THE USE OF NON-INVASIVE FIBROSIS MARKERS IN STRATIFICATION CARE PATHWAYS FOR THE MANAGEMENT OF CHRONIC LIVER DISEASE

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DECLARATION

I, Ankur Srivastava, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature …….

Date ……12th January 2022…….

ABSTRACT

The health, societal and economic consequences of chronic liver disease (CLD) are substantial and increasing exponentially. Cirrhosis is typically detected in the latter stages when prognosis is poor. Timely diagnosis is hindered by reliance on non-discriminatory tests for fibrosis. I explored the role of non-invasive tests (NITs) of liver fibrosis in primary care to promote earlier disease detection.

In this thesis, a systematic review revealed a paucity of published studies evaluating NIT in the community setting.

A national survey demonstrated that UK specialists consider current fibrosis assessment methods to be sub-optimal, and NIT are important in improving disease stratification in primary care.

To benchmark standard care, a one-year retrospective study of GP referrals for non-alcoholic fatty liver disease (NAFLD) established 93% of referrals to have non-significant fibrosis (Brunt ≤ F2) as assessed by liver specialists. Over two-thirds had a low-risk FIB-4 (<1.30) and could have avoided referral, although a quarter of patients with indeterminate FIB-4 (1.30 – 3.25) had significant liver fibrosis suggesting patients in this subgroup warrant further evaluation.

As part of the Camden and Islington liver working group, I developed and evaluated a NAFLD pathway that employs FIB-4 and ELF to identify patients

with advanced fibrosis or cirrhosis (Brunt ≥ F3 fibrosis). The pathway processed nearly 1500 patients over two years, resulting in a reduction in the proportion of total patients referred and an 81% decrease in referral of patients with non-significant fibrosis. The pathway achieved a 5-fold increase in the referral of patients with advanced fibrosis and 3-fold increase in the detection of liver cirrhosis.

To further extrapolate these findings, I developed a probabilistic decision analytical model which tested FIB-4, ELF and fibroscan, either alone or in combination in primary care pathways. Cost consequence analyses revealed all strategies to be clinically effective and cost-saving compared to standard care.

IMPACT STATEMENT

The work presented in this thesis evaluated the use of non-invasive liver fibrosis tests (NIT) in the primary care setting. The burden that chronic liver disease (CLD) imposes on healthcare systems is increasing exponentially. The development and validation of primary care pathways employing NIT to permit the earlier identification of significant liver disease is a key strategy to improve outcomes for patients with CLD.

A retrospective study of GP referrals for patients with non-alcoholic fatty liver disease (NAFLD) revealed over ninety percent of referrals had non-significant fibrosis and could have avoided referral. This strongly suggests that current standard care models, which are employed throughout the world, are ineffective, require adaptation and mandates change in community risk-stratification strategies to promote earlier disease detection and more effective use of specialist referral.

The Camden and Islington multidisciplinary liver working group described in this work provides the framework for other healthcare organizations that wish to adopt a similar model to tackle CLD in their locality. The Camden and Islington NAFLD pathway evaluation tracked over 3000 patients with NAFLD over two years, the largest primary care cohort of its kind. The ‘real-life’ nature of the service evaluation ensures the results are generalisable and highlighted the ability of the pathway to function at scale and manage the rising prevalence of NAFLD. The increase in referrals of patients with advanced fibrosis or

cirrhosis coupled with a reduction in referrals of patients with non-significant fibrosis is desirable and represents enhanced service efficiency. The reduction in proportion of cases referred is topical given over-stretched outpatient clinic capacity. The clinical and cost benefits were further validated by the probabilistic decision analytical model which was developed as part of this work.

The NAFLD pathway has directly benefitted patients by reducing unnecessary referrals and the associated inconvenience and anxiety. Furthermore, by increasing the detection of undiagnosed advanced fibrosis and cirrhosis, this work has increased the possibility to initiate screening and treatment of complications of cirrhosis and potentially reduce morbidity and mortality. These outcomes warrant further evaluation.

The outcomes from this thesis add substantial weight to proposals for services throughout the country and beyond to adapt their pathways and incorporate NIT in line with recently published national and international guidelines, some of which have drawn on my work. I believe the outcomes from the NAFLD pathway directly influenced the 2016 British Society of Gastroenterology guidelines on the management of abnormal liver function tests, whose authors included a member of the Camden and Islington Liver Working Group.

From an academic perspective, the approach employed in this thesis has established a framework to evaluate the role of NIT in primary care for other aetiologies of CLD including excessive alcohol consumption. To date, there

have been two peer review publications resulting from work in this thesis, and several presentations at national and international conferences. The outcomes are likely to be of interest to hepatologists, general practitioners, healthcare commissioners, public health professionals and those involved in the planning of healthcare delivery for patients with chronic liver disease.

DEDICATION

My thesis is dedicated to my wonderful, beautiful and supportive wife Shreya, my two cheeky and adorable boys Aditya and Aarav and my inspirational and loving parents Anil and Madhuri. Special mention should also go to my caring brothers Amit and Arpit and my extended family who have always been by my side. I would not be where I am today without their endless wisdom, support, love, and devotion.

ACKNOWLEDGMENTS

The work presented in this thesis would not be possible without the support, dedication and expertise of many friends and work colleagues during my period of research.

I would like to express my deep gratitude to my primary supervisor Professor William Rosenberg for his supervision and friendship. His continuous guidance and mentorship have always meant I have been well supported during my journey. I will cherish our ad-hoc discussions and research meetings which allowed ideas to flourish and resulted in a body of work that I am proud to present in this thesis. The skills I have learnt have not only been central to my development in academic medicine but have undoubtedly made me a better doctor. Above all, I would like to thank Professor Rosenberg for being a wonderful friend and mentor.

I am indebted to my secondary supervisors Professor Manolis Tsochatzis and Professor Julie Parkes for their support and expertise during this time. Professor Tsochatzis's knowledge and experience of the field of non-invasive liver fibrosis tests was invaluable, whilst Professor Parkes introduction into biostatistics and translational research was irreplaceable.

I am indebted to a number of friends and professionals at UCL, the Royal Free London hospital and beyond that I met during this journey. The partnership with primary care colleagues described in this thesis relied on the multidisciplinary working of an extensive group of individuals including patients

and colleagues from primary care, public health, and commissioning departments. We all embarked on a novel and ambitious project that integrated the primary care and secondary care interface. Our collective efforts, enterprise and expertise made our work a huge success and a desirable model to be replicated elsewhere. The hard work of the data analysts at the commissioning groups needs special mention, as we strived to develop a data search strategy which tested the limitations of the systems involved but now provides a framework for future works.

I am very grateful for the expert guidance and support provided by Associate Professor Simcha Jong, Dr Anna Gola and Dr Elena Pizzo for the health economics component of this thesis.

My studies took me to all corners of the United Kingdom, from Plymouth to Bristol to Birmingham to Newcastle and beyond. I am thankful to all the national experts who gave me their time to contribute to this valuable piece of work.

Finally, I thank my consultant and work colleagues at North Bristol Trust who have been supportive as I finalise my thesis.

RELEVANT PUBLICATIONS AND AWARDS

Peer reviewed publications – related to this thesis

Please refer to Appendix 1

Srivastava A, Gailer R, Morgan S, Sennet K, Warner A, Tanwar S, Trembling P, Hogan B, Parkes J, O'Beirne J, Patch D, Thorburn D, Tsochatzis E, Rosenberg W. Prospective evaluation of a primary care referral pathway for patients with non-alcoholic fatty liver disease. Journal of Hepatology 2019, 71: 371 – 378

Srivastava A, Jong S, Gola A, Gailer R, Morgan S, Sennet K, Fenlon L, Tanwar S, Parkes J, O'Beirne J, Thorburn D, Tsochatzis E, Rosenberg W. Cost-comparison analysis of FIB-4, Enhanced Liver Fibrosis Panel and Fibroscan in the primary care risk stratification of non-alcoholic fatty liver disease. BMC Gastroenterology 2019, 19: 122

Peer reviewed publications – not related to this thesis

Patel P, Connoley D, Rhodes F, **Srivastava A**, Rosenberg W. A review of the clinical utility of the enhanced liver fibrosis test in multiple aetiologies of chronic liver disease. Ann Clin Biochem 2020, 57 (1): 36-43

Hussain A, Patel P, Rhodes F, **Srivastava A**, Patch D, Rosenberg W. Decompensated cirrhosis is the commonest presentation for NAFLD patients undergoing liver transplant assessment. Clin Med 2020, 20 (3): 313-318

Tanwar S, Rhodes F, **Srivastava A**, Trembling P, Rosenberg W. Inflammation and fibrosis in chronic liver diseases including non-alcoholic fatty liver disease and hepatitis C. World J Gastroenterol. 2020, 26 (2): 109-133

Crossan C, Majumdar A, **Srivastava A,** Thorburn D, Rosenberg W, Pinzani M, Longworth L, Tsochatzis E. Referral pathways for patients with NAFLD based on non-invasive fibrosis tests: diagnostic accuracy and cost analysis. Liver International 2019, 39 (11): 2052-2060

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Younossi Z, Brown A, Buti M, Fagiuoli S, Mauss S, Rosenberg W, Serfaty L, **Srivastava A,** Smith N, Stepanova M, Beckerman R. Impact of eradicating hepatitis C virus on the work productivity of chronic hepatitis C (CH-C) patients: an economic model from five European countries. Journal of Viral Hepatitis J Viral Hepat. 2016 Mar;23(3):217-26

Srivastava A, Tanwar S, Nixon G, Sennett K, Morgan S, Rosenbeg W. Seizing the Opportunity: Hepatitis C Treatment has improved – but how do we find those who need it? Viral Hepatitis in Practice 2014; 6 (2) 2-4

Oral presentations

1. **Association for Clinical Biochemistry and Laboratory Medicine National Meeting**

Manchester, June 2018

Non-invasive liver fibrosis tests and their clinical application in the NHS.

