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# Expanding hepatocellular carcinoma surveillance strategies in high-risk patients in Switzerland: a cost-effectiveness analysis

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## Summary

BACKGROUND: European and Swiss guidelines recommend hepatocellular carcinoma surveillance of high-risk patients every 6 months using ultrasound (US), with/without α-fetoprotein (AFP). Other surveillance strategies are available, but evidence of their comparative cost-effectiveness is lacking. This study evaluated the cost-effectiveness of current hepatocellular carcinoma surveillance strategies in Switzerland, including the novel GAAD (gender [biological sex], age, α-fetoprotein, protein induced by vitamin K absence or antagonist-II [PIVKA-II]) serum-based algorithm in high-risk patients.

METHODS: A micro-simulated Markov model estimated the cost-effectiveness of hepatocellular carcinoma surveillance strategies (no surveillance, US, US+AFP, GAAD) performed at 6-monthly intervals in a simulated cohort of 100,000 patients with compensated liver cirrhosis over a lifetime horizon. Performance parameters were sourced from published meta-analyses and multicentre study data. Epidemiological parameters were estimated based on literature identified during a previous systematic literature review. Similarly, utility parameters were sourced from published literature. Costs were sourced from TARMED, the Analysis List, the Swiss Federal Statistical Office, publicly available data and published literature. Primary outcomes were life years lived, quality-adjusted life years, and costs per patient and per cohort. The cost-effectiveness of each strategy was analysed through incremental cost-effectiveness ratios at a cost-effectiveness threshold of Swiss Franc (CHF) 100,000/quality-adjusted life year.

RESULTS: Overall, the total costs and quality-adjusted life years per patient, respectively, were CHF 43,493.61 and 5.893 for no surveillance; CHF 48,702.79 and 6.018 for US; CHF 49,980.60 and 6.042 for US+AFP; and CHF 49,983.10 and 6.048 for GAAD. Compared with US+AFP and US alone, GAAD was cost-effective, with higher quality-adjusted life years and the highest rate of early-stage hepatocellular carcinoma detection (56%). Compared with no surveillance, incremental cost-effectiveness ratios for US, US+AFP and GAAD were considered to be cost-effective, ranging from CHF 41,509.01 to CHF 43,321.81.

CONCLUSIONS: The current model indicates that hepatocellular carcinoma surveillance with any of these strategies was cost-effective in Switzerland. GAAD was nearly cost-neutral versus US+AFP, although these findings were dependent on the performance of GAAD and operator-dependent US combined with AFP. Compared with US alone, GAAD was the most cost-effective strategy. Further investigations are required to confirm these findings and to optimise hepatocellular carcinoma surveillance.

## Introduction

Hepatocellular carcinoma (HCC) accounts for approximately 90% of primary liver cancer cases and a third of all cancer-related deaths globally [1, 2]. Studies have shown that in Switzerland there were 910 deaths caused by hepatocellular carcinoma in 2020 alone (age-standardised rate: 4.0

per 100,000) [3]. The primary risk factor for the development of hepatocellular carcinoma is cirrhosis caused by underlying chronic liver disease, such as metabolic dysfunction-associated steatotic liver disease (MASLD), hepatitis B virus (HBV) or hepatitis C virus (HCV) infection [1, 4–8]. However, as hepatocellular carcinoma is often asymptomatic in the early stages, timely diagnosis is rare [9]. As such, prognosis tends to be poor, as patients are often no longer suitable for surgical resection or liver transplantation by the time hepatocellular carcinoma is detected [9, 10]. Active surveillance of patients with certain high-risk aetiologies has been shown to improve overall survival by identifying tumours at an earlier stage and thereby enabling treatments to be initiated [11, 12].

Current guidelines recommend hepatocellular carcinoma surveillance with abdominal ultrasound (US) every 6 months in patients at risk of hepatocellular carcinoma. Research has shown that the diagnostic accuracy of US alone for the detection of hepatocellular carcinoma is poor, with the results of a meta-analysis demonstrating that US had a sensitivity of only 45% for the detection of early-stage hepatocellular carcinoma [13]. Several studies have suggested that serum biomarkers, such as α-fetoprotein (AFP) and protein induced by vitamin K absence or antagonist-II (PIVKA-II), have the potential to support a diagnosis of hepatocellular carcinoma [14, 15]. As such, European Association for the Study of the Liver guidelines recommend lifelong hepatocellular carcinoma surveillance with abdominal US, with or without AFP, in patients with cirrhosis, as long as they remain eligible for curative or disease-modifying treatment [16, 17]. The Swiss Association for the Study of the Liver recommends US, with or without AFP, for the surveillance of patients at risk of hepatocellular carcinoma, similar to practice guidance issued by the American Association for the Study of Liver Diseases [18, 19]. When used in combination, these surveillance strategies result in increased sensitivity for the detection of hepatocellular carcinoma compared with US alone, but with reduced specificity [20]. While the diagnostic value of AFP in isolation is debatable [21], combining AFP and PIVKA-II has been shown to improve detection of hepatocellular carcinoma compared with either biomarker alone [22].

GAAD (gender [biological sex], age, AFP, PIVKA-II]), a serum-based algorithm, is a novel *in vitro* diagnostic tool that combines gender (biological sex) and age with the serum biomarkers AFP and PIVKA-II (previously des-gamma carboxyprothrombin) to produce a semi-quantitative result. Notably, the GAAD algorithm has shown similar clinical performance for the diagnosis of hepatocellular carcinoma as the established GALAD algorithm, which combines the components of GAAD plus another biomarker, *Lens culinaris* agglutinin-reactive fraction of AFP (AFP-L3) [23].

Despite guideline recommendations, outside of tertiary centres, surveillance programmes are not always implemented owing to factors such as limited knowledge of guidelines in primary care, leading to some high-risk patients not being referred for surveillance. Additionally, patient-reported barriers to surveillance completion, such as scheduling difficulties and transportation concerns, have also been acknowledged [24]. Therefore, novel cost-effective surveillance strategies are needed to improve adherence to hepatocellular carcinoma surveillance. The objective of the current study was to perform a cost-effectiveness analysis of current hepatocellular carcinoma surveillance strategies in Switzerland, including the novel GAAD algorithm, in patients with compensated liver cirrhosis.

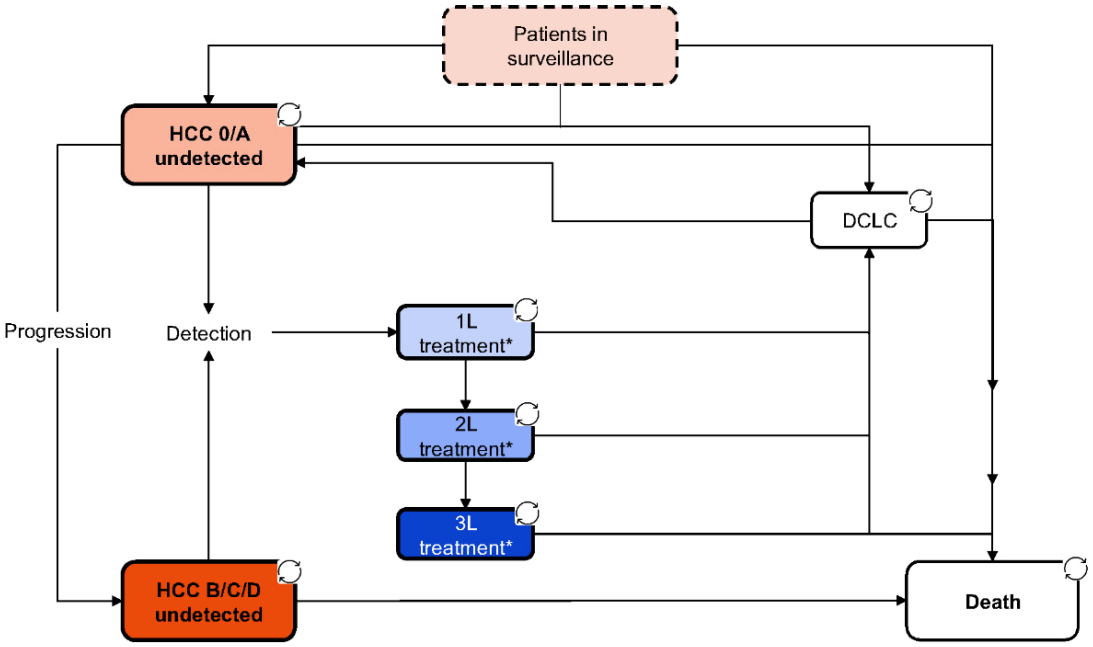
## Materials and methods

### Model structure

A micro-simulated Markov model was used to estimate the costs and performance of hepatocellular carcinoma surveillance strategies from the perspective of the Swiss healthcare system. The model was based on a recently published UK cost-effectiveness analysis in patients with compensated liver cirrhosis [25]. Each health state was associated with costs and health-related quality of life weights, with arrows representing transition probabilities (figure 1). A simulated cohort of 100,000 patients aged ≤75 years with compensated liver cirrhosis with any of the four underlying cirrhosis aetiologies (alcohol-associated liver disease [ALD], HBV, HCV or MASLD) were considered eligible for hepatocellular carcinoma surveillance and included in the model. The following surveillance strategies were evaluated: no surveillance, surveillance with US, surveillance with US+AFP and surveillance with GAAD alone. Active surveillance was performed at 6-month intervals. Patients were simulated individually, and outcomes were obtained for a lifetime horizon on a 6-month cycle. Disease stage was scored using the Barcelona Clinic Liver Cancer staging system, with stages 0/A representing early-stage hepatocellular carcinoma, and B/C/D representing late-stage hepatocellular carcinoma. In the simulation, patients started in the “compensated liver cirrho-

sis" state and either developed decompensated liver cirrhosis, developed early-stage hepatocellular carcinoma (Barcelona Clinic Liver Cancer stage 0/A undetected), which could progress to late-stage hepatocellular carcinoma (B/C/D undetected), or death (figure 1).

**Figure 1:** Model structure. *Treatment: liver transplantation, resection, radiofrequency thermal ablation, transarterial chemoembolisation, systemic therapy, best supportive care. Treatment for patients with decompensated liver cirrhosis liver transplantation or best supportive care only. Arrows indicate progression of patients through different states throughout the simulation. 1L: first-line; 2L: second-line; 3L: third-line; DCLC: decompensated liver cirrhosis; HCC: hepatocellular carcinoma.




Detection occurred in all stages via active surveillance or incidentally; incidental detection was assumed to be higher for late-stage hepatocellular carcinoma. The probability of progression from early- to late-stage hepatocellular carcinoma was predicted using expected tumour volume doubling times and assumed baseline tumour sizes. Adherence to hepatocellular carcinoma surveillance was assumed based on probability of attendance. Patients who developed decompensated liver cirrhosis either moved to the "waiting list" for liver transplantation, remained in the "decompensated liver cirrhosis" state until death or moved to the "hepatocellular carcinoma" state. The probability of tumour detection under surveillance was based on the probability of attendance at appointments, the diagnostic performance of the surveillance strategy used, and the probability of incidental/symptomatic detection. All patients with a positive test for hepatocellular carcinoma underwent confirmatory screening. After hepatocellular carcinoma diagnosis, patients received one of six possible first-line treatments: resection, orthotopic liver transplantation, radiofrequency ablation, transarterial chemoembolisation, best supportive care or systemic treatment. Patients eligible for orthotopic liver transplantation moved to the "waiting list" state, where the outcome was predicted according to stage-specific mortality. Based on calculated probability, patients could also receive any of the above treatments as second- or third-line therapy. Patients treated for hepatocellular carcinoma moved back into the "decompensated liver cirrhosis" state of the model (based on a survival probability for post-hepatocellular carcinoma treatment) unless they received orthotopic liver transplantation. The model assumed that no patient died with undetected hepatocellular carcinoma and that all patients diagnosed with and treated for hepatocellular carcinoma received palliative care in the last cycle of life.

Model parameters are reported in tables 1–3. Epidemiological and performance parameters are reported in table 1. Epidemiological parameters were estimated based on literature identified during a previous systematic literature review [25]. Adherence to surveillance was set at 52.0% (38.0–63.0%) for each surveillance strategy [26]. Performance of GAAD was based on data from the results of a multicentre analysis, in line with a previous UK-based cost-effectiveness analysis

[23, 25]. Performance of US and US+AFP was based on the Tzartzeva et al. meta-analysis in 2018 [13]. Utility parameters (table 2) included health-related quality of life weights for all health states and palliative care, and they fell between 0 and 1, where 0 corresponded with death and 1 with perfect health. Utility parameters were sourced from published literature [27, 28]. Cost parameters (table 3) included costs for all surveillance strategies, together with treatment-related costs for compensated and decompensated liver cirrhosis, hepatocellular carcinoma confirmatory testing (true and false positive test results), symptomatic detection, follow-up and treatment. Further information on the management of false-positive results is reported in the appendix (page 2) and in appendix figure S1. All costs were obtained from Swiss sources: TARMED 2025 tariffs [29], the Analysis List [30], the Swiss Federal Statistical Office [31], publicly available data [32, 33] and published literature [34, 35]. Costs from published literature were not adjusted for inflation [34, 35].

**Table 1:** Model parameters: epidemiology, surveillance and treatment.

| Parameters | | Base case (minimum to maximum) | Source |
|---|---|---|---|
| Age at start of surveillance in years (95% CI) | CLC (ALD) | 50.00 (34.81–73.23) | Base case: Kim et al., 2019 [38]. Range: Garay et al., 2024 [25] |
| | CLC (HBV) | 50.00 (21.83–67.70) | Base case: Kim et al., 2019 [38]. Range: Garay et al., 2024 [25] |
| | CLC (HCV) | 50.00 (30.84–71.22) | Base case: Kim et al., 2019 [38]. Range: Garay et al., 2024 [25] |
| | CLC (MASLD) | 50.00 (43.81–84.19) | Base case: Kim et al., 2019 [38]. Range: Garay et al., 2024 [25] |
| | Upper age limit for surveillance in years (95% CI) | 75.00 (70.00–80.00) | Assumption based on UK analysis [25] |
| Annual incidence of HCC, % (95% CI) | CLC (ALD) | 1.10% (0.99–1.21%) | Marot et al., 2017 [39] |
| | CLC (HBV) | 3.35% (3.02–3.69%) | Thiele et al., 2014 [40] |
| | CLC (HCV) | 2.90% (2.61–3.19%) | Marot et al., 2017 [39] |
| | CLC (MASLD) | 3.10% (2.79–3.41%) | Marot et al., 2017 [39] |
| Annual incidence of DCLC, % (95% CI) | CLC (ALD) | 7.30% (6.50–8.20%) | NICE guideline NG50 [41]; Fleming et al., 2010 [42] |
| | CLC (HBV) | 5.00% (4.50–5.50%) | NICE guideline NG50 [41]; Dakin et al., 2010 [43] |
| | CLC (HCV) | 4.00% (3.60–4.40%) | NICE guideline NG50 [41]; Wright et al., 2006 [44] |
| | CLC (MASLD) | 3.80% (3.42–4.18%) | Estes et al., 2018 [45] |
| DCLC-related parameters, % (95% CI) | DCLC after HCC treatment | 15.50% (13.95–17.05%) | Kondo et al., 2022 [46] |
| | DCLC, listed for OLT | 3.00% (2.40–3.60%) | Assumption |
| Annual incidental detection, % (95% CI) | HCC 0/A | 6.85% (0.00–23.25%) | Thompson et al., 2007 [47] |
| | HCC B/C/D | 31.05% (0.00–65.15%) | |
| Diagnostic performance by HCC stage in patients with cirrhosis: US, % (95% CI) | Sensitivity, early | 47.00% (33.00–61.00%) | Tzartzeva et al., 2018 [13] |
| | Specificity, early | 91.00% (86.00–94.00%) | |
| | Sensitivity, all | 84.00% (76.00–92.00%) | |
| | Specificity, all | 91.00% (86.00–94.00%) | |
| Diagnostic performance by HCC stage in patients with cirrhosis: US+AFP, % (95% CI) | Sensitivity, early | 63.00% (48.00–75.00%) | Tzartzeva et al., 2018 [13] |
| | Specificity, early | 84.00% (77.00–89.00%) | |
| | Sensitivity, all | 97.00% (91.00–99.00%) | |
| | Specificity, all | 84.00% (77.00–89.00%) | |
| Diagnostic performance by HCC stage in patients with cirrhosis: GAAD, % (95% CI) | Sensitivity, early | 67.40% (58.80–75.20%) | Subanalysis from Piratvisuth et al., 2023 [23], published in Garay et al., 2024 [25]. See appendix table S6. |
| | Specificity, early | 86.60% (78.90–92.30%) | |
| | Sensitivity, all | 81.90% (76.90–86.20%) | |
| | Specificity, all | 86.60% (78.90–92.30%) | |
| Treatment distribution for early-stage HCC detected, % (95% CI) | OLT | 5.34% (4.81–5.87%) | Kirstein et al., 2017 [48] |
| | Resection | 22.33% (20.10–24.56%) | |
| | RFA | 39.32% (35.39–43.25%) | |
| | TACE | 18.93% (17.04–20.83%) | |
| | SYS | 3.88% (3.50–4.27%) | |
| | BSC | 10.19% (9.17–11.21%) | |

| | | | |
|---|---|---|---|
| Treatment distribution for late-stage HCC detected, % (95% CI) | OLT | 1.18% (1.06–1.29%) | Kirstein et al., 2017 [48] |
| | Resection | 19.69% (17.72–21.65%) | |
| | RFA | 10.99% (9.89–12.09%) | |
| | TACE | 28.12% (25.31–30.94%) | |
| | SYS | 14.06% (12.66–15.47%) | |
| | BSC | 25.96% (23.37–28.56%) | |
| | OLT waiting time (in 6-month cycles) | 3.00 | Schwab et al., 2024 [49] |

