**Key Idea**

We want to measure the cost-effectiveness of screening MASLD non-cirrhosis patients. We assume that screening improves earlier detection and so lowers the death rate from HCC classes.

The graph represents the actual health states of patients and not what doctors know. So a false negative result should not affect the NC to HCC transition probability, the patients still develops HCC. However, earlier detection gives doctors more information so does reduce the death rate from HCC classes and there is an additional cost for false positive tests, which we process by creating a new node in the testing scenario.

Finally, we screen all people that we think do not have cirrhosis, we thus screen the NC and the CC groups.

**Data to collect:**

**Population characteristics (non-cirrhotic MASLD)**

* Age distribution
* Male (%)
* Diabetes (%)
* Overweight (%) and/or Obese (%)
* Race/ethnicity
* Platelet level distribution
* INR level distribution
* FIB-4 distribution

We could get these from large national databases (NHANES, Truven) or from published real-world data.

**Modelling Approach**

We generate 100,000 MASLD non-cirrhosis individuals, we conduct a simulation for each of the patients through the health states and collect a QUALY (utility) and a total cost (reward) value. This allows us to measure cost-effectiveness after running scenarios for each individual and then deduce group outcomes.

**Utility and Reward Definitions**

We calculate these values statically, not dynamically. If a health state sequence is [CC, HCC, HCC, D],then the utilities/rewards are based on values assigned to the states CC, HCC, HCC, D and not the transitions CC- HCC and HCC-HCC and HCC-D. We use uniform discounting.

**Subgroups Detection**

Based on our model, we can do the following:

* Analyze CE for the whole population
* Calculate CE for a given subgroup
* Deduce from the whole-population simulation which subgroups are most CE
* Derive mathematical parameterizations that are sufficient for a future subgroup to be CE (in expectation)

Joanne’s Idea: Look at Older male patients which are obese/that diabetes

And patients who are likely to have undiagnosed cirrhosis.

**Probability of transitioning:**

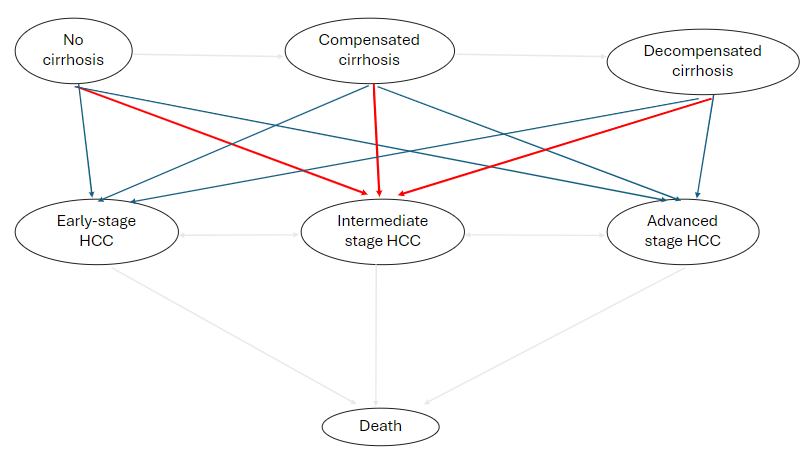
* **No cirrhosis to no cirrhosis** (US/AFP true negative rate)
* No cirrhosis to CC (from literature)
* **No cirrhosis to HCC** (incidence rate of CC in HCC, incidence rate depends on the population)
* No cirrhosis to death (from literature)
* CC to CC (from literature)
* CC to DC (from literature)
* CC to HCC (from literature)
* CC to death (from literature)
* DCC to DCC (from literature)
* DCC to HCC (from literature)
* DCC to death (from literature)
* **HCC to HCC** (actually we model different grades)
* **HCC to Death (**f-parameter, screening decreases this parameter by ensuring earlier detection, false negatives increase f-parameter, true positives decrease the f-parameter)
* **No Cirrhosis to False Positive Cirrhosis** (US/AFP false positive rate, they stay one year in that state and incur a higher cost to prove that this is a false positive)
* **False Positive Cirrhosis to No Cirrhosis (1)**
* **Death to Death (1)**

Probability of transitioning can depend on population characteristics, but may also be fixed.

Probabilities of transitioning are assumed to follow a uniform distribution, we take a range of values for each to conduct scenario testing.

