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Cost-effectiveness of non-invasive screening for alcohol-related liver fibrosis

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List of abbreviations: ALD, alcohol-related liver disease; AST, Aspartate Aminotransferase; ELF, enhanced liver fibrosis; GGT, Gamma-Glutamyl Transpeptidase ; ICER, incremental cost-effectiveness ratio; INR, international normalised ratio; LSM, liver-stiffness measurement; QALY, quality-adjusted life-years

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Abstract

Alcohol-related liver disease is often undetected until irreversible late-stage decompensated disease manifests. Consequently, there is an unmet need for effective and economically reasonable pathways to screen for advanced alcohol-related fibrosis. We used real-world data from a large biopsy-controlled study of excessive drinkers recruited from primary and secondary care, to evaluate the cost-effectiveness of four primary care initiated strategies: 1) routine liver function tests with follow-up ultrasonography for test-positives, 2) the enhanced liver fibrosis (ELF) test, with hospital liver stiffness measurement (LSM) for positives, 3) three-tier strategy using Forns Index to control before strategy two, 4) direct referral of all to LSM. We used linked decision trees and Markov models to evaluate outcomes short-term (cost-per-accurate-diagnosis) and long-term (quality-adjusted life-years, QALYs). For low-prevalence populations, ELF with LSM follow-up was most cost-effective, both short-term (accuracy 96%, 196$ per patient), and long-term incremental cost-effectiveness ratio (ICER) $5,387-8,430/QALY, depending on whether diagnostic testing had lasting or temporary effects on abstinence rates. Adding Forns Index decreased costs to $72 per patient and accuracy to 95%. The strategy resulted in less QALY's due to more false negatives, but an ICER of $3,012, making this strategy suited for areas with restricted access to ELF and TE, or lower willingness-to-pay. For high-prevalence populations, direct referral to LSM was highly cost-effective (accuracy 93%, $297 per patient), with ICERs between $490 and $1,037/QALY. **Conclusion:** Non-invasive screening for advanced, alcohol-related fibrosis is a cost-effective intervention when different referral pathways are used according to the prevalence of advanced fibrosis. Patients in the primary healthcare sector should be tested with the ELF test followed by LSM if test-positive, whereas direct referral to LSM is highly cost-effective in high-prevalence cohorts.

Alcohol is the seventh leading risk factor for death globally and the leading cause of mortality in adults aged 15-49.(1) Liver related death is a major consequence of excessive alcohol consumption, already in moderate drinkers without alcohol addiction disorder.(2) Since alcohol related liver mortality is on the rise, this calls for action.(3) There is an unmet need for cost-effective, clinically applicable referral strategies for diagnosis of early stage alcohol-related liver disease (ALD) to enable timely prevention and treatment. If committing to abstinence from alcohol, fibrogenesis will be halted.(4)

Diagnostic investigations in primary care are usually initiated with routine blood tests followed by abdominal ultrasonography.(5) While inexpensive, these tests have poor accuracy, and leads to unnecessary follow-up testing in hospital liver clinics and inefficient use of resources. Direct serum markers of fibrosis, such as the Enhanced Liver Fibrosis (ELF) test, have high discriminatory accuracy for advanced fibrosis and could be applied in primary care.(6) However, the ELF test is several times more costly than routine blood tests, and it is not known whether ELF's superior accuracy would offset higher testing costs by resulting in fewer unnecessary follow-ups. Liver stiffness measurements (LSM) by transient elastography (FibroScan, Echosens, France) is the non-invasive state of the art, but for now limited to secondary care (7, 8).

Previous economic evaluations of referral pathways for non-alcoholic fatty liver disease has shown favourable cost-effectiveness.(9, 10) However, only one study has evaluated the cost-effectiveness of similar efforts in ALD patients, but patients were assumed alcohol-dependent and testing compared to liver biopsy, which is not suited for primary care.(11) We therefore aimed to evaluate whether strategies based on non-invasive tests for advanced fibrosis can cost-effectively improve lifetime health outcomes in patients with excessive alcohol intake, using 45-year-old males and females in the Danish health care sector as an exemplar and deriving diagnostic test performance from a real-world, biopsy-controlled cohort of 241 primary care and 221 secondary care patients. Our objective was to calculate costs-per-accurate-diagnosis, lifetime costs and quality-adjusted life-years (QALYs) for four referral strategies using an economic decision model, with separate analyses for low-prevalence (primary care) and high prevalence (secondary care) settings. The four strategies formed a spectrum from low cost and low accuracy to high cost and high accuracy, benchmarked against a no testing alternative.

Materials and methods

Study design

We developed a cost-effectiveness model with two time perspectives: A short-term perspective to calculate which referral strategy would be cost-effective in terms of correctly classified individuals; and a long-term perspective to analyse the potential effects of screening on the quality-adjusted life-years (QALYs) and lifetime healthcare costs.

For the short-term perspective, we used a decision tree based on observed diagnostic yield and test accuracies for advanced fibrosis from a real-world, biopsy-controlled cohort to classify patients into four cardinal outcomes: true positives, false positives, true negatives, or false negatives (Figure 1). With patients distributed into these four diagnostic test outcomes, we proceeded with a Markov state-transition model, to test the long-term cost-effectiveness of the referral strategies (Figure 2).

Screening strategies

We evaluated four testing strategies to screen for advanced fibrosis, and compared them to no testing:

(A) Standard-of-care: routine liver function tests applied in parallel with follow-up ultrasonography for test-positives. We considered patients test-positive when exceeding the upper limit of normal for gamma-glutamyl transpeptidase (GGT), international normalized ratio (INR) or aspartate aminotransferase (AST), and lower limit of normal for platelet count. These blood tests are routine indicators of alcohol-related liver damage (GGT and AST) and liver function (INR and platelets). Patients testing positive were referred to outpatient ultrasonography. We assumed a majority of physicians would apply liver function tests in parallel such that a positive on either would warrant ultrasonography (see supplementary information).