**AFP**: α-fetoprotein; **ALD**: alcohol-associated liver disease; **BSC**: best supportive care; **CI**: confidence interval; **CLC**: compensated liver cirrhosis; **DCLC**: decompensated liver cirrhosis; **GAAD**: gender (biological sex), age, AFP, PIVKA-II; **HBV**: hepatitis B virus; **HCC 0/A**: hepatocellular carcinoma stage 0/A; **HCC B/C/D**: hepatocellular carcinoma stage B/C/D; **HCV**: hepatitis C virus; **MASLD**: metabolic dysfunction-associated fatty liver disease; **OLT**: orthotopic liver transplantation; **RFA**: radiofrequency thermal ablation; **SYS**: systemic therapy**; TACE**: transarterial chemoembolisation; **US**: ultrasound.

**Table 2:** Model parameters: utility weights (QoL).

| **Parameters** | **Base case (minimum to maximum)** | **Source** |
|---|---|---|
| CLC | 0.75 (0.68–0.83) | McLernon et al., 2008 [27] |
| DCLC | 0.67 (0.60–0.74) | McLernon et al., 2008 [27] |
| HCC undetected | 0.75 (0.68–0.83) | Assumed asymptomatic and equal to CLC |
| Waiting list | 0.70 (0.63–0.77) | McLernon et al., 2008 [27] |
| OLT and post | 0.71 (0.64–0.78) | McLernon et al., 2008 [27] |
| Resection and post | 0.70 (0.63–0.77) | Lima et al., 2019 [28] |
| RFA and post | 0.76 (0.68–0.84) | |
| TACE and post | 0.65 (0.59–0.72) | |
| BSC and post | 0.40 (0.36–0.44) | |
| SYS | 0.76 (0.68–0.84) | |
| Palliative | 0.40 (0.36–0.44) | |

**BSC**: best supportive care; **CLC**: compensated liver cirrhosis; **DCLC**: decompensated liver cirrhosis; **HCC**: hepatocellular carcinoma; **OLT**: orthotopic liver transplantation; **QoL**: quality of life; **RFA**: radiofrequency thermal ablation; **SYS**: systemic therapy; **TACE**: transarterial chemoembolisation.

**Table 3:** Model parameters: costs.

| Parameter | | Base case (minimum to maximum) | Source |
|---|---|---|---|
| Surveillance costs, CHF (95% CI) | US | 121.00 (110.00–131.00) | Determined using the average from TARMED codes for non-radiologists (TARMED codes: 39.3250, 39.3800, 39.0020) and radiologists (TARMED codes: 39.3250, 39.3800, 39.0015) [29] |
| | AFP | 17.40* | Determined via the official "List of analyses with tariff"; code 1034.00 [30] |
| | GAAD | 139.00 (111.20–166.80) | As GAAD is not reimbursed in Switzerland, the assumption was based on the medical value of GAAD and analogues based on the "List of analyses with tariff" [30] |
| Confirmatory testing costs, CHF | CT | 203 | Determined using TARMED code (39.4080) [29] |
| | MRI | 296 | Determined using TARMED code (39.5060) [29] |
| Treatment costs, CHF (95% CI) | CLC (annual) | 2715.00 (1841.00–3806.00) | Blach et al., 2019 [35] |
| | DCLC (annual) | 20,347.00 (16,561.00–24,517.00) | Pfeil et al., 2015 [34] |
| | True positive for HCC | 615.00 (553.50–676.50) | See appendix page 2 |
| | False positive for HCC | 824.00 (741.60–906.40) | |
| | Incidental diagnosis | 412.00 (370.80–453.20) | |
| | Follow-up after HCC, per cycle | 319.00 (287.10–350.90) | |
| | OLT, per operation | 125,102.00 (105,665.00–144,540.00) | Blach et al., 2019 [35] |
| | Post-OLT follow-up (year 1) | 19,323.00 (16,321.00–22,325.00) | |
| | Post-OLT follow-up (year 2+) | 19,323.00 (16,321.00–22,325.00) | |
| | Resection | 22,709.63 (18,935.31–27,936.06) | Office fédéral de la statistique, Section Services de santé, Switzerland [31] |
| | RFA | 19,586.34 (11,048.04–57,813.84) | |
| | TACE | 8617.70 (8013.19–9295.56) | |
| | BSC, per month | 1244.31 (1187.26–1295.86) | |
| | SYS, annual | 54,629.00 (49,395.00–59,863.00) | Average of yearly costs for lenvatinib (CHF 59,863) –Eisai Pharma AG [33] and sorafenib (CHF 49,395) –Bayer (Switzerland) Ltd [32] |

* No variability assumed.
**AFP**: α-fetoprotein; **BSC**: best supportive care; **CHF**: Swiss franc; **CI**: confidence interval; **CLC**: compensated liver cirrhosis; **CT**: computed tomography; **DCLC**: decompensated liver cirrhosis; **GAAD**: gender (biological sex), age, AFP, PIVKA-II; **HCC**: hepatocellular carcinoma; **MRI**: magnetic resonance imaging; **OLT**: orthotopic liver transplantation; **RFA**: radiofrequency thermal ablation; **SYS**: systemic therapy; **TACE**: transarterial chemoembolisation; **US**: ultrasound.

In line with previous cost-effectiveness analyses for hepatocellular carcinoma surveillance [36, 37] and as such costs are not incurred by the Swiss healthcare system, indirect costs associated with diagnosis (such as productivity costs due to absenteeism) were omitted from the analysis.

A description of the software used to perform the analyses is reported in the appendix (table S1). A summary of the quality of evidence of the studies used for parameter inputs is reported in the appendix (table S2).

### Analyses

Primary outcomes were life years lived, quality-adjusted life years and total costs per patient and per cohort. The cost-effectiveness of each surveillance strategy was analysed through incremental cost-effectiveness ratios and net monetary benefit for a cost-effectiveness threshold of Swiss Franc (CHF) 100,000/quality-adjusted life year. Cost-effectiveness acceptability curves were generated for each comparison. Incremental cost-effectiveness ratios were defined as the ratio between the change in cost to change in effect of one surveillance strategy compared with that of another surveillance strategy. A discount rate of 3.5% was applied. The net monetary benefit was calculated using willingness-to-pay thresholds and quality-adjusted life years.

### Sensitivity analyses

Multi-way sensitivity analyses were performed to assess joint parameter uncertainty and to build cost-effectiveness planes and cost-effectiveness acceptability curves. Due to computational burden, cost-effectiveness planes and cost-effectiveness acceptability curves were developed using cohorts with 10,000 patients/simulations each with 250 first-order samples. The probability distri-

butions for multi-way sensitivity analyses were assumed following standard recommendations [50]. Tables 1–3 include the parameter ranges used for one-way sensitivity analyses. Net monetary benefits were displayed in tornado plots for a cost-effectiveness threshold of CHF 100,000/quality-adjusted life year; positive net monetary benefit indicated the results were cost-effective, and negative net monetary benefit indicated that the results were not cost-effective. The incremental net monetary benefit of each strategy, with 95% confidence intervals (CIs), was calculated using the simulations of the cohorts that were used for the cost-effectiveness acceptability curves.

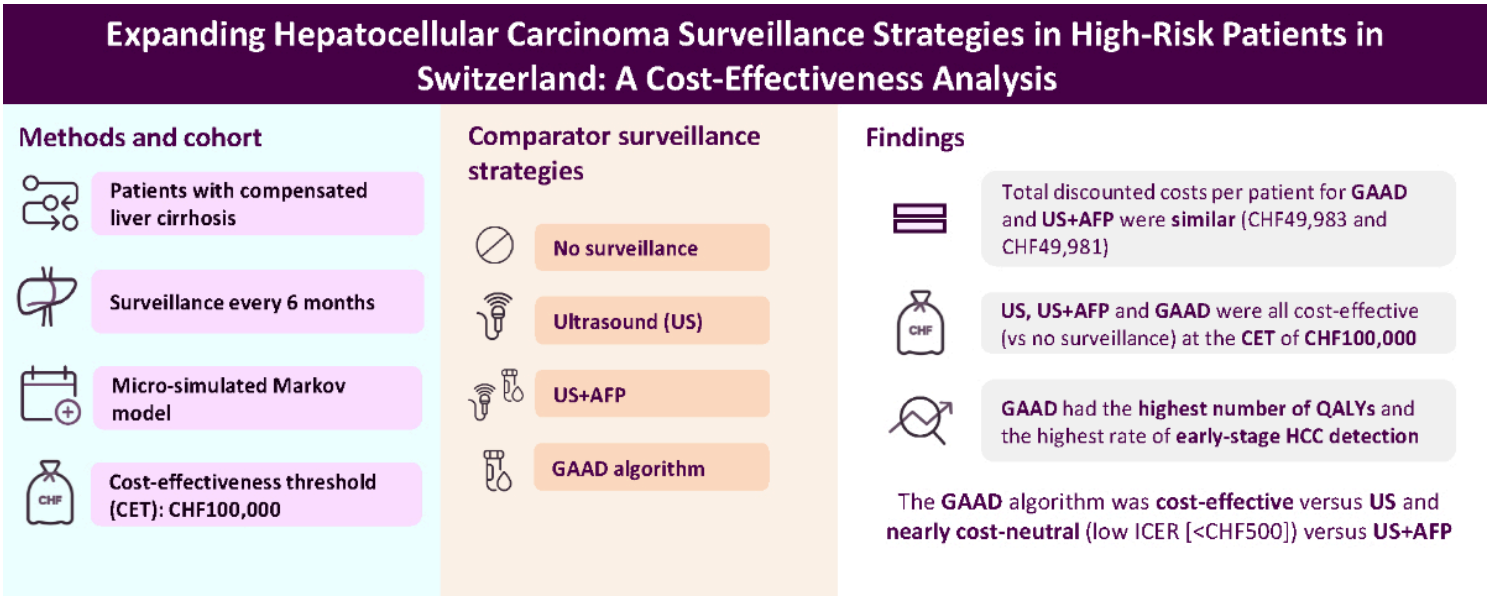
Several scenario analyses were modelled, and a deterministic base case with 10,000 simulations/patients was calculated to serve as a reference for comparison with the scenarios. The following scenario analyses were modelled: (A) surveillance of patients with compensated liver cirrhosis, non-cirrhotic HBV and Metavir FIB-3, (B) surveillance of patients with FIB-3 only, (C) patients with cirrhotic MASLD only, (D) patients with FIB-3 MASLD only, (E) 10% increased adherence rate for GAAD, (F) 25% increased adherence rate for GAAD, (G) 50% increased adherence rate for GAAD, and (H) surveillance with GALAD. Additional parameters for scenario analyses are listed in appendix tables S3–S7. The performance of GALAD for early-stage (0/A) and any-stage hepatocellular carcinoma were derived from the meta-analysis of Guan et al. [51]. Given that performance estimates were not reported by hepatocellular carcinoma stage for cirrhotic patients in this study, a novel random effects meta-analysis was conducted using studies identified by Guan et al. [51], which comprised at least 90% of individuals with cirrhosis with early-stage [52–56] and all-stage hepatocellular carcinoma [52, 54–58]. The meta-analysis was conducted using MetaDTA: Diagnostic Test Accuracy Meta-Analysis v2.1.3. [59–61]. Forest plots for the sensitivity and specificity of GALAD in the meta-analysis are shown in appendix figures S2–S3, and sensitivity and specificity point estimates for each study are shown in appendix figure S4. The estimates for sensitivity and specificity for GALAD by hepatocellular carcinoma stage in cirrhotic patients can be found in appendix table S7. An explanation of cost parameters for GALAD is reported in the appendix (page 2).

## Results

### Base case

A summary of the study design and base case results is reported in figure 2. In the base case analysis of 100,000 patients/simulations, the costs and quality-adjusted life years per patient, respectively, were CHF 43,493.61 and 5.893 for no surveillance, CHF 48,702.79 and 6.018 for US, CHF 49,980.60 and 6.042 for US+AFP, and CHF 49,983.10 and 6.048 for GAAD alone (table 4). In terms of quality-adjusted life years, GAAD was the preferred surveillance strategy, followed by US+AFP, US and no surveillance. Compared with no surveillance, incremental costs and quality-adjusted life years, respectively, were CHF 5209.18 and 0.125 for US; CHF 6486.99 and 0.150 for US+AFP; and CHF 6489.49 and 0.155 for GAAD, with incremental cost-effectiveness ratios below the willingness-to-pay threshold in the range CHF 41,509.01–43,321.81. Compared with US, incremental costs and quality-adjusted life years were CHF 1277.81 and 0.024, respectively (resulting in an incremental cost-effectiveness ratio of CHF 52,705.29), for US+AFP, and CHF 1280.30 and 0.030 (CHF 43,020.48) for GAAD. GAAD showed similar outcomes compared with US+AFP, with an incremental cost-effectiveness ratio of CHF 452.30 per quality-adjusted life year (incremental costs and quality-adjusted life years of CHF 2.49 and 0.006, respectively).

**Figure 2:** Summary of study design and base case results. AFP: α-fetoprotein; CHF: Swiss francs; GAAD: gender (biological sex), age, AFP, PIVKA-II; HCC: hepatocellular carcinoma; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; US: ultrasound.




An extended table of results detailing cost and health outcomes per cohort are reported in appendix table S8. Of the 100,000 patients with compensated liver cirrhosis in the simulation, 19,933 were considered to have developed hepatocellular carcinoma within their lifetime. In comparison with no surveillance, patients with hepatocellular carcinoma gained an average of 0.63 discounted quality-adjusted life years with US, 0.75 with US+AFP and 0.78 with GAAD. GAAD had the highest rate of early-stage hepatocellular carcinoma detection with surveillance (56%), followed by US+AFP (53%) and US (44%). US+AFP generated the highest number of false-positives (n = 123,687), followed by GAAD (n = 103,643) and US (n = 69,764). GAAD produced the fewest false-negatives (n = 5678), followed by US+AFP (n = 6361) and US (n = 10,378).

