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# Evaluating a population-based screening programme for early detection of liver fibrosis and cirrhosis in primary care in Germany: a cost assessment study

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## ABSTRACT

**Objectives** Structured Early detection of Asymptomatic Liver fibrosis and cirrhosis (SEAL) is a population-based screening programme using non-invasive tests for the early detection of liver fibrosis. This study evaluates the cost implications if the SEAL programme were to be implemented in routine care in Germany.

**Design** This study models cost differences with and without the SEAL screening programme. We regress costs of care on patient characteristics (age, comorbidities, sex, liver diseases, liver cancer and liver fibrosis and cirrhosis (LCI) stage) using statutory health insurance (SHI) data from routine care patients with LCI (n=4177). Based on these results, we predict per-patient costs for the patients newly diagnosed with LCI by SEAL (n=45). Costs with and without screening are estimated using patient age and LCI stage distributions from either SEAL or routine care.

**Setting** SEAL was conducted in two German states. Initial screening was performed by patients' primary care physicians.

**Participants** Individuals insured by SHI without a prior diagnosis of LCI, eligible for Check-up 35, a general health check-up programme primarily targeting adults aged 35 and older, conducted by primary care physicians.

**Interventions** Screening via aspartate aminotransferase to platelet ratio index in primary care, for further evaluation serological diagnostics and ultrasound examinations in secondary care and specific assessment for definite diagnosis including transient elastography and liver biopsy for selected cases in tertiary care.

**Primary and secondary outcome measures** Primary outcome measures: expected 5-year cost changes for SEAL patients diagnosed with fibrosis or cirrhosis compared to costs without a screening programme. Secondary outcome measures: case mix of leading chronic liver disease and LCI stages among patients diagnosed with advanced fibrosis or cirrhosis in SEAL versus routine care without screening.

**Results** Screening leads to fewer decompensated cases at initial diagnosis (4.6% in SEAL vs 22.8% in routine care) and thus savings in the costs of care within the first years of diagnosis: total expected costs per case were €2175 lower (bias-corrected bootstrap CIs (BCI): €527 to 3734), and LCI-associated costs were reduced by €1218 (BCI: €296 to 2164). Comparing the savings to the additional costs of diagnosis (range: €1575–1726 per detected LCI case) reveals that average changes in costs with screening range from moderate savings to moderate extra costs.

**Conclusions** SEAL liver screening identifies patients in less advanced stages of LCI. If only costs were considered that are directly attributable to LCI, savings within 5 years are unlikely to fully outweigh the costs of screening. However, since this approach might miss additional LCI-related costs, SEAL appears to be cost-neutral compared with routine care when considering total healthcare costs.

**Registration number** The SEAL registration number is DRKS00013460. This study relates to its results.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ First analysis to (1) study the expected savings in costs of care due to Structured Early detection of Asymptomatic Liver fibrosis and cirrhosis screening, (2) compare them to the screening costs and (3) analyse the underlying diseases and clinical disease stages with versus without screening programme.

⇒ The analysis is based on a small number of prospectively identified index cases with short-term follow-up and hence relies on cost modelling instead of incurred individual costs.

⇒ Quantification of the range of changes in both total healthcare costs (moderate savings) and costs that are directly attributable to liver fibrosis and cirrhosis (LCI) (moderate extra costs), as the quality of data did not always allow us to unambiguously identify all LCI-associated costs.

## INTRODUCTION

In routine care, patients with cirrhosis are often only diagnosed when they already show

decompensation, which is the painful and expensive state of the disease. As earlier treatment reduces the risk of decompensation,[1 2] screening pathways can play a critical role for improving patients' health and reducing costs. To date, there is no structured liver fibrosis or cirrhosis screening programme in routine care for the general population.[3–5] Simple non-invasive surrogate tests represent potential screening tools for advanced liver disease and have been proposed as first steps in population-based screening algorithms.[6–8]

In this context, a non-invasive screening pathway using the aspartate aminotransferase (AST) to platelet ratio index (APRI) for Structured Early detection of Asymptomatic Liver cirrhosis and fibrosis (SEAL) in the general population was implemented and tested in Germany. 45 (3.8‰) of 11 859 patients screened within SEAL were diagnosed with advanced liver fibrosis or cirrhosis. A medical effectiveness evaluation provides evidence that SEAL might increase the detection rate of compensated advanced liver fibrosis and cirrhosis (LCI).[9] However, at best, the benefits of the screening should outweigh its costs.[3 10] The present study analyses whether the clinical disease stage at initial diagnosis shifts because of screening and evaluates the cost implications if the early detection programme SEAL were to be implemented into routine care. We compare screening costs to economic benefits from the perspective of the statutory health insurance (SHI). Economic benefits are defined as savings in average costs of care compared with a scenario in which fibrosis or cirrhosis diagnosis occurs in routine care. However, the SEAL study does not provide empirical data on longer-term costs. Hence, we apply a model to estimate potential changes in costs with and without screening programme.

