**Methods**

***Comparators***

In this study, we evaluate the cost-effectiveness of HCC screening in patients with non-cirrhotic MASLD. The control arm does not receive routine HCC screening while the intervention arm receives semiannual abdominal ultrasound and AFP test. We conduct sub-group analyses to determine the cost effectiveness of conducting HCC screening in patients with various combinations of demographic and clinical characteristics, including older age, male sex, and presence of diabetes, that could impose higher HCC incidence.

***Overview of Model***

We use 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 have non-cirrhotic (or undiagnosed) cirrhosis. Patients start at the non-cirrhotic MASLD node and may transition to other states including HCC, false positive HCC, treated or untreated HCC, cirrhosis (at which point they are censored), and death (**Figure 1**). Patients who transition to the false positive HCC node will stay for one cycle then return to the non-cirrhotic MASLD node.

The health states are based upon clinical diagnosis; for example, patients in the non-cirrhotic MASLD node may truly be non-cirrhotic or have undiagnosed cirrhosis and patients move to the HCC node when they are diagnosed with HCC. 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 are weighed by the proportion of patients with undiagnosed cirrhosis (based on literature). All other transition probabilities, in addition to all costs and utilities, are not weighed by the proportion of undiagnosed cirrhosis as we assume these to be the similar for both patients with undiagnosed cirrhosis and no cirrhosis.

We model all HCC states (early, intermediate, and late) as a single HCC node. The utilities, costs, and probability of being treated in the HCC node are weighed by the distribution of patients diagnosed at the early, intermediate, and late stages. We estimate these distributions for patients who were diagnosed with HCC upon screening and those who were not, according to the literature. We differentiate 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. The details for this and the related data inputs can be found in the **Supplementary Methods.** After patients transition to the HCC node, they stay for one cycle, then transition either to the treated HCC or untreated HCC node, where they stay until death. The annual probability of death from the treated or untreated HCC nodes are also weighed by the

***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 ----

***Measurement of effectiveness and costs***

The utility and costs will be evaluated across a lifetime horizon for each patient. One cycle length is defined to be one year. 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 2024. 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 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 find the ratio of the average incremental cost and average incremental effectiveness of the control and intervention arms, each consisting of 1,000,000 simulated patients. The ICER is then interpreted with reference to the contemporary willingness to pay threshold (WTP) of $100,000 or $150,000.

We use a screening adherence rate of 60% in the base-case analysis [reference].

In our analysis of the overall cohort, we assume an equal proportion of male and female patients. The starting age of patients reflects the distribution of age upon MASLD diagnosis (18-30, 31-40, 41-50, 51-60, …, 91-100+) according to a large nationwide claims database [reference: Truven]. The age-dependent probability of death is 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): <https://www.ssa.gov/oact/STATS/table4c6.html>). This is added onto the annual rate 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***

In our subgroup analysis of only male patients, we use the age-dependent probability of death for male individuals. In our subgroup analysis of only older patients, we adjusted the age distribution to be only patients 60 years of age or above. We also adjust the transition probability from non-cirrhotic MASLD to cirrhosis and non-cirrhotic MASLD to HCC, and the proportion of patients with undiagnosed cirrhosis for each of these subgroups (**Table X**).

***Characterizing uncertainty and heterogeneity***

One-way sensitivity analysis is performed by varying the value of a parameter across a range of possible values, derived from current literature or reasonable assumption. This is 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) is calculated across each parameter’s range and plotted in a tornado diagram.

Additionally, probabilistic sensitivity analysis is conducted by randomly sampling 10,000 values within the range for every parameter for all 1,000,000 patients.

Both one-way ad probabilistic sensitivity analysis is conducted for the overall cohort and in subgroups by age, sex, and the presence of diabetes.