Hep C Calculator

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The *Hep C Testing Calculator* is an interactive tool designed to evaluate the cost-effectiveness of different testing pathways for hepatitis C virus (HCV). The tool uses a mathematical model to simulate HCV disease progression. Users can select a country of interest and then input costs, HCV prevalence, screening rate, and custom testing pathways. Users can then evaluate the effectiveness and cost-effectiveness of each diagnostic pathway. For the testing pathways, the type of test used, cost of the test, testing location (on-site or off-site), and patient follow-up rate for each stage in the screening pathway can be changed. The customizability allows users to determine which testing strategies would be appropriate in various localized settings, as HCV prevalence can vary substantially by jurisdiction, and differences in population characteristics and resources create different opportunities for testing and engaging patients in care.

To estimate lifetime disease management costs and outcomes for HCV patients who receive treatment compared to those who do not receive treatment, the tool using a previously validated microsimulation model of the natural history of HCV.[1, 2]

Input and Output Panels

An input panel at the top of the *Hep C Testing Calculator* allows users to select a country, cohort size (total population to be considered for screening), screening rate, HCV antibody and viremia rates, and local prices of direct-acting antivirals (DAAs) for treatment. Changing the country changes the underlying disease burden model as well as the default parameters in the tool. Then, users can input up to 8 testing pathways. An interactive interface allows users to create custom testing pathways, which are defined by different steps in the pathway: screening, confirmation, liver staging 1, liver staging 2, genotyping, monitoring, and SVR12. The type of test used, cost of the test, testing location (on-site or off-site), and patient follow-up rate for each stage in the screening pathway can be changed. In addition to adding customized testing pathways, users can also add 5 default pathways.

When results are generated, each testing pathway is compared to all of the other user-input pathways, as well as what happens when no testing for hepatitis C occurs. The total costs and outcomes associated with each testing pathway (over a 30-year period) are displayed, and incremental cost-effectiveness ratios are calculated. A preferred testing pathway is recommended based on a cost-effectiveness threshold. The cost-effectiveness threshold is based on a willingness to pay (WTP) of 1 - 3 times the gross domestic product per capita (depending on the income level of the country) per quality-adjusted life-year gained. This WTP threshold can also be changed by the user. Users can evaluate the following outcomes for each strategy: diagnostic costs per treated patient, total screening costs, total lifetime healthcare costs (including the cost of DAA treatment and of downstream events such as liver cancer), quality-adjusted life years (QALYs), and the cumulative incidences of decompensated cirrhosis, liver cancer, and HCV-related deaths.

Testing Pathways

Patient flow is customized in each testing pathway based on user-input values. The number of people in the cohort who receive the screening test is dependent on the user-input screening rate. Both the

screening and confirmation tests will generate false positive and false negative results based on the sensitivity and specificity of the test used (table 1). The percentage of people that follow up to all stages of testing after the? screening will depend on the user-input follow-up rate for that test—however, only people with a positive antibody test will move forward to confirmation, and only people with a positive confirmation result will move on to subsequent stages. Table 1 provides the performance characteristics of different tests.

Table 1. Performance characteristics of tests used in Hep C Calculator

Test	Sensitivity	Specificity
HCV Antibody Screening [3]	0.980	1.000
RNA [4]	0.998	0.997
cAg [5]	0.934	0.988

Treatment is assumed to happen after whichever is the latest of: liver staging 1, liver staging 2, or genotyping (depending on if any of these stages are skipped). People who have received a false positive confirmation test will incur treatment costs with no benefit if genotyping is skipped in the pathway, however, if genotyping occurs these false positives are assumed to be detected and will not incur treatment costs. Any tests occurring after treatment (such as SVR12) will only affect costs, not outcomes.

For any stage in the pathway, all people who follow up for that stage will receive the test, which is a limitation based on some liver-staging strategies. For example, if there is a second round of liver staging, all people who follow up will receive this test—there is no option to only conduct this test for a small portion of patients based on the first round of liver staging.

Natural History of Hepatitis C Virus

The life course of HCV-infected populations is simulated through the use of a previously validated mathematical model, the *Markov-based Analyses of Treatments for Chronic Hepatitis C* (*MATCH),*[1, 2] and utilized to determine the cost-effectiveness of DAAs.

