Economically-Efficient Hepatitis C Virus Treatment Prioritization Improves Health Outcomes

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Appendix S2

This document contains

- Excel Model Documentation and User Guide
- Appendix Figures S6-S8

EXCEL MODEL DOCUMENTATION AND USER GUIDE

The spreadsheet model implemented in Microsoft Excel is available for download as Appendix S3.

Overview

The purpose of the HCV treatment budget allocation model is to evaluate and compare different HCV treatment prioritization strategies. The model simulates a population of individuals with chronic HCV infection from ages 40 to 79 in 3-month time steps. For a specific set of patient demand assumptions and patient prioritization decisions, the model calculates the budget impact of treatment for each of the next 25 years, health outcomes (the number of individuals with compensated cirrhosis, the number of individuals who develop hepatocellular carcinoma (HCC), and the number of individuals who progress to decompensated cirrhosis (DC)), and health economic outcomes for the entire population (total lifetime discounted costs and quality-adjusted life-years (QALYs)).

By changing the model inputs, users can tailor the model to their situation (changing the total number of individuals eligible for treatment and their budget constraint) and the characteristics of their patient population (age-, gender-, and fibrosis distribution). Users can explore the impacts of different budget levels, different prioritization policies, and use the optimization framework to identify the prioritization guideline that maximizes net monetary benefit.

This workbook was developed for Microsoft Excel 2007-2016 for Windows. Most of the workbook works without VBA macros. However, VBA macros must be enabled to use the optimization component and some of the buttons added to the spreadsheet for user convenience.

This is a large spreadsheet with many calculations. User experience may be improved by turning calculations from Automatic to Manual (found in the Formulas ribbon under "Calculation Options"). With calculations set to Manual, press F9 to recalculate the worksheet.

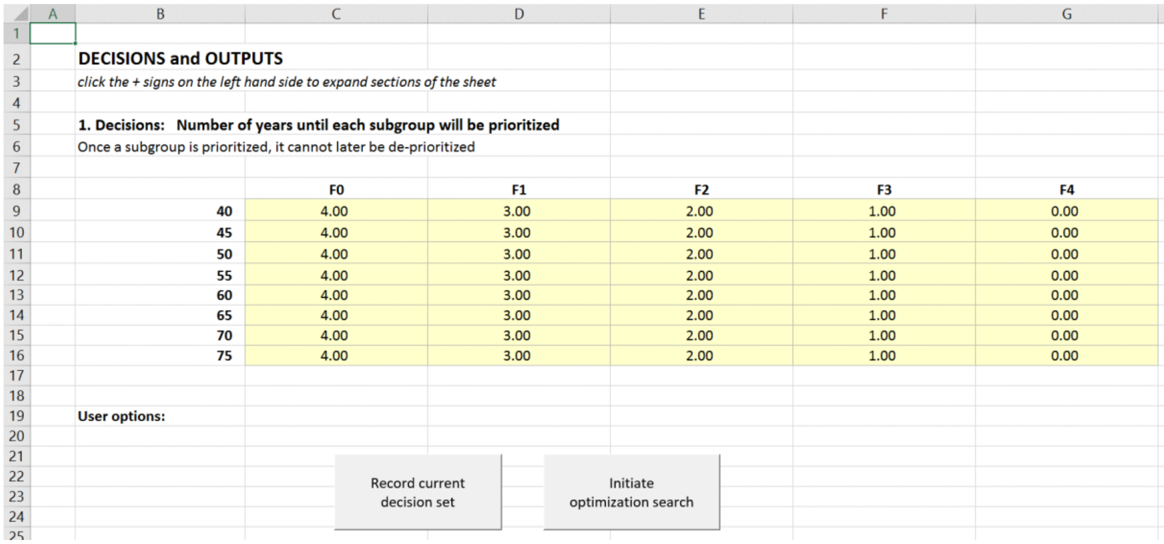
The spreadsheet model is organized over nine worksheets: Inputs, Decisions and Outputs, Intermediate Calculations – Markov, Markov WM, Markov WF, Markov BM, Markov BF, and Optimization Output, and Intermediate Calculations – Optimization. There are no hidden worksheets or protected cells. In the sections below, we provide a summary of how to use the model, a detailed description of each worksheet, a detailed description of the optimization process including the relevant sections of the spreadsheet and the Visual Basic for Applications (VBA) macros that run the optimization.

Using the model

To tailor the model to a specific population or to the perspective of a specific decision maker, users can update the inputs to values on the Inputs worksheet (described in detail in the sections below). After updating the model inputs, users can use the model in two primary ways: (1) Estimate the budget and health impacts of a user-defined, potential prioritization policy; and (2) Identify the guideline using optimization that maximizes net monetary benefit subject to a set of budget constraints.

1. **Estimate the budget and health impacts of a user-defined potential prioritization policy.**

On the Decisions and Outputs worksheet, the user can directly modify the decisions in the table at the top of the page:



DECISIONS and OUTPUTS

click the + signs on the left hand side to expand sections of the sheet

1. Decisions: Number of years until each subgroup will be prioritized

Once a subgroup is prioritized, it cannot later be de-prioritized

	F0	F1	F2	F3	F4
40	4.00	3.00	2.00	1.00	0.00
45	4.00	3.00	2.00	1.00	0.00
50	4.00	3.00	2.00	1.00	0.00
55	4.00	3.00	2.00	1.00	0.00
60	4.00	3.00	2.00	1.00	0.00
65	4.00	3.00	2.00	1.00	0.00
70	4.00	3.00	2.00	1.00	0.00
75	4.00	3.00	2.00	1.00	0.00

User options:

Record current decision set

Initiate optimization search

The model will then update (press F9 to update if you have set calculations to manual). A summary of health economic outputs, budget impacts, and population health outputs are then presented in the subsequent sections of the Decisions and Outputs worksheet.

The user can save sets of decisions by hitting the "Record current decision set" button. These sets of decisions are saved on the Optimization Output worksheet. The only output stored with the decision set is the net monetary benefit. If the user wants to calculate all model outputs for a previously saved set of decisions, call up that set of decisions by entering its solution number in cell C6 on the Optimization Outputs worksheet and then press the "Transfer this decision set to the model decisions" button.

2. Identify the guideline using optimization that maximizes net monetary benefit subject to a set of budget constraints.

On the Decisions and Outputs worksheet, just below the decisions is a button labelled "Initiate optimization search". Before the optimization begins, the user will be asked a series of questions:

- If you have previously saved results, a pop-up box will inform you of that and ask if you want to delete these results or to add to them with the results produced by the optimization search. Before deleting results, a second pop-up box will ask you to confirm your choice.
- An input box will ask how many iterations of the search procedure you want to do. The first time you run the optimization, choose a small number (i.e., five) to estimate the processing time. On a standard home desktop computer, we estimate it will take about 5 minutes per iteration. However, the larger the ratio of demand to budget, the longer the processing time for each iteration. In our experience, a single iteration can take as long as 15 minutes.

A pop-up box will announce when the runs are complete. If you need to stop the runs before the search is complete, hit the Esc key. You can then End the VBA script that this currently running.

