**Methods**

***Comparators***

In this study, we evaluated the cost-effectiveness of HCC screening in patients with non-cirrhotic MASLD. The intervention being evaluated is HCC screening using semiannual abdominal ultrasound and AFP test. In the control arm, no routine HCC screening is performed. We conducted sub-group analyses to determine the cost effectiveness of conducting HCC screening in patients with various combinations of demographic and clinical characteristics that could impose higher HCC incidence, including older age (above 60 years), male sex, and diabetes.

***Overview of Model***

We used a Markov model to simulate the health state transitions of a starting population of 1,000,000 adult patients (³18 years) in the U.S. who are diagnosed with MASLD without cirrhosis (or with undiagnosed cirrhosis). Patients start at the non-cirrhotic MASLD node and may transition to other states including HCC, false positive HCC, treated HCC, untreated HCC, cirrhosis (at which point they are censored), and death (**Figure 1**). The absorbing states are cirrhosis and death. Patients may transition to death from the non-cirrhotic MASLD, treated HCC, and untreated HCC nodes. Patients who transition to the false positive HCC node stay for one cycle and incur an additional cost for repeat CT/MRI, then return to the non-cirrhotic MASLD node. The cost and health state utilities of patients were calculated across a lifetime horizon with a cycle length of one year.

***Accounting for the proportion of patients with undiagnosed cirrhosis***

The health states were based upon clinical diagnosis; for example, patients in the non-cirrhotic MASLD node may truly be non-cirrhotic or have undiagnosed cirrhosis. The proportion of patients with undiagnosed cirrhosis were estimated from the literature. Because patients in the non-cirrhotic MASLD node may be truly non-cirrhotic or have undiagnosed cirrhosis, the transition probabilities from non-cirrhotic MASLD to HCC and non-cirrhotic MASLD to death were weighed by the proportion of patients with undiagnosed cirrhosis. Specifically, these transition rates were derived by combining that of non-cirrhotic and cirrhotic MASLD patients (found in literature), weighing each by the proportion of truly non-cirrhotic patients and patients with undiagnosed cirrhosis in our cohort, respectively. All other transition probabilities, in addition to all costs and utilities, were not weighed by the proportion of undiagnosed cirrhosis as we assumed these to be the similar for both patients with undiagnosed and no cirrhosis.

***HCC staging, treatment, and survival***

Patients transition to the HCC node when they are diagnosed with HCC. After patients transition to the HCC node, they stay for one cycle and incur a cost associated with CT/MRI to confirm the HCC diagnosis, then transition either to the treated HCC or untreated HCC node, where they stay until death.

We modeled all HCC states (early, intermediate, and late) as a single HCC node. We differentiated between the outcomes of the control and intervention groups by applying a different distribution of patients being diagnosed in each HCC stage, with the intervention group having a higher proportion of patients being diagnosed at an earlier stage (control arm: 45.7% early stage, 23.0% intermediate, 31.3% late; intervention arm: 70.7% early, 15.6% intermediate stage, 13.7% late [reference: [Daher 2024](https://pubmed.ncbi.nlm.nih.gov/38683607/)]). Then, these distributions were used to weigh the utilities, costs, probability of receiving HCC treatment, and survival after HCC diagnosis to take into account the differing values of these parameters for each HCC stage.

The probability of receiving HCC treatment (ablation, radiotherapy, resection, systemic chemotherapy, TACE, and liver transplant) for each HCC stage was collected from the SEER-Medicare database, including in this dataset only patients who have non-cirrhotic MASLD and were diagnosed with HCC between 2011-2017. We obtained a weighed average of treatment probabilities for each HCC stage, then further weighed this by the distribution of HCC stage upon diagnosis to obtain a single overall probability of receiving HCC treatment.

Furthermore, the annual probability of death after receiving ablation, radiotherapy, resection, systemic chemotherapy, TACE, and liver transplant for HCC treatment were individually collected from the literature for each HCC stage. The proportion of patients receiving each of these treatments within each HCC stage (obtained from the SEER-Medicare database) were used to weigh the annual death probabilities (obtained from the literature) to derive a weighed average death probability for each HCC stage. Then, the HCC stage distribution was applied to these weighed averages to get the overall annual probability of death for patients who were treated for HCC. Similarly, we obtained the annual probability of death for patients with untreated HCC for each HCC stage from the literature, then applied the HCC stage distribution to derive the overall annual probability of death for patients with untreated HCC. Detailed data inputs used to obtain these transition probabilities are included in the **Supplementary Methods.**

***Modeling parameters***

All modeling parameters are estimated from current literature or derived from the Truven Health Analytics MarketScan Databases and the linked Surveillance, Epidemiology, and End Results Program (SEER) and Medicare enrollment database (2000-2017).