(B) The enhanced liver fibrosis (ELF test), with follow-up liver stiffness measurement for positives. In this model, general practitioners referred excess drinkers with an ELF test above the 10.5 cut-off to outpatient, secondary care LSM by transient elastography.(12) An LSM-result 15 ≥ kPa gave a diagnosis of advanced fibrosis.(6, 13)

(C) Three-tier strategy using the indirect fibrosis marker Forns Index to control before strategy B. The Forns index is a diagnostic algorithm based on age, GGT, platelet count, and cholesterol level.(14) Patients exceeding 6.8 was eligible for the serial 'ELF followed by LSM' strategy. The aim of this strategy was to reduce the use of the costly ELF-test and LSM, by funnelling only patients with a high probability of having advanced fibrosis to these tests.

(D) Refer all excessive drinkers to LSM testing directly. This strategy was included to benchmark the cost-effectiveness of using any screening in primary care.

The strategies form a spectrum of the likelihood of referral to LSM in hospital based liver clinics. While strategy A improves net sensitivity, it reduces net specificity, yielding a low threshold for secondary care referral (see supplementary information). At the opposite side of the spectrum, restricting ELF testing to those with elevated Forns index (strategy C) improves specificity and results in a high threshold for referral.

Diagnostic test accuracies

We derived diagnostic test accuracies from a cohort of 462 patients with self-reported prior or current harmful alcohol consumption, included as part of a biopsy-controlled diagnostic test study (ethical ID S-20120071, S-20160021 and S-20170087). All diagnostic test results can be seen in the supplementary information. Study methods are described in detail previously.(6, 15) From May 2013 to September 2018, we included 241 asymptomatic patients recruited from primary care with an 8% prevalence of advanced fibrosis, and 221 patients recruited from secondary care with a 34% prevalence of advanced fibrosis. None of the patients had competing liver disease, alcohol-related hepatitis or evidence of decompensated cirrhosis. All study investigations were performed on the same day and included non-invasive testing with ELF test, Forns index and LSM, in addition to routine liver biochemistry and liver-specific B-mode ultrasonography. We used the Kleiner score for fibrosis staging.

Linking test outcomes to long term impact on health outcomes

As our target population are not alcohol dependent, a brief motivational intervention is standard practice for alcohol-rehabilitation. A 2018 meta-analysis found a reduction in alcohol consumption of 20 grams/week following a brief intervention in primary care.(16) This corresponds roughly to cutting a day per week of drinking for our target population, which is not effective enough to avoid progression. However, a diagnosis itself might also increase the motivation to stop drinking. This is to some extent backed-up by evidence, both from other chronic conditions and from non-invasive screening for ALD.(17-20) However, since knowledge is scarce regarding the short-term effects of testing on abstinence, and long-term effects are unknown, we took two scenarios into account. In one, we assumed a retained effect of diagnostic testing on abstinence. In the other, we assumed only a temporary response, that is after one model cycle the effect of diagnosis on abstinence vanishes and excessive drinking is resumed (Figure 3).

Diagnostic accuracies, transition probabilities and costs

The diagnostic input parameters to the decision model from the low prevalence, primary care patients and high prevalence, secondary care patients are shown in the supplementary appendix. Table 1 summarises all health state transition probabilities. They were derived from Danish cohort studies except the probability of developing compensated cirrhosis from advanced fibrosis if drinking, and the effect of diagnosis on abstinence. Table 2 lists health state costs and health state utilities. Costs were derived from the Danish health care service. We considered only direct medical costs from compensated cirrhosis and decompensated cirrhosis, as alcohol-related fibrosis (F0-3) is largely asymptomatic until cirrhosis occurs. We calculated costs for the excess morbidity of compensated cirrhosis, as approximately one third of compensated patients are hospitalised for other than liver-related events. We similarly assumed that loss of health-related quality-of-life happened from the onset of compensated cirrhosis. We used estimates from the 2004 study by Wells et al (21) where 114 cirrhotic patients were subjected to direct elicitation of health state preferences using the time-trade-off approach.

Analyses

We established short-term cost-effectiveness by assembling costs of administering, interpreting, and delivering the tests and their results. The effect was the tests' accuracy in terms of correctly classified patients. We ranked the strategies in ascending costs and calculated the incremental cost and effect of each strategy to the next least costly. Dominated strategies (higher costs and lower effect) were eliminated and the strategies' incremental costs and effects recalculated. The incremental cost-effectiveness ratios (ICERs) are the incremental costs relative to the incremental effects, and the strategy resulting in the highest ICER below a payer's economic constraint to realise one QALY is interpreted as the optimal strategy (22). While we report ICERs for the short term, these should be interpreted with caution for intermediate outcomes such as our cost-per-correct diagnosis because cost-effectiveness thresholds are typically only defined for final outcomes such cost-per-QALY.

For lifetime predictions, we considered the per-patient QALYs gained and lifetime health care costs as endpoints, calculated ICERs and ranked test strategies as in the short-term analysis. However, we added a 'no testing' alternative to benchmark against the natural disease development and its associated costs and QALYs.