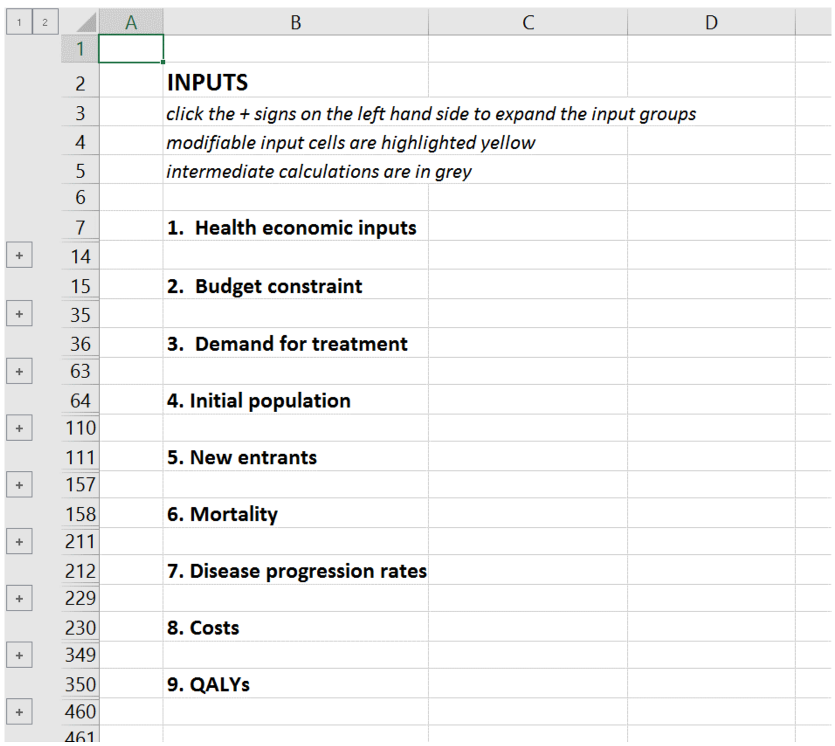
Each set of decisions evaluated during the search is saved on the Optimization Output worksheet. The only output stored with the decision set is the population net monetary benefit (NMB). To sort by NMB, press the button "Sort by NMB". We were confident that we had identified the global optimum when the top 10 solutions were identical or highly similar to each other.

If you want to calculate all model outputs for the top performing set of decisions, call up that set of decisions by entering its row number in cell C6 on the Optimization Outputs worksheet (i.e., row 1 for the decision set with the largest NMB) and then press the "Transfer this decision set to the model decisions" button.

Model layout: a detailed description of each worksheet

Inputs worksheet

The Inputs worksheet is organized into nine sections: Health economic inputs, Budget constraint, Demand for treatment, Initial population, New entrants, Mortality, Disease progression rates, Costs, and QALYs. This worksheet (and others in this book) are large and so to help with organization we have grouped sections of the sheet. To open a single section, click on the + sign to the left of the header. To show everything in the worksheet, click on the small number 2 in the upper right hand corner to the left of the row labels.



Throughout the workbook, inputs that can be modified by the user are highlighted in yellow. We describe the specific inputs in each section below:

1. Health economic inputs

Variable	Description
Cycle length	The cycle length is 3-months. This is a structural assumption in the model and is not modifiable.
Discount rate	3% per year is applied to both costs and QALYs in the model.
Willingness to pay	The marginal willingness to pay for one additional QALY.

2. Budget constraint

Variable	Description
Annual HCV treatment budget	This table contains the HCV drug treatment budget for the next 25 years. The value in year 10 is assumed to apply for years 11 through 25.
Budget over-run tolerance	The budget over-run tolerance is presented as a percent of the budget. This parameter is useful for the optimization so that good solutions are not rejected because of very small budget over-runs.

3. Demand for treatment

Variable	Description
Average uptake rate	The average uptake rate represents the weighted average demand over the entire population of individuals chronically infected with HCV.
Relative risk of uptake in cirrhosis	This parameter enables a higher rate of demand among individuals with stage F3 or F4 fibrosis (compared to individuals with F0, F1, and F2 fibrosis)
Approximate proportion F3 and F4	Intermediate calculation: the proportion of the initial population in stages F3 and F4
Update in F0-F2	Intermediate calculation: Calculating the uptake rate in F0-F2 given the overall uptake rate, the increased uptake rate in F3-F4, and the proportion of the population in F3-F4
Uptake in F3 and F4	Intermediate calculation: Calculating the uptake rate in F3-F4 given the overall uptake rate, the increased uptake rate in F3-F4, and the proportion of the population in F3-F4
Confirm overall demand rate	Intermediate calculation: Calculates the weighted average demand to confirm that it is consistent with the input (double checks the previous calculations)

Annual probability of seeking treatment	This table presents the uptake rate by age and fibrosis-stage. In our base case we assume a single rate for individuals with F0 to F2 fibrosis, a single rate for individuals for individuals with F3 and F4 fibrosis (with constant demand rate by age for both groups). Over-writing this table enables the user to specify demand rates for each fibrosis stage stratified by five-year age categories consistent with observed demand in their own population.
Cycle specific probability of seeking treatment	This table converts the annual probabilities, presented in the table to its left, to 3-month probabilities used in the model.
Proportion of individuals alive at the end of the model horizon who immediately receive treatment	At the end of the 25-year analysis horizon, some individuals may still have chronic HCV. This input specifies what should be assumed with respect to treatment of this population.

4. Initial population

Variable	**Description**
Number of people	The total number of individuals with chronic HCV infection.
Fraction treatment eligible	The fraction of the total number of individuals with chronic HCV infection who are treatment eligible.
Proportion of individuals in each race-gender-age group	This table presents the proportion of the population who are in each race-gender-age subgroup. Race is divided by black (B) and not-black (W). Gender is divided by male (M) and female (F). Age is divided into 5-year age categories (40-44, 45-49, …, 75-79). The sum of all the proportions in this table must be equal to 1.
Total number of treatment eligible individuals by race-gender-age group	Intermediate calculation: This table presents the total number of treatment eligible individuals with chronic HCV infection stratified by race, gender, and age.
Total number of treatment eligible individuals by fibrosis-stage and age group	Calculation for user interest: This table presents the total number of treatment eligible individuals with chronic HCV infection stratified by fibrosis-stage, and age.
Number of people who would demand treatment immediately	Calculation for user interest: This table applied the demand assumptions in the previous section to presents the total number of individuals who would demand treatment immediately stratified by fibrosis-stage, and age.

if their subgroup were prioritized	
Initial fibrosis stage distribution	This table presents the initial fibrosis distribution stratified by race, gender, and age. The proportions must sum to 1 for each race, gender, age group. So, for fibrosis stage F0 we calculate the probability remaining (1 – proportion of the population in F1 through F4).
Proportion of F0 who are non-progressors	This table presents the proportion of the F0 population who are non-progressors stratified by race, gender, and age.

5. New entrants

Variable	**Description**
Number of individuals by race-gender-age group in 2015	This table presents the number of individuals with chronic HCV infection who are ages 20-24, 25-29, 30-34, and 35-39. We use this table to estimate the number of individuals who will enter the model at age 40 each year over the 25-year analysis horizon. We assume no decrease in the number of infected individuals as they age (from their current age to age 40) from mortality or access to treatment and no increase in the number of infected individuals which may occur from disease transmission. The values in our model were estimated from NHANES and are based on small absolute counts of HCV infected individuals (including zeros for some race-gender-age categories). When NHANES reported zeros for a category, we crudely interpolated by using the estimated prevalence of the next age category.
Annual number of new model entrants	This table presents the annual number of individuals to enter the model as a chronically-infected treatment eligible 40-year old over the next 16 years. The value in year 15 is assumed to apply for years 15 through 25.
Fibrosis stage distribution of new entrants	This table presents the initial fibrosis distribution of new entrants to enter the model at age 40 stratified by race, gender, and age. The probabilities must sum to 1 for each race, gender, age group. So, for fibrosis stage F0 we calculate the proportion remaining (1 – proportion of the population in F1 through F4).
Proportion of new entrant F0 who are non-progressors	The proportion of the new entrant F0 population who are non-progressors.

