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Diagnostics Assessment Programme

FibroScan for assessing liver fibrosis and cirrhosis in primary or community care

The following documents are made available to stakeholders:

1. The **Stakeholder comments on the Diagnostics Consultation Document and responses (first consultation)** are available via hyperlinks to the webpage.

2. **Additional evidence and analysis submitted by Echosens**

3. **Critique of additional analysis provided by Echosens** prepared by Newcastle External Assessment Centre (EAC)

4. **Erratum to EAC critique of additional analysis**

5. **Further additional analyses submitted by Echosens**

6. **EAC's report on further additional Echosens analyses** prepared by Newcastle External Assessment Centre

7. **Factual Accuracy Check of EAC's report by Echosens, and EAG response** prepared by Newcastle External Assessment Centre

8. **Stakeholder comments on the Diagnostics Consultation Document and responses (second consultation)**

FibroScan for assessing liver fibrosis and cirrhosis in primary or community care [GID-MT562]

Medical Technologies Evaluation Programme (MTEP)

Additional Manufacturer Evidence and Analyses

Submitted by Echosens

National Institute for Health and Care Excellence

Submitted 9 March 2022

Contents

Introduction

Echosens supports the opportunity to present additional analyses recommended by NICE to reduce the uncertainty around the cost comparison of FibroScan delivered outside secondary care compared to FibroScan delivered inside secondary care and continues to be committed to provide support for the decision-making processes.

This additional analysis addresses the concerns around:

i. What happens after FibroScan fails
ii. Cost of FibroScan in secondary care
iii. Alternative costing model for FibroScan outside of secondary care
iv. Impact on long-term costs

Methods and revised inputs

What happens after FibroScan fails

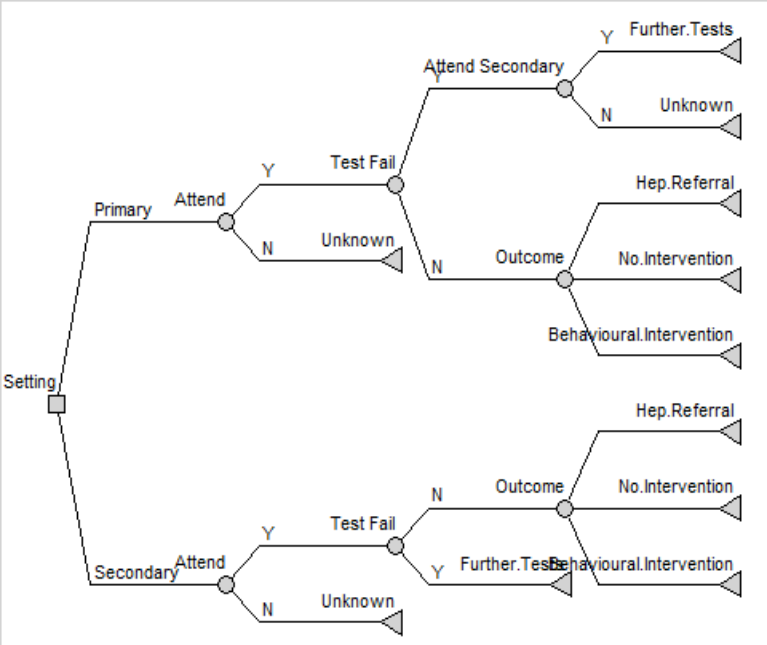
In the original Company model, if the patient attends the scan, then for a small proportion of patients (5%) the scan fails to produce results. For these patients, any diagnosis of liver disease was assumed to be missed and remained untreated.

The EAC considered this assumption to be incorrect. Feedback from clinical experts indicated that if FibroScan failed in primary care, a further fibrosis test, or secondary or specialist care should be sought. Therefore, the EAC applied a cost of “further tests” to both arms, where FibroScan has failed. The cost used by the EAC was set equivalent to the bundled HRG code RD48Z for ultrasound elastography (£43.93)[1], which they considered to reflect non-FibroScan ultrasound elastography or an appropriate average between a cheaper blood test or more expensive imaging modalities.

The EAC model assumes that, if FibroScan fails to produce results in secondary care, 100% of patients receive ‘further tests’, whereas if patients have a failed scan outside secondary care, then only the proportion of patients attending secondary care receive further tests. This is demonstrated by the decision tree in Figure 1, which implies that further tests are performed in the same secondary care

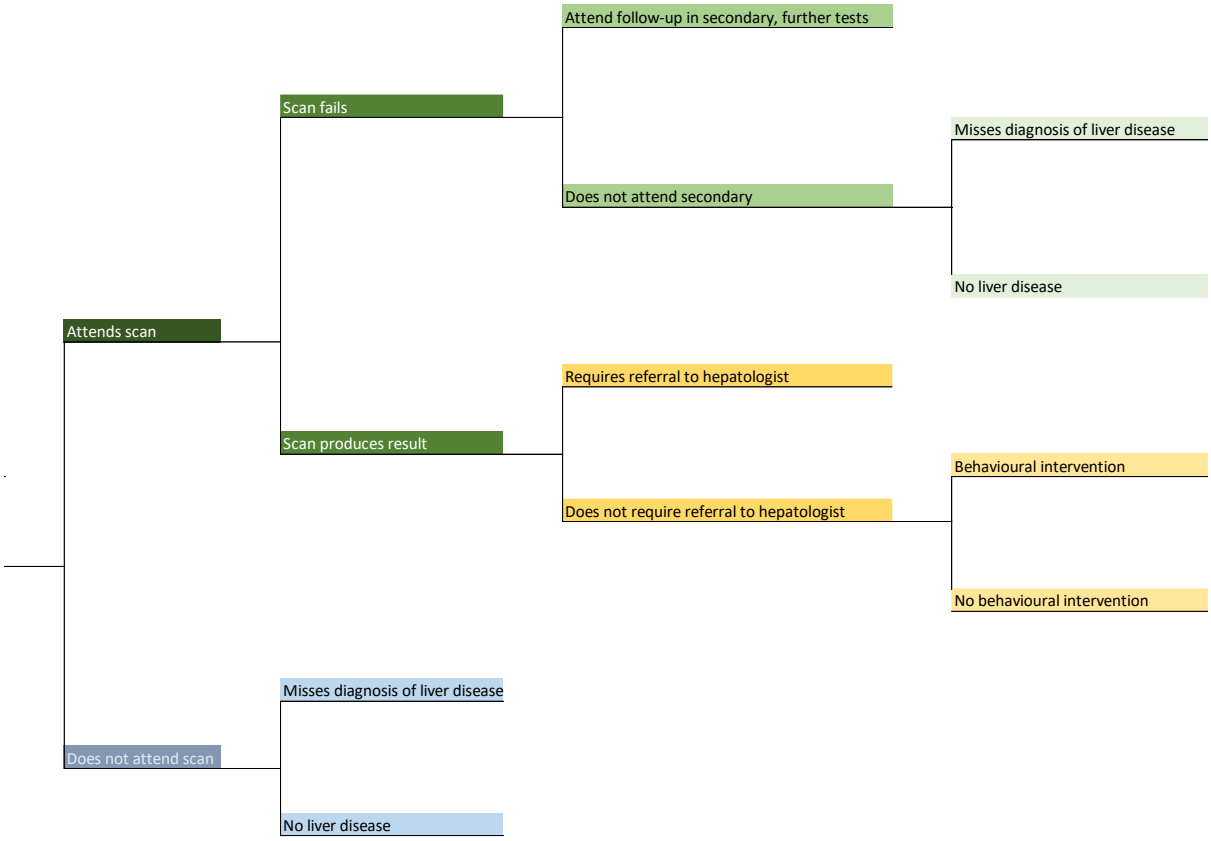
attendance for patients who have a scan that fails to produce a result in secondary care.

Figure 1 Decision tree for FibroScan (EAC base case model)



In response to this comment, the Company has added further tests after scan failure into the model structure as a scenario analysis (see Figure 2). This structure is applied to both patients receiving FibroScan inside and outside of secondary care. As the Company is uncertain that the further tests after scan failure in secondary care would be received in the same attendance, the probability of attending secondary care for the further tests in the secondary care scan arm is tested at 100% (i.e., equivalent to the EAC model) and 80% (the same probability used for attending secondary care in the first instance) in a sensitivity analysis.

Figure 2 Revised company structure for scenario analysis



Cost of FibroScan in secondary care

In the original Company model, staff time to interpret the scan result (non-Consultant led face-to-face appointment in hepatology department) was included with the HRG bundled cost (RD48Z).[1]

The EAC disagreed with this addition of staff time and claimed the time to evaluate scan is already incorporated within the HRG bundled cost. In response to this comment, the Company has provided an option to remove these additional staff time costs from the total cost of FibroScan in secondary care.

The EAC also tested a weighted average HRG cost for ultrasound elastography of £61.98. The Company have added a scenario using this cost in the results.

The EAC calculate the cost of a missed appointment in secondary or specialist care as the cost of nurse time if the appointment had been attended, which the EAC

considered to be £12.50 (15 minutes at £50 per hour PSSRU Unit Costs 2020; Hospital based nurse, band 6).[2] The Company has therefore also provided an option to apply the cost of nurse time to the HRG cost as an alternative cost of interpreting the scan result, as the Company does not consider the HRG code for ultrasound elastography alone to be reflective of performing and interpreting FibroScan in secondary care.

Alternative costing model for FibroScan outside of secondary care

In the original Company model, the cost of FibroScan outside secondary care was based on a Pay Per Exam business model, at a price of £58 per scan (excluding VAT). Under this model there would be no upfront cost for the machine, and the price captured training, installation, service and calibration costs, hardware, both probes M and XL and CAP/"SmartExam".

In clinical practice, some clinical commissioning groups will opt for the Pay Per Exam model, whereas others may choose to buy the machine outright. To reflect this, the Company has updated the economic model to include the option to calculate the cost per scan using a micro-costing approach, when the FibroScan equipment is purchased outright. Costs and resource use for this approach are provided in Table 1.

Table 1 FibroScan costs if machine is purchased

Item	**Cost**	**Number required over machine lifetime***
FibroScan 430 Mini+	£48,000	1
Additional probes	£16,700	1
Cost of CAP/SmartExam software	£18,500	1
Cost of 6-year Serenity service contract[†]	£28,560	1
Training costs (annual cost)	£1,180	7
Total	£120,020	

* Echosens guarantees the specification and performance characteristics of the FibroScan device for seven years, provided that all necessary precautions for use and maintenance have been taken in accordance with the recommendations of the user manuals provided to customers; †The lifetime of the machine is covered by an initial 12 month warranty + 6 years cover

Given the lifetime of the machine is 7 years (as stated in the instructions for use manual, provided with clinical evidence section), and the Southampton CCG group performed 500 scans in a year, this results in an average cost per scan of £34.29. The cost of a nurse's time to perform the scan is added to this cost for the total cost of FibroScan outside of secondary care (£10.50, calculated by £42/hour for Nurse (GP practice) incl. qualifications from the PSSRU 2020, multiplied by 0.25 to reflect 15 minutes)[2], making the total cost per a scan performed outside of secondary care £44.79.

Long-term time horizon

The time horizon of the original Company model was 1 year, which captures the FibroScan test in both settings, and differences in care pathway following the scan which are relevant to the decision problem. This may underestimate the true cost savings of performing Fibroscan outside secondary care, as the higher attendance rates to scan appointments leads to a lower rate of missed diagnosis of liver disease, which is expected to avoid long-term costs associated with undiagnosed liver disease being allowed to progress.

Due to the uncertainty and heterogeneity with patient pathways in the long term, long-term costs were not originally modelled. The EAC agreed that this was the most appropriate approach. The committee concluded that a longer time horizon considered in the model would have been preferable to help assess impact of the test. Based on this comment, the Company have added the ability to look at a 5-year time horizon into the model.

A 5-year time horizon has been incorporated by applying additional costs to the end of each branch in the decision tree, as outlined below.

For 'Misses diagnosis of liver disease' and 'Requiring referral to hepatologist'

The proportion of patients across three stages of liver disease was calculated and an annual cost of each stage was applied. These proportions were calculated using the liver stage by aetiology data published by El Gohary et al (Table 2).[3]

Table 2 Liver stage by aetiology

Liver stage	All patients N (%)	Non-alcoholic fatty liver disease N (%)	Alcohol-related liver disease N (%)	Hepatitis-related liver disease N (%)
Liver warning	220 (54%)	102 (51%)	89 (60%)	4 (50%)
Progressive fibrosis	141 (35%)	75 (37%)	44 (30%)	3 (38%)
Probable cirrhosis	44 (11%)	24 (12%)	16 (11%)	1 (13%)
Total	405	201	149	8

The model does not explicitly account for progression across these stages (e.g., liver warning progressing to progressive disease), i.e. due to the slow progression of liver disease, patients were assumed not to progress further from their initial severity level during the 5-year time horizon.

Annual costs for liver warning was assumed to be equivalent to behavioural intervention (GP appointment, applied twice per year). For progressive fibrosis and probable cirrhosis, a Health Technology Assessment Programme report was used (Wright et al, 2006).[4] Although this report is in relation to liver disease developed in those with hepatitis C, costs for treating each stage were assumed to be similar across aetiologies. Annual costs for each stage are outlined in Table 3.

Table 3 Annual cost by liver stage

Liver stage	Annual cost	Source/Comment
Liver warning	£78.46	GP consultation at £39.23 (PSSRU unit cost 2020), twice a year
Progressive fibrosis	£1,103.90	Wright et al 2006 ‘moderate disease’, inflated to 2021
Probable cirrhosis	£1,752.07	Wright et al 2006 ‘’cirrhosis’, inflated to 2021

For ‘behavioural intervention’

For patients receiving behavioural intervention, it was assumed that the long-term cost is the same as 'liver warning – e.g. continuing behavioural intervention, which consists of a GP consultation twice per annum (£78.46/year).[2]

This assumes that if the patient requires behavioural intervention within the first year after having a scan, then liver disease is manageable through behavioural intervention and does not progress. This would rely on patients following advice and does not account for non-compliance or progression of disease in this time frame.

For 'no liver disease' and 'no behavioural intervention'

No costs were applied. This assumes that these patients do not develop habits that lead to liver disease within a 5-year timeframe.

Model results

Original base case

The Company base case retains the inputs and structured used in the original submission and provided for reference in Table 4.

Due to the increased attendance rates at scans, the use of FibroScan outside of secondary or specialist care identifies more patients with liver disease requiring some form of intervention (specialist treatment by hepatologist or a behavioural intervention by a GP). Despite the increase of cases identified, FibroScan used outside of secondary or specialist care reduces costs by reducing the number of visits to hepatologist departments as well as reducing the opportunity costs of missed scan appointments.

Table 4 Base case results

	Mean using FibroScan outside of secondary or specialist care (technology)	**Mean using FibroScan in secondary or specialist care (comparator)**	**Difference in means: technology vs comparator**
Scan costs	£60.95	£109.70	-£48.74
Missed appointment costs	£1.16	£18.64	-£17.48
Hepatologist referral costs	£41.54	£29.60	£11.94
Behavioural intervention costs	£25.32	£22.77	£2.56
Total cost	**£ 128.97**	**£180.70**	**-£51.73**
Number of referrals to hepatologist after scan	0.20	0.18	0.02
Number of referrals to behavioural intervention	0.65	0.58	0.07
Missed diagnosis of liver disease	0.07	0.11	-0.04
Total number of visits to hepatology department	0.20	0.98	-0.78

Scenarios

Further tests after failed FibroScan

The addition of further tests after failed FibroScan results in a similar cost saving to the base case (scenario: £51.75-52.25 vs. base case: £51.73), both when 100% of patients who have a secondary care scan fail proceed to further tests, and when 80% of patients who have a secondary care scan fail proceed to further tests (Table 5 and Table 6).

This change to the decision tree results in less missed diagnosis of liver disease in both care settings.

Table 5 Further tests received after scan failure (100% of secondary care failures receive a further test)

	Mean using FibroScan outside of secondary or specialist care (technology)	**Mean using FibroScan in secondary or specialist care (comparator)**	**Difference in means: technology vs comparator**
Scan costs	£65.83	£115.92	-£50.09
Missed appointment costs	£1.99	£18.64	-£16.65
Hepatologist referral costs	£41.54	£29.60	£11.94
Behavioural intervention costs	£25.32	£22.77	£2.56
Total cost	**£134.68**	**£186.92**	**-£52.25**
Number of referrals to hepatologist after scan	0.20	0.18	0.02
Number of referrals to behavioural intervention	0.65	0.58	0.07
Missed diagnosis of liver disease	0.05	0.09	-0.04
Total number of visits to hepatology department	0.24	0.98	-0.74

Table 6 Further tests received after scan failure (80% of secondary care failures receive a further test)

	Mean using FibroScan outside of secondary or specialist care (technology)	Mean using FibroScan in secondary or specialist care (comparator)	Difference in means: technology vs comparator
Scan costs	£65.83	£114.68	-£48.84
Missed appointment costs	£1.99	£19.38	-£17.40
Hepatologist referral costs	£41.54	£29.60	£11.94
Behavioural intervention costs	£25.32	£22.77	£2.56
Total cost	**£134.68**	**£186.42**	**-£51.75**
Number of referrals to hepatologist after scan	0.20	0.18	0.02
Number of referrals to behavioural intervention	0.65	0.58	0.07
Missed diagnosis of liver disease	0.05	0.09	-0.04
Total number of visits to hepatology department	0.24	0.97	-0.74

Cost of FibroScan in secondary care

Removing (Table 7) or reducing (Table 8) the staff cost from the cost of FibroScan in secondary care results in FibroScan outside secondary care (pay per scan business model) being cost incurring compared to FibroScan in secondary care (by £28.96 – £38.96).

Using the weighted HRG RD48Z of £61.98 resulted in FibroScan outside secondary care (pay per scan business model) being cost incurring compared to FibroScan in secondary care, but to a lesser extent than removing or reducing the staff cost from the cost of FibroScan in secondary care.

It should be highlighted that the key uncertainty in this model is whether it is accurate to compare the cost of FibroScan in secondary care as reported in a bundled HRG cost for ultrasound elastography compared to a cost obtained by micro-costing in a non-hospital setting where an HRG code does not currently exist. Even with the changes made by the Company to the model, the uncertainty about whether it is accurate to compare these costs still exists.

The point is there is no standardisation regarding the way that hospitals charge/ capture costs relating to FibroScan delivery and how they code their activity.

Indeed, EAC and NICE highlighted that 3,561 scans were conducted in outpatients 2019/20 by using HRD RD48Z. We are aware that some large acute providers performed up to 3,000 scans each year by themselves.

Table 7 No additional staff costs added to HRG cost for ultrasound elastography

	Mean using FibroScan outside of secondary or specialist care (technology)	**Mean using FibroScan in secondary or specialist care (comparator)**	**Difference in means: technology vs comparator**
Scan costs	60.95	35.14	25.81
Missed appointment costs	1.16	2.50	-1.34
Hepatologist referral costs	41.54	29.60	11.94
Behavioural intervention costs	25.32	22.77	2.56
Total cost	**£128.97**	**£90.01**	**£38.96**
Number of referrals to hepatologist after scan	0.20	0.18	0.02
Number of referrals to behavioural intervention	0.65	0.58	0.07
Missed diagnosis of liver disease	0.07	0.11	-0.04
Total number of visits to hepatology department	0.20	0.98	-0.78

Table 8 Nurse staff costs added to HRG cost of ultrasound elastography

	Mean using FibroScan outside of secondary or specialist care (technology)	**Mean using FibroScan in secondary or specialist care (comparator)**	**Difference in means: technology vs comparator**
Scan costs	60.95	45.14	15.81
Missed appointment costs	1.16	2.50	-1.34
Hepatologist referral costs	41.54	29.60	11.94
Behavioural intervention costs	25.32	22.77	2.56
Total cost	**£128.97**	**£100.01**	**£28.96**
Number of referrals to hepatologist after scan	0.20	0.18	0.02
Number of referrals to behavioural intervention	0.65	0.58	0.07
Missed diagnosis of liver disease	0.07	0.11	-0.04
Total number of visits to hepatology department	0.20	0.98	-0.78

Table 9 Weighted average HRG cost (£61.98)

	Mean using FibroScan outside of secondary or specialist care (technology)	**Mean using FibroScan in secondary or specialist care (comparator)**	**Difference in means: technology vs comparator**
Scan costs	60.95	£49.58	£11.37
Missed appointment costs	1.16	£2.50	-£1.34
Hepatologist referral costs	41.54	£29.60	£11.94
Behavioural intervention costs	25.32	£22.77	£2.56
Total cost	**£128.97**	**£104.45**	**£24.52**
Number of referrals to hepatologist after scan	0.20	0.18	0.02
Number of referrals to behavioural intervention	0.65	0.58	0.07
Missed diagnosis of liver disease	0.07	0.11	-0.04
Total number of visits to hepatology department	0.20	0.98	-0.78

Alternative costing model

If a CCG were to buy FibroScan equipment outright for use outside secondary care, then with a large enough number of scans performed per year, the cost per scan would be lower compared to the pay-per-scan business model (£43.29 vs. £58, excluding staff costs). This results in larger cost saving for FibroScan performed outside secondary care compared to inside secondary care compared to the base case (£72.83 vs. £51.73) (Table 10).

Table 10 Microcosting model

	Mean using FibroScan outside of secondary or specialist care (technology)	**Mean using FibroScan in secondary or specialist care (comparator)**	**Difference in means: technology vs comparator**
Scan costs	£39.86	£109.70	-£69.84
Missed appointment costs	£1.16	£18.64	-£17.48
Hepatologist referral costs	£41.54	£29.60	£11.94
Behavioural intervention costs	£25.32	£22.77	£2.56
Total cost	**£107.87**	**£180.70**	**-£72.83**
Number of referrals to hepatologist after scan	0.20	0.18	0.02
Number of referrals to behavioural intervention	0.65	0.58	0.07
Missed diagnosis of liver disease	0.07	0.11	-0.04
Total number of visits to hepatology department	0.20	0.98	-0.78

Long-term time horizon

If a 5-year time horizon is incorporated into the model structure, the cost saving for FibroScan performed outside secondary care compared to inside secondary care increases from £51.73 in the base case, to £81.12.

There are strong assumptions associated with the way longer-term outlook has been incorporated, and the Company would still advise using the 1-year time horizon in the base case as there is less uncertainty associated with this approach. However, the Company hopes that including longer-term costs in the model reflects that the 1-year time horizon may underestimate the impact of scans performed outside secondary care to increase attendance at scans, increase early identification of liver disease, and thus decrease long term costs.

Table 11 Long term costs

	Mean using FibroScan outside of secondary or specialist care (technology)	**Mean using FibroScan in secondary or specialist care (comparator)**	**Difference in means: technology vs comparator**
Scan costs	£60.95	£109.70	-£48.74
Missed appointment costs	£1.16	£18.64	-£17.48
Hepatologist referral costs	£41.54	£29.60	£11.94
Behavioural intervention costs	£25.32	£22.77	£2.56
Long term costs	£1,082.47	£1,111.86	-£29.39
Total cost	**£1,211.44**	**£1,292.56**	**-£81.12**
Number of referrals to hepatologist after scan	0.20	0.18	0.02
Number of referrals to behavioural intervention	0.65	0.58	0.07
Missed diagnosis of liver disease	0.07	0.11	-0.04
Total number of visits to hepatology department	0.20	0.98	-0.78

Combined scenario 1: Furter tests after failed FibroScan + no staff cost in secondary care + alternative costing model

Combining the scenarios outlined in this report (excluding long term costs) results in FibroScan performed outside secondary care being marginally cost incurring compared to FibroScan performed inside secondary care (by £13.31). This is driven by higher hepatology referrals, as when FibroScan is performed outside secondary care, the number of attendances to the scan is higher and the probability of identifying liver disease is higher, which is reflected in a comparison of number of

referrals vs. missed diagnosis of liver disease. The absolute cost of the scan in both settings is almost identical (£0.05 difference).

Table 12 Combined scenario 1

	Mean using FibroScan outside of secondary or specialist care (technology)	**Mean using FibroScan in secondary or specialist care (comparator)**	**Difference in means: technology vs comparator**
Scan costs	£41.42	£41.37	£0.05
Missed appointment costs	£1.27	£2.50	-£1.23
Hepatologist referral costs	£41.54	£29.60	£11.94
Behavioural intervention costs	£25.32	£22.77	£2.56
Total cost	**£109.55**	**£96.24**	**£13.31**
Number of referrals to hepatologist after scan	0.20	0.18	0.02
Number of referrals to behavioural intervention	0.65	0.58	0.07
Missed diagnosis of liver disease	0.05	0.09	-0.04
Total number of visits to hepatology department	0.24	0.98	-0.74

Combined scenario 2: Furter tests after failed FibroScan + no staff cost in secondary care + alternative costing model + long term costs

Combining the scenarios outlined in this report (including long term costs) results in FibroScan performed outside secondary care being cost saving compared to FibroScan performed inside secondary care (by £8.78). This reflects the hepatology referrals being offset by the long-term cost savings from the earlier identification of liver disease.

Table 13 Combined scenario 2

	Mean using FibroScan outside of secondary or specialist care (technology)	**Mean using FibroScan in secondary or specialist care (comparator)**	**Difference in means: technology vs comparator**
Scan costs	£41.42	£40.12	£1.30
Missed appointment costs	£1.27	£2.60	-£1.33
Hepatologist referral costs	£41.54	£29.60	£11.94
Behavioural intervention costs	£25.32	£22.77	£2.56
Long term costs	£1,143.43	£1,166.67	-£23.24
Total cost	**£1,252.98**	**£1,261.76**	**-£8.78**
Number of referrals to hepatologist after scan	0.20	0.18	0.02
Number of referrals to behavioural intervention	0.65	0.58	0.07
Missed diagnosis of liver disease	0.05	0.09	-0.04
Total number of visits to hepatology department	0.24	0.97	-0.74

Conclusion

The Company have responded to requests to present additional recommended analyses.

The scenarios presented in this report show the difference in cost of performing Fibroscan outside secondary care compared to inside secondary ranges from saving £81.12 per person (base case + 5 year costs) to incurring £38.96 per person (base case + reduced cost of FibroScan in secondary care).

The costs of the scans were expected to be similar across care settings. Due to the increased scan attendance rates outside of secondary care, one would expect the number of referrals to secondary care to be reduced, and long-term costs to be

reduced due to earlier diagnosis and treatment. This is supported by the model and scenarios presented.

The Company would like to highlight that the key uncertainty in this model is whether it is accurate to compare the cost of FibroScan in secondary care as reported in a bundled HRG cost for ultrasound elastography compared to a cost obtained by micro-costing in a non-hospital setting where an HRG code does not currently exist. Even with the changes made by the Company to the model, the uncertainty about whether it is accurate to compare these costs still exists.

The point is there is no standardisation regarding the way that hospitals charge/ capture costs relating to FibroScan delivery and how they code their activity.

Just to give an example that support the previous statement, EAC highlighted that 3,561 scans were conducted in outpatients 2019/20 by using HRD RD48Z. To our knowledge, some CCG/providers performed up to 3,000 scans each year by themselves.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

MT562 FibroScan for assessing liver fibrosis and cirrhosis outside secondary and specialist care

EAC Critique of "Additional Manufacturer Evidence and Analysis"

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Date completed: 18/03/2022

Contains confidential information: No

Number of attached appendices: 2

Declared interests of the authors

None.

Acknowledgements

Prof Neil Guha, Professor of Hepatology, University of Nottingham

Louise Campbell, Clinical Director, Tawazun Health

Responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

Purpose of the Critique

The Company submitted an additional document during public consultation "Additional Manufacturer Evidence and Analysis", received by the EAC on 10/03/2022. The EAC has reviewed this additional report from the Company, and has provided a commentary on each results section in turn. Following a request, the Company sent (on 15/03/2022) instructions on model settings which should be used to generate the results of Table 4 to 13 of their additional analysis (Appendix A). The EAC sent a list of queries (on 11/03/2022) to nine Clinical experts, as of 16/03/2022 only two responded (Appendix B). For simplicity, the EAC will refer to FibroScan conducted in a non-secondary care setting as "primary care", and FibroScan conducted in a secondary or tertiary care setting as "secondary care".

Original base case

The Company states that the base case retains the inputs and structure used in the original submission and provided for reference in **Error! Reference source not found.** of the additional report. The EAC notes that the Company has corrected the per scan cost of FibroScan from £70 to £58, which was confirmed as an error in the original submission by the Company.

Further tests after failure FibroScan

The Company states that following review of the EAC assessment report, they have modified the economic model structure to incorporate additional diagnostic tests following an initial FibroScan test failure. The Company states that this was applied in both arms and that the probability of attending secondary care for the further tests in the secondary care scan arm is set at 100% (that is equivalent to the EAC model) and 80% (the same probability used for attending secondary care in the first instance) in a sensitivity analysis. However, in the EAC base case (FibroScan Assessment Report, 2021), it was assumed that the same proportion attending secondary care after test failure was the same as the proportion attending secondary care for the initial FibroScan measurement; this was set to 60% and not 100% as stated by the Company. The EAC considers it unlikely that 80% of patients will attend the first hospital appointment, but that 100% of patients experiencing a test failure will attend the second hospital appointment for FibroScan. Altering the proportion attending secondary care following test failure in the updated model has

little to no effect on the results, Table 1. The EAC would conclude that the proportion attending secondary care following test failure has not been appropriately incorporated into the updated model, and appears to remain fixed at 80% in both arms.

Table 1: Sensitivity analysis of attendance rate applied by the Company in the additional report

	Attendance			Cost			
Scenario [Table in additional Company report]	1st: Primary care	1st: Secondary care	2nd: Secondary care	FibroScan primary care	FibroScan secondary care	Difference (primary-secondary)	EAC Comment [Updated model detail]
Base case results [Table 4]	89%	80%	-	£128.97	£180.70	-£51.73	Represents base case with cost per scan corrected to £58. Additional diagnostic tests following FibroScan test failure not incorporated in base case.
Further tests received after scan failure (100% of secondary care failures receive a further test) [Table 5]	89%	80%	100%	£134.68	£186.92	-£52.25	There is only one parameter in the updated model which can be altered to represent attendance at secondary care following test failure. This parameter is applied equally to primary and secondary care arms. Despite the default setting of 100% attending scan in secondary care after scan failure in secondary care (all populations), the updated scenario model appears fixed at 80% [Engine_Scenario!N18 and Engine_Scenario!N73 are both multiplied by X_Sc = 80% regardless of Probabilities!H41 value]
Company updated model [Table 6]	89%	80%	80%	£134.68	£186.42	-£51.75	It is unclear to the EAC why the cost of FibroScan in primary care is unchanged.
EAC Scenario changing attendance at second healthcare appointment to 0%	89%	80%	0%	£134.68	£184.43	-£49.75	Setting the proportion attending scan in secondary care after scan failure in secondary care (all populations) to 0% [Probabilities!H41=0%], should replicate the base case, but does not. The EAC concludes that the additional proportion attending secondary care following test failure has little to no effect on the cost-difference.

Cost of FibroScan in secondary care

The Company explored changes to the costs of FibroScan when conducted in secondary care arm only. Changes included:

- removing additional staff time costs associated with interpreting the scan from the total scan costs completely (in line with the approach taken by the EAC to avoid double counting of staff costs incorporated within HRG code RD48Z),
- including 15 minutes of Band 6 hospital nurse time only, and
- using a weighted average HRG cost for ultrasound elastography (£61.98 instead of £43.93; in line with approach taken by EAC).

The EAC has summarised the results of the Company's additional sensitivity analysis to FibroScan costs in secondary care in Table 2.

Table 2: Sensitivity analysis of FibroScan costs in secondary care applied by the Company in the additional report

Scenario [Table in additional Company report]	Cost of scan in secondary care	FibroScan primary care	FibroScan secondary care	Difference (primary-secondary)	EAC comment
Base case results [Table 4]	£137.12: *[£43.93 (HRG) + £93.19 staff time]*	£128.97	£180.70	-£51.73	
No additional staff costs added to HRG cost for ultrasound elastography [Table 7]	£43.93 *[HRG cost only]*	£128.97	£90.01	+£38.96	Assuming fixed 80% attendance (with no subsequent testing due to test failure), the EAC would expect this modelled scenario to reduce the cost in secondary care by £74.55 (0.8*£93.19) when compared to base case; however this did not occur.
Nurse staff costs added to HRG: 15 minutes, band 6 hospital based nurse (secondary care only) [Table 8]	£56.43 *[£43.93 (HRG) + £12.50 staff time]*	£128.97	£100.01	+£28.96	The results from the model were as expected; an increase in cost of £10.00 from the above scenario (0.8*£12.50).
Weighted average HRG [Table 9]	£61.98	£128.97	£104.45	+£24.52	The results from the model were as expected; an increase in cost of £4.44 from the above scenario (0.8*(£61.98-£56.43)).

Within the additional report, the Company states that there is a lack of standardisation regarding the way hospitals charge or capture costs relating to FibroScan delivery and how they code their activity. The Company provides an example to support this statement, stating that some Clinical Commissioning Groups (CCG) or providers performed up to 3,000 scans each year, however the EAC had stated within the FibroScan Assessment Report (2021) that only 3,561 ultrasound elastography scans were documented (in England) as per HRG code RD48Z "transient elastography" obtained from the diagnostic imaging dataset of NHS Reference Costs 2019/20 in an outpatient setting.

The NICE adoption team has also investigated the Operating Procedure Codes Supplement (OPCS) code 'U36.4 - ultrasound elastography' within the Hospital Episode Statistics (HES) in the outpatient dataset (NHS Digital, Hospital Outpatient Activity) when coded as the *main* procedure, Table 3. Note that two Clinical experts have stated that FibroScan would be used in 60 to 80% of new hepatology referrals (Appendix B); if using data from 2019/20 (prior to the COVID-19 pandemic) this would result in an estimated number between 8,697 and 11,596 first appointment attendances requiring FibroScan. The EAC notes that coding of specific procedure (OPCS) codes in outpatient dataset is poor; coding of procedures is not mandatory within the outpatient dataset and is not driven by payment by results. To quantify data completeness of procedure codes in the outpatient dataset, the EAC has found that 74% outpatient attendances (92,472,497/124,927,781) in 2019/20, using local data extract from NHS Digital: DAR-NIC-17011-Z1B4J, had no main procedure coded. Additionally, for those with a procedure (OPCS) code recorded, the same caveats of HRG codes also apply: the code may include other interventions (for example ARFI, or other transient elastography) which do not use the FibroScan device, and is not specific to liver (and could involve ultrasound elastography of other anatomical areas). The EAC also note from Table 3 that a number of ultrasound elastography procedures have been coded as tele-consultations (e.g. 165 first and 216 subsequent tele-consultations in 2020/21), which further highlights issues with the quality of outpatient procedure coding. Therefore, the EAC would interpret the outpatient procedure coded data with caution.

Table 3: Outpatient data from NHS Digital, where U36.4 was recorded as the main procedure

Year	All Attendances	Attended first appointment	Attended first tele-consultation	Attended subsequent appointment	Attended subsequent tele-consultation
2017/18	17,514	6,726	3	10,784	1
2018/19	29,459	10,592	9	18,832	25
2019/20	37,845	14,495	23	23,307	20
2020/21	20,919	7,520	165	13,018	216

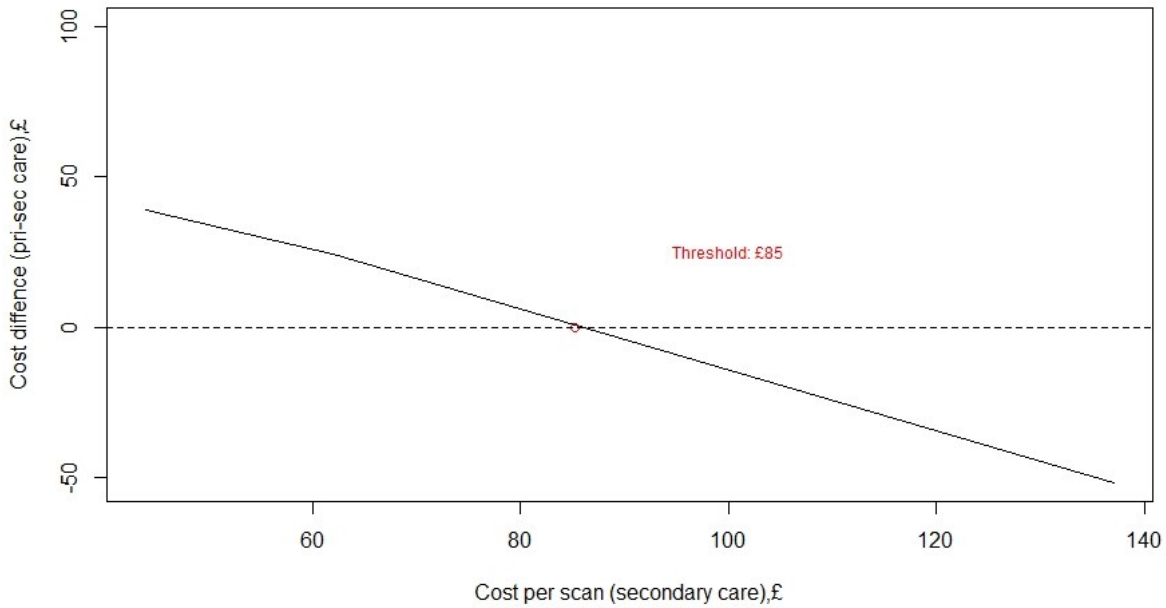
Due to large uncertainty, the EAC has queried the scale of use of FibroScan with the Clinical experts (Appendix B). From NHS Reference Costs 2019/20 there were a total of 333,333 outpatient hepatology attendances in 2019/20, which included 74,777 first appointments, 1,554 first telephone consultations, 245,056 subsequent appointments, and 11,946 subsequent telephone consultations. Whilst the EAC recognises that a number of specialties may request use of FibroScan, they have assumed that hepatology would be the most frequent user. Two Clinical experts have stated that FibroScan would be used in 60 to 80% of new referrals (Appendix B). Using NHS activity data for hepatology outpatient attendances (stated above), this would amount to between 44,866 to 59,822 scans within 2019/20 requiring FibroScan. However, one Clinical expert has stated that other non-invasive tests (other than FibroScan) may be carried out at a referral hepatology outpatient appointment (Appendix B). Based on the above the EAC is still uncertain to the scale of use of FibroScan within the NHS outpatient setting; with estimate ranging between 3,561 and 59,822 attendances using NHS Hospital Episode Statistics 2019/20 data, which would have a significant impact when considering centre throughput and estimation of costs.

