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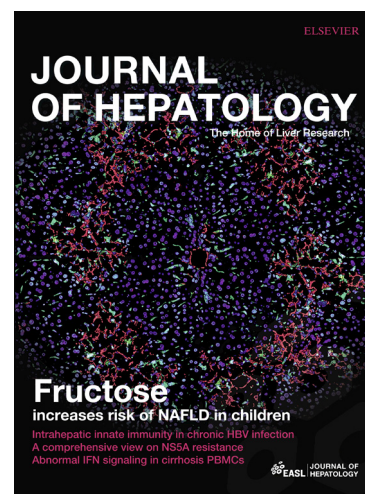
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Prospective evaluation of a primary care referral pathway for patients with non-alcoholic fatty liver disease

Ankur Srivastava[1,2], Ruth Gailer[1,2], Sudeep Tanwar[1,2], Paul Trembling[1,2], Julie Parkes[1,3], Alison Rodger[4,5], Deepak Suri[6], Douglas Thorburn[1,2], Karen Sennett[7], Sarah Morgan[8] , Emmanuel A. Tsochatzis[1,2,*], and William Rosenberg[1,2,*,$]

1. UCL Institute for Liver and Digestive Health, Division of Medicine, UCL Medical School, Rowland Hill Street, London NW3 2PF

2. Sheila Sherlock Liver Centre, Royal Free London NHS Foundation Trust, Pond Street, London NW3 2QG

3. Public Health Sciences and Medical Statistics, University of Southampton, University Hospital Southampton, Tremona Road, Southampton SO16 6YD

4. Department of Public Health, Royal Free London NHS Foundation Trust, Pond Street, London NW3 2QG

5. Infection and Population Health, Institute for Global Health, Faculty of Population Health Sciences, UCL Medical School, Rowland Hill Street, London NW3 2PF.

6. Department of Gastroenterology, The Whittington Hospital NHS Trust, Magdala Avenue, London, N19 5NF

7. Killick Street Practice, Islington Clinical Commissioning Group, 75 Killick Street, King's Cross, London N1 9RH.

8. Hampstead Group Practice, Camden Clinical Commissioning Group, 75 Fleet Street, Hampstead, London NW3 2QU.

* Joint senior authors

$ Corresponding author

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Corresponding author: Professor William Rosenberg, UCL Institute for Liver and Digestive health, Royal Free Hospital and UCL, Rowland Hill Street, London NW3 2PF, email: w.rosenberg@ucl.ac.uk or Dr Emmanuel Tsochatzis email: e.tsochatzis@ucl.ac.uk

List of abbreviations: NAFLD: non-alcoholic fatty liver disease, LFTs: liver function tests, GPs: general practitioners, CCG: clinical commissioning group, PPI: patient and public involvement, C&I: Camden and Islington

Conflict of interests:

WMR is an inventor of the ELF test but receives no related royalties. WMR, JP and AS have received speakers' fees from Siemens Healthineers. The other authors declare no competing interests.

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Abstract

Background & aims: We aimed to develop and evaluate a pathway for management of patients with non-alcoholic fatty liver disease (NAFLD) using blood tests to stratify patients in primary care to improve detection of cases of advanced fibrosis and cirrhosis, and avoid unnecessary referrals to secondary care.

Methods: This was a prospective longitudinal cohort study with before-and-after analysis and comparison to unexposed controls. We used a two-step algorithm combining the use of FIB-4 followed by the ELF test if required.

Results: In total, 3,012 patients were analysed. Use of the pathway detected 5 times more cases of advanced fibrosis **(Kleiner F3)** and cirrhosis (OR=5.18; 95%CI=2.97 to 9.04; p<0.0001). Unnecessary referrals from primary care to secondary care fell by 81% (OR=0.193; 95%CI 0.111 to 0.337; p<0.0001). Three times more cases of cirrhosis were diagnosed (OR=3.14; 95%CI=1.57 to 24; p=0.00011). Although it was used for only 48% of referrals, significant benefits were observed across all referrals from the practices exposed to the pathway. Unnecessary referrals fell by 77% (OR=0.23; 95% CI=0.658 to 0.082; p=0.006) with a 4-fold improvement in detection of cases of advanced fibrosis and cirrhosis (OR=4.32; 95% CI=1.52 to 12.25; p=0.006). Compared to referrals made before introduction of the pathway, unnecessary referrals fell from 79/83 referrals (95.2%) to 107/152 (70.4%) representing an 88% reduction in unnecessary referrals when the pathway was followed (OR=0.12; 95%CI=0.042 to 0.349; p<0.0001).

Conclusions: The use of non-invasive blood tests for liver fibrosis to stratify patients with NAFLD improves the detection of cases of advanced fibrosis and

cirrhosis and reduces unnecessary referrals to secondary care of patients with lesser degrees of liver fibrosis. This strategy improves resource use and benefits patients.

Lay summary: Non-alcoholic fatty liver disease effects up to 30% of the population but only a minority of cases develop liver disease. Our study has shown that established blood tests can be used in primary care to stratify patients with fatty liver disease to reduce unnecessary referrals by 80% and improve the detection of cases of advanced fibrosis 5 fold and cirrhosis 3 fold.

Non-alcoholic fatty liver disease (NAFLD) is the commonest cause of deranged liver blood tests (LFTs) in primary care in Europe and North America [1], and has an estimated prevalence of 25-30% in the adult population[2]. Only a minority of people with NAFLD (5%) develop clinically significant liver disease [2], but the burden is such that NAFLD is predicted to be the leading indication for liver transplantation within a decade[3].