## PATIENTS AND METHODS

### SEAL study and algorithm

SEAL was a population-based prospective cohort study in two German Federal states (Rhineland-Palatinate and Saarland (RPS)) between January 2018 and February 2021. The study investigated a non-invasive screening pathway for LCI. Participating primary care physicians (n=201) offered additional laboratory tests to participants of the Check-up 35 if insured by the major SHI 'AOK RPS' and not already diagnosed with LCI. Check-up 35 is a general health check-up programme that insurees can receive once between the ages of 18 and 34 and starting from age 35 every 3 years. (Before January 2020, insurees could receive a Check-up 35 every 2 years starting from age 35.) The Check-up 35 includes medical history, vaccination status, physical examination and laboratory tests (blood: total, low-density lipoprotein and high-density lipoprotein cholesterol, triglycerides, fasting plasma glucose and—once only—Hepatitis B surface antigen and Hepatitis C virus antibodies; urine: protein, glucose, erythrocytes, leucocytes and nitrite via urinalysis). Every year, 14–15 million adults participate in the Check-up 35 (eg, 2019: 14.7 million). The corresponding expenditures of the SHI for these check-ups amount to €571.7 million per year. The first stage of the screening involved additional collection of the serum markers alanine aminotransferase (ALT) and AST, as well as platelets. In case of elevated levels of ALT or AST, APRI>0.5 served as the decision criterion for referral to a specialist. APRI was calculated as (AST/AST upper limit of normal×100)/platelets ($10^9$/L). Because this study targets patients with advanced fibrosis or cirrhosis, the APRI cut-off serves primarily as a decision criterion for referral and hence, a low cut-off was chosen to maximise sensitivity. The APRI>0.5 criterion was based on findings in previous studies indicating its probable feasibility at low costs and its high negative predictive value in excluding cirrhosis and fibrosis.[6 7 11 12] Patients with APRI>0.5 were referred to a participating liver specialist (gastroenterologist in practice) for further evaluation of the tentatively diagnosed liver disease (eg, by serological diagnostics, ultrasound examinations). If LCI was ruled out by the liver specialist, the SEAL screening pathway was completed. After final consultation and counselling by the liver specialists, the patients were referred back to their primary care physicians. Patients with suspected or diagnosed LCI were referred to the university medical centres in Mainz, Rhineland-Palatinate or Homburg, Saarland, where definite diagnosis was ascertained via specific assessment, including transient elastography and, in selected cases, liver biopsy. The SEAL screening pathway also allowed patients to skip the secondary care specialist and directly consult the liver centre (tertiary care).

### Study populations and data

From the SEAL study population (2018–2021), we collect individual-level health and cost data from primary SEAL records and SHI. In addition, we use SHI data from Check-up 35 participants diagnosed with LCI in routine care between 2014 and 2017 without systematic liver screening. These Check-up 35 subpopulations differ with respect to the inclusion criterion concerning the timing of the check-up.

### SEAL check-up and SEAL LCI cohort

Due to the study setup, missing data were not an issue in the SEAL data. Of the 11 859 SEAL participants, 4.1% (488) showed elevated ALT or AST activities and an APRI>0.5, and 49.2% (240) of these patients visited a participating liver specialist in secondary care (179) and/or at a university liver centre (79). For most patients in whom advanced liver fibrosis or cirrhosis was excluded in secondary or tertiary care (195), the cause of elevated liver enzymes was identified by the liver specialists during the examinations conducted within SEAL. Advanced liver fibrosis or cirrhosis (stages F3/F4)[13] was diagnosed in 45 SEAL participants. Of these, 22 were diagnosed with cirrhosis sensu stricto (stage F4 only).

### SHI data

AOK RPS provided individual-level SHI data of Check-up 35 participants diagnosed with LCI between January 2013

and March 2021. The SHI data contain background characteristics and diagnoses, as well as associated costs from all care levels (primary, secondary and tertiary). In particular, the data contain fee schedule items according to the German Uniform Assessment Standard (EBM), medication data classified according to German Anatomical Therapeutic Chemical codes, diagnosis codes according to the 10th revision of the International Classification of Diseases and German Diagnosis Related Groups (G-DRGs) for inpatient stays. The supplementary material provides further details on exact operationalisations and definitions. Due to the latency in data transmission to SHI, cost data were only available until the second quarter of 2020. Since these data are the insurer's full administrative records, missing data are not an issue. If no diagnostic or cost entry is given over a certain period, this is not due to missingness but implies that no such diagnosis was made or no such service was rendered. Individuals with incomplete insurance periods were excluded from the study population.

### Control cohort

The control cohort was based on routine data from the AOK Rhineland-Palatinate/Saarland. This cohort was not based on a sample but included all adult patients from the general population (aged 35 years or older), who participated in a screening programme (Check-up 35) with their primary care physician between 2016 and 2017 (identified by fee schedule item 01732). Patients with a code for liver fibrosis or cirrhosis prior to the date of the Check-up 35 were excluded, resulting in n=348 977 individuals. During a 1-year follow-up to the Check-up 35 advanced liver fibrosis or cirrhosis (stages F3/F4) was newly diagnosed in 1016 Check-up participants. These LCI cases constitute the control cohort for empirical cost analyses.

### Routine care LCI cohort for cost modelling

The LCI cohort for cost modelling was also based on routine data from the AOK Rhineland-Palatinate/Saarland. AOK RPS provided individual-level SHI data of all their Check-up 35 participants diagnosed with advanced LCI (stages F3/F4) between 2013 and 2020. Consequently, this cohort represents the entire population of interest rather than a sample. Since the data do not contain a marker for 'initial diagnosis', we operationalise first diagnoses as a coding of fibrosis or cirrhosis after minimally four consecutive quarters without any such coding. For estimating the costs of care, we included all cases of patients *initially* diagnosed with LCI before 2018 (start of SEAL) whose underlying specific chronic liver disease (CLD) was also observed in SEAL, resulting in n=4177 cases. Thereof, n=3924 (n=3410) cases could be used for the short-term (medium and long term) cost analysis.