The EAC also queried with the Clinical experts what proportion of hospital attendances assigned the HRG code RD48Z would be attributed to transient elastography (FibroScan), liver ultrasound, or acoustic radiation force impulse (ARFI) (Appendix B). One expert stated that the majority would include FibroScan, another

expert stated that 100% of patients would be assigned this HRG. One expert also stated that an additional HRG code would be also be applied (WF01B: Non-Admitted Face-to-Face Attendance, First) as all would see a consultant. The EAC notes that this additional HRG code had a reference cost of £151, with limited activity of 2,731 attendances in the 2019/20 financial year. The Clinical expert did however acknowledge that FibroScan has not been developed as a pathway and this costing approach may not be uniform across hospitals, which may explain the low activity associated with the additional HRG code.

The EAC acknowledges that there is large uncertainty regarding the cost of FibroScan in secondary care, with the Clinical experts highlighting large variation across the NHS. However, using the Company's updated model (assuming no repeat testing after test failure) the threshold of *total* FibroScan costs in secondary care (combining equipment and staff time) is £85, below which FibroScan in primary care is considered cost-incurring, Figure 1. This threshold would represent 20 additional minutes of a consultant (£119 per hour, PSSRU 2020) to discuss results with the patient, assuming a FibroScan measurement cost in secondary care of £43.93, which the EAC considers plausible.

Figure 1: Threshold analysis of total scan costs using FibroScan in secondary care, using sensitivity analysis from Company's updated analysis



Cost of FibroScan in primary care

The Company also explored micro-costing of FibroScan assuming capital investment of equipment in primary care setting only. The costs assume a system (FibroScan, probe and software) lifetime of 7 years, and a patient throughput of 500 patients per year, Table 3. The EAC asked the Clinical experts to state how many patients were likely to have FibroScan in an NHS hospital setting in one year. Two Clinical experts responded, both acknowledging large variation across the NHS in terms of scale of use of FibroScan. One expert referenced a paper by Chalmers *et al.* (2020), which reported 968 patients attending a transient elastography clinic appointment in a tertiary hospital. Another expert stated that their previous unit (a large tertiary centre offering specialist liver clinics) conducted more than 3,500 scans in 2019, however referred to a recent survey conducted by the British Liver Trust (where 99% of CCGs responded) stating that only 25% of UK CCGs and Health Authorities (HA) used transient elastography (Jarvis *et al.* 2021).

The Company micro-costing calculation has only included the cost of the FibroScan 430 Mini+, which is a portable, battery-powered version of the device. The capital costs of FibroScan 630 Expert (mains powered) and FibroScan 530 Compact (battery powered), which are both cart-based versions, were not included in the Company micro-costings. The micro-costing also assumes that each primary care centre has one FibroScan device. The EAC acknowledges that some primary care centres may already have access to FibroScan, however the Clinical experts have highlighted that some existing devices are older generation, unable to be updated (EAC Correspondence Log, 2021) and unable to measure liver fat content (Appendix B). One Clinical expert also reported that there were approximately 480 FibroScan devices in the country with the majority located in large specialist and tertiary centres. Therefore, the EAC considers it unlikely that every primary care centre will be able to achieve 500 patients per year as incorporated in the updated Company model.

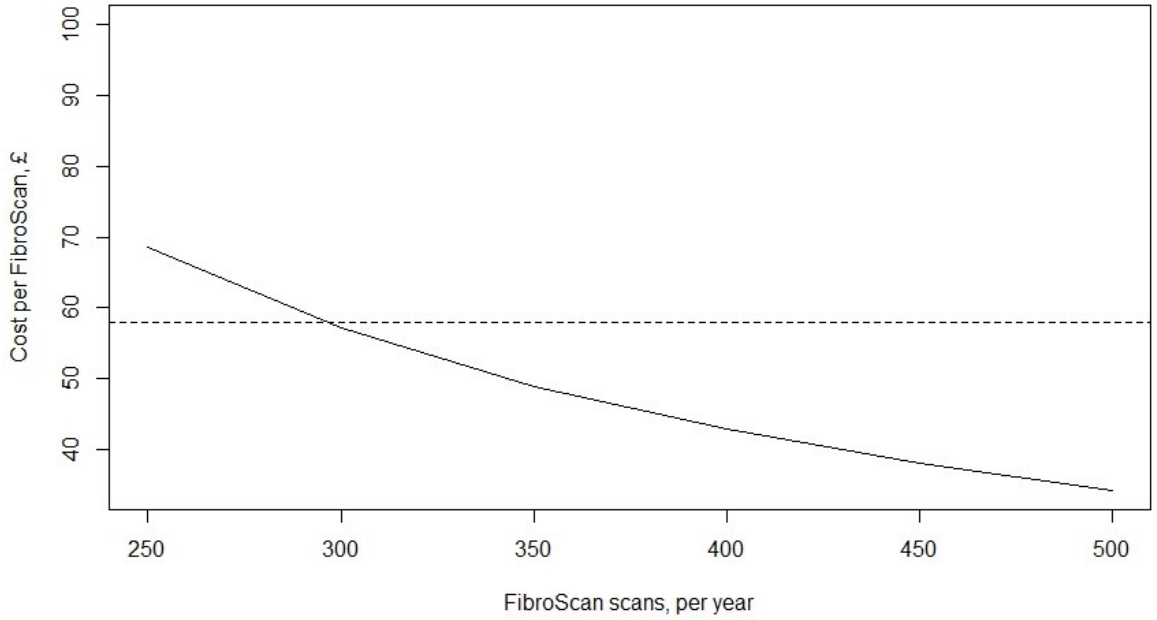
The EAC acknowledges there is large uncertainty regarding the *total* volume of FibroScan across the NHS in a secondary care setting, and large variation in the *per hospital* volume of FibroScan use, which would translate to large variation in *per primary care* volume of FibroScan use. However, the EAC has amended the Company micro-costing of FibroScan costs in primary care assuming a lower patient

throughput of 250 per year. This resulted in the FibroScan device costs exceeding those proposed by the company in their pay per scan model of FibroScan (£58 per scan). Threshold analysis conducted by the EAC found that a primary care centre would have to conduct more than 300 scans per year, for the cost to reduce to below £58 per scan, Figure 2.

Table 4: Company micro-costing of FibroScan per scan (*assumption of EAC).

Item	Unit cost	No. required (7 year lifetime)	Total cost	Total annual cost	Total cost per scan (500 per year)	Total cost per scan (250* per year)
FibroScan 430 Mini+	£48,000	1	£48,000	£6,857.14	£13.71	£27.43
Additional probes (small, medium or extra large)	£16,700	1	£16,700	£2,385.71	£4.77	£9.54
Cost of CAP/SmartExam software	£18,500	1	£18,500	£2,642.86	£5.29	£10.57
Cost of 6 year Serenity service contract	£28,560	1	£28,560	£4,080.00	£8.16	£16.32
Training costs (annual cost)	£1,180	7	£8,260	£1,180.00	£2.36	£4.72
		Total	**£120,020.00**	**£17,145.71**	**£34.29**	**£68.58**

Figure 2: Threshold analysis on the annual number of FibroScan scans conducted in a primary care centre using the Company micro-costing approach for calculating the cost per procedure (dashed line representing the £58 pay per scan cost proposed by the Company in primary care)



Additionally, the Company have included annual training costs of £1,180 (Table 4) within their micro-costing of FibroScan. The EAC did not assess FibroScan training material and it is not clear whether this annual costs is training of existing or new users, or both. The Company advised they provide training comprising a half-day on-site session for a maximum of three trainees (FibroScan Assessment Report, 2021). The EAC notes that at the Diagnostic Advisory Committee the Company stated that they encouraged users to ensure that competency is validated in practice, but did not provide guidance on requirements for the level of use. Clinical experts also confirmed that there is no independent accreditation scheme for FibroScan users. The EAC notes that there is no available evidence demonstrating equivalence of test performance or clinical outcomes, comparing FibroScan when used in a primary care setting to FibroScan when used in a secondary care setting. Due to unknown total volume of FibroScan in secondary care, and large variation in volume between centres (as highlighted by the Clinical experts), the EAC would recommend that competency in FibroScan measurement should be monitored in order to ensure test performance if implementing across the NHS.

Long-term time horizon

Within their updated model, the Company incorporated a 5-year time horizon. This assumed that higher attendance rates for the scan leads to a lower rate of missed diagnosis of liver disease. The updated model does not permit patients to change liver staging throughout the 5-year time horizon, which the EAC considers appropriate given the slow progression of liver disease, which was previously confirmed by the Clinical experts (EAC Correspondence Log, 2021) and reiterated at the Diagnostic Advisory Committee meeting. Therefore, long-term costs are attributed to each patient undergoing a successful FibroScan measurement, assuming a proportion are in liver warning (each with an annual cost of £78.46 attributed to account for GP consultations twice a year), a proportion with progressive fibrosis (each with £1,103.90 attributed ongoing care with moderate liver disease), and a proportion with probable cirrhosis (each with £1,752.07 attributed to ongoing care associated with cirrhosis). The Company stated that the proportion of patients with these severities of liver disease were derived from the study by El Gohary *et al.* (2018): 54.3% with liver warning, 34.8% progressive fibrosis and 10.9% probable cirrhosis. However, the EAC notes that the staging of liver disease applied in the updated model does not account for the majority of patients (55.5%, 505 of 910 patients from El Gohary *et al.* 2018) which reported no fibrosis, who would require no subsequent care, and thus would incur no additional cost. The appropriate proportions from El Gohary *et al.* (2018) would be 55.5% with no fibrosis, 24.2% with liver warning, 15.5% with progressive fibrosis, and 4.8% with probable cirrhosis, which the EAC applied in the updated Company model, results in Table 5. As the long-term costs are applied to both arms (primary and secondary care) equally, the cost difference after five years (-£50.58) is similar to that of the one year time horizon modelled in the base case (-£51.73).

Table 5: Costs associated with long-term (5-year) time horizon applied in Company updated model

	Liver stage aetiology				Cost per procedure			EAC comment
Scenario [Table in additional Company report]	No fibrosis	Liver warning	Progressive fibrosis	Probable cirrhosis	FibroScan primary care	FibroScan secondary care	Difference (primary-secondary)	
Long-term costs [Table 11]	0%	54.3%	34.8%	10.9%	£1,211.44	£1,292.56	-£81.12	
Long-term costs (proportions modified by EAC)	55.5%	24.2%	15.5%	4.8%	£750.53	£801.11	-£50.58	The EAC modified the updated Company model to account for the majority of patients having no fibrosis and therefore no subsequent healthcare costs associated. [Parameters!S49-S51]

Additionally, the Company applied annual costs for liver warning assuming two GP consultations per year, and annual costs associated with progressive fibrosis and probable cirrhosis derived from an HTA report of antiviral therapy for mild chronic hepatitis C (Wright *et al.* 2006), Table 6. Using these costs, the Company state that the cost-saving per patient increases from £51.73 per patient (base case) to £81.12 per patient (FibroScan primary care: £1,211.44; FibroScan secondary care: £1,292.56). As increased attendance in primary care leads to increased detection (at increased cost) it is unclear to the EAC how increasing the time-period of the model to include management costs can increase the potential cost saving.

The EAC notes that there is a lack of comparative evidence to suggest any difference in short- or long-term patient outcomes between FibroScan being used in a non-secondary (primary or community) care versus secondary care setting. The EAC notes that Clinical experts at the Diagnostic Advisory Committee acknowledged that there is a lack of evidence to confirm that delivery of behavioural therapy changes clinical outcomes. The Clinical experts previously advised that output of FibroScan would guide frequency of monitoring (EAC Correspondence Log, 2021).

Table 6: Annual cost applied in the update Company model by liver stage

Liver stage	Annual cost	Source/Comment	EAC Comment
No fibrosis	N/A	Not included in the updated model	The EAC reports that the majority of patients in the El Gohary *et al.* (2018) study had no fibrosis (55%, 505 of 910). The EAC would assume that patients with no fibrosis would be discharged back to GP and incur no additional cost £0).
Liver warning	£78.46	GP consultation at £39.23 (PSSRU unit cost 2020), twice a year	Cost for each GP consultation is consistent with updated PSSRU Unit Costs 2021, (Table 10.3b), £39.23. The Clinical experts previously advised that output of FibroScan would guide frequency of surveillance. Following previous advice, those with liver warning could undergo clinical review once every three years. The EAC would assume that patients with liver warning would incur an annual cost of £13.07 (£39.23/3).
Progressive fibrosis	£1,103.90	Wright *et al.* (2006) 'moderate disease', inflated to 2021	Inflation source not explicitly reported. Mean annual total cost of moderate disease was £717, and the highest cost items were outpatient visits and procedures (Wright et al. 2006, figure breakdown provided in Table 37). This was obtained from "Health benefits of antiviral therapy for mild chronic hepatitis C", with unit costs including drug costs, outpatient visits, investigations, procedures, inpatient days. This cost may not be representative of hospital resource usage of patients with suspected non-alcohol fatty liver disease (NAFLD), or alcohol-related liver disease (AFLD). The EAC would consider this is likely an upper estimate of ongoing care costs. The EAC has not identified any data regarding ongoing care of patients with progressive fibrosis. The Clinical experts did not provide any additional information on this subgroup of patients.
Probable cirrhosis	£1,752.07	Wright *et al.* (2006) 'cirrhosis', inflated to 2021	Inflation source not explicitly reported. The average total cost for managing patients with cirrhosis was £1,138 (Wright et al. 2006, figure breakdown provided in Table 37). Same limitations as above. One Clinical expert stated that most patients with cirrhosis would be invited to attend hepatology outpatient appointments twice a year. This could include endoscopy (to monitor varices), and ultrasound imaging (to monitor liver cancer). However, acknowledged that frequency of investigations would be dependent on centre and other factors (large, small or no varices). The EAC was unable to identify any national audit data, which reported ongoing care for patients with probable cirrhosis.

Combined scenarios

The Company produced two combined scenarios applying combinations of the above analyses, Table 7. The EAC altered both combined scenarios to incorporate the pay per scan model, which was applied in the original Economic Submission (as opposed to the micro-costing approach applied by the Company in the additional analysis).

Table 7: Combined scenarios

Scenario [Table in additional Company report]	FibroScan primary care	FibroScan secondary care	Difference (primary-secondary)	EAC comment
Combined scenario 1 [Table 12]	£109.55	£96.24	£13.31	Base case, with further tests after scan failure, micro-costing of FibroScan in primary care, 1 year time horizon, cost of FibroScan in secondary care using HRG cost only.
Same as above, however using cost per scan model in primary care	£130.64	£96.24	£34.41	Using pay per scan model is more cost-incurring.
Combined scenario 2 [Table 13]	£1,252.98	£1,261.76	-£8.78	Base case combined with further tests after scan failure (with 80% attending second hospital scan), micro-costing of FibroScan in primary care, 5 year time horizon, cost of FibroScan in secondary care using HRG cost only
Same as above, however using cost per scan model in primary care	£1,274.07	£1,261.76	£12.32	Using pay per scan model is more cost-incurring.

Conclusion

The EAC has reviewed the Company additional report and updated economic model and concludes that there remains substantial uncertainty regarding the volume of patients requiring FibroScan in an NHS secondary care outpatient setting, the cost of FibroScan in a secondary care outpatient setting, and the long-term healthcare costs associated with managing patients following FibroScan (across liver warning, progressive fibrosis, probable cirrhosis subgroups). Due to the uncertainty regarding the volume of patients requiring FibroScan, there remains ambiguity that the use of FibroScan in primary care would provide improved geographical coverage and accessibility to patients, while maintaining user competency through regular use. As stated by the EAC in the FibroScan Assessment report (section 8.1, 2021), the Clinical experts have advised that FibroScan is used across a range of specialties in a hospital setting including cardiology, dermatology, endocrinology, gastroenterology, heptatology, rheumatology as well as general practice, drug and alcohol, obesity care and cystic fibrosis teams. Therefore, secondary care services will need to maintain access to FibroScan, even if the technology is also implemented in primary care.

The EAC maintains there is potential for patient benefits in terms of increased quality of life associated with increased detection; however, there is no comparative or long-term data to support this.

Appendix A – Model settings to generate Tables 4-13 (provided by the Company on 15/03/2022)

Table in report	Settings used (all adjustable on Settings sheet, unless otherwise stated)
Table 4 Base case results	Population: All patients Include referral for further tests after scan failure: No further tests after scan failure Costing approach for Fibroscan: Pay per scan contract Time horizon: 1 year Cost of Fibroscan in Secondary Care: Non-consultant cost + IMAGOP/RD48Z
Table 5 Further tests received after scan failure (100% of secondary care failures receive a further test)	Population: All patients Include referral for further tests after scan failure: Further tests after scan failure Costing approach for Fibroscan: Pay per scan contract Time horizon: 1 year Cost of Fibroscan in Secondary Care: Non-consultant cost + IMAGOP/RD48Z
Table 6 Further tests received after scan failure (80% of secondary care failures receive a further test)	Population: All patients Include referral for further tests after scan failure: Further tests after scan failure Costing approach for Fibroscan: Pay per scan contract Time horizon: 1 year Cost of Fibroscan in Secondary Care: Non-consultant cost + IMAGOP/RD48Z Go to: Probabilities!H41 = 80%
Table 7 No additional staff costs added to HRG cost for ultrasound elastography	Population: All patients Include referral for further tests after scan failure: No further tests after scan failure Costing approach for Fibroscan: Pay per scan contract Time horizon: 1 year Cost of Fibroscan in Secondary Care: IMAGOP/RD48Z
Table 8 Nurse staff costs added to HRG cost of ultrasound elastography	Population: All patients Include referral for further tests after scan failure: No further tests after scan failure Costing approach for Fibroscan: Pay per scan contract Time horizon: 1 year Cost of Fibroscan in Secondary Care: Nurse cost + IMAGOP/RD48Z

Table 9 Weighted average HRG cost (£61.98)	Population: All patients Include referral for further tests after scan failure: No further tests after scan failure Costing approach for Fibroscan: Pay per scan contract Time horizon: 1 year Cost of Fibroscan in Secondary Care: IMAGOP/RD48Z Go to: Fibroscan cost!D14 = 61.98
Table 10 Microcosting model	Population: All patients Include referral for further tests after scan failure: No further tests after scan failure Costing approach for Fibroscan: Microcosting Time horizon: 1 year Cost of Fibroscan in Secondary Care: Non-consultant cost + IMAGOP/RD48Z
Table 11 Long term costs	Population: All patients Include referral for further tests after scan failure: No further tests after scan failure Costing approach for Fibroscan: Pay per scan contract Time horizon: 5 years Cost of Fibroscan in Secondary Care: Non-consultant cost + IMAGOP/RD48Z
Table 12 Combined scenario 1	Population: All patients Include referral for further tests after scan failure: Further tests after scan failure Costing approach for Fibroscan: Microcosting Time horizon: 1 year Cost of Fibroscan in Secondary Care: IMAGOP/RD48Z
Table 12 Combined scenario 2	Population: All patients Include referral for further tests after scan failure: Further tests after scan failure Costing approach for Fibroscan: Microcosting Time horizon: 5 years Cost of Fibroscan in Secondary Care: IMAGOP/RD48Z Go to: Probabilities!H41 = 80%

Appendix B – Additional questions to experts

Experts:

#	Name, Affiliation
1	Neil Guha
2	Louise Campbell

Q1: NHS Outpatient activity for 2019/20 states a total 319,833 outpatient attendances in that year. Can you estimate the proportion of these total hepatology outpatient (hospital) appointments would have included a transient elastography scan of the liver?

Response:

#1	No idea. One logical way of thinking about this is thinking about how many new patients are seen. A significant proportion of these new patients (70-80 %) will have had a fibroscan (or another non-invasive test of fibrosis) for workup of “abnormal liver enzyme “ tests..
#2	In my experience the majority (60%) of all our new referrals may require a scan where one has not previously been done, as it has a high negative predictor for fibrosis and depending on the disease being considered those not meeting the criteria >8KPa can be sent directly back to primary care with recomendations and advice. Follow ups will be guided by and dependent on the disease, diagnosis and access to available fibroscan is in the individual unit. If a trial location it will also look to be recruiting to clinical trials and all/majority of liver related clinical trials require fibroscan as a criteria for inclusion/exclusion/ disease monitoring I presume these figures detailed are only heaptology and would not therefore other routes to fibroscan including the combined fatty liver / endorine clinics, dermatalogy / rheumatology methotrexate patients or the sexual health / HIV clincs which all access and require fibroscan regularly?

Q2: For hospital attendances, can you estimate what proportion of hospital attendances assigned HRG RD48Z “ultrasound elastography”, would include each of the following:

- **Liver ultrasound**

- **Acoustic radiation force impulse (ARFI)**
- **Transient elastography (e.g. FibroScan)**

Response:

#1	The majority of this code should be fibroscan. Liver ultrasound is not an appropriate code and only a few places have ARFI.
#2	100% of all patients having Fibroscans performed would use the above code in my centre with the additional codes detailed below The coding given for the scan from our service team when performed was: NEW: All NEW patients had the following codes assigned The above RD48Z code, it would also have Nurse Specialist HRG code, all new patients had the HRG WF01B NEW non-admitted attendance as ALL new patients see the Consultant team. 3 codes assigned to the NEW fibroscan. For a Follow up - or repeat fibroscan for monitoring of the condition: The above RD48Z code, it would also have Nurse Specialist HRG code, and all Follow up patients had the HRG WF01A non-admitted follow up attendance code 3 codes assigned to the Follow up scan Fibroscan (VCTE) has not been developed as a pathway and this will not be uniform through all units and the transient elastography code was not previously developed or in use/communicated.

Q3: In an <u>NHS hospital setting</u>, how many patients will have a FibroScan scan *each year*?

Response:

#1	Huge variation depending on centre. For Nottingham you will have data in Chalmers et al Frontline Gastro paper which was a service evaluation . But… we are a tertiary centre and this will differ across the UK.
#2	Every unit will be different, and much will depend on the staffing resources available to the NHS trust. Fibroscan is a hepatology/gastro delivered scan by hepatology/gastro staff, not radiology or diagnostic units. This will therefore be different in every unit depending on their model of service/ staffing. Some trusts / units will only have 1 specialist nurse, some will have many. Medical staff do not perform regular patient lists even though they may be trained to scan.

	My previous unit would perform >3500 scans per year 2019, with a >91% increase between 2015 / 2019. This ceased to operate through much of the pandemic. approximatley 60% of our list would be Follow up to new, although as the follow up grows new capacity reduces or as new increases follow up witing lists lengthen as units to try and provide coverage with staff resources / availability. A model using health care assistant / non-HCP trained staff may have designated positions and job descriptions in place which protects time for fibroscan - in this case information is usually given at later time/appointment by HCP staff. With COVID this has pulled many of these resources to other areas, so the lists have stopped or significantly reduced creating back logs. A model using HCP delivered fibroscan, the appointment comes with the information from the scan are now more problematic to maintian as the patient sickness levels and numbers of patients have increased with and now post Covid, skilled staff are being utilised to deliver care/OPD mangment rather than scanning. I know of several units now with lists >12 months long with reduced staff resources to address this need.

Q4: How many FibroScan devices is <u>each hospital</u> likely to have?

Response:

#1	Again varies. We have about 10 !
#2	Approximatley 74% of the country currently have no access to fibroscan containing pathways - on a recent survey by the British Liver Trust where 99% ofCCG's responded. The majority of CCG's and NHS Trusts do not have fibroscan devices at all. There are approximatley 480 devices in the country, which given the number of specialist units may mean the spread is relativley low for the majority of providers in secondary care settings. We had 5 as an example so concentrated in small areas. The majority of devices are located in large specialist units - Transplant, specilalist tertiary centres / accademic trial units. NHSE gave all of the operational delivery networks for HCV a device and a few have been previously funded ny PHE for local projects in alcohol. The largest concentration of equipment is in London with my previous centre having 5, although 2 without fat ability are rarley used as no longer suitable and I understand more than 70 units are located in London area. Many devices will still without the ability/capability to assess liver fat content and thus only do stiffness measurements, which makes them poor for some liver conditions like NAFLD/NASH which is the most rapidly increasing conditionas obesity rises.

	There are Fibroscan devices in NHS trust locations where due to silo care and systems, they will only used for designated diseases/services and access is denied to other in trust specialisties. This currently acts as an obstruction to patient care in those areas such as alcohol / addiction and create an increased cost burden to purchase and staff other devices.

Q5: The Clinical Experts previously stated that the outcome of FibroScan would be used to guide the frequency of ongoing surveillance. In order to incorporate this into long-term economic modelling, can you please comment on whether the thresholds, ongoing surveillance type and frequency described in the below table are reasonable assumptions?

Transient elastography threshold	Liver stage	Frequency of surveillance	Type of surveillance
< 8 kPa	No liver disease	No further testing	N/A
8-14.9 kPa	Progressive fibrosis	Every 3 years	1 GP appointment
15 kPa	Probable cirrhosis	Annual	1 Hepatology outpatient appointment

Response:

#1	8-14.9 kPa, Type of surveillance 1 GP appointment: ? there is equipoise about whether these should be seen in primary care or secondary care … if you look at chalmers et al paper you can see breakdown of where they were seen for our centre… but this vary.. 15 kPa, Frequency of surveillance Annual: This does not make sense to me. If they have cirrhosis you would not repeat fibrocan but you would perform surveillance of complications of cirrhosis i.e. endoscopy to look at dilated veins (varices) and u/s to look for liver cancer … frequency of investigations dependent on centre and other factors (e.g. large or small varices or no varices) 15kPa, Type of surveillance 1 Hepatology outpatient appointment: Most places would have bi-annual follow up for cirrhosis
#2	Adjustmnents to the KPa scales have been increased in recent years from 7KPa to 8KPa, these have been primarily made on increasing patient volume as obesity rates rise and reduced capacity in regions/areas. The same applies to the frequency of surveillance.

	This has seen the threshold increase for KPa to addresss trying to locate those with the most severe disease and highest risk, <8KPa does not mean no disease. Those on the pathway are the ones who have usually had an abnormal liver blood test which is the few not the majority of those with liver damage. It does however identify those who may require urgent review. Southampton have form their report recently increased this to >10 KPa as an example to further address capacity issues to pick out those with even higher risks and for the development of liver cancer as in the setting of NASH the person does not have to have developed cirrhosis to get liver cancer. 8KPa is considered a safe pragmatic cut off for the majority, to manage the limited hepatology resources. Clinical trial access is 8KPa, this for pharma is financially the best option as the chance of finding the patients at high risk and recruitment into the study is greater above that level. This is not an exclusion of disease it is the enrichment of the population at risk. Most if not all of those patients above 8KPa will need to be seen by hepatology, many of those >7 KPa (old cut of) and <8KPa will progress yet do not currently qualify and as these are not included in the above. The risk therefore is we may miss progressive disease but also miss the opportunity to prevent progression to this level having had to increased the threshold. The quality of care patients recieive can be influenced significantly by the regularity of scans they get as well as lack of scans they get access to.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

MT562 FibroScan for assessing liver fibrosis and cirrhosis outside secondary and specialist care

Erratum

This erratum replaces pages 14 to 17 in the following document:

EAC Critique of "Additional Manufacturer Evidence and Analysis"

Long-term time horizon

Within their updated model, the Company incorporated a 5-year time horizon. This assumed that higher attendance rates for the scan leads to a lower rate of missed diagnosis of liver disease. The updated model does not permit patients to change liver staging throughout the 5-year time horizon, which the EAC considers appropriate given the slow progression of liver disease, which was previously confirmed by the Clinical experts (EAC Correspondence Log, 2021) and reiterated at the Diagnostic Advisory Committee meeting. The Company has attributed long-term costs to the patients at the end of each branch of the decision tree:

- 'no liver disease' attributes £0 cost;
- 'no behavioural intervention' attributes 0 cost;
- 'behavioural therapy' attributes £78.46 (equivalent to 2 GP consultations) per year;
- 'missed diagnoses', 'does not attend' and 'referred to hepatologist' arms each assume a proportion are in liver warning (annual cost of £78.46, equivalent to GP consultations each year), a proportion with progressive fibrosis (each with £1,103.90 attributed ongoing care with moderate liver disease per year), and a proportion with probable cirrhosis (each with £1,752.07 attributed to ongoing care associated with cirrhosis per year). The Company stated that the proportion of patients with these severities of liver disease were derived from the study by El Gohary *et al.* (2018): 54.3% with liver warning, 34.8% progressive fibrosis and 10.9% probable cirrhosis. The proportions are applied to each branch equally.

Using these costs, the Company state that the cost-saving per patient increases from £51.73 per patient (base case where ongoing care costs were not accounted for) to £81.12 per patient (FibroScan primary care: £1,211.44; FibroScan secondary care: £1,292.56). The EAC has identified that the additional savings are driven by the reduction in "does not attend", Table 5.

Table 5: Costs associated with ongoing care included in the long-term (5-year) time horizon applied in Company updated model

Decision tree outcome	FibroScan in primary care, number of patients (out of 1000 modelled patients)	FibroScan in secondary care, number of patients (out of 1000 modelled patients)	Difference in the number of patients, (Primary care – Secondary care; out of 1000 modelled patients)	Difference in cost (Primary care – Secondary care), per patient
Missed diagnosis of liver disease (attends scan)	19.80	17.80	2.00	£6.17
No liver disease (attends scan)	24.68	22.19	2.49	£0.00
Requires referral to hepatologist	199.83	179.66	20.17	£62.25
Behavioural intervention	645.46	580.34	65.143	£25.56
No behavioural intervention	0.00	0.00	0.00	£0.00
Missed diagnosis of liver disease (does not attend scan)	49.04	89.01	-39.97	-£123.37
No liver disease (does not attend scan)	61.15	110.98	-49.83	£0.00
			TOTAL	**-£29.39**

Additionally, the Company applied annual costs for liver warning assuming two GP consultations per year, and annual costs associated with progressive fibrosis and probable cirrhosis derived from an HTA report of antiviral therapy for mild chronic hepatitis C (Wright *et al.* 2006), Table 6. Therefore, these cost may not be representative of hospital resource usage of patients with suspected non-alcohol fatty liver disease (NAFLD), or alcohol-related liver disease (AFLD).

Table 6: Annual cost applied in the update Company model by liver stage

Liver stage	Annual cost	Source/Comment	EAC Comment
No fibrosis	£0	No cost associated	The EAC reports that the majority of patients in the El Gohary *et al.* (2018) study had no fibrosis (55%, 505 of 910). The assumes that patients with no fibrosis would be discharged back to GP and incur no additional cost £0.
Liver warning	£78.46	GP consultation at £39.23 (PSSRU unit cost 2020), twice a year	Cost for each GP consultation is consistent with updated PSSRU Unit Costs 2021, (Table 10.3b), £39.23. The Clinical experts previously advised that output of FibroScan would guide frequency of surveillance. Following previous advice, those with liver warning could undergo clinical review once every three years. The EAC would assume that patients with liver warning should incur an annual cost of £13.07 (£39.23/3).
Progressive fibrosis	£1,103.90	Wright *et al.* (2006) 'moderate disease', inflated to 2021	Inflation source not explicitly reported. Mean annual total cost of moderate disease was £717, and the highest cost items were outpatient visits and procedures (Wright et al. 2006, figure breakdown provided in Table 37). This was obtained from "Health benefits of antiviral therapy for mild chronic hepatitis C", with unit costs including drug costs, outpatient visits, investigations, procedures, inpatient days. This cost may not be representative of hospital resource usage of patients with suspected non-alcohol fatty liver disease (NAFLD), or alcohol-related liver disease (AFLD). The EAC would consider this is likely an upper estimate of ongoing care costs. The EAC has not identified any data regarding ongoing care of patients with progressive fibrosis. The Clinical experts did not provide any additional information on this subgroup of patients.
Probable cirrhosis	£1,752.07	Wright *et al.* (2006) 'cirrhosis', inflated to 2021	Inflation source not explicitly reported. The average total cost for managing patients with cirrhosis was £1,138 (Wright et al. 2006, figure breakdown provided in Table 37). Same limitations as above.

			One Clinical expert stated that most patients with cirrhosis would be invited to attend hepatology outpatient appointments twice a year. This could include endoscopy (to monitor varices), and ultrasound imaging (to monitor liver cancer). However, acknowledged that frequency of investigations would be dependent on centre and other factors (large, small or no varices). The EAC was unable to identify any national audit data, which reported ongoing care for patients with probable cirrhosis.

The EAC notes that there is a lack of comparative evidence to suggest any difference in short- or long-term patient outcomes between FibroScan being used in a non-secondary (primary or community) care versus secondary care setting. The EAC notes that Clinical experts at the Diagnostic Advisory Committee acknowledged that there is a lack of evidence to confirm that delivery of behavioural therapy changes clinical outcomes. The Clinical experts previously advised that output of FibroScan would guide frequency of monitoring (EAC Correspondence Log, 2021).

FibroScan for assessing liver fibrosis and cirrhosis in primary or community care [GID-MT562]

Medical Technologies Evaluation Programme (MTEP)

Response to NICE Suggested Further Analyses

Submitted by Echosens

National Institute for Health and Care Excellence

July 13th, 2022

Contents

Foreword

The committee asked Echosens to provide additional supporting evidence in the following three areas:

1. The extent of expected use of FibroScan in primary and community care.
2. The likely total cost of doing the test in secondary or specialist care
3. The long-term impacts on cost of testing in primary and community care.

This document elaborates on our original presentation to NICE with published and real-world evidence, confirming that current successful adoption and cost savings are achieved by using FibroScan in primary/community care. We estimate that 15% of FibroScan devices currently installed in the UK are used in a primary or community setting. The committee previously acknowledged that with appropriate training, quality assurance, and frequent use, FibroScan can be used equally effectively in primary or community care, when compared to its current use in secondary care, so we have not focussed on that aspect.

Expected use of FibroScan in primary or community care.

There are a number of potential models for the introduction and use of FibroScan in primary/community care. The evidence suggests that FibroScan devices should be used within a cluster of networks in primary or community care, and not placed in a single GP practice.

FibroScan can be shared effectively within different networks - typically 4 to 6 Primary Care Networks (PCN) - or additional Operational Delivery Networks (ODN). Examples of both these systems are already established - and/or in Community Diagnostic Centres/Community Rehabilitation Centres.

Expected numbers of patients

Using a model of a single FibroScan device shared across 5 PCNs (in the context of the typical number being 4 – 6 PCNs), the expected number of patients attending can be shown in one of two ways:

1. **Real-World Data:** Based on real-world data presented in Table 1 (below) the annual attendance was between 500 and 1000 patients per PCN, equivalent to 2500 – 5000 for a single device shared across 5 PCNs.
2. **National Data:** Based on National estimates the average annual attendance would be 1000 patients per PCN, or 5000 for a single device shared across 5 PCNs. There are good reasons that this figure is a little higher than the that from real world (see below).

3.

Real-World Data: Use of FibroScan in Primary or Community Care

FibroScan is increasingly being utilised in primary and community care – not least because it is painless and easy to use. NHS England and UK Health Service Agency (previously Public Health England) have commissioned care pathways which include FibroScan used in GP practices and community services. Examples include:

1. In 2015 NHS England funded 22 FibroScan devices to implement scanning in the community for Hepatitis C-induced liver fibrosis, through Operational Delivery Networks (ODNs) (one FibroScan per network).
2. In 2019 Public Health England (PHE) funded a further 11 FibroScan systems for use in community settings, to assess liver fibrosis and cirrhosis due to alcohol use disorder - 2 in Leeds City Council, 5 in Merseyside/Royal Liverpool, 1 in Manchester CGL (service provider), 1 in Nottingham, 2 in Brent and Hillington.
3. South Nottinghamshire: The Scarred Liver Project, which delivers a new diagnostic pathway to detect chronic liver disease across primary and secondary care.

Table 1 below presents a snapshot of the use of FibroScan in primary and community care, as reported in Gordon et al 2021[1]. This study found that implementation of FibroScan within primary care network (PCN) or community care settings was not only feasible, but both clinically effective, and cost saving.

Table 1 Typical sites currently using FibroScan in primary or community care

Location	**Area Covered**	**Number of machines**	**Number of scans**	**Any other information**
Southampton	2 GPs across 2 PCNs	2 systems	533 over 14 months	Systems are mobile across the different practices

Mid Hampshire	18 GPs across 4 PCNs	1 system	1,115 in a 12-month period	Systems are mobile across the different practices
South Nottinghamshire The Scarred Liver Project[2]	4 CCGs, Accessible to 100 GPs included within 9 PCNs serving a population of 700,000 people	2 systems	2,715 patients had a FibroScan from Sept, 2016 to Sept, 2018	GPs are able to refer patients with a defined risk factor for chronic liver disease directly for a specialised ultrasound test (Fibroscan®) before considering referral to secondary care.

Following a successful 18-month pilot across 2 PCNs and 2 GP practices, **Southampton** City CCG formally commissioned a local Community Fibro Scan Service in 2020. This service is operated in primary care (https://www.solentmedicalservices.co.uk/) alongside other community services. It now serves 6 PCNs and has been commissioned for 5 years.

In **Mid Hampshire** the PCN involvement started as a part of an integrated pathway in 2019 and is still in operation in 2022. The new pathway was noted in the paper by Gordon et al as having evidence of being clinically effective as well as cost effective when implemented at a collaborative PCN level.[1]

Summary of Real-World Data Findings

Based on the real-world data presented in Table 1 (above), the annual attendance was between 500 and 1000 patients per PCN, equivalent to 2500 – 5000 for a single device shared across 5 PCNs.