**Table 4:** Base case results.

| | | No surveillance | US | US+AFP | GAAD |
|---|---|---|---|---|---|
| Cost per patient, CHF | | 43,493.61 | 48,702.79 | 49,980.60 | 49,983.10 |
| QALYs per patient | | 5.893 | 6.018 | 6.042 | 6.048 |
| Surveillance strategies compared with no surveillance | Incremental costs, CHF | – | 5209.18 | 6486.99 | 6489.49 |
| | Incremental QALYs | – | 0.125 | 0.150 | 0.155 |
| | ICER per QALY, CHF | – | **41,509.01** | **43,321.81** | **41,798.74** |
| Surveillance strategies compared with US | Incremental costs, CHF | – | - | 1277.81 | 1280.30 |
| | Incremental QALYs | – | - | 0.024 | 0.030 |
| | ICER per QALY, CHF | – | - | **52,705.29** | **43,020.48** |
| Surveillance strategies compared with US+AFP | Incremental costs, CHF | – | - | - | 2.49 |
| | Incremental QALYs | – | - | - | 0.006 |
| | ICER per QALY, CHF | – | - | - | **452.30** |

**AFP**: α-fetoprotein; **CHF**: Swiss franc; **ICER**: incremental cost-effectiveness ratio; **QALY**: quality-adjusted life year; **WTP**: willingness to pay.
ICERs in bold indicate that the surveillance strategy is cost-effective within the WTP threshold of CHF 100,000 versus the comparator.

*Sensitivity analysis*

Analyses of paired comparisons are shown in figure 3. Compared with no surveillance, all strategies were cost-effective at a cost-effectiveness threshold of CHF 100,000. Compared with US, GAAD was the most cost-effective strategy, followed by US+AFP. GAAD was also cost-effective compared with US+AFP at the cost-effectiveness threshold depicted. Strategies were evaluated in terms of total discounted quality-adjusted life years, costs and the estimated probability of cost-effectiveness for different willingness-to-pay thresholds (figure 4). One-way sensitivity analyses comparing all surveillance strategies are shown in appendix figures S5–S10. Performance of diagnostic modalities, age at the start of surveillance and annual incidental detection were the most influential variables. In particular, tornado plots showed that the performance of GAAD and comparators were the key variables contributing to the cost-effectiveness of GAAD (appendix figures S9 and S10). The incremental net monetary benefit with 95% CIs for each surveillance strategy are reported in appendix table S9.

**Figure 3:** Cost-effectiveness plane depicting the incremental costs and effects of each surveillance strategy versus comparator. AFP: α-fetoprotein; CE: cost-effectiveness; CHF: Swiss franc; GAAD: gender (biological sex), age, AFP, PIVKA-II; QALY: quality-adjusted life year; US: ultrasound.

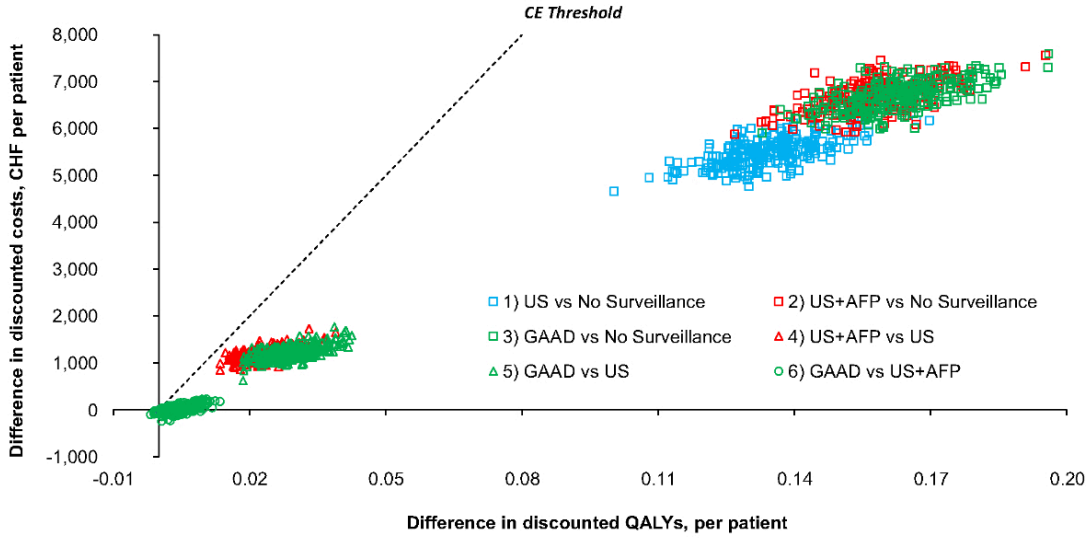
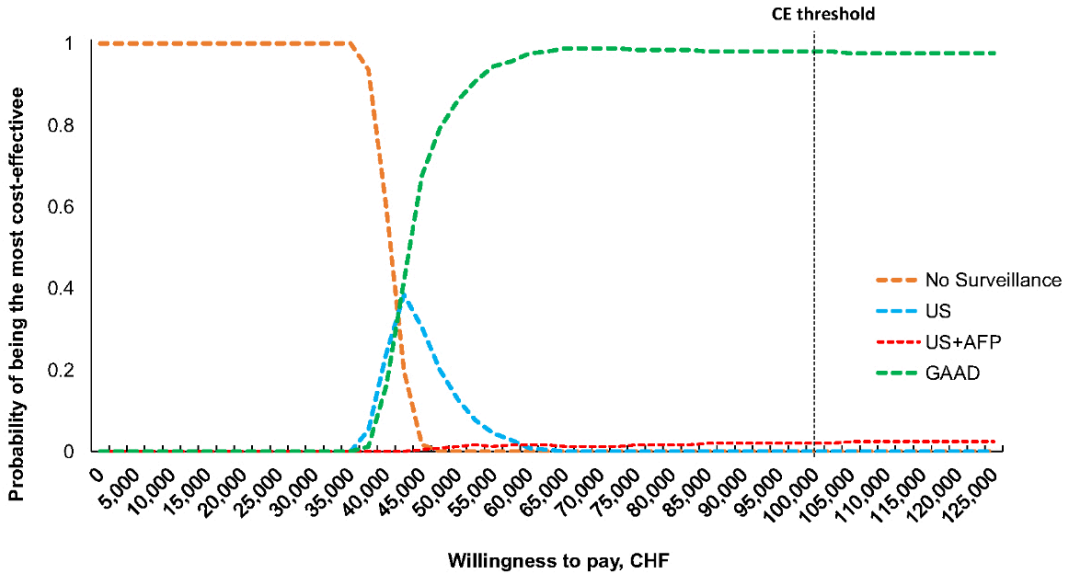


**Figure 4:** Probability of being the most cost-effective option at a willingness-to-pay threshold of CHF 100,000. AFP: α-fetoprotein; CHF: Swiss franc; CE: cost-effectiveness; GAAD: gender (biological sex), age, AFP, PIVKA-II; US: ultrasound.




*Scenario analysis*

The results of the deterministic base case for patients with compensated liver cirrhosis, the reference case against which the results of all scenario analyses were compared, are reported in appendix table S10. Compared with no surveillance, incremental quality-adjusted life years were 0.130 for US, 0.165 for US+AFP and 0.166 for GAAD. Incremental cost-effectiveness ratios compared with no surveillance were CHF 41,792.57, CHF 41,810.82 and CHF 40,921.24 for US, US+AFP and GAAD, respectively. Incremental quality-adjusted life years compared with US were 0.035 for US+AFP and 0.037 for GAAD. Compared with US, the incremental cost-effectiveness ratios were CHF 41,877.95 for US+AFP and CHF 37,835.73 for GAAD. Compared with US+AFP, GAAD was the dominant strategy in terms of incremental cost-effectiveness ratio.

In scenario analysis (A), where surveillance was performed in a combined group of patients with cirrhosis, non-cirrhotic HBV or FIB-3, incremental quality-adjusted life years were fewer in comparison to the deterministic base case (appendix table S11) as the incidence of hepatocellular carcinoma was lower than for patients with compensated liver cirrhosis only. Additionally, when compared with no surveillance, the cost-effectiveness of all surveillance strategies decreased when surveillance was performed in this combined patient group (cirrhosis, HBV or FIB-3) versus the deterministic base case. For example, compared with no surveillance, the incremental cost-effectiveness ratios for GAAD were CHF 40,921.24 in the deterministic base case versus CHF 75,090.80. Compared with no surveillance, the most cost-effective strategy was GAAD (incremental cost-effectiveness ratio: CHF 75,090.80), followed by US (CHF 92,351.85) and US+AFP (CHF 96,974.25). Compared with US alone, the incremental cost-effectiveness ratios for US+AFP and GAAD were CHF 113,824.80 and CHF 23,809.37, respectively. Compared with US+AFP, GAAD remained the dominant strategy.

For scenario analysis (B), which included patients with FIB-3 only, the cost-effectiveness of surveillance strategies, in comparison with no surveillance, was lower versus the deterministic base case (appendix table S12). In this scenario, US+AFP and US were no longer cost-effective, whereas GAAD remained cost-effective but with a greater incremental cost-effectiveness ratio. Compared with no surveillance, GAAD was the most cost-effective (incremental cost-effectiveness ratio: CHF 88,976.53), whereas US and US+AFP had incremental cost-effectiveness ratios above the willingness-to-pay threshold (incremental cost-effectiveness ratio: CHF 110,263.67 and 119,699.52, respectively). GAAD was cost-effective, in comparison to US, in the FIB-3-only population (incremental cost-effectiveness ratio: CHF 22,472.61). In contrast, US+AFP was not cost-ef-

fective in comparison to US with an incremental cost-effectiveness ratio of CHF 158,680.66. GAAD remained the dominant strategy compared with US+AFP, with an incremental cost of CHF -921.82 and 0.002 incremental quality-adjusted life years.

In scenario analysis (C), patients with cirrhotic MASLD only were included. Incremental cost-effectiveness ratios for each strategy compared with no surveillance were lower than in the deterministic base case: CHF 37,969.44 for GAAD, CHF 39,005.08 for US+AFP and CHF 39,237.15 for US (appendix table S13). The cost-effectiveness of each strategy compared with US also further improved versus that of the deterministic base case. Compared with US, the incremental cost-effectiveness ratio was CHF 33,476.53 for GAAD and CHF 38,111.15 for US+AFP. GAAD was the dominant strategy compared with US+AFP in this scenario (incremental cost: CHF -83.84; incremental quality-adjusted life years: 0.004).

Scenario analysis (D) showed that when surveillance was performed in patients with FIB-3 MASLD only, the costs per patient decreased and quality-adjusted life years increased versus the deterministic base case (appendix table S14). Compared with no surveillance, GAAD was the most cost-effective strategy (incremental cost-effectiveness ratio: CHF 75,776.81), followed by US (CHF 90,362.51) and US+AFP (CHF 96,910.72). Similarly, compared with US, GAAD was the most cost-effective strategy (incremental cost-effectiveness ratio: CHF 31,095.91). In this scenario, US+AFP was no longer cost-effective compared with US (incremental cost-effectiveness ratio: CHF 122,967.28). GAAD was the dominant strategy compared with US+AFP (incremental cost: CHF -828.44; incremental quality-adjusted life years: 0.003).

In scenario analyses (E), (F) and (G), the cost-effectiveness of GAAD was analysed after various increases to the GAAD adherence rate: 10% (from 52.0% to 57.2%), 25% (from 52.0% to 65.0%) and 50% (from 52.0% to 78.0%). With each increase, quality-adjusted life years were greater in comparison with the deterministic base case (appendix tables S15–S17). Incremental cost-effectiveness ratios for GAAD compared with each strategy were greater compared with the deterministic base case as GAAD adherence rates increased.

In scenario analysis (H), where GALAD was included as an additional surveillance strategy, costs were slightly greater for GALAD than GAAD and quality-adjusted life years were similar (CHF 50,227.81 and 6.014 versus CHF 49,694.07 and 6.013, respectively) (appendix table S18). Compared with no surveillance, GAAD was the most cost-effective strategy (incremental cost-effectiveness ratio: CHF 40,921.24), followed by US (CHF 41,792.57), US+AFP (CHF 41,812.45) and GALAD (CHF 43,832.44). When compared with US, GAAD was the most cost-effective (incremental cost-effectiveness ratio: CHF 37,835.73), followed by US+AFP (CHF 41,885.60) and GALAD (CHF 50,840.89). GAAD was the dominant strategy compared with US+AFP. GALAD was no longer cost-effective compared with US+AFP and GAAD, with incremental cost-effectiveness ratios of CHF 177,927.32 and 474,692.26, respectively.

## Discussion

The prognosis at diagnosis of hepatocellular carcinoma is often poor, so effective surveillance is required to facilitate earlier detection and thus improve treatment options. This study used a simulated model to evaluate the cost-effectiveness of different hepatocellular carcinoma surveillance strategies in Switzerland, which, to our knowledge, is the first such study conducted in a Swiss healthcare setting.

The findings of this study indicate that, at a cost-effectiveness threshold of CHF 100,000, 6-monthly surveillance with the GAAD algorithm was cost-effective compared with US and US+AFP, the current surveillance strategies recommended in Switzerland [16, 18]. These results are similar to those from a comparable analysis reporting perspectives from the UK National Health Service, which found that GAAD alone was the most cost-effective strategy compared with US and US+AFP in cirrhotic patients [25]. The results of the UK analysis also indicated that 6-monthly hepatocellular carcinoma surveillance with US or US+AFP is unlikely to be cost-effective at a cost-effectiveness threshold of £30,000, but it becomes cost-effective at a cost-effectiveness threshold of between £31,000 and £34,000. However, our findings were not consistent with the results of another recent North American cost-effectiveness analysis that found that US+AFP was dominant compared to both US alone and no surveillance for the detection of hepatocellular carcinoma in patients with compensated cirrhosis [37]. Despite these differences, these studies highlight that although US+AFP and US alone are currently the most widely recommended strategies for hepato-

cellular carcinoma surveillance, additional cost-effectiveness studies to assess the role of existing and novel strategies for hepatocellular carcinoma surveillance in a diversity of healthcare settings are needed.

GAAD alone was the preferred surveillance strategy in terms of quality-adjusted life years gained, with potential drivers of this benefit including early detection of hepatocellular carcinoma and the associated shift from late-stage treatment (e.g. systemic) to early-stage treatment (e.g. orthotopic liver transplantation and resection). The average increase in quality-adjusted life years per patient for GAAD compared with each strategy was, as expected, small (0.006 compared with US+AFP, 0.03 compared with US alone and 0.155 compared with no surveillance), due to the fact that only a small fraction of patients who underwent surveillance developed hepatocellular carcinoma. However, for these patients, the increase in quality-adjusted life years was greater (0.03, 0.15 and 0.78 for GAAD compared with US+AFP, US alone and no surveillance, respectively).

When determining the cost-effectiveness of surveillance strategies, the incidence of hepatocellular carcinoma in each patient population considered for surveillance is of importance. In the scenario analyses, incremental cost-effectiveness ratios with each surveillance strategy were lower in patients with cirrhotic aetiologies, particularly cirrhotic MASLD. Incremental cost-effectiveness ratios were greater in the scenario with patients with compensated liver cirrhosis, HBV and FIB-3, compared with the deterministic base case, likely due to the high incidence rate of hepatocellular carcinoma in the cirrhotic population [1]. When the analyses were performed in patients with FIB-3, whose risk of hepatocellular carcinoma was lower than those with cirrhosis, incremental cost-effectiveness ratios were higher for all hepatocellular carcinoma surveillance strategies compared with base case, with only GAAD remaining cost-effective. Previous studies have shown that hepatocellular carcinoma risk can be stratified based on clinical variables, including aetiology and molecular profiling [62–64]. Therefore, determining the modality of surveillance based on individual hepatocellular carcinoma risk may be more cost-effective than using a single strategy across all patient populations. For example, psychiatric outpatients are more likely to develop hepatitis C or cirrhosis and may therefore benefit from scaling-up of hepatocellular carcinoma screening with GAAD [65]. Despite this variability in cost-effectiveness, GAAD remained the most cost-effective option compared with other strategies across all aetiology scenario analyses and the deterministic base case, likely due to the quality-adjusted life years gained as a result of early-stage hepatocellular carcinoma diagnosis with GAAD.