### Patient and public involvement

Patients and/or the public were not involved in the design, conduction, reporting or dissemination plans of this cost analysis. When planning this cost analysis, we were in dialogue with the AOK RPS regarding the availability and quality of data, which influenced the operationalisations.

### Evaluation of costs

To compare the additional costs due to screening with the cost savings due to early detection, we determine the screening costs and estimate the expected costs of care per patient diagnosed with LCI for different time horizons with and without the screening programme. We assume that the detection rate of LCI does not change compared with SEAL when liver screening is implemented into routine care, and all patients detected in a prevention programme would eventually also show up in routine care without this programme.

### Screening costs

Screening costs include costs incurred by all SEAL participants for their complete diagnostic pathway (primary care physicians, and, if applicable, secondary care specialists and/or tertiary care centres). Costs for diagnosis are identified based on theoretical unit costs and empirical SHI billing data of SEAL participants. In primary care, SEAL built on an existing screening programme (Check-up 35) to which additional liver tests were added. The additional costs for screening are caused by the determination of the blood markers ALT, AST and platelets, as well as (additional) abdominal ultrasound examinations. Corresponding costs for the blood values were determined based on theoretical unit costs according to EBM. In contrast, for secondary and tertiary care, costs were derived from empirical data. In secondary care, screening costs occur, among others, for serological diagnostics and abdominal ultrasound examinations. All diagnostic services billed by liver specialists from the check-up quarter until the quarter of confirmed or excluded diagnosis were included. In tertiary care, university liver centres receive a flat rate compensation per outpatient (per quarter), and additional costs occur in case of a liver biopsy (eg, inpatient stay). Total screening costs are strongly influenced by liver biopsy practices, ie, type and frequency. Within SEAL, most biopsies were performed mini-laparoscopically, but this (expensive) diagnostic procedure is not representative. We thus assume biopsies to be performed percutaneously (G-DRG H62B). In many cases, a liver biopsy is not necessary to establish the diagnosis of cirrhosis. In the light of uncertainty concerning biopsy rates, results are reported for different weighted-average biopsy rates at the two liver centres (Mainz and Homburg): 3.54% for routine care and 13.92% for SEAL. We believe it is reasonable to expect biopsies to be performed in 3–4% of screening participants consulting a liver centre if the screening were to be rolled out in routine care. The high biopsy rate observed in SEAL is probably specific to its study character. For further details on screening costs, we refer to Ortner *et al*.[14] We report the screening costs as average costs per detected LCI case,

Table 1 Stages of disease based on D'Amico *et al*[15]

| Stage of disease | Stage of fibrosis | Characteristics |
|---|---|---|
| Stage 0 or 1 | F3 or F4; compensated | Complication free |
| Stage 2 | F4; compensated | Non-bleeding varices |
| Stage 3 | F4; decompensated | Ascites, hepatic encephalopathy or jaundice |
| Stage 4 | F4; decompensated | Bleeding varices |

based on the referral and attendance rates observed in SEAL.

### Costs of care

We collect empirical data on actual costs of care for fibrosis and cirrhosis cases diagnosed within the SEAL LCI cohort and the control cohort. Due to the prospective study design, these empirical cost data are only available for a subgroup of SEAL LCI cases and only for the short term. Hence, we fully model the costs of care in our main analyses and predict costs for all SEAL patients diagnosed with LCI. In particular, we estimate the difference in per-patient costs with versus without a liver screening programme. As the analysis requires the leading CLD (operationalisation: see online supplemental Table 1), and as progressive familial intrahepatic cholestasis cannot be identified in the SHI data, one SEAL patient was excluded from this analysis, resulting in a total of 44 patients. We assume that without a liver screening programme, an equal number of patients would be diagnosed, however, at a later stage of disease and at an older age. We estimate the resulting difference in costs for three different time periods (short-term, medium term and long term, corresponding to the quarter of initial diagnosis plus first quarter thereafter, 1 year thereafter and 5 years thereafter, respectively). We differentiate between costs that can be unambiguously attributed to LCI and total SHI costs.

We first set out to obtain the best possible estimation of per-patient care costs if SEAL were to be rolled out in routine care. Actual costs from the SEAL study are only available for a small subgroup with short follow-up. As the variance in costs is very high, estimating costs based on this small sample would lead to inaccuracy. Hence, we use routine care SHI data to regress costs of care on patient characteristics (age, comorbidities, sex, leading CLD, liver cancer and LCI stage at diagnosis (as defined in table 1).[15] Using these results, we predict per-patient costs for future treatment and surveillance for each of the 44 patients identified in SEAL based on these same characteristics. Next, we estimate what the costs of the same patients would have been *without* a screening programme. We follow the same procedure, but do not regard age and LCI stage. This implies that we assume that age and LCI stage of the 44 patients would have corresponded to their distributions in the population rather than to those observed in the screening programme. figure 1 illustrates the cost estimation procedure as described. As a robustness check, to address lead-time bias at least in part, we in addition control for age and assume only the LCI stage to correspond to the population distribution.