The majority of patients with NAFLD are **followed up** in the community by general practitioners (GPs). Liver fibrosis severity is the key determinant of liver-related outcomes in NAFLD [4-6]. However, identifying patients with significant fibrosis who might benefit from early specialist intervention is challenging. As clinical assessment is a poor discriminator of fibrosis, such patients progress silently until cirrhosis leads to complications. Accurate fibrosis assessment in primary care is limited by a reliance on LFTs, which correlate poorly with fibrosis [7, 8] and limited access to discriminatory fibrosis tests. Thus current management strategies are inefficient in identifying patients for specialist referral. Patients with mild disease are often referred for specialist review when the appropriate preventative interventions of lifestyle changes can be delivered effectively in primary care [9, 10]. Conversely, patients with advanced fibrosis or cirrhosis who will benefit from specialist interventions including clinical trials and cirrhosis surveillance often remain undetected until they present with cirrhosis complications including hepatocellular carcinoma. This ineffective management contributes to the poor outcomes associated with liver disease and the increasing trends in NAFLD-related morbidity and mortality.

The evolution of non-invasive liver fibrosis tests has created the opportunity for GPs to use these tests in innovative pathways that permit earlier identification of patients with chronic liver disease and subsequent access to specialist care [11]. An example of this approach is outlined in the recent British Society for Gastroenterology guidance on the management of abnormal LFTs that recommends the use of non-invasive tests to stratify patients at risk of CLD [12].

Whilst there is little evidence supporting the application of non-invasive tests in community settings, with only one study focusing on patients with NAFLD [13], guidelines recommend a two-tier approach to detect the presence of advanced fibrosis in NAFLD using either FIB-4 or NAFLD Fibrosis score, as an inexpensive first screen, in a combined cut-off approach with indeterminate scores retested using more sensitive and specific tests, ELF™ or FibroScan®, that are more costly[14].

Through broad consultation, a care pathway for patients identified with NAFLD in primary care was developed using non-invasive fibrosis assessment (FIB-4 followed by ELF™) to stratify patients to either remain in primary care or to be referred to secondary care. We present a prospective evaluation of the performance of the pathway performed two years after its introduction.

Materials and Methods

Study setting and Design

The Camden and Islington NAFLD Pathway (hereafter the "NAFLD pathway") was developed as a service innovation in conjunction with the primary care Clinical Commissioning Groups (CCG) of the London boroughs of Camden and Islington **(C&I)**, between April 2013 and March 2014 and then introduced into practice. The NAFLD pathway working group met regularly to develop a pathway for the management of patients with NAFLD aiming to identify patients with advanced liver fibrosis (≥**Kleiner** F3), who might benefit from referral to secondary care for specialist hepatology review while identifying and managing patients with lesser degrees of fibrosis in primary care. The composition and aims of the working group including patient and public involvement are described in the Appendix. The pathway evaluation was conducted between March 2014 and May 2016 with the aim of determining the impact of the pathway in reducing unnecessary referrals and increasing the detection and referral of patients with advanced fibrosis. The pathway was introduced into **C&I** CCGs representing two of the 25 CCGs making referrals to the liver specialist services at The Royal Free London NHS Foundation Trust, The Whittington Hospital NHS Trust and University College London Hospitals NHS Foundation Trust, accounting for 43% of the referrals in 2012-13. All practices within the two CCGs adopted the pathway but individual GPs within C&I were at liberty to follow it or to use Standard Care for each referral. The evaluation was conducted as a longitudinal study in which C&I

represented the CCGs exposed to the pathway and the remaining 23 CCGs represented the control CCGs.

The Camden and Islington NAFLD Pathway

All subjects aged 18 and over attending their GP with a new or established diagnosis of NAFLD were eligible for entry. For the pathway purposes, NAFLD was diagnosed in patients with steatosis on ultrasound, negative screens for other causes of liver disease and no alcohol excess (defined as >21 units of alcohol/week in males, >14 units/week in females).

The pathway consisted of a two-step non-invasive test assessment, starting with the calculation of the FIB-4 score (Figure 1). Patients with FIB-4<1.30 were deemed to be at low risk of advanced fibrosis (<F3) and remained in primary care [15]. Primary care management consisted of treatment of cardiovascular risks and diabetes, annual LFTs, and re-assessment of the risk of advanced fibrosis after 3-5 years. Patients with FIB-4>3.25 were deemed to be at high risk of advanced fibrosis and were recommended for referral to secondary care for specialist assessment. Patients with indeterminate FIB-4 values (≥1.30 and <3.25) had second tier testing with an ELF™ test. Patients with ELF™ scores <9.5 were recommended to remain in primary care while those with an ELF™ score ≥9.5 were recommended for referral to secondary care [16, 17].

Evaluation of Standard Care 2012-2013 prior to pathway introduction:
A retrospective audit of referrals to secondary care by GPs was undertaken between 01/03/2012 and 28//02/2013 to determine the referrers' ability to

identify patients with advanced fibrosis using Standard Care. The case records of all patients assigned a Read Code and referred with a diagnosis of NAFLD were reviewed by hepatologists in the receiving hospital and evaluated for evidence of advanced fibrosis/cirrhosis (≥F3) based on a composite of history, physical examination, blood tests, imaging, FibroScan®, and liver histology when available. FIB-4 scores were calculated and patients with FIB-4<1.30 were deemed to have no evidence of liver fibrosis and thus referred inappropriately. Referrals originating from primary care practices within the C&I CCGs were analysed separately from those referred from other CCGs.

Pathway evaluation:

Following introduction of the NAFLD pathway, data were collected on the outcomes of NAFLD referrals for patients seen at the secondary care sites. The CCG of the referral origin and use of the NAFLD pathway or Standard Care were recorded. The primary care electronic patient record systems (EMISWeb, Egton Medical Information Systems) were interrogated centrally to obtain data on NAFLD diagnosis and use of the pathway to stratify patients for referral using READ codes in primary care. Secondary care electronic medical records were interrogated to extract data related to patient demographics, secondary care management, fibrosis staging and clinical events.

The diagnostic performance of the NAFLD pathway in detecting cases of advanced fibrosis was assessed against a reference standard composite clinical evaluation performed by expert hepatologists blind to the use of the

NAFLD pathway, as described above. All decisions were reviewed by the study team (AS and WMR) and any differences of opinion between the experts and the study team (<10% of cases) were resolved through discussion.