2. **EASL International Liver Conference, Parallel Session.**

Amsterdam, April 2017

Primary care sequential use of FIB-4 and the Enhanced Liver fibrosis test to stratify patients with NAFLD doubles cirrhosis detection and reduces referrals of patients with mild disease.

3. **Institute of Biomedical Science Annual Conference**

Birmingham, September 2017

Use of the ELF Test in Primary care to stratify patients with Non-Alcoholic Fatty Liver Disease: The Camden and Islington Pilot Study.

4. **EASL International Liver Conference, Session: Alcohol, NASH and Public health.**

Vienna, April 2015

A one-year retrospective review of new patient attendances at a tertiary hepatology centre highlighting the increasing challenge of NAFLD and the need to develop clinical pathways.

Poster presentations

Ahmed A, **Srivastava A,** Rosenberg W. Decompensated cirrhosis is the commonest presentation for NAFLD patients undergoing liver transplant assessment. Journal of Hepatology 2017 (66) Abstract S596-S597. Poster presentation, European Association for the Study of the Liver International Liver Congress, Amsterdam 2017

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Hogan B, Parisi I, Patch D, Yu D, Dhillon A, Hall A, **Srivastava A**, Trembling P, Tanwar S, Parkes J, Meyer T, Rosenberg W, O'Beirne J. ELF™ and Angiopoietins accurately predict clinically significant portal hypertension. Hepatology 2015, Abstract. Poster presentation, European Association for the Study of the Liver International Liver Congress, Vienna 2015

Srivastava A, Gailer R, Gulati S, Warner A, Morgan S, Sennet K, Suri D, Thorburn D, Tsochatzis E, Rosenberg W. Analysis of new patient attendances for NAFLD at three London hospitals highlights the need to develop clinical risk stratification pathways. Gut 2015 (64) Abstract PWE-085. Poster presentation, British Society of Gastroenterology Annual Conference.

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the increasing challenge of NAFLD and the need to develop clinical pathways. Journal of Hepatology 2015 (62) Abstract S740

Younossi Z, Brown A, Buti M, Fagiuoli S, Mauss S, Rosenberg W, **Srivastava A**, Smith N, Stepanova M. The impact of sustained viral eradication with ledipasvir/sodosbuvir on the work productivity of patients with chronic hepatitis C in five European countries – insights from a work productivity economic model. Journal of Hepatology 2015 (62) Abstract

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LIST OF ABBREVIATIONS

AIH	Autoimmune Hepatitis
ALT	Alanine Aminotransferase
AMA	Antimitochondrial Antibody
APRI	AST: Platelet ratio
ARFI	Acoustic Radiation Force Impulse
ARLD	Alcohol Related Liver Disease
AS	Dr Ankur Srivastava
ASH	Alcoholic Steatohepatitis
AST	Aspartate Aminotransferase
AUDIT	Alcohol Use Disorder Identification Test
BMI	Body Mass Index
CCG	Clinical Commissioning Group
CHB	Chronic Hepatitis B
CHC	Chronic Hepatitis C
CLD	Chronic Liver Disease
CPRD	Clinical Practice Research Datalink
ECM	Extracellular Matrix
ELF	Enhanced Liver Fibrosis
EPR	Electronic Patient Records
ET	Dr Emmanouil Tsochatzis
ETOH	Ethanol (alcohol)
FBG	Fasting Blood Glucose

FDA	Food and Drug Administration
FIB-4	Fibrosis-4 score
FN	False negative
FP	False positive
FT	Fibrotest
GGT	Gamma Glutamyl-Transpeptidase
GP	General Practitioner
HA	Hyaluronic Acid
HCC	Hepatocellular Carcinoma
HELLP	Haemolysis Elevated Liver Low Platelets syndrome
HIV	Human Immunodeficiency Virus
HSC	Hepatic Stellate Cells
IMD	Index of Multiple Deprivation
IQR	Interquartile range
JP	Dr Julie Parkes
LFA	Liver Fibrosis Assessment
LFT	Liver Function Test
LSM	Liver Stiffness Measure
MDT	Multi-Disciplinary Team
MMP	Matrix Metalloproteases
MRE	Magnetic Resonance Elastography
MRR	Mortality Rate Ratio
MRI PDFF	Magnetic Resonance Imaging-estimated Proton Density Fat Friction

NAFLD	Non-Alcoholic Fatty Liver Disease
NASH	Non-alcoholic Steatohepatitis
NFS	NAFLD Fibrosis Score
NIT	Non-Invasive Tests
NILT	Non-Invasive Liver Fibrosis test
NHS	National Health System
NPV	Negative Predictive Value
PIIINP	N-Terminal peptide of type III procollagen
PBC	Primary Biliary Cirrhosis
PHG	Portal Hypertensive Gastropathy
PPV	Positive Predictive Value
PSC	Primary Sclerosing Cholangitis
QALY	Quality Adjusted Life Year
RFL	Royal Free London NHS Foundation Trust
SD	Standard Deviation
STL	Southampton Traffic Light
SVR	Sustained Virological Response
SWE	Shear Wave Elastography
TACE	Trans-Arterial Chemoembolization
T2DM	Type 2 Diabetes
TE	Transient Elastography
TGFβ	Transforming Growth Factor β
TIMP	Tissue Inhibitors of Metalloprotease

TN	True negative
TP	True positive
UCL	University College London
UCLH	University College London Hospital
UK	United Kingdom
US	Ultrasound
USA	United States of America
WMR	Professor William Rosenberg

CHAPTER 1 AIMS AND OBJECTIVES

1.1 Introduction

The burden of chronic liver disease (CLD) is rising in the United Kingdom and worldwide. The health, societal and economic consequences of CLD are substantial and ever-increasing [1-3]. In England and Wales, CLD is one of the 'top five' causes of premature mortality, and the only one to be rising in incidence [4]. With an increasing prevalence of excessive alcohol consumption, diabetes and obesity, all common risk factors for CLD, the burden of chronic liver disease is inevitably going to grow, intensifying pressure on healthcare systems and resources.

Diagnosis of chronic liver disease is typically at the advanced stages of the condition, when treatment options are limited and prognosis is poor [5]. Facilitating earlier detection of patients with advanced liver disease in primary care forms a key component of strategies to improve health outcomes and costs related to CLD [6]. The evolution and development of non-invasive liver fibrosis tests over the last two decades permit the development of novel pathways aimed at detecting patients with advanced liver disease earlier. The use of serum biomarkers and elastography based methods have become increasingly commonplace in hospital settings and form an integral component of liver disease assessment by a specialist.

The use of non-invasive liver fibrosis markers in the primary care setting is less well established. This thesis is structured to explore the utility of non-invasive

tests in primary care pathways of care, with the aim of appraising the existing evidence-base, to benchmark the performance of the current standard care model and to prospectively evaluate a primary care pathway for patients with non-alcoholic fatty liver disease employing non-invasive liver fibrosis tests.

1.2 Aims and objectives

The aims and objectives of this thesis were;

1. To systematically review the current evidence-base for use of non-invasive liver fibrosis tests in community-based pathways of care.
2. To evaluate the current practices of specialist physicians in the United Kingdom with regards to their attitudes to liver fibrosis assessment, their current knowledge and use of non-invasive liver fibrosis tests and use of such tests in designated patient pathways.
3. To assess the performance of “standard care” methods employed in primary care to identify patients with non-alcoholic fatty liver disease (NAFLD) with advanced liver fibrosis or cirrhosis (Brunt ≥F3).
4. To evaluate the performance of a novel primary care pathway employing FIB-4 and ELF to identify patients with NAFLD and advanced liver fibrosis or cirrhosis (Brunt ≥F3).
5. To develop a probabilistic decision analytical model to assess the clinical and cost utility of introducing competing pathways employing non-invasive liver fibrosis markers in primary care to identify patients with NAFLD and advanced liver fibrosis or cirrhosis (Brunt ≥F3).

1.3 Outline of thesis

In this thesis, I describe work performed during my doctoral studies at the University College London.

In Chapter 2, I set the background to this body of work by reviewing the anatomy and function of the liver and describing the pathogenic processes involved in the development of liver fibrosis. I will then discuss the current trends in chronic liver disease and NAFLD before describing the invasive and non-invasive methods available to assess liver fibrosis. Thereafter, I will make a case for change in current standard care by advocating the need to explore the use of non-invasive liver fibrosis markers in primary care pathways.

In Chapter 3, I will present a systematic review of the current literature to identify and appraise existing studies which have evaluated the performance of patient care pathways using liver fibrosis tests in the community setting.

In Chapter 4, I will present data from a national survey of UK specialists to explore current attitudes to liver fibrosis assessment and to review existing pathways of care using non-invasive liver fibrosis tests.

In Chapter 5 and Chapter 6, I will present a study evaluating the performance of a novel primary care pathway using FIB-4 and ELF for patients with NAFLD compared to standard care,

In Chapter 7, I will present a probabilistic decision analytical model assessing the clinical and cost utility of introducing non-invasive test strategies for patients with NAFLD in primary care.

In Chapter 8, I will present the main findings of the thesis with an outline of recommendations for future work.