Since costs of care do not occur for every individual in each period, a hurdle model was chosen for the above-mentioned regressions: in the first stage that uses logit regression, the probability is estimated that non-zero costs will occur for a given patient; in the second stage, only patients with non-zero costs are considered. Due to the right skewness of the cost distributions, we chose

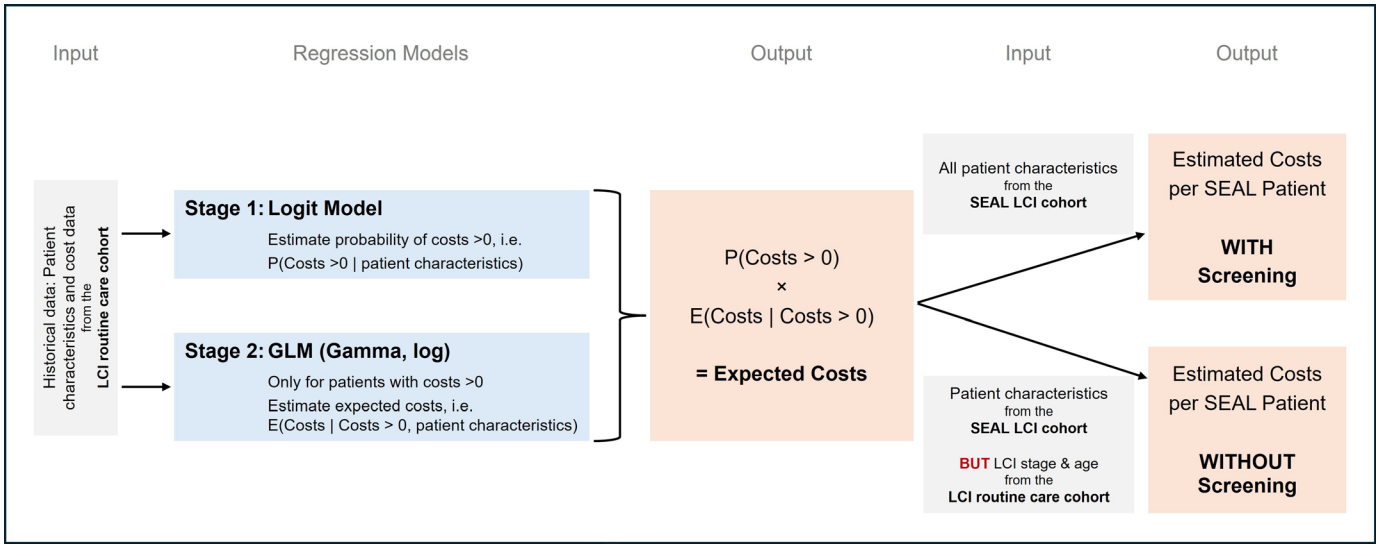


Figure 1 Cost estimation procedure. Costs of care are regressed on patient characteristics from routine data using a two-step hurdle model. Based on these results, costs are predicted twice for the SEAL patients, assuming screening and no screening. GLM, generalised linear model; LCI, liver fibrosis and cirrhosis; SEAL, Structured Early detection of Asymptomatic Liver fibrosis and cirrhosis.

a generalised linear model, which is based on a gamma distribution and uses a log-link function:

$$log\left(E\left[Costs_i|Costs_i>0\right]\right)=\beta_0+CLD_i'\gamma+\beta_1 LCI\_Stage_i+\beta_2 Age_i+\beta_3 Sex_i+X_i'\delta+u_i$$

in which CLD is a set of dummy variables indicating the leading CLD (alcohol-associated or metabolic dysfunction-associated steatotic liver disease, autoimmune hepatitis, malignant liver tumour, hepatitis C, hepatitis B, drug-induced liver injury, right heart failure, haemochromatosis) and X is a set of dummy variables indicating the presence of comorbidities (arterial hypertension, obesity, type 2 diabetes, insulin use among type 2 diabetes, hyperlipidaemia). The logit regressions in the first stage include the same set of covariates. To determine the average expected costs for a patient, the probability of occurrence of non-zero costs from the first stage is multiplied by the average predicted costs from the second stage. Costs were estimated separately with and without screening. When estimating costs without screening, age and LCI stage were not included as covariates. The model is estimated separately for the following dependent cost variables, capturing different categories of subsequent costs of care: total SHI costs, total LCI-associated costs, outpatient practice, specialist outpatient care (internist/gastroenterologist), outpatient clinics, inpatient clinical stays, LCI-associated inpatient clinical stays, medication costs, LCI-associated medication costs and other costs.

To account for the time effect that costs of treatment and surveillance partially occur some time after diagnosis, in addition to the undiscounted costs, we considered their present values based on a discount rate of 4% per year.[16] Potential future changes in costs (eg, due to price increases) were not considered, as no reasonable estimates could be made.