Further supporting evidence is available in Appendix 1, which summarises evidence from several studies on the use of FibroScan in Portsmouth, Southampton and

Gateshead, the Scarred Liver Project and the LOCATE study. They provide clear evidence of the feasibility, practicality, cost savings, ease of use, and reliability of using FibroScan in those settings. In addition, the Gordon et al study reported a high level of patient and GP satisfaction regarding the introduction and use of FibroScan in primary & community care [1].

Ease of Use in Primary or Community Care

The evidence (Gordon et al) shows that FibroScan can be used competently and reliably by operators ranging from health-care assistants (Band 2) to nurses (Band 6). The scan simply requires the placement of the FibroScan probe directly over the lower ribs of the patient and pressing predetermined buttons on the machine to start the scan. Training can be given within half a day at a cost of £1,150 (NICE 2020, +3% since then) for up to three people. Supervision from a competent user is needed for around the first 50 uses.

National Data: Numbers of Patients Based on National Estimates

Taking a national perspective on the numbers of people with liver fibrosis likely to be eligible for scanning, the table at Appendix 2 shows an estimated number based on the Liver Atlas, UK 2017.

Summary of data based on National estimates

The Atlas data show that an average of 1000 patients per annum per PCN would be eligible for screening by FibroScan per annum, which equates to 5000 patients per annum across our model group of 5PCNs.

Overall Summary

These two approaches (local real-world data and National Estimates) for modeling future patient numbers based on sharing a single FibroScan device across 5 PCNs show similar results, with a range between 2500 and 5000 patients per annum.

The trials reviewed show FibroScan devices are clinically effective and cost saving when shared across Primary and Community Care networks. The trials also confirmed that FibroScan devices are considered easy to use and found to be acceptable to both clinicians and patients.

Reasons for differences between the national estimate and the real-world figures

Reasons that not all the eligible patients, suggested by the national data would end up having a FibroScan (so the figure from real world data is somewhat lower) include:

1. Not every patient will be identified as being at risk and requiring a scan.
2. Other technologies available (ELF test or others).
3. No liver pathway available (https://britishlivertrust.org.uk/make-early-diagnosis-of-liver-disease-routine-maps/)
4. Local guidance to not conduct a FibroScan on patients with hazardous alcohol consumption, a high BMI or with Type 2 diabetes, etc.
5. Patient non-attendance.
6. The size of the PCN can be smaller (1% with less than 24,000 patients. Morciano et al 2020).

Numbers of Patients Based on Fibrosis Stage

We have also estimated these figures by Fibrosis stage to further support our studies, and the numbers are reassuringly similar. This evidence is presented at Appendix 3.

Appendix 1

Published evidence of feasibility, practicality, cost savings, and reliability

	Pathway goal	Pathway description	Fibrosis assessment		Study size (mean age; % female, % male)	Main findings	Fibrosis detection % (n/N)*	Transient elastography attendance rate
			First test	Second test				
(Continued from previous page)								
Portsmouth Hospitals NHS Trust NAFLD pathway;[20] England	Detection and risk stratification of NAFLD	Primary care practitioners managing patients with steatosis on ultrasound abnormal alanine aminotransferase in the absence of alcohol abuse and a negative non-invasive liver screen, are asked to send NFS; those with high NFS are referred directly to a hepatology clinic and intermediate scores are referred to a nurse-led one stop FibroScan clinic for transient elastography	NFS (-1·455 to 0·675)	Transient elastography (≥7·9 kPa)	904 (59 years; 47·1%, 52·9%)	87·4% of referrals through this pathway were diagnosed with NAFLD; among this group 70·6% had an liver stiffness; measurement <7·9 kPa, and the pathway was able to discharge 70·9% of referrals back to primary care overall	26·6% (210/790)	97·2%
Risk factors								
Gateshead pathway;[21] England	Detection of advanced fibrosis, primarily in NAFLD	Routine FIB-4 screening at annual review of type 2 diabetes; if intermediate or elevated and deemed appropriate to investigate further, the patient is referred for transient elastography	FIB-4 (≥1·3 if 35–65 years; ≥2·0 if >65 years)	Transient elastography (>8 kPa)	466 (63·8 years; 37·1%, 62·9%)	18·2% (85/467) of patients with diabetes screened had an elevated FIB-4; of the 58 patients referred, 43·1% had an elevated liver stiffness measurement of >8 kPa; over a fifth of patients referred for transient elastography had cirrhosis	43·1 % (25/58)	93%
LOCATE study;[22] England	Detection of advanced fibrosis, primarily in NAFLD and alcoholic liver disease	Cluster randomised feasibility trial; nurse-led primary care-based clinic accessible via primary care practitioner referral, community-based liver nurses doing case finding of patients with risk factors for liver disease (eg, type 2 diabetes), using electronic records, and patients with high AUDIT scores based on mailed questionnaires¶	Liver traffic light test (ie, green, amber, or red)	Transient elastography (6–8 kPa liver warning; 8–12·9 kPa	14 622 (49 years; 50·7%, 49·3%)	Of the 910 patients seen in community-nurse-led clinics 4·8% had probable cirrhosis and a further 15·5% had advanced fibrosis; 53·8% (218/405) of new cases of liver disease were identified through the nurse-led case finding intervention group; the intervention groups identified more than double the number of new cases of liver	15·5% (141/910)	N/A
Leeds Community Hepatology Clinic (CHEP);[25] England	Detection of advanced fibrosis, primarily in NAFLD and alcohol-related liver disease	Pilot study; patients with clinically suspected NAFLD or alcohol-related liver disease had an ELF test performed by primary care practitioners; if ELF test results were ≥9·5, patients had transient elastography in the community‖	ELF (> 9·5)	Transient elastography (≥15 kPa defined significant fibrosis)	1450 (age and sex demographics not stated)	Of 1450 patients assessed through the community pathway, 572 had an elevated ELF, with 71% attending their transient elastography appointment; 66% of these patients had NAFLD and 31% had alcohol-related liver disease; the pilot pathway was shown to be cheaper than standards of care; 53·3% of patients were discharged after clinic vs 9·6% in standards of care	11·1% (45/405)	71%
Scarred Liver Project;[5] England	Detection of advanced fibrosis of any cause	Patients with risk factors for NAFLD or alcohol-related liver disease (eg, obesity, type 2 diabetes, harmful alcohol consumption) can be referred to nurse-led transient elastography clinic; simultaneously patients with elevated liver function tests, a negative non-invasive liver screen, and aspartate aminotransferase to alanine aminotransferase ratio of ≥0·8 could be referred to the clinic**	Aspartate aminotransferase to alanine aminotransferase ratio (≥0·8) or fatty liver index‖ (≥60)	Transient elastography (8–14 kPa consider referral; ≥15 kPa all referred)	968 (56·3 years; 51%, 49%)	In >700 000 individuals, 968 patients were referred for transient elastography in 1 year, most commonly through the abnormal liver function tests pathway; of this group 22·9% had a liver stiffness measurement >8 kPa, with 5·9% having cirrhosis; the authors showed that without a case finding strategy, 38·7% of cases of liver disease would go undetected	22·9% (222/968)	Not stated

Appendix 2

Population subgroup in relation to liver diseases	**Numbers at risk/affected/concerned**	**Source/ Assumptions**
Proportion of the population with at risk liver damage and liver disease	5%	Liver Atlas UK 2017[i]
Average number of patients per PCN	40,000	30,000-50,000 patients per PCN on average Morciano et al, 2020[3]
Test per patient per year	0.5	NICE Guidance NG50. Provide a test every 2 years
Number of patients per year per PCN to scan	**1,000**	**5% x 40,000 x 0.5**

[i] https://fingertips.phe.org.uk/documents/FINAL_LiverAtlas.pdf

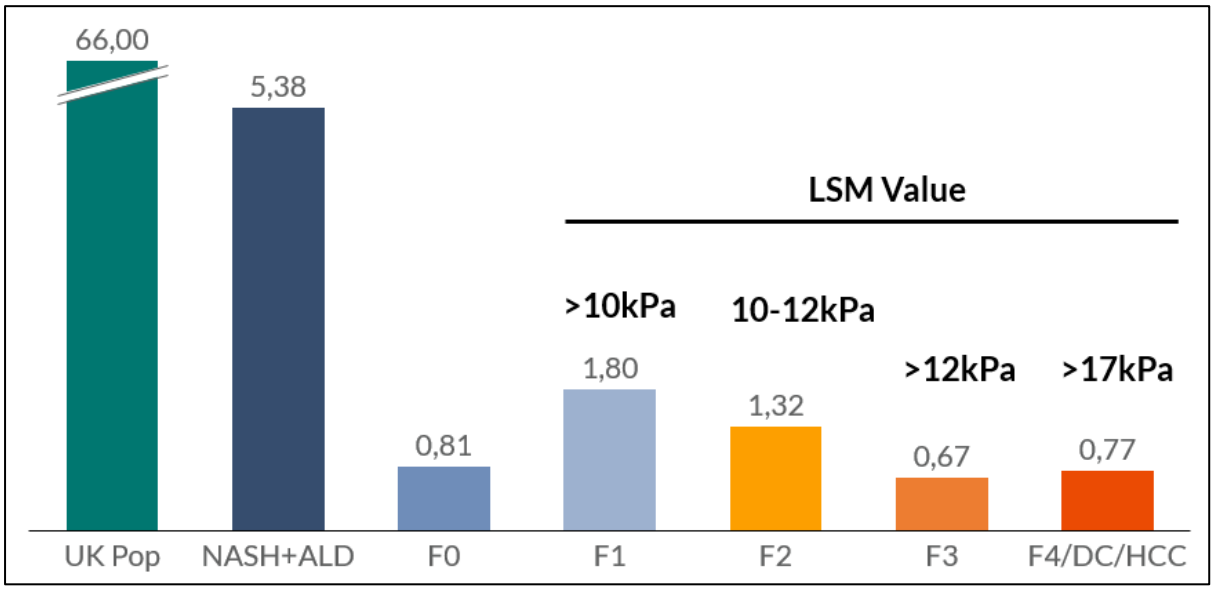
Appendix 3

Numbers of Patients Based on Fibrosis Stage

Figure 1 (below) represents patient numbers by liver fibrosis stage in the UK[4] with the associated LSM cut-offs for each fibrosis stage (F0 to F4), based on the FibroScan Interpretation Guide. Cut-off could vary depending on the condition[5].

Note: Alcoholic Liver Disease (ALD) and Non-Alcoholic Fatty Liver Disease (NAFLD) evolving to Non-Alcoholic Steatohepatitis (NASH) account for more than 90% of patients suffering from Chronic Liver Disease in the UK (British Liver Trust website).

Figure 1 Patient with NASH and ALD by Stage of Fibrosis in the UK (Millions)



DC: Decompensated cirrhosis; HCC: Hepatocellular carcinoma

The Southampton pilot (used as an example to implement the economic model with real-world evidence data) defined a minimum threshold of 10 kPa for a FibroScan procedure performed outside secondary care to refer patients to hepatology, regardless of the condition.

Considering the patients numbers revealed in Figure 1 and the threshold of 10 kPa based on the patient pathway, 1.4M (F3/F4 only) to 2.7M (F2 to F4) patients in the UK would be eligible to receive liver fibrosis assessment.

A recent paper presented the probable diagnosis ratio per liver fibrosis stage for NASH in the UK, which we can use to estimate the number of patients in the UK eligible for diagnosis using FibroScan. The data is presented below, for reference.

Table 2 Diagnosis probability and volume of patients (Morgan et al 2021)

Disease stage	F0	F1	F2	F3	F4/DC/HCC
Total patients (M)	0.81	1.80	1.32	0.67	0.78
Probability of Diagnosis	2,0%	2,0%	16,5%	58,3%	100%
Total patient diagnosed (M)	0.02	0.04	0.22	0.39	0.78

Considering these data, together with the threshold of 10 kPa and the probability of being diagnosed, 1.2M (F3/F4 only) to 1.4 M (F2 to F4) patients in the UK are likely to be diagnosed for liver fibrosis. This represents 2% of the UK population.

Considering a PCN has close to 50,000 patients on average[3] and the ratio of patients with chronic liver disease eligible to receive liver fibrosis assessment is approx. 2%, it represents a volume on average of 1,000 patients per year within a PCN. According to EASL (European Association for the Study of the Liver) Guidelines, for patients with NAFLD/NASH it seems reasonable to repeat a non-invasive test every 3 years in patients with early stage (F0 to F2) and every year in patients with advanced stage (F2/F3 to F4) NASH[6].

However, according to NICE Guidance, patients diagnosed with ALD should be offered retesting every 2 years.

These results are also in line with our estimates based on National statistics and real-world evidence, with an upper limit of approximately 5000 patients per annum across 5 PCNs.

Model-related responses

Introduction

Two concerns raised by the committee are related to model inputs: 1. The long-term impacts of testing in primary or community care on costs, and 2. The likely total cost of doing the test in secondary or specialist care. This section addresses both concerns and provides the Company recommended results.

Methods and revised inputs

Uncertainty about the likely total cost of doing the test in secondary or specialist care

Submission history of cost inputs used for FibroScan in secondary care

In the original Company model ('Model V1.0', file dated October 21), staff time to interpret the scan result (non-Consultant led face-to-face appointment in hepatology department) was added to the HRG bundled cost (RD48Z, IMAGOP Imaging: Outpatient Ultrasound Elastography).[7] The EAC disagreed with this addition of staff time and claimed the time to evaluate scan is already incorporated within the HRG bundled cost. In response to this comment, the Company provided an option to remove these additional staff time costs from the total cost of FibroScan in secondary care in Model V2.0 (file dated March 2022).

The EAC also tested a weighted average HRG cost for ultrasound elastography of £61.98. The Company also added a scenario using this weighted average HRG cost in Model V2.0.

For reference, a summary of the costs tested in Model V1.0 and V2.0, and by the Assessment Group are provided in Table 3.

Table 3 Previously suggested values for the cost of FibroScan in secondary care

	Value	Reference
Company used in initial submission (model V1)	43.93+93.19= £137.12	IMAGOP/RD48Z + non-admitted F2F attendance, first (non-consultant led)
Value used in Assessment Report	£43.93 for the base case, increased to £61.98 in scenario analysis	IMAGOP/RD48Z
Company values tested in scenarios (i) (model V2)	£43.93	IMAGOP/RD48Z
Company values tested in scenarios (ii) (model V2)	£61.98	Alternative weighted average HRG

Final Company preferred costing of FibroScan in secondary care

Since submitting Model V2.0, the Company has conducted a small survey of secondary care centres about the codes used by hospital coders when FibroScan in secondary care is performed. Two centres provided feedback: King's College Hospital NHS Foundation Trust and University Hospital Southampton NHS Foundation Trust. King's College reported that they use RD24Z (IMAGOP Imaging: Outpatient Computerised Tomography Scan of Two Areas, with Contrast) and Southampton reported the use of RD42Z (IMAGOP Imaging: Outpatient Ultrasound Scan with duration of 20 minutes and over, without Contrast). Given this feedback, the Company has chosen to select a weighted average across these codes in the base case (£88.15) as there is uncertainty between locations about which codes are currently being used in secondary care practice for FibroScan. The weights were calculated according to the reported number of examinations, and the Company is aware that these codes are used for other procedures and scans, and in other disease areas. The weighting calculations are presented in Table 4.

Table 4 HRG codes used for FibroScan in secondary care

Currency Description	Department Name	Currency Code	Department Code	Number of Examinations	National Average Unit Cost (£)	Weighting	Weight cost (£)
Computerised Tomography Scan of Two Areas, with Contrast	Imaging: Outpatient	RD24Z	IMAGOP	15829	145.36	3%	88.15
Computerised Tomography Scan of Two Areas, with Contrast	Imaging: Outpatient	RD24Z	IMAGOP	182364	114.36	34%	
Ultrasound Scan with duration of 20 minutes and over, without Contrast	Imaging: Outpatient	RD42Z	IMAGOP	38181	68.88	7%	
Ultrasound Scan with duration of 20 minutes and over, without Contrast	Imaging: Outpatient	RD42Z	IMAGOP	297365	71.50	56%	

Additional Scenario: Microcosting in secondary care

In the NICE 'Suggested further analyses for Echosens' document, it was commented that it would be "useful to provide a comparison of the individual costs that make up the total cost of FibroScan in secondary or specialist care… with those used to calculate the cost of FibroScan in primary or community care to help identify and compare equivalent costs between the 2 settings."

Microcosting procedures in secondary care is not standard practice in NICE submissions. However, given the uncertainty around which HRG bundled cost would be relevant for use of FibroScan in secondary care, an attempt has been made to calculate the cost of FibroScan in secondary care.

In the Company submitted report 'Additional Manufacturer Evidence and Analyses' the total cost of a FibroScan machine purchased outright was calculated to be £120,020. The breakdown of this cost is provided in Table 5. This figure is divided by the lifetime of the machine (7 years) and by the average number of scans performed per year.

Table 5 FibroScan costs if machine is purchased

Item	**Cost**	**Number required over machine lifetime***
FibroScan 430 Mini+	£48,000	1
Additional probes	£16,700	1
Cost of CAP/SmartExam software	£18,500	1
Cost of 6-year Serenity service contract[†]	£28,560	1
Training costs (per person)	£1,180	7
Total	**£120,020**	

To estimate the average number of scans per year in secondary care, four hospitals that were part of the small survey (one machine per hospital) were asked about the number of scans performed per year for calendar years where the machine has been in use throughout the time period. The responding hospitals and reported number of scans are provided in Table 6. The hospital-specific average number of scans across the years 2019-2021 were then weighted using the proxy of the number of beds per hospital to indicate the size of the hospital. This gave an average number of scans per year as 610.

Table 6 Number of scans performed by four hospitals

Hospital (one machine per hospital)	**2019**	**2019**	**2020**	**2021**	**Average across years**	**Number of beds per hospital**	**Weight applied to average**
Frimley Park Hospital	593	856	682	964	774	938	32%
Hairmyres Hospital	198	464	431	433	382	488	17%
Watford Hospital	115	200	191	114	155	521	18%
Wythenshawe Hospital	864	997	591	806	815	950	33%
Number of scans per year							**610**

Given the lifetime of the machine is 7 years, and the average number of scans performed by each hospital presented in Table 6 (N= 610), this results in an average cost per scan of £28.11. The cost of a nurse's time to perform the scan is added to this cost for the total cost of FibroScan outside of secondary care (£12.50, calculated by £50/hour for Nurse (in secondary care), multiplied by 0.25 to reflect the 15 minutes required to perform the test), making the total cost per a scan performed in secondary care £40.61. A breakdown of these costs and a comparison to the microcosting previously calculated for FibroScan outside secondary care has been provided in Table 7. Results generated using this value have been included in a scenario analysis in this report.

Table 7 Microcosting calculations for both care settings

Item no.	Item	Outside secondary care	Inside secondary care
i	Total cost of machine and training if purchased outright	£120,020	£120,020
ii	Lifetime of machine (years)	7	7
iii	Number of scans per year	500	610
iv	Cost per scan excluding staff costs ((i/ii)/iii)	£34.29	£28.11
v	Staff costs	£10.50	£12.50
vi	Cost per scan (iv + v)	£44.79	£40.61

Additional Scenario: Microcosting outside secondary care

Model V2.0 incorporated an approach which approximated the cost of FIbroScan outside secondary care using a microcosting approach. A key input for this approach is the number of scans performed per year. The Southampton CCG group performed 500 within a 12-month period, so this figure was used in the base case (see Table 1 in the 'Real-World Data' Section). However, this is also evidence of CCGs performing more scans than this, for example Mid Hampshire performed 1,115 (Table 1). For this reason, 500 is seen as a conservative estimate and 750/year is also tested in a scenario analysis. The calculated cost per scan when 750 are performed per year is provided in Table 8.

Table 8 Microcosting calculation outside secondary care scenario analysis

Item no.	Item	Outside secondary care

i	Total cost of machine and training if purchased outright	£120,020
ii	Lifetime of machine (years)	7
iii	Number of scans per year	750
iv	Cost per scan excluding staff costs ((i/ii)/iii)	£34.29
v	Staff costs	£10.50
vi	Cost per scan (iv + v)	£33.36

Long-term impacts of testing in primary or community care on costs are uncertain

The time horizon of the Company Model V1.0 was 1 year, which captures the FibroScan test in both settings, and differences in care pathway following the scan which are relevant to the decision problem. This may underestimate the true cost savings of performing FIbroScan outside secondary care, as the higher attendance rates to scan appointments lead to a lower rate of missed diagnosis of liver disease, which is expected to avoid long-term costs associated with undiagnosed liver disease being allowed to progress.

Due to the uncertainty and heterogeneity with patient pathways in the long-term, long-term costs were not originally modelled. The EAC agreed that this was the most appropriate approach. The committee concluded that a longer time horizon considered in the model would have been preferable to help assess the impact of the test. Based on this comment, the Company added the ability to look at a 5-year time horizon into Model V2.0.

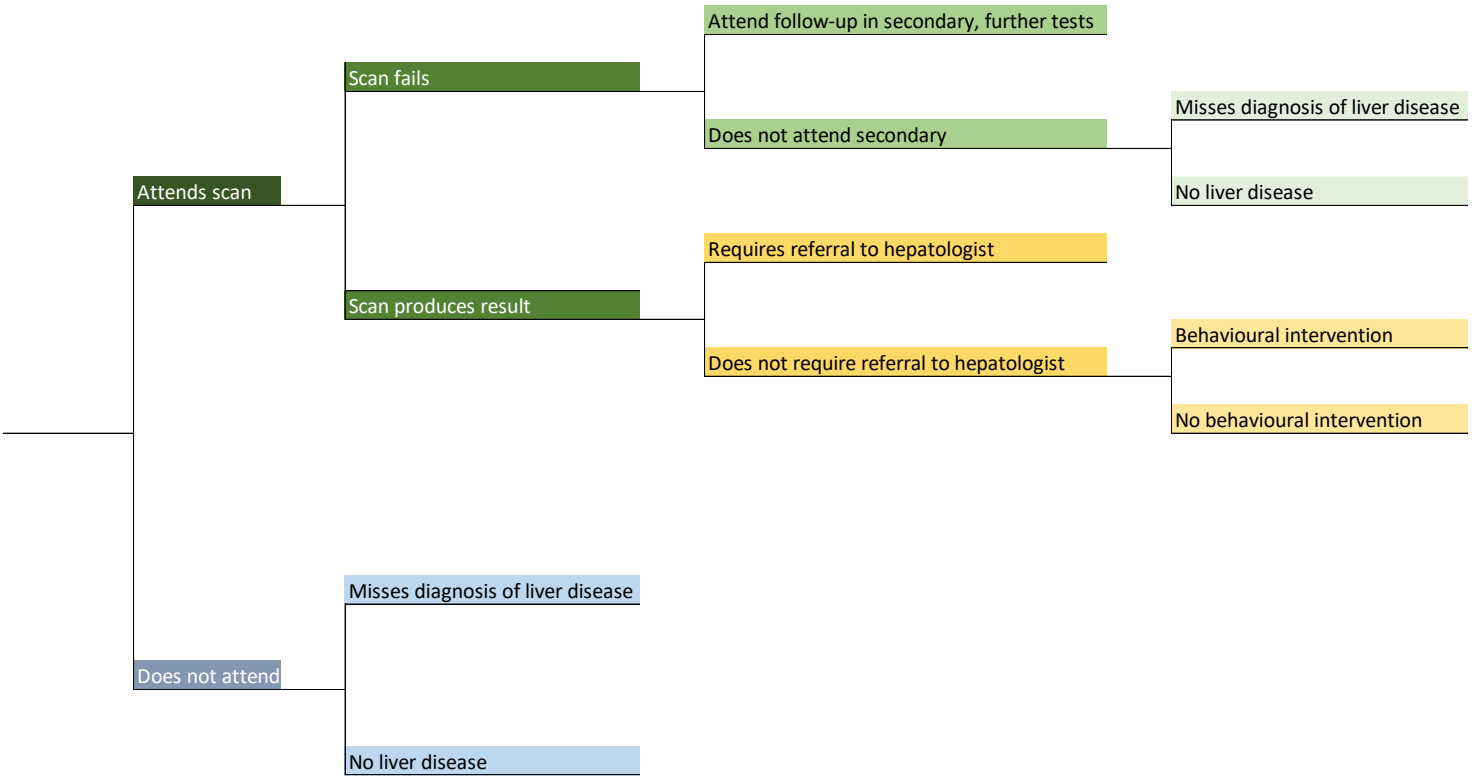
A 5-year time horizon was incorporated by adding the estimated long-term costs to the end of each branch in the decision tree. Model V2.0 did not incorporate progression across liver disease stages because liver disease is known to progress slowly, and any progression occurring over a 5 year time frame was not thought to substantially impact costs.[8]

NICE and the EAC have since requested that the Company add clarity to the assumptions used in the long-term modelling, and that the Company incorporate progression of liver disease into the long-term modelling. This section clarifies the Company's approach to long-term costing.

Model structure

This section provides a summary of the model structure. This decision tree model is initiated at the point from which an individual is identified as requiring FibroScan. The model structure in both treatment arms (FibroScan performed outside secondary care and FibroScan performed inside secondary care) is as outlined in Figure 2.

Figure 2 Model structure*



*one arm, structured is mirrored in both arms

The patient first may decide to attend or not attend the scheduled scan. If the patient does not attend the scan, then for patients with underlying liver disease, the diagnosis will be missed and the liver disease will remain untreated. If the patient attends the scan, then for a small proportion of patients the scan may fail to produce

results. If these patients do not attend secondary care for further tests, the diagnosis will be missed and the liver disease will remain untreated for a proportion of patients with underlying liver disease. When a long-term perspective is modelled, patients in these branches can be classified as having 'liver warning', 'progressive fibrosis' or 'probable cirrhosis', the distribution of which depends on the disease aetiology. Patients are modelled to progress through these categories. This is well described in the section below titled "For branches ending 'Misses diagnosis of liver disease'".

When the scan produces a result, depending on the severity of the liver fibrosis, the patient may require specialist treatment, or they may only require a behavioural intervention or no intervention at all. Alternatively, the scan may fail but the patient is referred to a follow-up in secondary care. The long-term assumptions for these scenarios are also well descried below, and for these branches it is assumed that liver disease does not progress.

For branches ending 'Misses diagnosis of liver disease'

The undiagnosed liver disease may be at different severity stages. The model used the liver staging definitions and the reported proportion of patients across three stages of liver disease by aetiology as published by El Gohary et al (Table 9)[9].

Table 9 Liver stage by aetiology

Liver stage	All patients N (%)	Non-alcoholic fatty liver disease N (%)	Alcohol-related liver disease N (%)	Hepatitis-related liver disease N (%)
Liver warning	220 (54%)	102 (51%)	89 (60%)	4 (50%)
Progressive fibrosis	141 (35%)	75 (37%)	44 (30%)	3 (38%)
Probable cirrhosis	44 (11%)	24 (12%)	16 (11%)	1 (13%)
Total	405	201	149	8

Progression was incorporated using transition probabilities reported in previously published economic models in liver disease. As liver disease can progress at

different rates depending on aetiology, progression is calculated separately for each liver disease aetiology. Transition probabilities are provided in Table 10. It is assumed that all patients either stay in the same state or progress (i.e., no improvement in liver disease is modelled).

Srivastava 2019 presents a cost-comparison analysis of non-invasive liver fibrosis tests for non-alcoholic fatty liver disease, and Wright 2006 presents a cost-effectiveness model for mild hepatitis C.[10,11] No economic model reporting transition probabilities for people with alcohol-related liver disease was identified. However, Poynard 2003 and Shoreibah 2016 report that people with alcohol-related liver disease have a higher rate of progression compared to those with both non-alcoholic fatty liver disease and hepatitis-related liver disease.[12,13] For the transition from progressive fibrosis to cirrhosis, according to Shoreibah 2016, the 10-year probability of developing cirrhosis in an alcohol-related liver disease population is 67%. If it is assumed that these patients had to have progressive fibrosis at baseline, then the annual probability of developing cirrhosis from progressive fibrosis can be calculated to be 10.5%. Incidentally, the assumption that alcohol-related liver disease leads to double the 10-year probability of developing cirrhosis from progressive fibrosis from non-alcoholic fatty liver disease as reported by the progression rates in Srivastava 2019, also leads to the estimate of the annual probability of developing cirrhosis from progressive fibrosis being 10.5%. Since two sets of assumptions and two data sources (Srivastava 2019 and Shoreibach 2016) lead to very similar results, the same logic was applied to calculate the annual probability of progressing from ‘liver warning’ to ‘progressive fibrosis’ (i.e., we calculated the 10-year probability of progression for non-alcoholic fatty liver disease based on Srivastava 2019 and assumed that the 10 year probability would be double for alcohol-related liver disease to then calculate an annual rate, see Table 10).

Table 10 Liver disease progression

Population	Annual transition probability	Value	Source and assumptions
Non-alcoholic fatty liver disease	From liver warning to progressive fibrosis	0.001	Srivastava 2019 'develop F3 disease'

	From progressive fibrosis to probable cirrhosis	0.04	Srivastava 2019 'develop F4 disease'
Hepatitis-related liver disease	From liver warning to progressive fibrosis	0.025	Wright 2006, ‘mild to moderate fibrosis’
	From progressive fibrosis to probable cirrhosis	0.037	Wright 2006, ‘moderate to cirrhosis’
Alcohol-related liver disease	From liver warning to progressive fibrosis	0.002	Calculated assuming ALD leads to double 10-year probability compared to NAFLD
	From progressive fibrosis to probable cirrhosis	0.105	

The resulting impact of incorporating progression on the distribution of patients across the liver warning, progressive fibrosis and probable cirrhosis categories over five years is provided in Table 11, which highlights that slow progression of liver disease.

Table 11 Distribution of liver disease over time

Year in model	**All patients**			**NAFLD**			**ALD**			**Hepatitis-related**		
	LW	*PF*	*PC*	*LW*	*PF*	*PC*	*LW*	*PF*	*PC*	*LW*	*PF*	*PC*
Year 1	54%	34%	11%	51%	37%	12%	60%	30%	11%	50%	38%	13%
Year 2	54%	32%	14%	51%	36%	13%	60%	27%	14%	49%	37%	14%
Year 3	54%	30%	16%	51%	34%	15%	59%	24%	17%	48%	37%	15%
Year 4	54%	28%	17%	51%	33%	16%	59%	21%	19%	46%	37%	17%
Year 5	54%	27%	19%	51%	32%	18%	59%	19%	21%	45%	37%	18%

NAFLD: non-alcoholic fatty liver disease, ALD: alcohol-related liver disease; LW: liver warning; PF: progressive fibrosis; PC: probable cirrhosis

The model does not account for mortality occurring over the 5-year time frame. Haflidadottir 2014 states that "the survival for patients with moderate to severe fibrosis was significantly worse than for patients with mild fibrosis", indicating that the reduction in the number of missed diagnoses due to the placement of FibroScan in primary care which stops, or at least slows down progression with treatment will also likely reduce number of liver disease-related deaths.[14]

Annual costs for liver warning was based on a recommendation by the EAC, based on clinical opinion.[15] For progressive fibrosis and probable cirrhosis, a Health Technology Assessment Programme report was used (Wright et al, 2006).[11] Although this report is in relation to liver disease developed in those with hepatitis C, costs for treating each stage were assumed to be similar across aetiologies. Annual costs for each stage are outlined in Table 12.

Table 12 Annual cost by liver stage

Liver stage	Annual cost	Source/Comment
Liver warning	£13.07	Recommended value by the EAC
Progressive fibrosis	£1,103.90	Wright et al 2006 'moderate disease', inflated to 2021
Probable cirrhosis	£1,752.07	Wright et al 2006 ''cirrhosis', inflated to 2021

For branches ending 'Requiring referral to hepatologist' or 'Attend follow-up in secondary, further tests'

These patients were assumed to be diagnosed and to be receiving appropriate treatment for their liver disease. Therefore, branches ending 'requiring referral to hepatologist' or 'attend follow-up in secondary, further tests' follow the same approach to determine the proportion of patients falling in each liver disease stage category as those ending 'misses diagnosis of liver disease', but patients are not modelled to progress. It is assumed that patients are treated after receiving the

diagnosis, and that treatment stops progression within the 5-year time horizon, i.e. that treatment does not revert liver damage, but does prevent it from getting worse.

For the tree including further tests after scan failure, it is assumed that patients in the 'attend follow-up in secondary, further tests' after scan failure will all require further treatment for liver disease, although it is unlikely that all patients who have a scan failure will have liver disease.

For branches ending 'behavioural intervention'

Patients receiving behavioural intervention should by definition have only mild disease. It was assumed that the long-term cost for these patients is the same as those with 'liver warning' – e.g. £13.07/year.

This assumes that if the patient requires behavioural intervention within the first year after having a scan, then liver disease is manageable through behavioural intervention and does not progress. This would rely on patients following advice and does not account for non-compliance or progression of disease in this time frame.

For branches ending 'no liver disease', 'no behavioural intervention'

No costs were applied. This assumes that these patients do not develop habits that lead to liver disease within a 5-year timeframe.

Summary of Company preferred base case settings

In the base case, the Company advise the following settings to be used in the base case:

- Include referral for further tests after scan failure? "Further tests after scan failure"
    - Justification: As advised in Assessment Group report
- Costing approach for FibroScan outside of secondary care: "Microcosting"
    - Justification: It is anticipated that the majority of machines will be purchased outright
- Time horizon: "5 years"

    - Justification: The MedTech Funding Mandate policy 2021/22 ‘Guidance for NHS commissioners and providers of NHS-funded care’, suggests that devices should be cost-saving within three years[16]
- Cost of Fibroscan in secondary care: “Weighted IMAGOP/RD24Z + IMAGOP/RD42Z”
    - Justification: These codes are used in currently in clinical practice. Microcosting secondary care procedures is not standard practice for NICE models

Model results

Company preferred base case

Due to the increased attendance rates at scans, the use of FibroScan outside of secondary or specialist care identifies more patients with liver disease requiring some form of intervention (specialist treatment by hepatologist or a behavioural intervention by a GP, community nurse and/or healthcare assistant). Despite the increase of cases identified, FibroScan used outside of secondary or specialist care reduces costs by reducing the number of visits to hepatologist departments as well as reducing the long-term costs due to missed scan appointments (and missed diagnosis of disease).

Table 13 Base case results

	Mean using FibroScan outside of secondary or specialist care (technology)	Mean using FibroScan in secondary or specialist care (comparator)	Difference in means: technology vs comparator
Scan costs	£42.99	£76.74	£-33.75
Missed appointment costs	£1.27	£2.50	£-1.23
Hepatologist referral costs	£41.54	£29.60	£11.94
Behavioural intervention costs	£8.44	£7.59	£0.85
Long term costs	£1,151.50	£1,193.91	£-42.42
Total cost	£1,245.73	£1,310.34	£-64.61
Number of referrals to hepatologist after scan	0.20	0.18	0.02
Number of referrals to behavioural intervention	0.65	0.58	0.07
Missed diagnosis of liver disease	0.05	0.09	-0.04
Total number of visits to hepatology department	0.24	0.98	-0.74

Scenarios

Extensive scenario analysis was presented previously, based on Model V2.0 (Additional Manufacturer Evidence and Analyses 9 March 2022). Two scenarios are presented in this report around the microcosting.

Microcosting in secondary care

Table 14 shows that when microcosting is used in secondary care that the results are similar to the base case (overall cost saving). The use of HRG codes is still the Company preferred base case.

Table 14 Secondary care microcosting scenario results

	Mean using FibroScan outside of secondary or specialist care (technology)	**Mean using FibroScan in secondary or specialist care (comparator)**	**Difference in means: technology vs comparator**
Scan costs	£41.30	£38.71	£2.59
Missed appointment costs	£1.27	£2.50	£-1.23
Hepatologist referral costs	£41.54	£29.60	£11.94
Behavioural intervention costs	£8.44	£7.59	£0.85
Long term costs	£1,151.50	£1,193.91	£-42.42
Total cost	£1,244.04	£1,272.31	£-28.27
Number of referrals to hepatologist after scan	0.20	0.18	0.02
Number of referrals to behavioural intervention	0.65	0.58	0.07
Missed diagnosis of liver disease	0.05	0.09	-0.04
Total number of visits to hepatology department	0.24	0.98	-0.74

Microcosting outside secondary care

Table 15 shows that when the number of scans increases from 500 to 750 the cost saving increases by £10.17 per person (from -£64.61 to -£74.78). The conclusions from this scenario are similar to the base case.

Table 15 Outside secondary care microcosting scenario results

	Mean using FibroScan outside of secondary or specialist care (technology)	**Mean using FibroScan in secondary or specialist care (comparator)**	**Difference in means: technology vs comparator**
Scan costs	£32.82	£76.74	£-43.92
Missed appointment costs	£1.27	£2.50	£-1.23
Hepatologist referral costs	£41.54	£29.60	£11.94
Behavioural intervention costs	£8.44	£7.59	£0.85
Long term costs	£1,151.50	£1,193.91	£-42.42
Total cost	£1,235.56	£1,310.34	£-74.78
Number of referrals to hepatologist after scan	0.20	0.18	0.02
Number of referrals to behavioural intervention	0.65	0.58	0.07
Missed diagnosis of liver disease	0.05	0.09	-0.04
Total number of visits to hepatology department	0.24	0.98	-0.74

Conclusion

The Company have responded to requests to present additional recommended analyses. The recommended Company base case predicts that FibroScan performed outside secondary care compared to FibroScan performed inside secondary care will be cost saving by £-64.61 per person scanned. It is worth noting that the model omits several factors which mean that this estimate may underestimate the true cost saving of performing FibroScan outside secondary care, including:

- Model does not capture mortality and the impact of increased diagnosis rate and proportions treated on mortality in the long term

- Model does not consider the opportunity/economic cost for the patient and how this will improve quality of life– e.g., the reduced need for long patient journeys, car parking, and carer costs, loss of economic, productivity, decrease in hospital visits and reduction of waiting times
- Model does not capture the additional freed up time/capacity for a secondary care hospital. Liver specialists will see patients who require secondary care intervention in a more timely way with reduced waiting times.