Secondary care evaluation of the patients consisted of more analyses and in most cases a Fibroscan independently of the use of the pathway. A subset of 35/152 referrals from C&I deemed to have advanced fibrosis underwent liver biopsy following clinical assessment. Biopsies were staged for fibrosis by a single histopathologist who was blinded to use of the pathway (Supplementary Table 1).

The distribution of FIB-4 scores in patients assessed by C&I GPs before and after introduction of the pathway was compared to look for evidence of bias in patient selection.

Outcomes

The primary outcome was the reduction in the proportion of patients with NAFLD referred to secondary care who did not have evidence of advanced fibrosis based on clinical evaluation and were thus deemed to have been referred unnecessarily.

Secondary outcomes included:

- The number of cases and proportion of those referred who were deemed to have advanced fibrosis or cirrhosis after assessment by a liver specialist (true positive rate).

- Proportion of patients diagnosed with NAFLD avoiding referral after primary care stratification.

- Number of patients coded for NAFLD by GP before and after introduction of the pathway.

Sensitivity analyses were conducted to determine the impact of using age-specific cut-offs for FIB-4 to triage patients [18]. The impact of using alternative ELF™ cut-offs for detection of advanced fibrosis was investigated including the manufacturer's recommendation (ELF™=9.8) and the threshold recommended in recent NICE guidance on NAFLD (ELF™=10.51)[19].

In order to determine the effectiveness of the pathway compared to Standard Care, the outcomes of patients referred using the NAFLD pathway were compared to those of patients referred from C&I prior to introduction of the pathway; and to those of patients referred using Standard Care from C&I and from other CCGs during the evaluation period following introduction of the pathway.

In order to determine the effectiveness of the introduction of the pathway to all general practices across the two CCGs of C&I, outcomes for all patients referred from C&I, irrespective of the use of the NAFLD pathway, were compared to those of patients referred from all other CCGs where the pathway was not introduced during the evaluation period.

Statistical Analyses

Statistical analyses were performed using SPSS (version 22, SPSS Inc., Chicago, IL, USA). The odds ratios for differences in outcomes for patients managed in accordance with the pathway and those managed using Standard Care were calculated, along with 95% confidence intervals and chi-square tests for statistical significance using Medcalc statistical software (MedCalc Software 2018).

Ethical Approval:

The Royal Free London NHS Foundation Trust Research and Development Department judged this study to be an evaluation of a service improvement innovation, therefore this was registered for audit **(EDGE ID:122031)** but not subject to review by an independent ethics committee and individual patient consent was not sought. All activities were performed in accordance with the guidelines of the Helsinki Declaration.

RESULTS

Participants:

Between 01/03/2014 and 31/05/2016 in C&I CCGs, 3,012 patients were coded as having NAFLD, with an equal distribution in the numbers entered into the NAFLD pathway and Standard Care (Table 1). Seventy-two per cent of eligible practices (52/72) used the NAFLD pathway to stratify a proportion of their patients. Patients entered into the NAFLD pathway compared to Standard Care were older (54.4 years vs. 51.5, P<0.001), had a higher prevalence of treated type 2 diabetes (27.6% vs. 21.0%, P<0.001) and hypertension (41.7% vs. 33.0%, P<0.001), and less dyslipidaemia (13.5% vs. 14.6%, P<0.001). There were no significant differences in Q-Risk2 score, HbA1c, transaminases, platelet counts or HDL. The distribution of calculated FIB-4 scores in 695 cases for which the data were available was identical between the patients managed using the NAFLD pathway and those managed using Standard Care <1.30: 513/695 (73.8%); 1.30-3.25: 162/695 (23.3%); >3.25: 20/695 (2.9%).

Stratification of NAFLD patients in primary care using the NAFLD Pathway

Between 2012-13 and 2014-16 the number of patients assigned READ codes in the electronic patient records per annum by GPs in C&I increased from 601/year to 1,506/year, representing a 2.5-fold increase. The number of cases of NAFLD referred from C&I GPs nearly doubled from 83 in 2012-13 to 329 in 2014-16 (164.5/year). However, taking into account the increased coding, the

proportion of NAFLD coded patients referred to secondary care from all C&I GPs fell from 13.8%(**83/601)** to 10.9%(**165/1506).**

Comparison of the distribution of FIB-4 scores of patients referred for NAFLD by C&I GPs before and after introduction of the NAFLD pathway revealed no evidence of bias in patient selection (Supplementary Table 2).

Over two years, 1,452 patients were risk-stratified for the presence of advanced fibrosis using FIB-4 (Figure 2). FIB-4 score <1.30 was calculated in 1,022 patients (71.3%), whilst 43 patients (3.0%) had FIB-4 >3.25. The remaining 387 patients had an indeterminate FIB-4 score (1.30-3.25) and proceeded to an ELF test. Of these, 155 (40.0%) had ELF<9.5, and 232 (60.0%) had ELF>9.5. In total, 1,177 patients were stratified as being at low risk of advanced fibrosis (81.1%) and remained in the primary care setting. The remaining 275 patients (18.9%) were recommended for referral to a specialist for further investigation. The GPs referred 152 of these 275 patients (55.3%) for specialist investigation within the follow up period (Figure 3). **To interrogate the reasons for non-referral, 3 surgeries were audited including 32 of the non-referrals. In this sub-group, reasons for non-referral included: patient already under the care of a hepatologist (n=4), inappropriate for pathway due to alcohol excess (n=2), comorbidity precluding need for specialist review (n=1), continued monitoring in primary care (n=3) awaiting outpatient appointment at time of evaluation (n=2), and lost to follow up (n=2). Reasons were not recorded for 18 patients.** Process evaluation revealed that 37/152 (24.3%) referrals had normal LFT's, and therefore should not have been on the pathway. Of the patients referred to secondary care using the NAFLD pathway, hepatologists

judged that 29.6% had advanced fibrosis and 14.5% had cirrhosis compared to 4.8% and 3.6% respectively prior to introduction of the NAFLD pathway. **Advanced fibrosis or cirrhosis was identified by liver biopsy (n=14, 31.1%), Fibroscan (n=25, 55.6%) or radiological features of cirrhosis (n=6, 13.3%). Of the 45 patients with advanced fibrosis or cirrhosis, 7 patients were referred due to FIB-4 alone (of which 6 were cirrhotic) and 38 due to the combination of FIB-4 and ELF.**