To show model responsiveness to single-changes in parameter values we used one-way sensitivity analysis (supplementary information). We used probabilistic sensitivity analysis to show the influence on decision uncertainty arising from the model input parameters. This

approach assigns probability distributions to the model parameters based on their variation (beta for binomial probabilities, dirichlet for multinomial probabilities, and gamma for costs). From the resulting joint distribution of costs and QALYs, we calculated the net monetary benefit of each strategy. This gives one measure of the strategies' costs and QALYs relative to a payer's economic constraint, or cost-effectiveness threshold. The strategy with the highest expected net monetary benefit is interpreted as the optimal strategy for a given level of willingness to pay (23). To facilitate decision makers with different economic constraints our analysis considered a range of willingness to pay per QALY from 0 (only cost-saving new interventions accepted) to $50,000.

Results

Short-term cost-effectiveness

Strategy B, the ELF-test with LSM follow-up, was the most accurate strategy with an accuracy of 96.0%, at a cost of $194 per patient (Table 3). Strategy B was followed by the Forns/ELF/LSM serial strategy (C), which correctly classified 95.1% of patients and was also the least costly, at $72 per patient. The standard-of-care strategy (A) was the least accurate, and resulted in $8 higher testing costs per patient than strategy C because of the high false positive rate requiring follow-up ultrasonography. The strategy was therefore ruled out from the set of alternatives. The most expensive approach, direct referral to LSM, was also ruled out as it failed to achieve the accuracy of the Forns/ELF/LSM serial strategy. The ELF/LSM strategy yielded a 0.9% better accuracy than the Forns-initiated counterpart and cost an additional $122 per patient. The short-term ICER for the ELF/LSM strategy was therefore $12,200. If considering only short-term effects the very low additional accuracy of ELF/LSM and substantially lower per-patient cost of the Forns/ELF/LSM strategy, stratifying first with the Forns index in a likely low prevalence setting could therefore in practice be the best option.

For the secondary care cohort, the LSM directly strategy was most accurate, correctly identifying 93% of the patients. Furthermore, because a third of the patients in this cohort had advanced fibrosis, a larger proportion would require the follow-up tests in the other strategies than in the primary care cohort. This resulted in higher testing costs across all strategies with follow-up tests, favouring directly using the highly accurate LSM with an additional cost of $30 per patient compared to the next most effective ELF/LSM option. Although the per patient cost of LSM directly is the same in both cohorts at $297, the incremental cost of $30 for the incremental effect of 3% accuracy resulted in an ICER of only $1,154 in the short-term perspective.

Lifetime cost-effectiveness

The rank of the strategies from the lifetime simulation were the same as in the short term for both patient cohorts. Furthermore, the two scenarios for the effect of diagnostic testing on abstinence were in agreement, although the predicted lifetime costs were higher and QALYs gained were lower across all strategies in the temporary response on abstinence scenario than in the retained response on abstinence scenario. In a primary care setting, serial testing with ELF/LSM would be cost-effective given a payer's willingness to pay per QALY gained exceeding $8,430. If patients only temporarily stop drinking, QALYs gained are lower, however ICER is also lower compared to the next most effective strategy (table 4).

In a secondary care setting with higher prevalence of advanced alcohol-related liver fibrosis, direct testing with the LSM can improve lifetime health outcomes for payers with cost-effectiveness thresholds even below $500 per QALY gained if testing has lasting effect on abstinence, or approximately $1,000 if the effect is only temporary (table 4).

Figure 4 show the influence of uncertainty in model input parameters on lifetime predictions of cost-effectiveness. These results reinforce the base case findings: for both the primary care cohort and the secondary care cohort the identified cost-effective strategies are consistently optimal strategies above their ICERs.

Discussion

From an economic perspective, the expected lifetime healthcare costs associated from undetected ALD is between $6,600 - $10,000 depending on prevalence. This gives relatively low additional costs to introduce screening efforts. Our cost-effectiveness analysis indicates that the optimal short- and long-term strategy to screen for alcohol-related liver fibrosis among primary care patients is ELF-testing with referral to liver stiffness measurement at a hospital liver clinic, in case of a positive ELF. In secondary care settings, where the prevalence of advanced fibrosis is substantially higher, direct LSM in all patients was the superior diagnostic pathway. This strategy had the highest accuracy and most QALYs gained, resulting in very low incremental cost effectiveness ratios between $490 and $1,037.

The ELF/LSM strategy is most accurate in the setting of low-prevalence of advanced fibrosis. The higher cost of using the ELF rather than a cheaper, non-invasive marker for initial screening is offset by more patients being correctly diagnosed which results in more QALYs gained. The incremental cost-effectiveness ratio was between $5,387 and $8,430 per quality-adjusted life-year gained, depending on how screening was modelled to affect drinking behaviour. Adding Forns test as a first selection step helped reduce the number of expensive ELF and LSM tests, but at the expense of fewer QALYs gained. Using the cheap indirect fibrosis markers to initiate screening could therefore be an option in countries with lower cost-effectiveness thresholds or limited access to ELF and LSM.

Evidence, albeit scarce, suggests that screening for liver damage can influence patients to change their drinking habits. There seem to be a stronger motivation to sustain abstinence if given a positive test result, than if given a negative. Since there is no evidence to suggest whether this motivation is sustained or temporary, we modelled both scenarios. Despite the standard-of-care strategy having the highest proportion test-positives, it resulted in the fewest lifetime QALYs gained, as the pathway also resulted in the second-highest proportion false-negatives, and lowest true-negatives. The prolonged time to diagnosis for the false negatives offset the improved abstinence rates among false positives. This finding underlines the importance of implementing new referral strategies with higher sensitivities for detection of advanced fibrosis.

Timely alcohol rehabilitation is essential to improve survival.(24) A strength of our study is that we based our model on patients with a heavy, daily alcohol use, but not severe addiction disorder, in line with the literature. The non-dependent patients can more easily give up drinking when motivated and a brief intervention is effective even when delivered in primary care, outside

alcohol rehabilitation clinics. If we had included more intensive alcohol rehabilitation strategies, such as acamprosate treatment, the effect of a correct diagnosis may have been even stronger, however costs would also increase.