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GID-MT562 FibroScan

Critique of additional Company economic modelling and analysis

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Start date	15/07/2022
Completion date	15/09/2022

Declared competing interests of the authors:

None

Acknowledgements:

- Louise Campbell, Clinical Director, Tawazun Health;
- Neil Guha, Professor of Hepatology, University of Nottingham;
- Coral Hollywood, Consultant Hepatologist, Gloucestershire Hospitals NHS Foundation Trust;
- Helen Jarvis, GP Partner, NIHR clinical doctoral research fellow, Newcastle University;
- Michael Moore, Professor of Primary Care Research, University of Southampton;
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Tables 1, 3 and 4 were taken from the Company's updated submission: "Response to NICE Suggested Further Analyses", received by the Newcastle EAG on 15/07/2022.

Responsibility for report:

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

Version no.	Date	Author	Purpose
0.01	18/07/2022	K Keltie	Starting draft
0.02	19/07/2022	K Keltie C Fernandez-Garcia R Parker M Reiling	Adding content to methods and results
0.03	27/07/2022 28/07/2022	K Keltie R Parker	Review Adding content to methods and results
0.4	02/08/2022	E Belilios M Reiling K Keltie C Fernandez-Garcia	Adding Clinical Expert responses Adding content to methods and results
0.05	05/08/2022	K Keltie R Parker C Fernandez-Garcia	Adding responses to questions received from the Company
0.06	09/08/2022 10/08/2022 11/08/2022	K Keltie C Fernandez-Garcia R Parker	Adding content from Company Engagement meeting Review and adding detail Adding responses from Clinical Experts to methods and results
0.07	12/08/2022	K Keltie	Adding additional EAG scenarios
0.07	12/08/2022	AJ Sims	Oversight
0.08	12/08/2022	K Keltie	Addressing review comments

Version no.	Date	Author	Purpose
0.09	15/08/2022	C Fernandez-Garcia	Review
0.10	15/08/2022	E Belilios	Pre-submission checks Adding latest notes from company call Adding expert response
0.11	16/08/2022	K Keltie	Review
1.00	16/08/2022	K Keltie	Clean version sent to NICE
1.01	18/08/2022	R Parker K Keltie	Addressing NICE comments
1.02	18/08/2022	C Fernandez-Garcia E Belilios	Addressing NICE comments Adding expert response
1.03	07/09/2022	K Keltie R Parker AJ Sims	Review Oversight
1.04	08/09/2022	K Keltie	Review
2.00	08/09/2022	K Keltie	Final version sent to NICE
2.01	14/09/2022	K Keltie	Response to Company fact check
3.00	15/09/2022	K Keltie	Clean version sent to NICE

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Emma Belilios: Project co-ordinator and comms lead

Andrew Sims: oversight

Table of Contents

Abbreviations

Term	Definition
AFLD	Alcoholic fatty liver disease
ALD	Alcohol-related liver disease
ALT	Alanine transaminase
AST	Aspartate aminotransferase
BMI	Body mass index
CCG	Clinical Commissioning Group
DAC	Diagnostics Advisory Committee
EAG	External Assessment Group
EASL	European Association for the Study of the Liver
ELF	Enhanced liver fibrosis
FIB-4	Fibrosis-4 index for liver fibrosis
HCV	Hepatitis C Virus
HRG	Health Resource Group
ICS	Integrated Care System
LSM	Liver Stiffness Measurement
NAFLD	Non-alcoholic fatty liver disease
NITs	Non-invasive tests
PCN	Primary Care Networks
PSA	Probabilistic sensitivity analysis
TE	Transient elastography

Background

Following the second Diagnostics Advisory Committee (DAC) meeting the Company (Echosens) were asked to provide additional supporting evidence in three specific areas:

1. Extent of expected use of FibroScan in primary or community care

2. Uncertainty about likely total cost of doing the test in secondary or specialist care

3. Long-term impacts of testing in primary or community care on costs are uncertain

Objectives

The Newcastle EAG was asked to critique the additional information provided by the Company against each of the three specific uncertainties listed above.

Methods

The EAG received an updated economic model (v4.0) in Microsoft Excel, and a "Response to NICE Suggested further analyses" report on 15 July 2022. A list of questions was sent to the Company on 20 July 2022; responses were received 05 August 2022 including a later version of the economic model (v5.0).

Objective 1: Extent of expected use of FibroScan in primary or community care

The Company claimed that FibroScan should be shared across within a cluster of networks in primary or community care, for example shared across 5 Primary Care Networks (PCNs) or additional Operational Delivery Networks; and have clarified that FibroScan should not be placed in a single GP practice. The Company included a tabulation of 3 examples of real-world UK NHS data (Table 1 of their submission) to demonstrate annual FibroScan attendance between 500 and 1,000 patients per PCN, equivalent to 2,500 and 5,000 for a single FibroScan device shared across 5 PCNs. Five Clinical Experts stated that sharing one device amongst five PCNs was

plausible in some scenarios, however two Experts stressed that this was dependent upon careful appointment scheduling, two Experts stated that this would only be feasible in an urban setting (where PCNs are in proximity), one stated that a portable device would need to be used to move around, otherwise patients could visit one fixed location. One Expert noted that this would be ambitious depending on the size of the network and whether the device would be used in all or a selection of sites. Another Expert noted concerns for service delivery when the equipment requires servicing or repair.

To demonstrate the extent of expected use (in line with the first uncertainty raised by the Committee), the EAG calculated the annual attendance *per PCN* for FibroScan using the same three studies tabulated by the Company. The number of patients undergoing FibroScan *per year per PCN* was between 92 and 278 in the 3 examples shared by the Company, Table 1; however, the EAG notes that South Nottinghamshire achieved this with two FibroScan devices across nine PCNs. The Company provided additional data in confidence from the Southampton Clinical Commissioning Group (CCG) which has had a commissioned FibroScan pathway for five years. The data included an average of [redacted] FibroScan measurements per year for initial visits and follow-up appointments (Appendix A – Question 2d); therefore, the number of *patients* per year per PCN will be lower. This established service (which has been running for 5 years) has not met the expected throughput of between 500 and 1,000 patients per year per PCN. Therefore, using the real-world data of FibroScan used in a primary or community care setting, the EAG considers that the assumption of a single FibroScan device being used for between 500 and 1,000 patients per year per PCN, or in 2,500 to 5,000 patients per year across 5 PCNs may not be achievable across the NHS.

Table 1: Sites currently using FibroScan in primary or community care (from Table 1 of Company submission, amended using response from Company received 05/08/2022 Appendix A - Question 2a) with additional column showing EAG calculation of annual use of FibroScan per PCN.

Location [reference]	**Area Covered**	**Number of FibroScan machines**	**Number of scans**	**Any other information**	**EAG calculation of number of scans per year per PCN**	**Additional information from EAG**
Southampton [unpublished]	50 GPs across 5-6 PCNs (as of August 2022) referring on to 2 GPs where the measurements are conducted	1	533 over 14 months from Jan 2020 and March 2021 based on a commissioned pathway.	Systems are mobile across the different practices	**92** *Calculation: [(533 scans/14 months)x12 months]/5* PCNs	ELF threshold of >9.5 used as referral criteria for FibroScan (Appendix B2). EAG has assumed 5 PCNs for calculation (number of annual FibroScan per PCN would be lower, i.e. 77, if assumed 6 PCNs). The EAG notes that the Company corrected the number of devices (from 2 to 1) and provided additional data from Southampton (January 2021 to June 2022; see Appendix A-Question 2d). [redacted] The Company advised that following the 18-month pilot, that the Southampton CCG formally commissioned the local community FibroScan service in 2020. The service has been commissioned for 5 years. However, the Company have advised that the large majority of patients are referred from only 5 of the 50 GP centres (Appendix A-Question 2d).
Mid Hampshire CCG [†Gordon *et al.* 2021]	18 GPs across 4 PCNs	1	1,115 in a 12-month period	Systems are mobile across the different practices	**278** *Calculation: [1,115 scans/1 year]/4 PCNs*	FIB-4 between 1.3 and 3.24 was used as referral criteria for FibroScan. Threshold of 8-15 used for lifestyle advise and consideration of hepatology referral (159 of 1115, 14.3%), >15 referred to hepatology (60 of 1115, 5.4%). Did not attend rate was 1% for FibroScan.
South Nottinghamshire The scarred liver project [NICE Shared Learning Awards, 2019]	4 CCGs, Accessible to 100 GPs included within 9 PCNs serving a population of 700,000 people	2	2,715 patients had a FibroScan from Sept, 2016 to Sept, 2018	GPs are able to refer patients with a defined risk factor for chronic liver disease directly for a specialised ultrasound test (FibroScan) before considering referral to secondary care.	**153** *Calculation: [2,751 scans/2 years]/9 PCNs*	2 systems were used to conduct this. Threshold of >15 kPa was applied to define patients with advanced liver disease (145 of /2,751, 5.3%). The EAG note that the Company stated the number of patients incorrectly as 2,715.

†Available as abstract only

Abbreviations: CCG, clinical commissioning group, EAG, external assessment group, FIB-4, Fibrosis 4 index for liver fibrosis, PCN, primary care network

The EAG acknowledges that the number of patients using FibroScan in primary or community care will be defined by the eligibility criteria, which for the purposes of the final scope should be considered the same as the population referred to secondary care for measurement FibroScan. However, the EAG notes that the eligibility for FibroScan differed amongst the three real-world examples highlighted by the Company:

- Southampton: unpublished, the EAG clarified the referral criteria with a Clinical Expert as ELF greater than 9.5; Fib-4 is not calculated (Appendix B2).
- Mid Hampshire [Gordon *et al.* 2021]: FIB-4 was calculated from blood test results for patients with diabetes, BMI greater than 35 kg per m^2, alcohol intake greater than 50 units per week for men, greater than 35 units per week for women. Patients with FIB-4 between 1.3 and 3.24 were referred for FibroScan.
- South Nottinghamshire [NICE Sharing Learning Awards, 2019]: heavy alcohol use, diabetes, and obesity (poster states that GPs followed an algorithm however details not provided).

The EAG also considered evidence included in the original Assessment Report (November 2021) to demonstrate extent of expected use in the UK NHS primary care setting. This included 3 additional studies that reported the number of patients attending FibroScan measurement in UK NHS within GP practices:

- The abstract by Hosack *et al.* (2019), conducted in 4 GP practices in West Berkshire, identified 476 patients with one or more risk factors (type 2 diabetes, obesity, and excess alcohol use, undefined) over a 27-month time-period. This equates to 53 patients per GP practice per year (((476 scans/27 months)*12 months)/4 GP practices) or 265 patients assuming 5 GP practices per PCN.
- The LOCATE study (El-Gohary *et al.* 2018), conducted within 10 GP practices across Southampton between July 2014 and March 2016, invited 2,082 patients to a liver clinic from 3 different pathways (GP referral, screening for excess alcohol using the AUDIT questionnaire, and case-finding for risk factors: abnormal blood test, type 2 diabetes, CIRRUS algorithm, alcohol misuse). Focusing on the subgroup of patients who were invited from a GP or

practice nurse referral (n=627), the attendance was 43.4% (272/627). This equates to 17 patients per GP practice per year (((272 patients/20 months)*12 months)/10 GP practices) or 82 patients assuming 5 GP practices per PCN.

- The study by Harman *et al.* (2015), conducted in 2 GP practices in Nottingham identified 920 at risk patients over 14 months (hazardous alcohol use, type 2 diabetes, raised alanine amino transferase). However, of the patients eligible, only 41.1% (378/920) underwent transient elastography measurement with FibroScan. This equates to 162 patients per GP practice per year (((378 patients/14 months)*12 months)/2 GP practices) or 810 patients assuming 5 GP practices per PCN.

The Company then reported the following sourced from national data:

- 40,000 as the average number of patients within a PCN, which was the midpoint of the recommended range of between 30,000-50,000 (Morciano *et al.* 2020). However, the EAG notes that the cross-sectional study by Morciano *et al.* (2020), which reported 1,250 PCNs in January 2020, stated that the PCN size was higher at a mean of 48,000 registered patients (median: 44,000). The EAG identified a more recent source of data, using NHS England and Improvement PCN raw administrative data (published 01 April 2022, using data from 01 January 2022). This data showed a total of 1,255 PCNs across 42 Integrated Care Systems (ICS) which included a total of 6,458 GP practices; an average of 5 GP practices within each PCN. The mean and median number of registered patients within each PCN (48,822 and 44,723 respectively), were in broad agreement with those reported in Morciano *et al.* (2020). However, NHS England reported 466 (37.1%) PCNs included over 50,000 patients, 26 (2%) including over 100,00 patients.
- 5% as the proportion of the population with or at risk of liver damage and liver disease (Atlas of Variation, 2017). However, the EAG notes that this report estimated that between 10 and 20% of the population of England were at some risk of developing a degree of liver damage during their lifetime and at any single timepoint that between 600,000 and 700,000 individuals may have a significant degree of liver damage (between 1.00% and 1.25% assuming a population of 56 million in England). The decision problem does not propose using FibroScan within national screening of liver disease (this is outside the

NICE Final Scope, 2021), therefore it is unclear to the EAG how this 5% "at risk" population would be identified as eligible for FibroScan. No further detail was provided by the Company in their updated submission; however, the assumption would remain that the same patient population currently being referred for FibroScan in secondary care would be eligible for referred for FibroScan in a primary or community care setting. The EAG notes from the previous economic submission that the decision to refer for FibroScan was based on FIB-4, however the Clinical Experts advised that non-alcoholic fatty liver disease (NAFLD) fibrosis score, ELF, AST to ALT ratio, BMI, AUDIT questionnaire, presence of comorbidities such as diabetes, obesity, hypertension, use of certain medications (for example, tamoxifen and methotrexate), or family history of liver disease may also indicate patients for FibroScan. The previous assessment report by the EAG (2021) noted that transient elastography conducted in secondary care setting was recommended in three guidelines from NICE:

  - hepatitis B (chronic) (NICE CG165, 2017),
  - cirrhosis in over 16s (NICE NG50, 2016),
  - non-alcoholic fatty liver disease (NAFLD) (NICE NG49, 2016),

  Within the previous Assessment Report, the EAG also listed the British Society of Gastroenterology Guidelines on the management of abnormal liver blood tests in children and adults in both primary and secondary care. Variation in eligibility criteria applied with the UK NHS primary care setting was also reflected in the published literature, which adds uncertainty when considering the extent of expected use of FibroScan if implemented in a non-secondary care setting.
- 0.5 tests per patient per year, assuming each patient is scanned every 2 years (NG50, 2016). The EAG notes that NG50 recommends offering retesting for cirrhosis every 2 years in 3 specific subgroups:
  - people diagnosed with alcohol-related liver disease,
  - people with hepatitis C virus infection who have not shown a sustained virological response to antiviral therapy, and
  - people with NAFLD and advanced liver fibrosis (as diagnosed by a score of 10.51 or above using the enhanced liver fibrosis (ELF) test).

- using the above parameters, the Company assumed that 1,000 patients per PCN per year could be referred for FibroScan (5% of 40,000 with liver disease having 0.5 scans per year).

Using real-world data and national data, the Company have provided 2 estimates of the number of patients per PCN where FibroScan could be used; national data estimated 1,000 patients per PCN, real-world data between 500 and 1,000 patients per PCN. The Company provide six reasons to describe the differences between these estimates, Table 2.

Table 2: Reasons for differences between the national estimate and real-world figures as reported by the Company.

#	Reason provided by the Company	EAG comment
1	Not every patient will be identified as being at risk and requiring a scan.	The Company have not proposed how "at risk" patients will be identified. NICE Guidelines (NG50, 2016) recommend offering transient elastography to diagnose cirrhosis for: • people with hepatitis C virus infection, • men who drink over 50 units of alcohol per week and women who drink over 35 units of alcohol per week and have done so for several months, • people diagnosed with alcohol-related liver disease. NG50 also recommends offering either transient elastography or acoustic radiation force impulse imaging (whichever is available) to diagnose cirrhosis for people with NAFLD and advanced liver fibrosis (as diagnosed by a score of 10.51 or above using the enhanced liver function, ELF, test). The EASL practice guideline update 2021 recommends: • Non-invasive fibrosis tests should be used for ruling out rather than diagnosing advanced fibrosis in low prevalence populations. • Non-invasive fibrosis tests should be preferentially used in patients at risk of advanced liver fibrosis (such as patients with metabolic risk factors or harmful use of alcohol) and not in unselected general population. • ALT, AST, and platelet count should be part of the routine investigations in primary care in patients with suspected liver disease, so that simple non-invasive scores can be readily calculated. • The automatic calculation and systematic reporting of simple non-invasive fibrosis tests such as FIB-4, in populations at risk of liver fibrosis (individuals with metabolic risk factors or harmful use of alcohol) in primary care is recommended in order to improve risk stratification and linkage to care.

#	Reason provided by the Company	EAG comment
2	Other technologies available (ELF test or others)	The Company model does not include use of other technologies within the clinical pathway in detecting liver disease in primary or community setting.
3	No liver pathway available	The Company have stated that there are examples of established pathways for FibroScan in primary and community settings within the NHS as indicated by Table 1 of their submission.
4	Local guidance to not conduct FibroScan on patients with hazardous alcohol consumption, a high BMI or with Type 2 diabetes etc.	This contradicts the eligibility criteria outlined by the real-world evidence summarised by the Company, and the EASL Clinical Practice Guideline 2021. This also excludes specific subgroups which were listed in the NICE Final Scope, 2021: "Use of FibroScan in specific populations, for example for people with: • Non-alcoholic fatty liver disease • Suspected non-alcoholic fatty liver disease (for example, people with metabolic syndrome or type-2 diabetes) • Alcohol-related liver disease • Suspected alcohol-related liver disease (for example, based on hazardous alcohol use) • Hepatitis" The EAG notes that the Company responded (05/08/2022; Appendix A - Question 3) stating that this was due to local variations in practice, and that some PCNs/community centres may not scan with FibroScan due to lack local liver guidance.
5	Patient non-attendance	The EAG note that the original economic submission reported that more patients were likely to attend FibroScan visit in primary or community care than in secondary or specialist care setting, leading to increased detection of liver disease. The abstract (Gordon *et al.* 2021) provided by the Company stated that the "did not attend" rate of community FibroScan was 1% across 18 GP surgeries in West Hampshire CCG. However, the EAG notes that published examples of using FibroScan in primary care setting within the UK NHS, non-attendance can be much higher, for example, 56.6% (El-Gohary *et al.* 2018; of the 627 invited from GP referral, 355 did not attend).
6	The size of the PCN can be smaller (1% with less than 24,000 patients, Morciano *et al.* 2020)	Data regarding PCN size was taken from NHS Digital in January 2020. Using the same data source 5% of PCN had more than 80,000 registered patients. As the model assumes one device across 5 PCNs, it is likely that this is not a major contributory factor.

#	Reason provided by the Company	EAG comment
Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; EASL, European Association for the Study of the Liver; PCN, primary care network		

The EAG would consider the real-world examples of FibroScan in primary and community care setting as more robust than the estimates using national data (where the assumptions made are not explicit). All eight Clinical Experts stated that the assumption of each PCN being able to conduct 500 scans per year was clinically plausible (Appendix B1 – Question 3). Four Clinical Experts stated that this estimate would depend on the size of the PCN, four Clinical Experts noted that the number of patients eligible for FibroScan would be dependent on the criteria applied for identifying those considered 'at risk', and one Clinical Expert stated that this may be conducted with joined up working between primary and secondary care (although noted that this was only in exceptional cases). Using 6 sources of information (1 unpublished) provided by the Company, the EAG has found only 1 example where the extent of FibroScan use was within the range defined by the Company (between 500 and 1,000 patients per year per PCN); the remaining 5 examples were between 92 and 278 per year per PCN. The EAG additionally highlights the variation in referral criteria used for FibroScan across the identified studies which add uncertainty to how the expected use can be achieved across the NHS. The EAG notes that the decision problem within the NICE Final Scope, 2021 assumes that the same patient population would be eligible for FibroScan if used in secondary or non-secondary care setting; however, the EAG would highlight that clear eligibility criteria for FibroScan are currently lacking.

Models of primary care service delivery

The Company did not consider micro-costing approaches relevant to a specific model of delivering FibroScan in primary care due to variation in delivery options. The Company did not consult with users of FibroScan in primary care to inform micro-costs (Appendix C) [At fact check the Company clarified that they consulted with stake holders in both primary (including clinical experts, commissioners and directors within primary care) and secondary care]. The EAG consider that this may

impact their assumptions regarding the resources needed for the use of FibroScan as well as the achievable number of scans per machine.

Of the eight Clinical Experts consulted by the EAG, five have experience in delivering FibroScan in a primary or community setting (including two from Nottingham and two from Southampton). There was variation in delivery approaches used including the delivery of scans at a fixed location, the use of a dedicated FibroScan equipped van, transporting the scanner between locations with the nursing staff by taxi or bus (Appendix B1). Another Clinical Expert noted the use of a FibroScan device purchased by the NHS Trust and transported from the hospital base for scanning within GP practices by secondary care specialist hepatology nurses (Appendix B2). One Clinical Expert noted that the FibroScan device was loaned from the Company with charges negotiated between the CCG and the Company and transported to practices from a central location in primary care (Appendix B2). The EAG consider that it would have been beneficial for the Company to consider models of service delivery (for example administrative costs in booking appointments) and run sensitivity analysis around these scenarios to address some of the uncertainties (Appendix C).

One of the Experts also noted in addition to the costs associated with the staff delivering FibroScan in primary care that costs associated with staff turnover and additional training should be considered (Appendix B1). Furthermore one Expert stated that the time taken to develop, build and resource a FibroScan service should be considered, particularly in settings with no experience or knowledge base.

The EAG asked three secondary care Experts with experience of implementing FibroScan in three different NHS primary care settings regarding the impact of on secondary care services, specifically the impact on proportion of scans conducted (Appendix B2). One Expert noted that there was a reduction in consultant-led appointments due to the specialist hepatology nurses conducting FibroScan prior to consideration of a consultant-led referral (some patients managed by GP, some by the hepatology nurse-led clinics). The Clinical Expert noted that the use of the FIB-4 as a screening tool reduced the overall number of patients being seen in hospital.

The EAG note that this pathway utilises secondary care device and staff to deliver FibroScan in primary care settings and the addition of an ultrasound test (conducted by radiologists in secondary care) was introduced as part of the referral criteria for FibroScan. One Expert noted that 30% of patients with fatty liver due to alcohol or metabolic conditions are scanned and referred to hepatology (with the remaining 70% discharged back to the GP); prior to the service all were referred to hepatology (Appendix B2).

One Expert also highlighted that not all eligible patients would attend their appointment. The EAG considers placement within a fixed location, such as a community diagnostic centre to minimise transportation costs, ensure high patient throughput to maintain staff competency in FibroScan measurement and access to infrastructure (including clerical staff to book appointments, additional diagnostic tests conducted if required, and access to trained staff to discuss results) may be more appropriate. However, it is unclear whether patients would be more likely to attend a FibroScan appointment at 1 of 40 proposed community diagnostic centres (including multi-disciplinary staff, open 7 days a week) across England than secondary care setting; particularly as a large number of the diagnostic centres are proposed to remain within a hospital setting.

Objective 2: Uncertainty about likely total cost of doing the test in secondary or specialist care

The Company conducted a survey of clinical coding within two NHS Hospital Trusts using FibroScan:

- HRG RD24Z: Computerised Tomography scan of two areas (King's College Hospital NHS Foundation Trust)
- HRG RD42Z: Ultrasound scan with duration of 20 minutes and over, without contrast (University Hospital Southampton NHS Foundation Trust).

The Company then applied a weight average (weighted by the number of examinations) to determine an average cost of £88.15 per scan when FibroScan is conducted in a secondary care outpatient setting, Table 3. However, given FibroScan uses transient elastography (ultrasound), of a single anatomical location (liver), and does not require contrast, the EAG considers that the response from one

trust (RD24Z: King's College) may be a typographical error. The Company have also agreed that this is likely a typographical error, that they contacted the centre to clarify but were unable to gain a response as of 04 August 2022 (see Appendix A – Question 5). If this HRG was removed, the weighted average cost of FibroScan in secondary care would reduce to £71.20.

The EAG noted that the two NHS Trusts who provided feedback on the HRG codes used for FibroScan provided by the Company (King's College Hospital NHS FT and University Hospital Southampton NHS Foundation Trust), were different to the four NHS Trusts who provided the number of FibroScan scans per year (Frimley Health Foundation Trust, Manchester University NHS FT, University Hospital Hairmyres (NHS Lanarkshire), West Hertfordshire Teaching Hospitals NHS Trust). Due to concerns regarding selection bias, particularly since the Company have confirmed widespread use in hospital setting (see Appendix A – Question 7), the EAG requested from the Company further detail regarding the clinical coding of FibroScan procedures from those four latter NHS Trusts. The Company confirmed that responses from three of the four NHS Trusts included the OPCS coding which led to HRG RD48Z Ultrasound elastography (see Appendix A - Question 6); an HRG code which was included in the original economic model (Assessment Report 2021) at a cost of £43.93. The EAG note that this HRG (RD48Z) was available as an option in the latest economic model (v5.0).

The EAG notes that the economic studies included within the Assessment Report (2021) considered different costs for FibroScan in secondary care;

- Crossan *et al.* (2019) applied £47.00 as the cost of FibroScan sourced from NHS Reference costs 2013/14 using HRG code RA23Z (Ultrasound Scan, less than 20 minutes; Imaging Direct Access).
- Srivastava *et al.* (2019) applied £43.00 as the cost of FibroScan sourced from local costing tariffs from the Royal Free, February 2015 with 3.5% discount rate applied.
- Tanajewski *et al.* (2017) applied £37.30 as the cost of FibroScan sourced from the Centre for Evidence-Based Purchasing Economic Report (2009).

- Serra-Burriel *et al.* (2019) was based on previously published cost-effectiveness model by Tanajewski *et al.* (2017).

Table 3: HRG codes used for FibroScan in secondary care [Table 4 in Company's updated submission]

Currency Description	Department Name	Currency Code	Department Code	Number of Examinations	National Average Unit Cost (£)	Weighting	Weight cost (£)
Computerised Tomography Scan of Two Areas, with Contrast	Imaging: Outpatient	RD24Z	IMAGOP	15829	145.36	3%	88.15
Computerised Tomography Scan of Two Areas, with Contrast	Imaging: Outpatient	RD24Z	IMAGOP	182364	114.36	34%	
Ultrasound Scan with duration of 20 minutes and over, without Contrast	Imaging: Outpatient	RD42Z	IMAGOP	38181	68.88	7%	
Ultrasound Scan with duration of 20 minutes and over, without Contrast	Imaging: Outpatient	RD42Z	IMAGOP	297365	71.50	56%	

The EAG would note that there remains variation in clinical coding to capture FibroScan conducted in a secondary care outpatient setting. The EAG would advise that a micro-costing approach in assessing the costs of all diagnostic pathways being considered, accounting for device, staff, and infrastructure costs would be more appropriate when comparing costs in secondary care with those in a non-secondary care setting.

The EAG acknowledge that the Company included a micro-costing of FibroScan if the device was purchased outright within their updated submission. The EAG critiqued this approach previously in the Assessment Report and noted the following limitations with the Company micro-costing approach:

- the micro-costing calculation included the cost of the FibroScan 430 Mini+ in both secondary and non-secondary care settings, which is a portable, battery-powered version of the device. The capital costs of FibroScan 630 Expert (mains powered) and FibroScan 530 Compact (battery powered), which are both cart-based versions, were not included in the Company micro-costings in either setting. Two Clinical Experts stated that FibroScan 430 Mini+ model was appropriate if delivering a mobile service. One Clinical Expert stated that if delivering the service from a fixed location that the FibroScan 530 Compact model would be suitable. The Expert stated that a new FibroScan Go model was also suitable but that this was only available on a “pay per scan” contract. The EAG can confirm that the “pay per scan” scenario (£58 in the original Assessment Report, 2021) was not described by the Company in their updated submission, however the scenario was still available within the economic model (can be changed in “Settings” worksheet but only in non-secondary care arm). In a secondary care setting, two Experts stated that FibroScan 430 Mini+ was a suitable model for all clinical areas, two Experts stated that FibroScan 430 Mini+ could be used but that older versions already existing in secondary care setting would continue to be used if still working, and two Experts stated that FibroScan 430 Mini+ would not be used or the preferred model in a secondary care setting (no further reasons offered). One Expert highlighted that the probes used are the same across all models.

- the micro-costing assumes that each hospital (or PCN in the non-secondary care arm) will conduct a capital purchase of one single FibroScan device. Three Clinical Experts stated that some NHS hospitals may have one FibroScan device, where used, while another Expert noted that there may be variation where some larger hospitals may have more than one machine to cover larger networks or for the provision of existing community services. One Expert highlighted that the functionality of models across the NHS may not be consistent (some with capability to measure steatosis), Appendix B1. The Company confirmed that as of 01 August 2022 more than 340 FibroScan devices are used in hospitals (Appendix A – Question 7); and that 49% of NHS Trusts using FibroScan have more than 1 FibroScan device. The EAG notes that this illustrates the uncertainty in the number of machines needed in a secondary care setting to achieve the number of scans assumed by the Company.
- the micro-costing assumes that each provider will purchase additional CAP or SmartExam software. Within their Assessment Report, the EAG previously noted that none of the peer-reviewed publications included reported CAP as an outcome measure. The Company estimated that more than 50% of existing FibroScan devices in NHS Trusts have CAP or SmartExam software (Appendix A - Question 7). The EAG notes that CAP or SmartExam software may not be required in a primary or community care setting. Assuming the same population are scanned with the same device but in a different setting, in line with the decision problem, the EAG would consider the removal of CAP software from both arms of the economic model would reduce the point-estimate of costs in both arms by the same amount.
- the micro-costing includes annual onsite training costs (increased to £1,180 in 2022, previously £1,150, see Appendix A – Question 8) which includes half a day for a maximum of 3 staff. The Company recommends that supervision from a competent user is needed for the first 50 uses (on average), however the additional staff costs in this supervisory role was not included within the micro-costing. The Company further clarified that the Company is not involved in the supervision of these 50 scans after training and that the Company does not reassess competence after 50 scans (see Appendix A – Question 19a).

The EAG notes that supervision of 3 staff, each conducting 50 scans during training, each scan taking approximately 20 minutes, would require a total of 50 hours of supervisory staff time (£2,500 if assuming this supervision was provided by a Band 6 hospital nurse at £50 per hour, or £1,900 if assuming conducted by a GP practice nurse at £38 per hour). The EAG acknowledge that staff in both settings would require training (therefore, additional supervisory staff costs are applicable to both arms of the economic model). In contrast, the Company have estimated that 15% of FibroScan devices currently installed in the UK are used in primary or community setting, therefore implementing this new care pathway across the non-secondary care settings would likely require substantially more staff to be trained and supervised. Furthermore, rates of staff turnover in each setting should be explored as these may have an impact on the level of additional internal and external (company delivered) training that may need to be incorporated into the micro-costing. The Company also advised (Appendix C) a Competency Framework has been developed, and that they encourage fewer operators to ensure skills are maintained.

The Company surveyed 4 NHS hospitals to determine the number of FibroScan scans conducted in a secondary care setting between 2018 and 2021; reporting a weighted average of 610 scans per hospital per year (weighted by the number of number of beds per hospital). The EAG notes that activity stated for 2020 and 2021 may be lower due to the COVID-19 pandemic. The EAG highlights that the four hospitals providing FibroScan activity data are from different NHS Hospital Trusts to the two who responded regarding their clinical coding practices, which may indicate selection bias.

The Company have applied the total device costs, assuming a 7-year lifetime of a single FibroScan device, used by an average of 610 scans per year in secondary care, would result in a cost per scan of £28.11. The Company assumes costs associated with staff time, including 15 minutes of a Band 6 hospital-based nurse (£50 per hour, PSSRU Unit Costs 2020) are used to perform each scan. The EAG note that this duration of scanning is shorter than that assumed by the HRG code

RD42Z “Ultrasound scan with duration of 20 minutes and over, without contrast” suggested by the Company in their updated submission. This micro-costing did not include staff time to set up the appointment, record results or sterilise the device between patients. However, the EAG notes that a consultation exercise would have helped to itemise the exact resource items and costs associated with the use of FibroScan in secondary care. The combined device and staff time costs presented by the Company resulted in a total cost of £40.61 per scan when conducted in a secondary care setting.

The Company have applied the same approach assuming an average of 500 scans per year in a primary or community setting, and 15 minutes of a GP practice nurse with qualifications (£42 per hour, PSSRU Unit Costs, 2020) resulting in a total cost of £44.79 per scan. The EAG notes that the use of FibroScan in primary or community care setting is £4.18 more than that of secondary care. The EAG also notes that to calculate the cost per scan, the Company has assumed a lower use per device in primary or community care (500 per year) than that of secondary care (610 per year). The Company clarified (Appendix C) the proposal is to expand the utilisation of FibroScan into primary care to increase the early diagnosis of liver disease, but that existing services should not be removed from secondary care where FibroScan is used by multiple specialties. The EAG also notes, as per its previous critique, that Clinical Experts advised that FibroScan is used across a range of specialties in a hospital setting including cardiology, dermatology, endocrinology, gastroenterology, hepatology, rheumatology as well as general practice, drug and alcohol, obesity care and cystic fibrosis teams. Therefore, secondary care services will need to maintain access to FibroScan, even if the technology is also implemented in primary care. Therefore, the costs of implementing FibroScan in primary or community setting cannot directly replace those in secondary care setting and may represent additional costs to the health system (potentially with additional benefits) if the total number of patients scanned as a result in both settings increases. Furthermore, their use across different disease areas in secondary care may yield additional health benefits (outside liver disease), which the current model is not able to capture. However, the EAG notes that the economic model is sensitive to change in the assumed number of average uses per device. The EAG acknowledges that the Company included an

additional scenario where the use of FibroScan in primary or community care was increased from 500 per device, to 750 per device (reducing the cost per scan to £33.36; £7.25 less than FibroScan used in a secondary care setting), but that lower use was not considered in the Company's submission. Given the real-world evidence submitted by the Company (in response to Objective 1), and lack of criteria to define who would be eligible for FibroScan in a primary or community care setting, the EAG considers it unlikely that every FibroScan device would be able to achieve this high extent of use across the UK NHS in a non-secondary care setting. The Company did not consider the implications of a decreased use of FibroScan.

The EAG also highlights that the Company's micro-costing includes only one single FibroScan device (see Appendix A-Question 2b), however would consider that multiple devices may be required when sharing across PCNs, particularly those covering a large geographical area. Additionally, one Clinical Expert raised concerns relating to impact on service delivery if the device required repair or servicing (planned or unplanned) (Appendix B1). The EAG notes that the use of multiple devices may alter the estimated average number of scans per machine as the ratio between machine and scans may not be linear. For example, the use of two machines may not necessarily lead to twice as many scans. Issues relating to the GP's own delivery pathway, scheduling conflicts, machine being faulty, distance between GPs or spread of patient population may mean that more than one machine is needed to reach the target population.

When considering the expertise of staff required to deliver a FibroScan service, three Clinical Experts noted that GP practice nurses could be trained to offer results and guidance at the time of the FibroScan measurement (Appendix B1). However, five Clinical Experts also noted that depending on the case complexity, abnormalities detected, or requirement for an onward referral, that additional GP or specialist advice or appointment(s) may be appropriate. One Clinical Expert also highlighted that a call from the nursing team or GP may also be considered. Another Clinical Expert highlighted a pathway were FibroScan was carried out with results discussed by secondary care specialist hepatology nurses within a primary care setting (Appendix B1, Appendix B2). The EAG notes that additional GP face-to-face or

telephone appointments to discuss results prior to a referral to hepatology were not considered within the updated Company model. This omission may lead to an underestimation of costs when delivering FibroScan in a primary or community care setting.

The EAG consulted with eight Clinical Experts, five of which had experience in delivering a FibroScan service, who advised that the following additional costs should be considered:

- operator time, including training time with supervision, and accounting for staff turnover,
- clerical staff time (to arrange appointments and ensure uploading of results),
- time associated with building business model to support adoption across GP or PCNs,
- IT costs (providing electronic uploading of FibroScan data into NHS systems),
- technology and software upgrade costs including consumables,
- insurance for the FibroScan device to be transported between sites,
- time to provide feedback to patients, including written advice, which may require a separate appointment (for example with a GP if delivered in primary care pathway dependent upon results),
- room costs (with a bed) in primary or community settings, including storage of FibroScan when not in use,
- hygiene and waste disposal standards and equipment,
- if providing a mobile service, costs associated with transportation of device including vehicle costs (lease, insurance, parking), Appendix B1.

These were not included in the updated economic model, and therefore the EAG would consider that the Company have not fully acknowledged the cost to the NHS in delivering FibroScan in a non-secondary care setting. The EAG would acknowledge that some of these additional cost considerations would also be applicable in a secondary care arm (for example, building a business case, transport costs). Furthermore, the scale of these costs may differ between settings potentially affecting the cost implications associated with delivering the services within and outside secondary care. The need to consider the costs associated with the implementation of a new service was further highlighted by one Expert who noted

the time taken to develop build and resource a FibroScan service should be considered, particularly in settings with no experience or knowledge base (Appendix B1). The EAG would therefore consider the cost per scan, particularly when conducted in a primary or community care setting, to be an underestimation of the true costs of implementing a FibroScan service.

The EAG notes that as per best practice, the costing of the capital equipment within the updated Economic model which included a 5-year time horizon should have been conducted using the Equivalent Annual Cost methodology. This method incorporates both the depreciation and cost-opportunity aspects of the acquired equipment over its lifetime (Drummond *et al.* 2015). The Company confirmed that original model, which had a one-year time horizon, was not updated to account for Equivalent Cost methodology (Appendix A – Question 19). The EAG notes that as this applied to both arms, that using Equivalent Cost methodology had minimal impact on the cost-difference.

