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Referral pathways for patients with NAFLD based on non-invasive fibrosis tests: diagnostic accuracy and cost analysis

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Abbreviations: NAFLD: non-alcoholic fatty liver disease, PC: primary care, SCR: secondary care referrals, NIT: non-invasive test, NASH: non-alcoholic steatohepatitis, TP: true positive, FP: false positive, TN: true negative, FN: false negative

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Abstract

Background/aims: Non-invasive fibrosis tests (NITs) can be used to triage non-alcoholic fatty liver disease (NAFLD) patients at risk of advanced fibrosis (AF). We modeled and investigated the diagnostic accuracy and costs of a two-tier NIT approach in primary care (PC) to inform secondary care referrals (SCRs).

Methods: A hypothetical cohort of 1,000 NAFLD patients with a 5% prevalence of AF was examined. Three referral strategies were modeled: refer all patients (Scenario 1), refer only patients with AF on NITs performed in PC (Scenario 2) and refer those with AF after biopsy (Scenario 3). Patients in Scenarios 1 and 2 would undergo sequential NITs if their initial NIT was indeterminate (FIB-4 followed by Fibroscan®, ELF® or Fibrotest®). The outcomes considered were true/false positives and true/false negatives with associated mortality, complications, treatment and follow-up depending on the care setting. Decision curve analysis was performed, which expressed the net benefit of different scenarios over a range of threshold probabilities (Pt).

Results: Sequential use of NITs provided lower SCR rates and greater cost savings compared to other scenarios over 5 years, with 90% of patients managed in PC and cost savings of over 40%. On decision curve analysis, FIB-4 plus ELF was marginally superior to FIB-4 plus Fibroscan at Pt≥8% (1/12.5 referrals). Below this Pt, FIB-4 plus Fibroscan had greater net benefit. The net-reduction in SCRs was similar for both sequential combinations.

Conclusions: The sequential use of NITs in PC is an effective way to rationalize SCRs and is associated with significant cost savings.

Lay summary: Only a minority of people with non-alcoholic fatty liver disease develops progressive liver injury, therefore effective and efficient tools are required to appropriately select patients for secondary care referrals. We present modeling and cost data of a two-step pathway to appropriately triage patients in primary care.

Keywords: FIB-4; Fibroscan; ELF; Fibrotest

Non-alcoholic fatty liver disease (NAFLD) has an estimated prevalence of 20-25% in industrialized countries and is the leading cause of referrals for liver test abnormalities from primary to secondary care (1). It is considered the hepatic manifestation of the metabolic syndrome and is closely associated with the current epidemic of obesity.

NAFLD encompasses a wide range of liver abnormalities, from simple steatosis to steatohepatitis, progressive fibrosis and cirrhosis (2). Only a minority of patients with NAFLD, estimated at 15—20%, have non-alcoholic steatohepatitis (NASH), which is considered the progressive form of the disease from a liver perspective (3). The

primary cause of mortality in unselected patients with NAFLD is cardiovascular disease, followed by non-liver related malignancies, while liver-related deaths are only third in the list (4). Recent data suggest that liver-related mortality is dictated by the presence of advanced fibrosis rather than the presence of NASH (5, 6). Therefore, NAFLD is a disease of high prevalence and relatively low severity in the majority of patients. Its high prevalence dictates the need for triaging patients in primary care in terms of their severity of liver disease, in order to accurately select those who would mostly benefit from targeted interventions and also minimize unnecessary secondary care referrals (7).

Although liver biopsy remains the gold standard for diagnosing NASH and staging fibrosis, it is practically impossible to biopsy every patient with NAFLD. The explosive development and use of non-invasive fibrosis tests (NITs) has greatly reduced the need for liver biopsy (8). Several NITs have been validated in patients with NAFLD, and range from simple readily available serum tests (such as FIB-4 and NAFLD fibrosis) score to patented serum tests (such as ELF score and Fibrotest) and elastography methods (such as Fibroscan). Given the low prevalence of advanced fibrosis in unselected patients with NAFLD, such tests or their combination have high negative predictive value and can be used to guide referrals for dedicated hepatology input and provide an efficient solution for improving outcomes (7).

We therefore modeled a pathway using non-invasive fibrosis tests in primary care to triage patients for secondary care referrals based on diagnostic accuracy and decision curve analysis. We subsequently carried out a cost analysis of different scenarios of this pathway.

Methods

Referral pathway using non-invasive fibrosis tests

We evaluated the single use of NITs or their sequential use, starting from a simple NIT and followed with Fibroscan or a patented serum NIT. For the two-tier approach, we modeled the initial use of FIB4, with a combined diagnostic threshold cut off. As this test may return a number of indeterminate results, we assumed that this subgroup of patients would receive a second test. We modeled a choice of three second tier tests: Fibroscan, ELF and Fibrotest to confirm a diagnosis. We sourced the summary sensitivity and specificity of these NITs from a systematic review and meta-analysis of the diagnostic accuracy of NITs compared to liver biopsy in adult patients with NAFLD (9). This was part of a larger project funded by UK NIHR Health Technology Assessment Program that determined the cost-effectiveness of NITs in patients with HBV, HCV, ALD and NAFLD (9-11).

We set the prevalence of advanced fibrosis (≥F3) in the primary care population at 5%, similar to what is expected in unselected cohorts with NAFLD (1). We assumed that the NITs would perform equally well when used sequentially, i.e. their performance is unchanged at different prevalence of advanced fibrosis.

This was a modelling study that did not include patient data therefore ethical approval was not required.