Referrals made using the NAFLD Pathway compared to Standard Care during the evaluation period

Comparison was made for referrals from C&I GPs using the pathway to GPs in C&I using Standard Care; and to GPs using Standard Care in other CCGs where the pathway had not been discussed or introduced (tables 2 and 3). The NAFLD pathway was 5 times better at selecting cases of advanced fibrosis and cirrhosis than Standard Care. When compared to Standard Care referrals from C&I, use of the pathway improved detection of advanced fibrosis and cirrhosis 4.9-fold (OR=4.90; 95%CI=2.56-9.36; $p<0.0001$) and when compared to referrals made by GPs outside C&I using Standard Care the pathway improved detection 5.2-fold (OR=5.18; 95%CI=2.97-9.04; $p<0.0001$). This equates to an 81% reduction in unnecessary referrals from primary care (OR=0.193; 95%CI=0.111-0.337; $p<0.0001$) when the pathway was used.

Hepatologists diagnosed more cases of cirrhosis amongst patients referred using the NAFLD pathway compared to those referred by C&I GPs using

Standard Care (22/152 (14.5%) compared to 10/177 (5.6%)). This equates to nearly a 3-fold improvement in the detection of cases of cirrhosis (OR=2.83; 95%CI=1.29-6.18; p=0.009). The number of referrals required to detect one case of advanced fibrosis was 3.4 using the pathway compared to 12.6 using Standard Care.

Comparison of the NAFLD pathway with Standard Care provided by other CCGs during the evaluation period revealed similar results to those observed when comparing the pathway and Standard Care used by GPs within C&I (see Table 3 and Supplementary Data).

Referrals made from Camden and Islington Before and After Introduction of the NAFLD Pathway

Due to the increased awareness of NAFLD in 2014-16 compared to 2012-13, rates of referral to secondary care were analysed proportionate to the number of contemporaneously coded NAFLD cases, rather than comparing the absolute numbers of cases referred and detected per year.

Prior to the pathway introduction in one year 79/83 (95.2%) referrals made to secondary care were deemed unnecessary. Following introduction of the NAFLD pathway over a period of 2 years, the number of unnecessary referrals fell to 107/152 (70.4%) representing an 88% reduction when the pathway was followed (OR=0.12; 95%CI=0.042-0.349; p<0.0001) (Tables 2,3). The improvement in selection of cases of advanced fibrosis led to an increase in the number of cases of cirrhosis detected from 3/83 (3.6%) to

22/152 (14.5%), a 74% improvement (OR=0.259; 95%CI=0.075-0.892; p=0.0323) representing 8 additional cases of cirrhosis per year.

There were no statistically significant differences in the outcomes for patients managed using Standard Care before or after introduction of the pathway suggesting that there was no Hawthorne or bystander effect [20] from diffusion of the benefits of the pathway to patients managed using Standard Care.

The impact of using age-adjusted FIB-4 thresholds

Subsequent to the design and implementation of the NAFLD pathway the influence of age on FIB-4 was investigated, leading to a recommendation to adjust the threshold of FIB-4 score in people aged over 65[18]. While adopting this higher threshold would have reduced the number of unnecessary referrals to secondary care by 29 from 122 to 93, (23% reduction), this would result in the loss of 12 cases with advanced fibrosis of which 4 had cirrhosis (Table 2).

Modelling of the impact of other ELF™ Thresholds

The effect of using the ELF threshold proposed by NICE (10.51) [19] and the manufacturers of ELF (9.8) [21] rather than the threshold selected by the NAFLD pathway working group was investigated in the referral population (Table 4). Employing a threshold of 9.8 would have avoided 11 (7.2%) unnecessary referrals but with a concomitant loss of 3 (6.7%) cases of advanced fibrosis. Use of an ELF™ threshold of 10.51 would reduce the number of inappropriate referrals by 34 (22%), at a cost of missing 10 cases

of advanced fibrosis (22%) comprising 7 cases F3 fibrosis and 3 cases of cirrhosis.

Discussion

In this study, we report the results of a prospective, pragmatic, real world pathway to triage patients with NAFLD in primary care using non-invasive fibrosis tests based on their risk of advanced fibrosis. This represents the largest reported primary care cohort of patients with NAFLD to date. The NAFLD pathway reduced the proportion of unnecessary referrals of NAFLD cases while at the same time improved detection of advanced fibrosis and cirrhosis. When the NAFLD pathway was followed, it resulted in a reduction in unnecessary referrals by 81%, a 5-fold increase in the referral of cases of advanced fibrosis and cirrhosis and a 3-fold improvement in the detection of cases of cirrhosis.

Prior to introduction of the pathway, the vast majority of referrals made to secondary care hepatologists could have been managed in primary care. We believe that this pattern of referral is common for NAFLD. Reducing inappropriate referrals represents an opportunity to reduce unnecessary investigations, inconvenience and even harm for patients, pressure on secondary care services and costs for the healthcare system. The NAFLD pathway processed 1,452 patients in 2 years demonstrating the ability to function at scale and manage the rising prevalence of NAFLD.

Compared to other studies in the general population, this is the first that specifically focused in patients with established NAFLD and also provided a comprehensive algorithm for referral to secondary care. Other studies in primary cared screened patients with risk factors for NAFLD or alcohol-related liver disease or general population cohorts

based on specific age cut-offs[22]. Moreover, most such studies have failed to report on the outcome of positive screening results, i.e. on the proportion of patients who truly had advanced fibrosis or cirrhosis.