Another factor that significantly impacted cost-effectiveness was patient adherence to surveillance, as reflected in scenario analyses E–G. When adherence to GAAD was increased by 10%, 25% and 50%, the clinical effectiveness of GAAD improved. Although the overall cost-effectiveness of GAAD was slightly reduced when adherence was increased, GAAD remained cost-effective across all adherence rates. This reduction in overall cost-effectiveness was due to increased costs with greater adherence despite increased quality-adjusted life years.

While appropriate data for GAAD in overweight, obese and diabetic populations were not available at the time of the analysis, future research should investigate both the performance and cost-effectiveness of surveillance strategies in such populations. In particular, the increasing prevalence of non-cirrhotic MASLD in overweight populations is a point of interest. Moreover, a recent phase III cohort study demonstrated greater predictive value for the composite biomarker score, HES V2.0, which combines changes in AFP, AFP-L3 and PIVKA-II over 12 months with age, platelets, alanine transaminase and underlying disease aetiology, compared with GALAD and ASAP scores (age, sex, AFP and PIVKA-II) [66]. However, it should be noted that the cut-offs for GALAD used in this study are not those validated for clinical use and the sample size was relatively small [66]. As such, future research should aim to further validate the performance of the HES V2.0 strategy and once costs are available, its cost-effectiveness compared with other available strategies warrants investigation.

It is important to consider that data on the performance of GAAD were only available from studies of case-control design, which have inherent limitations that can result in the overestimation of test performance. These data can be considered less extensive and robust than the meta-analysis data available for the performance of the other surveillance strategies, such as US±AFP [67]. Nevertheless, we expect that the potential differences in performance estimations coming from the study designs were captured in the various sensitivity analyses. When all surveillance interventions were compared with no surveillance, changes in performance estimates did not play a relevant role (appendix figures S5–S7). Similarly, when compared with US, a lower sensitivity or specificity for GAAD, even below the 95% CI limit, did not change the conclusions. However, as GAAD

and US+AFP have similar total costs and quality-adjusted life years, the results for this comparison were more sensitive to changes in performance estimates. Despite this, the 95% CIs around the incremental net monetary benefit values for each comparison were small, indicating a low level of variability in the data.

Although the base case probabilistic results suggest that GAAD was nearly cost-neutral compared with US+AFP, with a low incremental cost-effectiveness ratio per quality-adjusted life year of CHF 452, this result was dependent on performance data (appendix figure S10). GALAD, for which performance data from prospective cohort studies are available [68], has shown similar performance to GAAD [51]. Despite the inclusion of GALAD in scenario analysis H, GAAD remained the most cost-effective strategy compared with no surveillance, US and US+AFP. Although the inclusion of AFP-L3 in GALAD led to slightly higher quality-adjusted life years than GAAD, this was not cost-effective due to the extra cost of the additional biomarker test. These data indicate that GAAD is the preferred strategy over GALAD in terms of cost-effectiveness. However, as AFP-L3 is not available in Switzerland, it should be noted that the costs of GALAD were based on assumptions involving other available test prices, as detailed in the appendix (page 2).

There were several limitations associated with the analysis. Several parameters were obtained using non-Swiss databases or patients, including the survival curves stratified by hepatocellular carcinoma, which were taken from a German study [48]; the model only considered early- and late-stage hepatocellular carcinoma owing to a lack of data on the surveillance strategies by hepatocellular carcinoma stage, and a number of parameters were assumed to be equal irrespective of patient sex owing to a lack of data and for model simplification, including progression rates, incidence rates and statistics for survival curves. The absence of a single source providing a comprehensive performance estimate for all the strategies under comparison could also have created biases and potentially impacted the results. Additionally, in the scenario analyses, similar performance of US and US+AFP was assumed for both cirrhotic and non-cirrhotic disease. However, there is evidence to suggest that US performs better in non-cirrhotic aetiologies compared with cirrhotic aetiologies, due to decreased nodularity and better-defined margins, resulting in a clearer image [69]. Due to a lack of data and suitable sources for utilities, for some parameters, the most appropriate sources were slightly dated and based on viraemic HCV patients. TARDOC tariffs were not considered as they were not yet finalised at the time of the analysis. However, according to the deterministic sensitivity analysis, the cost elements concerned were not considered to have a substantial impact on the final results. Comparisons with GAAD+US were not included in the sensitivity analysis owing to the lack of robustness of the data available. Therefore, further investigation is needed for this comparison. Finally, external validity may be limited outside of a Swiss healthcare setting. However, the Swiss setting was selected due to the high standard of healthcare quality, comprehensive data availability and well-studied patient population, which enhances generalisability and comparisons to other healthcare settings. Furthermore, the conclusions were similar to those found in the UK-based cost-effectiveness analysis [25], indicating that these data are likely applicable to other healthcare systems.

### Conclusion

Our analyses found that hepatocellular carcinoma surveillance is cost-effective in Switzerland, regardless of the modality used. Notably, GAAD was the most cost-effective strategy when compared with US alone. GAAD was nearly cost-neutral compared with US+AFP, with similar costs but higher quality-adjusted life years, although this was dependent on the performance data of both GAAD and the operator-dependent US combined with AFP. Further investigations are required to confirm these findings and to optimise surveillance of patients at risk of hepatocellular carcinoma.

## Data availability statement

The data supporting the conclusions of this article are publicly available and fully reported in the publication. Further data requests can be addressed to the corresponding author and data will be made available on reasonable request. The study protocol is described throughout the publication; however, any methodological questions can be addressed to the corresponding Methods author (Osvaldo Ulises Garay, MSc; Global Access & Policy, Roche Diagnostics International; Forrenstrasse 2, Switzerland, 6343 Rotkreuz ZG).

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**Author contributions:** All authors made substantial contributions to the conception or design of the work, or acquisition, analysis or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; provided final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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## Potential competing interests

VK and LA were employed by Roche Diagnostics (Schweiz), AG, Switzerland, at the time of the study. VK owns stock in F. Hoffmann-La Roche AG. FG is the representative of Swiss hospitals at the Federal Drug Commission (Federal Office of Public Health) and is an expert for InnoSuisse, the Federal Agency for Innovation (Life Sciences section). CW is employed by Roche Diagnostics (Schweiz), AG, Switzerland and owns stock in F. Hoffmann-La Roche. OUG is employed by Roche Diagnostics International and owns stock in F. Hoffmann-La Roche. NG reports research funding from Gilead and Novo, congress funding from AbbVie and Gilead, and attends advisory boards for Roche Diagnostics and Novo Nordisk.

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# Appendix

## Diagnostic pathway – confirmatory screening

It was assumed that patients with a positive diagnosis for hepatocellular carcinoma (HCC) underwent subsequent confirmatory screening. If the patient was considered a true positive (TP), they would receive confirmation after magnetic resonance imaging (MRI), a medical appointment, and a computed tomography (CT) scan, then receive treatment. If the patient was considered a false positive (FP), additional examinations would be required to confirm the FP. For approximately 50% of cases, it was assumed that an MRI and a medical consultation would be sufficient; however, for the remaining 50%, it was assumed that repeated imaging, including MRI (×3) and medical consultations (×3), would be required for a period of 12 months. If the surveillance modality provided a negative result (for underlying true and false negative), then the patient continued with the surveillance program (figure S1). The costs for confirmatory testing were set to CHF 203 for CT and CHF 296 for MRI, as per TARMED tariffs (TARMED codes: CT 39.4080, MRI 39.5060) (1). The cost of a medical appointment was set at CHF 116 (2).

## Scenario analysis parameters

In scenario analysis H, the cost of Elecsys® GALAD was assumed to be the same as that for Elecsys GAAD, plus the cost of AFP-L3. However, as AFP-L3 is not available in Switzerland and therefore there is no current price, the cost was assumed to be the same as for Elecsys PIVKA-II minus the cost of Elecsys AFP, following the same cost structure of each test in the list of Current Procedural Terminology codes and their associated Medicare costs in the United States **(3)**.

## Supplementary tables

**Complete, Transparent, Accurate and Timely account (CTAT)**

**Table S1:** CTAT (software).

| Software name | Manufacturer | Version |
|---|---|---|
| Microsoft Excel (Micro-simulated Markov transition model analysis) | Microsoft | Microsoft Excel 2016 |

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**Table S2.** Summary of the quality of evidence of input parameter sources

| First author | Year | Title | Study objective | Study design | Sample size | Location | Study perspective/population |
|---|---|---|---|---|---|---|---|
| **Kim (4)** | 2019 | Magnetic resonance imaging is cost-effective for hepatocellular carcinoma surveillance in high-risk patients with cirrhosis | To compare the cost-effectiveness of semiannual surveillance using MRI versus US in patients with compensated cirrhosis and to identify the population that would gain optimal cost-effectiveness through MRI surveillance | Markov model | 10,000 | Korea | Health system perspective<br><br>CLC, aged 50 years |
| **Garay (5)** | 2024 | Cost-effectiveness of hepatocellular carcinoma surveillance strategies in patients with compensated liver cirrhosis in the United Kingdom | To evaluate the cost-effectiveness of 4 hepatocellular carcinoma surveillance strategies in the United Kingdom, the GAAD algorithm; US; US+AFP and GAAD+US | Markov model | 100,000 | UK | UK NHS perspective<br><br>CLC, aged up to 75 years at the start of surveillance |
| **von Hessen (6)** | 2021 | High subcutaneous adipose tissue density correlates negatively with survival in patients with hepatocellular carcinoma | To assess the association between different body composition parameters and overall survival in two different newly diagnosed HCC populations | Prospective cohort | 403 | Switzerland/ UK | N/A<br><br>Newly diagnosed HCC, aged > 18 years |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Fattovich (7)** | 2008 | Natural history of chronic hepatitis B: Special emphasis on disease progression and prognostic factors. | To review the natural history of chronic hepatitis B, with emphasis on summarizing the available data to estimate the rates of disease progression according to the stage of the disease and factors influencing its course | Systematic review | N/A | Global | N/A<br><br>Chronic hepatitis B |
| **Marot (8)** | 2017 | Alcoholic liver disease confers a worse prognosis than HCV infection and non-alcoholic fatty liver disease among patients with cirrhosis: An observational study | To assess the impact of the underlying liver disease on the occurrence of HCC and death | Observational study | 932 | Switzerland | N/A<br><br>Patients with cirrhosis related to ALD, chronic HCV infection or MASLD, aged > 18 years |
| **Thiele (9)** | 2014 | Large variations in risk of hepatocellular carcinoma and mortality in treatment naïve hepatitis B patients: systematic review with meta-analyses | To estimate the incidence and predictors of HCC and in untreated HBV patients | Systematic review and meta-analyses | 27,584 | Global | N/A<br><br>Untreated patients with HBV infection, mean age range 26–65 years across studies |
| **Sánchez-Azofra (10)** | 2021 | Hepatocellular carcinoma risk in hepatitis C stage-3 fibrosis after sustained | To investigate the risk of HCC in a large cohort of patients with well-defined stage 3 fibrosis | Multicentre, ambispective, | 506 | Spain | N/A |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | virological response with direct-acting antivirals | | observational study | | | Patients with chronic hepatitis C and stage 3 fibrosis, aged > 50 years |
| **Toshikuni (11)** | 2014 | Clinical differences between alcoholic liver disease and nonalcoholic fatty liver disease | To comprehensively characterize ALD by comparing its clinical features and outcomes with those of MASLD | Comprehensive review | N/A | Global | N/A<br><br>Patients with ALD and MASLD |
| **Ieluzzi (12)** | 2014 | Progression to cirrhosis, hepatocellular carcinoma and liver-related mortality in chronic hepatitis B patients in Italy | To evaluate some of the risk factors for cirrhosis, hepatocellular carcinoma and liver-related mortality in Italian patients with chronic hepatitis B | Prospective, longitudinal cohort | 105 | Italy | N/A<br><br>Untreated patients with chronic HBV infection without cirrhosis at diagnosis |
| **Erman (13)** | 2019 | Estimation of fibrosis progression rates for chronic hepatitis C: a systematic review and meta-analysis update | To obtain updated estimates of fibrosis progression rates in treatment-naïve patients with chronic HBV and to explore sources of heterogeneity | Systematic review and meta-analysis | 42,693 | Global | Broad population perspective, specific treatment interventions, and screening or diagnostic management strategies<br><br>Untreated patients with chronic HCV infection |
| **Gruneau (14)** | 2023 | Disease Progression Modeling for Economic Evaluation in Nonalcoholic | To investigate modeling of the natural history of MASLD | Systematic review of Markov models | NR (28 studies included) | Global | N/A<br><br>Patients with MASLD |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Fatty Liver Disease—A Systematic Review | | | | | |
| **Fleming (15)** | 2010 | The rate of decompensation and clinical progression of disease in people with cirrhosis: a cohort study | To determine the rate of decompensation and clinical progression of disease in patients with cirrhosis based upon clinical symptoms recorded electronically in general practice data | Cohort study | 4,537 | UK | General practice<br><br>Patients with cirrhosis, aged ≥ 25 years |
| **Dakin (16)** | 2010 | Cost-utility analysis of tenofovir disoproxil fumarate in the treatment of chronic hepatitis B | To assess the cost-effectiveness of tenofovir disoproxil fumarate in the treatment of chronic hepatitis B versus alternative nucleos(t)ides from a UK NHS perspective | Markov model | 6,500 | UK | UK NHS perspective<br><br>Patients with HBV mono-infection and compensated liver disease, aged ≥ 18 years |
| **Wright (17)** | 2006 | Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation | To determine whether combined therapy with interferon- and ribavirin was more effective and cost-effective than no treatment for patients with mild chronic hepatitis C | RCT and Markov model | RCT, 204<br><br>Markov model, 1000 | UK | UK NHS perspective<br><br>Patients with mild chronic HCV infection |
| **Estes (18)** | 2018 | Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an | To develop a dynamic model of MASLD to assess the health burden of the disease at a | Markov model | N/A | United States | United States population perspective |