Objective 3: Long-term impacts of testing in primary or community care on costs

Within their original submission the Company applied a time horizon of less than one year. The premise of the original submission was that higher attendance rate outside of secondary care setting (for example, in primary or community care) may lead to fewer missed diagnoses of liver disease and may avoid associated long-term costs. Therefore, to address the uncertainties regarding long-term benefit of FibroScan, the Company extrapolated the costs over five years and estimated the progression of liver disease in patients over a five-year period only in those with a missed diagnoses of liver disease.

The economic model includes 1,000 people per cohort in order to observe how people move through each pathway and hence estimate average costs and effects on a per patient basis. The model still assumes that 80% attend a FibroScan appointment in a secondary care setting and that 89% attend in a non-secondary care setting. The EAG acknowledges that there is no evidence comparing FibroScan services in secondary care with those in a non-secondary care setting. The EAG

would consider that there remains uncertainty on how and where patients may be reached to achieve higher attendance rate outside a secondary care setting. As a result, lower attendance rates outside secondary care could have been considered in the scenario analysis in order to explore their effect on the cost-savings associated with FibroScan delivery in this setting.

The Company model assumes that the subset of patients who attend their FibroScan appointment and whose results meant that they *do not* require further treatment, remain free of liver disease for the full five-year timeframe. Five Clinical Experts confirmed that it was unlikely that a patient would progress from a no liver disease state to significant liver disease within five years, however one Clinical Expert stated that patients with no liver stiffness but high liver steatosis may progress and an additional expert stated that 5 year may be too long an interval for some patients (Appendix B1, Question 8). The Company model includes the assumption that patients who attend their FibroScan appointment and receive treatment based on the results, are assumed to remain in that same stage of liver disease for the five-year duration and do not progress further. Five Clinical Experts advised that this assumption was inappropriate, with two Experts noting it is the patient adoption of behavioural intervention advice or change in risk factor that would stop the progression of disease, Appendix B1. Two Clinical Experts highlighted the UK study by Reinson *et al.* (2021; which reported follow-up of the intervention arm of the LOCATE study) which reported that at follow-up (mean interval of 4.5 years when compared to baseline) that 32.2% (n=19 patients) had no change in fibrosis stage, 49.1% had a decrease in fibrosis stage (n=29 patients) and 18.7% (n=11 patients) had progression of liver fibrosis stage. The Company justifies not incorporating progression across liver disease stages based on its slow progression over five years (Bataller and Brenner 2005). However, the natural history of liver fibrosis, as stated by Bataller and Brenner (2005), also indicated that most morbidity and mortality associated with a progression to cirrhosis occurs after an interval of 15 to 20 years. One Clinical Expert highlighted that the meta-analysis by Singh *et al.* (2015), demonstrated a 1 stage of progression over 14.3 years for patients with NAFLD, and over 7.1 years with patients with non-alcoholic steatohepatisis. This suggests that adopting a longer timeframe would have allowed the Company to

capture in full the expected outcomes and the differences in resource use, costs and benefits of delivering FibroScan in different settings. This approach is also considered best practice in the development of health economic models (Gray *et al.* 2010). The Company confirmed that there is no evidence available related to liver disease management and behavioural intervention specific to FibroScan (Appendix A – Question 12). The Company state that non-adherence to behavioural interventions were considered but were omitted from the model to avoid introducing more uncertainty (Appendix A – Question 12).

The Clinical Experts previously advised that FibroScan measurements may be repeated in some patients (with frequency dependent upon severity of fibrosis). One Clinical Expert acknowledged that the optimal interval period between scans is uncertain. The Clinical Expert also noted that patients with known cirrhosis would be under secondary care, and therefore would not have a repeated scan in primary or community care. Another Clinical Expert stated that fast progressors who require more frequent scanning would allow for the majority of others to be monitored every 3 to 5 years. One Clinical Expert shared the Quality standards for the management of non-alcoholic fatty liver disease (NAFLD): consensus recommendations from the British Association for the Study of the Liver and British Society of Gastroenterology NAFLD Special Interest Group which states reassessing fibrosis using non-invasive tests every 3 years. The Company stated that repeated investigations were assumed within long-term costs applied from Wright *et al.* (2006) (see Appendix A – Question 24). However, as noted by the EAG in its prior critique (of v2.0 of the economic model), Wright *et al.* (2006) was an HTA report of antiviral therapy for mild chronic hepatitis C and the annual costs applied included medication, outpatient visits, investigations, procedures and inpatient days (breakdown provided in Table 37 of Wright *et al.* 2006). The EAG notes that Wright *et al.* (2006) did not explicitly include FibroScan as one for the investigations conducted during follow-up.

The Company applied transition probabilities (Table 4) to the three stages of liver disease (liver warning, progressive fibrosis, probable cirrhosis) considered in the analysis. The decision tree assumes that the proportion of patients with liver warning, progressive fibrosis, and probable cirrhosis liver disease stages differ by

aetiology (NAFLD, AFLD, hepatitis) and follows that reported in the study by El-Gohary *et al.* (2018) that included 405 patients with liver disease. The Company applied a weighted average to estimate “all patients” progression percentages, which is a reasonable approach to take. However, the EAG notes that these proportions are from a single study, where the number of patients within each subgroup was small (201 NAFLD, 149 AFLD, and 8 hepatitis respectively). The EAG additionally note that the percentage progression from liver warning to fibrosis, and from fibrosis to cirrhosis was obtained from three separate studies for NAFLD (economic model by Srivastava *et al.* 2019), hepatitis C (Wright *et al.* 2006) and ALD (Shoreibah *et al.* 2016) subgroups; with only the study by Srivastava *et al.* (2019) explicitly including FibroScan as an intervention of interest. Furthermore, Wright *et al.* (2006) acknowledged difficulties in finding literature around transition probabilities for disease progression, which adds uncertainty to the economic model. Additionally, both Srivastava and Wright used secondary sources for their transition probabilities. Some of the cited sources (Teli *et al.* 1995) had very small samples and predated the lower bound date recommended for the search of clinical evidence (2003). The EAG was unable to replicate the transition probabilities cited on these studies.

Table 4: Liver disease progression (Table 10 – Company submission)

Subgroup	Annual transition probability	Value	Source and assumptions	EAG Comments
Non-alcoholic fatty liver disease	From liver warning (F0,F1,F2) to progressive fibrosis (F3)	0.001	Srivastava *et al.* (2019) 'develop F3 disease'	The EAG note that the progression rates in Srivastava *et al.* are derived from 2 studies: • Teli *et al.* (1995): followed a very small sample of 26 patients with NAFLD between 7.6 and 16 years. • Pais *et al.* (2013): reviewed 70 patients with untreated NAFLD with two biopsies performed more than 1 year apart and reported that fibrosis progressed (by 1 or more stages) in 20 patients (29%), and regressed (by 1 or more stages) in 20 patients (29%). The EAG could not replicate the progression rate cited by Srivastava *et al.* 2019. The EAG notes that Srivastava also modelled all-cause mortality for patients with mild or no

Subgroup	Annual transition probability	Value	Source and assumptions	EAG Comments
				fibrosis (F0, F1, F2), with transition probability of 0.005.
	From progressive fibrosis (F3) to probable cirrhosis (F4)	0.04	Srivastava *et al.* (2019) 'develop F4 disease'	The EAG note that the progression rates in Srivastava *et al.* are derived from 3 studies: • Ekstedt *et al.* (2006): followed 129 patients with biopsy proven NAFLD, mean follow-up was 13.7 years. 5.4% (1/129) developed end-stage liver disease including 3 patients with HCC. Progression of liver fibrosis occurred in 41%. • Bhala *et al.* (2011): included 247 patients with NAFLD with advanced fibrosis (F3, 47.7%) or cirrhosis (F4, 52.2%) confirmed by biopsy, followed for mean 7.1 years where 26 cases developed gastroesophageal varices, 19 developed ascites, liver failure, hepatopulmonary syndrome and or encephalopathy, and 6 developed HCC (4 of which were initially in stage 4 fibrosis). • Adams *et al.* (2005): included 103 patients with NAFLD who underwent serial liver biopsies with mean interval between biopsies of 3.2 years (range 0.7 to 21.3 years). Fibrosis progressed in 37%, remained stable in 34%, and regressed in 29%. As above, Srivastava cites 3 different studies as a source for the 0.04 transition probability, and the EAG could not replicate the progression rate cited by Srivastava *et al.* 2019. The EAG notes that Srivastava also modelled all-cause mortality for patients with advanced fibrosis (F3) and compensated cirrhosis (F4), with transition probabilities of 0.005 and 0.02 respectively. The EAG also notes that Shoreinah *et al.* 2016 also reported development of cirrhosis in 34% of 201 NAFLD patients followed for up to 10 years.
Hepatitis-related liver disease	From liver warning to progressive fibrosis	0.025	Wright *et al.* (2006), 'mild to moderate fibrosis'	The EAG acknowledges the difficulties the Company faced in identifying transition probabilities for disease progression for this aetiology due to

Subgroup	Annual transition probability	Value	Source and assumptions	EAG Comments
	From progressive fibrosis to probable cirrhosis	0.037	Wright *et al.* (2006), 'moderate to cirrhosis'	lack of data. The EAG can confirm that Wright *et al.* 2006 (Table 22) stated that the mean estimated annual probability of progression for the main group of interest (mean age of 25 years at infection) was 0.025 for mild to moderate disease, and 0.037 for moderate disease to cirrhosis. However, the source of these values was not explicitly reported, and therefore could not be verified by the EAG. The EAG notes that Bhala *et al.* 2011 also reported progression within 264 patients with hepatitis C who were naïve or non-responders to treatment, who were followed for a mean of 6.24 years, where 9 developed gastroesophageal varices, 20 developed ascites, liver failure and or encephalopathy and 18 developed HCC (10 of which were initially in stage 4 fibrosis).
Alcohol-related liver disease	From liver warning to progressive fibrosis	0.002	Calculated assuming ALD leads to double 10-year probability compared to NAFLD	Shoreibah *et al.* 2016 reported that in a cohort of 268 patients (201 with NAFLD) without cirrhosis at or within 6 months of presentation, that the cumulative probability of cirrhosis developing was higher in ALD patients (67% vs. 34%). The Company have assumed that if these patients had progressive fibrosis at baseline then the annual probability of progressing to cirrhosis was calculated to be 10.5%. The Company states that doubling the annual probability of developing cirrhosis from progressive fibrosis from Srivastava *et al.* 2019 was also calculated to be 10.5%.
	From progressive fibrosis to probable cirrhosis	0.105		
Abbreviations: ALD, alcohol-related liver disease, EAG, external assessment group, NAFLD, non-alcoholic fatty liver disease				

The EAG notes from the published economic studies reviewed within the original Assessment Report (2021):

- Srivastava *et al.* (2019) included early and late-stage complications, liver transplant and mortality within its cost analysis of patients with confirmed NAFLD modelled over one and five-year time horizon.

- Crossan *et al.* (2019) included progression to cirrhosis, screening and development of hepatocellular carcinoma (HCC), liver transplantation in adult patients with NAFLD over five-year time horizon.
- Tanajewski *et al.* (2017) included annual costs of no or mild liver disease, significant liver disease, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, transplantation cost to estimate lifetime costs of patients identified at risk of NAFLD.

However, within their long-term modelling, the Company did not account for mortality nor explored potential transitions and costs associated with health states (such as cancer or liver transplant) that may affect patients diagnosed with moderate or severe fibrosis or cirrhosis. The Company provides justification for its exclusion: "*Given the uncertainty with modelling over a 5-year time frame, it was considered that including mortality in the model would add further uncertainty and unnecessary complexity. The Company felt that there was a lack of data to model differential mortality according to the severity of liver disease*" (see Appendix A – Question 10). However, the EAG would consider that modelling all-cause mortality, cancer and transplantation and knowing the uncertainty associated with the estimates is considered an important step in building a health economic model. Likewise, including health states associated with diagnosis of different levels of fibrosis severity is in line with the outcomes defined in the decision problem. Moreover, they may have significant cost implications on the healthcare system and affect the cost-consequences of the technology being evaluated, particularly if an early diagnosis for those attending in one setting leads to different disease progression rates compared to another setting. The EAG notes that Crossan *et al.* (2015) explored the cost-effectiveness of non-invasive tests of fibrosis and cirrhosis in patients with hepatitis B and C and included progression from none or mild fibrosis to moderate or significant fibrosis to compensated cirrhosis. They also incorporated transition probabilities to allow for a proportion of the patient cohort to progress to hepatocellular cancer, liver transplant, or survival or death. In the absence of a lifetime model, it would have been good practice to report the probability of these events occurring for this patient cohort within the five-year perspective assumed by the Company's model.

The Company applied annual costs for each liver disease stage Table 5, which were reviewed by the EAG in its prior critique. The Clinical Experts also previously noted that behavioural therapy delivered in a primary or community care setting may not be adhered to the same extent as that delivered in secondary care setting. The EAG notes that the cohort study by Reinson *et al.* (2021) followed patients with a baseline FibroScan reading between 6 and 12 kPa for an average of 54 months. The authors summarised that there was no substantial impact on weight or alcohol consumption after 54 months follow-up, and that further support is required for patients to make positive and sustained lifestyle changes. The EAG considers that the annual cost of ongoing care applied by the Company for patients with progressive fibrosis and probable cirrhosis (which are based on the annual costs reported for mild chronic hepatitis C in the HTA by Wright *et al.* 2006) may not be representative of hospital resource usage of patients with suspected non-alcoholic fatty liver disease (NAFLD), alcoholic fatty liver disease (AFLD) or alcohol-related liver disease (ALD).

Table 5: Annual cost by liver stage [Table 12 of Company's submission; with EAG comment].

Liver stage	Annual cost	Source/Comment	EAG comment (from previous critique)
Liver warning	£13.07	Recommended value by the EAG	Assumes patients with liver warning would undergo clinical review within GP once every 3 years (GP consultation: £39.23, PSSRU Unit Costs 2020).
Progressive fibrosis	£1,103.90	Wright et al 2006 'moderate disease', inflated to 2021	Inflation source was not explicitly reported in the Company submission. Mean annual total cost of moderate disease was £717, and the highest cost items were outpatient visits and procedures (Wright *et al*. 2006, figure breakdown provided in Table 37). This was obtained from "Health benefits of antiviral therapy for mild chronic hepatitis C", with unit costs including drug costs, outpatient visits, investigations, procedures, inpatient days. The financial year used in Wright *et al.* is 2002/2003. The EAG inflated these 2003 prices to 2021 using the Campbell and Cochrane Economics Methods Group (CCEMG) and the Evidence for Policy and Practice Information and Coordinating Centre (EPPI-Centre) Cost Convertor, £1,023. An alternative convertor would be the Bank of England inflation calculator, £1,059. The EAG notes that the costs used by the Company are higher than both estimates determined by the EAG.

			This cost may not be representative of hospital resource usage of patients with suspected non-alcohol fatty liver disease (NAFLD), or alcohol-related liver disease (AFLD). The EAG would consider this is likely an upper estimate of ongoing care costs. The EAG has not identified any data regarding ongoing care of patients with progressive fibrosis. The Clinical Experts did not provide any additional information on this subgroup of patients.
Probable cirrhosis	£1,752.07	Wright *et al.* 2006 ''cirrhosis', inflated to 2021	Inflation source not explicitly reported in the Company submission. The average total cost for managing patients with cirrhosis was £1,138 (Wright *et al*. 2006, figure breakdown provided in Table 37). Same limitations as above. The EAG inflated this to 2021 prices using: a) CCEMG – EPPI-Centre Cost Converter, £1,623, and b) Bank of England Inflation Calculator, £1,680. The EAG notes that the costs used by the Company is higher than both estimates determined by the EAG. One Clinical expert stated that most patients with cirrhosis would be invited to attend hepatology outpatient appointments twice a year. This could include endoscopy (to monitor varices), and ultrasound imaging (to monitor liver cancer). However, acknowledged that frequency of investigations would be dependent on centre and other factors (large, small or no varices). The EAG was unable to identify any national audit data, which reported ongoing care for patients with probable cirrhosis.
Abbreviations: AFLD, alcoholic fatty liver disease, EAG, external assessment group, NAFLD, non-alcoholic fatty liver disease			

The EAG also considers the variable thresholds in defining liver warning, progressive fibrosis and probable cirrhosis across the studies shared by the Company. The EAG also note the European Association for the Study of the Liver (EASL) clinical practice guideline recommendations (2021):

- In patients with alcohol-related liver disease (ALD), liver stiffness measurement (LSM) by transient elastography (TE) less than 8 kPa is recommended to rule-out advanced fibrosis in clinical practice, with the following non-invasive tests (NITs) as alternatives, if TE is not available:

    - Patented test: ELF less than 9.8, or FibroMeter less than 0.45, or FibroTest less than 0.48
    - Non-patented test: FIB-4 less than 1.3
- Upon referral of patients at risk of ALD, LSM by TE greater than or equal to 12 to 15 kPa is recommended to rule-in advanced fibrosis, after considering causes of false positives.
- In patients with elevated liver stiffness and biochemical evidence of hepatic inflammation (aspartate aminotransferase or glutamyl transpeptidase greater than two times the upper normal limit), LSM by TE should be repeated at least one week of alcohol abstinence or reduced drinking.

Results

The results of the Company updated economic model, with some additional scenario modelled by the EAG, including probabilistic sensitivity analysis (PSA) results are shown in Table 6. The EAG noted:

- The inclusion of discounting in the latest version of the economic model, gave approximately the same cost saving between arms (as discounting is applied to both arms equally), but a 6% reduction in the absolute costs of each arm, and narrower confidence interval in PSA. Using the Company's micro-costing approach resulted in the cost saving reducing from £61.68 to £25.34 per patient.
- The economic model is sensitive to changes to the average number of scans conducted per device, such that if each device is used less than 275 times per year within a primary or community care setting then the point estimate of FibroScan when used in primary or community care setting is more expensive than when used in secondary care.
- The economic model is also sensitive to the costing methodology and attendance rate. Expert opinion suggests that there are some key items (Appendix A) that should have been part of a detailed micro-costing exercise in primary care. The diversity of diagnostic pathways in primary care also highlights the potential variability of resource use in each setting. The EAG notes that a consultation stage with relevant PCNs may have helped the

Company in the development of their costing exercise. The EAG has also noted that evidence from the literature shows considerable variability in FibroScan uptake in primary care. However, this variability has not been incorporated in the economic model. In order to explore this uncertainty the EAG has conducted some additional scenarios outlined in Table 6. When the micro-costing submitted by the Company is applied to both settings (due to variability in coding practice, and to align with costing approach in primary care setting) and attendance is assumed to be 80% in each arm (equivalent to the base-case attendance in secondary care) the cost saving is £6.45 per patient. When the attendance rate is changed to 89% in each arm (equivalent to the base-case attendance in primary or community care setting) the delivery of FibroScan in primary care is cost neutral to secondary care. When assuming attendance of 60% in secondary care, and 80% in primary or community care, then FibroScan is considered cost saving.

- The model is sensitive to changes in long-term costs. When applying the annual costs of care reported in Tanajewski *et al.* (2017), we used the reported annual costs from year 2 onwards. Year 1 costs were excluded in order to avoid double counting of the diagnostic costs associated with FibroScan both inside and outside secondary care. These costs were chosen as they represented an average annual cost whilst the other economic papers required additional assumptions regarding proportions to calculate a cost. Furthermore, the use of the average annual costs reported in Tanajewski helped illustrate how these can vary considerably between patient groups. The annual costs by liver stage used by the company related to patients diagnosed with Chronic Hepatitis C and differ from those reported for NAFLD patients by Tanajewski *et al.* (2017). The EAG noted that FibroScan became cost neutral in primary care if applying micro-costing in secondary care, and cost saving in primary care if applying HRG costing in secondary care.

The EAG considers there still remains substantial uncertainty which has not been addressed by the sensitivity, scenario or PSA analysis included in the Company's updated submission. In order to address some of this remaining uncertainty the EAG has provide additional scenarios exploring the effect that changes to a shift of patient

load from secondary to primary care would have on the results of the cost-analysis, Table 6. The EAG modified the Company model so that changes in attendance rates could be incorporated into PSA. The results derived from the economic model are sensitive to small changes to the parameters of interest incorporated in the economic model developed by the Company.

The EAG included a scenario which combined changes in costing approach (micro-costing in both arms), included the same number of annual scans in both settings (305 in each arm, assuming that 50% of FibroScan measurements in secondary care are referred from primary care), 60% attendance rates in secondary care and 80% attendance rates in primary care, removal of CAP/SmartExam software costs from both primary and secondary care arms, and applied long-term annual costs associated with liver warning, significant liver disease, probable cirrhosis (excluding year 1 costs to avoid double counting FibroScan and other appointment and staff costs already included by the Company, inflated to 2021 prices). This scenario, and PSA, were cost incurring.

Table 6: Results from the Company's updated economic modelling [EAG highlighted cells to indicate cost savings (green), cost incurrence (red) and uncertainty in costs where the 95% confidence interval crossed 0 (amber)].

Scenario [changes to the model]	Model version	Cost of FibroScan in secondary care setting (additional changes to the model)	FibroScan in primary/community care setting	FibroScan in secondary care setting	Difference (%)	PSA results [95%CI]
Company base-case HRG costs applied in secondary care	Company V4.0	Weighted IMAGOP/RD24Z + IMAGOP/RD42Z	£1,245.73	£1,310.34	-£64.61 (4.9%)	-£64.59 [-£91.87 to -£38.02]
Company base-case HRG costs applied in secondary care	Company V5.0	Weighted IMAGOP/RD24Z + IMAGOP/RD42Z	£1,170.21	£1,231.89	-£61.68 (5.0%)	-£61.29 [-£86.79 to -£35.29]
Micro-costing in secondary care	Company V5.0	Micro-costing	£1,168.52	£1,193.86	-£25.34 (2.1%)	-£25.31 [-£51.40 to £0.62]
Increased user per device in non-secondary care only [Resource use worksheet: "Number scans per year per CCG: 750"]	Company V5.0	Weighted IMAGOP/RD24Z + IMAGOP/RD42Z	£1,160.04	£1,231.89	-£71.85 (5.8%)	-£71.44 [-£97.89 to -£46.82]
EAG scenario: "pay per scan" (*£58) cost approach in non-secondary care only	Company V5.0	Pay per scan contract	£1,191.31	£1,231.89	-£40.58 (3.3%)	-£40.01 [-£70.13 to -£12.11]
EAG scenario: Number of scans in secondary care being the same as primary care (decreasing from 610 to 500) [Resource use worksheet: "Number scans per year per CCG: 500"]	Company V5.0	Micro-costing	£1,168.74	£1,198.81	-£30.07 (2.5%)	-£29.86 [-£54.67 to -£5.98]
EAG scenario: Average number of scans in secondary care reduced from 610 to 305 (assuming that 50% were referrals from primary care) and that the same number could be scanned in primary care in line with the final scope. [Resource use worksheet: - "Number scans per year per CCG: 305" - "Number scans per year per hospital: 305"]	Company V5.0	Micro-costing	£1,189.03	£1,216.34	-£27.32 (2.2%)	-£26.58 [-£53.36 to -£0.58]
EAG scenario: Average number of scans in secondary care reduced from 610 to 410 in secondary care, assuming the remaining 200 are able to move to primary care. [Resource use worksheet: - "Number scans per year per CCG: 200" - "Number scans per year per hospital: 410"]	Company V5.0	Micro-costing	£1,214.78	£1,204.83	£9.95	£10.56 [-£18.43 to £39.95]
EAG scenario: Assume attendance rate is 80% in both secondary and non-secondary care settings, and apply micro-costing in secondary care. [Probabilities worksheet: "Does not attend scan: 20" outside of secondary or specialist care]	EAG V5.0	Micro-costing	£1,187.41	£1,193.86	-£6.45 (0.5%)	-£6.07 [-£30.85 to £19.20]
EAG scenario: Assume attendance rate is 89% in both secondary and non-secondary care settings, and apply micro-costing in secondary care. [Probabilities worksheet: "Attends scan: 89" secondary or specialist care]	EAG V5.0	Micro-costing	£1,174.76	£1,175.43	-£0.67 (0.0%)	-£0.08 [-£19.04 to £20.17]
EAG scenario: Assume attendance rate is 60% in secondary care and 80% in non-secondary care settings. [Probabilities worksheet: - "Attends scan: 60" secondary or specialist care - "Does not attend scan: 20" outside of secondary or specialist care]	EAG V5.0	Micro-costing	£1,174.87	£1,234.81	-£59.94 (4.9%)	-£59.32 [-£101.59 to -£19.36]
EAG scenario: Remove costs associated with CAP/SmartExam software [FibroScan costs worksheet: "Cost of CAP/SmartExam software: 0"]	Company V5.0	Micro-costing	£1,163.66	£1,190.39	-£26.73 (2.2%)	-£26.42 [-£51.78 to -£3.79]

<table>
<tr><th>Scenario [changes to the model]</th><th>Model version</th><th>Cost of FibroScan in secondary care setting (additional changes to the model)</th><th>FibroScan in primary/community care setting</th><th>FibroScan in secondary care setting</th><th>Difference (%)</th><th>PSA results [95%CI]</th></tr>
<tr><td>EAG scenario: Applying long-term costs from Tanajewski et al. (2017) NAFLD population using costs from years 2-5 to avoid double counting of FibroScan costs in year 1.

Costs have been re-calculated as follows:
<table>
<tr><th></th><th>Year 1</th><th>Year 2</th><th>Year 3</th><th>Year 4</th><th>Year 5</th><th>Average annual costs (excluding Year 1)</th><th>Costs concerted from 2013 to 2021 using EPPI centre cost converter</th></tr>
<tr><td>NMD</td><td>£1223.18</td><td>£65.44</td><td>£65.44</td><td>£65.44</td><td>£65.44</td><td>£65.44</td><td>£75.24</td></tr>
<tr><td>SLD</td><td>£1223.18</td><td>£367.51</td><td>£367.51</td><td>£367.51</td><td>£367.51</td><td>£367.51</td><td>£422.53</td></tr>
<tr><td>CC</td><td>£1655.98</td><td>£849.61</td><td>£849.61</td><td>£849.61</td><td>£849.61</td><td>£849.61</td><td>£976.80</td></tr>
</table>
[Other costs worksheet:
- “Liver warning: £75.24”
- “Significant liver disease: £422.53
- “Probable cirrhosis: “£976.80”]</td><td>Company V5.0</td><td>Micro-costing</td><td>£722.06</td><td>£717.03</td><td>£5.03 (0.7%)</td><td>£5.53 [-£11.95 to £22.90]</td></tr>
<tr><td>EAG scenario: Applying long-term costs from Tanajewski et al. (2017) NAFLD population using costs from years 2-5 to avoid double counting of FibroScan costs in year 1.

[Other costs worksheet:
- “Liver warning: £75.24”
- “Significant liver disease: £422.53
- “Probable cirrhosis: “£976.80”]</td><td>Company V5.0</td><td>Weighted IMAGOP/RD24Z + IMAGOP/RD42Z</td><td>£723.76</td><td>£755.07</td><td>-£31.31 (4.1%)</td><td>-£30.79 [-£50.24 to -£10.21]</td></tr>
<tr><td>EAG scenario: removal of long-term costs.

[Other costs worksheet:
- “Liver warning: £0”
- “Significant liver disease: £0”
- “Probable cirrhosis: “£0”]</td><td>Company V5.0</td><td>Micro-costing</td><td>£92.54</td><td>£78.40</td><td>£14.15 (18.0%)</td><td>£14.40 [-£1.67 to £29.68]</td></tr>
<tr><td>EAG scenario: (multiple changes from base case)
Micro-costing approach in both primary and secondary care arms
305 scans per year per PCN and 305 scans per year per hospital (assuming 50% of FibroScan in secondary care is from referrals from primary care)
60% attendance in secondary care
80% attendance in primary care
Removal of CAP/SmartExam software from FibroScan costs
Long-terms annual costs associated with liver warning, progressive fibrosis and probable cirrhosis taken from Tanajewski et al. (2017) year 2 onwards: £75.24, £422.53, £976.80 (inflated to 2021)</td><td>EAG V5.0</td><td>Micro-costing</td><td>£722.38</td><td>£718.44</td><td>£3.93 (0.5%)</td><td>£4.09 [-£16.59 to £26.48]</td></tr>
<tr><td colspan="7">Abbreviations: CCG, Clinical Commissioning Group; EAG External Assessment Group; HRG, Health Resource Group
Key: *pay per scan was included in the original submission from the Company for non-secondary setting only, with minimum 36-month contract, and minimum 25 scans per month that would support the use of upgraded devices and includes training, installation, service and calibration costs, hardware, M+ and XL+ probes, and CAP (EAG Assessment Report, 2021).</td></tr>
</table>

Conclusions

The EAG considers that the updated economic submission from the Company has not provided robust evidence to support any of the three objectives outlined by Committee following DAC2:

1) The proposed expected use (500 scans per device) is not supported by the majority of real-world data. If the device is used less than 275 times per year in primary care, FibroScan would be cost incurring compared with secondary care, using micro-costing. The EAG notes that, from the evidence submitted, it is not clear that attendance rates in primary care will be higher than in secondary care. This variability has not been explored by the company, however scenario analysis conducted by the EAG shows that the cost-savings associated with the use of FibroScan are sensitive to small changes in attendance rates.

2) Proposed costs in secondary care included an inappropriate HRG code. Variation in clinical coding justifies taking a micro-costing approach (particularly when comparing with the cost of a new pathway), however the approach to micro-costing taken by the Company was top-level in both arms. The Company did not develop this in consultation with key stakeholders such as commissioners, managers and healthcare professionals involved in the implementation and delivery of the service. The micro-costing omitted important factors which need to be considered when developing a new pathway from an NHS perspective. Although multiple categories of cost would be applicable in both primary and secondary care settings, the actual cost may differ by setting and models of service delivery (for example room, staffing or implementation costs). This results in the Company's estimates of costs of FibroScan used in a primary, community care or secondary care setting not being an accurate representation of the full cost to the NHS.
3) The EAG considers that the long-term impacts have not been appropriately modelled. Progression was only included in missed patients, and mortality and related health states such as cancer and transplantation were not included. The time horizon could have also been extended beyond 5 years to estimate the longer-term benefits of FibroScan across the healthcare system.

The EAG acknowledges there remains a lack of comparative evidence comparing FibroScan in primary care to secondary care setting, and there is a lack of evidence to demonstrate adherence to behavioural therapy, limited evidence per NAFLD, AFLD and hepatitis subgroups. However, the Company could have conducted additional sensitivity analysis to demonstrate the impact of additional assumptions on the economic analysis.

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Appendix

Appendix A: Questions to the Company (sent 20/07/2022, response received 05/08/2022)

[Note: the EAG highlighted key questions and requested a rapid response (within 3 days); Questions 1a-c, 2a-b, 5, 7, 8, 11, 15, 18, 19a, 22]

1. Table 1 provided by the Company provides details on sites using FibroScan in primary and community care and the number of scans. The EAG has added a column to convert this to an average number of scans per year per PCN; this ranges from 153 to 278 (see below).
    a. Can you therefore advise why it has been assumed that the annual attendance is between 500 and 1000 patients per PCN (on page 4 of submission)?

Response: No response

    b. Additionally, it does not appear as though the micro-costings have accounted for multiple systems requiring capital purchase (as stated in the third column of the below table). Can you explain?

Response: The microcosting approach in the economic model calculates the cost per scan based on the total number of scans performed per machine, rather than per PCN (PCNs may have multiple machines or conversely, a single machine may be used across different PCNs).

The main point of interest for the economic evaluation of FibroScan is the cost of each scan. Therefore, the microcosting approach relied on the average number of scans performed by a single machine in a year regardless of how many GP practices the machine was shared across or if other machines are operated in parallel. The submitted data shows that the value used for the average number of scans per machine (500) is actually a conservative estimate.

In addition to the number of scans performed by PCNs being irrelevant, the calculations presented by the EAC in the table below are not consistent and, therefore, do not even always calculate numbers of scans per PCN:

- Some of the calculations account for the number of PCNs. For example, for mid-Hampshire, 1,115 divided by four (assumed to represent the 4 PCNs), whilst the Southampton calculation does not seem to take the number of PCNs into account.
- Some of the calculations adjust for the time frame. For example, for Southampton, the figure is divided by 14 and multiplied by 12 to reflect an annual number, whilst the South Nottinghamshire 24-month time frame does not appear to be accounted for.

The Company has provided the calculations for the number of scans per machine per year in question 2, based on updated data. Given this range of figures (457-1,115), as well as the other information presented in the submission on the prevalence of liver disease and potential numbers of patients eligible for scans, we maintain that 500 scans per year per machine represents a conversative average for the microcosting approach in the model.

c. Can you provide a specific reference for the Southampton row of this table (so that we can verify the numbers used) please?

Location	Area Covered	Number of machines	Number of scans	Any other information	EAC calculation of number of scans per year per PCN
Southampton	2 GPs across 2 PCNs	2 systems	533 over 14 months	Systems are mobile across the different practices	228 *Calculation: [(533/14)x12]/2* *Additional notes: 2 systems were used to conduct this.*
Mid Hampshire	18 GPs across 4 PCNs	1 system	1,115 in a 12-month period	Systems are mobile across the different practices	278 *Calculation: 1115/4*
South Nottinghamshire The Scarred Liver Project[2]	4 CCGs, Accessible to 100 GPs included within 9 PCNs serving a population of 700,000 people	2 systems	2,715 patients had a FibroScan from Sept, 2016 to Sept, 2018	GPs are able to refer patients with a defined risk factor for chronic liver disease directly for a specialised ultrasound test (Fibroscan®) before considering referral to secondary care.	153 *Calculation: [2751/2]/9* *Additional notes: 2 systems were used to conduct this, the number of patients was incorrectly stated as 2715 in updated company submission*

Response: No response

2. The EAG note that the unpublished Southampton CCG Pilot study has been used as the value for the number of scans per year in primary care;
   a. Table 1 notes that 2 scanners were used across 2 GP practices and 2 PCNs; please can you clarify whether there is an error in the number of GP practices covered?

Response: This is a mistake; it is only 1 FibroScan. This is a commissioned pathway including 5 to 6 PCNs for a total of 50 GP practices as of August 2022. However, the scans are performed at 2 GP locations where the other GPs refer in.

For clarity we have provided a revised table below. We have also provided a column which calculates the number of scans per year per machine, which we believe should replace the EACs calculations in question 1a/b.

Location	Area Covered	Number of machines	Number of scans	Any other information	Company calculation of scans per year per machine
Southampton	5-6 PCNs covering 50 GP practices as of August 2022	1 system	533 from Jan 2020 to March 2021 based on a commissioned pathway	System is mobile only within two locations where the scans take place	(533/14)x12 = 457
Mid Hampshire	18 GPs across 4 PCNs	1 system	1,115 in a 12-month period	Systems are mobile across the different practices	1,115
South Nottinghamshire The Scarred Liver Project[2]	4 CCGs, Accessible to 100 GPs included within 9 PCNs serving a population of 700,000 people	2 systems	2,715 patients had a FibroScan from Sept, 2016 to Sept, 2018	GPs are able to refer patients with a defined risk factor for chronic liver disease directly for a specialised ultrasound test (Fibroscan®) before considering referral to secondary care.	(2,715/2)/2= 679

b. Please can you clarify why 2 scanners have not been costed as 2 were used during this pilot trial (resulting in 1 scanner per PCN/GP practice or 250 patients per PCN/scanner)?

Response: Not relevant as this pathway only includes 1 FibroScan, please see correction above. As mentioned, the evaluation is interested in the average cost per scan, and it does not form part of the submission to determine how many machines a PCN should obtain or what the placement of the equipment should be.

c. From the information shared previously relating to this pilot trial, the EAG note that there was an aim to link into the Mid Hampshire pilot trial (row 2 in Table 1). Please can you confirm that there is no overlap in the patient cohorts?

Response: The Mid Hampshire and Southampton pathways are separate pathways, with separate cohorts. However, even if there was overlap with patients, this would not matter as patients would still require the scan (i.e., since the aim is to assess the number of scans performed by machine, it does not matter if multiple data points are from the same individual).

d. Given the pilot data is from 2018/19 and the service was formally commissioned in 2020 with 6 PCNs, is there any updated data that the Company can share?

Response: We can provide the monthly consumption of this FibroScan since January 2021 to June 2022 in the Southampton (see table below).

Now 50 GPs have access to FibroScan through this pathway, however the large majority of patients are referred from 5 GPs [redacted] and the scans are performed in 2 GP practices (as mentioned above). This pathway is commissioned, ramp up of volume is due to increase pools of GPs having access to the pathway (expending from initially Southampton PCNs to Southeast and Southwest Hampshire PCNs) plus patients being rescanned for follow up in addition to new referrals.

[redacted]	[redacted]
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3. The submission states that some patients may not undergo FibroScan due to 6 reasons (listed on page 9). Reason number 4 states: “local guidance to not conduct Fibroscan on patients with hazardous alcohol consumption, a high-BMI or type 2 diabetes”. However, these are subgroups of interest within the final scope/decision problem and reflect the eligibility criteria of the real-world evidence submitted. Can you please explain?

Response: This comment was in relation to local pathways only.
These subgroups (high-BMI, Type 2 Diabetes, alcohol use disorders) are eligible to undergo a FibroScan as listed in the final scope of MTG 562 from August 21st, 2021. However not all PCNs and community centres routinely scan due to lack of local liver guidance for these specific subgroups.

4. Please can you provide a full reference for Morgan *et al.* 2021 which is referenced in Table 2 of the Company submission?

Response: This has been uploaded with this document through NICE Docs.

5. The Company have explained that they surveyed two NHS Trusts to query which HRG codes were used to code FibroScan used in secondary care. They propose that “RD24Z” was used by King’s College, which is computerised tomography scan of two areas with contrast. Given FibroScan is ultrasound of one area, without contrast, can you check with Kings to ensure that there was not a typo and transpose of numbers in the HRG (i.e. did they mean RD42Z instead of RD24Z)? As contrast CT has a higher cost, and contributes 37% to the weighted cost, its inclusion is increasing costs of the comparator arm.