The NAFLD pathway working group elected to use blood tests to stratify liver fibrosis severity rather than transient elastography that has been used in other successful pathways[23]. Blood tests have the advantages that they are easily incorporated into routine investigations in primary care, require no specialist equipment, training or operation and have a lower diagnostic failure rate compared to elastography-based methods including FibroScan®, which has failure rates between 5-15% of cases, especially in NAFLD[24].

Application of the first stage "simple" **and inexpensive** test, FIB-4, allowed us to prevent referral of 70.3% of cases of NAFLD detected in primary care who did not have evidence of advanced fibrosis. However use of FIB-4 alone only permitted the selection of just 3.0% of cases for referral to secondary care with high probability of cirrhosis. Addition of the "direct biomarker" ELF™ test was only required in 26.7% of cases in the pathway, but the additional use of ELF avoided inappropriate referral for 40.1% of those with indeterminate FIB-4 results. **It is therefore important to underline that over two thirds of patients with NAFLD can be reassured with the use of readily available inexpensive tests.**

Following introduction of the pathway, only 19% of cases of NAFLD diagnosed in primary care were deemed suitable for referral to secondary care. Although not appropriate to compare this proportion with referral practice prior to the pathway introduction, it is noteworthy that using the same

criteria, 93% of patients referred to secondary care prior to the pathway introduction were judged to have been unnecessary.

The beneficial effects of the pathway were restricted to cases that followed the pathway. During the evaluation period, despite evidence of improved awareness of NAFLD, suggested by increased coding of NAFLD, there was no evidence of improvement in case detection or any reduction in unnecessary referrals when Standard Care was followed rather than the pathway. **This demonstrates the value of use of the pathway but also shows that there was no diffusion of the pathway benefits to patients managed with Standard Care or any significant change in "standard" practice due to emerging awareness of NAFLD during the evaluation period.**

Only 48% of referrals from C&I were made using the NAFLD pathway. **Despite this, introduction of the pathway produced significant improvements in referral practice even when referrals made using Standard Care were included in the analysis. This demonstrates the success of the service improvement delivered in the context of routine clinical care despite moderate adoption and suggests that the results are generalizable.** More widespread use of the NAFLD pathway could result in even greater improvements in efficiency and the detection of cases of advanced fibrosis. This might be achieved with more extensive efforts to disseminate the pathway and insistence that the pathway should be adopted for all NAFLD referrals.

Use of an age-adjusted FIB-4 threshold or of a higher ELF™ threshold according to the manufacturer's or the NICE recommendation would have improved the positive predictive value of the NAFLD pathway for detection of advanced fibrosis at the expense of increased number of false negative cases. **We believe that the use of such thresholds is not justified in this context as the reduction in referral numbers carries significant risks of missing cases that would benefit from specialist care and would be difficult to implement in primary care.** Individual healthcare commissioners may decide to prioritize the detection of advanced fibrosis and long-term cost effectiveness over shorter term cost savings associated with avoiding referral of patients with lesser degrees of fibrosis.

Prior to introduction of the NAFLD pathway, funders expressed concern that the pathway might lead to a marked increase in referrals to secondary care leading to greater costs. Despite an increase in the diagnosis of NAFLD between 2012-2016 denoted by the increase in the coding of patients for NAFLD, use of the pathway resulted in a 3% reduction in the proportion of NAFLD cases that were referred to secondary care per year whether or not the pathway was followed and only a modest increase in the number of patients referred.

The strengths of this study **include the prospective collection of real world data, the size of the cohort, which is the largest primary UK cohort with regards to NAFLD,** and the engagement of appropriate stakeholders in the pathway design.

The limitations mostly stem from the nature of the implementation design, which was designed to evaluate a health service innovation. It was not possible to conduct a randomized controlled trial because of the commitment to adopt the pathway once it was discussed with GPs and public health clinicians who formed the opinion that there was sufficient evidence to implement the pathway without a trial. This view was subsequently endorsed by NICE in the NAFLD Guidance[24].

The NAFLD pathway evaluation lacked a hard outcome measure of liver fibrosis and rather used the composite clinical judgement of an expert clinician blinded to the pathway use. **The secondary care evaluation of the included patients thus reflects real world practice, with an inevitable degree of selection bias in the patients undergoing liver biopsy.**

Similarly the lack of formal evaluation of the prevalence of fibrosis amongst patients allocated to remain in primary care prevented assessment of the "false negative" rate for the pathway allocation. However longer term follow-up for clinical outcomes and more detailed health economic analyses will reveal the clinical impact of stratification and the true cost effectiveness of the pathway. Patient and service provider acceptance is being gathered and will be reported in due course.

Conclusions

The Camden and Islington NAFLD pathway improved the selection of patients with advanced fibrosis and cirrhosis for referral to secondary care, reducing unnecessary referrals. This in turn delivers improvements in the detection of serious liver damage, better use of healthcare resources and immediate cost

savings. The reduction in referrals to secondary care reduces strain on services that are confronting a rising prevalence of obesity and NAFLD as well as benefitting patients' experiences by avoiding unnecessary clinic appointments and investigations. This is the first study to incorporate the BSG guidance on the management of NAFLD and validates the recommendation to use FIB-4 and ELF™ for two-stage stratification. The NAFLD pathway is highly generalizable, as GPs will have access to both FIB-4 and ELF tests through most biochemistry laboratories.

It remains to be seen if the use of the NAFLD pathway delivers benefits in terms of a reduction in the incidence and complications of NAFLD cirrhosis.