**Probability of transitioning (HCC grades)**

We consider three HCC-grades: early, intermediate and advanced. Here is the graph representation:



We estimate the red arrows:

* DCC,CC-> Intermediate HCC from literature, we assume no additional screening for scenario analysis

We derive the blue arrows based on the probability of the red arrows:

* DCC,CC -> Early HCC using the above (this would increase in the intervention group that receives HCC screening)
* DCC,CC -> Late HCC using the above (this would increase in the control group that does not receive HCC screening)

We estimate Early->Intermediate->Late using the literature.

**Scenarios**

* No screening on Non-Cirrhosis MALSD
* US/AFP screening on MASLD non-cirrhosis

**Validation Approach**

Model will output survival curves, QUALYs and costs. Estimating from literature if these are reasonable are important.

**Determining the differing death rates in the control vs intervention groups**

**Accounting for cirrhosis and HCC that are diagnosed vs undiagnosed**

In the Compensated Cirrhosis and the HCC states, whilst the health state is known in the Markov model, in the real world, the doctor may not know the true health state. We calculate a weighted average cost and death rate for these two groups. Better screening increases the proportion of “doctor knows” patients and thus improves the death rate but increases costs.

How we account for patients in the cirrhosis health state who are unaware of their cirrhosis. The % of patients who are aware vs unaware of their cirrhosis will be the same in both the intervention and the control arms. In the table below (example), we show how the weighted average of the cost and probabilities will be applied to determine the cost and probabilities of the overall cirrhosis population.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| % Patients | Health State | Cost | P(Death) | P(early stage HCC) |
| 70% | Compensated cirrhosis – doctor knows | $20,000 | 5% | 50% |
| 30% | Compensated cirrhosis – doctor doesn’t know | $0 | 10% | 100% |
| 100% | All cirrhosis patients | $14,000 | 6.5% | 65% |

We account for the difference in % of HCC patients who have HCC diagnosed by splitting the group into patients who has been diagnosed and those are unaware of the diagnosis. Then, in the overall HCC population, we assign costs and probabilities as the weighted average of the splitted groups.

Example: These are for patients in the HCC early health state, control group with a default 70% and 30% split.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| % Patients | Health State | Cost | P(Death) | P(intermediate stage HCC) |
| 70% | Early Stage HCC – doctor knows | $20,000 | 5% | 50% |
| 30% | Early Stage HCC – doctor doesn’t know | $0 | 10% | 100% |
| 100% | All population | $14,000 | 6.5% | 65% |

These are for patients in the HCC early health state, intervention group with a default 100% and 0% split. Here, the % of patients who knows the diagnosis goes up because they receive HCC screening.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| % Patients | Health State | Cost | P(Death) | P(intermediate stage HCC) |
| 100% | Early Stage HCC – doctor knows | $20,000 | 5% | 50% |
| 0% | Early Stage HCC – doctor doesn’t know | $0 | 10% | 100% |
| 100% | All population | $20,000 | 5% | 50% |

**Accounting for sensitivity and specificity of HCC surveillance...**

In our actual model, the split for the intervention group shown in the table above will be determined by the sensitivity of the HCC surveillance technique. For example, if sensitivity of US+AFP is 60% for example, then the split will be 60% and 40% for the intervention group.

Additionally, the specificity will be accounted for by considering false positive scenarios. If the specificity of HCC + AFP is 80% for example, then 20% of patients who were screened for HCC will incur an additional cost (while being in the no HCC health state) due to the additional testing and time lost that is a consequence of the false positive result.

The sensitivity and specificity will be difference depending on whether the HCC is early/intermediate/advanced stage.

**Assumptions**

* Distribution of male vs. Female and <50 vs >=50 are the same in both cirrhosis and no cirrhosis starting populations.
  + Winnie will pull from Truven
  + Plt<140 and high FIB-4>=2.67 in Truven – check what % of these have diagnosis for cirrhosis
  + Stratify by sex and age (</>= 50)
  + Cirrhosis dx any time before defining lab or within 12 months after the lab
* Annual transition from early to late stage HCC is the same for all age/sex groups
* When we simulate each age/sex/cirrhosis diagnosis subgroup, we assume the same size for greater simulation accuracy
  + When we simulate the total population, we will add weights to reflect the more accurate distribution to age/sex in the total population
* Screening compliance is 100%

**Data inputs from Winnie:**

We are trying to get a sense of the distribution of male vs. female and age <50 and >50 for our starting populations, as well as for our diagnosed vs. undiagnosed cirrhosis populations.