Characteristics of Base Case Population

Our base case population included HCV-infected persons with a user-defined age (in years), distribution of HCV genotype (G1, G3, or G4), and METAVIR fibrosis score (no fibrosis [F0], portal fibrosis without septa [F1], portal fibrosis with few septa [F2], numerous septa without fibrosis [F3], or cirrhosis [F4]). On choosing a country, data on HCV genotype distribution and fibrosis distribution for the particular country, as extracted from the Polaris Observatory (http://polarisobservatory.org/), are fed into the *Hep C Calculator*. However, a user can also choose to manually change the patients' mean age and the relative frequency of fibrosis distribution.

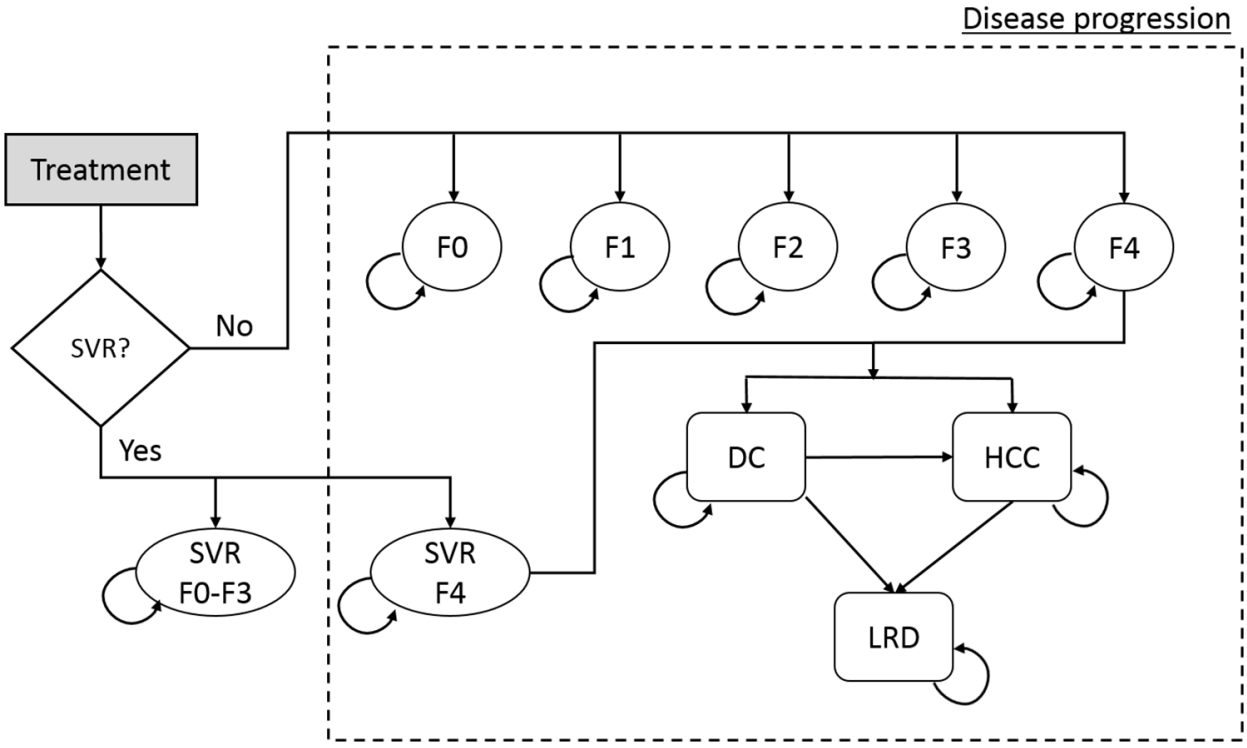
Treatment Regimens and Efficacy

The treatment regimen and duration are dependent on HCV genotype and fibrosis stage. Treatment efficacy, adverse events, and premature treatment discontinuation rates for each treatment regimen are modeled on data from clinical trials of DAAs in treatment-naïve patients.[6-9]

Natural History of HCV Infection

The natural history of HCV infection and progression are defined as transition rates between Markov health states. Each patient starts in one of five METAVIR liver fibrosis states (F0–F4; as defined by the user's input) (**Figure 1**), and can, at the end of each cycle (i.e., month), remain in the same state, die from background mortality, move into a higher fibrosis state, or progress to decompensated cirrhosis and/or HCC, or liver-related death. Patients in F0-F3 states who achieved SVR are assumed to be cured and to follow background mortality thereafter; however, those initially in F4 state who achieve SVR can progress to more advanced states (decompensated cirrhosis and hepatocellular cancer), albeit at a slower rate. Patients who fail to achieve SVR or who discontinue treatment are assumed to continue to progress over time at their baseline rate. **Table 2** provides the base case values of transition probabilities, i.e., the probability of a person progressing from one health state to the other.