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Table 1: Patient demographics

| | Standard Care | Pathway Patients | p value | Camden and Islington Pathway Split by FIB4 | | | |
				FIB-4 <1.30	FIB-4 1.30-3.25	FIB-4 >3.25	P value (<1.30 vs. >1.30)
	n=1560	*n=1452*		*1022 (71.3%)*	*387 (25.7%)*	*43 (3.0%)*	
FIB-4 range	-	0.20 – 15.61		0.20-1.29	1.30-3.24	3.30-15.6	-
Age, years	51.5±14.1	54.4±13.7	<0.001	50.5±12.8	63.4±11.2	64.2±11.9	<0.001
Male, n(%)	570 (50.5%)	788 (54.3%)	N.S.	560 (54.7%)	204 (71.1%)	24 (55.8%)	N.S.
BMI (kg/m^2) mean±S.D. (n)	30.5 ± 7.1 (1082)	30.4 ± 5.9 (1238)	N.S.	30.4 ± 5.6	30.7 ± 6.3	27.3 ± 5.7	N.S.
T2DM, n(%)	237/1126 (21.0%)	344/1245 (27.63)	<0.001	190/846 (22.5%)	141/364 (38.7%)	13/35 (37.1%)	<0.001
HBA1c, mmol/mol (mean±S.D)	4212.8 (585)	42.5±13.35 (1059)	N.S.	42.3±13.6 (769)	43.4±13.4 (267)	41.4±15.2 (23)	N.S.
Hypertension, n(%)	371/ 1124 (33.0%)	521/1248 (41.7%)	<0.001	266/ 849 (31.3%)	234/364 (64.2%)	21/35 (60.0%)	<0.001
Hyperlipidaemia, n(%)	95/650 (14.6%)	168/1248 (13.5%)	<0.001	96/ 849 (11.3%)	64/364 (7.5%)	8/35 (22.8%)	<0.001
Total Cholesterol, mmol/L (mean±S.D)	4.9 ± 1.1 (602)	4.8 ± 1.1 (1084)	0.03	4.8±1.1 (792)	4.6±1.2 (267)	4.8±1.1 (25)	0.02
HDL, mmol/L	1.3 ± 0.4	1.3 ± 0.4	N.S.	1.3±0.4	1.4±0.4	1.3±0.4	0.006

(mean±S.D)	(602)	(1084)		(792)	(267)	(25)	
IHD, n(%)	49/1127 (3.9%)	84/1248 (6.7%)	<0.001	30/849 (3.5%)	48/364 (5.6%)	6/35 (17.1%)	N.S.
Q-risk,% (n)	12.1±10.7 (501)	13.6±11.3 (900)	N.S.	11.9±10.7 (670)	18.6±12.1 (211)	16.1±9.9 (19)	<0.001
ALT, IU/L (mean±S.D)	43.0±36.5 (1096)	45.1±36.5 (1254)	N.S.	45.3±29.5	42.8±27.4	59.5±39.2	N.S.
AST, IU/L (mean±S.D)	33.7±22.1 (704)	33.7±22.6 (1206)	N.S.	29.4±17.3	37.8±23.9	70.2±52.1	<0.001
Bilirubin, mmol/L (mean±S.D)	8.9±5.9 (1094)	8.9±5.7 (1250)	N.S.	8.6±5.2	9.2±5.1	14.2±13.3	0.02
Albumin, g/L (mean±S.D)	45.3±5.9 (1101)	45.3±3.1 (1249)	N.S.	45.7±2.7	44.8±3.6	42.4±6.4	<0.001
Ferritin, ng/ml (mean±S.D)	190.1±231.6 (436)	190.21±227.5 (753)	N.S.	172.1±186.6	202.8±220.3	468.2±612.9	0.001
INR (mean±S.D)	1.1±0.5 (245)	1.2±0.6 (266)	N.S.	1.1±0.48	1.3±0.7	1.3±0.5	N.S.
Platelets, 10^9/L (mean±S.D)	260.4±70.1 (1092)	255.1±65.8 (1254)	N.S.	271.4 ± 61.5	226.4 ± 56.6	159.0 ± 65.8	<0.001

Abbreviations: BMI: Body Mass Index, T2DM: type II diabetes mellitus, HDL: high density lipoprotein, SD: standard deviation, INR: international normalized ratio

Table 2: Clinical estimates of liver fibrosis for patients diagnosed with NAFLD before and after introduction of the Camden and Islington NAFLD Pathway

	2012-2013			2014-2016						Age adjusted FIB-4
	C&I	Other CCGs	All CCG	C&I Path	C&I STANDARD CARE	All C&I	Other CCG STANDARD CARE	All STANDARD CARE	All CCGs	C&I Path *FIB-4* *>2.0*
n=	83	109	192	152	177	329	293	470	622	93
<F3	79	100	179	107	163	270	271	434	541	60
<F3 %	*95.2%*	*91.7%*	*93.2%*	*70.4%*	*92.1%*	*82.1%*	*92.5%*	*92.3%*	*87%*	*64.5%*
F3&F4	4	9	13	45	14	59	22	36	81	33
F3&F4%	*4.8%*	*8.3%*	*6.8%*	*29.6%*	*7.9%*	*17.9%*	*7.5%*	*7.7%*	*13%*	*35.5%*
F4	3	4	7	22	10	32	15	25	47	18[2]
F4%	*3.6%*	*3.7%*	*3.6%*	*14.5%*	*5.6%*	*9.7%*	*5.1%*	*5.3%*	*7.5%*	*19.4%*

Abbreviations: C&I: Camden and Islington. CCG: Clinical Commissioning Group

Table 3: Impact of Implementation of The Camden and Islington NAFLD Pathway

Intervention	Comparator	Referrals Avoided			Advanced Fibrosis/Cirrhosis Detection			Cirrhosis Detection		
		Proportion	95%CI	*Significance*	Odds Ratio	95%CI	*Significance*	Odds Ratio	95%CI	*Significance*
C&IP	C&I Before	88%	75-96%	*p=0.0001*	8.30	2.87-24.05	p=0.0001	4.51	1.31-15.56	*p=0.017*
C&IP	C&I STANDARD CARE	80%	61-89%	*p<0.0001*	4.90	2.56-9.36	p<0.0001	2.83	1.29-6.18	*p=0.0092*
C&IP	Other CCGs	81%	66-89%	*p<0.0001*	5.18	2.97-9.04	p<0.0001	3.14	1.57-6.24	*p=0.0011*
All of C&I	Other CCG	77%	35-92%	*p=0.006*	4.32	1.52-12.25	p=0.006	2.87	0.86-9.62	*p=0.0871*