### Statistical analyses for between-group comparisons

We compared the characteristics and costs of patients diagnosed through SEAL with those diagnosed in routine care. Differences were analysed using t-tests for continuous variables (age and costs) and $\chi^2$-tests for most categorical variables. Due to small expected cell counts, Fisher's exact tests were applied to compare insulin use among individuals with type 2 diabetes and the overall distribution of CLD, irrespective of stage. To assess differences in LCI severity (ie, disease stage), a Wilcoxon rank-sum test was performed. Given the small sample size and non-normal distribution, differences in empirical costs between the SEAL LCI and the control cohort were assessed using the Wilcoxon rank-sum test. Differences in modelled costs with and without screening were analysed using t-tests based on bootstrapping (B=2000 replications) and the assumption of normal distribution. In addition, 95% bootstrap CIs (BCIs) for the mean differences (ie, expected savings) were calculated.

## RESULTS

### Screening results in the detection of earlier liver disease stages than routine care

Table 2 provides the characteristics of patients diagnosed with LCI (F3/F4) in the SEAL screening programme versus patients from the full routine care LCI cohort. The mean age of SEAL patients was lower (60 vs 65 years), and SEAL patients were less likely to be diagnosed with cirrhosis sensu stricto or to have arterial hypertension. While the first two differences can likely be explained by screening-based detection, we account for differences in arterial hypertension in our cost analysis. Table 3 presents the case mix of CLD and stages of diseases. While the overall CLD distribution (irrespective of stage) differs significantly (p=0.01) between the screening and routine care cohorts, the most frequent leading CLD in both

**Table 2** Characteristics of patients diagnosed with advanced liver fibrosis or cirrhosis (F3/F4)

| | SEAL n=44 | Routine care n=4.177 | Group comparison (p values) |
|---|---|---|---|
| Age (in years) | 60.0<br>SD: 12.1; min: 36; max: 83 | 64.8<br>SD: 13.2; min: 14, max:106 | 0.016* |
| Women | 38.6% | 37.1% | 0.837† |
| Cirrhosis (F4 only) | 47.7% | 82.8% | <0.001† |
| Obesity | 52.3% | 38.5% | 0.062† |
| Type 2 diabetes | 43.2% | 37.2% | 0.417† |
| Insulin-requiring type 2 diabetes | 6.8% | 11.1% | 0.813‡ |
| Hyperlipidaemia | 43.2% | 38.1% | 0.493† |
| Arterial hypertension | 45.5% | 65.8% | 0.005† |

*t-test.
†$\chi^2$-test.
‡Fisher's exact test.
SEAL, Structured Early detection of Asymptomatic Liver fibrosis and cirrhosis.

Table 3 LCI stages and leading CLD in the SEAL LCI and the routine care LCI cohorts

| | | ALD or MASLD | Autoimmune hepatitis | Malignant liver tumour | Chronic viral hepatitis (C) | Drug-induced liver injury | Right heart failure | Haemo-chromatosis | Total |
|---|---|---|---|---|---|---|---|---|---|
| Stage 1 | SEAL | 55% | 9% | 9% | 7% (5%) | 5% | 5% | 0% | **89%** |
| | Rountine Care | 50% | 1% | 3% | 8% (6%) | 5% | 5% | 1% | **73%** |
| Stage 2 | SEAL | 2% | 0% | 0% | 2% (2%) | 0% | 0% | 2% | **7%** |
| | Rountine Care | 3% | 0% | <1% | 1% (1%) | <1% | <1% | 0% | **4%** |
| Stage 3 | SEAL | 5% | 0% | 0% | 0% (0%) | 0% | 0% | 0% | **5%** |
| | Rountine Care | 12% | <1% | 2% | 2% (1%) | 1% | 5% | <1% | **22%** |
| Stage 4 | SEAL | 0% | 0% | 0% | 0% (0%) | 0% | 0% | 0% | **0%** |
| | Rountine Care | <1% | 0% | 0% | <1% (<1%) | 0% | <1% | 0% | **1%** |
| **Total** | SEAL | **61%** | **9%** | **9%** | **9% (7%)** | **5%** | **5%** | **2%** | **100%** |
| | Rountine Care | **66%** | **1%** | **4%** | **11% (8%)** | **6%** | **10%** | **1%** | **100%** |

Casemix of LCI stages and leading CLD in patients diagnosed with advanced fibrosis or cirrhosis in SEAL (n=44) and in routine care (n=4177). ALD, alcohol-associated liver disease ; CLD, chronic liver disease; LCI, liver fibrosis and cirrhosis; MASLD, metabolic dysfunction-associated steatotic liver disease; SEAL, Structured Early detection of Asymptomatic Liver fibrosis and cirrhosis.

was metabolic dysfunction-associated and/or alcohol-associated fatty liver disease, which occurred in more than 60% of patients. Within the SEAL programme, it was followed by chronic viral hepatitis (9%), malignant liver tumour (9%) and autoimmune hepatitis (9%).

Importantly, for LCI severity, there was a significant shift of disease stage (p=0.004). The portion of patients with decompensated cirrhosis at initial diagnosis (disease stages 3 or 4) was considerably lower in SEAL (5%) than in routine care (23%). Whereas the percentage of patients with decompensated cirrhosis in disease stage 4 at initial diagnosis was low in both routine care and SEAL, the positive effect was particularly evident in the different frequencies of disease stage 3 (table 3). Hence, SEAL is indeed suitable for early detection. Note that costs of cirrhosis are driven by complications resulting from decompensation (online supplemental Table 2). In this light, despite additional costs for screening, surveillance and earlier treatment, SEAL may prove to be cost-effective in the longer term, as long as progression of cirrhosis can be slowed down and complications are less likely to occur by controlling or healing the underlying CLD.