Figure 1: State-transition model schematic showing the natural history of hepatitis C virus infection.



Abbreviations: DC = decompensated cirrhosis; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; LRD = liver-related death; SVR = sustained virologic response; F0–F4 = METAVIR fibrosis score.

Table 2: Annual transition probabilities for different Markov states of the mathematical model used in Hep C Calculator.

Transition *probabilities (annual)*	Base case
F0 to F1 [10]	0.117
F1 to F2 [10]	0.085
F2 to F3 [10]	0.120
F3 to F4 [10]	0.116
F4 to DC [11]	0.039
F4 to HCC [11]	0.014
Post F4-SVR to DC [12]	0.008
Post F4-SVR to HCC [12]	0.005
DC to HCC [13]	0.068
DC (first year) to death from liver disease [13]	0.182
DC (subsequent year) to death from liver disease [13]	0.112
HCC to death from liver disease [11]	0.427

Abbreviations: SVR = sustained virologic response; F0–F4 = METAVIR fibrosis score; DC = decompensated cirrhosis; HCC = hepatocellular carcinoma; F4-SVR = post-SVR state of treated cirrhosis patient

Quality-of-life weights

The quality-of-life (QoL) weights for each health state are based on the disability weights (QOL = 1 – disability weight) as defined by the Global Burden of Disease study (0 for METAVIR scores F0–F4, 0.194 [range 0.127–0.273] for decompensated cirrhosis, and 0.508 [0.348–0.67] for HCC).[14] We have used these standard weights for all countries.

Hepatitis C Virus Sequelae Management Costs

Disease management costs, in U.S. dollars (USD), were estimated for each country in the tool. The overall cost estimates for each sequela were calculated through a five-step process.

First, the initial costs for inpatient and outpatient services were derived from the WHO-CHOICE tool for each country.[15] Next, these service costs were multiplied by the average quantity of that service (inpatient versus outpatient) consumed within each disease stage to obtain an estimate of the management cost for each hepatitis C sequela in international dollars (I$). For this calculation, the proportion of inpatient services was estimated to be 0.3807 for F0 through F3, 0.4329 for F4, 0.6589 for DC, and 0.5547 for HCC. These management costs were computed for each country in the tool and the United States. Third, these I$ management costs were next converted into USD. In order to convert these costs to U.S. dollars, a baseline annual cost for each health stage within the U.S. was obtained from Chhatwal et al. 2015.[1] Using the CPI inflation calculator, the dollar values reported in this paper were scaled from 2015 USD to 2020 USD to account for inflation.[16] After this conversion, the estimated annual costs (USD) in the U.S. for F0 and F1 were $802.32, $812.23 for F2, $1,648.73 for F3, $1,923.15 for F4, $21,368.47 for DC, and $39,295.00 for HCC. Fourth, a ratio of the WHO-choice tool management costs in I$ was calculated for each stage, within each country, relative to the U.S. estimate for that same stage. Lastly, the relative cost ratio for each stage was multiplied by the U.S. baseline annual cost for the

corresponding stage to compute country-specific disease sequelae management costs in USD. The table below contains these final values.

Table 3: Disease sequelae management costs for each country in the Hep C Calculator. These costs are derived from the WHO-CHOICE tool[15] and converted into 2020 USD.

Hepatitis C Management Costs	Georgia (in USD)	Malaysia (in USD)	India (in USD)	Pakistan (in USD)
F0	64.92	233.02	42.02	31.35
F1	64.92	233.02	42.02	31.35
F2	65.72	225.77	42.54	31.73
F3	133.41	458.29	86.34	64.42
F4	152.50	529.79	98.23	73.05
DC	1,599.89	5,742.59	1,016.28	748.14
HCC	3,007.16	10,658.13	1,920.62	1,419.46

Abbreviations: F0–F4 = METAVIR fibrosis score; DC = decompensated cirrhosis; HCC = hepatocellular carcinoma

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