Abbreviations: C&I: Camden and Islington. CCG: Clinical Commissioning Group

Table 4: Impact of using different ELF thresholds for patient stratification

	ELF≥9.8		ELF≥10.51	
Relative to ELF≥9.5	n	%	n	%
Referrals avoided	11	7.2	34	22.4
Missed Cases of F3/F4 fibrosis	3	6.7	10	22.2
Missed Cases of Cirrhosis	0		3	13.6

Figure 1

The Camden & Islington NAFLD Pathway

Raised ALT with no excess ETOH, negative CLD screen +/- fatty liver on Ultrasound

FIB-4

<1.30   1.30-3.25   >3.25

LOW risk of ≥F3 fibrosis   <9.5   ELF   >9.5   HIGH risk of ≥F3 fibrosis

Manage Fatty Liver in Primary Care
- Treat metabolic syndrome
- Weight loss
- Annual LFT's
- Re-assess fibrosis in 3-5 years using pathway

Refer to Hepatologist
- For assessment of CLD
- Consideration of clinical trials
- Consideration of HCC/ variceal surveillance

Figure 2

Primary Care Risk Stratification Using the Camden & Islington NAFLD Pathway
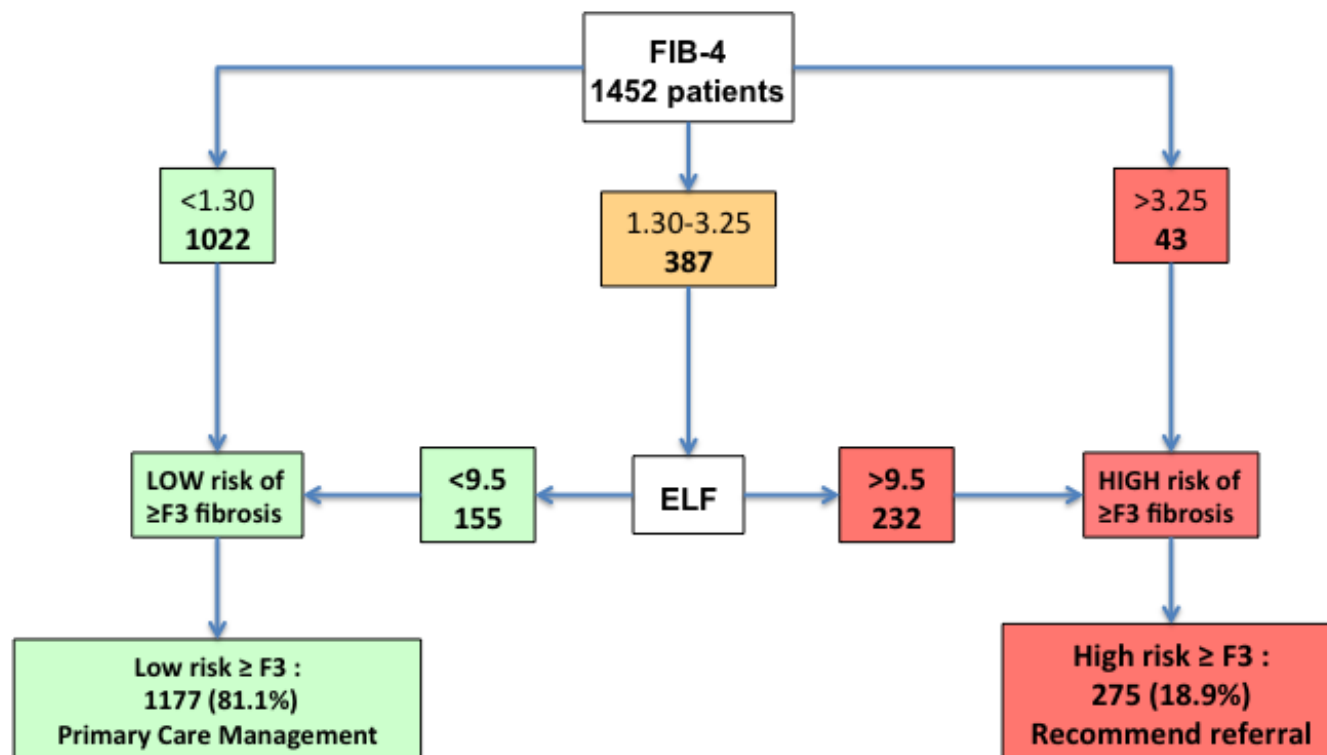2014 - 2016