## Screening costs per individual correspond to a small share of the check-up budget

The average additional screening costs for the complete diagnostic SEAL pathway range from €5.98 to 6.55 *per screened individual* (online supplemental Table 3), depending on the assumed rate of (percutaneous) liver biopsies (3.5% vs 13.9%). This corresponds to 15.4–16.8% of the current Check-up 35 reimbursement in Germany (€38.90). The average costs *per detected LCI case* range from €1575 to 1726. Of note, surveillance costs for outpatients with cirrhosis in tertiary care in Germany range from €290 to 384 per year only, based on the SHI rates for university hospitals (2020) and a consultation every 6 months. For more detailed information, see Ortner *et al*.[14]

## Empirical cost analysis provides preliminary evidence for cost reduction

Empirical billing data in the subgroup of SEAL LCI cases for whom these data were provided (n=28) suggested that total SHI costs of the SEAL screening cohort, which amount on average to €7173, might be lower than those of the control cohort (p=0.013). Of note, the difference manifested in lower inpatient costs (p<0.001). As expected for screening, costs in outpatient clinics are higher in SEAL as compared with the control cohort (p<0.001). However, detailed analyses are not possible due to the small sample size (n=28) and the short-term follow-up. In addition, this short-term effect might be attributable to lead-time bias, although the control cohort theoretically should also diagnose early fibrosis and cirrhosis because it was based on participants of the German prevention programme (Check-up 35), although non-liver-specific—in contrast to data from general routine care. Due to these limitations, we embarked on fully modelling to assess the costs for all SEAL LCI cases in the short-term medium term and long term.

## Modelling costs of care demonstrates savings in total long-term costs per patient identified by screening

### Short-term costs

Table 4 summarises the average expected costs of treatment and surveillance per patient diagnosed with LCI in the quarter of initial diagnosis plus the first quarter thereafter—once with and once without a liver screening programme. Table 4 further contains the bootstrap 95% BCI for the expected savings in costs of care and the normal-based bootstrapped p values of the difference in costs being equal to zero. On average, total predicted

Table 4 Modelling of average expected costs for the short-term treatment and surveillance for SEAL patients diagnosed with fibrosis or cirrhosis (in €)

| | Costs | | Cost savings with screening programme | | | |
|---|---|---|---|---|---|---|
| | Without screening programme | With screening programme | Expected savings (mean) | Normal-based p value | 95% bias-corrected bootstrap CI | |
| **Total SHI costs*** | **9959.77** | **8890.49** | **1069.28** | **<0.001** | **539.07** | **1528.87** |
| **Thereof LCI associated** | **3397.78** | **3169.61** | **228.17** | **0.401** | **−304.62** | **760.95** |
| Outpatient practice | 594.21 | 588.99 | 5.22 | 0.430 | −7.53 | 18.27 |
| Thereof internist or gastroenterologist | 33.67 | 35.49 | −1.82 | 0.002 | −2.95 | −0.72 |
| Outpatient clinics | 39.83 | 42.08 | −2.25 | 0.006 | −3.84 | −0.57 |
| Inpatient clinical stays | 6724.44 | 5832.71 | 891.73 | <0.001 | 429.10 | 1232.97 |
| Thereof LCI associated | 1547.53 | 987.39 | 560.14 | <0.001 | 298.09 | 779.66 |
| Medication costs* | 2369.05 | 2210.95 | 158.10 | 0.197 | −53.81 | 417.14 |
| Thereof LCI associated | 1816.58 | 2146.73 | −330.15 | 0.151 | −837.81 | 51.37 |
| Others | 232.23 | 215.76 | 16.47 | 0.918 | −289.74 | 328.70 |

Short-term, that is, quarter of initial diagnosis+subsequent quarter; costs, that is, costs of care; cost estimation using a two-stage model: stage 1: logistic regression; stage 2: generalised linear model with gamma distribution and log-link function; data basis for price structure: SHI data (n=3924). Prognosis under the assumption of characteristics being equal to those of the SEAL patients diagnosed with fibrosis (n=44); 95% bias-corrected bootstrap CI for mean difference in costs; replications B=2000.
*Adjusted medication costs for hepatitis C.
LCI, liver fibrosis and cirrhosis; SEAL, Structured Early detection of Asymptomatic Liver fibrosis and cirrhosis; SHI, statutory health insurance.

SHI costs in the short-term were slightly lower with than without screening programme (€8890 vs 9960; p<0.001; BCI: €539 to 1529). This effect was also reflected in the costs that could specifically be attributed to LCI, though not statistically significant (€3170 vs 3398; p=0.401; BCI: €−305 to 761). The strongest reduction is attained in costs for inpatient hospital stays, where both total costs and costs that can specifically be attributed to LCI-associated decrease significantly. This is intuitive, as LCI-associated inpatient stays most often occur due to complications, which should occur less frequently in patients identified in a screening programme.

### Medium-term costs

In the medium term (quarter of initial diagnosis plus 1 year afterwards), estimated total SHI, inpatient total and LCI-associated costs were significantly lower with the liver screening programme (online supplemental Table 4). For instance, the expected LCI-associated costs were on average €542 lower (€3993 vs 4535; p=0.034; BCI: €32 to 1050), driven by savings in costs for LCI-associated inpatient stays (€1450 vs 1967; p=0.002; BCI: €175 to 820). In contrast to that, as in the short-term analysis, costs for medication did not differ.