Response: We contacted the centre to confirm the HRG code with them, we were not able to collect feedback before August 4 due to summer holidays. We agree with you that this is likely to be typo but we are not able to confirm with the centre.

6. The EAG notes that two NHS Trusts provided feedback on the HRG codes used for FibroScan in primary care (King’s College Hospital NHS FT and University Hospital Southampton NHS Foundation Trust). However, 4 hospitals who are from 4 different NHS Trusts provided the number of scans per year ([redacted] Can you ask each of the above to provide the same information?

Response: All the centres used the same OPCS codes but they were not able to share the HRG.

Centres	Coding
[redacted]	OPCS: U364, Y981 & Z301
[redacted]	OPCS: U216, U364, Y981 & Z301
[redacted]	OPCS: U364 & Y981

[redacted] the coding will not be relevant.

All these OPCS codes lead to HRG RD48Z in the NHS HRG+ 2019/20 Local Payment Grouper which the EAC considered plausible (slides from March 22nd, 2022). The model provides an option to select RD48Z to reflect the cost of FibroScan in secondary care.

7. Can you advise how many NHS hospitals currently used FibroScan? Can you estimate the proportion of these hospitals that have more than one FibroScan? Can you also estimate the proportion of these hospitals which have CAP/SmartExam software?

Response: This question was addressed on July 29, 2021, to NICE [staff members]. Since then, the Company has sold additional systems to secondary care centres. As of August 1st, 2022, the Company has 340+ FibroScan used at a hospital level. 49% of NHS Trusts have more than 1 FibroScan. We do not have this data at a hospital level as our direct customers are Trusts. The Company estimates 50%+ of these devices have CAP/or Smart Exam.

8. Please can you clarify the training costs; Table 5 lists the cost as £1,180 per person with 1 training per year or 7 users during the equipment lifetime compared with half a day training for up to 3 people at a cost of £1,150?

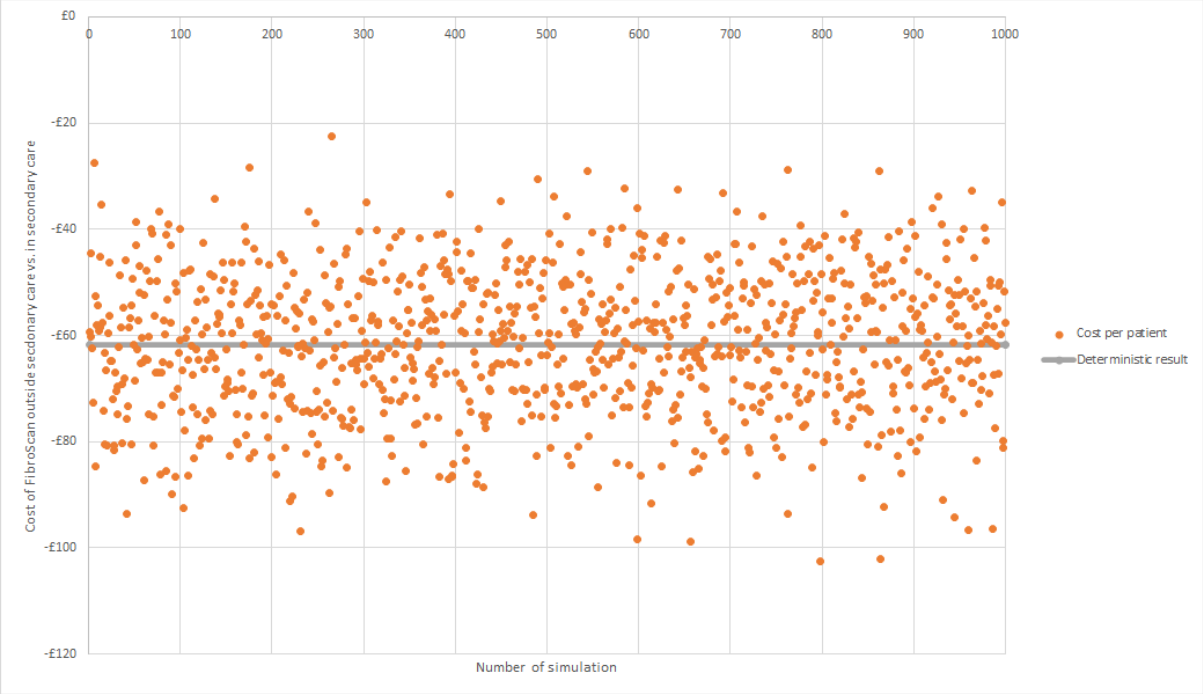
Response: Training for up to 3 persons for half a day was previously £1,150. In 2022, the cost for this training is £1,180 for up to 3 persons.
The cost of the training is not related to the number of attendees.

9. The EAG notes that the model applies a normal distribution to characterise the uncertainty in costs included in the analysis. However, the Gamma distribution, which is constrained to choose values between 0 and positive ∞ is generally considered more appropriate in order to reflect uncertainty in the costs used in economic models. Could the Company provide an option to change the type of distribution applied to explore whether there are any changes to the results?

Response: The normal distribution is always a candidate for any parameter based on expected values because of the role of the Central Limit Theorem, which essentially states that the sampling distribution of the mean will be normally distributed whatever the underlying distribution of the data with sufficient sample size.[1] Since it relies on all hospitals in England, the sample sizes relied upon when calculating costs for the NHS Reference Costs were deemed large enough. However, upon the EAG's request the gamma distribution has been added to the model (V5.0_29July22). The use of the gamma distribution for costs resulted in minimal difference in the results.
Results for 1000 simulations using normal distribution on costs:

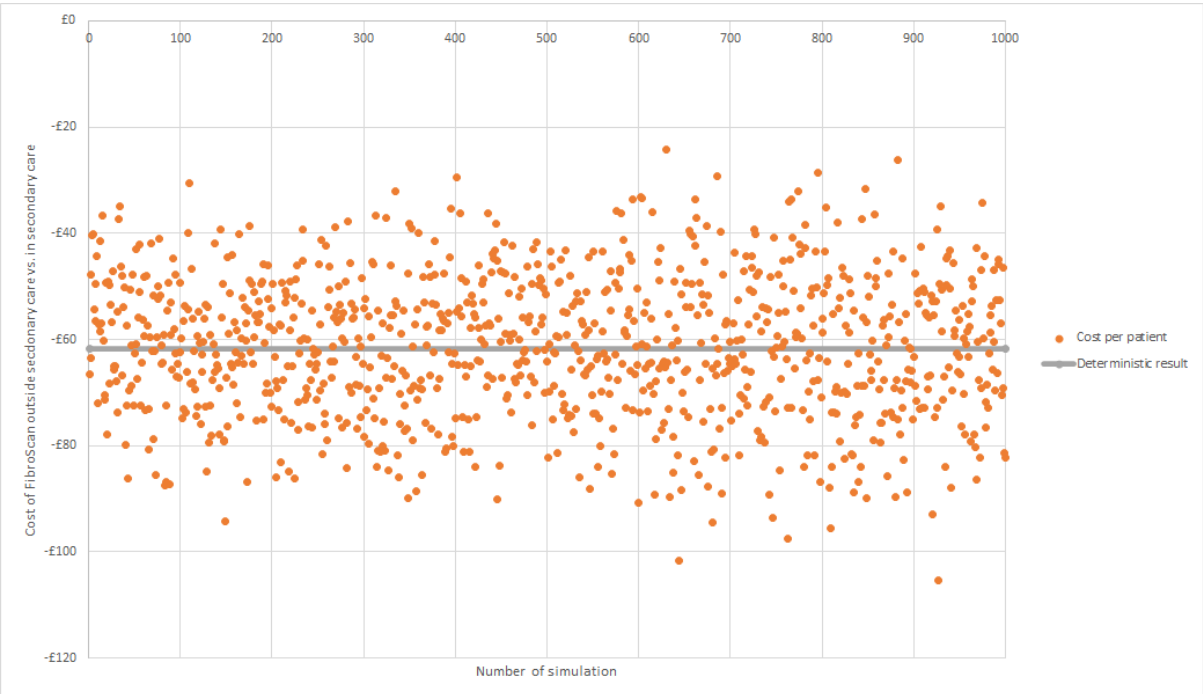
	Cost per person		
	Primary care	**Secondary care**	**Difference**
Average across 1000 simulations	£1,170.07	£1,231.52	-£61.46

[1] Briggs, A. 2005, Probabilistic Analysis of Cost-Effectiveness Models: Statistical Representation of Parameter Uncertainty. *Value in Health*. https://doi.org/10.1111/j.1524-4733.2005.08101.x



Results for 1000 simulations using gamma distribution on costs:

	Cost per person		
	Primary care	**Secondary care**	**Difference**
Average across 1000 simulations	£1,166.87	£1,228.19	-£61.32



10. The Company states that the model does not account for mortality occurring over the 5-year time frame citing Haflidadottir 2014 citing that "the survival for patients with moderate to severe fibrosis was significantly worse than for patients with mild fibrosis". However, the patient cohort included in the model includes patients with mixed disease severity which may have an impact on mortality rates. Furthermore, modelling all-cause mortality and knowing the uncertainty associated with the estimates is considered an important step in building a health economic model. Can the Company provide additional rationale for not including mortality in the model?

Response: Given the uncertainty with modelling over a 5-year time frame, it was considered that including mortality in the model would add further uncertainty and unnecessary complexity.
The Company felt that there was a lack of data to model differential mortality according to the severity of liver disease. The inclusion of mortality was considered but there was concern that mortality differences modelled between the two arms would be solely driven by higher numbers having missed diagnosis in the secondary care arm, unless the model also included assumptions about the distribution of patients who do not actually attend scanning between different levels of liver disease severity, therefore would add unnecessary complexity.

11. The EAG notes that NICE (2020) specifies preferred discount rates for costs and health effects in its reference case of 3.5% per year for both costs and health effects. The long term economic model however, does not include a discount. Can the company provide a rationale for this approach?

Response: The original time frame in Model V1.0 (file dated October 21) was 1 year. Given this time horizon, discounting was not applied. Based on NICE and EAC feedback, a longer-term perspective was then incorporated as an option. As this was still a scenario at this point, discount rates were unintentionally omitted.
To explore the impact of this omission, discount rates have now been added in the model. This results in a very minor change in the results (-£64.61 without discounting vs. £-61.68 with discounting at 3.5%).

12. The company assumes that if the patient requires behavioural intervention within the first year after having a scan, then liver disease is manageable through behavioural intervention and does not progress. Can the company provide any evidence for this claim?

Response: This was a simplifying assumption because the long-term scenario is highly uncertain. Non-adherence to behavioural intervention does exist and data on non-adherence to liver disease-related behavioural interventions are reported (e.g., in sophisticated models such as those presented by Crossan[2]). Since the model time frame is only 5 years and liver disease typically takes a long time to progress, it was believed that it would create more uncertainty to include assumptions about the behavioural patterns of patients over a short time frame and would not be warranted

[2] Crossan, C., *et al*. 2015. Cost-effectiveness of non-invasive methods for assessment and monitoring of liver fibrosis and cirrhosis in patients with chronic liver disease: systematic review and economic evaluation. *Health Technology Assessment*. 19(9).

in this model. Furthermore, this simplification does not bias the results, as there is no basis to assume that the behavioural patterns of patients would depend on whether they were originally scanned in secondary care or outside secondary care.
There is no evidence available related to liver disease management and behavioural intervention specific to FibroScan.

13. On page 18 (Table 5) can you advise what the superscript "†" symbol means?

Response: Table 5 FibroScan costs if machine is purchased

Item	Cost	Number required over machine lifetime*
FibroScan 430 Mini+	£48,000	1
Additional probes	£16,700	1
Cost of CAP/SmartExam software	£18,500	1
Cost of 6-year Serenity service contract†	£28,560	1
Training costs (per person)	£1,180	7
Total	**£120,020**	

* Echosens guarantees the specification and performance characteristics of the FibroScan device for seven years, provided that all necessary precautions for use and maintenance have been taken in accordance with the recommendations of the user manuals provided to customers.
†The lifetime of the machine is covered by an initial 12-month warranty + 6 years cover

14. In Table 6, which reports the number of scans performed by the 4 hospitals, there are 2 columns representing 2019. Can you explain?

Response: This is a typo, and table headings should be 2018, 2019, 2020, and 2021.

15. In Table 7, it states that 610 scans would be conducted each year in secondary care, but that 500 scans would be conducted each year in primary/community care. In the original economic submission and this updated submission the premise was that more patients would attend primary care and therefore would detect more liver disease. Can you explain why this basecase model assumes fewer patients would be scanned in primary care?

Response: This is a misunderstanding of the approach and the inputs' purpose (see also our response to question 1 above). These figures are used for predicting the number of scans performed by a single machine depending on where it is used to allow for calculation of the cost of a single scan and were not intended to reflect a prediction of the total number of scans performed by a PCN or in secondary care. Data presented in the submission shows that the attendance rate in primary care would be higher than in secondary care. Using 500 scans per year per machine and

testing 750 scans per year per machine in a scenario analysis, shows that both scenarios to lead to cost savings if FibroScan is performed in primary care (-£71.85 if 750 scans are performed per machine vs. -£61.68 if 500 scans performed per machine). Please note again, that these numbers represent assumptions about numbers of scans performed per machine, not total numbers of scans performed in primary care or secondary care settings.

16. In Table 8, the "Cost per scan excluding staff costs ((i/ii)/iii)" in the 750 scans year scenario is the same as the one listed for the 500 scan per year scenario. Could you please double check?

Response: This was an error, please see updated table below.
Table 1 Microcosting calculation outside secondary care scenario analysis

Item no.	Item	Outside secondary care
i	Total cost of machine and training if purchased outright	£120,020
ii	Lifetime of machine (years)	7
iii	Number of scans per year	750
iv	Cost per scan excluding staff costs ((i/ii)/iii)	£22.86
v	Staff costs	£10.50
vi	Cost per scan (iv + v)	£33.36

17. Also, in the previous model a "cost per scan" approach was taken in primary care. Can you explain why this scenario has been removed in this updated submission?

Response: If this is referring to the 'Pay per scan' contract, this option has not been removed from the model, and the user can still select to use this scenario.
The number of scenarios presented in the reported was reduced to keep the document concise, with a clearly stated base case.

18. The micro-costing for FibroScan in primary care only includes capital cost equipment (generator, probe, software, training, servicing) and nurse time costs. However, no costs have been included for transporting the device across the primary care network, need for multiple devices, multiple staff or room costs. Can you explain the approach to micro-costing in primary care?

Response: As explained above, the aim of the micro-costing approach is to estimate the average cost per scan. If multiple machines were required (and multiple staff) in a network, then the current assumption would be that costing is linear, i.e. use of two machines require two purchases and two times as much staff time to cover a two times larger population. This would still make the cost per scan the same.

Room costs are not typically included separately. For example, if a patient requires a GP attendance cost for a behavioural intervention, a room cost is not added to the cost of the GP appointment. It is not anticipated that a dedicated FibroScan room would be required, and that it could be located in nurse practice room given its size. Each PCN would have their own localised system for implementing FibroScan in primary care. Some devices would be static. For mobile devices, the FibroScan 430 Mini+ is easily portable by an individual. The operator with a FibroScan can put it in a suitcase to move by car or take on public transport during already scheduled visits. This would not incur an extra cost.

19. The EAG has identified the following issues with the micro-costing that need further clarification from the Company:
    a. The company have stated that for the competent use of FibroScan, supervision from a competent user is needed for around the first 50 uses. However, this additional cost does not seem to have been included in the micro-costing exercise. Can the Company provide a rationale for this exclusion?

Response: The 50 scans are an average based on feedback from customers. This is managed internally at a centre level by the competent operator. The Company is not involved in the supervision of these 50 scans (on average) after the training and is not reassessing competence after 50 scans.

    b. The EAG notes that the costing of the capital equipment should have been conducted using the Equivalent Annual Cost methodology as per best practice. This would apply to both the micro-costing exercises (in secondary care and outside secondary care) This method incorporates both the depreciation and cost-opportunity aspects of the acquired equipment over its lifetime (Drummond, M.F., Sculpher, M.J., Claxton, K., Stoddart, G.L. and Torrance, G.W., 2015. Methods for the economic evaluation of health care programmes. Oxford university press.) This method allowed us to convert the initial capital cost into an annual sum that equals the resources invested plus their opportunity cost.

Tables 1 and 2 below have been created by the EAG in order to incorporate the equivalent annual cost of the Fibroscan equipment (scan plus probes) using this methodology.

The following assumptions were made:

- Fibroscan lifespan: 7 years (as per Company submission)
- Number of scans per year: 610 (as per company submission)
- Discount rate: A discount factor of 3.5% was applied to account for the individual's time preference for costs to be incurred later rather than sooner. This follows NICe guidance which NICE guidelines recommend that costs and health outcomes should be discounted at 3.5% per year.
- All costs are assumed to be incurred at the beginning of the year – in this case capital costs for year 1 will not be discounted

- The capital cost of Fibroscan was spread over its lifetime (7 years)

Table 1: Step 1- Calculation of annual annuity factor

Life years of capital equipment	Annuity factor calculated using 3.5% discount rate *= 1(1+r)^n where r = discounting rate (e.g. 3.5%)*
Year 1	1.000 (no discount rate applied to year 1)
Year 2	0.9662
Year 3	0.9335
Year 4	0.9019
Year 5	0.8714
Year 6	0.8420
Year 7	0.8135
Total annuity factor, 7 years, discount rate of 3.5%	6.3286

Table 2: Step 2 - Microcosting calculation outside secondary care scenario analysis

Item number	Item	Outside secondary care
i.	Annual equivalized cost of FibroScan equipment (including 1 purchased probe – purchase cost £48,000 + 16,700)	£10,224 (£64,700/6.3286)
ii.	Capital cost per scan (£10,224 / 500)	£20.45
iii.	Cost of CAP/SmartExam software per scan (£18,500 / 7years/ 500 scans)	£5.29
iv.	Maintenance costs per scan (28,560/7 years/500 scans)	£8.16
v.	Training costs per scan (£1,180 / 500 scans)	£2.36
vi	Staff costs - Nurse to perform scan £42.00 *0.25	£10.50
vii	Cost per scan (ii + vi)	£46.76

The EAG notes that using the Equivalent Cost methodology (applied to the outside secondary care scenario) only minimally alters the cost difference between the use of Fibroscan in secondary care and outside secondary care.

Response: Thank you for confirming that this does not result in significant differences in the cost per scan. For continuity with the previously submitted material, the Company has not updated the model based on Equivalent Cost methodology.

20. Thank you for providing the conference abstract for Gordon *et al*. (2021); which was published in November 2021 after the original literature search conducted by the EAG in the Assessment Report. On page 7 of the Company submission it states that the study by Gordon reported that FibroScan was used reliably by operators ranging from healthcare assistants Band 2 to nurses Band 6. However,

the conference abstract states that the “undertaken by a trained Band 3, moving between each practice each day”. Please can you explain? Can you please provide a reference to the full peer-reviewed paper, if available?

Response: We know from customers that FibroScan can be used by HCA Band 2 to Band 6. Gordon et al 2021 shows that FibroScan used by a Band 3 nurse is in line with what we see in the field.
There is no full peer-reviewed paper for this conference abstract.

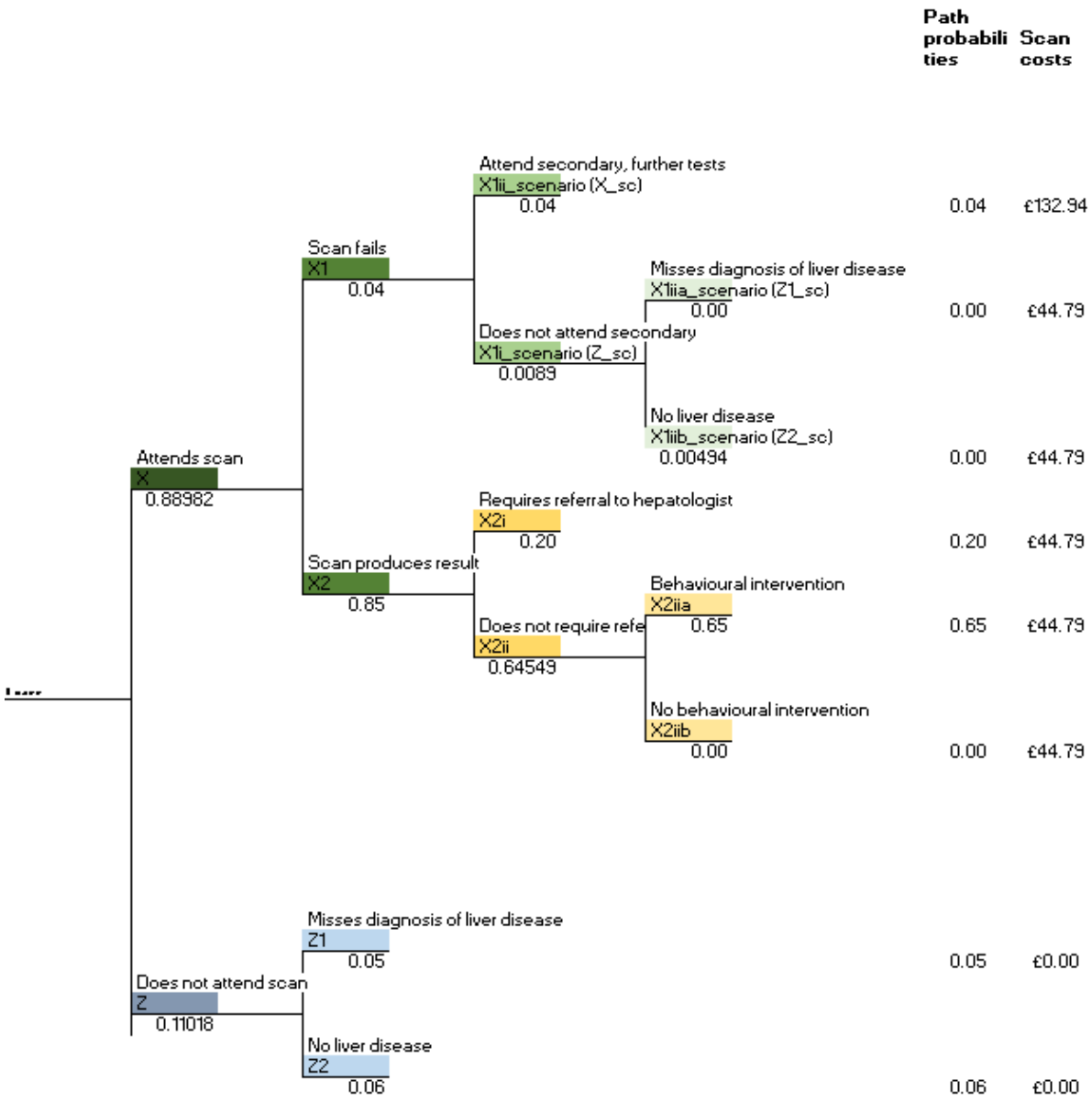
21. Can you please provide justification of the scan costs included in Tables 13, 14 and 15, as these values do not appear elsewhere in the report?

Response: The scan costs in table 13, 14 and 15 are the total costs associated with use of FibroScan in the given branch of the decision tree.
For example, the scan costs in Table 13: ‘Mean using FibroScan outside of secondary or specialist care (technology)’ are listed as £42.99. This is calculated from the weighted average of each branch in the decision tree, e.g. the first branch represents a patient pathway where the patient attends the scan in primary care (cost of £44.79), however, the scan fails, therefore the patient has to attend secondary care for further tests (cost of £88.15) giving a total of £44.79+£88.15=£132.94. The probability of the patient ending up on this whole pathway is obtained my multiplying the probability of each branch: the probability that the patient attends a scan in primary care (89%), the probability that the scan fails (5%) and then the probability that the patient attends the follow-up tests in secondary care (80%) resulting in pathway probability of 89%*5%*80%=0.036.

Branch in model	Probability of pathway	Total scan costs for pathway	Weighted cost
End of branch X1ii_scenario: Attends scan, scan fails, attends scan in secondary with further tests	0.036	£132.94	£4.73
End of branch X1iia_scenario: Attends scan, scan fails, does not attend scan in secondary, misses diagnosis of liver disease	0.004	£44.79	£0.18
End of branch X1iib_scenario: Attends scan, scan fails, does not attend scan in secondary, no liver disease	0.005	£44.79	£0.22

End of branch X2i: Attends scan, scan produces result, requires referral to hepatologist	0.200	£44.79	£8.95
End of branch X2iia: Attends scan, scan produces result, does not require referral to hepatologist, behavioural intervention	0.645	£44.79	£28.91
End of branch X2iib: Attends scan, scan produces result, does not require referral to hepatologist, no behavioural intervention	0.000	£44.79	£0.00
End of branch Z1: Does not attend scan, misses diagnosis of liver disease	0.049	£0.00	£0.00
End of branch Z2: Does not attend scan, no liver disease	0.061	£0.00	£0.00
Total			£42.99

The figure below provides a screen shot of where these numbers are featured in the model calculating the pathway probabilities and the total scan-related costs for each branch in the decision tree:



22. Can you advise why the cost attributed to liver warning is stated as £78.76 in the economic model in the "Other costs" worksheet and is not £13.07 as stated in table 12 of the submission?

Response: See explanation above on differentiation between unit costs of resource use items in the model from expected costs per patient (which is calculated as the branch-specific resource use times the unit costs multiplied by the patient pathway probability for each branch and then summed across for all possible patient pathways. Therefore £78.76 is the unit cost for a year of treatment for a patient with liver warning, whereas £13.07 is the expected cost per patient for liver warning (since only a proportion of patients are identified with liver warning).

23. Can you confirm that within long-term modelling that repeated testing of FibroScan (in either primary/community or secondary care) has not been incorporated, and provide a rationale for this?

Response: Repeat scanning after scan failure is built into the model. The source used for the long-term costs (Wright et al 2006[3]) includes disease monitoring (labelled 'investigations' in the publication), and any requirements for further investigation with FibroScan or other means of imaging is included in these costs.

24. In Appendix 2 of the updated submission, the given value for "proportion of the population with at risk liver damage and liver disease" is 5%, but the Atlas report states the at risk population to be between 10-20%. Can you explain the reason for using 5%?

Response: The figures come from the Liver Atlas 2017, page 16 Table A.1.

Population subgroup in relation to liver diseases	**Numbers at risk/affected/concerned**
At risk of liver damage	2.24 million inhabitants
With significant liver disease	0.6 million inhabitants
UK inhabitants	56 million
Proportion of the population with at risk liver damage and liver disease.	= (2.24 + 0.6)/56 = 5%

25. On page 8 of the updated submission it is discussed that 1000 patients per annum per PCN would be 'eligible for screening' using FibroScan. Could you explain what criteria would be used to identify the 1000/40,000 patients per PCN per year who would be eligible for FibroScan?

Response: The Company consider this question to be outside of NICE scope. The scope defines the patient population as those who would be already identified for screening in secondary care - therefore the criteria are the same for primary care.

[3] Wright M, Grieve R, Roberts J, Main J, Thomas HC, Alexander G, *et al*. Health benefits of antiviral therapy for mild chronic hepatitis C: randomized controlled trial and economic evaluation. Health Technol Assess 2006;10(21). http://dx.doi.org/10.3310/hta10210

Appendix B1: Questions to the Clinical Experts (sent 20/07/2022)

Questions sent 20/07/2022 to 8 Clinical Experts, 8 responses received

	Question	Responses
01	The Company have assumed that a single FibroScan device can be used across 5 Primary Care Networks. Do you think this is feasible?	**Expert #1:** Yes but it will require careful scheduling. I have personal experience of this and a single scanner was adequate over time, it is never urgent to obtain a reading so waits are not a clinical issue. Waits were an issue for the primary care referrer and patient however so this would need managing to avoid unrealistic expectations
		Expert #2: This would be feasible in urban areas where several PCNs are in close proximity. Maybe more difficult in more rural areas but possible if the device moved around between operation centres.
		Expert #3: If it remains on one site and the patients can access it there, this would be possible. If it needs to go to different sites it would need to be fully portable.
		Expert #4: This would be primarily dependant on the average size of the PCN, population over their geographic area. A large PCN with a high liver disease prevalent area may require more for demand It would be reasonable to calculate this based on the model of scanning – daily, weekly – full time service / part time, fixed or different clinic locations.
		Expert #5: Mobile Fibro Scan machines can be easily transported to outreach area and if there is good scheduling done can be used across multiple sites. A dedicated room will need to be booked across each of these five sites to ensure that the procedure is carried out appropriately.
		Expert #6: That sounds ambitious- each network might have 5-10 individual sites so it depends on the model of delivery but 5 networks might then have 50 sites spread across a reasonable area so each site would have access to a fibroscanner for just one week per year. There is a model in place for locality delivery of retinal screening in which the camera is moved from site to site. So it would be worth looking to see how many cameras are used per GP network bearing in mind that retinal screening is a planned once a year service.
		Expert #7: What happens if one breaks or needs servicing … At least 2 would seem prudent …
		Expert #8: Yes
02	Do you think it is likely that a NHS Hospital currently using FibroScan would only have one FibroScan device?	**Expert #1**: It will vary considerably. Larger hospitals will have more than one machine and machines are available through the NHS England HCV networks for example which may well be

		accessible to the community. Some hospitals will have one dedicated to this community service which would be required to provide adequate PCN cover.
		Expert #2: I think this is the normal at the minute although I don't work in the hospital setting. The company should know how many scanners are in different hospitals.
		Expert #3: Yes
		Expert #4: This is certainly the situation for many hospitals. It must also be noted many of which do NOT have steatosis capability and are restricted to stiffness measurements only. Fat in the liver requires measurement as this is now known not to be benign and NON-CAP fibroscan devices are no longer fit for purpose in the setting of NAFLD, NASH or alcohol related liver conditions. With NAFLD rising exponentially and becoming the leading cause of poor liver health, risk of fibrosis and associated other conditions (Type 2 DM, CVD etc) these devices miss a significant at- risk population
		Expert #5: Most hospitals have one machine at their disposal with built in service contracts with the company in case repairs are needed. This is built into the budget. In the ideal world, a back up machine would be useful for outreach work and in case of emergencies.
		Expert #6: No response
		Expert #7: No
		Expert #8: Yes
03	The Company have assumed an attendance of between 500 and 1000 patients per year per PCN. The Company extrapolate this to 5000 patients being eligible for FibroScan screening across 5 PCNs over 1 year. Does scale of expected use of FibroScan in primary/community care setting seem feasible?	**Expert #1:** Yes, these numbers seem reasonable. The Nottingham system shows that the demand can be managed quite effectively by minor tweaks to the referral/request criteria but I think the numbers here are very much in accord with our direct experience.
		Expert #2: Assuming each PCN is roughly 30 000 patients (they vary in size) then 5 x PCN would be 150 000 so 5000 patients being eligible is reasonable given the likely incidence of those meeting current national guidelines for Fibroscan assessment. Actual attendance is obviously not the same as being eligible and this relies on pathways of care into Fibroscan and GP awareness/education which is outside the scope of this NICE assessment.
		Expert #3: Yes

		Expert #4: Possible – My experience in a specialist NHS trust – we performed >3500 scans and increased by 91.5% between 2015 and 2019. PCN with high-density, known high-risk patient populations – Alcohol, T2 DM, Obesity …. may require larger numbers of scans
		Expert #5: Obviously, this is partly dependant on size of patient populations. The prevalence of significant NASH is estimated to be 1 in 40 so a PCN of 50,000 population size would theoretically have 6250 subjects that needs scanned so the numbers given are reasonable. We have no data on incidence of NASH and the effectiveness of community screening and these two factors will also determine numbers coming through the system annually.
		Expert #6: As I understand it PCNs are likely to be 30-50000 registered patients. So if we assume 50 000 the figures they are working with represent 1-2% of the population. It depends then on what we are envisaging the population being screened to look like. It might include those at risk, those with suspected liver disease due to abnormal results and those being followed up with established but early liver disease. In our published feasibility study 5 practices in the intervention group had 27000 adults aged over 25 of whom 4000 (14%) had a risk factor for liver disease. So the figures look on the low side if screening of those with liver risk factors is envisaged.
		Expert #7: I think the numbers are large because undiagnosed liver disease has been neglected .. if the population of a PCN is 50,000 to 100,000 then these estimates are not unreasonable. Whether there is capacity to provide this service is more challenging . Certain areas have done this with joined up working between primary and secondary care … but the exception rather than the rule…
		Expert #8: Yes
04	Within primary/community care setting is it likely that an additional GP appointment is needed to discuss the results of the scan? Or would the GP practice nurse be qualified and able to deliver the results at the same time as the scan?	**Expert #1**: It is essential that the fibroscan operator delivers the result and brief advice verbally and in writing on that result, there are good examples of this which can be used across the country. Appointments with the GP should be restricted to those who have abnormal values or require onward referral.
		Expert #2: Any XRay, US, blood test that is currently done in primary care needs some communication/discussion with the patient. Depending on practice care models and staffing this may be done by messages through admin, text/email directwto patients, phone call from

		nursing team or GP. Depending on the result and the complexity of the information passed on this may be deemed to count as an extra 'appointment' or 'patient contact'. If the results are normal for bloods/swabs/scans this is quite often relayed by the admin team. A practice nurse if trained to carry out the Fibroscan could easily be qualified to give out the results and related advice at the time of the scan.
		Expert #3: The GP practice nurse could give the results and the guidance, most of it will be brief interventions.
		Expert #4: The current skill set used in most areas are skilled liver nurses and where these are used the majority of units support them discussing the results with the patients. As a CQC regulated provider of fibroscan services – We have never been asked NOT to discuss the results and this is often specifically requested as our team are very familiar with discussing these results in an appropriate and supportive manner with context and guideline supported information. These are always discussed at the time of appointment and time of highest patient engagement and teaching moment. Additional appointments would be required in the setting of no knowledge there would be a level of education required. In settings unfamiliar with fibroscan and its indications/limitations such as primary care and non-hepatology / gastroenterology areas lack of knowledge, skill and context of use are the most common barriers reported in surveys. In high stiffness levels and additional appointment may be required with the GP if the nurse is unfamiliar with this area, biopsy may be an outcome of referral, this could also be provided virtually or discussed with the local specialist team. Where only technicians are used then this will always necessitate an appointment for results discussion with either a nurse with knowledge or the physician.
		Expert #5: This is predominantly determined by a robust pathway for assessment and treatment of these patients. I've attached a pdf document outlining the change of a consultant led service to a nurse led service in NHS Grampian and this can be easily replicated in primary care.
		Expert #6: It would depend on the model of service delivery, in our feasibility study we used an experienced nurse/doctor to do the scanning and they would be capable of interpretation and delivery of the results. A practice nurse with no prior training would be unlikely to have the confidence to do this. In our study the results of

		scans and fibrosis blood tests were all reviewed by a consultant hepatologist to arrive at a putative diagnosis and a management plan put in place. So I think the minimum here would be an experienced GP appointment in someone who had training in interpretation and subsequent management options (El-Gohary *et al.* 2018)
		Expert #7: GPs should not be used to discuss the results. Who does this Is debatable . A practice nurse may not have the confidence or experience to do this… we have trained our HCA nurses to provide brief intervention and summary of scan results.
		Expert #8: If person performing the fibroscan is appropriately trained and there is a set outcome pathway then they should be able to inform the patient, give lifestyle advice and send outcome records to GP or refer directly to secondary care.
5	Would the FibroScan 430 Mini+ model be the standard model to be used in a primary/community care setting?	**Expert #1**: Probably-this is a good machine but any would be fine so long as both standard and XL probes available.
		Expert #2: No idea - not sure there is a standard model in the community yet.
		Expert #3: Not sure.
		Expert #4: It would certainly be the best current primary/community option currently – highly mobile, relatively light. The 530 compact model whilst mobile is bulky and would require transport costs and possible manual handling assessments for all locations. If fixed primary/community setting this would be a suitable model. The latest software should be installed – Continuous CAP and SmartExam – this maximises the scope of use of the devices. Other models would be suitable –new Fibroscan GO model although this is I believe only available on a per scan charge.
		Expert #5: This has the advantage of being used in multiple sites, but innovation will continue and other manufacturers may come into play in the future.
		Expert #6: No response
		Expert #7: This model should be fine
		Expert #8: This is a portable device which can be taken around the PCN region to where the patients are.