6. Mortality

Variable	Description
Hazard ratios, increase in mortality rate to account for HCV+ infection status	The hazard ratios representing the increased rate of non-liver-related death in individuals with chronic HCV infection.
Average age-specific mortality rates (per 100,000)	This table presents the average age-specific mortality rate (per 100,000 person-years) for individuals in the population stratified by race and gender. Deaths from liver causes have not been removed because they represent a small fraction of deaths in the general population.
HCV+ mortality rates (per 100,000)	Intermediate calculation: This table presents the age-specific rates of death from non-liver causes for individuals with chronic HCV infection stratified by race and gender. Rates are presented per 100,000 person-years.

7. Disease progression rates

Variable	Description
Progression rates: F0→ remission	The annual rate (per 100,000 person-years) of spontaneous clearing HCV, represented by the transition from chronic HCV with no fibrosis (F0) to remission.
Progression rates F4→ HCC	The annual rate (per 100,000 person-years) of transition from chronic HCV with compensated cirrhosis (F4) to liver cancer (also called hepatocellular carcinoma (HCC)).
Progression rates: F4 → DC	The annual rate (per 100,000 person-years) of transition from chronic HCV with compensated cirrhosis (F4) to decompensated cirrhosis (DC)
Cycle-specific probability of transitions (F0→Remission; F4→HCC; F4→DC)	Intermediate calculations: The 3-month probabilities associated with each of the transitions immediately to the left on the worksheet.
Age-specific progression rates	This table presents the annual age-specific HCV infection progression rates stratified by race and gender (per 100,000 person-years). These rates inform the probability of transition from F0 → F1, F1 → F2, F2 → F3, and F3 → F4.

8. <u>Costs</u>

Variable	Description
Cost of HCV treatment	This table presents the cost of a complete course of HCV treatment stratified by fibrosis stage (enabling the use to assume a longer course of treatment for individuals with later-stage disease).
Annual cost; patients who did not get treated this cycle	The annual cost of baseline health care including costs unrelated to HCV infection and routine care for HCV prior to initiating treatment such as HCV disease progression monitoring. Costs are stratified by race, gender, fibrosis-stage, and age.
Lifetime discounted cost; patients who are treated this cycle	The lifetime discounted cost for an individual who receives treatment this cycle. This cost is the expected value incorporating the probability treatment is curative and the probability that treatment fails and all the downstream potential consequences of each treatment outcome (such as the probability of progression to HCC or DC in an individual in whom treatment fails and HCV disease progression continues). Costs are stratified by race, gender, fibrosis-stage, and age.
Lifetime discounted cost; patients who will never receive treatment	The lifetime discounted cost for an individual who will never receive treatment. This input is only used to assign lifetime costs to the individuals who remain alive and untreated at the end of the analysis horizon (25-years). Costs are stratified by race, gender, fibrosis-stage, and age.
Lifetime discounted cost; patients who achieved remission this cycle	The lifetime discounted cost for an individual who transitions from F0 to remission this cycle. Costs are stratified by race, gender, fibrosis-stage, and age.
Lifetime discounted cost; patients who progressed to HCC this cycle	The lifetime discounted cost for an individual who transitions from F4 to liver cancer (HCC) this cycle. This cost is the expected value incorporating the possibility of liver transplant. Costs are stratified by race, gender, fibrosis-stage, and age.
Lifetime discounted cost; patients who progressed to DC this cycle	The lifetime discounted cost for an individual who transitions from F4 to decompensated cirrhosis (DC) this cycle. Costs are stratified by race, gender, fibrosis-stage, and age.
Lifetime discounted cost; patients who reached age 80 this cycle	The lifetime discounted cost for an individual who transitions from age 79.75 to age 80 this cycle. Costs are stratified by race, gender, and fibrosis-stage.

9. QALYs

Variable	Description
Annual QALY; patients who did not get treated this cycle	The annualized utilities of a individuals with chronic HCV infection stratified by race, gender, fibrosis-stage, and age.
Lifetime discounted QALY; patients who are treated this cycle	The lifetime discounted QALYs for an individual who receives treatment this cycle stratified by race, gender, fibrosis-stage, and age. This is the expected value incorporating the probability treatment is curative and the probability that treatment fails and all the downstream potential consequences of each treatment outcome (such as the probability of progression to HCC or DC in an individual in whom treatment fails and HCV disease progression continues).
Lifetime discounted QALY; patients who will never receive treatment	The lifetime discounted QALYs for an individual who will never receive treatment stratified by race, gender, fibrosis-stage, and age. This input is only used to assign lifetime QALYs to the individuals who remain alive and untreated at the end of the analysis horizon (25-years).
Lifetime discounted QALY; patients who achieved remission this cycle	The lifetime discounted QALYs for an individual who transitions from F0 to remission this cycle stratified by race, gender, fibrosis-stage, and age.
Lifetime discounted QALY; patients who progressed to HCC this cycle	The lifetime discounted QALYs for an individual who transitions from F4 to liver cancer (HCC) this cycle stratified by race, gender, fibrosis-stage, and age. This is an expected value incorporating the possibility of liver transplant.
Lifetime discounted QALY; patients who progressed to DC this cycle	The lifetime discounted QALYs for an individual who transitions from F4 to decompensated cirrhosis (DC) this cycle stratified by race, gender, fibrosis-stage, and age.
Lifetime discounted QALY; patients who reached age 80 this cycle	The lifetime discounted QALYs for an individual who transitions from age 79.75 to age 80 this cycle stratified by race, gender, and fibrosis-stage.

Decisions and Outputs worksheet

The Decisions and Outputs worksheet is organized into four sections: Decisions, Budget impact and health economic outputs, Population health outcomes, and Additional budget required to provide treatment earlier.

1. <u>Decisions: The year each subgroup will be prioritized</u>

   The first section of this worksheet is a table in which the user can enter a prioritization policy:

DECISIONS and OUTPUTS

click the + signs on the left hand side to expand sections of the sheet

1. Decisions: Number of years until each subgroup will be prioritized

Once a subgroup is prioritized, it cannot later be de-prioritized

	F0	F1	F2	F3	F4
40	4.00	3.00	2.00	1.00	0.00
45	4.00	3.00	2.00	1.00	0.00
50	4.00	3.00	2.00	1.00	0.00
55	4.00	3.00	2.00	1.00	0.00
60	4.00	3.00	2.00	1.00	0.00
65	4.00	3.00	2.00	1.00	0.00
70	4.00	3.00	2.00	1.00	0.00
75	4.00	3.00	2.00	1.00	0.00

User options:

Record current decision set

Initiate optimization search

In the policy depicted above, all individuals with F4 fibrosis are prioritized for treatment immediately, individuals with F3 fibrosis are prioritized in year 1, individuals with F2 fibrosis are prioritized in year 2, and so on. We will refer to this table in the spreadsheet many times throughout this document; to be clear we will call it the Current Decisions. Users can change the values in the Current Decisions and recalculate the model by pressing F9.

This section also has two buttons which activate Visual Basic with Applications (VBA) macros. The first button will record the current set of decisions. The second button will initiate a search to identify a set of decisions that will maximize net monetary benefit. Both of these user options will be described in greater detail in the optimization process section of this document.

2. Budget impact and health economic outputs

This section contains two tables reporting model outputs that result from the Current Decisions. The first reports the total lifetime discounted costs, QALYs, and net monetary benefit (NMB). The second table reports the treatment expenditures by year, calculates whether the expenditures exceed the budget, and calculates the percent the expenditures are over or under budget.