### Long-term costs

The estimated long-term costs indicate the average financial burden to the SHI within the first 5 years after the initial diagnosis of LCI. Table 5 shows the results of the corresponding cost estimations with and without liver screening. Without screening, the expected total and LCI-associated SHI costs were €53 502 and €7770 on average, respectively. There is evidence for a significant decrease of these 5-year costs in the presence of a liver screening programme: total expected costs were €2175 lower (€51 327 vs 53 502; p=0.009; BCI: €527 to 3734) and LCI-associated total costs were reduced by €1218 (15.7%) (€6552 vs 7770; p=0.010; BCI: €296 to 2164). In particular, the expected average LCI-associated inpatient costs were significantly lower with a screening programme (€3094 vs 4186; p=0.008; BCI: €254 to 1904).

To address lead-time bias, at least in part, we also controlled for patient age in our model (online supplemental Table 5): In this case, expected savings are moderately lower, but more significant. Expected reduction in total costs on average amounts to €1623 (p=0.005; BCI: 350 to 2696) and to €1108 for LCI-associated costs (p=0.003; BIC: 282 to 1736), which is again mainly driven by expected savings in LCI-associated inpatient costs (€978; p=0.005; BCI: 182 to 1558). LCI-associated costs for medication did differ only when taking age into account (p<0.001; BCI: 66.52 to 208.63).

### Liver screening is no less than cost-neutral

The average additional cost of diagnosis per detected LCI case ranges from €1575 to 1726 for biopsy rates of 3.54% and 13.92%, respectively. Comparing these additional costs of diagnosis to the expected 5-year savings in total SHI costs of €2175 indicates that the screening

Table 5 Modelling of average expected costs for the long-term treatment and surveillance for SEAL patients diagnosed with fibrosis or cirrhosis (in €)

| | Costs | | Cost savings with screening programme | | | |
|---|---|---|---|---|---|---|
| | Without screening programme | With screening programme | Expected savings (mean) | Normal-based p value | 95% bias-corrected bootstrap CI | |
| **Total SHI costs*** | **53 502.12** | **51 326.90** | **2175.22** | **0.009** | **526.83** | **3733.88** |
| **Thereof LCI associated** | **7769.97** | **6552.08** | **1217.89** | **0.010** | **295.88** | **2163.66** |
| Outpatient practice | 5553.38 | 5379.73 | 173.65 | 0.116 | −35.93 | 394.18 |
| Thereof internist or gastroenterologist | 181.01 | 187.30 | −6.29 | 0.212 | −16.05 | 3.79 |
| Outpatient clinics | 454.91 | 450.18 | 4.73 | 0.829 | −34.63 | 51.94 |
| Inpatient clinical stays | 25 764.6 | 24 714.49 | 1050.11 | 0.027 | 55.78 | 1937.88 |
| Thereof LCI associated | 4186.26 | 3094.18 | 1092.08 | 0.008 | 253.79 | 1904.17 |
| Medication costs* | 14 677.97 | 13 841.63 | 836.34 | 0.061 | 43.19 | 1781.25 |
| Thereof LCI associated | 3402.70 | 3270.60 | 132.10 | 0.453 | −239.76 | 442.64 |
| Others | 7051.26 | 6940.87 | 110.39 | 0.773 | −680.82 | 818.73 |

Long-term, that is, quarter of initial diagnosis+subsequent 5 years; costs, that is, costs of care; Cumulated 5-year costs resulting from a year-by-year cost estimation using a two-stage model: stage 1: logistic regression; stage 2: generalised linear model with gamma distribution and log-link function; data basis for price structure: SHI data (n=3410). Prognosis under the assumption of characteristics being equal to those of the SEAL patients diagnosed with fibrosis (n=44); bootstrap CI for mean difference in costs; replications B=2000.
*Adjusted medication costs for hepatitis C.
LCI, liver fibrosis and cirrhosis; SEAL, Structured Early detection of Asymptomatic Liver fibrosis and cirrhosis; SHI, statutory health insurance.

programme is likely cost-neutral with expected cost-saving of €600 (95% BCI: −1048 to 2159) (€449 (BCI: −1199 to 2008)). These numbers do not yet consider discounting. For a discount rate of 4%, expected cost-savings amount to €398 (BCI: −1097 to 1810) (€247; BCI: −1249 to 1658)).

For a more conservative analysis, the costs of diagnosis were compared with the expected savings in LCI-associated costs only, which were €1218 on average. This comparison suggested that SEAL increases costs within the first 5 years (expected savings: €−357; BCI: −1279 to 589) (€−508; BCI: −1430 to 438). Assuming a discount rate of 4%, expected extra costs amount to €471 (BCI: −1306 to 388) (€−622; BCI: −1458 to 236). To justify these expected extra costs, SEAL would need to improve health outcomes by at least 0.016 quality-adjusted life years (QALYs) (0.009 QALYs) to be considered cost-effective at a threshold of €30 000 (€50 000) per QALY gained (online supplemental Table 6).

In summary, the costs of liver fibrosis screening depend on which costs are taken into account. If only costs are considered for which it was specifically possible to attribute them to LCI, then screening seems unlikely to be cost-neutral. However, if total SHI costs are considered, then the screening programme appears to be cost-neutral.