6	Would the FibroScan 430 Mini+ model be the standard model to be used in secondary care setting?	**Expert #1**: Generally yes although many of us continue to use older models, they still work!
		Expert #2: No idea - company will know
		Expert #3: No
		Expert #4: Predominantly the models used in secondary care are the 502 touch, 530 compact, 430 mini and 430 mini+ with some larger liver units having the 630-expert model. The 430 mini+ It is a suitable model for all areas, specialist units often have a range of devices and various software versions installed throughout.
		Expert #5: If this is being used in one site other models would be preferred.
		Expert #6: No response
		Expert #7: Lost track of all the devices they produce .. Quite frankly the company make a big deal about this but the main aspects are size and portability . For the purpose of community liver disease they are all fine.
		Expert #8: This can vary depending on funding and historical models used. The probes are the same across the models.
7	Within long-term modelling the Company have assumed that only patients who do not attend the FibroScan appointment have liver disease progression. The Company has assumed that patients who undergo FibroScan and are identified as liver warning, probable fibrosis or probable cirrhosis do not progress to the next stage of disease within a 5-year time horizon. Is this a reasonable assumption?	**Expert #1**: Are you sure this is right and this is what the company are saying? It doesn't sound right to me! A fibroscan isn't a treatment for liver disease and I do not think anyone would suggest it is. Therefore the fibroscan tells people they are at risk and hopefully provide a basis for lifestyle change, alcohol reduction and weight management being the most important. Liver disease will only stop progressing if that risk factor is addressed. This may be a misinterpretation of the rates of progression, for non alcoholic fatty liver progression (assuming no change in risk factor) is slow so the risk of a patient going from moderate fibrosis to cirrhosis or cirrhosis to decompensated cirrhosis in a 5 year period would be low (but not zero). In alcohol related liver disease progression can be faster although still the proportion changing a liver disease state over a 5 year period will still be relatively small. Clearly if the risk factors are no longer there then progression would be halted so the assumption then of no progression over 5 years is correct.
		Expert #2: The progression will depend on the uptake and success of lifestyle interventions/other interventions as a result of making the above diagnoses. The location of the scan (primary v secondary care) is unlikely to have an impact on this - rather the quality and intensity of the follow

		up intervention. It is unrealistic to assume that none of the patients who have been given a liver warning will progress.
		Expert #3: No
		Expert #4: This has been based largely on the meta-analysis (Clin Gastroenterol Hepatol. 2015 Apr;13(4):643- 54. e1-9; quiz e39-40.doi: 10.1016/j.cgh.2014.04.014. Epub 2014 Apr 24) where the findings corresponded to 1 stage of progression over 14.3 years for patients with NAFL (95% CI, 9.1-50.0 y) and 7.1 years for patients with NASH (95% CI, 4.8-14.3 y). It is now evidenced that there are fast and slow progressors and the identification and monitoring of these categories of patients is of importance. Locating the fast progressors who require more frequent scanning would allow for the majority of others to be monitored 3- 5 yearly most likely. This would also increase the ability to locate those at highest risk of HCC development in the next 10 years and those at high risk now. NAFLD and NASH is a liver disease which confers an increased liver cancer risk in the setting of NO cirrhosis unlike most other disease areas and should be monitored.
		Expert #5: No, it is not, progression occurs in a proportion of subjects whether or not Fibro Scan is done or not. The test identifies patient who can have behavioural interventions and referred for putative drug trials at the moment as no licensed drugs exist. Without any effective intervention, the patients who have had the test will also progress.
		Expert #6: No, we have observed only modest behaviour changes following the feedback of liver screening results. Even in those admitted to hospital with catastrophic liver decompensation only half will modify their subsequent behaviour. So I would imagine there would be disease progression in those attending for screening. In a follow up study of our pilot study above in those who were rescreened after 4.5 years 20% had evidence of disease progression. https://bjgpopen.org/content/5/6/BJGPO.2021.0145
		Expert #7: Reasonable assumption . Based on biopsy to biopsy longitudinal studies which show progression of approx. 0.2 units per year… old data but can be extrapolated ..
		Expert #8: Tina Reinson, Christopher D Byrne, Janisha Patel, Magdy El-Gohary and Michael Moore BJGP Open 2021; 5 (6): BJGPO.2021.0145. DOI: https://doi.org/10.3399/BJGPO.2021.0145

		18.7% who had been provided lifestyle change advice had progressed at an interval of 53.6 months. The optimal interval period between scans remains uncertain and for some 5 years is too long. People with known liver cirrhosis need to be under secondary care and therefore do not need repeated fibroscans the community.
8	The Company has assumed that those patients who have had a negative result showing no liver disease and therefore no treatment will remain liver disease free within a 5-year time frame. Does this seem likely? Is there any data that confirms that this is the case?	**Expert #1**: Generally yes with the caveats above. Someone with non alcoholic liver disease and no liver fibrosis will have a very low risk of developing liver fibrosis in a 5 year period even if they remain at risk of fatty liver. Alcohol related liver disease can progress faster but even then a no fibrosis scan would be a pretty good way of saying the chance of progressing to serious liver disease in 5 years is very low.
		Expert #2: Due to the slow rate of progression of NAFLD these patients would be v unlikley to develop significant liver disease within the next 5 years. The progression with alcohol related liver disease can be faster and less predictable. There is lots of literature on the natural history of liver disease progression which I'm sure the committee are capable of searching for.
		Expert #3: It does seem likely, especially if the opportunity to address risk factors for liver disease are taken at the time of the scan
		Expert #4: NOTE: Liver disease is a multi-system disease and thus requires consideration in relation to this evidence by Tracey Simon et al (Simon TG, Roelstraete B, Hartjes K, Shah U, Khalili H, Arnell H, Ludvigsson JF, Non-alcoholic fatty liver disease in children and young adults is associated with increased long-term mortality, Journal of Hepatology (2021), doi: https://doi.org/10.1016/j.jhep.2021.06.034) suggests increased mortality from associated conditions in the setting of children and young adults of 1:15 over a 20 year period of CVD and non-hepatic cancer in the setting of fatty liver. The EASL Lancet report 2021 – (Published Online December 2, 2021, https://doi.org/10.1016/ S0140-6736(21)01701-3) details and provides significant evidence of the growing burden of other conditions associated with poor liver health. This will not necessarily be the case these patients are likely to progress as noted above at slower rates per stage of fibrosis as detailed previously. In context to only of LIVER disease / diagnosis – in those with no stiffness but high liver steatosis – the risks relate to associated metabolic conditions developing – pre-diabetes, T2DM, hypertension, hypercholesteremia, CVD etc... Maintaining and optimising lifestyle remains the primary treatment option and a key factor –

		should this alter rapidly then additional assessment can be offered.
		Expert #5: Again, this is a flawed assumption. The recently published BSG / BASL quality standards (https://www.bsg.org.uk/clinical-resource/quality-standards-for-the-management-of-non-alcoholic-fatty-liver-disease-nafld-consensus-recommendations-from-the-basl-and-bsg-nafld-special-interest-group/) suggest that this group needs a pragmatic relook every 3 years. This is based on studies documenting progression of disease which is slow.
		Expert #6: I am not sure there is data to support this. The optimal period for rescreening is not currently known.
		Expert #7: Not sure we have strong data to guide us on this. Pts with negative results are often reassured and not given followed up … so they are known unknowns … Anecdotally we have pts presenting with advanced disease who have had recent negative results … this however is not scientific data and clincians will have recall bias in remembering these. The NPV of >90 % is what is used to justify the approach of reassuring -ve results … i.e. extrapolated data and I am not aware of robust studies that have actively found the negative scan results and robustly offered them follow up scans five years later.
		Expert #8: See above. 5 years may be too long an interval for some.
9	In order to consider the cost-case, for those with experience in delivering FibroScan within a non-secondary care setting: a) can you please list some components that contribute to the cost of delivering FibroScan in a non-secondary setting? For example, healthcare/clerical staff, consumables, facilities, storage costs etc.	**Expert #1**: fibroscan operator (band 3) time and training which includes learning curve of 30or so supervised readings. Clerical staff to arrange appointments and ensure results uploaded to correct systems. There is an IT cost to provide electronic uploads of data from the fibroscanner into NHS systems. If this is not done then it is quite a significant manual process which will require quite a lot of time to deliver. There is also time to ensure that the feedback to patients is available in written form so that the brief advice post scan is backed up in writing. There is a room cost in primary and community settings for fibroscan and this needs to be up to clinical standards for hygiene and waste disposal. We hire rooms in general practices which isn't a fortune but will be around £200 per session.
		Expert #2: N/A

		Expert #3: I do not deliver fibroscans outside the hospital setting.
		Expert #4: 1: Within my NHS experience: This would include • Time and cost taken to progress business cases– I wrote the anonymised case currently used by NICE for obtaining Fibroscan – this took 15 months to write and progress through internal structures and divisional staff changes despite being a specialist setting. • Equipment, software upgrades. • Healthcare staff (dedicated/released from current role), secretarial, clinic staff, scan staff training needs, clerical support, appointment scheduling, staff turnover. • Device transport cost, location, device not in use time, consumables. • Insurance costs, maintenance costs for each device. • The time taken to develop, build and resource a fibroscan service are also costs to be considered in the setting of no experience or knowledge base. 2: Within my current role as a CQC regulated supplier of complete fibroscan services we hold all capital expenditure and other costs above. The costs attributable to the local non-secondary setting or any purchaser is usually the clerical support to schedule appointments and in clinic. The location / room costs unless use of one of our mobile clinic vans is required for more rural locations where parking would be required. GP surgery, golf course etc…
		Expert #5: 1. Room booking and space costs in primary care 2. Admin costs for booking appointments 3. Nurse led clinics to deliver clinics 4. Nursing time for result documentation 5. Admin staff for maintaining database 6. Storage of fibro scan machine in centralised facility
		Expert #6: I would look to the diabetes retinal screening services which are already in place to get some estimates of costs. I don't think this would be dissimilar.
		Expert #7: admin staff costs to book appts , fibroscan staff costs, Room costs , travel , IT costs e.g laptops (if secondary staff using primary care) are the major ones I can think of.
		Expert #8: Trained staff perform the scan and provide brief intervention and explain the results. In our setting there is a Community Wellbeing Service and the nurses are trained to provide lifestyle

		advice who have been now trained to perform the fibroscan. Ongoing training and appraisals Clerical staff Facility – clinic room with a bed to be able to perform the scan and the consumables required for the room Storage of the fibroscan when not in use Insurance for the fibroscan to be transported between sites Purchase and service of the fibroscan
	b) do you transport the FibroScan around multiple GPs/PCNs? Or do you have a central location (GP/diagnostic hub) where FibroScan stays at the same location?	**Expert #1**: Can do either and it very much depends on the PCNs. The options are to use a flexible space in a general practice (this just uses GP rooms free on a session basis and works) which can rotate round the PCN. We have used rooms in multiple practices within a PCN but others have very good more central facilities which are easy for patient access and also woks with a relatively fixed location. The NHS England initiative via the hep C ODNs uses mobile facilities, essentially fibroscan equipped vans. This works very well and has the advantage that you can use any convent space (eg Sainsbury's car park) but there is cost, most services lease the vehicles rather than buy it and you do need to have a driver and insurance but it can stil be very cost effective. NHS England HCV programme will be able to tell you the costs as they dealt with funding bids from the ODNs.
		Expert #2: N/A
		Expert #3:I do not deliver fibroscans outside the hospital setting
		Expert #4: In my previous NHS role providing into the community, this was primarily to drug and alcohol in support on the HCV ODN program, we provided to 7 locations on service level agreements. All other referrals came through the specialist referral pathway to hepatology. NO direct access is available to primary care. In my current role as a CQC regulated provider we travel to any location or can be based in the hospital, a diagnostic hub/GP, providing the number required, in the location required at short notice. This is where the patients engage best, maximising attendance. Where there are barriers, non-attendance occurs and where these barriers are multiple this increase. The following is unpublished data from March 2022, may show some current context to the importance of access in non-secondary care locations and also the needs of fibroscan units post pandemic backlog issues. We were commissioned by a large NHS Trust with their own fibroscan service who had no ability to

		undertake their fibroscan's as a result of the increase in sick liver patients presenting and staff needed to support this. The waiting list for some was 1 year. We completed 143 scans in 5 half days brining the service up to date 100% of all 143 patients who attended (89%) their appointments were successfully scanned. The indications for the scan were spread throughout liver disease although only 5% were for alcohol concerns. This was surprising given the increased level of consumption that has been seen during the pandemic. The most common indication was for Non-alcoholic fatty liver disease (NAFLD) or Non-alcoholic steatohepatitis (NASH) which accounted for 50% (71) of the patients. In the 143 patients the level of significant fibrosis indicated by Fibroscan using the stiffness cut off of 8 KPa was 31% (45) which is alarming and indicates all of these patients would be retained by or referred to hepatology. Of more concern was the level of advanced fibrosis F3 (>9.5 KPa) and cirrhosis F4 (>13.5 KPa) which accounted for 23% of the patients scanned, 10% and 13% respectively. Of those patients with F4 on FibroScan 63% were referred for NAFLD/NASH. In the NAFLD/NASH group 56% were male, 31% of the patients required the XL probe to be used to obtain the FibroScan. The level of advanced fibrosis F2 (> 8.5 KPa) and above was 37% with 17% having stiffness compatible with cirrhosis (F4). A cut off of 8.0 KPa is often used to define those who require specialist liver follow up and has now been recommended in many recent international guidelines EASL (2021), AGA (2021), APSAL (2021).
		Expert #5: Yes the nurses transports the machine around practices from the main hospital where the machine is stored primarily
		Expert #6: I suspect this will vary by PCN depending on the geography and availability of a central site. It would be most efficient to have a central site but this would not work with wide geographical spread or registered patients
		Expert #7: Central hub and move fibroscans around – used to be a taxi but we now have had a bus delivered ….
		Expert #8: The fibroscan is transported between sites but is stored at a central location where the PCNs who perform the scan are based.

Appendix B2: Additional Questions to Three Clinical Experts (sent 11/08/2022 and 17/08/2022)

Questions sent to Clinical Expert 5 (sent 11/08/2022)

	Question	Responses
1	The pathway refers to 'ultrasound' being undertaken by the GP, and FibroScan being performed by a Hepatology Nurse later in the pathway. Please can you advise if the ultrasound is performed using the FibroScan device, or is there a separate ultrasound device? Who performs the ultrasound?	The ultrasound cannot be done on the fibroscan machine. It is booked in hospital and done by radiologists/radiographers.
2	You mention that the nurses transport the FibroScan device around practices from the main hospital which is its primary location; please can you clarify: a) Has the FibroScan device been purchased by PCN or secondary care services? Is it also used by the hospital where it is kept (shared resource)? b) Are the staff conducting the scans at the GP practices primary or secondary care staff?	a) Purchased by the hospital and utilised in peripheral clinics but not in primary care. (Scottish health system is different!!) b) Specialist nurses from our department
3	As a result of the new pathway, has there been an overall reduction or increase in FibroScans being conducted using secondary care services? If so, please can you estimate the proportion change?	I don't know the exact answer to that but the use of Fib-4 as screening tool has reduced patients coming to hospital and nurse led clinic has led to decease in consultant appointments. We are evaluating this as we speak.

Questions sent to Clinical Expert 7 (sent 11/08/2022)

	Question	Responses
1	You mention that the FibroScan device is transported around practices from a central location; please can you clarify: a) Has the FibroScan device been purchased by PCN or secondary care services? Is it also used by a hospital if this is the central base (shared resource)? b) Are the staff conducting the scans at the GP practices primary or secondary care staff?	a) Secondary care have purchased devices. Stored centrally (at hospital) and then used for primary and secondary pathways separately. Contract between primary and secondary care to provide "liver disease detection" in a community setting. b) Secondary care

2	As a result of the new pathway, has there been an overall reduction or increase in Fibroscans being conducted using secondary care services? If so, please can you estimate the proportion change?	I don't have data on this. Almost impossible to dissect : liver disease rising , COVID has decimated services, etc

Questions sent to Clinical Expert 8 (sent 17/08/2022 [questions 1 and 2] and 08/09/2022 [question 3])

	Question	Responses
1	You mention that the FibroScan device is transported around practices from a central location; please can you clarify: a) Has the FibroScan device been purchased by PCN or secondary care services? Is it also used by a hospital if this is the central base (shared resource)? b) Are the staff conducting the scans at the GP practices primary or secondary care staff? Who trains the staff?	a) Fibroscan is on loan to PCN with costs negotiated between ECHOsens and the CCG. In secondary care we have our own fibroscan and do not use the PCN machine b) For our pathway they are the Primary care staff. ECHOsens initially to train the operator and University Hospital Southampton Hepatology department and lead consultant provides on going updates and training, feedback on activity and support for any queries raised.
2	As a result of the new pathway, has there been an overall reduction or increase in Fibroscans being conducted using secondary care services? If so, please can you estimate the proportion change?	The workload increases continuously. In secondary care we only scan patients referred to us for fibroscan internally or those who need surveillance for progressive liver fibrosis eg Haemochromatosis patients or HBV patients. We scan patient for Dermatology, Rheumatology and endocrinology. In primary care patients with fatty liver due to alcohol of metabolic conditions are scanned and only 30% are now referred to hepatology for having advanced liver fibrosis. 70% are discharged back to the GP and therefore this workload has been redirected from hepatology. Prior this service all patients were referred to hepatology for fibroscan, if they did not have advanced liver fibrosis they would be discharged back. Now they are referred to the community service and only 30% are now forwarded to hepatology department because they have advanced fibrosis. The remaining 70% do not need hepatology input and GPs are encouraged to follow the pathway to consider a repeat fibrosis assessment in 3 years.
3	The Company shared some activity data from Southampton (50 GPs across 5-6 PCNs, referring on to 2 GPs where the measurements were conducted). They stated 533 scans over 14 months	I am not involved with the Mid-Hampshire pathway. I have worked on the Southampton CCG pathway. We use ELF of >9.5 as a threshold to refer for a community fibroscan. People with no treatable cause for liver disease (negative liver screen) and

	between January 2020 and March 2021 on a commissioned pathway. I'm assuming this data came from your work in Southampton. However the Company has not shared what the eligibility criteria are for this "commissioned pathway. You state in your responses below that the primary care pathway includes fatty liver due to alcohol or metabolic conditions. However can I check whether the eligibility criteria are similar to that of Mid Hampshire: • FIB-4 was calculated from blood test results for patients with diabetes, BMI greater than 35 kg per m2, alcohol intake greater than 50 units per week for men, greater than 35 units per week for women. Patients with FIB-4 between 1.3 and 3.24 were referred for FibroScan.	no biliary disease liver function test pattern are referred down the pathway to assess for fibrosis. We do not calculate Fib4.

Appendix C: Notes from Company Engagement Call (08/08/2022)

GID-MT562 Fibroscan for assessing liver fibrosis and cirrhosis in primary care
NICE EAG Meeting with Company
Monday 08 August 2022 @ 15:00

In Attendance:
Newcastle EAG: Andrew Sims (AJS), Kim Keltie (KK), Emma Belilios (EB), Ros Parker (RP), Cristina Fernandez-Garcia (CFG),
NICE: Thomas Walker (TW), Jacob Grant (JG), Toni Gasse (TG), Suvi Harmala (SH),
Echosens: Rachel Evans (RE), Quentin L'Huillier (QL), Mark Tyrrell (MT), Camille Manceau (CM)

1) **Background**

- At DAC2 meeting (March 2022), Committee felt that the Company could have done more in their additional analysis to show that the technology could be cost saving/cost neutral and to explore some of the uncertainties. The Company were given the opportunity to submit an addendum to their submission (a fourth model) to address this feedback, focusing on:
  i. Long-term impacts of testing in primary or community care on costs
  ii. Uncertainty about likely total cost of doing the test in secondary or specialist care (micro-costing in secondary care)
  iii. Extent of expected use of FibroScan in primary or community care

  The new model was received by the EAG 15 July 2022.

  Purpose of this meeting is to gain clarification on specific areas and to address additional queries from the EAG.

  JG clarified for the Company's benefit that the change from External Assessment Centre (EAC) to External Assessment Group (EAG) is a change in terminology only so that NICE can align across programmes; but stated that the group involved in the assessment of FibroScan is unchanged.

2) **Questions for the Company**
   i) **Thank you for your clarification regarding your approach to calculating an average cost per scan, per setting. Can you please specify whether the assumption is that FibroScan services would**

move from secondary care to primary care (i.e. direct replacement of services)? If so, the average number of uses per setting do not reflect this assumption.

MT clarified that the proposal is to expand the utilisation of FibroScan into primary care to increase the early diagnosis of liver disease. There is no suggestion that existing services should be removed from secondary care - FibroScan services in primary care will support more appropriate referrals. Patients scanned in primary care and referred into secondary care would not be re-scanned in secondary care (and some will also have their follow up scans in primary care), therefore some patients will move from secondary to primary care, but not all.

MT - the *primary care* usage figures in the model are based on real world evidence from early adopters.

ii) **The data provided by the Company stated 50 GP practices from 5-6 PCNs, however that the large majority of patients were referred from 5 GPs, with scans being conducted by 2 GPs. To assist with the objective relating to the extent of expected use of FibroScan in primary and community care, why are the remaining 45 GPs not referring? Are they newly added to the pathway? Are they continuing to refer to secondary care (barrier to implementation)? Could this mean that the expected number of scans per machine may result to be lower than the assumed 500 in primary care?**

The Company clarified that the Southampton pilot pathway was established in 2018 and commissioned in 2020 for five years.. At the time of the pilot there were 4-6 PCNs (27 GPs) in the pathway. Since then, with the introduction of Integrated Care Systems, some boundaries have changed. 5-6 GPs refer the bulk of the volume, number per PCN depends on factors such as size of PCN and GP awareness. As the pathway begins to mature, will start to see re-scans occurring. Then volume is likely to increase further.

Different care providers are all using different electronic patient record (EPR) systems and tracking their patients in different ways. CFG queried whether longer term, that would be a significant barrier? Will providers therefore need to update the way they work, potentially incurring additional costs? MT thought GP education was the key, which Echosens can help with, but local providers will need to take responsibility for too. MT thought that this would not substantially add to costs.

iii) **Thank you for your clarification regarding your approach to micro-costing. Can you please explain why other cost-contributors such as additional infrastructure, local implementation and transport costs, additional site training etc. have not been considered when costing a new pathway (i.e. delivering FibroScan in primary care setting)? These are likely to represent a cost to the NHS. As the perspective set by NICE is that of the NHS and PSS, the EAG believes that these costs would need to be included in order to fully consider the costs implications of moving FibroScan outside of secondary care.**

The model did not consider additional costs as there is a lot of variability in how FibroScan can be delivered in primary care, either from a fixed location or as a mobile unit. It is a small device, and doesn't need a dedicated room. It is also very portable, so there are many options for service delivery.

CFG suggested it would have been useful for the Company to pick up two or three ways of delivering the service and run sensitivity analysis around those scenarios. Even though the device is easy to transport, there will be costs associated, which will vary by locality. For example, the service might need a booking system (incurring cost of software, staff time and so on).

The training costs included in the model are the Echosens training costs only. The submission suggests that a user should perform 50 supervised scans to achieve competency - given the supervision costs will be incurred by the NHS, they should have been included. Higher staff turnover in primary care may increase these costs substantially.

MT clarified that the estimate of 50 scans is based on anecdotal evidence in secondary care. Echosens deliver thorough training to users, including a practical session and assess competence by supervising 3 to 4 scans on a range of patients. FibroScan is very easy to use - don't need to be a radiographer. The Company has developed a competency framework since the assessment started (not implemented yet). The Company are keen to encourage (although not enforce) that fewer operators are better, so the device is used more frequently. The number of supervised scans required in practice before competence is assumed is down to local guidance. Echosens claim competence after their training is completed.

CFG asked if there had been any consultation with FibroScan users to inform micro-costs? MT clarified that the Company had not consulted with users regarding the actual costs of providing the service.

iv) **Thank you for your clarification and corrections relating to the data from Southampton. As requested in Question 1c (which was not previously addressed) can you provided a specific reference for this information so that the EAG can verify the data?**

MT clarified that the most recent data is not published anywhere. Pathway piloting data is published (and has been shared with the EAG). The Company receives regular updates from users on scan numbers and can potentially get a contact if this would be helpful for verification purposes. KK asked if the data should be highlighted for redaction if they are not currently in the public domain. MT agreed that they probably should be. TW advised that the Company will therefore need to resubmit their submission with the confidential information marked up for redaction (no content highlighted as confidential currently). QL will check the submission and re-submit with confidential information marked up.

ACTION: QL to re-submit Company submission with confidential information highlighted for redaction.

NICE National Institute for Health and Care Excellence

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

External assessment group's report on additional Company economic modelling and analysis - Factual check by Company and EAG response

FibroScan for assessing liver fibrosis and cirrhosis in primary or community care

Issue 1

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAG response
Global understanding of the economic model	The company acknowledges the approach from EAG likely to be more accurate however not achievable to model in the given timeframe, especially as the scope has been extended progressively throughout the assessment. The company prefers to stick with the initial NICE guidance scope and favours the model to be assessed within that scope, unless NICE would like to redefine a new scope.	The EAG report shows several deviations from initial scope from NICE as listed in the decision problem and misunderstanding to the model. <u>Microcosting approach:</u> The microcosting approach in the economic model calculates the cost per scan based on the total number of scans performed per machine, rather than per PCN (PCNs may have multiple machines or	Not a factual inaccuracy, no changes made. <u>Micro-costing approach:</u> The EAG has summarised the data *per year per PCN* from the evidence available to demonstrate the feasibility of patient throughput proposed by the Company in response to the first objective set by NICE DAC following the second committee meeting. The EAG have used the Company cost per scan values (based on number of scans per year per device) within the economic analyses.

		conversely, a single machine may be used across different PCNs). The main point of interest for the economic evaluation of FibroScan is the cost of each scan. Therefore, the microcosting approach relied on the average number of scans performed by a single machine in a year regardless of how many GP practices the machine was shared across or if other machines are operated in parallel. The submitted data shows that the value used for the average number of scans per machine (500) is a conservative estimate The Company thinks there is a clear misunderstanding Timeframe: Initial EAC report stated that a 5-year timeframe would be more complex than necessary to assess the economic case. The Company addressed the suggested further analyses to include the 5-year timeframe, which was a deviation from the initial scope. EAG new report suggests now an even longer timeframe would have been feasible, also considering liver transplant, HCC and non-liver disease. The Company thinks it is a deviation from the scope.	Timeframe: Within the original Assessment Report the EAG reported that due to the Scope (same device, same patient population) and lack of direct evidence available that a short-time horizon was appropriate. The NICE Committee requested long-term modelling to better understand the cost implications of diagnosing liver disease earlier as per the third objective. The EAG would note that the additional modelling provided by the Company does not meet the request of the Committee, and that uncertainty remains.

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAG response
		If this is part of the scope, we are willing to address these different items, as long the scope is set and not likely to evolve after each EAG report. The Company sees a disconnect between experts' interviews when related to number of scans per year per system, foreseen used within a network of PCNs and the assumptions taken by the EAG to model To conclude, the Company sees a misunderstanding of the EAG of the initial NICE scope.	

Issue 2

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAG response
Uncertainty of long-term impacts of testing in primary or community care on costs and modelling all-cause mortality. Starting page 27	The Company acknowledges the uncertainty impacts of long-term costs despite non-being part of the initial costs. It is likely the Company would have anticipated more and build the model potentially differently if it has been part of	The Initial EAC report from October 16, 2021 statement was: • *"Crossan et al. (2019) modelled pathways over a five-year time horizon, with repeated testing in primary*	Not a factual inaccuracy, no changes made. Note the EAG is unchanged (same group conducted initial assessment report and subsequent critique, just a

	the scope since the beginning in order to capture in full the expected outcomes. The original base case was only 1 year. The company selected 1 year following initial conversations with the NICE technical team to keep cost modeling simple. The cost modelling would then also better lend itself to the NHS Funding Mandate Criteria at the which stipulated technologies would have to demonstrate savings within 12 months The extension to 5 years and addition of progression was specifically requested by the previous EAG.	*care for patients with fibrosis levels less than F3, and repeated follow-up in tertiary care for those with F3 fibrosis or higher. The EAC considered this pathway and time horizon more complex than necessary to assess the economic case for adopting FibroScan outside of secondary or specialist care.* • *Srivastava et al. (2019) modelled a diagnostic pathway over a one-year time horizon, followed by a five-year timeframe to assess longer term disease progression, complications, and outcomes. The EAC also considered this more complex than necessary for the decision problem (where the same FibroScan device would be used in the same at-risk population, but with measurement taken in different setting by different staff).”*	name change from EAC to EAG to align across NICE programmes). Longer term modelling was request by the NICE Diagnostic Advisory Committee (not the EAG) to better understand the long-term cost implications of diagnosing liver disease in primary or community care as the third objective. However, due to the approach taken by the Company to long-term modelling, the EAG would note that uncertainty remains.

		Other topics of interest: • Attendance rates (both in an outside secondary care) were included in the sensitivity analyses • The model makes the same assumption in both settings (liver steatosis and liver disease progress), therefore even if there are a few patients who may progress, it does not bias the results • Full expected outcomes and the differences in resource use, with substantially increasing uncertainty. The use of the shorter timeframe is therefore conservative, as there may be additional benefits in the long-term, i.e. the current results could be even better • EAG notes that Wright et al. (2006) did not explicitly include FibroScan as one for the investigations conducted during follow-up → It did not have to. The issue was whether follow-up investigations were included (which were).	

		None of the guidelines state that the patients have to be reassessed with the same technique / same type of scan. The company believes that the aforementioned examples show that there has been a clear deviation from the original scope. Nonetheless the company has endeavoured to address these additional parameters as suggested by the NICE Technical on 4th April 2022. The use of the shorter timeframe is therefore conservative, as there may be additional benefits in the long-term, i.e. the current results could be even better.	

Issue 3

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAG response
EAG Report states the Company did not consult with users of FibroScan in primary care to inform micro-costs - Page 16	The company consulted stake holders in both primary and secondary care. The company provided NICE with cost examples from Southampton, and Mid Hampshire. The company also consulted with a variety of service managers in secondary care to capture codes used to cost fibro scan activity. The	We apologise for the misguidance on August 8th. We have spoken with clinical experts, commissioners, and directors within primary care.	Not a factual inaccuracy at the time of writing report (EAG explicitly asked the Company if they consulted with service users). However, in light of this new information the EAG has updated the report (new text in red):

	company cannot be held accountable for the wide deviation and variation in how services are managed, commissioned, coded, or reimbursed.		"The Company did not consult with users of FibroScan in primary care to inform micro-costs (Appendix C) [At fact check the Company clarified that they consulted with stake holders in both primary (including clinical experts, commissioners and directors within primary care) and secondary care]."

Issue 4

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAG response
Excessive additional costings identified by clinical experts on - Page 26.	The company acknowledges the approach from EAG likely to be more accurate however not achievable to model in the given timeframe, especially as the scope has been extended progressively throughout the assessment.	Exhaustive list of costs listed on page 26 of the EAG report. Most of these costs was not part of the previous EAC report and not part as well of our previous rounds of discussions. They were not highlighted as missing in the previous iterations of the model. Furthermore, from speaking with current providers of community fibro scan services we feel it is reasonable that many of the "additional costs" could be mitigated as follows:	Not a factual inaccuracy, no changes made. The HRG approach was debated at length at Committee and within previous EAG critiques, therefore a micro-costing approach (to capture all associated costs as highlighted in this Company response) was requested by Committee to better understand cost implications of delivering FibroScan in both arms. The Clinical Experts consulted by the EAG highlighted the list of additional cost considerations if implementing FibroScan in a primary care setting on page 26. The Company submission did not consider these costs in their micro-costing approach.

		- Room costs = by effectively using existing resources already in place and efficient facilities management GP surgeries with availability or free clinic spaces/rooms on certain days: Clerical staff time = existing reception and admin staff already running and book patents into similar community-based services (ophthalmology, dermatology, etc.) could be used to administer FibroScan clinics. Storage of fibro scan when not ii use? = Its small and should not create a burden at all. No additional costs to model here. Mobile Service & Transportation costs? = The device for primary care is a 430 MINI, this is light weight and can be easily wheeled, carried, or placed into a car by a community nurse as she moves from one to location to the next - this is precisely what currently happens in the 22 Hep C ODN's. Hygiene and waste disposal standards and equipment = This cost is negligible; use of fibro scan	

		will not create a significant increase in cleaning costs. Time to provide feedback to patients = Not applied for parity; the secondary care costings/HRG tarrifs used were for the time to perform scan only. Some hospital nurses will scan intervene/discuss results in more detail than others. Some scan and a consultant will interpret and feedback. This significantly increases cost in secondary care. insurance for the FibroScan device to be transported between sites = Yes a potential cost, however, most Community and Acute Trusts have insurance policies that will cover the use and movement of medical equipment. technology and software upgrade costs including consumables = covered in part by pay per exam option, or a service contract. The Company thinks it is not part of the initial scope to consider the implementation of the service.	

Issue 5

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAG response
The Company recommends that supervision from a competent user is needed for the first 50 uses (on average), however the additional staff costs in this supervisory role was not included within the micro-costing. – page 22	Echosens claim competence after their training is completed. The first 50 scans are based on anecdotal evidence in secondary care from local initiatives. Otherwise Echosens would require all trainees to perform 50 scans before issuing a training certificate. It is the customers responsibility to deem, assess "competence in practise" as per local guidelines. Furthermore, as discussed at the meeting 8th August 2022 Echosens have prepared a competency assessment framework that may be used by both liver and non-liver specialists performing fibro scan.	Upon initial NICE feedback, the Company took action and has developed a competency framework since the assessment started (not implemented yet). The Company are keen to encourage (although not enforce) that fewer operators are better, so the device is used more frequently. The number of supervised scans required in practice before competence is assumed is down to local guidance.	Not a factual inaccuracy, no changes made. The EAG highlights that the cost of the supervisor, identified from this anecdotal evidence, has not been included in the micro-costing. The EAG has acknowledged that the Company has developed a Competency Framework on page 24 of the report.

Issue 6

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAG response
Volume of scans depending on the settings - Page 38 EAG considers that the assumption of a single FibroScan device being used for between	The company acknowledges the approach from EAG likely to be more accurate however not achievable to model in the given timeframe, especially as the scope has been extended progressively throughout the assessment.	The Company sees a disconnect in EAG modelling. The volume of scans used in EAG model (305 patients) per arms is disconnected from real world evidence	Please see response to Comment 1.

500 and 1,000 patients per year per PCN, or in 2,500 to 5,000 patients per year across 5 PCNs may not be achievable across the NHS. - Page 8		(Southampton CCG, Harman 2015 study), feedback from expert interviews (6 out of 8 declare the volume of scans in primary care are achievable and 5 out of 8 declare the network of 5 PCN being reasonable) and attendance rates from literature. Patients can and should be rescanned if needed. We need number of scans per machine to calculate cost per scan. The Company thinks this is factual inaccuracy.	

Issue 7

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAG response
The Company did not consider other technologies available (ELF test or others) – page 15	The Company did not consider other technologies available (ELF test or others) because it is not part of the initial scope from the decision problem.	NICE scope is to scan those who otherwise would have received scan in secondary care and not to make an extensive review of the available technologies in the patient flow. The referral technique as listed in the initial scope is the FibroScan, no other technologies, to be compared across settings.	Not a factual inaccuracy, no change to report. The Company stated “Other technologies available (ELF test or others)” as a potential reason for difference in national estimate and real-world figures reported in their updated submission. However, the eligibility criteria for using FibroScan in community care in Southampton does include an ELF greater than 9.5. This sentence from the EAG is acknowledging that the

		The Company thinks this is outside of the initial scope	use of ELF in defining eligibility was not incorporated in the economic model, which remains true.

Issue 8

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAG response
The EAG would note that there remains variation in clinical coding to capture FibroScan conducted in a secondary care outpatient setting. The EAG would advise that a micro-costing approach in assessing the costs of all diagnostic pathways being considered, accounting for device, staff, and infrastructure costs would be more appropriate when comparing costs in secondary care with those in a non-secondary care setting. – page 21.	The Company followed the recommendation to not pursue a micro-costing approach for the secondary care arm as it was not a concerned in previous iterations of the model.	For the secondary care arm, the bundled HRG costing was considered plausible by the EAC report from October 2021, as well as the in the NICE committee slide deck presented on March 8, 2022. The Company thinks this is outside of the initial scope	Not a factual inaccuracy, no change to the report. Uncertainties relating to the variation and robustness of HRG approach was raised by the Company and prior EAG critiques. Consideration of micro-costing approach was requested by the NICE Committee in response to these concerns. The EAG maintain that using the same approach in both arms is more robust (for example, HRGs do not exist in primary care).

Issue 9

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAG response
The EAG notes that additional GP face-to-face or telephone appointments to discuss results prior to a referral to hepatology were not considered within the updated Company model.	The interpretation and the results discussions are part of the examination as the FibroScan is a point of care medical device with immediate results. Patients do not have additional appointment to discuss the results of the exam.	The FibroScan is a point of care delivery system with immediate results. In the first model submission, for the secondary arm, we included the physician consultation on top of the HRG. It was recommended by NICE and EAC to remove the physician consultation as it was double counting, the results discussion being part of the HRG For parity and consistency, we should include the cost of hep or GI consultant time and or model the 1st multidisciplinary outpatient appointment for secondary care then. The micro-costing approach for secondary care was never discussed prior to this EAG report. The Company thinks this is a factual inaccuracy and a deviation from the initial scope and from previous EAC report	Not a factual inaccuracy, no change to the report. The EAG note that Clinical Experts (which included 3 users of FibroScan in primary/community care) stated that additional costs for *"time to provide feedback to patients, including written advice, which may require a separate appointment (for example with a GP if delivered in primary care pathway dependent upon results"* [see page 26 of EAG report]. The NICE Committee requested consideration of micro-costing in their second objective [page 7 of the EAG report], due to uncertainties relating to the variation and robustness of HRG costs raised by the Company and Committee.

Issue 10

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAG response
Local guidance to not conduct FibroScan on patients with hazardous alcohol consumption, a high BMI or with Type 2 diabetes etc.	Local guidance not following national guidance is not part of the problem. This is the everyday clinical practice. Local practice, or rather clearly defined local guidelines is not part of the decision tree problem. This is unfortunately a reality that we cannot model.	NICE scope is to scan those who otherwise would have received scan in secondary care. The Company thinks this is outside of the initial scope.	Not a factual inaccuracy, no change to the report. These words were extracted from the Company submission directly, and queried by the EAG (see Appendix A, Question 3 of the EAG report). The report [page 15] already states: *"The EAG notes that the Company responded (05/08/2022; Appendix A - Question 3) stating that this was due to local variations in practice, and that some PCNs/community centres may not scan with FibroScan due to lack of local liver guidance."* The EAG considered the plausibility of the reasons provided by the Company for discrepancies between national estimates and real-world figures.