2. Budget impact and health economic outputs

Lifetime discounted costs, QALYs, and NMB

	WM	WF	BM	BF	Total
Costs	$418,804,557,589	$295,360,796,780	$66,749,171,633	$68,589,977,817	$849,504,503,819
QALYs	15,714,339	11,380,501	2,375,984	2,503,682	31,974,506
NMB	1,152,629,324,459	842,689,317,716	170,849,196,160	181,778,268,341	**2,347,946,106,676**

Budget impact

Year	Treatment expenditures	Budget Limit	Surplus / (Deficit)	% over budget	% under budget
0	$ 4,154,150,879	$ 8,686,000,000	$ 4,531,849,121		52.17%
1	$ 6,849,408,459	$ 8,686,000,000	$ 1,836,591,541		21.14%
2	$ 8,191,869,079	$ 8,686,000,000	$ 494,130,921		5.69%
3	$ 9,029,337,757	$ 8,686,000,000	$ (343,337,757)	3.95%	
4	$ 9,315,295,754	$ 8,686,000,000	$ (629,295,754)	7.24%	
5	$ 8,167,635,253	$ 8,686,000,000	$ 518,364,747		5.97%
6	$ 7,131,848,545	$ 8,686,000,000	$ 1,554,151,455		17.89%
7	$ 6,223,906,333	$ 8,686,000,000	$ 2,462,093,667		28.35%
8	$ 5,428,207,642	$ 8,686,000,000	$ 3,257,792,358		37.51%
9	$ 4,731,402,738	$ 8,686,000,000	$ 3,954,597,262		45.53%
10	$ 4,102,226,268	$ 8,686,000,000	$ 4,583,773,732		52.77%

In this example, the Current Decisions do not use the entire budget in the first three years and then exceed the budget for the next two years.

3. Population health outcomes

This section also contains two tables reporting model outputs that result from the Current Decisions.

The first table presents a summary of health outcomes:

- The number of individuals who are chronically infected and treatment eligible but remain untreated after 2 years, after 5 years, and after 10 years.
- The number of individuals with compensated cirrhosis (fibrosis stage F4) who remain untreated after 2 years, after 5 years, and after 10 years.
- The cumulative number of individuals who have received treatment after 2 years, after 5 years, and after 10 years.
- The cumulative number of individuals who progress to liver cancer (HCC) after 2 years, after 5 years, and after 10 years.
- The cumulative number of individuals who progress to decompensated cirrhosis (DC) after 2 years, after 5 years, and after 10 years.

The second table presents the number of individuals in each fibrosis stage and the total number of HCV treatment eligible individuals in each year over the model horizon (25-years).

4. Additional budget required to provide treatment earlier

This section also contains one large table presenting the additional budget required in each year to provide treatment to a specific subgroup earlier than the Current Decisions. The first column of this table reports the current decisions in column format (rather than a grid). The next three columns describe the subgroups (by fibrosis stage and age group). Columns F through AD report the additional budget required to provide treatment to each subgroup earlier. For example, consider the subgroup of

40-44 year olds with F1 fibrosis (row 146 in the screenshot below). This group is currently prioritized in year 3. To prioritize this subgroup one year earlier (in year 2), there must be at least $146,703,164 remaining currently unused in the year 2 treatment budget (or the budget needs to be increased to accommodate this additional responsibility). To prioritize this subgroup two years earlier (in year 1), there must be at least $162,184,082 remaining currently unused in the year 1 treatment budget and approximately, but somewhat less than, $146,703,164 remaining currently unused in the year 2 treatment budget. The reason $146,703,164 is greater than the exact amount of treatment budget required is that the values in this table are calculated using the number of individuals in each subgroup under the Current Decisions. If treatment were provided to this subgroup in year 1, the number of people remaining in the subgroup after one year will be less than with the current policy because some individuals will have already received treatment. This table is primarily useful for identifying the budget impact of prioritizing a subgroup one or two years earlier than the Current Decisions.

4. Additional budget required to provide treatment earlier

Budget required to provide treatment access in year

0 indicates access provided by current policy

	Priority sub-group			Year			
Current prioritization decision	**Fibrosis stage**	**Age group**	**Subgroup number**	**0**	**1**	**2**	**3**
4	0	40	1	168,265,754	148,874,344	132,101,207	117,692,024
4	0	45	2	323,037,877	276,473,426	233,747,346	194,533,957
4	0	50	3	427,195,350	375,698,618	331,884,860	294,401,749
4	0	55	4	421,075,487	391,090,281	363,217,783	337,280,143
4	0	60	5	296,017,384	293,409,047	289,660,391	284,998,121
4	0	65	6	123,287,526	144,672,819	161,219,308	174,120,761
4	0	70	7	43,293,992	52,395,456	59,678,516	65,488,749
4	0	75	8	25,515,683	24,905,889	24,276,691	23,608,402
3	1	40	9	178,517,148	162,184,082	146,703,164	0
3	1	45	10	392,434,404	338,534,724	287,453,392	0
3	1	50	11	585,274,149	514,314,651	453,231,765	0
3	1	55	12	601,141,532	553,538,255	512,557,813	0
3	1	60	13	366,907,740	362,035,528	358,863,661	0
3	1	65	14	106,295,326	133,491,786	150,610,981	0
3	1	70	15	21,700,282	28,662,079	32,462,737	0
3	1	75	16	7,416,820	7,367,023	6,985,307	0
2	2	40	17	93,689,389	88,746,877	0	0
2	2	45	18	255,884,396	224,524,113	0	0
2	2	50	19	502,990,260	451,947,162	0	0
2	2	55	20	692,977,849	633,839,555	0	0
2	2	60	21	558,067,963	540,280,975	0	0

Intermediate Calculations – Markov worksheet

The purpose of the intermediate calculations sheet is to convert inputs organized compactly on the Inputs worksheet into vectors (columns), potentially with many repeating values, for easy use in the

Markov models. The first table organizes inputs that are race-, gender-, fibrosis-stage-, and age specific inputs. This table has a row for every health state in the Markov models. The second table organizes inputs that are race-, gender, and age-specific.

1. Race-, gender-, fibrosis-stage, and age-specific model inputs

This table has 960 rows, one for each unique health state in the model. Health states are characterized by five fibrosis stages (F0, non-progressors; F0, progressors; F1; F2; F3; F4) and 160 age categories (40.00, 40.25, 40.50, 40.75, 41.00, … , 79.50, 79.75).

- States 1 through 160: fibrosis stage F0 (no fibrosis) and non-progressors
- States 161 through 320: fibrosis stage F0 (no fibrosis) and progressors
- States 321 through 480: fibrosis stage F1
- States 481 through 640: fibrosis stage F2
- States 640 through 800: fibrosis stage F3
- States 801 through 960: fibrosis stage F4

The first four columns (columns E through H) report the initial population in each health state stratified by race and gender. This calculation divides the number of individuals in the 5-year age category by 5 to estimate the number of individuals in each single age (i.e., 40, 41, …). This number is then multiplied by the cycle length (0.25) to estimate the number of individuals in each 3-month age category (i.e., 40.00, 40.25, 40.50, …). The number of individuals in each 3-month age category is then multiplied by the proportion of individuals in the fibrosis stage. For individuals in F0 fibrosis an IF statement further divides the group into 'non-progressors' and 'progressors'.

Columns I through L report the 3-month baseline health care costs stratified by race and gender.

Columns M through P report the average lifetime discounted costs of an individual who receives treatment this cycle (excluding the costs of treatment which are captured elsewhere).

Columns Q through T report the average lifetime discounted costs of an individual who never receives treatment. This cost is only used at the end of the 25-year model horizon to assign lifetime costs to the individuals who remain alive and treatment naïve.

Columns U through X report the average lifetime discounted costs of an individual who turns 80 years of age this cycle. The costs are only non-zero for individuals aged 79.75.

Columns Y through AB report the 3-month baseline health care QALYs stratified by race and gender.