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|---|---|---|---|---|---|---|---|
| | | exponential increase in burden of disease | population level that allows a forecast of the health care impact of MASLD. It is designed to be a "living document" by creating a conceptual framework that can be periodically updated based on emerging data | | | | Patients with MASLD and MASH |
| **Thompson Coon (19)** | 2007 | Surveillance of cirrhosis for hepatocellular carcinoma: systematic review and economic analysis | To evaluate the effectiveness, cost-effectiveness and cost-utility of surveillance of patients with cirrhosis (ALD-, HBV- and HCV-related, using periodic serum AFP testing and/or liver ultrasound examination, to detect HCC, followed by treatment with liver transplantation or resection, where appropriate | Systematic review and Markov model | Systematic review, 214 studies<br><br>Markov model, 10,000 simulations | UK | UK NHS perspective<br><br>Markov:<br>Patients with compensated cirrhosis (ALD, HBV and HCV), aged ≤ 70 years |
| **Kondo (20)** | 2022 | Impact of acute decompensation on the prognosis of patients with hepatocellular carcinoma | To clarify features and impact of acute decompensation/acute-on-chronic liver failure on the prognosis of patients after treatment for HCC | Retrospective study | 556 | Japan | N/A<br><br>Patients with HCC, mean age 70 years |
| **Kirstein (21)** | 2017 | Patterns and challenges of treatment sequencing in | To analyze initial treatments and treatment sequencing in regard | Retrospective cohort study | 2,101 | Germany | German healthcare system |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | patients with hepatocellular carcinoma: Experience from a German referral center | to tumor burden and liver function at first diagnosis | | | | Patients with HCC, median age 65 years |
| **Schwab (22)** | 2024 | Selection Bias in Reporting of Median Waiting Times in Organ Transplantation | To apply competing-risk multistate models to calculate probabilities for transplantation and adverse outcomes on the Swiss national transplant waiting list | Retrospective cohort | 3,643 | Switzerland | Swiss healthcare system<br><br>Candidates for heart, liver, lungs, kidney, or pancreas and/or islet transplant |
| **Zhao (23)** | 2017 | Poor adherence to hepatocellular carcinoma surveillance: A systematic review and meta-analysis of a complex issue | To evaluate adherence rates to HCC surveillance | Systematic review and meta-analyses | 19,511 | Global | N/A<br><br>Patients with cirrhosis owing to any aetiology, chronic HCV with advanced fibrosis or chronic HBV regardless of fibrosis stages |
| **Ong (24)** | 2008 | Health-related quality of life in chronic hepatitis B patients | To determine the relationship between health-related quality of life and stages of chronic hepatitis B infection compared with normal and with a disease control | Prospective cohort | 432 | Singapore | N/A<br><br>Patients with HBV, aged > 16 years |

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|---|---|---|---|---|---|---|---|
| **McLernon (25)** | 2008 | Health-state utilities in liver disease: a systematic review | To conduct a systematic review of health-state utilities in liver disease, to look at the variation of study designs used, and to pool utilities for some liver disease states | Systematic review | NR (30 studies included) | Global | N/A<br><br>Patients with liver disease |
| **Younossi (26)** | 2019 | Reduced Patient-Reported Outcome Scores Associate With Level of Fibrosis in Patients With Nonalcoholic Steatohepatitis | To assess patient-reported outcomes in patients with histologically proven NASH by using a number of well-validated instruments | Collated randomized clinical trial data | 1,667 | Global | N/A<br><br>Patients with MASH, mean age 58 years |
| **Lima (27)** | 2019 | Cost-Utility Analysis of Imaging for Surveillance and Diagnosis of Hepatocellular Carcinoma | To compare imaging-based surveillance and diagnostic strategies in patients at risk for HCC while taking into account technically inadequate examinations and patient compliance | Markov model | NR | Canada | Canadian healthcare system<br><br>Patients with cirrhosis initiating HCC surveillance at age 50 years |
| **Blach (28)** | 2019 | Cost-effectiveness analysis of strategies to manage the disease burden of hepatitis C virus in Switzerland | To quantify the clinical and economic burden of HCV intervention strategies over the next 15 years | Markov model | 1,000 | Switzerland | Swiss healthcare system<br><br>Patients with HCV infection treated with HCV intervention strategies |

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|---|---|---|---|---|---|---|---|
| **Pfeil (29)** | 2015 | Cost-Effectiveness Analysis of Sofosbuvir Compared to Current Standard Treatment in Swiss Patients with Chronic Hepatitis C | To estimate clinical effectiveness in terms of quality-adjusted life years gained, the direct medical cost, and the cost-effectiveness in terms of cost per QALY gained, of sofosbuvir-based treatment strategies compared with the current standard treatment of mono-infected patients with chronic HCV genotypes 1–4 | Markov model | 10,000 | Switzerland | Swiss healthcare system<br><br>Mono-infected patients with chronic HCV genotypes 1–4, aged ≥ 18 years |
| **Tzartzeva (30)** | 2018 | Surveillance imaging and alpha fetoprotein for early detection of hepatocellular carcinoma in patients with cirrhosis: A meta-analysis | To compare the performance of surveillance imaging, with or without AFP, for early detection of HCC in patients with cirrhosis | Meta-analysis | 13,367 | Global | N/A<br><br>Patients with cirrhosis undergoing HCC surveillance |
| **Piratvisuth (31)** | 2023 | Development and clinical validation of a novel algorithmic score (GAAD) for detecting HCC in prospective cohort studies | To develop, implement, and clinically validate the GAAD algorithm for differentiating HCC (early and all-stage) and benign chronic liver disease, across disease stages and etiologies | Prospective cohort study | 1,084 | Hong Kong, Germany, Spain and Thailand | N/A<br><br>Patients with HCC or chronic liver disease, aged ≥ 18 years |
| **Janssen (32)** | 2021 | General population normative data for the EQ- | To generate a pooled set of population norms including France, Germany, Italy, Spain and | Population-based survey data | 21,425 | France, Germany, | N/A<br><br>General population |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | 5D-3L in the five largest European economies | the UK that represent the five largest European economies and drug markets (EUR5), which could facilitate communication and interpretation of results for these purposes for this important geographical and economical area | | | Italy, Spain and the UK | |

AFP: α-fetoprotein; ALD: alcohol-associated liver disease; CLC: compensated liver cirrhosis; GAAD: gender (biological sex), age, AFP, PIVKA-II; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; MASH: metabolic dysfunction-associated steatohepatitis; MASLD: metabolic dysfunction-associated steatotic liver disease; MRI: magnetic resonance imaging; N/A: not applicable; NHS: National Health Service; NR: not reported; PIVKA-II: protein induced by vitamin K absence or antagonist-II; QALY: quality-adjusted life year; RCT: randomised controlled trial; UK: United Kingdom; US: ultrasound.

**Parameters – scenario analyses**

**Table S3:** Epidemiology, surveillance, and treatment parameters for scenario analyses.

| Parameters | Base case (minimum to maximum) | Source |
|---|---|---|
| Patient type distribution | | |
| CLC | 9.80% | Defined by authors based on clinical/country-specific experience |
| NC.CHB | 4.10% | |
| FIB-3 | 86.10% | |
| Age at start of surveillance, years (95% CI) | | |
| NC.CHB | 50.00 (45.00–55.00) | Assumption |
| FIB-3 | 50.00 (45.00–55.00) | Assumption |
| CLC/FIB-3 aetiology, % (95% CI) | | |
| ALD | 36.90 (29.40–45.00) | Von Hessen et al., 2021(6) |
| HBV | 15.90 (10.60–22.60) | Von Hessen et al., 2021(6) |
| HCV | 32.50 (25.20–40.40) | Von Hessen et al., 2021(6) |
| MASLD | 14.60 (9.50–21.20) | Von Hessen et al., 2021(6) |
| Annual incidence of HCC, % (95% CI) | | |
| FIB-3 (ALD) | 0.18 (0.16–0.20) | Calculated based on the ratio of FIB-3 HCV/CLC HCV |
| FIB-3 (HBV) | 0.54 (0.49–0.60) | Calculated based on the ratio of FIB-3 HCV/CLC HCV |
| FIB-3 (HCV) | 0.47 (0.42–0.52) | Sánchez-Azofra et al., 2021(10) |
| FIB-3 (MASLD) | 0.50 (0.45–0.55) | Calculated based on the ratio of FIB-3 HCV/CLC HCV |
| NC.CHB | 0.30 (0.12–0.41) | Fattovich et al., 2008(7) |
| Annual incidence of CLC, % (95% CI) | | |
| FIB-3 (ALD) | 7.70 (3.20–12.20) | Toshikuni et al., 2014(11) |
| FIB-3 (HBV) | 1.56 (1.10–2.21) | Ieluzi et al., 2014(12) |
| FIB-3 (HCV) | 11.60 (10.40–13.10) | Erman et al., 2019(13) |
| FIB-3 (MASLD) | 7.90 (4.00–11.80) | Gruneau et al., 2023(14) |
| NC.CHB | 3.80 (1.65–5.96) | Fattovich et al., 2008(7) |
| Diagnostic performance by HCC stage in patients with non-cirrhotic aetiologies: US, % (95% CI) | | |
| Sensitivity, early (FIB-3) | 47.00 (33.00–61.00) | Tzartzeva et al., 2018(30) |
| Specificity, early (FIB-3) | 91.00 (86.00–94.00) | |
| Sensitivity, all (FIB-3) | 84.00 (76.00–92.00) | |
| Specificity, all (FIB-3) | 91.00 (86.00–94.00) | |
| Sensitivity, early (NC.CHB) | 47.00 (33.00–61.00) | Tzartzeva et al., 2018(30) |
| Specificity, early (NC.CHB) | 91.00 (86.00–94.00) | |
| Sensitivity, all (NC.CHB) | 84.00 (76.00–92.00) | |
| Specificity, all (NC.CHB) | 91.00 (86.00–94.00) | |
| Diagnostic performance by HCC stage in patients with non-cirrhotic aetiologies: US+AFP, % (95% CI) | | |
| Sensitivity, early (FIB-3) | 63.00 (48.00–75.00) | Tzartzeva et al., 2018(30) |
| Specificity, early (FIB-3) | 84.00 (77.00–89.00) | |
| Sensitivity, all (FIB-3) | 97.00 (91.00–99.00) | |
| Specificity, all (FIB-3) | 84.00 (77.00–89.00) | |
| Sensitivity, early (NC.CHB) | 63.00 (48.00–75.00) | Tzartzeva et al., 2018(30) |
| Specificity, early (NC.CHB) | 84.00 (77.00–89.00) | |
| Sensitivity, all (NC.CHB) | 97.00 (91.00–99.00) | |
| Specificity, all (NC.CHB) | 84.00 (77.00–89.00) | |
| Diagnostic performance by HCC stage in patients with non-cirrhotic aetiologies: GAAD, % (95% CI) | | |
| Sensitivity, early (FIB-3) | 79.50 (63.50–90.70) | Subanalysis in non-cirrhotic patients from Piratvisuth et al., 2023(31), published in Garay et al., 2024(5) (see table S6) |
| Specificity, early (FIB-3) | 97.90 (94.70–99.40) | |
| Sensitivity, all (FIB-3) | 87.30 (78.00–93.80) | |
| Specificity, all (FIB-3) | 97.90 (94.70–99.40) | |
| Sensitivity, early (NC.CHB) | 80.00 (61.40–92.30) | Subanalysis in patients with NC.CHB from Piratvisuth et al., 2023(31), published in |
| Specificity, early (NC.CHB) | 98.30 (93.90–99.80) | |
| Sensitivity, all (NC.CHB) | 87.00 (75.10–94.60) | |

| | | |
|---|---|---|
| Specificity, all (NC.CHB) | 98.30 (93.90–99.80) | Garay et al., 2024(5) (see table S6) |

AFP: α-fetoprotein; ALD: alcoholic liver disease; CI: confidence interval; CLC: compensated liver cirrhosis; FIB-3: fibrosis-3; GAAD: gender (biological sex), age, AFP, PIVKA-II; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; MASLD: metabolic dysfunction-associated steatotic liver disease; NC.CHB: non-cirrhotic chronic hepatitis B; US: ultrasound.

**Table S4:** Utility parameters for scenario analyses.

| Parameters | Base case (minimum to maximum) | Source |
|---|---|---|
| Utility weights (QoL) | | |
| NC.CHB | 0.87 (0.78–0.96) | Janssen et al., 2021[32]; Chin Ong et al., 2008[24] |
| FIB-3 | 0.84 (0.70–0.97) | Younossi et al., 2019[26] |

FIB-3: fibrosis-3; NC.CHB: non-cirrhotic chronic hepatitis B; QoL: quality of life.

**Table S5:** Cost parameters for scenario analyses.

| Parameters | Base case (minimum to maximum) | Source |
|---|---|---|
| Treatment costs, CHF (95% CI) | | |
| NC.CHB (annual, other than surveillance) | 3,385.00 (2,539.00–4,231.00) | Swiss Compendium of Medicinal Products(33) |
| FIB-3 (annual, other than surveillace) | 0.00 (0.00–0.00) | Assumption |

CI: confidence interval; FIB-3: fibrosis-3; NC.CHB: non-cirrhotic chronic hepatitis B; CHF: Confoederatio Helvetica franc; QoL: quality of life.

**Table S6:** Clinical performance of GAAD (cut-off of 2.57) for the detection of HCC for different aetiologies.

| Parameters | Elecsys GAAD | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Etiology** | **Cirr.** | **Cirr. HBV** | **Cirr. HCV** | **Cirr. MASH** | **Cirr. ALD** | **Cirr. other** | **Non-cirr.** | **Non-cirr. HBV** | **Non-cirr. HCV** | **Non-cirr. MASH** | **Non-cirr. ALD** | **Non-cirr. other** |
| N (early/all/ control) | 399 (135/287/112) | 238 (97/178/60) | 60 (22/44/16) | 28 (7/21/7) | 73 (14/54/19) | 80 (23/51/29) | 270 (39/79/191) | 169 (30/54/115) | 51 (5/6/45) | 64 (2/9/55) | 6 (0/2/4) | 57 (4/10/47) |
| | | | | | | | | | | | | |
| Sensitivity, early HCC | | | | | | | | | | | | |
| TP | 91 | 64 | 16 | 4 | 11 | 16 | 31 | 24 | 4 | 2 | 0 | 3 |
| FN | 44 | 33 | 6 | 3 | 3 | 7 | 8 | 6 | 1 | 0 | 0 | 1 |
| Sensitivity (95% CI) | 67.4 (58.8–75.2) | 66 (55.7–75.3) | 72.7 (49.8–89.3) | | | 69.6 (47.1–86.8) | 79.5 (63.5–90.7) | 80 (61.4–92.3) | | | | |
| | | | | | | | | | | | | |
| Sensitivity, late HCC | | | | | | | | | | | | |
| TP | 144 | 76 | 21 | 13 | 39 | 26 | 38 | 23 | 1 | 7 | 2 | 6 |
| FN | 8 | 5 | 1 | 1 | 1 | 2 | 2 | 1 | 0 | 0 | 0 | 0 |
| Sensitivity (95% CI) | 94.7 (89.9–97.7) | 93.8 (86.2–98) | 95.5 (77.2–99.9) | | 97.5 (86.8–99.9) | 92.9 (76.5–99.1) | 95 (83.1–99.4) | 95.8 (78.9–99.9) | | | | |
| | | | | | | | | | | | | |
| Sensitivity, all HCC | | | | | | | | | | | | |
| TP | 235 | 140 | 37 | 17 | 50 | 42 | 69 | 47 | 5 | 9 | 2 | 9 |
| FN | 52 | 38 | 7 | 4 | 4 | 9 | 10 | 7 | 1 | 0 | 0 | 1 |
| Sensitivity (95% CI) | 81.9 (76.9–86.2) | 78.7 (71.9–84.4) | 84.1 (69.9–93.4) | 81 (58.1–94.6) | 92.6 (82.1–97.9) | 82.4 (69.1–91.6) | 87.3 (78–93.8) | 87 (75.1–94.6) | | | | |
| Specificity | | | | | | | | | | | | |
| TN | 97 | 59 | 12 | 5 | 11 | 26 | 187 | 113 | 45 | 53 | 4 | 46 |
| FP | 15 | 1 | 4 | 2 | 8 | 3 | 4 | 2 | 0 | 2 | 0 | 1 |
| Specificity (95% CI) | 86.6 (78.9–92.3) | 98.3 (91.1–100) | | | | 89.7 (72.6–97.8) | 97.9 (94.7–99.4) | 98.3 (93.9–99.8) | 100 (92.1–100) | 96.4 (87.5–99.6) | | 97.9 (88.7–99.9) |

Source: Subanalysis in Piratvisuth et al., 2023 (31), published in Garay et al., 2024(5).

ALD: alcohol-associated liver disease; CI: confidence intervals; Cirr, cirrhosis; FN: false negative; FP: false positive; GAAD: gender (biological sex), age, AFP, PIVKA-II; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; MASH: metabolic dysfunction-associated steatohepatitis; PIVKA-II: protein induced by vitamin K absence or antagonist-II; TN: true negative; TP: true positive.