## DISCUSSION

Early detection of LCI using a non-invasive screening pathway with APRI was tested as an additional component to the existing general health check-up programme in Germany (Check-up 35). Our comparative analysis of the case mix of clinical disease stages at the time of initial diagnosis revealed that patients diagnosed with LCI in SEAL have fewer and less severe complications than in the routine care LCI cohort. Following this evidence, combined with that by Labenz *et al*, the SEAL algorithm appears suitable for the early detection of LCI. Considering the evidence of the medical effectiveness of this SEAL programme in terms of LCI detection rates,[9] the question of its economic balance of costs arose. As reported previously,[14] screening with the SEAL pathway is feasible at low screening costs. The present study entails a full cost evaluation of SEAL by including the subsequent treatment and surveillance costs.

This analysis revealed that earlier detection probably leads to savings in costs of care within the first years of diagnosis. However, we could neither prove nor rule out the cost-neutrality of SEAL when taking the screening costs into account. In fact, the evaluation critically depends on the type of costs considered (ie, total SHI costs vs LCI-associated costs only). When focusing on savings in total costs, SEAL appears to be cost-neutral within a 5-year timeframe with a probability of 76.4% (68.4% for a discount rate of 4%). Meanwhile, in a stricter sense, for savings that can specifically be attributed to LCI, SEAL does not seem to be cost-neutral within a 5-year time period (probability less than 25%). However, it is possible that SEAL would also be cost-neutral in this stricter sense when considering a longer-term follow-up (eg, 10 or 20 years). Furthermore, it should be noted that the costs that we could attribute to LCI do not cover all LCI-associated

costs, as we were unable to extract costs from some healthcare providers, such as costs for specific laboratory tests or outpatient treatment in clinics. Hence, the true LCI-associated costs and savings are likely to be higher than captured. Moreover, the observed reduction in total SHI costs potentially includes health conditions that are indirectly related to LCI. Hence, the present calculations will have missed potential cost-savings occurring within and after 5 years.

In addition, it should be noted that screening results may lead to behavioural changes among participants. A negative screening result in primary care might cause patients to delay further consultation and exhibit health-risk behaviours (eg, increased alcohol consumption), which affects cost-effectiveness by underestimating screening costs. However, in our setting, we believe that the effect of adding two laboratory parameters to the Check-up 35 tends to be small: patients underwent a comprehensive evaluation, making it unlikely that physicians emphasised liver-specific findings to such an extent that it would induce additional behavioural changes concerning liver health. Negative screening also occurred at the second level: In total, 195 out of 240 patients (81.3%) who visited a liver specialist did not have LCI. The realisation that they had abnormal liver function tests plus the consultation with a liver specialist communicating the potential cause of these findings might lead patients at risk of developing LCI to improve their health behaviour, and this would lead to additional cost savings. Overall, 248 participants were referred to a liver specialist but did not show up. The referral to a liver specialist may have increased their awareness of potentially poor liver health and promoted lifestyle changes. In fact, such positive effects of liver screening have been reported recently.[17] Again, this could lead to cost savings not captured here.

There were some limitations to this study. First, the cost evaluation is based on a small number of prospectively identified index cases with short follow-up. As we could not expand the sample size or recruit validation cohorts, the assessment relies on cost modelling instead of incurred individual costs. We have adjusted for changes in medication costs for hepatitis C; however, we cannot rule out potential other cost changes. Second, the quality of the SHI data did not allow us to unambiguously identify LCI and their associated costs. Third, as in most prevention programme evaluations, lead-time bias issues cannot be completely ruled out. Patients who are detected earlier might cause costs over a longer time period if the early detection does not reduce fibrosis progression or the occurrence of cirrhosis complications. However, due to our modelling approach and robustness check, we are confident that this would only be a critical issue if earlier detection had no effect on disease progression at all. Fourth, we assumed that liver biopsies in routine care are performed percutaneously. In settings in which biopsies are performed (mini-)laparoscopically, screening costs would be considerably higher and cost-neutrality less likely. This underlines the need to provide follow-up of screening results with diagnostic algorithms that are sufficient, appropriate and economical. Such a screening for CLDs not only has the potential to change the paradigm of how and when these diseases are diagnosed and treated,[18] but at best could be implemented at little extra costs or even be cost-neutral. Still, questions regarding cost-effectiveness, targeting, as well as implementation and intervention strategies remain, which further research needs to address. Taking this into account and to enable a more comprehensive cost evaluation, we recommend further research on population-based screening for LCI using non-invasive testing, ideally with longer follow-up periods, as well as the inclusion of patient-reported outcomes (such as QALYs) and behavioural data.

## CONCLUSIONS

Taken together, our findings suggest that liver screening is worth it, and even when considering a small increase in LCI-associated costs per patient, this does not appear economically substantial, since it would correspond to approximately 2% of the annual health expenditures of the SHI for Check-Up 35 only. Clearly, the earlier detection of LCI is expected to improve the patients' long-term health and quality of life,[1 2 19–22] and patient-reported outcomes could be included in a more holistic health economic evaluation. In conclusion, the evaluation of SEAL indicates that screening for CLD has not only the potential to change the paradigm from the current scenario of late diagnosis with complications and high costs to early diagnosis and cure of specific CLD but to be cost-neutral or even cost-saving in the long term.

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