Columns AC through AF report the average lifetime discounted QALYs of an individual who receives treatment this cycle.

Columns AG through AJ report the average lifetime discounted QALYs of an individual who never receives treatment. This value is only used at the end of the 25-year model horizon to assign lifetime QALYs to the individuals who remain alive and treatment naïve.

Columns AK through AN report the average lifetime discounted QALYs of an individual who turns 80 years of age this cycle. The QALYs are only non-zero for individuals aged 79.75.

2. Race-, gender, and age-specific model inputs

This table has 160 rows, one for each age category in the model. The inputs in this section may vary by race, gender, and age, but do not vary by fibrosis stage.

The first four columns (columns E through H) report the 3-month probability of death stratified by race and gender. We convert the input (the annual rate per 100,000 population) to a 3-month probability using the formula:

$$\text{3-month probability} = 1 - e^{-(\text{Annual rate per 100,000} \times \text{Cycle length / 100,000})}$$

Columns I through L report the 3-month probability of disease progression.

Columns M through P report the average lifetime discounted costs of an individual who transitions from F0 to remission this cycle.

Columns Q through T report the average lifetime discounted costs of an individual who transitions from F4 to HCC (liver cancer) this cycle.

Columns U through X report the average lifetime discounted costs of an individual who transitions from F4 to decompensated cirrhosis this cycle.

Columns Y through AB report the average lifetime discounted QALYs of an individual who transitions from F0 to remission this cycle.

Columns AC through AF report the average lifetime discounted QALYs of an individual who transitions from F4 to HCC this cycle.

Columns AG through AJ report the average lifetime discounted QALYs of an individual who transitions from F4 to decompensated cirrhosis this cycle.

Markov WM, Markov WF, Markov BM, and Markov BF worksheets

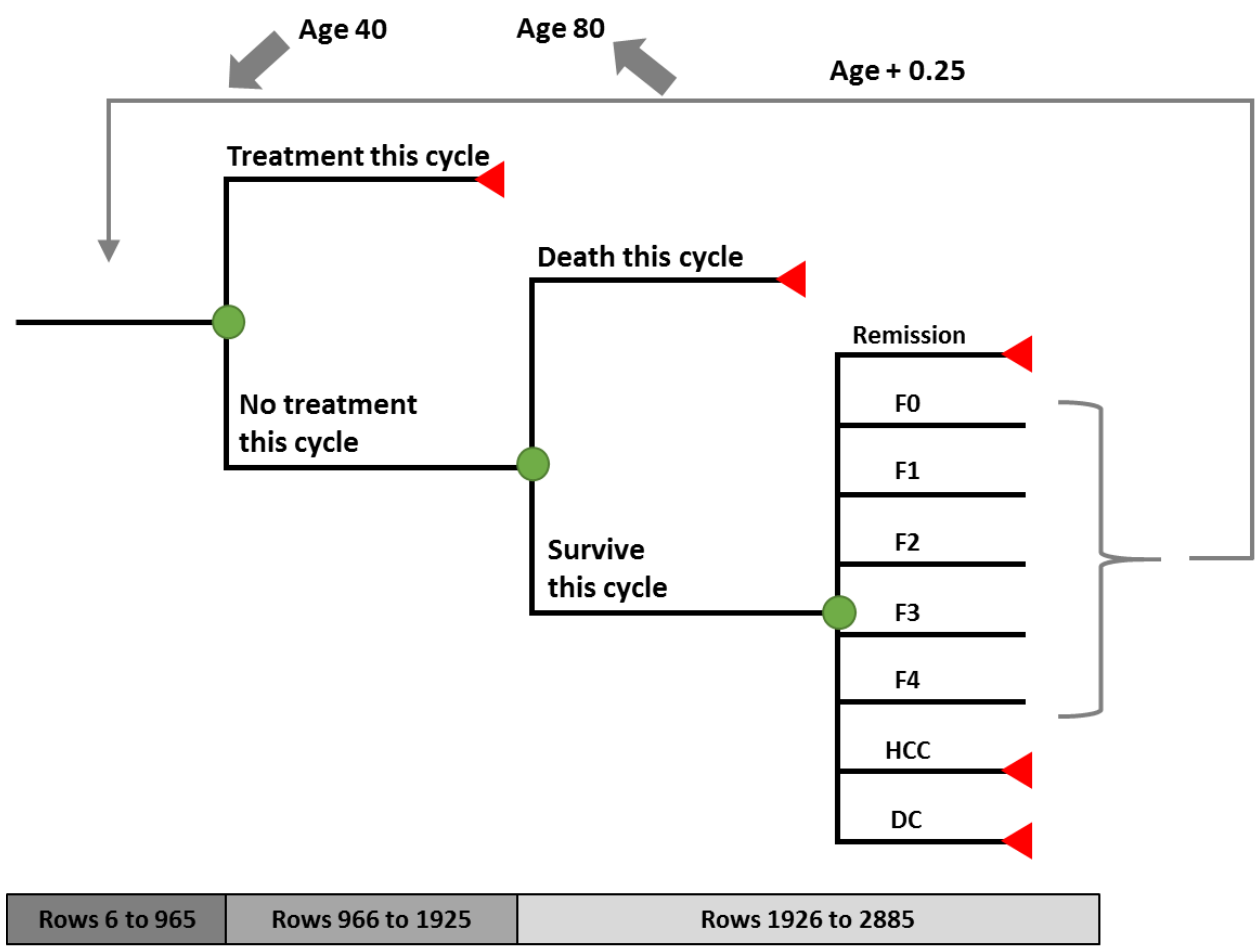
These four worksheets are identical in structure. On each sheet, cell C2 identifies the "race-gender group" where 1 indicates white males, 2 indicates white females, 3 indicates black males, and 4 indicates black females. Any formulas in the sheet that require a race and gender stratified input will reference this cell.

To maintain relatively easy to debug formulae the sequence of events that may occur in each cycle have been divided into three steps on the spreadsheet (**Appendix Figure S6**):

1. Rows 6 to 965 report the number of individuals in each state at the beginning of the cycle.

2. Rows 966 to 1925 report the number of individuals who remain untreated. Some intermediate calculations used in the calculation of the number of individuals treated appear in columns D and E of these rows. This is calculated as follows:
   - If the Current Decisions indicate that the subgroup is not yet prioritized (identified by comparing the time at which priority begins, tracked in cells D966 to D1925, to the current time tracked in row 4), then no individuals receive treatment in the cycle.
   - If the Current Decisions indicate that the subgroup is prioritized at or before the current time, specifically that the priority time is less than or equal to the current time, then the number of individuals who receive treatment from the subgroup is determined by the age- and fibrosis-stage specific rate of demand (reported in cells E966 to E1925).
   - If the Current Decision is a point in time between two cycle times (i.e., at 1.1 years, then a proportional fraction of demand will receive treatment in the cycle for 1.0-1.25 years).

APPENDIX FIGURE S6. A schematic of the sequential calculations in each cycle of the Markov model (in worksheets labelled Markov WM, Markov WF, Markov BM, and Markov BF).