**Table S7:** Estimates for sensitivity and specificity for GALAD by HCC stage in patients with cirrhosis.

| **Parameters** | **Meta-analysis (90% CLC)** |
|---|---|
| Sensitivity early-stage HCC (0/A) | 73 (63.9–80.5) |
| Specificity early-stage HCC (0/A) | 83.9 (77.3–88.9) |
| Sensitivity all-stage HCC | 79.6 (72.3–85.3) |
| Specificity all-stage HCC | 85.3 (82.0–88.1) |

CLC: compensated liver cirrhosis; GALAD: gender (biological sex), age, AFP, AFP-L3, PIVKA-II; HCC: hepatocellular carcinoma; HCC 0/A: hepatocellular carcinoma stage 0/A.

**Table S8.** Extended results: Total costs, life years, and quality-adjusted life years (discounted and undiscounted); HCC cases by detection status; HCC treatments and tests; and main cost categories, by surveillance strategy.

| | No surveillance | US (biannual) | US+AFP (biannual) | GAAD (biannual) |
|---|---|---|---|---|
| **Cohort size, n** | 100,000 | 100,000 | 100,000 | 100,000 |
| **Main results, discounted** | | | | |
| Costs, CHF | 4,349,361,150 | 4,870,279,411 | 4,998,060,422 | 4,998,309,910 |
| Life years | 800,453 | 817,260 | 820,341 | 820,999 |
| QALYs | 589,272 | 601,822 | 604,246 | 604,798 |
| **Per patient** | | | | |
| Costs, CHF | 43,494 | 48,703 | 49,981 | 49,983 |
| Life years | 8.00 | 8.17 | 8.20 | 8.21 |
| QALYs | 5.89 | 6.02 | 6.04 | 6.05 |
| **Main results, undiscounted** | | | | |
| Costs, CHF | 5,960,516,671 | 6,751,571,560 | 6,941,994,604 | 6,949,436,678 |
| Life years | 1,044,924 | 1,076,263 | 1,082,128 | 1,083,469 |
| QALYs | 767,880 | 791,063 | 795,602 | 796,668 |
| **Per patient** | | | | |
| Costs, CHF | 59,605 | 67,516 | 69,420 | 69,494 |
| Life years | 10.45 | 10.76 | 10.82 | 10.83 |
| QALYs | 7.68 | 7.91 | 7.96 | 7.97 |
| **Main results, discounted, HCC patients only** | | | | |
| Cohort size, n | 19,933 | 19,933 | 19,933 | 19,933 |
| Costs, CHF | 691,181,978 | 1,113,644,371 | 1,203,596,345 | 1,214,278,151 |
| Life years | 167,270 | 184,077 | 187,158 | 187,816 |
| QALYs | 122,464 | 135,013 | 137,438 | 137,989 |
| **Per patient** | | | | |
| Costs, CHF | 34,675 | 55,869 | 60,382 | 60,918 |
| Life years | 8.39 | 9.23 | 9.39 | 9.42 |
| QALYs | 6.14 | 6.77 | 6.89 | 6.92 |
| **HCC cases by detection status, n** | | | | |
| Total cases | 19,933 | 19,933 | 19,933 | 19,933 |
| Detected in surveillance: early | 0 | 8,689 | 10,592 | 11,107 |
| Detected in surveillance: late | 0 | 2,558 | 2,230 | 2,698 |
| Detected incidentally | 3,833 | 1,203 | 952 | 958 |
| Detected symptomatically | 16,087 | 7,470 | 6,146 | 6,002 |
| Early detection, % cases | 0 | 44 | 53 | 56 |
| **HCC treatment type, n** | | | | |
| OLT | 111 | 498 | 600 | 621 |
| Resection | 927 | 2,809 | 3,097 | 3,156 |
| RFA | 822 | 4,139 | 4,756 | 4,908 |
| TACE | 1,119 | 2,814 | 3,042 | 3,023 |
| Systemic therapy | 464 | 846 | 839 | 803 |
| BSC | 390 | 1,344 | 1,440 | 1,407 |
| Total | 3,833 | 12,450 | 13,774 | 13,918 |
| **Test results, n** | | | | |
| True positive | 0 | 11,247 | 12,822 | 12,960 |
| True negative | 0 | 704,397 | 650,474 | 670,518 |
| False negative | 0 | 10,378 | 6,361 | 5,678 |
| False positive | 0 | 69,764 | 123,687 | 103,643 |
| **Main costs (undiscounted), millions CHF** | | | | |
| Surveillance | 0.00 | 96.27 | 109.82 | 110.28 |
| HCC treatment (stage 0/A) | 114.72 | 828.85 | 1,000.87 | 1,050.77 |
| HCC treatment (stages B/C/D) | 181.85 | 196.94 | 172.42 | 148.42 |
| False positive test result | 0.00 | 57.49 | 101.90 | 85.39 |
| CLC | 2,368.41 | 2,320.13 | 2,311.81 | 2,310.09 |
| DCLC | 3,166.01 | 3,166.01 | 3,166.01 | 3,166.01 |
| Palliative care | 120.03 | 55.70 | 45.82 | 44.74 |
| True positive test result | 0.00 | 6.92 | 7.89 | 7.97 |
| Total | 5,960.52 | 6,751.57 | 6,941.99 | 6,949.44 |
| **Costs of first-line HCC treatment (undiscounted), millions CHF** | | | | |
| OLT | 43.21 | 209.43 | 255.50 | 265.29 |
| Resection | 82.93 | 245.22 | 273.26 | 278.69 |

| | | | | |
|---|---|---|---|---|
| RFA | 63.85 | 321.44 | 370.92 | 384.77 |
| TACE | 42.12 | 115.65 | 126.54 | 128.06 |
| Systemic therapy | 60.67 | 117.12 | 127.85 | 122.87 |
| BSC | 3.78 | 16.92 | 19.22 | 19.50 |
| Total | 296.57 | 1,025.79 | 1,173.30 | 1,199.19 |

AFP: α-fetoprotein; BSC: best supportive care; CHF: Confoederatio Helvetica franc; CLC: compensated liver cirrhosis;

DCLC: decompensated liver cirrhosis; GAAD: gender (biological sex), age, AFP, PIVKA-II; HCC, hepatocellular carcinoma;

HCC 0/A: hepatocellular carcinoma stage 0/A; HCC B/C/D: hepatocellular carcinoma stage B/C/D; OLT: orthotopic liver transplantation;

QALYs: quality-adjusted life years; RFA: radiofrequency thermal ablation; TACE: transarterial chemoembolization; US: ultrasound.

**Table S9:** Incremental net monetary benefit, CHF (95% CI) by surveillance strategy

| Incremental net monetary benefit, CHF (95% CI) | US | US+AFP | GAAD |
|---|---|---|---|
| Surveillance strategies compared with no surveillance | 7,553 (7,450–7,657) | 9,604 (9,496–9,712) | 9,831 (9,720–9,943) |
| Surveillance strategies compared with US | – | 2,051 (2,001–2,101) | 2,278 (2,223–2,334) |
| Surveillance strategies compared with US+AFP | – | – | 227 (199–256) |

AFP: α-fetoprotein; CI: confidence interval; GAAD: gender [biological sex], age, AFP, PIVKA-II; PIVKA-II: protein induced by vitamin K absence or antagonist-II; US: ultrasound.

## Scenario analyses

Deterministic base case – cirrhotic patients only

**Table S10:**
Deterministic base case – cirrhotic patients only (model results for 10,000 simulations/patients, Switzerland, 2025)

| | No surveillance | US | US+AFP | GAAD |
|---|---|---|---|---|
| Cost per patient, CHF | 42,884.26 | 48,307.56 | 49,785.16 | 49,694.07 |
| QALYs per patient | 5.846 | 5.976 | 6.011 | 6.013 |
| Surveillance strategies compared with no surveillance | | | | |
| Incremental costs, CHF | - | 5,423.30 | 6,900.90 | 6,809.81 |
| Incremental QALYs | - | 0.130 | 0.165 | 0.166 |
| ICER, CHF | - | 41,792.57 | 41,810.82 | 40,921.24 |
| Surveillance strategies compared with US | | | | |
| Incremental costs, CHF | - | - | 1,477.61 | 1,386.51 |
| Incremental QALYs | - | - | 0.035 | 0.037 |
| ICER, CHF | - | - | 41,877.95 | 37,835.73 |
| Surveillance strategies compared with US+AFP | | | | |
| Incremental costs, CHF | - | - | - | -91.10 |
| Incremental QALYs | - | - | - | 0.001 |
| ICER, CHF | - | - | - | Dominant |

AFP: α-fetoprotein; CHF: Confoederatio Helvetica franc; ICER: incremental cost-effectiveness ratio; GAAD: gender (biological sex), age, AFP, PIVKA-II; QALY: quality-adjusted life year; US: ultrasound.

*Scenario analysis A: Cirrhotic, FIB-3, and HBV patients*

**Table S11:**
Cirrhotic, FIB-3, and HBV patients (model results for 10,000 simulations/patients, Switzerland, 2025).

| | **No surveillance** | **US** | **US+AFP** | **GAAD** |
|---|---|---|---|---|
| Cost per patient, CHF | 29,321.14 | 32,706.62 | 33,851.24 | 33,000.40 |
| QALYs per patient | 9.933 | 9.969 | 9.979 | 9.982 |
| Surveillance strategies compared with no surveillance | | | | |
| Incremental costs, CHF | - | 3,385.47 | 4,530.10 | 3,679.26 |
| Incremental QALYs | - | 0.037 | 0.047 | 0.049 |
| ICER, CHF | - | 92,351.85 | 96,974.25 | 75,090.80 |
| Surveillance strategies compared with US | | | | |
| Incremental costs, CHF | - | - | 1,144.63 | 293.78 |
| Incremental QALYs | - | - | 0.010 | 0.012 |
| ICER, CHF | - | - | 113,824.80 | 23,809.37 |
| Surveillance strategies compared with US+AFP | | | | |
| Incremental costs, CHF | - | - | - | -850.84 |
| Incremental QALYs | - | - | - | 0.002 |
| ICER, CHF | - | - | - | Dominant |

AFP: α-fetoprotein; CHF: Confoederatio Helvetica franc; FIB-3: fibrosis-3; GAAD: gender (biological sex), age, AFP, PIVKA-II; HBV: hepatitis B virus; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; US: ultrasound.

*Scenario analysis B: FIB-3 patients only*

**Table S12:**
FIB-3 patients only (model results for 10,000 simulations/patients, Switzerland, 2025).

| | **No surveillance** | **US** | **US+AFP** | **GAAD** |
|---|---|---|---|---|
| Cost per patient, CHF | 27,194.60 | 30,450.60 | 31,584.83 | 30,663.01 |
| QALYs per patient | 10.264 | 10.294 | 10.301 | 10.303 |
| Surveillance strategies compared with no surveillance | | | | |
| Incremental costs, CHF | - | 3,256.00 | 4,390.23 | 3,468.41 |
| Incremental QALYs | - | 0.030 | 0.037 | 0.039 |
| ICER, CHF | - | 110,263.67 | 119,699.52 | 88,976.53 |
| Surveillance strategies compared with US | | | | |
| Incremental costs, CHF | - | - | 1,134.23 | 212.41 |
| Incremental QALYs | - | - | 0.007 | 0.009 |
| ICER, CHF | - | - | 158,680.66 | 22,472.61 |
| Surveillance strategies compared with US+AFP | | | | |
| Incremental costs, CHF | - | - | - | -921.82 |
| Incremental QALYs | - | - | - | 0.002 |
| ICER, CHF | - | - | - | Dominant |

AFP: α-fetoprotein; CHF: Confoederatio Helvetica franc; FIB-3: fibrosis-3; GAAD: gender (biological sex), age, AFP, PIVKA-II; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; US: ultrasound.

*Scenario analysis C: Cirrhotic MASLD patients only*

**Table S13:**
Cirrhotic MASLD patients only (model results for 10,000 simulations/patients, Switzerland, 2025).

| | **No surveillance** | **US** | **US+AFP** | **GAAD** |
|---|---|---|---|---|
| Cost per patient, CHF | 39,550.29 | 46,887.70 | 48,737.90 | 48,654.06 |
| QALYs per patient | 6.005 | 6.192 | 6.241 | 6.245 |
| Surveillance strategies compared with no surveillance | | | | |
| Incremental costs, CHF | - | 7,337.42 | 9,187.61 | 9,103.78 |
| Incremental QALYs | - | 0.187 | 0.236 | 0.240 |
| ICER, CHF | - | 39,237.15 | 39,005.08 | 37,969.44 |
| Surveillance strategies compared with US | | | | |
| Incremental costs, CHF | - | - | 1,850.19 | 1,766.36 |
| Incremental QALYs | - | - | 0.049 | 0.053 |
| ICER, CHF | - | - | 38,111.15 | 33,476.53 |
| Surveillance strategies compared with US+AFP | | | | |
| Incremental costs, CHF | - | - | - | -83.84 |
| Incremental QALYs | - | - | - | 0.004 |
| ICER, CHF | - | - | - | Dominant |

AFP: α-fetoprotein; CHF: Confoederatio Helvetica franc; GAAD: gender (biological sex), age, AFP, PIVKA-II; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; MASLD: metabolic dysfunction-associated steatotic liver disease; US: ultrasound.

*Scenario analysis D: FIB-3 MASLD patients only*

**Table S14:**
FIB-3 MASLD patients only (model results for 10,000 simulations/patients, Switzerland, 2025).

| | **No surveillance** | **US** | **US+AFP** | **GAAD** |
|---|---|---|---|---|
| Cost per patient, CHF | 26,916.42 | 30,523.84 | 31,757.53 | 30,929.09 |
| QALYs per patient | 10.291 | 10.331 | 10.341 | 10.344 |
| Surveillance strategies compared with no surveillance | | | | |
| Incremental costs, CHF | - | 3,607.42 | 4,841.10 | 4,012.66 |
| Incremental QALYs | - | 0.040 | 0.050 | 0.053 |
| ICER, CHF | - | 90,362.51 | 96,910.72 | 75,776.81 |
| Surveillance strategies compared with US | | | | |
| Incremental costs, CHF | - | - | 1,233.68 | 405.24 |
| Incremental QALYs | - | - | 0.010 | 0.013 |
| ICER, CHF | - | - | 122,967.28 | 31,095.91 |
| Surveillance strategies compared with US+AFP | | | | |
| Incremental costs, CHF | - | - | - | -828.44 |
| Incremental QALYs | - | - | - | 0.003 |
| ICER, CHF | - | - | - | Dominant |

AFP: α-fetoprotein; CHF: Confoederatio Helvetica franc; FIB-3: fibrosis-3; GAAD: gender (biological sex), age, AFP, PIVKA-II; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; MASLD: metabolic dysfunction-associated steatotic liver disease; US: ultrasound.

*Scenario analysis E: GAAD adherence rate increased by 10%*

**Table S15**. GAAD adherence rate increased by 10% (model results for 10,000 simulations/patients, Switzerland, 2025).

| | **No surveillance** | **US** | **US+AFP** | **GAAD** |
|---|---|---|---|---|
| Cost per patient, CHF | 42,884.26 | 48,307.56 | 49,785.16 | 50,130.36 |
| QALYs per patient | 5.846 | 5.976 | 6.011 | 6.021 |
| Surveillance strategies compared with no surveillance | | | | |
| Incremental costs, CHF | - | 5,423.30 | 6,900.90 | 7,246.10 |
| Incremental QALYs | - | 0.130 | 0.165 | 0.175 |
| ICER, CHF | - | 41,792.57 | 41,810.82 | 41,501.09 |
| Surveillance strategies compared with US | | | | |
| Incremental costs, CHF | - | - | 1,477.61 | 1,822.81 |
| Incremental QALYs | - | - | 0.035 | 0.045 |
| ICER, CHF | - | - | 41,877.95 | 40,657.41 |
| Surveillance strategies compared with US+AFP | | | | |
| Incremental costs, CHF | - | - | - | 345.20 |
| Incremental QALYs | - | - | - | 0.010 |
| ICER, CHF | - | - | - | 36,147.82 |

AFP: α-fetoprotein; CHF: Confoederatio Helvetica franc; GAAD: gender (biological sex), age, AFP, PIVKA-II;

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; US: ultrasound.