CHAPTER 2 CHRONIC LIVER DISEASE AND ASSESSMENT OF LIVER DISEASE

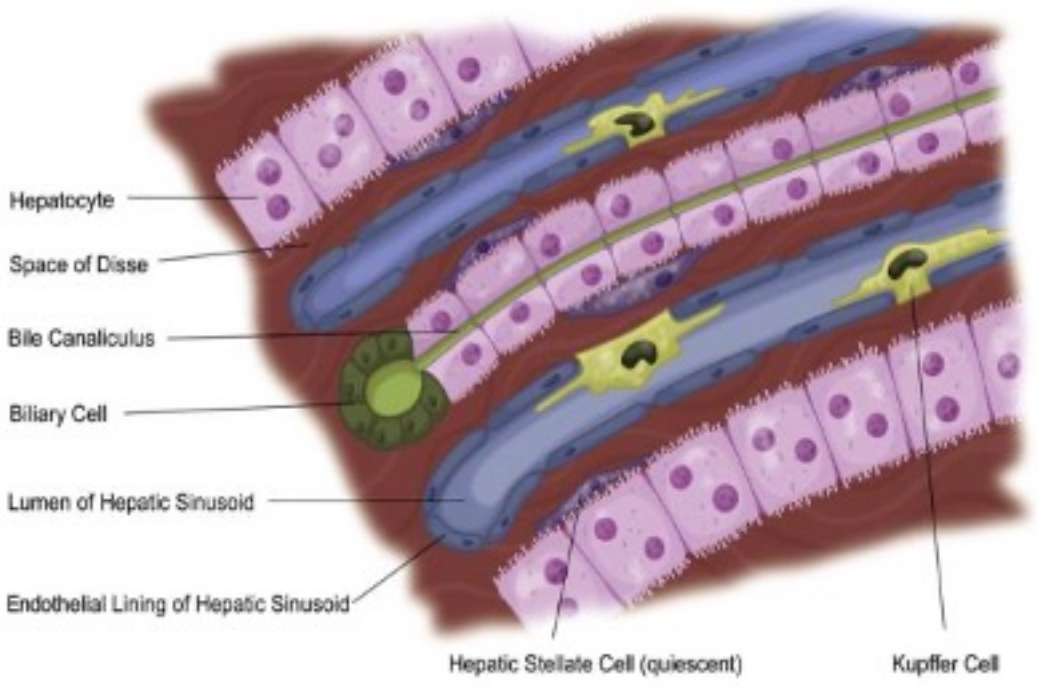
2.1 Structure of the liver

The liver is the largest visceral organ in the human body and is estimated to have a median weight of 1.5 kilograms in healthy individuals [7]. It is located in the upper abdominal cavity, inferior to the diaphragm and adjacent to the stomach. The organ is divided into four lobes; namely the right, left, caudate and quadrate lobes but is subdivided, based on biliary drainage and vascular territories into eight functional sub-segments [8]. The vascular supply to the liver differs to other organs in that the blood is supplied by two afferent vessels, namely the hepatic artery which originates from coeliac trunk and accounts for approximately 25% of oxygen-rich blood supply and the portal vein, which accounts for the remainder. The portal vein transports bloods from the capillary system of the gastrointestinal tract, gallbladder, pancreas and spleen. The blood from the terminal branches of the portal vein and hepatic artery mixes as they enter hepatic sinusoids, which are distensible and lined by highly fenestrated endothelial cells which are circumferentially bordered by hepatocytes (Figure 2.1) [9]. The blood passes at a low pressure through the sinusoidal spaces. The Space of Disse separates the sinusoidal cells and the hepatocytes and acts as a molecular sieve as the passing plasma undergoes ultrafiltration and reabsorption prior to release into the systemic circulation via the hepatic veins and then the inferior vena cava. Within this structure, Kupffer cells and hepatic stellate cells (HSC) are found. Kupffer cells are non-

parenchymal macrophage cells that are found in the hepatic sinusoid and aid in the phagocytosis of potential toxins from the portal and arterial blood supply. Their function includes clearance of endotoxins and exotoxins, and their activation results in the release of reactive oxygen species and multiple pro-inflammatory cytokines. HSC are a mesenchymal cell found in the space of Disse. They have a number of roles including promoting a response to liver injury and wound healing and, in their resting state, are a major storage site in the body for vitamin A [9].

Figure 2.1 Schematic presentation of hepatic sinusoid

Diagram of the organisation of different cell lineages in the liver. Reproduced with permission from Baxter et al [9]



Bile salts are excreted by the liver via biliary canaliculi into bile ducts and travel in the opposite direction to sinusoidal blood flow. The bile ducts converge to

form the common hepatic duct and bile is stored in the gallbladder until it is released via the common bile duct into the duodenum. The primary function of this process is to aid digestion of fats and lipids.

2.2 Function of the liver

The liver has a broad range of functions. The liver is important in the storage of essential nutrients, minerals, vitamins and cholesterol. It has critical homeostatic functions in carbohydrate, lipid and protein metabolism. It is the site of synthesis of cholesterol, triglycerides, glycogen, and albumin. Insulin promotes storage of glucose by synthesis of glycogen in hepatocytes, whilst fatty acids are stored after conversion from digested triglycerides. The liver has a crucial role in digestion. Bile salts including conjugated bilirubin, glutathione, chenodeoxycholic acid, cholic acid and other organic anions are stored in the gallbladder. The presence of fat in the duodenum stimulates cholecystokinin release, which promotes motility of bile in the biliary tree and contraction of the gallbladder propelling bile into the duodenum. This aids fat emulsification and ingestion.

The liver has a central role in the detoxification of both endogenous and exogenous substances. Approximately 20% of the blood flow in each cardiac cycle passes through the liver. The hepatocytes serve to remove toxic substances, predominantly from the portal blood that has passed through the gut. This process can include cleansing the blood of toxic substances including alcohol and paracetamol which are metabolized by the liver into inactive

metabolites. Another example includes the deamination of ammonia to produce urea.

The liver has several other functions including protein synthesis encompassing production of albumin, fibrinogen, pro-thrombin, and complement. The liver also plays a crucial role in the immune defence system.

2.3 Fibrogenesis

2.3.1 Pathophysiology of fibrogenesis

The development of fibrosis can be considered a “wound healing process” and one of ageing in all organs that contributes to natural deterioration and death [10, 11].

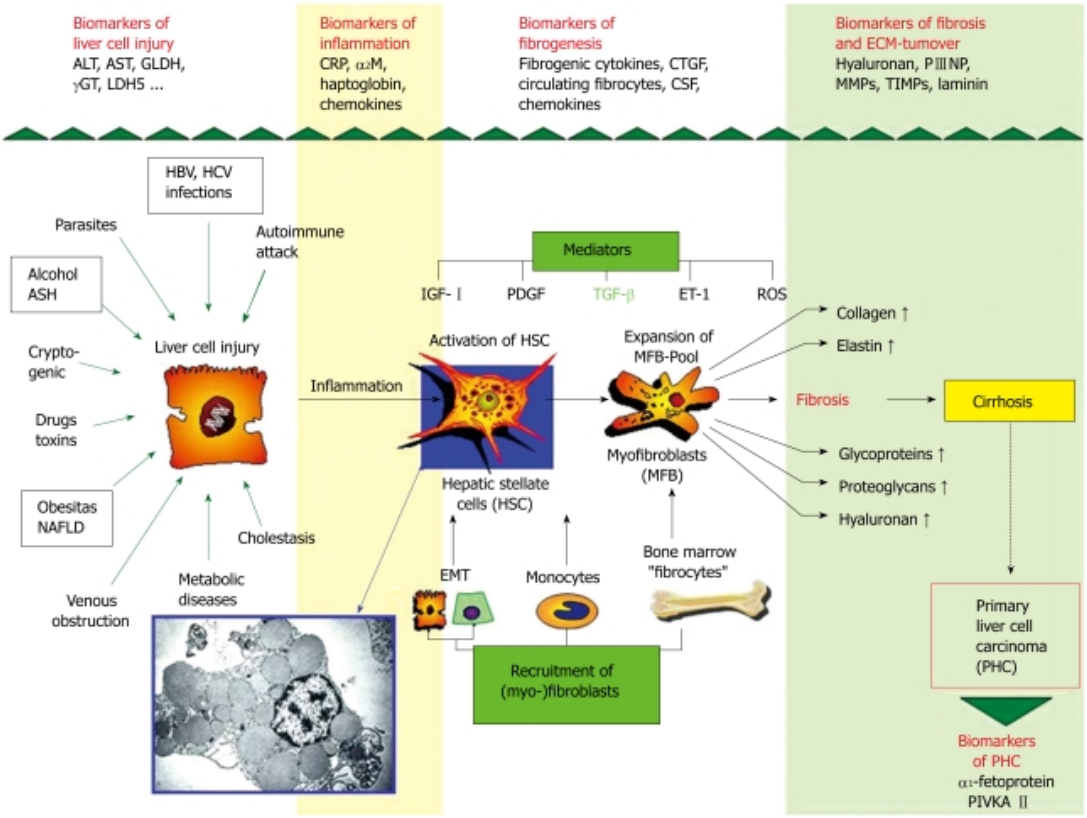
The distortion of the normal liver architecture and replacement with fibrous tissues can result in impaired liver function through disruption of the normal anatomical organization of the liver acinus and if the number of functioning cells drops below a certain threshold. Therefore, liver fibrosis is the key feature in the development of chronic liver disease. Liver fibrosis results from continuous or repetitive injury such as may follow instigation of an inflammatory response triggered by a viral infection. As the liver architecture recovers from the original insult and subsequent inflammatory response, fibrogenesis is central to recovery and the maintenance of hepatic integrity. Fibrogenesis is a dynamic process involving the deposition, degradation and remodelling of liver matrix. The key hallmark of fibrogenesis is the deposition

of extracellular matrix (ECM) resulting in the molecular and histological changes of various molecules including collagen (types I and III), structural glycoproteins, proteoglycans and hyaluronan [12]. In the normal liver, this occurs in a balanced fashion resulting in a stable extracellular matrix equilibrium [13, 14]. However, chronic and sustained inflammation can lead to structural change and progressive fibrosis, which can eventually lead to liver cirrhosis. The insult to the liver may be caused by viruses, alcohol, steatosis, autoimmune diseases or biliary injury. Regardless of the injury, the pathway of inflammation and fibrosis is multifaceted but very similar (Figure 2.2).

