=&year;
  ini={0.10 0.10 0.10 0.10 };
  x={1 0 0 0};

do i=1 to 30000;
  tran=j(5,5,0);
  tran[1,2]=ini[1];tran[2,3]=ini[2];tran[3,4]=ini[3];
  tran[4,5]=ini[4];tran[5,5]=1;
  tran[1,1]=1-ini[1];tran[2,2]=1-ini[2];tran[3,3]=1-ini[3];
  tran[4,4]=1-ini[4];

tran5=tran**year;
xtran5=x*tran5;
rs=xtran5-p; rs2=rs*rs`;

if rs2<=0.000001 then do;
  tranrate=ini; p_end=xtran5;p_begin=p; residual=rs2;
  iteration=i;
  print"Estimated transition probability";
  print p_begin;
  print p_end residual;
  print tranrate iteration;
  stop;
end;
do j=1 to 4;
  if rs26 < 0 then ini26 = ini26-0.00001;
  if rs26 > 0 then ini26 = ini26+0.00001;
end;
end;
if rs2>0.000001 then do;
print"Estimated transition probability without converge";

  print xtran5;
  print ini;
  print p rs2 i;
end;
quit;
%mend;

*****example: *****;
*****Kenny Walsh (excluding 20% RNA-)*****;
```

```
data tt;  
input f0 f1 f2 f3 f4;  
cards;  
0.490 0.34 0.10 0.05 0.02  
;  
run;      %transition(tt,17)
```

Appendix C. Survey

P. Peter Wang, M.D., Ph.D
Assistant Professor
Department of Public Health Sc
University of Toronto
Fax: 416-340-4105
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Date: Nov. 22, 2004

Dear Dr. xxx,

You may recall that in 2001 we sent you a questionnaire about your antiviral treatment practices for hepatitis C patients. We very much appreciated your help then. Your clinical insights were incorporated into the prognostic models we developed for the Joint Committee administering the \$1.1 billion compensation agreement for individuals who acquired hepatitis C through the blood supply.

Three years have passed and now we have been asked to revise our prognostic models. Once again, the effects of antiviral treatment remain as important part of our predictions of the long term prognosis of these individuals. As you know, peginterferon, which has been proven to be more effective in treating chronic hepatitis patients, has become a mainstream therapy in the past few years. Thus we suspect that these changes may have affected or will affect physicians' practice. We are writing to ask for your help by answering two brief questions. I realize that this request is only one of many demands on your time and trust that you can help with this very important task. To save your time, you can either fax or e-mail your answers with question numbers back to me.

Thank you

Peter

Questions 1.

By June, year 2001, 2466 Canadian hepatitis C patients filed claims for financial compensation. In the 2001 data set, the proportion who had ever received anti-viral treatment was **14.1%**. By June 2004, the number of claimants (including deceased) increased to 4,530. In the 2004 data, the proportion of those who ever received antiviral treatment increased to **16.2%**. Now we would like to ask your opinions (your best estimate) in terms of the proportion of patients who will have received antiviral treatment 10 years from now. _____%

For your reference, the following two tables provide disease and patient characteristics associated with the patients of interest.

Table 1. **Estimated Fibrosis stage** distribution in compensation claimants in June, 2004.

	F0	F1	F2-F3	Cirrhosis	Transplant	Decompensated cirrhosis	HCC	Others
N	1751	929	490	255	62	24	22	36
%	49.2	26.1	13.5	7.2	1.74	0.67	0.62	1.01

Table 2. Other selected characteristics

Age Mean ≈53	<40	25%
	>40	75%
Sex	Male	53%
	Female	47%
Hemophilia	Yes	27.3%
	No	72.7%

Question 2.

2A: What percentage of patients with mild hepatitis/no-fibrosis do you treat? _____%

2B: What percentage of patients with moderate-severe hepatitis with fibrosis do you treat? _____%

2C: What percentage of patients with well compensated cirrhosis do you treat? _____%

2D: What percentage of patients with decompensated cirrhosis do you treat? _____%

2004 Hepatologist survey

Physician	Q1 (%)	Q2a (%)	Q2b (%)	Q2c (%)	Q2d (5)	
1	35	10	70	40	0	
2	60	10	95	99	20	
3	30	5	90	80	0	
4	50	15	75	75	25	
5	27	30	60	60	0	
6	50	25	90	80	0	
7	30	20	60	20	0	
8	40	10	90	100	0	
9	25	10	70	10	2	
Average	38.6%	15.0%	77.8%	62.7%	5.2%	
Result from last survey		13.8	80	75	0	

Q2.

Q2a: What percentage of patients with mild hepatitis/no-fibrosis do you treat? ____%

Q2b: What percentage of patients with moderate-severe hepatitis with fibrosis do you treat? ____%

Q2c: What percentage of patients with well compensated cirrhosis do you treat? ____%

Q23: What percentage of patients with decompensated cirrhosis do you treat? ____%

Based on currently treating pattern and HCV stage distribution, we have estimated the proportion who are under treatment of 39.1%. $P = \sum d_i \times p_i$ where P is the proportion of people receiving anti-viral treatment; d_i is proportion of adjusted HCV stage i in current cohort, p_i is the physician estimated proportion receiving treatment for people in stage i.

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