A limitation of our lifetime analysis is that we were unable to identify good quality evidence on transition rates between the discrete Kleiner stages, but had to consider F2 and F3 together. While advanced fibrosis is a strong predictor of liver-related events in ALD, presence of significant fibrosis at baseline predicts later fibrosis progression.(25, 26) Therefore, we are confident that ALD patients with both F2 and F3 will be at high risk of progressing to symptomatic disease if drinking continues.

We investigated clinically relevant diagnostic cut-offs, but acknowledge that they may not be optimal thresholds from a cost-effectiveness and long-term, outcome point of view.(27) However, no studies have presented relevant cut-offs for prognostication using ELF, LSM and indirect markers. Another unexplored factor is that we restricted our analysis to direct health care costs associated to liver disease and excluded other alcohol-associated healthcare cost such as cancer and cardiovascular disease. Consequently, our analysis does not include larger societal benefits from reduced drinking such as accidents and sick leave. It is possible that by widening the perspective, more abstinent individuals in the at-risk population could offset screening costs resulting in lower ICERs.

We benefit from a number of analytical strengths: First, our employed estimates for test performance came, except ultrasonography, exclusively from a real-word diagnostic test study including patients similar to the model population. This is an advantage, because test performance may change dramatically between cohorts with different disease prevalence.(28) We thereby avoid spectrum bias. Second, our explicit reporting on model sensitivity to the link between test outcomes and lifetime outcomes strengthens the credibility of our predictions. Third, we took into account that elastography is the more expensive option due to its availability exclusively in secondary care.(29)

In conclusion, this analysis is the first to show cost-effectiveness of precise, diagnostic strategies that improve correct referrals of alcohol over-users to secondary care. This is an area with large unexplored potential, as the use of cost-effective diagnostic pathways in primary and secondary care may ultimately lead to improvement in quality-adjusted life years for patients with alcohol-related liver disease.

References

1. Collaborators GA. Alcohol use and burden for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet (London, England). 2018;392(10152):1015-35.

2. Wood AM, Kaptoge S, Butterworth AS, Willeit P, Warnakula S, Bolton T, et al. Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. The Lancet. 2018;391(10129):1513-23.

3. Tapper EB, Parikh ND. Mortality due to cirrhosis and liver cancer in the United States, 1999-2016: observational study. BMJ. 2018;362.

4. Takahashi H, Shigefuku R, Maeyama S, Suzuki M. Cirrhosis improvement to alcoholic liver fibrosis after passive abstinence. BMJ Case Rep. 2014;2014:bcr2013201618.

5. Mueller S, Seitz HK, Rausch V. Non-invasive diagnosis of alcoholic liver disease. World J Gastroenterol. 2014;20(40):14626-41.

6. Thiele M, Madsen BS, Hansen JF, Detlefsen S, Antonsen S, Krag A. Accuracy of the Enhanced Liver Fibrosis Test vs FibroTest, Elastography, and Indirect Markers in Detection of Advanced Fibrosis in Patients With Alcoholic Liver Disease. Gastroenterology. 2018;154(5):1369-79.

7. Gines P, Graupera I, Lammert F, Angeli P, Caballeria L, Krag A, et al. Screening for liver fibrosis in the general population: a call for action. The lancet Gastroenterology & hepatology. 2016;1(3):256-60.

8. Thiele M, Detlefsen S, Møller L, Madsen BS, Hansen JF, Fialla AD, et al. Transient and 2-dimensional shear-wave elastography provide comparable assessment of alcoholic liver fibrosis and cirrhosis. Gastroenterology. 2016;150(1):123-33.

9. Tapper EB, Hunink MG, Afdhal NH, Lai M, Sengupta N. Cost-Effectiveness Analysis: Risk Stratification of Nonalcoholic Fatty Liver Disease (NAFLD) by the Primary Care Physician Using the NAFLD Fibrosis Score. PloS one. 2016;11(2):e0147237.

10. Tanajewski L, Harris R, Harman DJ, Aithal GP, Card TR, Gkountouras G, et al. Economic evaluation of a community-based diagnostic pathway to stratify adults for non-alcoholic fatty liver disease: a Markov model informed by a feasibility study. BMJ open. 2017;7(6):e015659.

11. Soto M, Sampietro-Colom L, Lasalvia L, Mira A, Jimenez W, Navasa M. Cost-effectiveness of enhanced liver fibrosis test to assess liver fibrosis in chronic hepatitis C virus and alcoholic liver disease patients. World journal of gastroenterology. 2017;23(17):3163-73.

12. Byrne CD, Patel J, Scorletti E, Targher G. Tests for diagnosing and monitoring non-alcoholic fatty liver disease in adults. BMJ (Clinical research ed). 2018;362:k2734.

13. de Franchis R. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. Journal of hepatology. 2015;63(3):743-52.

14. Forns X, Ampurdanes S, Llovet JM, Aponte J, Quinto L, Martinez-Bauer E, et al. Identification of chronic hepatitis C patients without hepatic fibrosis by a simple predictive model. Hepatology (Baltimore, Md). 2002;36(4 Pt 1):986-92.

15. Thiele M, Detlefsen S, Sevelsted Moller L, Madsen BS, Fuglsang Hansen J, Fialla AD, et al. Transient and 2-Dimensional Shear-Wave Elastography Provide Comparable Assessment of Alcoholic Liver Fibrosis and Cirrhosis. Gastroenterology. 2016;150(1):123-33.

16. Kaner EF, Beyer FR, Muirhead C, Campbell F, Pienaar ED, Bertholet N, et al. Effectiveness of brief alcohol interventions in primary care populations. Cochrane Database Syst Rev. 2018;2:Cd004148.

