Statistical analysis- Apendix

The primary fit used the multi-state model shown in Supplemental Figure 1, where each box is a state and each arrow represents a transition (rate) from one state to another. The analysis interest focused on 1) the two transitions to death; and 2) the overall probabilities that a subject is in each of the three states as a function of age (shown in Figure 2).

The underlying multi-state model creates rate estimates for all 3 arrows in Supplemental Figure 1, and these were combined using the Aalen-Johansen estimate to produce the overall probability in state. The underlying hazard models were fit on an age scale, and the important confounders of obesity status at time of diagnosis (BMI <18, 18-24, 25-29, 30-34, 35-39, and ≥40), as well as smoking, diabetes, hypertension, and dyslipidemia. Thus, the comparison group for any death is the set of subjects who have attained the same age as those who died, and with the same values of these variables. Stratifying on multiple variables requires a large sample size, but provides the most comprehensive balance with respect to a potential confounder. It is worth noting that the more common Fine-Gray approach does not extend to general multi-state models such as this (the Fine-Gray model is limited to the simple competing risks case, in which all of the arrows emanate from a single location).

To examine the performance of PCE in men and women with NAFLD compared to the referent cohort, predicted 10-year rates of primary ischemic CV events (composite of MI or stroke) were calculated using the sex- and race-specific equations, using age, total cholesterol, HDL cholesterol, treated or untreated systolic blood pressure, smoking status and diabetes as covariates. Because the PCEs are used to predict first-time events, subjects with a history of myocardial infarction or stroke were excluded for this part of the analysis. The expected number of events for each subject based on the ASCVD model was computed from the PCE by first converting the PCE 10-year probability into a yearly hazard rate. For subjects with over 10 years of follow-up their status and cumulative hazard at 10 years was used. For subjects with less than 10 years of follow-up, the predicted cumulative hazard and status based on the subjects' last follow-up time was used17. The ASCVD performance was assessed using 2 parameters: discrimination and calibration. Discrimination was measured by the c-statistic, which was calculated assuming that the predicted rates are fixed and the observed events follow a Poisson distribution. Calibration is a measure of the calculator's ability to accurately estimate the observed absolute risk and it was assessed using the standardized incidence ratio (SIR)=observed events/predicted events. Good calibration is achieved if the SIR is close to 1.

Statistical analyses were performed in SAS v9.4 (SAS Institute; Cary, NC) and R statistical software, version 3.2.0 (R Foundation for Statistical Computing, Vienna). The study was approved by the Institutional Review Boards of Mayo Clinic and Olmsted Medical Center.