Issue 11

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAG response
Number of scans per PCN – page 7 and page 8	The use per PCN is irrelevant - we are estimating scan per machine. We do not state that each PCN should get a machine, but that we foresee a number of PCN working as a cluster of PCNs within a given healthcare system or ICS can comfortably achieve 500 scans or more	The microcosting approach in the economic model calculates the cost per scan based on the total number of scans performed per machine, rather than per PCN (PCNs may have multiple machines or conversely, a single machine may be used across different PCNs). The main point of interest for the economic evaluation of FibroScan is the cost of each scan. Therefore, the microcosting approach relied on the average number of scans performed by a single machine in a year regardless of how many GP practices the machine was shared across or if other machines are operated in parallel. The submitted data shows that the value used for the average number of scans per machine (500) is a conservative estimate. Even if All eight Clinical Experts stated that the assumption of each PCN being able to conduct 500 scans per year was clinically plausible (Appendix B, Question 3)	Not a factual inaccuracy, no change to the report. Please see response to Comment 1. The EAG has described the reasoning behind calculating use per year per PCN within the report [see page 8]: *"To demonstrate the extent of expected use (in line with the first uncertainty raised by the Committee), the EAG calculated the annual attendance per PCN for FibroScan using the same three studies tabulated by the Company.*

		We believe that this has been consistently misunderstood throughout the assessment and critique of our proposal.	

Issue 12

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAG response
The time taken to develop, build and resource a FibroScan service should be considered, particularly in settings with no experience or knowledge base. Expert point of view page 17	Time taken to develop, build and resource a FibroScan is a local consideration in support with ICS clinical director, commissioner, and other NHS team.	The Company thinks this is a deviation of the initial scope. NICE scope is to scan those who otherwise would have received scan in secondary care. The scope of the guidance is not to identify how to implement the service in a primary care setting Agree, this is up to local commissioners and service leads. The Company thinks this is a deviation from the initial scope.	Not a factual inaccuracy. This was one cost consideration of the use of FibroScan within primary or community care that was highlighted by one of the Clinical Experts, we have clarified this in the report [see page 17] (new text in red below): *"Furthermore one Expert stated that the time taken to develop, build and resource a FibroScan service should be considered, particularly in settings with no experience or knowledge base."*

Issue 13

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAG response
Tanajewski et al. (2017) included annual costs of no or mild liver disease, significant liver disease, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, transplantation cost to estimate lifetime costs of patients identified at risk of NAFLD – page 33		Our model utilises estimates of treatment costs after the patient has been diagnosed. However, the Tanajewski estimates used by the EAG also include the costs for the diagnosis of patients too (this is why the first-year costs for no/mild disease are the same as significant liver disease in Tanajewski). This double counts costs. If we were to include just the year 2-5 estimates in our model (in order not to double count diagnostic costs), then the results still show cost saving for use in primary care. So, the costing scenarios would turn green on page 40.	Thank you for raising this. We have included costs from years 2 to 5 as indicated by the Company and updated the table of results to reflect this change (including inflation to 2021 prices). Note that the use of FibroScan in primary/community care is cost-neutral when compared to secondary care when using micro-costing approach, and cost-saving when using HRG approach.

Issue 14

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAG response
The Company have not proposed how “at risk” patients will be identified and eligibility criteria for FibroScan are currently lacking Furthermore, their use across different disease areas in secondary care may yield additional health benefits (outside liver disease), which the current model is not able to capture. However, the EAG notes that the eligibility for FibroScan differed amongst the three real-world examples highlighted by the Company	NICE scope is to scan those who otherwise would have received scan in secondary care. Patient populations in the model are in line with the initial scope and decision problem.	Use of Fibroscan in specific populations, for example for people with: • Non-alcoholic fatty liver disease • Suspected non-alcoholic fatty liver disease (for example, people with metabolic syndrome or type-2 diabetes) • Alcohol-related liver disease • Suspected alcohol-related liver disease (for example, based on hazardous alcohol use) • Hepatitis EAC report from October 16, 2021, confirmed the population and its identification. *“The Company defined the population, broadly in line with the scope, as “people having FibroScan to assess for liver fibrosis or cirrhosis (as per current NHS practice).”*	Not a factual inaccuracy, no change to the report. The Company provided a reason for the discrepancy between their national estimate and real-world figures were “Not every patient will be identified as being at risk and requiring a scan”. The EAG acknowledges that as per the Final Scope that the referral criteria to FibroScan in primary care should be the same as referral criteria in secondary care. However, the EAG is highlighting that there is a lack of defined referral criteria across the NHS. This may lead to variation in patient throughput, and subsequently cost per scan.

		Regarding real-world examples, per the research by the British Liver Trust, many former CCGs do not have commissioned pathways for early liver disease detection OSC. Just like some ICS systems have access to ELF in PC and others do not, there will be variation - Echosens cannot control this. The examples we included are early adopters/pioneers The Company believes this is a deviation from the initial scope. We would support drawing up clinical guidelines for the use of Fibroscan. However, this does not impact the assessment at all, as the assessment's starting point is when. have already been identified and referred into the diagnostic pathway	

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Comment number	Name and organisation	Section number	Comment	NICE response
1	Royal College of General Practitioners		Fibroscan technology appears to be relatively newly used technology in specialist care. We assume NICE have reviewed the value of the intervention in terms of case finding in people who are at risk or have abnormal liver function tests and that an earlier diagnosis will result in improved outcomes like any other screening programme. This would need to be explicit and clear.	Thank you for the comment which has been considered. Use of transient elastography (FibroScan) is recommended in NICE and other UK clinical guidelines and its use in secondary and specialist care was considered current NHS practice in this assessment. Sections 2.3 to 2.5 of the diagnostics guidance document provide an overview of the relevant guidelines. This guidance has considered the use of FibroScan in a different location, rather than to assess a wider, or different, population than recommended in existing guidance. The population in this assessment (as specified by the scope for the assessment) was “People having a FibroScan to assess for liver fibrosis or cirrhosis (as per current NHS practice)” [underlining added]. The committee’s adoption recommendation in section 1.1 of the diagnostics guidance document specifies that the use of FibroScan should be in accordance with national guidelines. The full guidance document also captured committee concern that using FibroScan in primary or community care could lead to its use

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Comment number	Name and organisation	Section number	Comment	NICE response
				in a wider population than assessed in this guidance (see section 3.8 of the diagnostics consultation document). Further text has now been added to section 1 of the guidance document to make this clearer.
2	Royal College of General Practitioners		We are not aware that Fibroscan technology is currently robustly undertaken in a specialist environment for those at risk nor in annual review programmes – hence seems unusual to want to recommend use in primary care when specialist colleagues are not providing this.	Thank you for the comment which has been considered. Use of transient elastography (FibroScan) is recommended in several NICE guidelines (such as Cirrhosis assessment and management and Hepatitis B [chronic] diagnosis and management) and is included in a British Society of Gastroenterology algorithm for diagnosis of NAFLD and non-invasive assessment of liver fibrosis. Sections 2.3 to 2.5 of the diagnostics guidance document provide an overview of relevant guidelines. Clinical experts (from secondary and specialist care) who attended committee meetings for this topic also described their current use of FibroScan. A national UK survey of community liver disease management completed by 159 clinical commissioning groups carried out on behalf of the British Liver Trust cited by the external assessment group in their

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				report (Jarvis et al. 2021) suggested that 25% of CCGs use transient elastography (FibroScan). Jarvis, H. et al. (2021) Engagement with community liver disease management across the UK: a cross-sectional survey. BJGP Open 2021; 5 (5)
3	Royal College of General Practitioners		At the current time, this is not a procedure that is routinely ordered in primary care (nor is it available) and we are not aware that it is undertaken routinely across secondary care settings for all patients or in annual reviews.	Thank you for the comment which has been considered. The purpose of this assessment was to see if use of FibroScan in primary or community care could be recommended (please see the scope for the assessment for further detail). Please see the response to the above comment on current use of FibroScan in secondary or specialist care.
4	Royal College of General Practitioners		We note (page 13) that pre-pandemic, 3,500 tests were done in England (though this value is an underestimate and some tests would be repeat tests over this term). It would appear this value would fit in with a need in specialist care for testing of (assuming England population 56 million) around 1:16,000 which would not be feasible to maintain expertise in an average area – as the recommended 500 tests per	Thank you for your comment which has been considered. As noted in the comment and diagnostics consultation document (section 3.11), the estimate of about 3,500 is likely to be an underestimate of the number of FibroScan assessments done. Text in the section 3.11 of the diagnostics guidance document has been

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			year would need a population of 8 million (or considerably larger than an average region – hence local testing in primary care would not be feasible).	amended to further clarify that scans may be done during outpatient appointments and recorded using different HRG codes, potentially at higher cost. The committee's discussion on the expected use of FibroScan in primary or community care is described in sections 3.5 and 3.12 of the diagnostics guidance document. The committee considered that sufficient levels of use may not be achieved if the test was available in individual GP practice populations, but use in locations which cover larger populations, such as community diagnostic hubs or across a primary care network, would likely mean the users do enough tests to be sure it is being used correctly. The company provided real world data and national data sources to support their assertion that at least 500 scans per year was feasible. Of the 8 experts consulted by the external assessment group, 5 said sharing 1 device between 5 primary care networks was plausible in some scenarios and all thought a single network would be able to do 500 scans per year (see section 3.12 of the diagnostics consultation document). Clinical experts at the diagnostic advisory committee meeting supported this view.

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				The committee's adoption recommendation in section 1.1 of the diagnostics guidance document includes that training for healthcare professionals on doing the test should be provided and that the company should provide supporting materials to ensure that user competency after initial training is maintained. As noted in the comment, section 1.1 also includes that the use is recommended if each FibroScan device is expected to be used for at least 500 scans per year, with local decision-makers considered best placed to decide if this can be achieved in their area.

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5	Royal College of General Practitioners		The RCGP would support the early identification of disease where we are able to make an important difference to patient care – and would encourage appropriate testing and input, though are wary of workload implications and the evidence base behind the decision being considered.	Thank you for the comment which has been considered. The use of FibroScan in this assessment was based on testing being done in hubs and diagnostic centres, or as a service across a number of practices, rather than in individual GP practices (see section 3.12 in the diagnostics guidance document for further detail). Use is only recommended if each FibroScan device is expected to be used for at least 500 scans per year (see section 1.1), which experts indicated was unlikely to be achievable in single GP practices. Text has been added to the recommendations in the guidance (section 1.1) to highlight that this is an option. The guidance has identified potential patient benefits, particularly around increased access for patients, but the recommendations are not mandated.
6	Royal College of General Practitioners		There is a suggestion that the plan is to assess liver fibrosis and cirrhosis in primary and community care rather than a hospital setting. We did not see an estimate of the prevalence in a population (how many	Thank you for the comment which has been considered.

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			would be needed to be performed per year) – nor the workload implications of annual screening (and indeed its value and implications), we believe that there are workload implications and capacity issues for those undertaking the procedure and those that will be interpreting the result clinically (assuming the test is not going to a secondary care colleague).	See the response to the comment above, and additional text added to the guidance document, concerning workload implications for primary and community care. To help reduce uncertainty and burden interpreting a result for testing done outside secondary or specialist care, the recommendations for use (section 1.1) specify that a clear care pathway with advice for healthcare professionals on what to do based on a FibroScan result should be established locally in collaboration between primary or community care and secondary or specialist care providers. This is further discussed in section 3.9 of the diagnostics consultation document.
7	Royal College of General Practitioners		The workload in primary care is currently under intense pressure – hence additional resource would need to be identified to undertake this work, and if significant could worsen the current workforce crisis.	Thank you for the comment which has been considered. See the response to comment 5 above, and additional text added to the guidance document to highlight that this is an option, and is not mandated.

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Comment number	Name and organisation	Section number	Comment	NICE response
8	Siemens Healthineers	committee-discussion There may be benefits to local testing 3.2	Adoption of FibroScan in the primary and community care setting may be challenging in the context of current workforce shortages, whilst using the existing laboratory medicine and phlebotomy infrastructure may be preferable to deliver liver fibrosis risk assessment at scale, as well as simplifying access for patients in socially deprived areas which have an increased prevalence of liver disease. We agree with clinical experts and the committee that the prevalence of liver fibrosis, particularly associated with metabolic disorders, is such that it will risk overwhelming hepatology and gastro-enterology secondary services, and that more efficient diagnostic pathways are therefore required to optimise the referral from primary/community care to secondary care for patients at high risk of liver fibrosis. There is consensus among national and international clinical guidelines to recommend that patients who do not present with advanced fibrosis (i.e., patients with liver fibrosis stages F0 to F2) are managed in primary and community care, while patients with advanced fibrosis (stages F3 or F4) are referred for specialist	Thank you for the comment which has been considered. See the response to comment 5 above, and additional text added to the guidance document to highlight that this is an option and not mandated. This assessment evaluated using FibroScan outside of secondary or specialist care. Both the intervention and the population are described in the final scope. This assessment did not evaluate alternative tests such as blood tests or other ultrasound-based technologies. This diagnostics guidance will not replace any current recommendations for use of laboratory-based or ultrasound testing in existing NICE guidance.

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			consultation. A reduction in unnecessary referrals to secondary care is therefore a relevant metric considering the increasing burden of liver fibrosis for patients and on the NHS. It should however be considered by the committee that, although assessing a patient in primary care may be less costly to the NHS than referring them to a specialist, and that displacing some of the FibroScan testing activity in the former setting may therefore be associated with theoretical cost savings, it is currently unclear whether there is sufficient capacity in primary and community care to adopt an additional imaging activity. This issue is exacerbated by the requirement for a minimum level of FibroScan testing activity, as well as the requirements for training, certification and ongoing quality management. While these requirements are relevant in light of considerations raised in the diagnostics consultation document, we recommend for the committee to recognise that the implementation of FibroScan testing in primary and community care, particularly in individual GP offices, may be significantly challenged by the current capacity and workforce shortages issues faced by the NHS. It should also be recognised by the committee that while FibroScan is only intended for use in the	

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			diagnosis of liver fibrosis, current ultrasound equipment can also deliver liver elastography whilst also being capable of use in a wide variety of ultrasound assessments relevant to community diagnostic centres.	

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9	Perspectum		It is a positive step forward that there has been a focus on enhancing care for patients with liver disease and moving towards non-invasive testing as opposed to liver biopsy. However, we believe that in principle, and for setting guideline precedents, in nascent medical AI-enable device fields, there needs to be uniformity and greater relevance between and across all assessment programmes and guidelines that are currently underway. GID-MT562 has illustrated "that a clear pathway with advice for healthcare professionals should be established locally in collaboration between primary or community care and secondary or specialist care providers" however this has not been done for DAP59. There is an expectation that one secondary care pathway for diagnosing and monitoring NAFLD will be correct for every trust in England. For there to be better care for these patients, clinical and cost effectiveness modelling should be done encompassing and accounting for both primary and secondary care. The current modelling should reflect and incorporate standards for evaluation that will ultimately support the achievement of NHS's national health inequalities priorities and programmes that are	Thank you for the comment which has been considered. This assessment is comparing whether FibroScan can be done in a different location rather than whether it should be introduced to test a new population. This diagnostics guidance will not replace any current recommendations for use of other diagnostic testing in existing NICE guidance. The committee's adoption recommendation is in section 1.1 of the diagnostics guidance document specifies that the use of FibroScan should be in accordance with national guidelines. The committee's considerations of the need for FibroScan to be used in primary or community care as part of a clear pathway is discussed in section 3.9 of the diagnostics consultation document. This concerns making sure that healthcare professionals in primary or community care know what steps to take next based on the FibroScan result, rather than the pathway itself (such as further tests or interventions to offer) being unclear. Guidance on the use of transient elastography (such as FibroScan) and what to do based on results are available and are cited in the

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Comment number	Name and organisation	Section number	Comment	NICE response
			already using and/or prognosticating the utilisation of non-invasive tests are not available in all areas of England. Updating NG49 would be a great space for this to occur and it is our recommendation that the planned publication of GID-MT562 should be paused until this is confirmed.	diagnostics consultation document (see sections 2.3 to 2.5). Further text has been added to section 3.9 of the guidance to further clarify that the care pathways should be based on existing national guidelines. Modelling done for this assessment included the initial FibroScan test (done in or outside secondary or specialist care) and a consideration of subsequent care, including referral to a hepatologist. A surveillance review of NG49 is ongoing. If this is updated, this diagnostics assessment of FibroScan can be updated in the future if, for example, there are changes to relevant care pathways that are likely to change the recommendation. The process of reviewing and updating existing guidance is described in the CHTE programme manual on the NICE website.
10	Perspectum	the-diagnostic-test Clinical need and practice 2.5	It has not been confirmed in writing whether the current NICE NAFLD guidelines (NG49) are going to be updated, and as of submission (1st December 2022), there was still no confirmation on the guideline update – the most recent contact that has been received regarding this potential update was on 1st August 2022.	Thank you for the comment which has been considered. A surveillance review of NG49 is ongoing. If this is updated, this diagnostics assessment of FibroScan can be updated in the future if, for example, there are changes to relevant care pathways that are likely to change the

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			Any programme relating to a guideline that could potentially be updating in the coming months, should be postponed so that the most recent, robust and credible information can be used to inform assessments.	recommendation. The process of reviewing and updating existing guidance is described in the CHTE programme manual on the NICE website.

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Comment number	Name and organisation	Section number	Comment	NICE response
11	Perspectum		With FibroScan recommended for use in primary or community care to assess liver fibrosis or cirrhosis it is important to recognise well reported limitations associated with its use in terms of staging earlier phases of fibrosis and its performance in patients with Non-alcoholic fatty liver disease (NAFLD) and obesity. It has been well-documented that NAFLD is the most common cause of chronic liver disease, affecting approximately 25% of the general population worldwide (Younossi et al, 2016). The more aggressive form, non-alcoholic steatohepatitis (NASH) occurs in approximately 30% of those with NAFLD and is predicted to become the leading cause of liver transplant over the coming decade (Younossi, 2016). A significant proportion of those presenting with NAFLD/NASH are overweight/obese. FibroScan is not effective in NAFLD and/or obesity (Caussy et al., 2018, Wagner et al., 2017, Castera et al., 2009, Liang and Li et al., 2020, and Wentworth and Caldwell et al., 2021). Given its high failure rate, FibroScan performs poorly in the real world for prognostication in NAFLD (Jayaswal et al., 2020) and due to its high coefficient	Thank you for the comment which has been considered. As noted in response to comments above, this guidance does not recommend when or in which population to use FibroScan, but rather if it should be used in primary or community care setting for the same uses as currently recommended and used in secondary or specialist care. The committee's adoption recommendation is in section 1.1 of the diagnostics guidance document specifies that the use of FibroScan should be in accordance with national guidelines. The failure rate of FibroScan was considered in the model used for this assessment. To help healthcare professional in primary or community care interpret FibroScan results, the recommendations specify that a clear care pathway with advice for healthcare professionals on what to do based on a FibroScan result should be established locally in collaboration between primary or community care and secondary or specialist care providers.

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			of variation of up to 46% (Harrison et al 2018) is regarded as a sub-optimal tool for monitoring liver disease. This variability issue is highly problematic in a chronic, slowly progressing/regressing condition as liver disease whereby patients' conditions can change gradually between visits. These factors should be taken into consideration and made clear within guidelines so that primary care clinicians can interpret FibroScan results considering the appropriate degree of error. The fact that the above factors have not been only accentuates the uncertainty inherent in this assessment. References Andersson, A., et al. (2021). Clinical utility of MRI biomarkers for identifying NASH patients at high risk of progression: A multicenter pooled data and meta analysis. Clinical Gastroenterology and Hepatology, 20, 2451-2461. https://doi.org/10.1016/j.cgh.2021.09.041 Castera, L., et al. (2010). Pitfalls of liver stiffness measurement: A 5-year prospective study of 13,369 examinations. Hepatology, 51, 828-835.	

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			Caussy, C., et al. (2018). Association and discordance in fibrosis stage determination by magnetic resonance vs transient elastography in patient with nonalcoholic liver disease. Clinical Gastroenterology and Hepatology, 16. 1974-1982. https://doi.org/10.1016/j.cgh.2017.10.037 Harrison, S. A., et al. (2018). Utility and variability of three non-invasive liver fibrosis imaging modalities to evaluate efficacy of GR-MD-02 in subjects with NASH and bridging fibrosis during a phase-2 randomised clinical trial. Plos One, 13. https://doi.org/10.1371/journal.pone.0203054 Imajo, K., et al. (2021). Quantitative multiparametric magnetic resonance imaging can aid non-alcoholic steatohepatitis diagnosis in a Japanese cohort. World Journal of Gastroenterology, 27, 609-623. https://dx.doi.org/10.3748/wjg.v27.i7.609 Jayaswal, N. A. A., et al. (2020). Prognostic value of multiparametric magnetic resonance imaging, transient elastography and blood based fibrosis markers in patients with chronic liver disease. Liver International, 40, 3071-3082. https://doi.org/10.1111/liv.14625 McDonald, N., et al. (2018). Multiparametric magnetic resonance imaging for quantitation of liver disease: a	

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			two centre cross sectional observational study. Scientific Reports, 9. 10.1038/s41598-018-27560-5 Wagner, M., et al. (2017). Technical failure of MR elastography examination of the liver: Experience from a large single-center study. Radiology, Gastrointestinal Imaging, 284, 401-412. Wentworth, B. J., and Caldwell, S. H., (2021). Pearls and pitfalls in nonalcoholic fatty liver disease: tricky results are common. Metabolism and Target Organ Damage, 1, 1-15. 10.20517/mtod.2021.02 Younossi, Z. M., et al. (2016). Global epidemiology of non-alcoholic fatty liver disease – meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology, 64, 73-84. 10.1002/hep.28431.	
12	Perspectum	committee-discussion FibroScan should be used as part of a clear care pathway 3.9	"It noted that performance of the test would depend on the population being tested and that the value of testing would depend on the availability and effectiveness of interventions for the population tested, based on test results." – GID-MT562 CDC There are no current approved NAFLD/NASH pharmacological treatments in the UK. It is well-know and incorporated into UK clinical practice that lifestyle advice is the most common treatment and can support disease regression. The statement above	Thank you for the comment which has been considered. The statement cited in the comment is quoted out of context. The preceding sentences in section 3.8 of the diagnostic consultation document highlight that: "…the population in this assessment was restricted to those who would have FibroScan as in current NHS practice (see section 2.10). The test was only assessed for use in people it is already recommended for". The quoted statement is not a statement about the

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			implies that there is limited value in assessing patients with suspected NAFLD as there is not a readily available and effective treatment in the UK. Given that liver disease, and in particular NAFLD and NASH is a rising public health issue, extra attention, or value, should be given to identifying these patients.	size of likely value of testing, but a statement that the level of benefit of doing the test in further populations (for which use is not already recommended) will differ, is uncertain, and crucially (as stated in the preceding sentence in section 3.8 of the diagnostic consultation document) that this has not been considered in this assessment. As stated elsewhere in responses, this assessment compared whether FibroScan can be done in a different location rather than what population it should be used in. The committee's adoption recommendation is in section 1.1 of the diagnostics guidance document and specifies that the use of FibroScan should be in accordance with national guidelines. Existing guidance on assessment of NAFLD is referenced in the diagnostics consultation document (see section 2.5).

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Comment number	Name and organisation	Section number	Comment	NICE response
13	Tawazun Health	3.4 (page 7)	The development and maintenance of quality metrics for fibroscan can be assessed and measured for users – electrograms reviewed, IQR consistency. With protocols adapted from specialist care or providers to promote Point of Care accuracy and competency	Thank you for this comment which has been considered. The committee concluded that with appropriate training and quality assurance, and frequent use, FibroScan can be done effectively in primary or community care. This is described in section 3.7 of the diagnostics guidance document. The committee's adoption recommendation in section 1.1 of the diagnostics guidance document includes that training for healthcare professionals on doing the test should be provided and that the company should provide supporting materials to ensure that user competency after initial training is maintained. The recommendation also specifies that a clear pathway is established locally, with advice and guidance on what to do based on a FibroScan result.
14	Tawazun Health	3.5 (pages 7 and 8)	Attending multiple practices for set clinics at the frequency required the number of scans is not difficult to achieve in our experience. Concentrating on those liver pathways where patients are most frequently returned to care post first fibroscan – abnormal LFT, NAFLD – (90% in my previous center were within these referral reasons)	Thank you for the comment which has been considered.

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FibroScan for assessing liver fibrosis and cirrhosis in primary or community care

Diagnostics Consultation Document – Comments
Diagnostics Advisory Committee date: 28 September 2022
THEME: Ensuring performance of FibroScan in primary or community care

Comment number	Name and organisation	Section number	Comment	NICE response
15	Tawazun Health	3.6 (page 8)	Fully support the assessment and supervision of users. Fibroscan is now a CQC regulated diagnostic test which is supportive for patient safety and quality.	Thank you for the comment which has been considered.
16	Tawazun Health	3.8 (page 9)	The use of fibroscan has now been made a CQC regulated activity to support the quality and use which would support this area.	Thank you for the comment which has been considered.

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THEME: Other non-invasive tests

Comment number	Name and organisation	Section number	Comment	NICE response
17	Perspectum		Our opinion is that throughout the consultation document and committee discussion, there is documentation of uncertainty regarding the methodology, and evidence within this assessment. Examples of this can be found in sections, 3.9, 3.10, 3.11, 3.12, 3.13 and despite this uncertainty FibroScan will be recommended for use in primary care. Given that the use of FibroScan is being limited to those listed in the national guidelines, this is an expensive exercise with limited utility - especially for NHS purposes. Investing in non-invasive tests in secondary care, such as MRI (whose use is not limited to either liver disease or fibrosis detection) would be a more worthwhile investment.	Thank you for this comment which has been considered. The diagnostics advisory committee considered uncertainties associated with this assessment in its decision-making, as described in section 3.13 of the diagnostics consultation document. It concluded that there was enough certainty that the immediate cost of using FibroScan for assessing liver fibrosis and cirrhosis in primary or community care are likely to be lower than the cost of referring people for testing in secondary or specialist care to allow it to recommend use in this setting. The topic was considered and selected by the NICE Topic selection oversight panel (TSOP) as suitable for the production of NICE guidance. Use of MRI-based technologies was not included in the scope for this assessment, but is being assessed in a further guidance topic (MRI-based technologies for assessing non-alcoholic fatty liver disease).

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Comment number	Name and organisation	Section number	Comment	NICE response
18	Siemens-Healthineers	the-diagnostic-test Clinical need and practice 2.5	Adoption of ELF in each of the 29 pathology networks in England would be sufficient to provide universal service coverage for primary care. We recommend for the committee to note that one of the main barriers against nationwide availability of the enhanced liver fibrosis (ELF) test is the current need to secure local commissioning for a diagnostic pathway including the ELF test in individual integrated care systems (ICSs). We would therefore encourage NICE to develop guidance and implementation tools that may facilitate the nationwide adoption of the ELF test, developing on current NICE guideline NG49 as well as other national clinical guidelines referenced in the diagnostics consultation document for patients with non-alcoholic fatty liver disease. In addition, it should be recognised by the committee that testing for liver fibrosis using ELF does not require that specific laboratory analysers are available in each pathology network. The national pathology exchange (NPEx) deployed in all UK hospital laboratories allows electronic requesting and receipting of ELF scores from any UK laboratory	Thank you for the comment which has been considered. This assessment evaluated using FibroScan outside of secondary or specialist care, as described in the final scope. It did not evaluate alternative tests such as blood tests. This diagnostics guidance will not replace any current recommendations for use of laboratory-based testing in existing NICE guidance. The committee's adoption recommendation is in section 1.1 of the diagnostics guidance document specifies that the use of FibroScan should be in accordance with national guidelines.

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			requesting the test, therefore facilitating a networked approach.	

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THEME: Assessment documents and health economic analysis

Comment number	Name and organisation	Section number	Comment	NICE response
19	Royal College of General Practitioners		We would suggest a fuller documentation highlighting prevalences, benefits and value is produced. That more understanding is made of the current workload in specialist care – and if considered for primary care implementation considerably more evidence of benefit in this environment is produced.	Thank you for the comment which has been considered. In addition to the guidance document, the full company submissions made for this topic and critiques of these, and further analyses, done by an external assessment group are also published on the NICE website. This provides the full data and analyses considered by the committee in its decision-making. This included data used in the economic modelling on a proposed benefit of greater use of the technology in primary or community care: improved attendance at appointments. This was based on data from a pilot study done by the Southampton CCG.
20	Perspectum	committee-discussion Cost modelling 3.9	There are many uncertainties within the cost modelling that need to be accounted for: • Patients with a false positive test result that may be referred unnecessarily to secondary care and potentially undergo invasive, expensive procedures such as liver biopsy. • Patients with a false negative test result that may be inappropriately discharged and potentially return with more advanced disease. • The cost of a failed FibroScan and having to repeat the tests. It is unclear what happens to those for	Thank you for the comment which has been considered. The produced model and accompanying documentation, as well as the external assessment group's critique of these, were provided in full to the committee for consideration in decision-making for this assessment. Uncertainties were considered by the committee in producing their recommendations. The

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			whom transient elastography is unsuitable to assess fibrosis. • The absence of natural disease progression within the model. Section 3.10 states that "The company's model did not allow people's liver disease to progress in the 5-year time period model". To assume that a patients liver disease could not progress within 5 years is an unrealistic assumption and should be accounted for in the modelling. These points need to be addressed in the model, to help account for numerous uncertainties within the assessment.	existence of uncertainties is not a barrier to committee decision making, unless these uncertainties mean the committee is too unsure about whether a technology is likely to be cost saving or cost effective to make a recommendation for routine use. In this assessment, the committee concluded that there was enough certainty that the immediate cost of using FibroScan for assessing liver fibrosis and cirrhosis in primary or community care are likely to be lower than the cost of referring people for testing in secondary or specialist care to allow it to recommend use in this setting (see section 3.13 of the diagnostics consultation document). As noted above, this assessment concerned the use of FibroScan done in a different setting, rather than introducing the test to a care pathway, or changing how it was used. While there were no data directly comparing the performance of FibroScan when used in primary or community care with its use in secondary or specialist care (see section 3.3 in the diagnostics consultation document), after extensive discussion the committee agreed that with appropriate training

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				and quality assurance, and frequent use, FibroScan can be done effectively in primary or community care (see section 3.7 in the diagnostics consultation document). Failure rates for a FibroScan test were included in modelling. In advance of the third committee meeting, the company provided a revised model, and accompanying description, of the long-term implications of missing liver disease. This included allowing liver disease to progress within the modelled time period. Section 3.10 of the guidance document has been updated to reflect this.
21	Tawazun Health	3.12 (page 14)	The cost models were only based on NHS pathways, new models are available, where expertise, volume and mobility reduce cost. Reviewing in comparison to current.	Thank you for the comment which has been considered. The costs included in the analysis followed the NICE medical technologies evaluation programme methods guide. The guide states that the decision problem, as defined in the scope, determines the construction and assumption of any models. Models should quantify the effect of introducing a new technology into current healthcare pathways and routine health and social care system use. Costs resulting from or

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				associated with the use of the technology should be estimated using prices relevant to the health and social care system and personal social services.

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THEME: Evidence and uncertainties

Comment number	Name and organisation	Section number	Comment	NICE response
22	Perspectum		There are many instances in the consultation document where no evidence is cited to validate claims made by the company and clinical experts, making the claims seemingly unsubstantiated, including: • The reduction in health inequalities (section 1.1) • The behavioural changes that patients may undergo based on FibroScan results (section 3.1) • The performance of FibroScan in primary care (section 3.3) • The performance of FibroScan in differing patient populations (Alcohol related liver disease, NAFLD, Hepatitis B, C) (Section 3.8) • Reallocation of resources and workload (Section 3.12) In contrast the quality standards upheld during the ongoing NICE Diagnostic Assessment Programme DAP59 assessment 'MRI based technologies for the assessment of NAFLD' clearly require extensive documentation as well as reviewed with what appears to be much higher standards or thresholds from which analysis is based. Given that the outcome of GID-MT562 would directly impact the patient population for DAP59, the same scrutiny should be applied. During	Thank you for the comment which has been considered. The type and extent of evidence required to support adoption recommendations can vary by technology and how its use is being assessed. DAP59 assesses the introduction of a new test into a care pathway, whereas this assessment as described in the scope, does not assess the introduction, or change to existing recommendations for the use, of FibroScan into a care pathway, but rather where the test can be done. Use of the technology (in terms of when it should be used and how results interpreted) are as per existing guidance (as described in sections 2.3 to 2.5 in the diagnostics consultation document). On the points raised for this guidance: • The potential benefit in terms of reducing health inequalities (discussed in 'Why the committee made these recommendations' section) describes how moving tests closer to people may improve access and may therefore reduce health inequalities

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			DAP59, quantitative evidence was required for the following: • The reduction in health inequalities • The behavioural changes that patients may undergo based on MRI results • The performance of MRI in differing patient populations. NICE is displaying double standards in its approach to health technology assessment by not insisting on the same level of rigour across the programs. It is our position that guidelines without clear evidence should not guide standards, especially if it shows disparity in the evidence requirements necessary in NICE assessments.	for people from disadvantaged or high-risk communities, which the committee found plausible. • Section 3.1 in the diagnostics consultation document describes committee consideration of behavioural changes that may occur based on FibroScan results, and notes that that there was no evidence showing long-term behavioural change after FibroScan use. There was no discussion that the impact of the test result would differ based on where the test was done. • The lack of data comparing the performance of FibroScan when used in primary or community care with its use in secondary or specialist care was noted by committee (described in section 3.3 of the diagnostics consultation document). But in considering expert opinion on the impact of doing the same test in a different setting, the committee concluded that if the test was done in a primary or community care setting where appropriately trained operators do enough

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				scans to maintain their expertise, that it was likely that test performance could be maintained outside of secondary or specialist care, if there are ongoing measures to ensure quality such as those proposed by the company (described in section 3.7 of the diagnostics consultation document). • Section 3.8 in the diagnostics consultation document highlights the committee's concern that that greater availability of FibroScan in primary or community care could lead to wider use. As noted in this section, and captured in the recommendations, the committee recommended use of the test in primary or community care only as recommended in national guidelines. • Section 3.12 in the diagnostics consultation document details committee consideration of the uncertainty in cost of testing in different settings, and the analyses done by the company and external assessment group to assess this. The committee acknowledged that there is

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				still uncertainty about the true cost of doing a test both in secondary or specialist care and in primary or community care, but on balance, it concluded that there was enough certainty that the immediate cost of using FibroScan for assessing liver fibrosis and cirrhosis in primary or community care are likely to be lower than the cost of referring people for testing in secondary or specialist care to allow it to recommend use in this setting (described in section 3.13 of the diagnostics consultation document).
23	Tawazun Health	3.14 (page 16)	I fully support the need to monitor the effect of fibroscan in all settings. It maybe a consideration to monitor the additional aspect of the level of high liver fat and metabolic risks.	Thank you for the comment which has been considered.

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THEME: Equality considerations

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24	Royal College of General Practitioners		The aim to provide scanning close to the patients home and hence reduce some health inequality would be dependent on the estimates of usage across a population which was not particularly evident in the documentation.	Thank you for the comment which has been considered. Any improvement in access to testing as a result of making FibroScan available in primary or community care was noted as a potential, rather than definite, benefit (see section 3.2 of the diagnostics consultation document). Section 3.2 of the diagnostics guidance describes the committee discussion on the potential for using FibroScan in primary or community care to reduce health inequality by making testing more accessible. This section of the guidance has been updated to note that this will depend on how community or primary testing is provided locally. Because this will depend on features that vary locally, such as how testing in primary or community care is set up and local transport links, it is not possible to definitely state the size of any benefit. Further text has been added to the recommendations to highlight to local decision makers that they should consider how this would improve access to people in the local population, in comparison to

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				testing available only in secondary or specialist centres.

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25	Royal College of General Practitioners		The cost implications to the NHS are not clear in the documentation. Are NICE confident that this intervention fulfils the criteria for implementation.	Thank you for the comment which has been considered. The committee's consideration of cost impact and conclusions are described in section 3.13 of the diagnostics consultation document. The committee concluded that there is some uncertainty about the overall long-term costs of using the test in primary or community care. But, on balance, it concluded that there was enough certainty that the immediate cost of using FibroScan for assessing liver fibrosis and cirrhosis in primary or community care are likely to be lower than the cost of referring people for testing in secondary or specialist care to allow it to recommend use in this setting. In addition to the guidance document, results of the full cost analyses done by the company and external assessment group, which were used by the committee in its decision making, are published on the NICE website.
26	Siemens Healthineers	committee-discussion	In light of the committee's considerations and the company's stated intended use for FibroScan in primary and community care, we encourage the	Thank you for the comment which has been considered.

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		There is no evidence on how often FibroScan would need to be used to maintain competence 3.5	committee to clarify their current recommendation regarding the setting FibroScan should be used in. Indeed, this recommendation may currently be interpreted as recommending the test for implementation in individual GP practices, whereas the diagnostics consultation document is highlighting a consensus that FibroScan should instead be used in diagnostic hubs or across a primary care network to represent a cost-effective use of NHS resources. It should further be noted that there is no quality assurance framework for performing FibroScan, emphasising the requirement for minimum volumes of activity to maintain a level of competence, which cannot be objectively quantified or assessed. In contrast hospital laboratories which could run ELF are subject to UKAS inspection, run internal and external quality assurance schemes for all parameters measured, whilst being managed by state registered biomedical scientists	The committee's recommendation in section 1.1 of the diagnostics guidance document includes that the use of FibroScan in primary or community care is recommended if each FibroScan device is expected to be used for at least 500 scans per year, which experts indicated to be unlikely to be achieved if the test was available in individual GP practices (see section 3.5 of the diagnostics consultation document). Section 3.12 of the diagnostics consultation document also makes the company's intended use, in hubs and diagnostic centres rather than single GP practices, clear. The committee considered quality assurance for use of FibroScan in a primary or community care setting. It concluded that if appropriately trained operators do enough scans to maintain their expertise it was likely that test performance could be maintained outside of secondary or specialist care, if there are ongoing measures to ensure quality such as those proposed by the company (described in section 3.7 of the diagnostics consultation document).
27	Tawazun Health	1.1 (page 3)	I thank the committee and fully support the recommendation 1.1, As a CQC regulated provider of	Thank you for the comment which has been considered.

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			fibroscan services, the CQC approval process supports the recommendations made, the establishment of protocols, pathway and quality metrics.	