17. Day C, Gilvarry E, Butler T, James O. Moderate alcohol intake is not deleterious in patients with alcoholic liver disease. Hepatology (Baltimore, Md). 1996;24.

18. Crossan C, Tsochatzis EA, Longworth L, Gurusamy K, Davidson B, Rodriguez-Peralvarez M, et al. Cost-effectiveness of non-invasive methods for assessment and monitoring of liver fibrosis and cirrhosis in patients with chronic liver disease: systematic review and economic evaluation. Health technology assessment (Winchester, England). 2015;19(9):1-409, v-vi.

19. Stevenson M, Lloyd-Jones M, Morgan MY, Wong R. Non-invasive diagnostic assessment tools for the detection of liver fibrosis in patients with suspected alcohol-related liver disease: a systematic review and economic evaluation. Health technology assessment (Winchester, England). 2012;16(4):1-174.

20. Newsom JT, Huguet N, Ramage-Morin PL, McCarthy MJ, Bernier J, Kaplan MS, et al. Health behaviour changes after diagnosis of chronic illness among Canadians aged 50 or older. Health reports. 2012;23(4):49.

21. Wells CD, Murrill WB, Arguedas MR. Comparison of health-related quality of life preferences between physicians and cirrhotic patients: implications for cost-utility analyses in chronic liver disease. Digestive diseases and sciences. 2004;49(3):453-8.

22. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. Methods for the Economic Evaluation of Health Care Programmes. OUP Catalogue. 2005.

23. Phelps CE, Mushlin AI. On the (near) equivalence of cost-effectiveness and cost-benefit analyses. International journal of technology assessment in health care. 1991;7(1):12-21.

24. Takahashi H, Shigefuku R, Maeyama S, Suzuki M. Cirrhosis improvement to alcoholic liver fibrosis after passive abstinence. BMJ Case Rep. 2014;2014.

25. Mathurin P, Beuzin F, Louvet A, Carrie-Ganne N, Balian A, Trinchet JC, et al. Fibrosis progression occurs in a subgroup of heavy drinkers with typical histological features. Aliment Pharmacol Ther. 2007;25(9):1047-54.

26. Lackner C, Spindelboeck W, Haybaeck J, Douschan P, Rainer F, Terracciano L, et al. Histological parameters and alcohol abstinence determine long-term prognosis in patients with alcoholic liver disease. Journal of Hepatology. 2017;66(3):610-8.

27. Laking G, Lord J, Fischer A. The economics of diagnosis. Health economics. 2006;15(10):1109-20.

28. Brenner H, Gefeller O. Variation of sensitivity, specificity, likelihood ratios and predictive values with disease prevalence. Statistics in medicine. 1997;16(9):981-91.

29. Harman DJ, Ryder SD, James MW, Jelpke M, Ottey DS, Wilkes EA, et al. Direct targeting of risk factors significantly increases the detection of liver cirrhosis in primary care: a cross-sectional diagnostic study utilising transient elastography. BMJ open. 2015;5(4):e007516.

30. Teli MR, Day CP, Burt AD, Bennett MK, James OF. Determinants of progression to cirrhosis or fibrosis in pure alcoholic fatty liver. Lancet (London, England). 1995;346(8981):987-90.

31. Jepsen P, Ott P, Andersen PK, Sorensen HT, Vilstrup H. Clinical course of alcoholic liver cirrhosis: a Danish population-based cohort study. Hepatology (Baltimore, Md). 2010;51(5):1675-82.

32. Denmark [Internet]. 2018 [cited Februar 5, 2018]. Available from: http://www.mortality.org/.

33. Stefansdottir J, Christensen E, Schiodt FV. Hepatocellular carcinoma in Danish patients: a single Copenhagen center experience. Scand J Gastroenterol. 2017;52(6-7):768-72.

34. Day C, Gilvarry E, Butler T, James O. Moderate alcohol intake is not deleterious in patients with alcoholic liver disease. Hepalogogy. 1996;24.

35. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC medical research methodology. 2012;12:9.

36. Helse - og omsorgsdepartementet. Forskrift om stønad til dekning av utgifter til undersøkelse og behandling hos lege https://lovdata.no/dokument/SF/forskrift/2018-06-29-11532017 [updated June 20, 2018. June 26, 2017:[Available from: https://lovdata.no/dokument/SF/forskrift/2018-06-29-1153.

37. InteraktivDRG [Internet]. 2017 [cited June 21, 2018]. Available from: http://drgservice.ssi.dk/grouper/Modules/Home/.

38. Praktiserende lægers organisation. Honorarer og takster https://www.laeger.dk/PLO-honorarer-og-takster2018 [Available from: https://www.laeger.dk/PLO-honorarer-og-takster.

39. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. Health economics. 2001;10(8):779-87.

Table 1 Annual transition probabilities between health states

Parameter	Expected value	(95% CI)	Reference
Relapse non-invasive test positive*	0.48	(0.34, 0.58)	(17-19)
Relapse non-invasive test negative*	0.79	(0.67, 0.91)	(17-19)
Progression F-0/1 to F-2/3 in drinking state	0.03	(0.00, 0.07)	(30)
Progression F-2/3 to F4 in drinking state	0.20	(0.10, 0.30)	(18)
Progression from F4 to DC	0.14	(0.08, 0.20)	(31)
of which less severe complications**	0.80	(0.76, 0.85)	(31)
of which more severe complications**	0.20	(0.15, 0.24)	(31)
Progression from F4, DC to HCC	0.006	(0.00, 0.02)	(31)
F-0/1, F-2/3 to death	Life-table based all-cause mortality		(32)
F4 to death	0.16	(0.13, 0.21)	(31)
DC death			
mild complications***	0.17	(0.15, 0.20)	(31)
severe complications***	0.49	(0.44, 0.55)	(31)
HCC to death	0.83	(0.75, 0.89)	(33)

*Assumption based on clinical advice in (18, 19) for biopsied patients in (34). ** Less severe complications: ascites or bleeding oesophageal varices, severe complications: hepatic encephalopathy or ascites and bleeding oesophageal varices (31).