Figure 2.2 Pathogenic mechanisms of fibrogenesis.

Summary of the pathogenetic mechanisms of fibrosis development (fibrogenesis) in the liver. After an injury or insult, activated hepatic stellate cells (HSC) promote extracellular matrix deposition. The insert shows an electron micrograph of hepatic stellate cells containing numerous lipid droplets

Reproduced with permission from Gressner et al (2009) [12]



In response to an insult or toxin, the activation of the hepatic stellate cell is a key step in the development of fibrosis. Quiescent HSC are a major store of vitamin A but on activation they transform into myofibroblasts in response to interactions between injured hepatocytes, activated Kupffer cells, and cytokines such as Transforming Growth Factor β (TGFβ) [13]. The activated HSCs migrate and aggregate to the site of injury. Their myofibroblast functions

promote the deposition of ECM which disrupts the architecture and damages the sinusoidal structure. This leads to a disrupted barrier between hepatocytes and the sinusoidal blood flow and therefore impaired function and resistance to sinusoidal blood flow. This is a dynamic process whereby there are inhibitors of fibrogenesis including matrix metalloproteinases (MMP). These are proteolytic molecules and have the ability to degrade the extracellular matrix. The MMPs are inhibited by Tissue Inhibitors of Metalloproteinases (TIMPs). The deposition of matrix is therefore partly a balance between TIMPs and activated metalloproteinases. A major determinant of progressive fibrosis is the inability to degrade the fibril-forming scar matrix, or a relative excess of fibrogenesis relative to fibrinolysis. The removal of the insult can often lead to a reversal of this process [15, 16]. Whilst the fibrogenesis pathway is similar irrespective of the injury, disease specific mechanisms do exist with different factors triggering HSC activation. In non-alcoholic steatohepatitis (NASH) and alcoholic steatohepatitis (ASH), adipokines mediate fibrogenesis and many hepatic manifestations of obesity [17], whilst leptin, a circulating adipogenic hormone, promotes both HSC related fibrogenesis and TIMP-1 expression [18]. Insulin resistance is likely to have a pivotal role in hepatic fibrosis, in particular when associated with hepatic steatosis [19]. Ethanol subjects the liver to oxidative stress, which promotes hepatocyte necrosis and apoptosis. Individuals who drink alcohol to excess are often deficient in antioxidants including glutathione and vitamin E and therefore are prone to fibrosis development, where collagen is deposited in a typical perivenular and

pericellular pattern. In hepatitis caused by some viruses, the direct cytopathic effect of the virus on hepatocytes results in damage which is attenuated by a cytokine driven host immune response to viral proteins expressed by the infected hepatocyte [20]. In hepatitis C and hepatitis B the immune response to infected cells triggers fibrogenesis. This leads to fibrosis which often originates in the portal areas and then progresses to involve the lobules toward the central vein. Primary biliary cirrhosis differs in that it is characterised by immune dysregulation mediated by interleukin-12 and interferon- γ. Disease specific antimitochondrial antibodies (AMA) activate immunodominant inner mitochondrial membrane epitopes in epithelial cells lining the intra-lobular and septal bile ducts. This leads to a lymphocytic cholangitis and cell apoptosis which causes progressive fibrosis and biliary cirrhosis [21].

A defining feature of cirrhosis is the development of nodules of regenerating hepatocytes surrounded by scar tissues. The activation of HSC, as described above, leads to the formation and subsequent deposition of ECM in the Space of Disse. This reduces hepatocyte integrity with loss of both endothelial fenestrations and hepatocyte microvilli [22] and leads to progressive accumulation of scar matrix and fibrosis. Extensive fibrosis linking all areas of the hepatic structure between central and portal areas is the histological characterization of liver cirrhosis. These changes lead to diminished sinusoidal blood flow resulting in diminished hepatic flow and increased vascular resistance within the portal venous system resulting in portal hypertension. Patients with liver cirrhosis are predisposed to complications of chronic liver

disease including ascites, variceal bleeding, encephalopathy, jaundice, hepatocellular carcinoma, and death.

2.3.2 Histological grading of fibrosis

Liver biopsy and histological assessment is considered the reference or “gold” standard of liver fibrosis assessment. A number of semi-continuous categorical fibrosis scores have been developed to describe the histological findings in a variety of liver diseases (Table 2.1).

Table 2.1 Liver histological scores for liver fibrosis

Scoring system	
Metavir [23]	
F0	No fibrosis
F1	Periportal fibrotic expansion without septae formation
F2	Periportal expansion with occasional septae
F3	Fibrosis connecting to other areas of fibrosis (bridging)
F4	Cirrhosis
Brunt [24]	
F0	No fibrosis
F1	Zone 3 perisinusoidal fibrosis or periportal fibrosis
F2	Zone 3 fibrosis and portal and periportal fibrosis
F3	Fibrosis connecting to other areas of fibrosis (bridging)
F4	Cirrhosis
Ishak [25]	
F0	No fibrosis
F1	Fibrous expansion of some portal areas +/- septa
F2	Fibrous expansion of most portal areas +/- septa
F3	F2 + occasional portal to portal bridging
F4	F3 + some portal – central bridging
F5	Marked bridging with occasional nodules
F6	Cirrhosis

Scheuer [26]	
F0	No fibrosis
F1	Enlarged, fibrotic portal tracts
F2	Peri-portal or portal-portal septa, but intact architecture
F3	Fibrosis with architectural distortion, but no clear cirrhosis
F4	Probable or definite cirrhosis

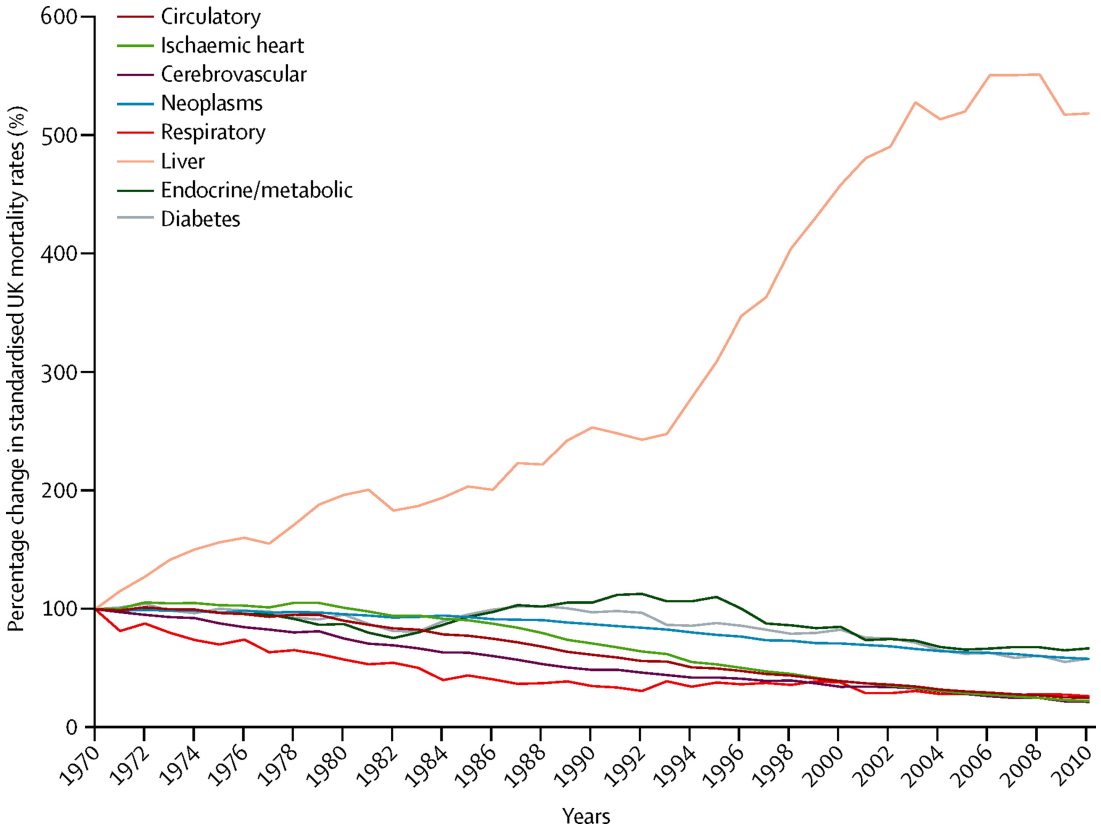
2.4 Chronic liver disease

2.4.1 The increasing burden of chronic liver disease

Chronic Liver Disease (CLD) represents a significant global healthcare burden and a major public health concern. The health, societal and economic consequences of CLD are substantial and increasing [1-3]. In England and Wales, CLD is one of the 'top five' causes of premature mortality, and the only one to be rising in incidence [4]. In 2012, 60,000 patients had a diagnosis of cirrhosis in the United Kingdom (UK), representing a 40% increase compared to the preceding decade and resulting in 57,682 hospital admissions and 10,948 annual deaths [27]. Rates of chronic liver disease in adolescents and young adults (aged < 40 years) have doubled since the late 1980s [28]. The Chief Medical Officer's report (2012) commented that deaths from CLD and cirrhosis had increased by over 20% between 2000-2009 [29]. The National Health Service (NHS) National End of Life Care Intelligence Network quoted 9,231 deaths from liver disease in 2001 rising to 11,575 in 2009, representing 2% of all deaths in the UK [30]. Since 1970, there has been a 400% increase in standardized liver mortality rates in the United Kingdom, and a 500% increase in patients aged less than 65 years old [6] (see Figure 2.3).