Referral scenarios assessed

We considered a hypothetical cohort of 1000 unselected patients with NAFLD who are tested for the presence of advanced fibrosis. The outcomes of non-invasive testing can be true positive (TP), false positive (FP), true negative (TN) or false negative (FN). Our analysis compared three different scenarios **(Figure 1).**

1. Immediate referral of all patients diagnosed with NAFLD (irrespective of fibrosis level) to secondary care for non-invasive fibrosis testing, treatment and management.
2. At primary care level, testing all patients with NAFLD with a NIT. If the NIT is suggestive of ≥F3 (advanced fibrosis), refer patients to secondary care for treatment and management. If the NIT score indicates low risk for advanced fibrosis (<F3), treat and manage patient in primary care. We also considered a variation of this scenario, where patients tested as ≥F3 receive a subsequent liver biopsy, and are followed-up in secondary or primary care if TP and FN respectively (scenario 2b).
3. Biopsy all patients; treat and manage all patients with advanced fibrosis at secondary care. Refer those with <F3 for treatment and management in primary care.

Input Parameters

Assumptions regarding resource use

The time frame adopted in the analysis was five years and a discount rate of 3.5% was applied (12). **We assumed that the cardiovascular management would be done by the general practitioner (as is customary in the UK) irrespective of the referral or not to the liver specialist, therefore such costs were not considered in our calculations. The input parameter costs are shown in Table 1 of the Supplementary material.**

High Risk (≥ F3) Treated in Secondary Care

We assumed that patients with a fibrosis score of ≥F3 would have two assessments per year with a consultant hepatologist.

Exercise and diet programs would be initiated and monitored by specialists (dietician, physiotherapist, and psychologist) with a six-monthly assessment.

Treatment would involve aggressive management of metabolic syndrome components with statins, pioglitazone and anti-hypertensives. We modeled that patients who tested true positive (4%) would have a 0.4% probability of progressing to a cirrhotic health state per year (13).

In the absence of data on the percentage of persons who may be offered bariatric surgery as additional treatment if all other options have failed, we built into our model that a small proportion (0.8%) of the high-risk cohort (TP and FP) will undergo surgery. We sourced this proportion using the costing report for the NICE clinical guidelines for obesity (14).

We also assumed that a proportion of patients (1%) who tested true positive and were treated in secondary care would progress to a cirrhotic state during the time period and would receive subsequent screening and associated costs for HCC and varices.

Twenty per cent of patients (TP patients) who progressed to cirrhosis would receive screening for hepatocellular cancer (HCC) twice per year (using a combination of ultrasound and monitoring of alpha-fetoprotein levels). For those patients who developed HCC each year, we allowed for a thirty-minute consultation with the hepatologist. We also applied a cost for those patients who developed HCC. For the proportion that did not develop HCC, we allowed for thirty minutes of a hospital based nurse's time to feedback results via letter.

We assumed that 3.5% of the patients who developed HCC would undergo liver transplantation (0.04% progression rate to HCC health state) (13). In the absence of specific data, we sourced this cost from a study that evaluated liver transplantation (15). The model assumed a cost per year of £38,870.54

Low Risk (<F3) Treated in Secondary Care

We assumed that patients with a Kleiner score of <F3 would receive an initial assessment with a consultant hepatologist and thereafter would receive one assessment per year. Exercise and diet programs would be initiated and monitored by a hepatologist and 20% of this population cohort would see a dietician (initial assessment and once per year thereafter). Treatment would also involve aggressive management of metabolic syndrome components with statins, pioglitazone and anti-hypertensives. This patient cohort would also have annual liver function tests administered by the clinical hepatologist at the yearly assessment. We assumed that an arbitrary proportion of this group (5%) would have an additional assessment by the hepatologist to feedback results. The remaining 95% would have results fed back via letter (we identified the resource use for this as thirty minutes of a hospital based nurse's time). This group would also receive a re-test with an NIT to check progression of fibrosis at five years. We conservatively assumed that for the annual liver function tests and the five year NIT re-test, a hospital based nurse would spend thirty minutes administration time (non-face to face time) for each contact episode organizing tests, sending samples to laboratory's for analysis and compiling results.

Low Risk (< F3) Treated in Primary Care

We assumed that patients who have a Kleiner score of <F3 would receive one thirty minute assessment per year with a general practitioner who would advise on and monitor diet and exercise programs. As in secondary care, treatment would also involve aggressive management of metabolic syndrome components with statins, pioglitazone and anti-hypertensives. This patient cohort would also have annual liver function tests (administered by a practice nurse during a thirty minute assessment) and would receive a re-test with an NIT to check progression of fibrosis at five years. We conservatively assumed that for the annual liver function tests and the five year NIT re-test, a nurse based at a GP practice would spend thirty minutes administration time for each contact episode (non-face to face time) organizing tests, sending samples to laboratory's for analysis and compiling results.

Cost of complications due to missed diagnosis (FN diagnoses)

We modeled a cost due to complications from missed diagnosis for patients who tested FN and were treated in primary care or secondary care. We assumed that a higher proportion of these patients would progress to cirrhosis (6%) and of these (0.6%) would progress to a HCC health state per year (assumption 50% higher than progression rates for TP patients). We applied the same cost for HCC for FN patients as applied for TP patients (15).

Proportion of patients receiving combination of drugs or drugs alone (for treatment of metabolic conditions)

We modeled that patients could receive more than one drug: pioglitazone, vitamin E, statins or anti-hypertensives. The proportion or combination would remain the same if patients were treated in a secondary or a primary care setting. Simvastatin was chosen as the statin of choice as this is the most commonly prescribed. Lisinopril was chosen as an antihypertensive drug as per NICE Guidance which advised that the first line drug of choice for hypertension should be an angiotensin converting enzyme (ACE) inhibitor or an angiotensin ll receptor blocker (ARB) (16). We sourced the dosage for pioglitazone and vitamin E suspension (alpha tocopheryl acetate) from the British National formulary (BNF 64). It was assumed in this exploratory analysis that the formulation of the drugs prescribed would be the cheapest non-proprietary drug available. Estimates were based on clinical opinion.