*** Mortality rate mild complications: mortality with ascites, mortality severe complications: mortality with hepatic encephalopathy. Probability distributions are available in the supplementary information. For the transition probabilities to death from cirrhosis and decompensated cirrhosis, we performed enhanced secondary analysis of published Kaplan Meier curves in order to recreate the individual patient data.(35) This allowed estimating survival with the correct number at risk, and censoring information. We fitted the data using exponential survival regression to derive transition probabilities reflecting constant hazard. Comparisons of published and recreated survival curves are available in the supplementary information.

Abbreviations: F0-1: no/mild fibrosis. F2-3: moderate/advanced fibrosis. F4: compensated cirrhosis. DC: decompensated cirrhosis. HCC: hepatocellular carcinoma. CI: confidence interval.

Table 2 Health state costs and health state utilities

Parameter	Expected value	(95% confidence interval)	Reference
Diagnostic test costs			
Liver function tests	$37.2	(27.9, 46.5)	
ELF testing	$155.3	(116.5, 194.1)	*
Forns index testing	$35.6	(26.7, 44.5)	(36)
Ultrasonography	$97.2	(72.9, 121.5)	(37)
LSM	$297	(222.8, 371.3)	(37)
Treatment costs**			
Brief intervention	$124	(93, 155)	(38)
Treatment compensated cirrhosis	$4 883	(3 662, 6 103)	(37)
Treatment cirrhosis with ascites	$5 650	(4 237.5, 7 062.5)	(37)
Treatment cirrhosis with bleeding oesophageal varices	$9 463	(7 097.3, 11 829)	(37)
Treatment for cirrhosis with ascites and bleeding oesophageal varices	$9 463	(7 097.3, 11 829)	(37)
Treatment hepatic encephalopathy	$6 791	(5 093.3, 8 488.8)	(37)
Treatment hepatocellular carcinoma	$4 438	(3 328.5, 5 547.5)	(37)
Health state utility values			
Health states with severity < F4	1		***
Compensated cirrhosis	0.88	(0.85, 0.91)	(21)
Decompensated cirrhosis			
Less severe complications	0.74	(0.70, 0.78)	(21)
More severe complications	0.55	(0.51, 0.59)	(21)
Hepatocellular carcinoma	0.30	(0.25, 0.35)	(21)

*Cost for test (2017) at the Department of Clinical Biochemistry, Odense University Hospital Svendborg (personal communication). **Treatment costs for decompensated cirrhosis were weighted with probabilities for the specific complications (supplementary information). ***We assumed patients would have asymptomatic disease progression until cirrhosis occurred. Costs were calculated in Danish kroner (DKK), or Norwegian kroner (NOK) where Danish costs could not be obtained, and adjusted to 2018 US dollar (USD) using the yearly average exchange rates 7.45 DKK/USD and 8.14 NOK/USD. We calculated the present value of future costs and QALYs with an annual discount rate of 4%. Individual treatment costs from the national diagnosis related groups database(37), which contains reimbursement tariffs for individual diagnoses and procedure codes, can be seen in the supplementary information. Estimation details and probability distributions are provided in the supplementary information.

Abbreviations: ELF: Enhanced Liver Fibrosis test. LSM: Liver stiffness measurement. F4: compensated cirrhosis.

Table 3 Short-term cost-effectiveness: cost per correct diagnosis

Cohort	Strategy	Expected per-patient costs	Accuracy	Incremental costs	Incremental accuracy	ICER
Primary care (low prevalence)	C	$ 72	0.948	-	-	-
	A	$ 80	0.886	$ 8	-0.06	Dom.
	B	$ 194	0.958	$ 122	0.01	$ 12 200
	D	$ 297	0.932	$ 103	-0.03	Dom.
Secondary care (high prevalence)	A	$ 116	0.745	-	-	-
	C	$ 152	0.836	$ 36	0.09	$ 396
	B	$ 267	0.902	$ 115	0.07	$ 1 742
	D	$ 297	0.928	$ 30	0.03	$ 1 154

A: Standard-of-care using routine liver function tests applied in parallel with follow-up ultrasonography for test-positives;

B: The enhanced liver fibrosis (ELF test), with follow-up liver stiffness measurement for positives;

C: Three-tier strategy using the indirect fibrosis marker Forns Index to control before strategy B;

D: Refer all excessive drinkers to LSM testing directly.

Abbreviations: ICER: incremental cost-effectiveness ratio (compared to next least costly non-dominated strategy). QALYs: quality-adjusted life-years. ELF: enhanced liver fibrosis test, LSM: liver stiffness measurement. Dom: dominated strategy, costlier and less effective than at least one other strategy. Ext. Dom.: extendedly dominated, higher ICER than a more effective strategy.