Figure 2.3 Standardised mortality data in the United Kingdom

Data were normalised to 100% in 1970, and data from the WHO-HFA database used to plot trends using statistical software. Reproduced with permission from Williams et al (2014) [6]



This trend is replicated internationally, with retrospective autopsy-based studies estimating the global prevalence of liver cirrhosis to be between 4.5% to 9.5% [31, 32]. In the United States, a population-based study estimated the prevalence of cirrhosis to be 0.27%, corresponding to over 630,000 US adults [33]. The prevalence of disease was higher in ethnic minorities, those with lower income status, and those who did not complete university education [33]. Evidence suggests that CLD disproportionately affects younger people compared to other conditions. Ninety percent of liver-related deaths are in patients aged under 70, whilst greater than 10% are in their forties [30]. This

has an appreciable impact on society and liver disease was the leading cause of potential working life years lost in 2016 and 2017, overtaking both ischaemic heart disease and accidental poisoning [34]. This equates to an estimated loss of over 60,000 working life years each year in England and Wales [34]. The mortality of a condition, and consequent years of life lost is a relevant endpoint by which to measure the impact of a condition. In 2001, The World Bank Global Burden of Disease database ranked worldwide deaths from liver cirrhosis as the 14th and 10th leading cause of death in the world and in developed countries respectively, with over 771,000 deaths [35]. Updated reports from the same organisation in 2013 revealed worldwide deaths from cirrhosis was now the 13th leading cause of mortality, and 4th commonest chronic disease in terms of life years lost behind coronary heart disease, cerebrovascular disease and chronic obstructive pulmonary disease [36]. Deaths from liver cancer ranked 21st in the list, with an estimated 1.2 million deaths from cirrhosis and 818,000 deaths from liver cancer every year [36].

The morbidity associated with chronic liver disease is reflected in the burden placed on healthcare services by the condition. In 2012, there were 57,682 hospital admissions for patients with liver cirrhosis, representing a 62% increase compared to the preceding decade [27].

The economic impact is an additional barometer of the true burden of a health condition on healthcare systems. The costs of cirrhosis include direct costs such as drugs and hospitalization which are calculable and accountable.

Healthcare budgets dedicated to the care of patients with CLD have increased exponentially, with inpatient hepatology admissions accounting for approximately £460 million annual spend in the United Kingdom [27]. Another document estimated the direct cost of liver disease in the NHS was in excess of £500 million every year and rising by ten percent annually [37]. Indirect costs such as loss of work and productivity are harder to quantify. In 2004, the direct and indirect costs of chronic liver disease in the United states was estimated at $2.5 billion and $10.6 billion dollars respectively [38].

2.4.2 Aetiology

In Europe and North America, NAFLD is the commonest cause of deranged liver bloods tests in primary care [39] and has a prevalence ranging between 10% and 50% [40]. Alcohol use disorders, diabetes, obesity, hepatitis B and C, male sex and older age are all independently associated with cirrhosis [33]. The three commonest causes of chronic liver disease are non-alcoholic fatty liver disease (NAFLD), alcohol related liver disease (ARLD) and chronic viral hepatitis (chronic hepatitis B (CHB) and chronic hepatitis C (CHC)). A quarter of the population accounts for over 75% of alcohol consumption in the United Kingdom [41] and this sub-population are at risk of CLD from harmful or hazardous drinking. The main causes of chronic liver disease are listed in Table 2.2.

Table 2.2 Common aetiologies of chronic liver disease

	Disease
Metabolic	Non-alcoholic fatty liver disease
Toxins	Alcohol Drugs (i.e. methotrexate/ amiodarone)
Viral hepatitis	Chronic hepatitis B Chronic hepatitis C
Autoimmune	Autoimmune hepatitis Primary biliary cholangitis Primary sclerosing cholangitis
Genetic	Haemochromatosis Wilson disease Alpha-1 antitrypsin deficiency Porphyria Glycogen storage disorders Cystic fibrosis
Others	Chronic congestive heart failure Veno-occlusive disease Budd Chiari syndrome Sarcoidosis Schistosomiasis Secondary sclerosing cholangitis

2.4.3 Clinical manifestations of chronic liver disease

The development of liver cirrhosis is typically silent and insidious. The presence of liver fibrosis is usually asymptomatic, even at the stage of advanced fibrosis (Brunt F3) and compensated liver cirrhosis (Brunt F4) [42, 43]. By definition, the transition to decompensated liver disease is signalled by

the clinical manifestations of impaired liver function and the onset of complications of portal hypertension, a point at which patients will likely present to healthcare services. Compromised liver synthetic function can result in jaundice, whilst low serum albumin levels and deranged prothrombin time can be detectable on routine blood tests. The inefficient clearance of toxins including nitrogen containing substrates can manifest with neuropsychiatric symptoms labelled as hepatic encephalopathy. Portal hypertension can present with fluid in the abdomen called ascites or development of varices, which are spontaneous shunts between the systemic and portal circulation which are prone to bleeding. Another serious complication of liver cirrhosis is the development of hepatocellular carcinoma (HCC). Annual incidence is estimated at approximately 5% [44], whilst a study in patients with NAFLD suggest annual cumulative incidence was between 2% and 12% [45]

2.4.4 Management

Currently, there are no licenced pharmaceutical agents that treat or reverse liver cirrhosis. However, the treatment or removal of the insult, for example reducing alcohol consumption or treating active viral hepatitis, may prevent the progression of fibrosis and allow for healing of the liver infrastructure. In addition, the mainstay of management of patients with liver cirrhosis is to screen for complications of liver cirrhosis.

High quality evidence supports the cost-effectiveness reductions in morbidity and mortality in cirrhosis through the use of treatments for portal hypertension

[46] and the early detection of HCC through targeted screening [47] as well as changes in lifestyle, particularly abstinence from alcohol [48] and weight loss [49]. Patients with liver cirrhosis are screened for HCC. HCC is commonly classified using the Barcelona Clinic staging system, which allows for prognostication and informs management decisions [50]. Staging is dictated by tumour size, number of lesions, the presence of metastases, liver disease status and performance status. Patients with Stage 0 (very early stage) and stage A (early) disease usually have compensated liver cirrhosis, low tumour burden and good performance status, and are considered for curative treatment with liver resection, liver transplantation or radiofrequency ablation [51]. Patients have an estimated 5-year survival of 40 to 70%. Patients with stage B (indeterminate) and stage C (advanced stage) usually have evidence of decompensated liver disease, have a poorer performance status and higher tumour burden, and options are limited to life extending but non curative options including trans-arterial chemoembolization (TACE), Sorafenib and clinical trials. Median survival is quoted at 11 months. Patients with stage D (end stage) disease have no therapeutic options and management is limited to symptom control with a median survival of less than three months. Screening for liver cancer aims to identify patients with earlier stages of liver cancer.

In addition to the aforementioned interventions, patients referred to secondary care with advanced liver disease may benefit from consideration for clinical trials of emerging therapies [3, 52].

2.5 Non-Alcoholic Fatty Liver Disease

2.5.1 Burden of disease

In 1980, Ludwig and colleagues first described the clinical entity of non-alcoholic fatty liver disease (NAFLD) [53] . The condition was defined by the pathological macrovesicular accumulation of fat cells (>5% of hepatocytes on histological assessment) in the absence of others causes of chronic liver disease including excessive alcohol consumption, as detailed in section 2.4.2. Excessive alcohol consumption has been defined as more than 20 grams of ethanol per day in women (approximately 14 units per week) and 30 grams per day in men (approximately 21 units per week) [54]. Other causes of liver steatosis are detailed in Table 2.3 [55].