*Scenario analysis F: GAAD adherence rate increased by 25%*

**Table S16**. GAAD adherence rate increased by 25% (model results for 10,000 simulations/patients, Switzerland, 2025)

| | **No surveillance** | **US** | **US+AFP** | **GAAD** |
|---|---|---|---|---|
| Cost per patient, CHF | 42,884.26 | 48,307.56 | 49,785.16 | 50,783.26 |
| QALYs per patient | 5.846 | 5.976 | 6.011 | 6.033 |
| Surveillance strategies compared with no surveillance | | | | |
| Incremental costs, CHF | - | 5,423.30 | 6,900.90 | 7,899.00 |
| Incremental QALYs | - | 0.130 | 0.165 | 0.187 |
| ICER, CHF | - | 41,792.57 | 41,810.82 | 42,335.70 |
| Surveillance strategies compared with US | | | | |
| Incremental costs, CHF | - | - | 1,477.61 | 2,475.70 |
| Incremental QALYs | - | - | 0.035 | 0.057 |
| ICER, CHF | - | - | 41,877.95 | 43,576.29 |
| Surveillance strategies compared with US+AFP | | | | |
| Incremental costs, CHF | - | - | - | 998.09 |
| Incremental QALYs | - | - | - | 0.022 |
| ICER, CHF | - | - | - | 46,359.63 |

AFP: α-fetoprotein; CHF: Confoederatio Helvetica franc; GAAD: gender (biological sex), age, AFP, PIVKA-II;

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; US: ultrasound.

*Scenario analysis G: GAAD adherence rate increased by 50%*

**Table S17**. GAAD adherence rate increased by 50% (model results for 10,000 simulations/patients, Switzerland, 2025)

| | **No surveillance** | **US** | **US+AFP** | **GAAD** |
|---|---|---|---|---|
| Cost per patient, CHF | 42,884.26 | 48,307.56 | 49,785.16 | 51,615.15 |
| QALYs per patient | 5.846 | 6.976 | 6.011 | 6.047 |
| Surveillance strategies compared with no surveillance | | | | |
| Incremental costs, CHF | - | 5,423.30 | 6,900.90 | 8,730.89 |
| Incremental QALYs | - | 0.130 | 0.165 | 0.200 |
| ICER, CHF | - | 41,792.57 | 41,810.82 | 43,599.51 |
| Surveillance strategies compared with US | | | | |
| Incremental costs, CHF | - | - | 1,477.61 | 3,307.59 |
| Incremental QALYs | - | - | 0.035 | 0.070 |
| ICER, CHF | - | - | 41,877.95 | 46,926.20 |
| Surveillance strategies compared with US+AFP | | | | |
| Incremental costs, CHF | - | - | - | 1,829.98 |
| Incremental QALYs | - | - | - | 0.035 |
| ICER, CHF | - | - | - | 51,986.25 |

AFP: α-fetoprotein; CHF: Confoederatio Helvetica franc; GAAD: gender (biological sex), age, AFP, PIVKA-II;

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; US: ultrasound.

*Scenario analysis H: Surveillance with GALAD*

**Table S18:**
Surveillance with GALAD (model results for 10,000 simulations/patients, Switzerland, 2025).

| | **No surveillance** | **US** | **US+AFP** | **GAAD** | **GALAD** |
|---|---|---|---|---|---|
| Cost per patient, CHF | 42,884.26 | 48,307.56 | 49,785.43 | 49,694.07 | 50,227.81 |
| QALYs per patient | 5.846 | 5.976 | 6.011 | 6.013 | 6.014 |
| Surveillance strategies compared with no surveillance | | | | | |
| Incremental costs, CHF | - | 5,423.30 | 6,901.17 | 6,809.81 | 7,343.55 |
| Incremental QALYs | - | 0.130 | 0.165 | 0.166 | 0.168 |
| ICER, CHF | - | 41,792.57 | 41,812.45 | 40,921.24 | 43,832.44 |
| Surveillance strategies compared with US | | | | | |
| Incremental costs, CHF | - | - | 1,477.88 | 1,386.51 | 1,920.26 |
| Incremental QALYs | - | - | 0.035 | 0.037 | 0.038 |
| ICER, CHF | - | - | 41,885.60 | 37,835.73 | 50,840.89 |
| Surveillance strategies compared with US+AFP | | | | | |
| Incremental costs, CHF | - | - | - | -91.37 | 442.38 |
| Incremental QALYs | - | - | - | 0.001 | 0.002 |
| ICER, CHF | - | - | - | Dominant | 177,927.32 |
| Surveillance strategies compared with GAAD | | | | | |
| Incremental costs, CHF | - | - | - | - | 533.75 |
| Incremental QALYs | - | - | - | - | 0.001 |
| ICER, CHF | - | - | - | - | 474,692.26 |

AFP: α-fetoprotein; CHF: Confoederatio Helvetica franc; GAAD: gender (biological sex), age, AFP, PIVKA-II; GALAD: gender (biological sex), age, AFP, AFP-L3, PIVKA-II; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; US: ultrasound.

## Supplementary figures

### Diagnostic pathway

**Figure S1:** Diagnostic pathway of the intervention and comparator. CT: computed tomography; FN: false negative; FP: false positive; HCC: hepatocellular carcinoma; MRI: magnetic resonance imaging; TN: true negative; TP: true positive.

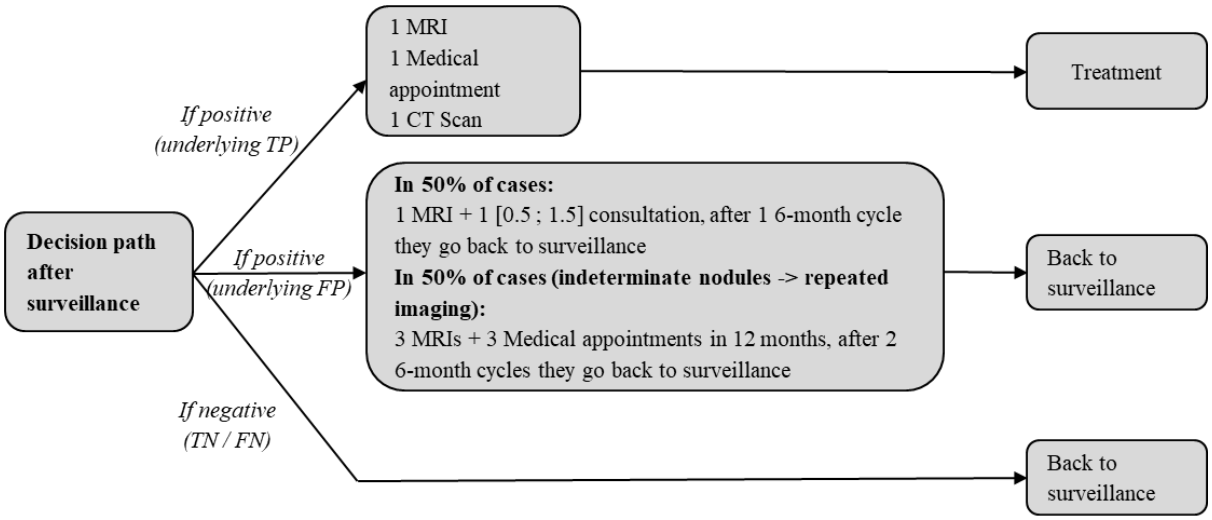


**Figure S2:** Sensitivity and specificity of GALAD for early-stage HCC in studies identified in Guan et al. (2023) (34). Extraction from MetaDTA: Diagnostic Test Accuracy Meta-Analysis v2.1.3(35-37)
GALAD: gender (biological sex), age, AFP, AFP-L3, PIVKA-II; HCC, hepatocellular carcinoma.

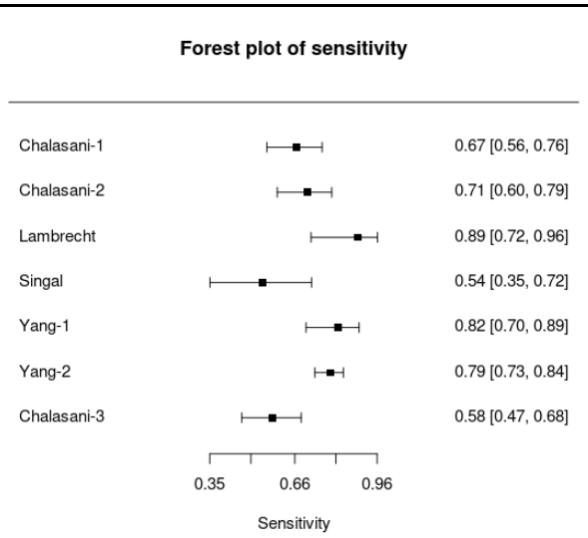
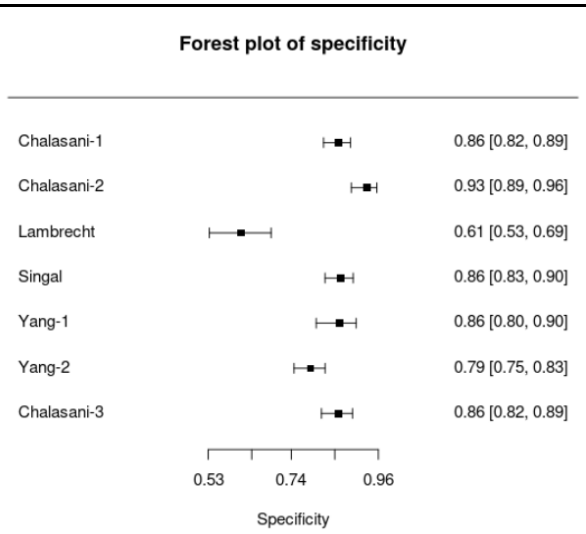
| Sensitivity | Specificity |
|---|---|
|  |  |

**Figure S3.** Sensitivity and specificity of GALAD for all-stage HCC in studies identified in Guan et al. (2023) (34). Extraction from MetaDTA: Diagnostic Test Accuracy Meta-Analysis v2.1.3. (35-37). GALAD, gender (biological sex), age, AFP, AFP-L3, PIVKA-II; HCC, hepatocellular carcinoma.

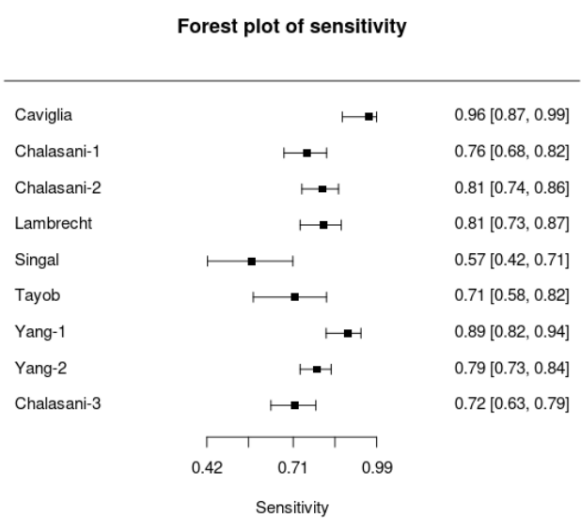
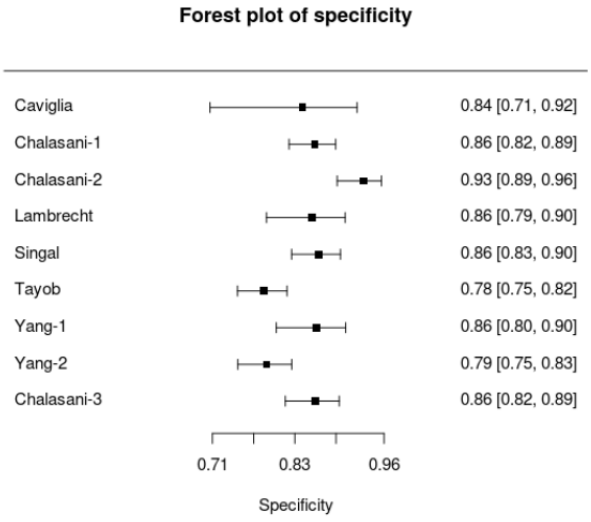
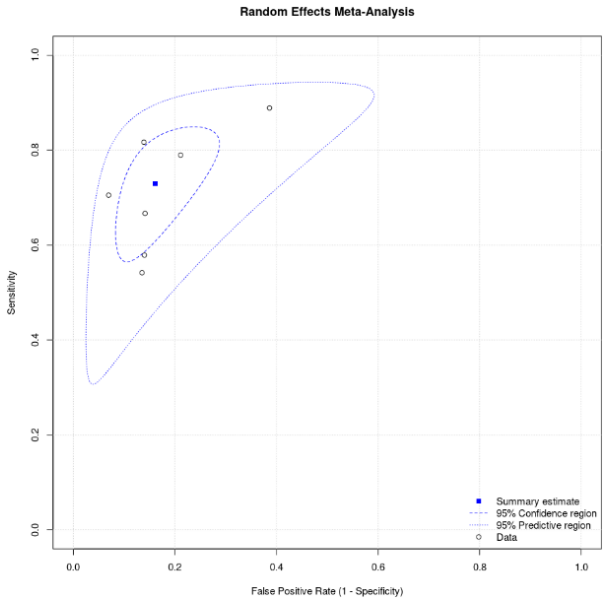
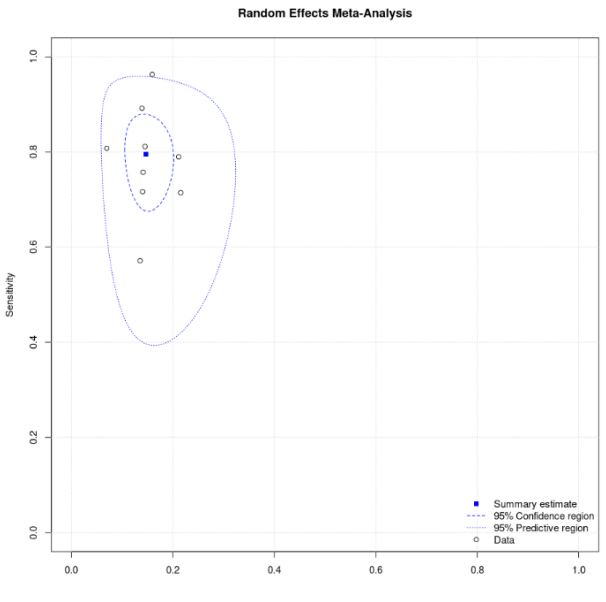
| Sensitivity | Specificity |
|---|---|
|  |  |

**Figure S4.** GALAD sensitivity and specificity point estimates for each study and the meta-analysed results. Extraction from MetaDTA: Diagnostic Test Accuracy Meta-Analysis v2.1.3 (35-37). GALAD, gender (biological sex), age, AFP, AFP-L3, PIVKA-II.

| Early-stage | All-stage |
| --- | --- |
|  |  |

**One-way sensitivity analyses**

**Figure S5:**
One-way sensitivity analysis (US [biannual] vs no surveillance; NMB of CHF 100,000; Switzerland, 2025)
Graph is centered at INMB (CHF 7,553). Arrows indicate which strategy is favored. CHF: Confoederatio Helvetica franc; CLC: compensated liver cirrhosis; HCC: hepatocellular carcinoma; INMB: incremental net monetary benefit; NMB: net monetary benefit; QoL: quality of life; RFA: radiofrequency thermal ablation; US: ultrasound.
*modifies more than one variable (early and late estimates).