Sensitivity analyses

We performed the following sensitivity analyses

1. **We increased the prevalence of advanced fibrosis to 15%, in order to capture populations at higher risk of fibrosis (such as patients with type II diabetes).**
2. **We used the NAFLD fibrosis score instead of the FIB-4 as first tier testing.**
3. **We used dual Fibroscan cut-offs in the two tier approach (scenario 2), namely 10 KPa to rule out and 15 KPa to rule in advanced fibrosis as per the Baveno VI criteria (17). Patients in the indeterminate range had a liver biopsy.**

Decision analysis and net benefit

We used decision curve analysis to determine the clinical utility of NITs (Scenario 2) in comparison to a "biopsy all" (Scenario 3) or "refer all" (Scenario 1) strategy. The cost component is not included within this analysis. The primary advantage of this method over traditional statistical measures such as sensitivity and specificity is that the impact of patients who are misclassified is quantified. Decision curve analysis uses the concept of net-benefit, which aims to quantify the harms and benefits of using a diagnostic test or strategy in clinical practice. This is achieved by multiplying the harm of a test by a threshold probability so that it is placed on the same scale as benefit and therefore can be directly compared. Threshold probability refers to the probability of a correct diagnosis that a patient or a clinician is willing to accept to undergo a test. For example, if a clinician was willing to subject 10 patients to a liver biopsy for one diagnosis of advanced fibrosis, then the threshold probability would be 10% (18). Net-benefit was calculated and expressed across a range of threshold probabilities as decision curves and net-reduction in intervention curves, according to the method described by Vickers and Elkin (19). Input variables for sensitivity and specificity were the same as used for the cost-effectiveness analysis in a hypothetical cohort of 1,000 patients. Only sequential use of NITs was examined, as this leads to lower referral rates with no increase in the false negative rate. All decision analysis calculations were performed using STATA v14.2 (STATACorp ®, USA) software.

Results

Non-invasive fibrosis assessment of patients with NAFLD

The summary sensitivity and specificity of the NITs used is shown in table 1 (9). We applied these values in a population with a low prevalence of advanced fibrosis, which was set at 5%. For **the main analysis**, we selected FIB4 over NAFLD fibrosis score, as it is based on less parameters and therefore is easier to calculate with similar diagnostic accuracy (9). We also selected Fibroscan, Fibrotest and ELF as they are well validated in patients with NAFLD. For FIB-4, we considered dual cut-offs of <1.30 and >3.25. Patients with a FIB-4 score of <1.30 were considered as having a low risk for advanced fibrosis and could therefore be managed in primary care, while those with scores >3.25 were considered as high risk and were referred to secondary care. Those with indeterminate results (between 1.30 and 3.25) either had second tier testing with Fibroscan, Fibrotest or ELF or were referred to secondary care. For Fibroscan, Fibrotest and ELF, we used a single cut-off to diagnose patients at low or high risk of advanced fibrosis, who were subsequently managed in primary and secondary care respectively.

Single use of NITs

The single use of FIB-4 would result in a 29% referral rate, 25% false positives and a 1% false negatives. **The single use of NFS would result in a 36% referral rate, 32% false positives and a 1% false negatives.** The single use of ELF would result in a 14% referral rate, 10% false positives and a 1% false negatives. The single use of Fibrotest would result in a 30% referral rate, 25% false positives and 0.6% false negatives. The single use of Fibroscan would result in a 19% referral rate, 15% false positives and a 1% false negatives.

Sequential use of NITs

Taking into account the increased cost of ELF, Fibrotest and Fibroscan, we evaluated a sequential approach, where all patients had a FIB-4 as a baseline test, followed by an ELF or a Fibroscan for those with indeterminate results. This would result in 24.1% patients having indeterminate results and requiring a second tier test. The prevalence of advanced fibrosis in the population of indeterminate FIB4 testing would be 9.5%, This approach resulted in referral rates of 9-11%, with 5-7% of false positives and 1% of false negatives. This reduced referral rate was also associated with lesser costs. All this is summarized in table 2. A schematic representation of this sequential approach is shown in Figure **2.**

Cost analysis

The summary results of the economic analysis are shown in tables 3 and the detailed results in supplementary table 2. We assumed that all patients who tested negative at baseline (TN and FN) would be re-tested at 5 years in order to diagnose those with disease progression and those who tested FN in the first instance. Irrespective of the combination of NITs, scenario 2 i.e. testing patients with a two-tier non-invasive test strategy and referring only those at high risk of advanced fibrosis was the most cost-saving and at least 40% cheaper than using liver biopsy for all patients. Within scenario 2, performing a liver biopsy in those at high risk of advanced fibrosis according to NITs, was more cost saving than treating all of them as if they had advanced fibrosis.

Decision curve analysis and net-benefit

The sequential use of FIB-4 plus ELF resulted in the greatest net benefit compared to FIB-4 plus Fibroscan or FIB-4 plus Fibrotest, the "biopsy none" (Scenario 1) and the "biopsy all" (Scenario 3) strategies in the detection of advanced fibrosis (see Figure 3). The benefit was observed if the threshold probability was between 8% and 42%, which includes all clinically relevant probability thresholds. Put alternatively, FIB-4 plus ELF provides marginally greater net benefit to other strategies if the chance of finding advanced fibrosis is between 1:2.4 and 1:12.5. FIB-4 plus Fibroscan provided the greatest net benefit at threshold probabilities between 2% and 7%. In terms of the net reduction in biopsies, FIB-4 plus ELF provided comparable benefit to FIB-4 plus Fibroscan (Figure 4, Table 4).