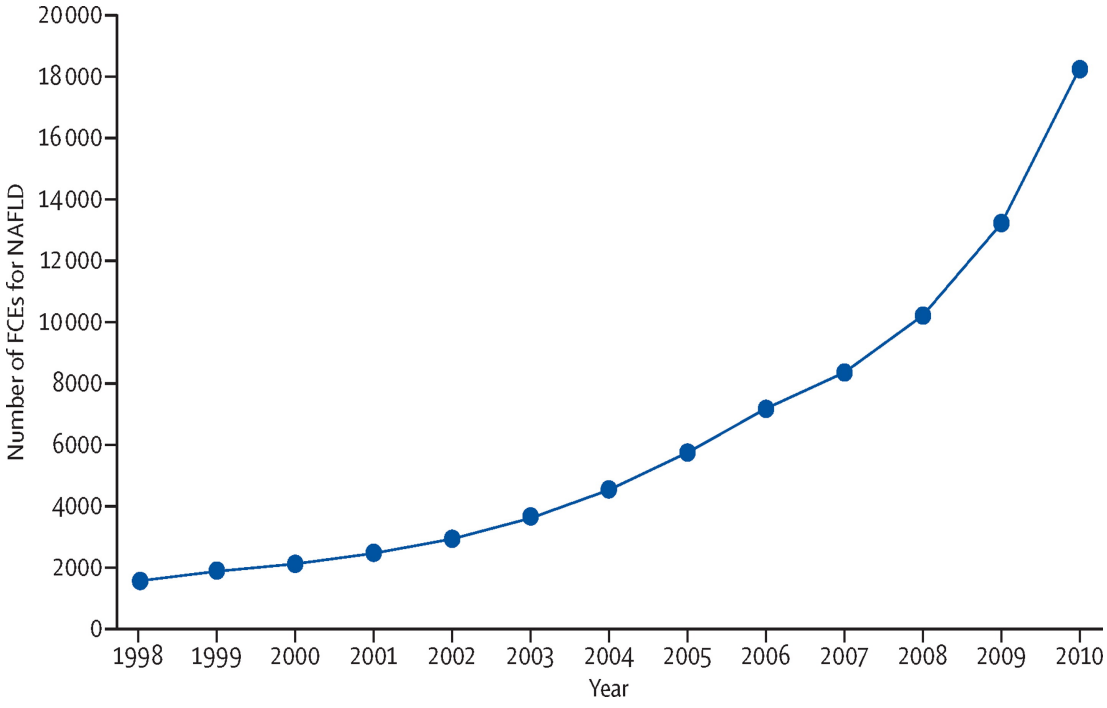
Table 2.3 Causes of hepatic steatosis

Macrovesicular hepatic steatosis
Non-alcoholic fatty liver disease Alcohol related liver disease Other causes of chronic liver disease i.e. hepatitis B/ C, autoimmune hepatitis etc. Abetalipoproteinaemia Lipodystrophy Nutritional causes (prolonged starvation, parenteral feeding Medications i.e. amiodarone, corticosteroids, methotrexate, tamoxifen
Microvesicular hepatic steatosis
Inborn errors of metabolism e.g. Lecithin cholesterol acyltransferase deficiency, cholesterol ester storage disease Reyes syndrome Acute fatty liver of pregnancy HELLP (haemolysis elevated liver enzymes low platelets) syndrome Medications i.e. anti-epileptic, anti-retroviral drugs

Globally, NAFLD is the commonest cause of chronic liver disease [40] and cases are rising exponentially. Population studies in Europe, the United States of America and Asia have estimated the prevalence of NAFLD to be between 14% and 31% in the general population [56]. Studies focussed on high-risk groups have suggested the prevalence of NAFLD can be as high as 70% in patients with diabetes [57, 58] and 90% in obese patients [59]. In the United Kingdom, hospital admissions for patients with NAFLD have increased from less than 2000 per annum in 1998 to over 18,000 per annum in 2010 [6] (Figure 2.4).

Figure 2.4 Number of hospital admissions for NAFLD 1998 – 2010

Hospital admissions defined as first finished consultant episodes. Reproduced with permission from Williams et al [6]



NAFLD is a leading cause for hepatocellular carcinoma [60], liver related and all-cause mortality [61-63]. Liver transplantation for patients with NAFLD has increased by 170% in the past 10 years, compared to 14% for viral hepatitis C and 45% for alcoholic cirrhosis [64]. It is the second commonest indication for liver transplantation in Europe and the United States and predicted to be the leading indication within the next few decades [65-67].

2.5.2 Risk factors

NAFLD can be considered as the hepatic manifestation of the metabolic syndrome, the components of which are listed in Table 2.4 [68].

Table 2.4 Definition of metabolic syndrome.

Metabolic syndrome
Defined as ≥ 3 of the following
Fasting plasma glucose ≥ 6.1 mmol/l or anti-hyperglycaemic therapy Waist circumference > 102 cm in men and > 88 cm in women HDL cholesterol < 1.03 mmol/l in men and < 1.29 mmol/l in women or on drug therapy for low HDL Triglyceride concentration > 1.7 mmo/l or on drug therapy for hypertriglyceridemia Systolic BP ≥ 130mmHg or diastolic BP ≥ 85mmHg or on anti-hypertensive therapy

The main risk factors for NAFLD are type II diabetes, insulin resistance, obesity (in particular central adiposity) hyperlipidaemia and hypertension [69, 70]. It is estimated that over 80% of patients with metabolic syndrome have NAFLD, of whom 25% have steatohepatitis on liver biopsy [71]. However, it is estimated a significant minority of patients (approximately 5%) are not overweight or obese [72].

2.5.3 Spectrum of liver disease

NAFLD encompasses a spectrum of disease [73] as illustrated in Figure 2.5. NAFLD usually refers to ‘simple’ or ‘bland’ steatosis, namely the presence of fat cells in hepatocytes. Over fifteen years of follow up, less than one percent of patients developed liver cirrhosis [74]. Approximately ten percent of patients with NAFLD will develop non-alcoholic steatohepatitis (NASH), of whom up to 15% are likely to develop liver cirrhosis [74]. Although bland steatosis is considered a benign entity, patients with NAFLD (regardless of fibrosis stage) were found to have a 70% increased rates of all-cause mortality compared to the general population. The majority of deaths were cardiovascular or cancer-related [62].

Figure 2.5 Natural history of NAFLD, NASH and NASH-fibrosis.

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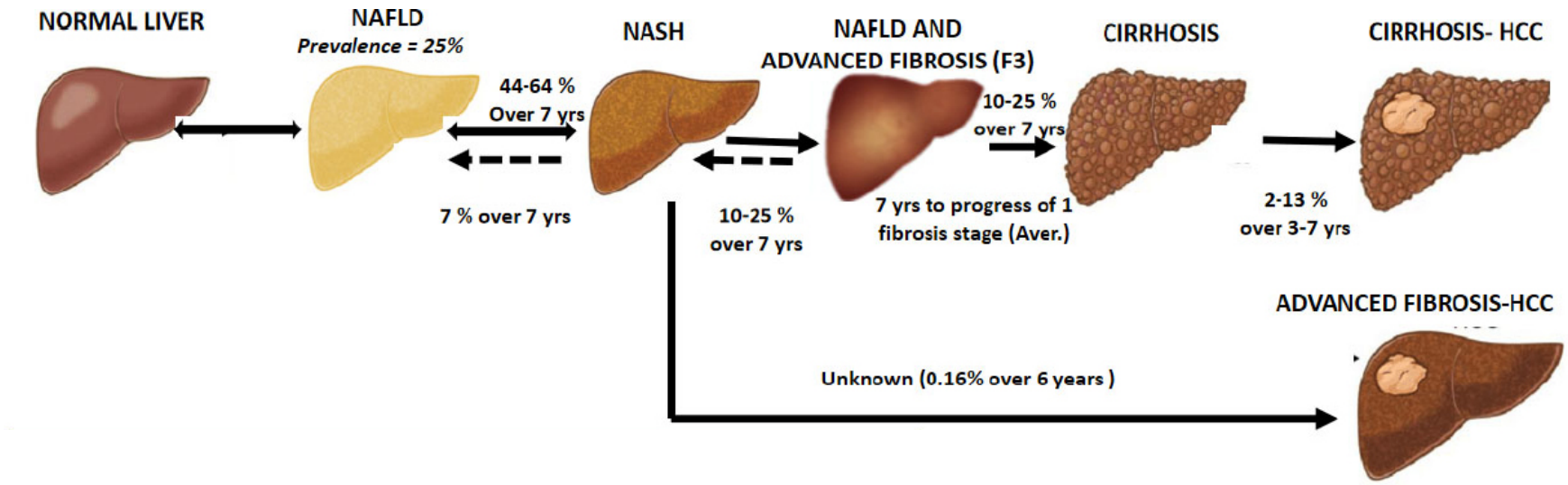


2.5.4 Liver fibrosis key predictor of patient outcomes

Longitudinal follow-up studies of patients with NAFLD have demonstrated liver fibrosis as the key predictor of liver related events and mortality [75, 76]. Angulo and colleagues retrospectively evaluated 619 biopsy staged patients with NAFLD and followed them up for a median of 12.6 years. Fibrosis stage, but no other histological features on the liver biopsy including steatohepatitis were found to be associated with liver related events and mortality. Compared to Brunt stage F0 fibrosis, hazard ratios for death or liver transplantation were 1.88, 2.89, 3.76 and 10.9 for fibrosis stages F1, F2, F3 and F4 respectively [75]. A Swedish cohort study of 229 biopsy characterised patients with NAFLD were followed up for a mean of 26.4 years [76]. Compared to a reference population, no increase in overall mortality was observed in patients with F0, F1 and F2 fibrosis, irrespective of steatohepatitis activity (hazard ratio 1.41, $p= 0.07$). Conversely, patients with advanced fibrosis (stage F3) and cirrhosis (stage 4) had increased mortality (hazard ratio 3.3, $p < 0.001$) regardless of the presence or absence of steatohepatitis.

2.5.5 Treatment

The management of patients with non-alcoholic fatty liver disease requires a multidisciplinary approach to enable treatment of not only the liver disease but also the associated co-morbidities.

Lifestyle modification with an emphasis on diet and exercise remain the mainstay of treatment for NAFLD and are beneficial for its associated cardiovascular risk factors [77, 78]. The role of bariatric surgical interventions remains under evaluation with insufficient evidence to consider them a standard treatment option [77]. However, a meta-analysis of 15 studies revealed bariatric surgery improved hepatic steatosis in 91.6% of cases, steatohepatitis in 81.3% and liver fibrosis in 69.5% [79]. Pharmacological options remain limited for both steatohepatitis and fibrosis [80]. However, there are several agents at advanced stages of development [81].