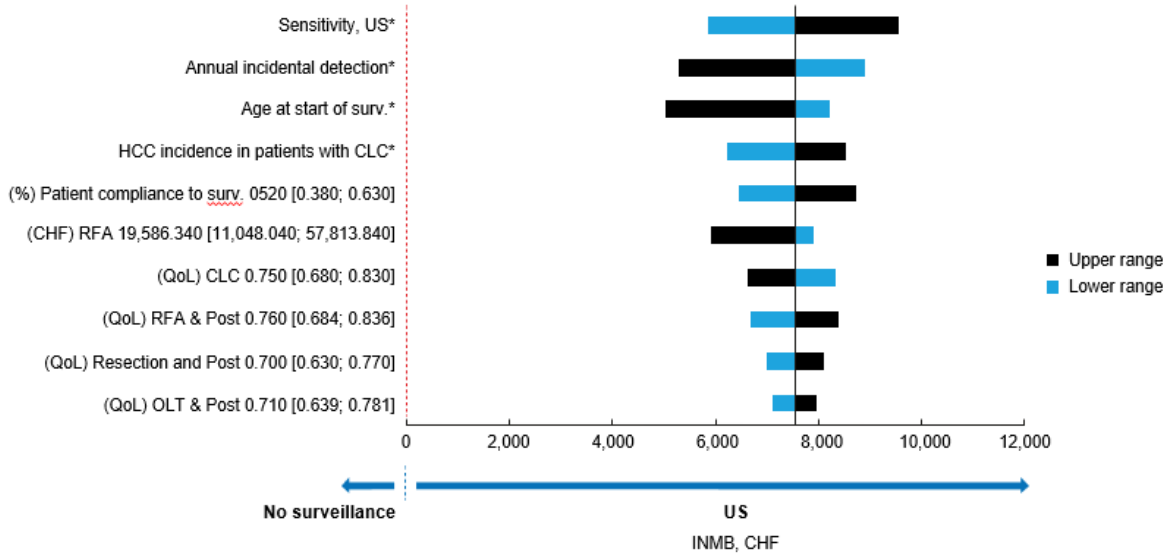


**Figure S6:**
One-way sensitivity analysis (US+AFP [biannual]) vs no surveillance, NMB of CHF 100,000; Switzerland, 2025).
Graph is centered at INMB (CHF 9,604). Arrows indicate which strategy is favored. AFP: α-fetoprotein; CHF: Confoederatio Helvetica franc; CLC: compensated liver cirrhosis; HCC: hepatocellular carcinoma; INMB: incremental net monetary benefit; NMB: net monetary benefit; QoL: quality of life; RFA: radiofrequency thermal ablation; US: ultrasound.
*modifies more than one variable (early and late estimates).

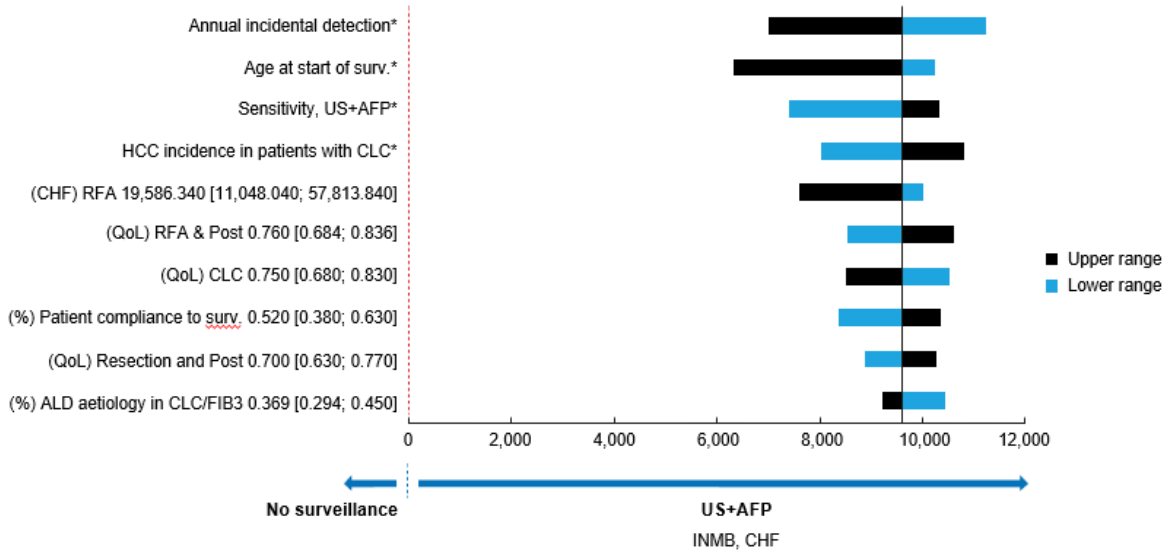


**Figure S7:**
One-way sensitivity analysis (GAAD [biannual] vs no surveillance; NMB of CHF 100,000; Switzerland, 2025).
Graph is centered at INMB (CHF 9,831). Arrows indicate which strategy is favored. CHF: Confoederatio Helvetica franc; CLC: compensated liver cirrhosis; GAAD: gender (biological sex), age, AFP, PIVKA-II; HCC: hepatocellular carcinoma; INMB: incremental net monetary benefit; NMB: net monetary benefit; QoL: quality of life; RFA: radiofrequency thermal ablation; US: ultrasound.
*modifies more than one variable (early and late estimates).

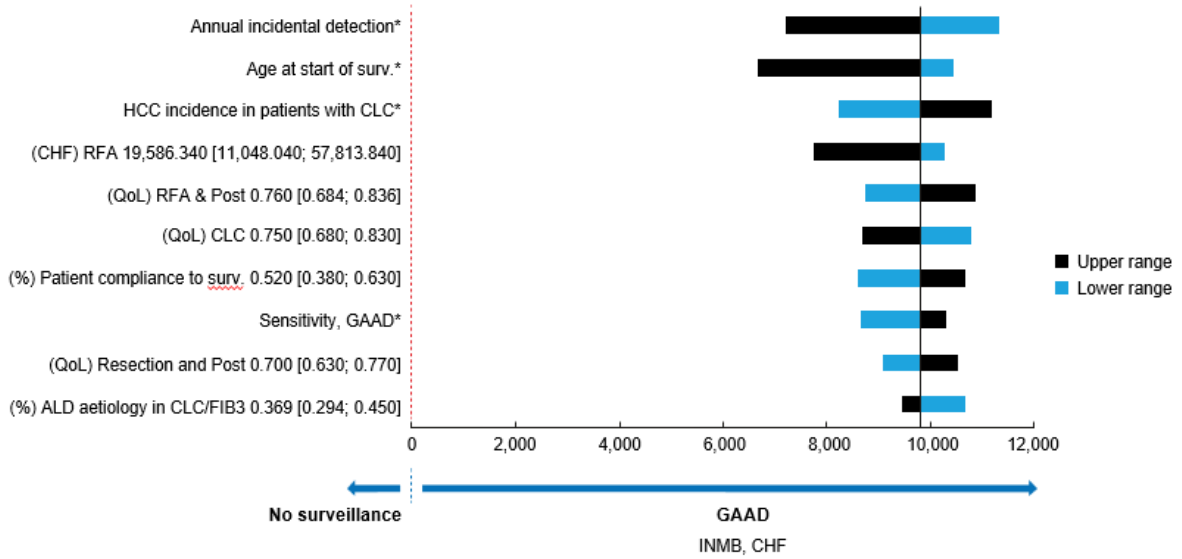


**Figure S8:**
One-way sensitivity analysis (US+AFP [biannual] vs US [biannual]; NMB of CHF 100,000; Switzerland, 2025).
Graph is centered at INMB (CHF 2,051). Arrows indicate which strategy is favored. AFP: α-fetoprotein; CHF: Confoederatio Helvetica franc; CLC: compensated liver cirrhosis; HCC: hepatocellular carcinoma; INMB: incremental net monetary benefit; NMB: net monetary benefit; QoL: quality of life; RFA: radiofrequency thermal ablation; US: ultrasound.
*modifies more than one variable (early and late estimates).

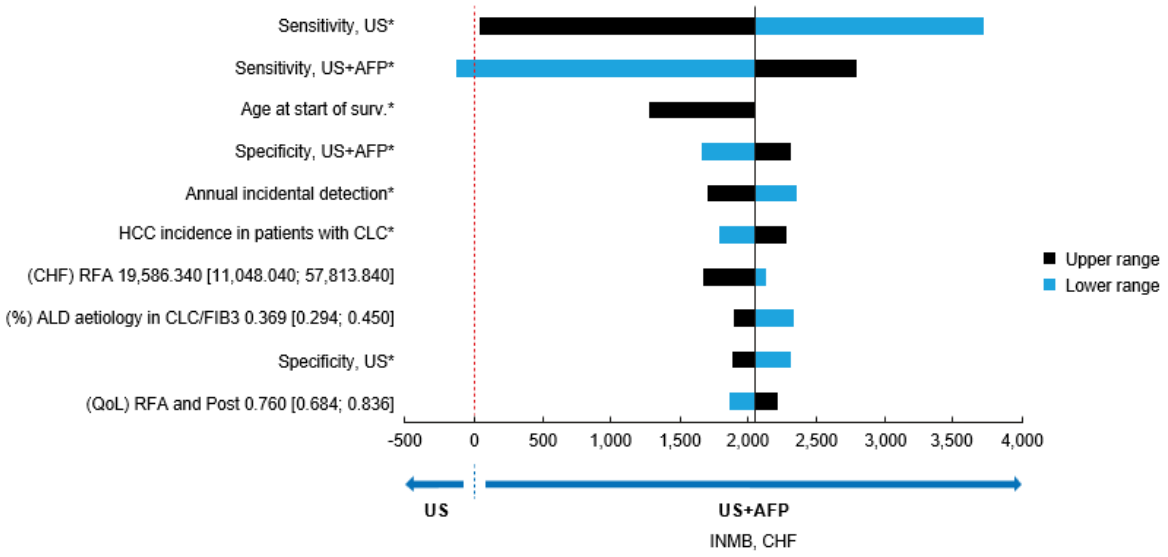


**Figure S9:**
One-way sensitivity analysis (GAAD [biannual] vs US [biannual]. NMB of CHF 100,000; Switzerland, 2025. Graph is centered at INMB (CHF 2,278). Arrows indicate which strategy is favored.
CHF: Confoederatio Helvetica franc; CLC: compensated liver cirrhosis; GAAD: gender (biological sex), age, AFP, PIVKA-II; HCC: hepatocellular carcinoma; INMB: incremental net monetary benefit; NMB: net monetary benefit; QoL: quality of life; RFA: radiofrequency thermal ablation; US: ultrasound.
*modifies more than one variable (early and late estimates).

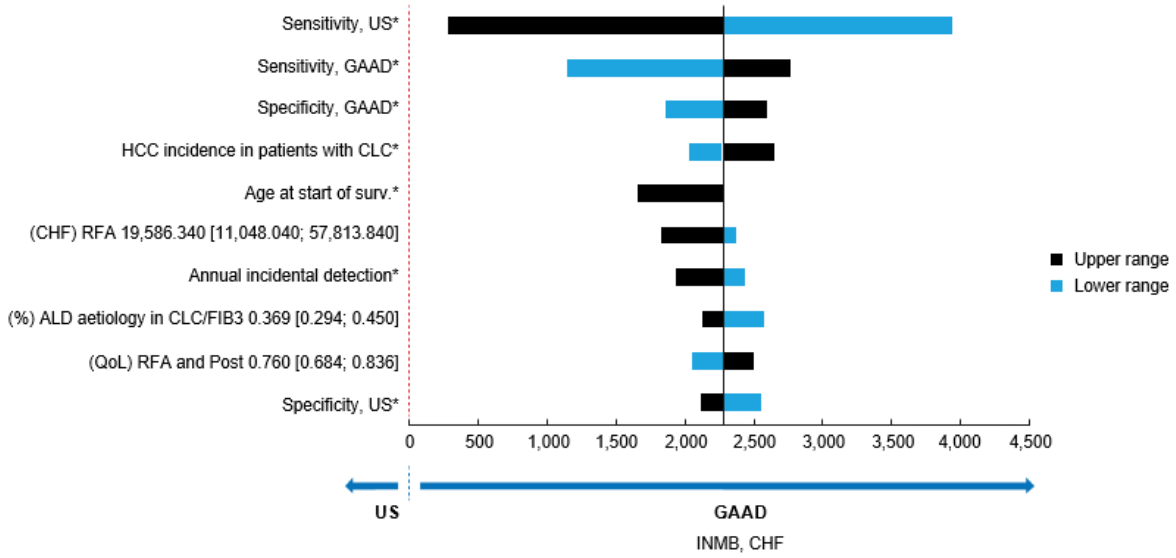
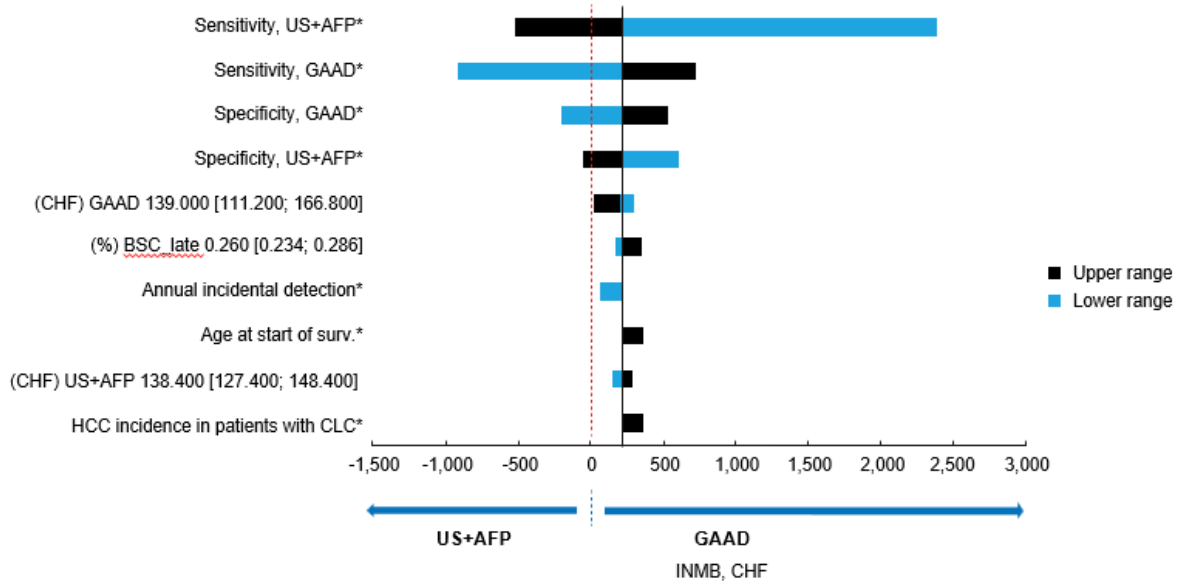


**Figure S10:**

One-way sensitivity analysis (GAAD [biannual] vs US+AFP [biannual], NMB of CHF 100,000; Switzerland, 2025). Graph is centered at INMB (CHF 227). Arrows indicate which strategy is favored. BSC, best supportive care; CLC, compensated liver cirrhosis; AFP: α-fetoprotein;
CHF: Confoederatio Helvetica franc; CLC: compensated liver cirrhosis; GAAD: gender (biological sex), age, AFP, PIVKA-II; HCC: hepatocellular carcinoma; INMB: incremental net monetary benefit; NMB: net monetary benefit; QoL: quality of life; RFA: radiofrequency thermal ablation; US: ultrasound.
*modifies more than one variable (early and late estimates).



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