Table 4 Lifetime cost-effectiveness predictions

Simulated cohort	Scenario	Strategy	Expected per-patient costs	Expected per-patient QALYs	Incremental costs	Incremental QALYs	ICER
Primary care (low prevalence)	Retained benefit	No testing	$6 673	13.69	-	-	-
		A	$6 777	16.23	$104	2.55	$41
		D	$8 158	16.79	$1 380	0.56	$2 475
		C	$8 429	16.69	$271	-0.10	Dom.
		B	$8 882	16.88	$724	0.09	$8 430
	Temporary benefit	No testing	$6 673	13.69	-	-	-
		A	$7 396	15.51	$732	1.83	$401
		D	$8 871	15.92	$1 475	0.41	Ext. Dom.
		C	$9 072	15.99	$201	0.07	$3 012
		B	$9 587	16.09	$515	0.10	$5 387
Secondary care (high prevalence)	Retained benefit	A	$9 567	14.36	-	-	-
		No testing	$10 636	10.09	$1 069	-4.27	Dom.
		D	$10 664	16.60	$1 097	2.24	$490
		B	$11 704	15.78	$1 040	-0.82	Dom.
		C	$11 811	14.73	$107	-1.05	Dom.
	Temporary benefit	A	$10 468	12.38	-	-	-
		No testing	$10 636	10.09	$168	-2.30	Dom.
		D	$11 817	13.68	$1 349	1.30	$1 037
		C	$12 738	12.78	$921	-0.90	Dom.
		B	$12 763	13.32	$946	-0.36	Dom.

A: Standard-of-care using routine liver function tests applied in parallel with follow-up ultrasonography for test-positives;

B: The enhanced liver fibrosis (ELF test), with follow-up liver stiffness measurement for positives;

C: Three-tier strategy using the indirect fibrosis marker Forns Index to control before strategy B;

D: Refer all excessive drinkers to LSM testing directly.

Abbreviations: ICER: incremental cost-effectiveness ratio (compared to next least costly non-dominated strategy). QALYs: quality-adjusted life-years. ELF: enhanced liver fibrosis test, LSM: liver stiffness measurement. Dom: dominated strategy, costlier and less effective than at least one other strategy. Ext. Dom.: extendedly dominated, higher ICER than a more effective strategy.

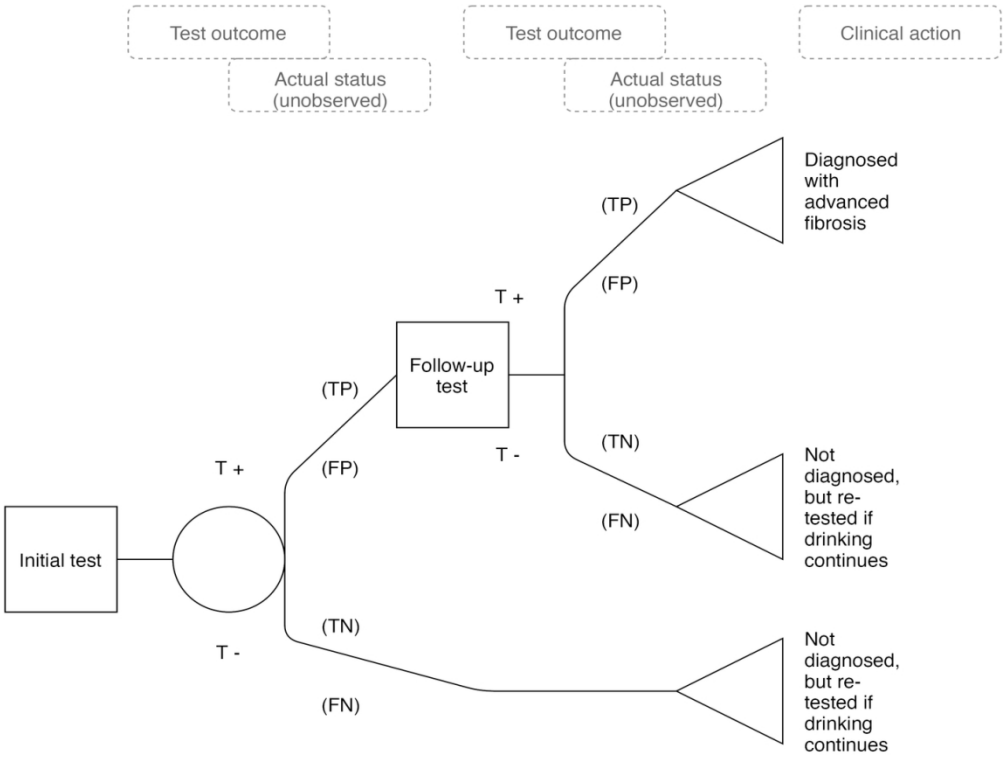

Figure 1 Decision tree. Used to calculate test outcomes and costs in short term analysis, and to distribute patients to initial health states and potential repeat testing in the Markov state transition model for lifetime simulation. We based our model on the assumption that patients who tested negative was invited to a re-test the following year if relapsed or continued drinking. Patients initially testing positive were not re-tested.