2.6 Diagnostic test performance

2.6.1 Assessing test performance

The accuracy and performance of diagnostic tests are defined by the sensitivity and specificity of a test [82] (Table 2.5).

Table 2.5 Evaluation of a diagnostic test

2x2 contingency table comparing diagnostic test result to true disease state

		Disease state		
		Positive	Negative	Total
Test result	Positive	True positive (TP)	False positive (FP)	TP + FP
	Negative	False negative (FN)	True Negative (TN)	FN+ TN
	Total	TP + FN	FP + TN	TP + FP + FN + TN

The sensitivity of a test (true positive rate) is the proportion of those who have the condition that are correctly identified as having the condition (TP / TP + FN). A sensitive test will correctly identify patients with the condition, and therefore a negative test will correctly rule out the condition.

The specificity of a test (true negative rate) is the proportion of those without the condition that are correctly identified as not having the condition (TN / TN + FP). A specific test will correctly identify patients without the condition, and therefore a positive test will correctly rule in the condition.

The positive predictive value (PPV) of a test is the proportion of positive results that do have the condition (TP / TP + FP). In a test with a high PPV, a positive result is more probable to mean the individual has the condition.

The negative predictive value (NPV) of a test is the proportion of negative results that do not have the condition (TN/ TN + FN). In a test with a high NPV, a negative result is more probable to mean the individual does not have the condition.

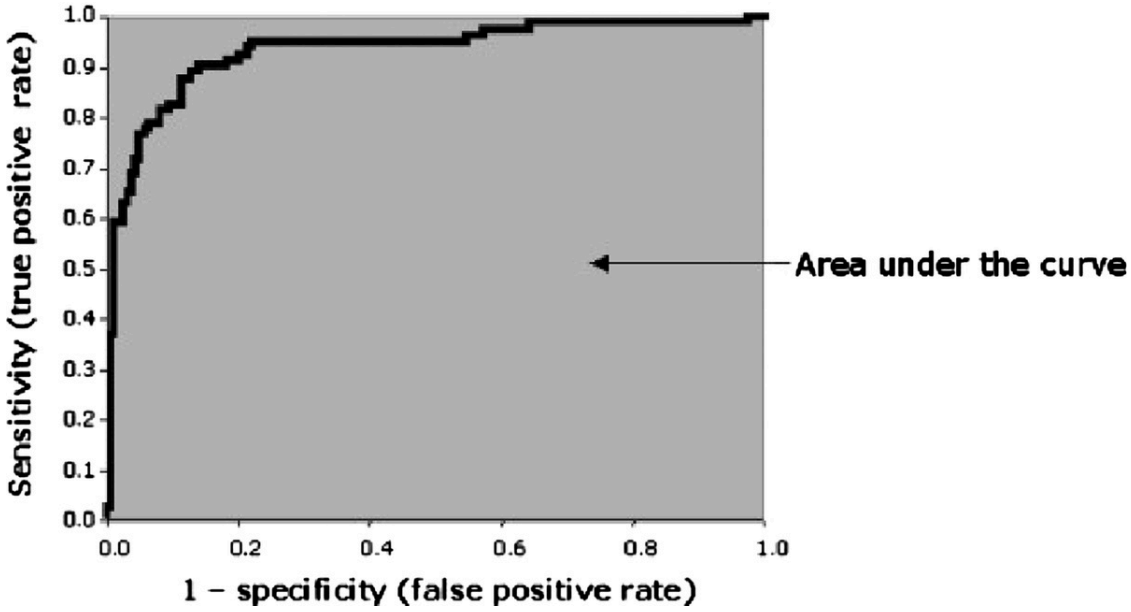
The accuracy of a diagnostic test is determined by calculating the area under the receiver operator characteristic (AUROC) curve. Sensitivities and specificities are calculated for a diagnostic test across a broad scale of diagnostic thresholds. Sensitivity is plotted against 1 – specificity to produce a receiver operator characteristic (ROC) curve.

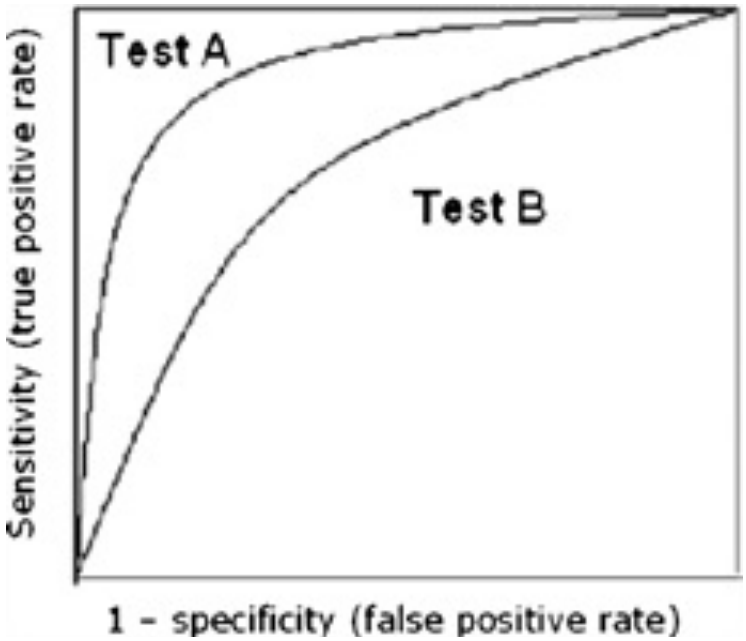
Figure 2.6 Example of area under receiver operator characteristic

Top figure: Area under receiver operator characteristic (AUROC) curve is calculated by plotting sensitivity against 1 – sensitivity and is used to measure a diagnostic test's discriminative performance.

Bottom figure: Test A is superior to Test B as at all cut-offs, it has a higher true positive rate and lower false positive rate.

Reproduced with permission from Ekelund [83]





The area under the curve is the AUROC. An AUROC > 0.90 is considered excellent, between 0.80 – 0.90 good, 0.70 – 0.80 fair, 0.60 0.70 poor, 0.50 – 0.60 failed. An AUROC less than 0.5 equates to a test that performs worse than chance [84].

2.6.2 Spectrum bias

The performance of a diagnostic test will vary depending on the clinical setting and the patient characteristics within that setting. The sensitivity and specificity of a diagnostic test are influenced very little by the prevalence of the index condition in the test population. By contrast, the PPV and NPV of a test are influenced by the prevalence of the condition in the population studied, which directly impacts on the pre-test probability. The over-representation of either end of the spectrum - the 'diseased' or 'non-diseased' state, will result in falsely elevated 'rule-in' or 'rule-out' characteristics [85]. For example, in the context of patients with liver cirrhosis, in a population with a high proportion of cases of cirrhosis (i.e., 50% of cohort), a test at a set threshold for the identification of patients with liver cirrhosis will have a high PPV (proportion of positive cases that have condition) when evaluated in that population compared to another population with a low prevalence of cirrhosis. Using the same test (at the same threshold and therefore same sensitivity and specificity characteristics) in a different population where the prevalence of cirrhosis is less (i.e., 5% of cohort), the PPV will be lower as the number of people with liver cirrhosis is lower. In the context of this thesis, a high prevalence population could be

considered to be carefully selected patients in secondary care clinical trials in whom non-invasive liver fibrosis tests have been validated, and the low prevalence population can be considered to be a primary care population in whom we are considering employing these tests in designated primary care pathways.

2.7 Assessment of liver fibrosis

2.7.1 Liver blood tests

Liver function tests (LFTs) are also known as liver blood tests and are used routinely to screen for liver dysfunction and liver disease in both primary care and hospitals settings. However, it is recognised that LFTs correlate poorly with liver fibrosis stage. In a large primary care-based study of 95,977 patients, 21.7% had abnormal LFT's. Over a median of 3.7 years follow up, only 1.15% of patients developed liver disease [86]. Harman and colleagues followed a community cohort of patients with diabetes and alcohol excess and found the alanine aminotransferase (ALT) level to be normal (using local laboratory cut-offs; >35 u/l women, >45 u/l men) in 72.4% patients with increased liver stiffness (LS), 60% with liver fibrosis on biopsy, and 90.9% with confirmed liver cirrhosis. Even reverting to more conservative cut-offs (>19 u/l women, >30 u/l men), 41.8% patients with increased LS and 18.2% cirrhotics had normal ALT [87]. In another study of 222 biopsy staged NAFLD patients, comparing patients with normal ALT to those with elevated ALT, no difference in the rate of advanced fibrosis was identified (26.8% vs 18.1%, p= 0.19) [88], although a

raised ALT was a predictor for the presence of steatohepatitis (10.7% vs. 28.9%, $P < 0.01$). The study showed that 53% of patients with elevated ALT had no NASH or advanced fibrosis, whereas 37.5% of patients with normal ALT had evidence of NASH or advanced fibrosis on liver biopsy.

2.7.2 Imaging

Radiological methods including ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) have a role in identifying hepatic steatosis. However, their accuracy in distinguishing bland steatosis from steatohepatitis and progressive fibrosis is limited [89, 90]. At the latter stages of liver cirrhosis, when morphological changes in the hepatic architecture or portal hypertension are evident, definitive evidence of liver cirrhosis including surface irregularity and signs of portal hypertension are strongly predictive of liver cirrhosis [91] but overall sensitivity is modest [92, 93].