---- insert input tables ----

***Extrapolating transition probabilities for subgroup analysis***

[write this section later after finalizing our strategy]

***Measurement of effectiveness and costs***

The utility and costs will be evaluated across a lifetime horizon for each patient. The quality adjusted life years (QALYs) will be calculated using the estimated quality (quantified value ranging from 0-1) and length of life. All costs will be determined from the payer’s perspective and will be converted to USD in 2025. Costs for HCC treatment account for all services related to HCC care, including inpatient and outpatient physician services, medications, imaging, and procedures. A 3% annual decrease in both cost and utility is applied as recommended by the Public Health Service Panel on Cost-Effectiveness in Medicine [reference: Lipscomb et al., 1996].

***Measuring cost-effectiveness in the base-case analysis***

The primary outcome is the incremental cost effectiveness ratio (ICER) calculated for the intervention arms compared to the control. To evaluate the ICER, we found the ratio of the average incremental cost and average incremental QUALYs of the control and intervention arms, each consisting of 1,000,000 simulated patients, using the same seed for both the control and intervention arms. The ICER was then interpreted with reference to the contemporary willingness to pay threshold (WTP) of $100,000 or $150,000. In the base-case analysis, we used a screening adherence rate of 60% [reference: [Singal 2024](https://karger.com/lic/article/13/6/643/909485/Cost-Effectiveness-of-a-Biomarker-Based-Screening)].

In our analysis of the overall cohort, we assumed an equal proportion of male and female patients. The starting age of patients reflects the distribution of patient age at the time of MASLD diagnosis according to the Truven Health Analytics MarketScan Databases [reference: Truven] (**Supplementary Table X**). The age-dependent probability of death was determined from the Actuarial Life Table provided by the Social Security (2021 period life table for the Social Security area population, as used in the 2024 Trustees Report (TR) [reference: <https://www.ssa.gov/oact/STATS/table4c6.html>]. In the base case, we used the age-dependent probability of death that is averaged between that of male and female individuals. The incremental increase in death probability due to aging was added to the annual probability of liver-related death for patients in the MASLD node. Once a patient reaches an age of 100, the patient is transitioned to the death node regardless of their health state. More details regarding the age distribution and age-adjusted probability of death can be found in the **Supplementary Methods**.

***Measuring cost-effectiveness in subgroups of high-risk populations***

We conducted subgroup analyses for cohorts that are male, older than 60 years of age, and with diabetes. In our analysis of male patients, we used the age-dependent probability of death from the Actuarial Life Table for male individuals only. In our analysis of older patients, we created a cohort of patients older than 60 years and applied the age distributions (for age groups: 61-70, 71-80, 81-90, 91-100+) according to the Truven Health Analytics MarketScan Databases [reference: Truven]. For each subgroup analyzed, we also adjusted the transition probability from non-cirrhotic MASLD to cirrhosis and non-cirrhotic MASLD to HCC, and the proportion of patients with undiagnosed cirrhosis (**Table X**). For the subgroup of patients older than 60 years, these three parameter values were obtained from literature reporting data for patients older than 60 or 65 years.

***Characterizing uncertainty and heterogeneity***

Sensitivity analyses were performed by varying the value of a parameter across a range of possible values, derived from 95% confidence intervals reported in the literature or professional opinion. In the one-way sensitivity analysis, this was conducted for each parameter individually, such that only one parameter is changed while the others remain fixed at the base case value. The net monetary benefit (NMB) was calculated across each parameter’s range and plotted in a tornado diagram. We also conducted a threshold analysis to determine the screening adherence rate required for the intervention to be cost effective. To evaluate the change in cost-effectiveness with respect to the distribution of HCC stage upon diagnosis, we varied the percentage of patients diagnosed with early- and late-stage HCC and plotted the region where the intervention was cost-effective.

Additionally, probabilistic sensitivity analysis was conducted by randomly sampling 10,000 values within the range for every parameter, for all 1,000,000 patients. The results of this analysis were plotted on a cost-effectiveness plane and cost-effectiveness acceptability curve. [include details about beta, gamma, normal distributions after deciding with Malvyn]

Both one-way and probabilistic sensitivity analyses were conducted for the overall cohort and in subgroups by age, sex, and diabetes [add details later for combinations of these factors].