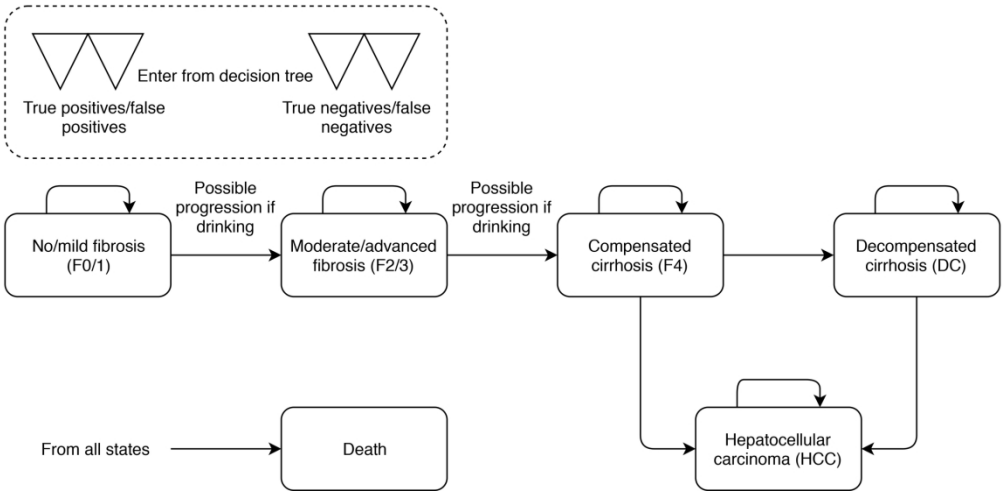

Figure 2 Markov state transition model for lifetime simulation over discrete health states. The state transition model simulated disease history as annual transitions between six discrete health states: 1) no/mild fibrosis (F0/1), 2) moderate/advanced fibrosis (F2/3), 3) compensated cirrhosis (F4), 4) decompensated cirrhosis, 5) hepatocellular carcinoma, and 6) death. In addition to these states, F0/1 and F2/3 had sub-states for either staying abstinent following a brief motivational intervention or continued drinking, influencing the likelihood of progressing to more severe fibrosis stages. If relapsed upon their annual physician follow-up, testing was repeated. The decompensated cirrhosis health state had two sub-states indicating which type of cirrhosis complication patients could develop, one with less severe complications, and one with more severe complications. We used ascites to exemplify less severe complications, and hepatic encephalopathy for more severe complications.(30) Hepatocellular carcinoma could develop from both compensated and decompensated cirrhosis, and death could be transitioned to from any state. We did not include the option of a liver transplantation, as occurrence of this event is negligible in the average ALD population. Patients were followed until death or 100 years of age.

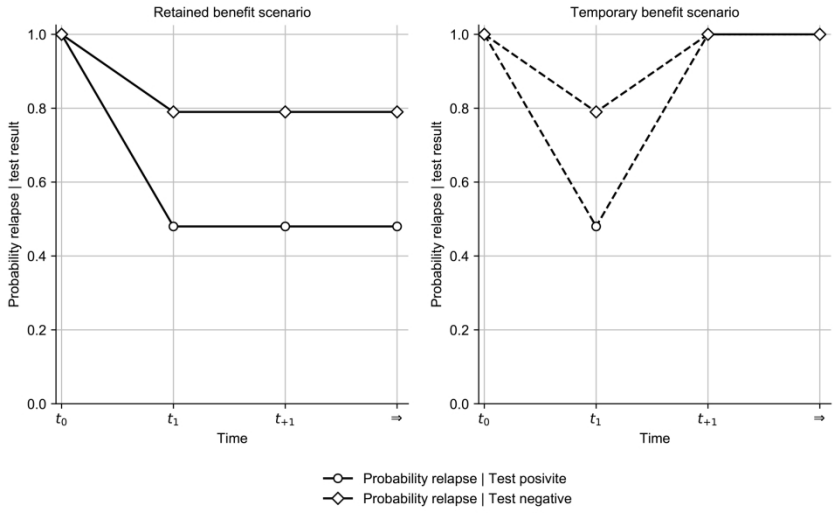

Figure 3 The impact of diagnostic testing on drinking pattern. Probability of relapse to excessive drinking after diagnostic testing. We assumed that the probability of relapse would be higher in patients with a negative test result, than in patients with a positive test result, regardless of whether the test was correct. In the retained benefit scenario, we assumed that testing's effect on abstinence would be lasting, whereas in the temporary benefit scenario, we assumed that testing would have a temporary (one cycle) effect on abstinence, after which the patient would relapse to excessive drinking.

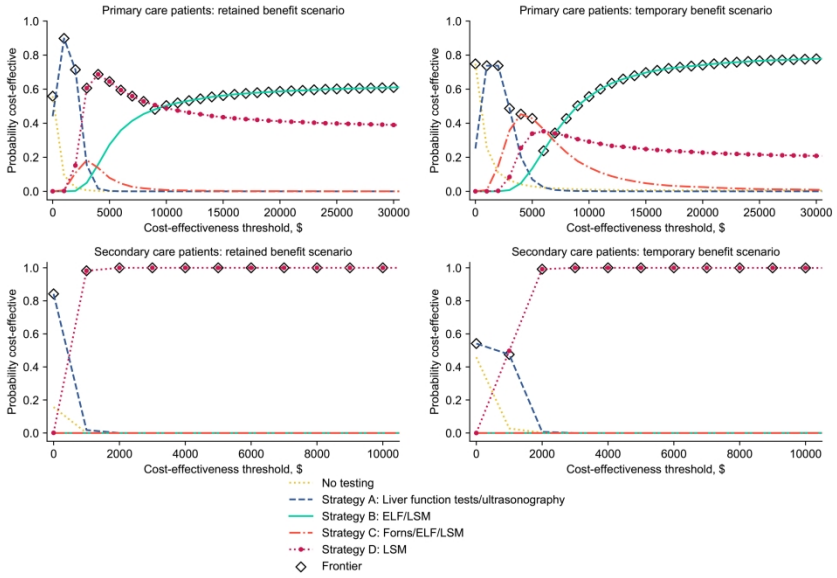

Figure 4 Cost-effectiveness acceptability curves and frontier. The figure show the influence of uncertainty in model input parameters on lifetime predictions of cost-effectiveness assessed with probabilistic sensitivity analysis. 10,000 net health benefits (QALYs – cost/willingness to pay) of each testing strategy was calculated with input parameters varying over their distributions (supplementary information). The cost-effectiveness acceptability curves show the proportions highest net health benefit for the strategies at increasing cost-effectiveness thresholds. The curves with superimposed diamonds show the strategy maximising expected net health benefit which is the frontier, interpreted as the optimal strategy.(31) The switch points of optimal strategy correspond to the calculated ICERs in the baseline analysis.