Original cohort: Please include patients who have **MASLD diagnosis** (in any year) without cirrhosis at the time of MASLD diagnosis. The cirrhosis group should only include patients who have lab data so that we can compare the time difference between lab data showing cirrhosis and when they received a cirrhosis diagnosis. This lets us differentiate between patients who had diagnosed vs. undiagnosed cirrhosis.

We have the following scenarios. Please provide the following information for each scenario:

1. Out of the original cohort, what is the number and % breakdown of male vs female and age <50 vs. age >= 50 years old (see table shell below)?
2. Out of the original cohort, what is the number and % that develops cirrhosis? (defined as having a cirrhosis diagnosis OR platelet <140 and FIB-4>=2.67).
3. Out of the patients who develop cirrhosis, what is the number and % that has had a lab showing platelet <140 and FIB-4>=2.67 and without a cirrhosis diagnosis within 12 months after this lab date? This is the **undiagnosed cirrhosis group**.
   1. Out of the **undiagnosed cirrhosis group**, what is the % breakdown of male vs female and age <50 vs. age >= 50 years old (see table shell below)?
4. All other cirrhosis patients are in the **diagnosed cirrhosis group.** 
   1. Out of this diagnosed cirrhosis group, what is the number and % breakdown of male vs female and age <50 vs. age >= 50 years old (see table shell below)?

|  |  |  |
| --- | --- | --- |
|  | | |
| Overall (N=) | Male | Female |
| Age <50 | N (%) | N (%) |
| Age >=50 | N (%) | N (%) |
| Undiagnosed cirrhosis (N=, %) | Male | Female |
| Age <50 | N (%) | N (%) |
| Age >=50 | N (%) | N (%) |
| Diagnosed cirrhosis (N=,%) | Male | Female |
| Age <50 | N (%) | N (%) |
| Age >=50 | N (%) | N (%) |

* Sensitivity and specificity of US+AFP for HCC screening
  + By early, intermediate, and advanced HCC stage
* Quality of life (QUALY)
  + MASLD without cirrhosis
  + MASLD with compensated cirrhosis
  + MASLD with decompensated cirrhosis
  + MASLD with HCC
    - for early, intermediate, advanced stage
* Cost parameters
  + MASLD without cirrhosis
  + MASLD with compensated cirrhosis
  + MASLD with decompensated cirrhosis
  + MASLD with HCC
    - for early, intermediate, advanced stage
* Annual incidence of:
  + No cirrhosis --> compensated cirrhosis
  + No cirrhosis --> early, intermediate, and advanced stage HCC
    - By sex
    - By age <50, and age >=50
  + No cirrhosis --> death
  + Compensated cirrhosis --> decompensated cirrhosis
  + Compensated cirrhosis --> HCC
  + Compensated cirrhosis --> death
  + Decompensated cirrhosis --> HCC
  + Decompensated cirrhosis --> death
  + HCC --> curative or palliative treatment
    - By early, intermediate, advanced stage HCC
  + HCC --> death
    - By age <50 and age>=50
    - By sex
    - By early, intermediate, advanced stage HCC (untreated)
    - By early, intermediate, advanced stage HCC (palliative treatment)
    - By early and intermediate HCC (curative treatment)
* Questions to discuss:
  + For the transitions that could be impacted by age and sex, can we just collect data on the incidences above by sex, and by age, individually (instead of finding the incidence of each sex/age combination)?
  + How can we account for the cases in which patients are censored or excluded, as was outlined by Dr. Nguyen?
    - Exclude: Cirrhosis (diagnosed) --> HCC (grace period of 6 months after cirrhosis dx)
    - Censor: Cirrhosis --> no HCC
    - Censor: HCC --> cirrhosis
* Questions for Dr. Nguyen:
  + Following up on our discussion last Thursday, are the only incidences impacted by age/sex: no cirrhosis --> HCC and HCC --> death?
    - Primary treatment received is not affected by sex: [Sex differences in disease presentation, treatment and clinical outcomes of patients with hepatocellular carcinoma: a single-centre cohort study | BMJ Open Gastroenterology](https://bmjopengastro.bmj.com/content/3/1/e000107)
  + Can we combine intermediate and advanced stage HCC into one category (non-early stage) to simplify the analysis?

Control

* Probability of accidental diagnosis of HCC