3. Rows 1926 to 2885 report the number of individuals in each health state after mortality and disease progression are accounted for. Each fibrosis-stage category has its own formulas which we write here in plain language:

- Rows 1926 to 2085 (F0, non-progressors):

$$\begin{aligned}&\text{Number in the F0 non-progressor state } (\textit{at age } x)\\&= \text{Number in the F0 non-progressor state after treatment } (\textit{at age } x)\\&\quad \times (1 - \text{probability of death}) \times (1 - \text{probability of transition to remission})\end{aligned}$$

- Rows 2086 to 2245 (F0, progressors):

$$\begin{aligned}&\text{Number in the F0 progressor state } (\textit{at age } x)\\&= \text{Number in the F0 progressor state after treatment } (\textit{at age } x)\\&\quad \times (1 - \text{probability of death})\\&\quad \times (1 - \text{probability of transition to remission} - \text{probabilitiy of transition to F1})\end{aligned}$$

- Rows 2246 to 2405 (F1):

$$\begin{aligned}&\text{Number in the F1 state } (\textit{at age } x)\\&= \Big[\text{Number in the F1 state after treatment } (\textit{at age } x)\\&\quad \times (1 - \text{probability of death}) \times (1 - \text{probability of transition to F2})\Big]\\&\quad + \Big[\text{Number in the F0 progressor state after treatment } (\textit{at age } x)\\&\quad \times (1 - \text{probability of death}) \times (1 - \text{probability of transition to F1})\Big]\end{aligned}$$

- Rows 2406 to 2565 (F2):

$$\begin{aligned}&\text{Number in the F2 state } (\textit{at age } x)\\&= \Big[\text{Number in the F2 state after treatment } (\textit{at age } x)\\&\quad \times (1 - \text{probability of death}) \times (1 - \text{probability of transition to F3})\Big]\\&\quad + \Big[\text{Number in the F1 state after treatment } (\textit{at age } x)\\&\quad \times (1 - \text{probability of death}) \times (1 - \text{probability of transition to F2})\Big]\end{aligned}$$

- Rows 2566 to 2725 (F3):

$$\begin{aligned}&\text{Number in the F3 state }(at\ age\ x)\\&=\Big[\text{Number in the F3 state after treatment }(at\ age\ x)\\&\quad\times\ (1\ -\ \text{probability of death})\times\ (1\ -\ \text{probability of transition to F4})\Big]\\&\quad+\Big[\text{Number in the F2 state after treatment }(at\ age\ x)\\&\quad\times\ (1\ -\ \text{probability of death})\times\ (1\ -\ \text{probability of transition to F3})\Big]\end{aligned}$$

- Rows 2726 to 2885 (F4):

$$\begin{aligned}&\text{Number in the F4 state }(at\ age\ x)\\&=\Big[\text{Number in the F4 state after treatment }(at\ age\ x)\\&\quad\times\ (1\ -\ \text{probability of death})\\&\quad\times\ (1\ -\ \text{probability of transition to HCC}-\ \text{probability of transition to DC})\Big]\\&\quad+\Big[\text{Number in the F3 state after treatment }(at\ age\ x)\\&\quad\times\ (1\ -\ \text{probability of death})\times\ (1\ -\ \text{probability of transition to F4})\Big]\end{aligned}$$

At the end of each cycle, the individuals aged 79.75 turn age 80 and exit the model. Individuals aged 40.00 to 79.50 become the individuals aged 40.25 to 79.75 in the next cycle (with no change in fibrosis stage). Finally, new individuals enter the model at age 40 (for an example see cell J6). The new entrants are distributed across all fibrosis stage categories.

The remaining sections of these worksheets calculate the number of individuals who exited the model this cycle, perform error checks for debugging, record summary information about the population, and calculate the costs and benefits accrued in the cycle.

- Rows 2887 to 2892: These rows report the number of people who exit the model this cycle – those who transition to death, receive treatment, transition to remission, transition to liver cancer (HCC), transition to decompensated cirrhosis (DC), and who turn 80 years.
- Rows 2894 to 2896: These rows check to ensure that all individuals are accounted for in each of the intermediate calculation steps.
- Rows 2898 to 2905: These rows report the number of individuals in the total population and in each fibrosis-stage.
- Rows 2907 to 2946: These rows report the number of individuals who would demand treatment in each of the 40 decision subgroups (by fibrosis stage and 5-year age category) if the subgroup were to be prioritized.
- Rows 2948 to 2961: These rows report the number of individuals who received treatment this cycle stratified by fibrosis stage and then stratified by 5-year age category.
- Rows 2963 to 2972: These rows report the costs for each cycle. The costs are divided by type: baseline costs, cost of treatment, and lifetime discounted costs of transition to each of the absorbing health states (remission, treatment, HCC, DC, turning age 80).
- Rows 2974 to 2982: These rows report the QALYs for each cycle. The QALYs are divided by type: baseline, QALYs of treatment, and lifetime discounted QALYs of transition to each of the absorbing health states (remission, treatment, HCC, DC, turning age 80).
- Rows 2984 to 2986: These rows calculate the present value of costs and QALYs.

Beginning in row 2989, outputs for the worksheet are organized into tables with the same format as appears on the Decisions and Outputs page for ease of combining the information from each of the Markov model sheets.

Optimization Output worksheet

The optimization output worksheet stores and reports on potential decision sets in three sections. Decision sets are stored as single rows in the third section. Therefore, for user convenience, the first section provides an opportunity to convert any stored decision set from the third section into the grid layout with fibrosis stages across the top and 5-year age categories in rows. To do so, enter the row number into cell C6 and press F9 to calculate the sheet. If you are interested in calculating all of the model outputs for this set of decisions, press the “Move to model decisions” button.

	A	B	C	D	E	F	G
1							
2		**STORED OUTPUT**					
3							
4		**1. Review a single solution from the saved trials table below**					
5							
6		**Show solution row #**	1				
7							
8			*1*	*2*	*3*	*4*	*5*
9			**F0**	**F1**	**F2**	**F3**	**F4**
10	*1*	**40**	4.0	3.0	2.0	1.0	0.0
11	*2*	**45**	4.0	3.0	2.0	1.0	0.0
12	*3*	**50**	4.0	3.0	2.0	1.0	0.0
13	*4*	**55**	4.0	3.0	2.0	1.0	0.0
14	*5*	**60**	4.0	3.0	2.0	1.0	0.0
15	*6*	**65**	4.0	3.0	2.0	1.0	0.0
16	*7*	**70**	4.0	3.0	2.0	1.0	0.0
17	*8*	**75**	4.0	3.0	2.0	1.0	0.0
18							
19		**NMB**	2,347,946,106,676				
20				Transfer this decision set to model decisions			
21							
22							
23							

The second section of this worksheet converts the grid of the Current Decisions into the row format of the table in the third section for compact storage.

The third section of this worksheet stores potential decision sets, the net monetary benefit of each decision set, and a grid number which classifies areas of the decision space. Users can store decision sets using a button on the Decisions and Outputs worksheet. Similarly, the model stores all decision sets considered in the optimization procedure in this table. The decision set that maximizes net monetary benefit is identified at the top of the table in cells C39 and C40. Users can sort the table by NMB using the button provided.