Sensitivity analyses

By increasing the prevalence of advanced fibrosis to 15%, the referral rate increased in scenario 2 to 15.7% (FIB4 plus ELF), 17.1% (FIB4 plus Fibroscan) and 19.7% (FIB4 plus Fibrotest). The respective costs per patient also increased accordingly. FIB4 plus ELF was marginally less costly in all scenarios, apart from scenario 2b where FIB4 plus Fibroscan was less costly (Table 3). In decision curve analysis, between threshold probabilities of 0.05-0.14, FIB-4 plus FibroTest followed by FIB-4 plus TE had the highest net benefit. Above the threshold probability of 0.15 (1 in 6.7 or lower), FIB-4 plus ELF had the greatest net benefit. The above is shown in detail in the supplementary material (Tables 3,4 and Figures 1, 4).

By using NAFLD fibrosis score as first tier testing instead of FIB4, the referral rate in scenario 2 increased by 0.6-2.4% depending on the second-tier test used. These results are presented in detail in the supplementary material (Table 5, Figures 2 and 5).

Using dual cut-offs of Fibroscan only marginally improved the performance of the testing strategy with no benefit in the decision curve analysis (supplementary Figures 3 and 6).

Discussion

In this paper, we present a comprehensive pathway for triaging patients with NAFLD in primary care and deciding on further specialist referral and management. We use a stepwise approach with widely available and well-validated non-invasive fibrosis tests as first tier testing and a choice of second tier tests for a subgroup of patients with indeterminate first tier results. We have taken into account diagnostic accuracy, resource utilization and clinical decision making, in order to provide a holistic view on a pragmatic tool that is readily available for use in clinical practice. Our findings support a two-tier approach, with FIB-4 as the initial triaging test, followed by ELF, Fibroscan or Fibrotest in patients with an indeterminate FIB-4. This would result in a referral rate of approximately 10% and cost savings of at least 40% compared to a "refer all" strategy.

NAFLD is common and was overlooked by most primary care physicians until recently. The increasing awareness of NAFLD could potentially lead to the overburdening of secondary care, due to the high prevalence of this disease in the general population, but also to unnecessary patient anxiety and testing. Therefore, a simple triaging algorithm is key in order to accurately select patients who need further investigation, educate

primary care physicians, reassure patients who are not at risk of progression and rationalize resource use (7, 20).

Simple non-invasive fibrosis tests, namely FIB-4 (21) and NAFLD fibrosis score (22), have dual cut-offs: a high cut-off with a high specificity and a low cut-off with a high sensitivity for advanced fibrosis. The low cut-offs have a high negative likelihood ratio for advanced fibrosis, thus safely excluding patients who do not have this condition. Even more reassuringly, low cut-offs of both tests have been associated with minimal liver-related events in over 10 years of mean follow-up (23). Since these two scores have similar diagnostic accuracy, we used FIB-4 in our model as it is based on fewer parameters and is therefore easier to calculate. As solely using FIB-4 for triaging would result in a referral rate of 29%, we further refined the pathway with a second non-invasive test. ELF score (24) and Fibrotest (25) are proprietary serum tests while Fibroscan requires dedicated equipment (26). All second line tests provided similar results in terms of diagnostic accuracy and referral rate and the choice should be based on local availability.

In our pathway, the diagnosis of interest is advanced fibrosis rather than NASH. Although NASH is the potentially progressive form of NAFLD, it is now well established that advanced fibrosis, rather than other histological features, is associated with adverse long-term outcomes in such patients (5, 6). Of the high-risk population that is referred to secondary care using the proposed two-tier pathway, approximately 40-50% will truly have advanced fibrosis. We postulate, however, that the majority of those who are false positive, will have some degree of fibrosis and might therefore benefit from secondary care input and/or participation in clinical trials.

In order to capture those patients with disease progression or the minority who tested false negative with the pathway, we propose re-testing of the low risk population with the same pathway every 3-5 years. Cohort studies have shown that patients with NASH and advanced fibrosis have significant decrease in their survival at 7 years after their first presentation (4, 5), therefore re-testing will provide an adequate safety net. The low risk population, rather than being discharged from medical follow-up, should be encouraged to lose weight and managed for cardiovascular risk factors at a primary care level. The message conveyed is that such patients, although at low risk for liver disease, still have an increased cardiovascular risk and would benefit from strategies to mitigate this.

We opted to use a rudimentary cost analysis rather than Markov modeling as there is too much uncertainty in the assumptions for the latter, due to the lack of relevant long term data about the natural history and treatment. Reported economic evaluations have used transition probabilities from studies with a high risk of selection bias, thus probably overestimating the risk of disease progression (27). Moreover, the lack of any approved therapy for NAFLD at the moment also makes this approach less relevant from a therapeutic point of view.

Importantly, this model is optimal for patients between 40 and 65 years old. For patients older than 65 years, FIB-4 has an unacceptably low specificity and leads to a high number of false positive results (28). This is because the derivation cohort for FIB-4 did not include elderly patients, therefore increasing age is inappropriately weighted in the equation. The same is true for the NAFLD fibrosis score (28). ELF score is not liver specific and might lead to false positive results when other fibrotic conditions, such as pulmonary fibrosis or chronic kidney disease, are present. Fibroscan might also lead to false positive results in patients with heart failure. All the above conditions have

an increasing prevalence with advanced age. We therefore recommend judicious use of the pathway in such patients, always in conjunction with the clinical history. Refined cut-offs for those over 65 years have recently been proposed for FIB-4 and NAFLD fibrosis score and could be used in this scenario (29). For patients younger than 40 years old, it is important to recognize those who might progress to advanced fibrosis, even if this is not present at baseline. We would therefore favor referrals based on the number of the metabolic syndrome components that are present, rather than the use of the pathway. As with patients above 65, the diagnostic accuracy of FIB-4 and NAFLD fibrosis score is reduced in younger patients, particularly to those who are younger than 35 years.