Figure 3

Liver Specialists' Evaluation of Secondary Care NAFLD Referrals
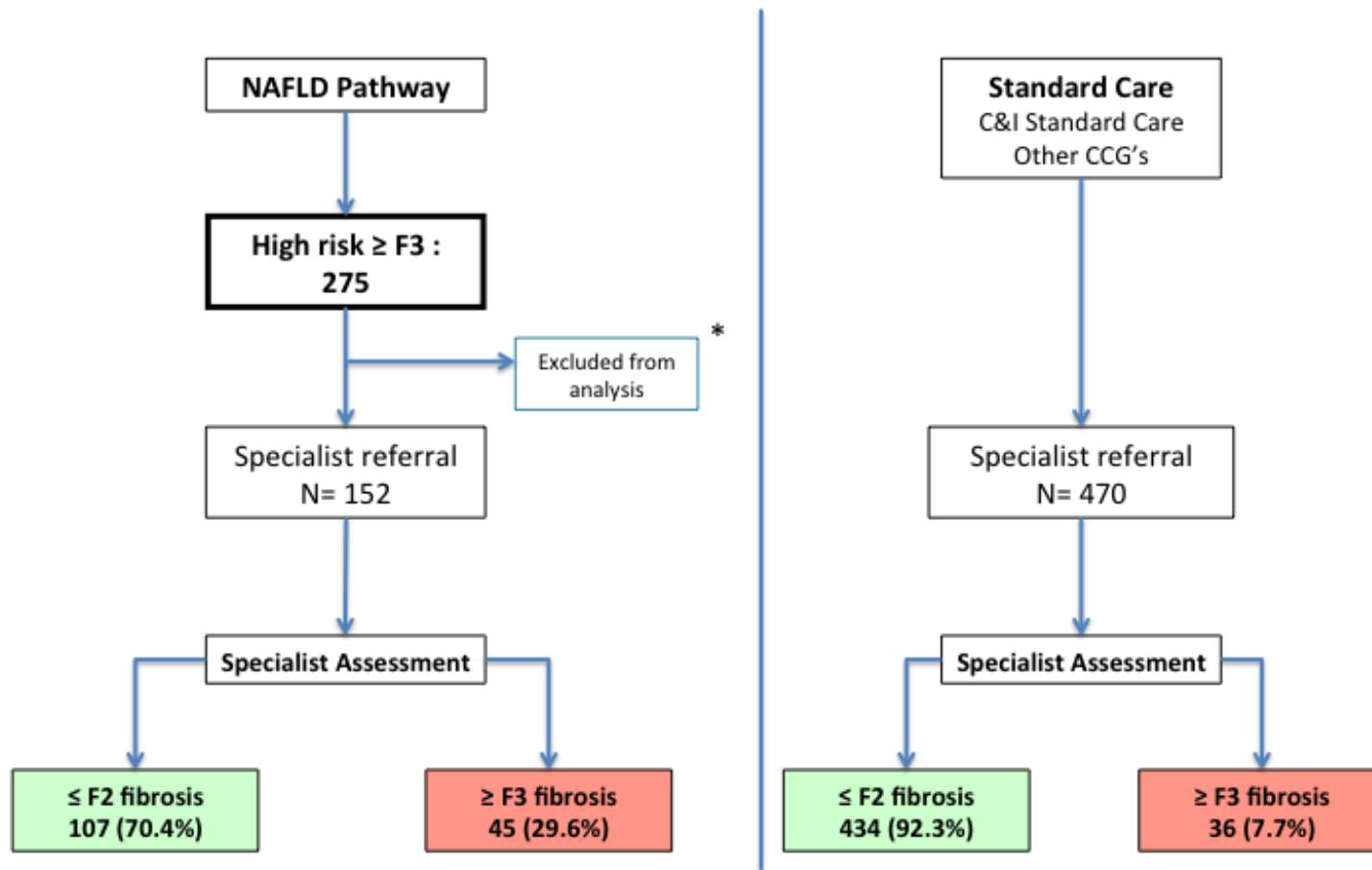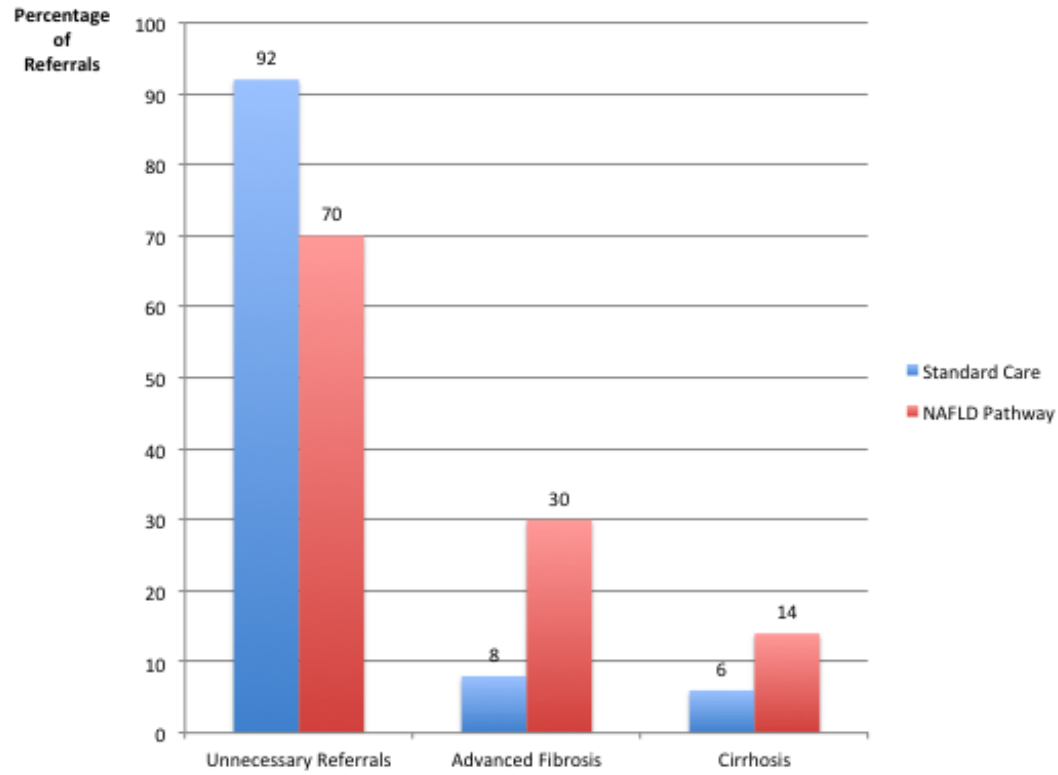2014 - 16

Figure 4

Evaluation of Patients Referred to Secondary Care From Camden and Islington 2014-2016

- Our study has shown that established blood tests can be used in primary care to stratify patients with fatty liver disease

- This two-step pathway (FIB-4 followed by ELF if required) reduced unnecessary referrals by 80% and improved the detection of cases of advanced fibrosis 5-fold and cirrhosis 3-fold.

- In the face of a growing burden of NAFLD established this pathway can be used in primary care to differentiate those patients who might benefit from referral to liver specialists from those who can be managed safely in primary care.

- This should reduce unnecessary referrals while at the same time improving the detection of cirrhosis, improving patient care and healthcare resource use.