3. Trials (from optimization or saved by user)

Max NMB trial #	21
Max NMB	2,365,906,772,110

Sort by NMB

	Subgroup number											
Trial number	**1**	**2**	**3**	**4**	**5**	**36**	**37**	**38**	**39**	**40**	**NMB**	**Base value set**
1	-	-	-	3.00	4.00	-	-	-	4.00	5.00	2,364,859,806,820	10
2	-	-	-	3.00	3.00	-	-	-	4.00	5.00	2,365,428,714,233	6
3	3.00	5.00	3.00	3.00	4.00	2.00	1.00	2.00	4.00	4.00	2,365,426,488,987	14
4	3.00	4.00	4.00	4.00	4.00	-	-	-	-	-	2,365,898,292,126	12
5	4.00	5.00	3.00	3.00	4.00	-	1.00	2.00	4.00	3.00	2,365,094,306,646	19
6	4.00	4.00	4.00	3.00	4.00	2.00	1.00	2.00	4.00	5.00	2,365,094,353,700	21
7	-	-	-	4.00	3.00	-	-	-	5.00	4.00	2,365,095,789,026	7
8	-	-	-	3.00	3.00	-	-	-	4.00	5.00	2,365,096,209,102	18
9	-	-	-	3.00	4.00	-	-	-	4.00	5.00	2,364,859,806,820	18
10	2.00	2.00	2.00	3.00	4.00	-	-	-	1.00	1.00	2,365,426,765,188	7
11	-	-	-	3.00	4.00	-	-	-	4.00	5.00	2,365,428,707,089	2
12	-	-	-	3.00	3.00	-	-	-	4.00	5.00	2,365,905,393,264	9
13	3.00	5.00	4.00	3.00	3.00	2.00	1.00	2.00	5.00	4.00	2,364,863,834,723	25
14	1.00	2.00	2.00	3.00	4.00	-	-	-	4.00	4.00	2,364,865,434,870	2
15	1.00	3.00	2.00	4.00	3.00	-	-	-	1.00	1.00	2,365,899,843,595	21
16	1.00	-	-	2.00	4.00	1.00	2.00	3.00	4.00	5.00	2,365,903,430,708	8
17	2.00	2.00	2.00	4.00	4.00	-	-	-	1.00	1.00	2,365,904,579,956	17
18	3.00	4.00	3.00	5.00	4.00	1.00	2.00	1.00	4.00	3.00	2,365,905,338,738	6
19	3.00	4.00	5.00	4.00	4.00	2.00	1.00	2.00	3.00	4.00	2,365,426,380,374	11
20	2.00	2.00	3.00	4.00	4.00	-	-	-	4.00	5.00	2,364,859,937,729	18
21	-	-	-	3.00	3.00	-	-	-	4.00	4.00	2,365,906,772,110	15
22	4.00	4.00	4.00	4.00	4.00	-	-	-	-	-	2,347,946,106,676	20

Intermediate Calculations - Optimization worksheet

Before we discuss the details of this spreadsheet, we review the big picture of our search strategy.

The decision space for this problem is very large – each of the 40 subgroups has 25 possible values resulting in 25^{40} $(=8.27\times10^{55})$ possible sets of decisions. Many of these possible sets of decisions, such as those that immediately prioritize all subgroups, are infeasible because they violate the budget constraints. Furthermore, many feasible sets of decisions leave a large portion of the budget unspent in the first few years (consider a guideline of prioritizing no subgroups until year 9 and then prioritizing all subgroups over years 9, 10, 11, and 12). Consistent with cost effectiveness analyses performed by others, our model indicates treatment has a positive incremental net monetary benefit (equivalent to an incremental cost effectiveness ratio of less than $100,000 per QALY gained) for all subgroups (Table S4 in Appendix S1). This implies that the optimal solution will include treating all subgroups as early as possible. Therefore, solutions that leave a large portion of the budget unspent in the first few years are easily improved upon by treating one or more subgroup earlier.

In order to search the large number of sets of decisions efficiently, we developed an algorithm to focus on searching only sets of decisions which spend nearly all, but do not exceed, the annual budget constraints using a two-step process. In the first step, we randomly generated the order in which patient subgroups would be considered for prioritization (each subgroup was assigned a number between 1 and 40). This first step is performed in the first table of the Intermediate Calculations – Optimization worksheet. In the second step, in the order determined in step 1, we sequentially identified the least possible time to prioritization for each subgroup as to not violate any annual budget constraint. The second table in the Intermediate Calculations – Optimization worksheet presents the subgroups in the order determined in step 1.

The first table has one row for each of the 40 decision variables and the purpose of this table is to generate a random order in which to prioritize subgroups. In this table, columns E through I describe the decision variables including position in the decision grid (row and column), subgroup number, fibrosis stage, and 5-year age category. To the left of these columns, in columns B through D, a random number is assigned to each of the subgroups (column D) and the rank of that random number is determined (column C, generating unique values 1 through 40). These values are the order in which the subgroups will be considered for prioritization. Because these values change every time the workbook recalculates, these values are copied and pasted as values into column B in the iterative search procedure. The VBA macro called MakeDecisions() will then identify the earliest possible year each subgroup can be prioritized evaluating the subgroups in the previously established randomly generated order.

This approach, on its own, will search the space of feasible decision sets using nearly all the budget without exceeding the budget constraints including prioritization sequences that do not have a pattern across the grid layout of the decisions. However, competing mortality risks, the risk of liver cancer or decompensated cirrhosis, and the benefits of treatment are similar for subgroups that are near each other in the grid layout of the decisions. Therefore, we hypothesized that the optimal solution would prioritize subgroups near each other similarly and that the order of priority would radiate from a yet unidentified 'high value' region of the decision space.

To further improve on our search algorithm, we created 26 sets of base values. These base values serve to direct the search to specific regions of the decision space. These sets of base values are in columns J through AI of the first table. We present four examples (laid out as a grid) in **Appendix Figure S7**. For example, using the set of base values in **Appendix Figure S7A**, the algorithm will focus on generating sets of decisions that are more likely to prioritize subgroups of patients aged 50-64 with F2 or F3 fibrosis first. Using the set of base values in **Appendix Figure S7B**, the algorithm will focus on generating sets of decisions that are more likely to prioritize subgroups of patients aged 40-54 with F1 fibrosis first. One of the 26 sets assigns a base value of one to all subgroups ensuring that any decision set can still be considered.

A schematic presenting an overview of the combined search procedure is presented in **Appendix Figure S8**. The VBA macro Search() executes the search procedure. To perform a single iteration of the search, the model first identifies a set of base values (identified by a number between 1 and 26). This number is stored on the Intermediate Calculations – Optimization worksheet in cell C4. Then, a random number uniformly distributed between zero and two is added to the base number for each subgroup (this calculation is performed in column D). The random numbers are then ranked to establish the order in which to consider subgroups for prioritization. The VBA macro MakeDecisions()

executes the procedure to identify the soonest possible time to prioritization, subject to not violating a budget constraint, for each subgroup in the order of those ranks.

APPENDIX FIGURE S7. Example base value sets. In each of the 26 sets of base values, each subgroup is assigned a value (between zero and six). These serve to identify a region of the decision space in which to focus the attention of the search algorithm.

A.

	F0	F1	F2	F3	F4
40	6.0	5.0	4.0	4.0	5.0
45	6.0	4.0	2.0	2.0	4.0
50	5.0	2.0	1.0	1.0	3.0
55	5.0	2.0	1.0	1.0	3.0
60	6.0	2.0	1.0	1.0	3.0
65	6.0	4.0	2.0	2.0	4.0
70	6.0	5.0	4.0	4.0	5.0
75	6.0	5.0	5.0	5.0	5.0

B.

	F0	F1	F2	F3	F4
40	2.0	1.0	2.0	3.0	5.0
45	2.0	1.0	2.0	3.0	5.0
50	2.0	1.0	2.0	3.0	5.0
55	3.0	2.0	3.0	4.0	5.0
60	3.0	2.0	3.0	4.0	5.0
65	3.0	2.0	3.0	4.0	5.0
70	4.0	4.0	4.0	5.0	5.0
75	4.0	4.0	4.0	5.0	5.0