Rather than just presenting the diagnostic test accuracy, we used net benefit in order to quantify the harms and benefits of using the proposed diagnostic test strategy. It is reassuring that the two-tier approach provided the greatest net benefit at all threshold probabilities.

In conclusion, we have devised a pathway based on the sequential use of non-invasive fibrosis tests in order to rationalize secondary care referrals of unselected patients with NAFLD. Modeling of this pathway resulted in reducing the burden of unnecessary referrals by 90%, reducing cost per patient by 40% and accurately selecting those patients at greatest risk of advanced fibrosis and disease progression. This model works optimally in patients aged 40-65 years and **was recently** prospectively evaluated and audited (30).

1. Armstrong MJ, Houlihan DD, Bentham L, et al. Presence and severity of non-alcoholic fatty liver disease in a large prospective primary care cohort. J.Hepatol. 2012;56:234-240.
2. Buzzetti E, Pinzani M, Tsochatzis EA. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). Metabolism 2016;65:1038-48.
3. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016;64:1388-402.
4. Ekstedt M, Franzen LE, Mathiesen UL, et al. Long-term follow-up of patients with NAFLD and elevated liver enzymes. Hepatology 2006;44:865-873.
5. Ekstedt M, Hagstrom H, Nasr P, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. Hepatology 2015;61:1547-54.
6. Angulo P, Kleiner DE, Dam-Larsen S, et al. Liver Fibrosis, but No Other Histologic Features, Is Associated With Long-term Outcomes of Patients With Nonalcoholic Fatty Liver Disease. Gastroenterology 2015;149:389-97.e10.
7. Tsochatzis EA, Newsome PN. Non-alcoholic fatty liver disease and the interface between primary and secondary care. Lancet Gastroenterol Hepatol 2018;3:509-517.
8. Buzzetti E, Lombardi R, De Luca L, et al. Noninvasive Assessment of Fibrosis in Patients with Nonalcoholic Fatty Liver Disease. Int J Endocrinol 2015;2015:343828.
9. Crossan C, Tsochatzis EA, Longworth L, et al. Cost-effectiveness of non-invasive methods for assessment and monitoring of liver fibrosis and cirrhosis in patients with chronic liver disease: systematic review and economic evaluation. Health Technol Assess 2015;19:1-409, v-vi.
10. Crossan C, Tsochatzis EA, Longworth L, et al. Cost-effectiveness of noninvasive liver fibrosis tests for treatment decisions in patients with chronic hepatitis B in the UK: systematic review and economic evaluation. J Viral Hepat 2016;23:139-49.
11. Tsochatzis EA, Crossan C, Longworth L, et al. Cost-effectiveness of noninvasive liver fibrosis tests for treatment decisions in patients with chronic hepatitis C. Hepatology 2014;60:832-43.
12. National Institute for Health and Clinical Excellence. Guide to the Methods of Technology Appraisal. In. London: NICE; 2013.
13. Mahady SE, Wong G, Craig JC, et al. Pioglitazone and vitamin E for nonalcoholic steatohepatitis: a cost utility analysis. Hepatology 2012;56:2172-9.
14. National Institute for Health and Clinical Excellence. Obesity guidance on the prevention, identification, assessment and managment of overweight and obesity in adults and children. In: NICE clinical guideline 43. London: NICE; 2006.
15. Longworth L, Young T, Buxton MJ, et al. Midterm cost-effectiveness of the liver transplantation program of England and Wales for three disease groups. Liver Transplantation 2003;9:1295-1307.
16. National Clinical Guideline Centre. Hyptertension The clinical managment of primary hypertension in adults. In: Clinical Guideline 127 Methods, evidence, and recommendations London: NICE; 2011.
17. de Franchis R. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. J Hepatol 2015;63:743-52.
18. Vickers AJ, Van Calster B, Steyerberg EW. Net benefit approaches to the evaluation of prediction models, molecular markers, and diagnostic tests. Bmj 2016;352:i6.

19. Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. Med Decis Making 2006;26:565-74.
20. Newsome PN, Cramb R, Davison SM, et al. Guidelines on the management of abnormal liver blood tests. Gut 2018;67:6-19.
21. Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology 2006;43:1317-25.
22. Angulo P, Hui JM, Marchesini G, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology 2007;45:846-854.
23. Angulo P, Bugianesi E, Bjornsson ES, et al. Simple noninvasive systems predict long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology 2013;145:782-9.e4.
24. Guha IN, Parkes J, Roderick P, et al. Noninvasive markers of fibrosis in nonalcoholic fatty liver disease: Validating the European Liver Fibrosis Panel and exploring simple markers. Hepatology 2008;47:455-460.
25. Imbert-Bismut F, Ratziu V, Pieroni L, et al. Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: a prospective study. Lancet 2001;357:1069-75.
26. Tsochatzis EA, Gurusamy KS, Ntaoula S, et al. Elastography for the diagnosis of severity of fibrosis in chronic liver disease: a meta-analysis of diagnostic accuracy. J.Hepatol. 2011;54:650-659.
27. Argo CK, Northup PG, Al-Osaimi AM, et al. Systematic review of risk factors for fibrosis progression in non-alcoholic steatohepatitis. J Hepatol 2009;51:371-379.
28. McPherson S, Hardy T, Dufour JF, et al. Age as a Confounding Factor for the Accurate Non-Invasive Diagnosis of Advanced NAFLD Fibrosis. Am J Gastroenterol 2016.
29. McPherson S, Hardy T, Dufour JF, et al. Age as a Confounding Factor for the Accurate Non-Invasive Diagnosis of Advanced NAFLD Fibrosis. Am J Gastroenterol 2017;112:740-751.
30. Srivastava A, Gailer R, Tanwar S, et al. Prospective evaluation of a primary care referral pathway for patients with non-alcoholic fatty liver disease. J Hepatol 2019 doi 10.1016/j.jhep.2019.03.033.