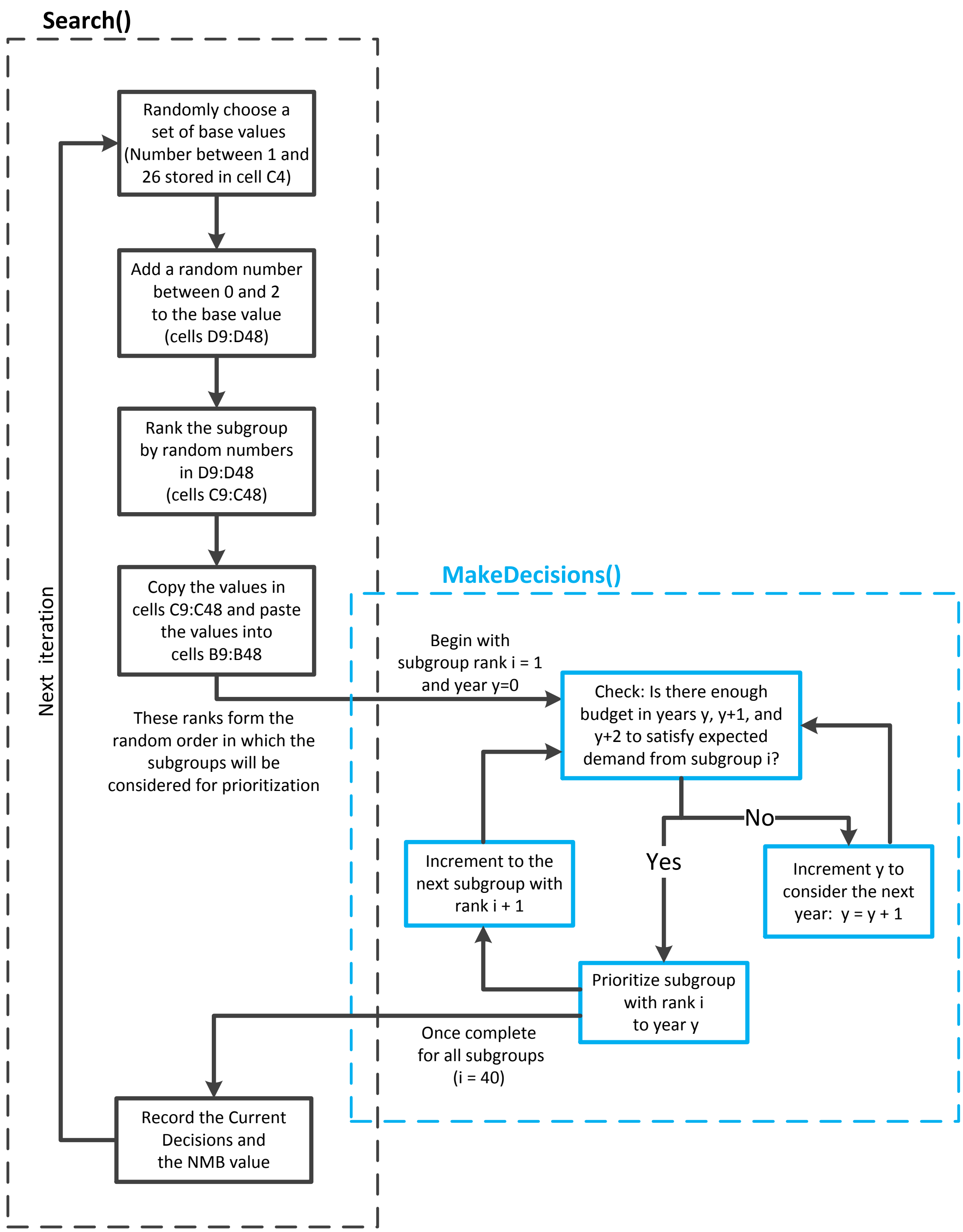
C.

	F0	F1	F2	F3	F4
40	4.0	4.0	5.0	5.0	5.0
45	2.0	2.0	3.0	4.0	5.0
50	1.0	1.0	2.0	3.0	4.0
55	1.0	1.0	2.0	3.0	4.0
60	1.0	1.0	2.0	3.0	4.0
65	2.0	2.0	3.0	3.0	5.0
70	2.0	2.0	3.0	4.0	5.0
75	4.0	4.0	5.0	5.0	5.0

D.

	F0	F1	F2	F3	F4
40	5.0	3.5	1.5	1.0	0.5
45	5.0	3.5	1.5	1.0	0.5
50	5.0	3.5	1.5	1.0	0.5
55	5.0	4.0	1.5	1.0	0.5
60	5.0	4.0	3.0	2.5	2.0
65	5.0	4.0	3.0	2.5	2.0
70	5.0	4.5	4.5	4.5	4.5
75	5.0	4.5	4.5	4.5	4.5

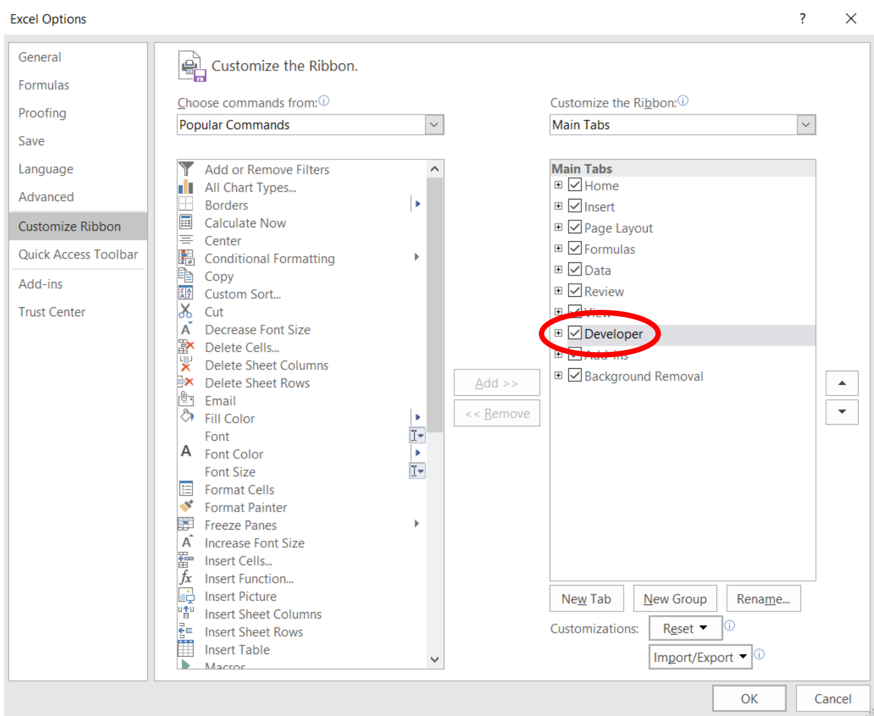
APPENDIX FIGURE S8. Overview of the two key VBA macros, Search() and MakeDecisions(). Search() creates a random ranking of the subgroups. MakeDecisions() identifies the soonest possible time to treatment prioritization, subject to not violating a budget constraint, for each subgroup in the order of those ranks.



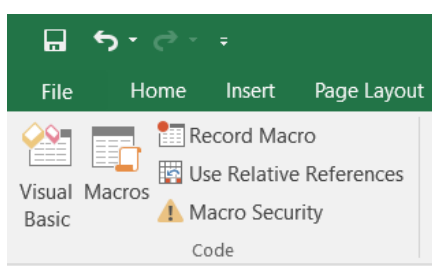
Troubleshooting if the VBA macros don't work

The model was developed and tested on Microsoft Excel for Windows 2007-2016.

If you have a problem running the VBA macros, you may be missing VBA reference libraries. To check your reference libraries, activate the Developer ribbon. This is can be found under File → Options → Customize Ribbon:



On the Developer ribbon, the icon on the left will open the Visual Basic window.



In the VBA window, open the Tools menu and choose References. The following menu will appear. Checkboxes are required beside Visual Basic for Applications, OLE Automation, Microsoft Forms 2.0 Object Library, Microsoft Excel 16.0 Object Library, and Microsoft Office 16.0 Object Library. In the latter two the number may be 14.0, 15.0, or 16.0 depending on which version of Microsoft Office you are running (14.0 for 2007, 15.0 for 2010, and 16.0 for 2013 and 2016, respectively).