Table 1. Diagnostic accuracy of non-invasive tests used in the NAFLD pathway

	Sensitivity	**Specificity**
1st Tier Test		
FIB-4 (low cut off)	0.84	0.74
FIB-4 (high cut off)	0.38	0.97
NFS (low cut-off)	**0.40**	**0.97**
NFS (high cut-off)	**0.80**	**0.66**
2nd Tier Test		
Fibroscan	0.82	0.84
Fibrotest	0.88	0.73
ELF	0.80	0.90

Table 2. Referral rates using single tier and two-tier testing strategies, assuming a prevalence of advanced fibrosis of 5%.

Test strategy	High risk (Referral)		Low risk (Primary care)		Referral rate
	True positive	False Positive	True Negative	False Negative	
FIB-4	42	247	703	8	28.9%
NFS	**40**	**323**	**627**	**10**	**36.3%**
Fibroscan	41	152	798	9	19.3%
ELF	40	95	855	10	13.5%
Fibrotest	43	257	694	6	30.1%
FIB4 plus Fibroscan	38	64	886	12	10.2%
FIB4 plus ELF	37	51	899	13	8.8%
FIB4 plus Fibrotest	39	88	862	11	12.7%
NFS plus Fibroscan	**36**	**76**	**874**	**14**	**11.2%**
NFS plus ELF	**36**	**58**	**892**	**14**	**9.4%**
NFS plus Fibrotest	**38**	**108**	**842**	**12**	**14.6%**

Table 3. Mean total cost per person (in £) over a five-year period of three different two tier non-invasive fibrosis testing strategies, **at 5% and 15% prevalence of advanced fibrosis.**

Test strategy	Scenario 1 (Refer all)	Scenario 2 (NIT)	Scenario 2b (NIT and biopsy)	Scenario 3 (Biopsy all)
5% prevalence of advanced fibrosis				
FIB4 followed by ELF	1,033	894	759	1,603
FIB4 followed by Fibroscan	1,100	963	839	1,603
FIB4 followed by Fibrotest	1,208	1,074	947	1,603
15% prevalence of advanced fibrosis				
FIB4 followed by ELF	**1,378**	**1,248**	**1,350**	**2,147**
FIB4 followed by Fibroscan	**1,444**	**1,318**	**1,304**	**2,147**
FIB4 followed by Fibrotest	**1,579**	**1,456**	**1,408**	**2,147**

Table 4: Net benefit of non-invasive testing strategies and net reduction in biopsies compared to a biopsy all strategy at various threshold probabilities assuming a prevalence of advanced fibrosis of 5%.

Threshold Probability	**Net Benefit**			**Net reduction in biopsies**		
	FIB-4 plus Fibroscan	FIB-4 plus ELF	**FIB-4 plus FibroTest**	FIB-4 plus Fibroscan	FIB-4 plus ELF	**FIB-4 plus FibroTest**
0.05	0.035	0.034	0.034	65.8%	65.2%	65.3%
0.10	0.031	0.031	0.029	77.8%	78.2%	76.3%
0.15	0.027	0.28	0.023	81.8%	82.5%	80.0%
0.20	0.022	0.024	0.017	83.8%	84.7%	81.8%
0.25	0.017	0.020	0.010	85.0%	86.0%	82.9%
0.30	0.011	0.015	0.001	85.8%	86.9%	83.6%

Figure 1: Schematic representation of the three scenarios of referral to secondary care.

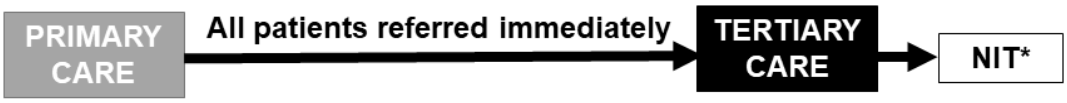
Figure 2: Test outcomes and referral rates of different non-invasive test strategies assuming a prevalence of advanced fibrosis of 5%.

Figure 3: Net benefit decision curves for non-invasive fibrosis test strategies.

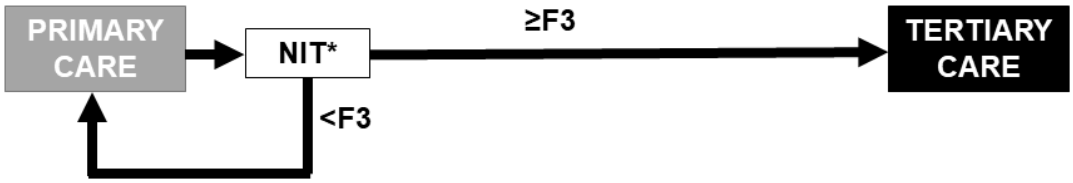
Figure 4: Net reductions in biopsies when using non-invasive fibrosis test strategies. At each threshold probability give on the x-axis, the net reduction in biopsies without missing a diagnosis of advanced fibrosis per 100 patients is given on the y-axis.

Specific author contributions: CC economic modeling, drafting of the manuscript, review for important intellectual content; AM decision curve analysis, drafting of the manuscript; AS review for important intellectual content; DT study concept, review for important intellectual content; WR study concept, review for important intellectual content; MP study concept, review for important intellectual content; LL study concept and design, economic modeling, review for important intellectual content; ET study concept and design, drafting of the manuscript, review for important intellectual content. All authors approved the final version of the manuscript.

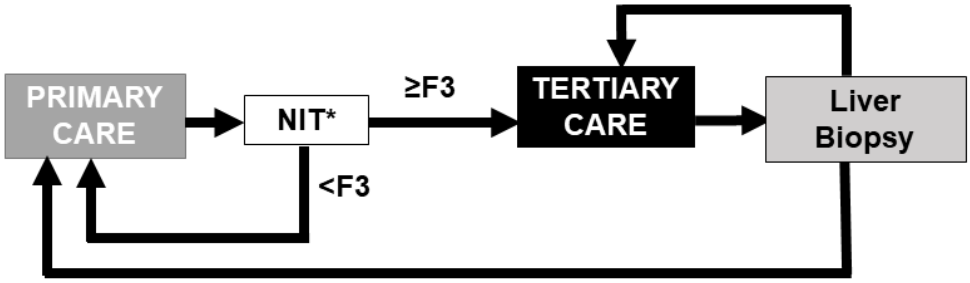
Scenario 1

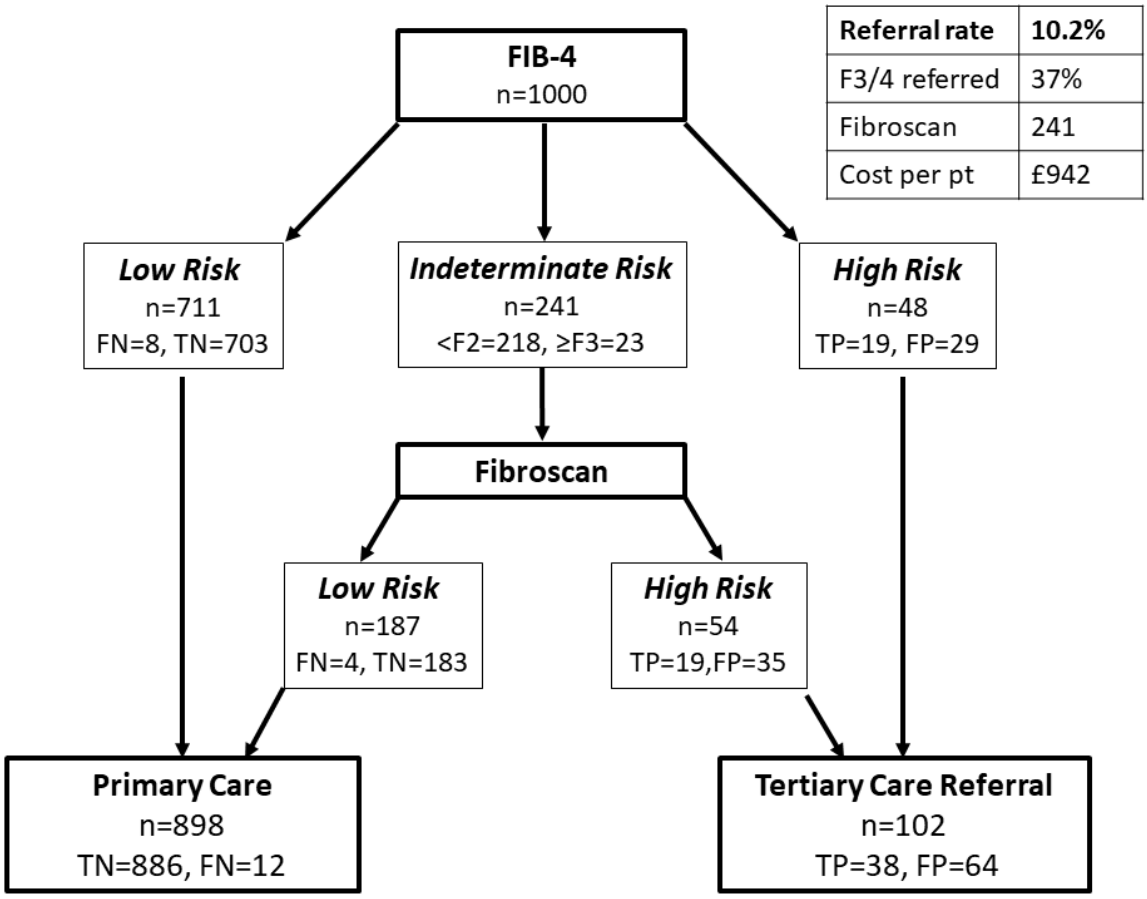


Scenario 2

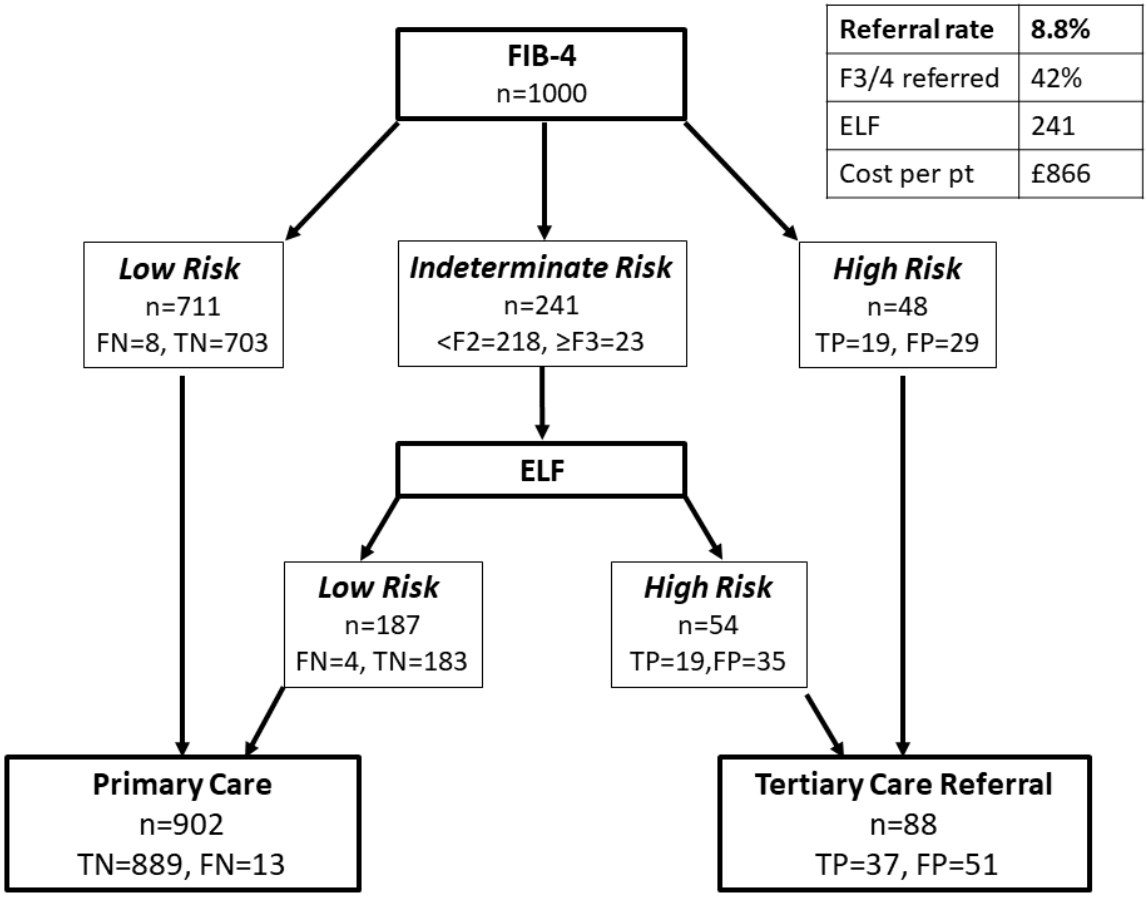


Scenario 2b

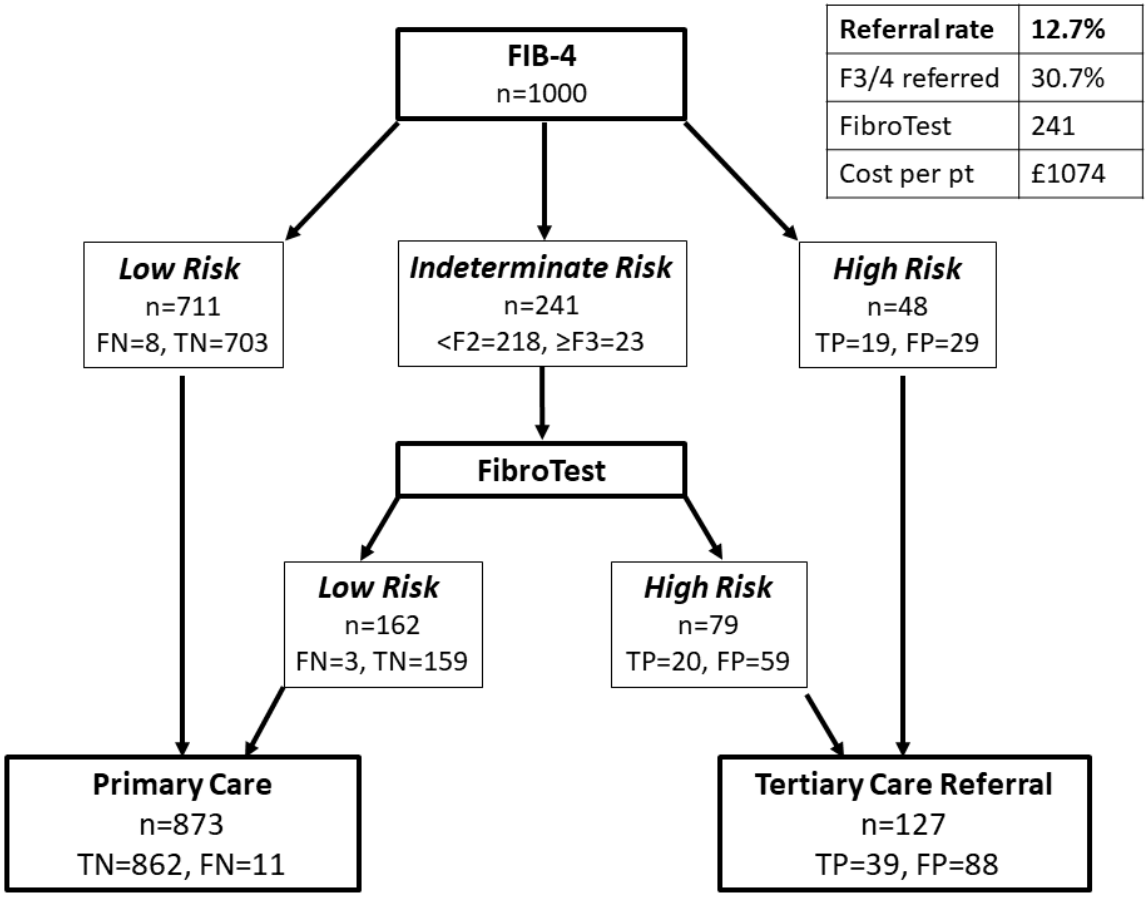




Referral rate	10.2%
F3/4 referred	37%
Fibroscan	241
Cost per pt	£942



Referral rate	8.8%
F3/4 referred	42%
ELF	241
Cost per pt	£866



Referral rate	**12.7%**
F3/4 referred	30.7%
FibroTest	241
Cost per pt	£1074