2.7.3 Liver biopsy

The histological assessment of a liver biopsy specimen is the reference standard for staging liver disease. However, biopsy is associated with pain, morbidity including bleeding, and rarely death [94, 95]. The diagnostic accuracy and reliability of biopsy is questionable due to sampling error and inter- and intra-observer variability.

The distribution of liver fibrosis is heterogenous and variable. A study of surgical liver biopsies using the Metavir scoring system and image analysis

showed a coefficient of variation of fibrosis assessment of 55% in liver biopsies of 15 mm length and 45% in liver biopsies of 25 mm length, highlighting sample variability as a major limitation [96]. A French study in which 51 patients with NAFLD underwent liver biopsy with samples from the right and left lobe of the liver demonstrated that most NAFLD related histological features including hepatocyte ballooning and fibrosis demonstrated considerable sample variability [94]. For example, out of seventeen patients with bridging fibrosis, six patients had bridging fibrosis on one sample and only mild or no fibrosis on the other sample. Similar observations have been made in patients undergoing liver biopsy for evaluation of hepatitis C [97].

Furthermore, liver biopsy requires technical skill and pathologist expertise, day-case hospital admission and is costly, limiting its applicability as a widely applied screening tool [98, 99].

2.8 Non-invasive liver fibrosis tests

In view of the limitations of the available tools for liver fibrosis assessment including LFT's, imaging and liver biopsy, there has been intense research activity over the last few decades to develop and validate non-invasive liver fibrosis tests with sufficient sensitivity and specificity to be clinically valuable. A summary for the diagnostic performance of non-patented serum biomarkers, patented serum biomarkers and elastography based methods are presented in Table 2.6, Table 2.7 and Table 2.8 respectively and discussed in detail in the following sections.

Table 2.6 Summary of diagnostic performance of non-patented serum biomarkers of liver fibrosis in mixed aetiology of chronic liver disease

Adapted with permission from Chin et al [100]

[a] values are for prediction of cirrhosis [b] meta-analysis

Test	Parameters	Year	Disease	N	Cut off F3	AUROC for F3	Sens	Spec	NPV	PPV	Reference
APRI	AST, platelet	2003	HCV	270	1.50	0.8-0.88	41-91	47-95	61-88	64-86	[101]
		2007	HCV	180	0.50	0.82	94	22	32	90	[102]
		2008	HBV	264	1.50	0.86	87	66	81	74	[103]
		2008	ALD	103	1.50	0.43	-	-	-	-	[104]
		2010	NAFLD	145	1.0	0.67	27	89	84	37	[105]
		2011	HCV	8739 [a]	1.0	0.80	61	64			[106] [a]
		2015	PBC	137	1.0	0.84	-	-	-	-	[107]
AST: ALT	AST, ALT	1998	HCV	139	1.0	-	53[a]	100[a]	91[a]	100[a]	[108]
		2000	HCV	151	1.0	-	47 [a]	96 [a]	88 [a]	74 [a]	[109]

Test	Parameters	Year	Disease	N	Cut off F3	AUROC for F3	Sens	Spec	NPV	PPV	Reference
		2010	NAFLD	145	0.8	0.83	74	78	93	44	[105]
		2015	PBC	137	0.8	0.59	-	-	-	-	[107]
BARD	Diabetes, BMI, AST, ALT	2008	NAFLD	827	2	0.81	-	-	-	-	[110]
		2010	NAFLD	145	2	0.77	89	44	95	27	[105]
		2011	NAFLD	138	2	0.67	51	77	81	45	[111]
		2016	NAFLD [b]	1038	2	0.76	74	66	-	-	[112] [b]
FIB-4	Age, AST, ALT, platelet count	2006	HCV/HIV	830	1.45	0.74-0.77	67	71	-	-	[113]
		2007	HCV	780	1.45	0.85	74.3	98.2	94.7	82.1	[114]
		2010	HBV	668	1.6	0.91	91.2	97.9	90.0	94.8	[115]
		2009	NAFLD	541	1.30	0.80	52	90	-	-	[116]

Test	Parameters	Year	Disease	N	Cut off F3	AUROC for F3	Sens	Spec	NPV	PPV	Reference
FIB-4	Age, AST, ALT, platelet count	2010	NAFLD	145	1.30	0.86	85	65	95	36	[105]
		2016	NAFLD [b]	1038	1.30	0.85	84	69	-	-	[112] [b]
		2015	PBC	137	1.45	0.71	-	-	-	-	[107]
Forns index	Age, platelet, GGT, cholesterol	2002	HCV	476	4.2	0.81-0.86	94	51	96	40	[117]
Hui score	BMI, platelet, albumin, bilirubin	2005	HBV	235	0.15	0.79	88	50	92	38	[118]
NAFLD fibrosis score	BMI, age, platelets, albumin, AST, ALT, diabetes	2007	NAFLD	733	-1.455	0.82-.88	77-82	71-77	88-93	52-56	[119]

Test	Parameters	Year	Disease	N	Cut off F3	AUROC for F3	Sens	Spec	NPV	PPV	Reference
		2010	NAFLD	145	-1.455/ 0.676	0.81	33-78	58-98	86-92	30-79	[105]
NAFLD fibrosis score	BMI, age, platelets, albumin, AST, ALT, diabetes	2016	NAFLD [b]		-1.455	0.84	77	70	-	-	[112] [b]
Pohl score	ALT, AST, platelet count	2001	HCV	221	AST/ALT >1 + platelet <150	-	41	99	93	85	[120]

Table 2.7 Summary of diagnostic performance of patented serum biomarkers of liver fibrosis in mixed aetiology of chronic liver disease

Adapted with permission from Chin et al [100]

[a] meta-analysis

Test	Parameters	Year	Disease	N	Cut off F3	AUROC for F3	Sens	Spec	NPV	PPV	Reference
ELF	Age, Hyaluronic acid, TIMP-1, PIIINP	2004	HCV	496	0.063	0.77	95	29	95	28	[121]
		2004	NAFLD	61	0.375	0.87	89	96	98	80	[121]
		2004	ALD	61	0.087	0.94	93	100	86	100	[121]
		2008	NAFLD	192	0.358	0.90	80	90	94	71	[122]
		2008	PBC	161	-	0.75	-	-	-	-	[123]
		2014	Mixed [a]	1645	-	0.87	78	76	-	-	[124] [a]
		2015	NAFLD [a]	-	10.35	-	80	90	-	-	[125] [a]

Test	Parameters	Year	Disease	N	Cut off F3	AUROC for F3	Sens	Spec	NPV	PPV	Reference
		2017	NAFLD	82	9.8	-	86.7	92.5	72	97	[126]
		2019	NAFLD	3173	9.8	0.80	74	73	53	87	[127]
		2020	NAFLD [a]	5366	9.8	0.83	65	86	-	-	[128] [a]
Fibrometer test	Platelet, prothrombin time, AST, α2 macroglobulin, hyaluronic acid, urea, age	2005	HCV/ HBV	383	0.30	0.89	81	84	77	86	[129]

Test	Parameters	Year	Disease	N	Cut off F3	AUROC for F3	Sens	Spec	NPV	PPV	Reference
Fibrometer A	Prothrombin time, AST, α2 macroglobulin, hyaluronic acid, age	2005	ALD	95	0.30	0.96	92	93	83	97	[129]
		2008	ALD	103	-	0.88	-	-	-	-	[104]
Fibrospect	Hyaluronic acid, TIMP-1, α2 macroglobulin	2004	HCV	696	0.36	0.82-8.83	77-83	66-73	-	74	[130]

Test	Parameters	Year	Disease	N	Cut off F3	AUROC for F3	Sens	Spec	NPV	PPV	Reference
Fibrotest	Haptoglobin, α2 macroglobulin, apolipoprotein A1, GGT, bilirubin, age, gender	2001	HCV	339	0.30	0.87	75	85	80	80	[131]
		2006	NAFLD	267	0.30	0.81	92	71	98	33	[132]
		2007 [a]	HCV	1679	0.60	0.81	47	90	-	-	[133] [a]
		2008	ALD	103	-	0.8	-	-	-	-	[104]
		2014[a]	HBV	2494	0.48	0.84	61	80	-	-	[134][a]

Test	Parameters	Year	Disease	N	Cut off F3	AUROC for F3	Sens	Spec	NPV	PPV	Reference
Hepascore	Age, gender, bilirubin, GGT, Hyaluronic acid, α2 macroglobulin	2005	HCV	221	0.5	0.9-0.96	74-81	88-95	95-98	-	[135]
		2008	ALD	103	-	0.83	-	-	-	-	[104]

Table 2.8 Summary of diagnostic performance of elastography based fibrosis assessment in mixed aetiology of chronic liver disease

Adapted with permission from Chin et al [100]

Year	Disease	Cut-off F3	AUROC for F3	Sens	Spec	Cut-off F4	AUROC for F4	Sens	Spec	Reference
Fibroscan										
2007	All	- [a]	0.87	70	84	- [a]	0.96	87	91	[136] [a]
2008	All	7.7	0.84	-	-	13.0	0.94	-	-	[137]
2010	All	7.7	-	71.9	82.4	15.1	-	84.5	94.7	[138]
2010	NAFLD	7.9	0.93	91	75	10.3	0.95	92.0	87.8	[139]
2011	All	- [a]	-	79.0	78.0	- [a]	-	83.0	89.0	[140] [a]
2015	NAFLD	7.5 – 10.4 [a]	-	0.82	0.84	-	10.3-17.5	0.96	0.89	[125] [a]
2019	NAFLD	9.9 [a]	0.80	83	61	-		-	-	[127] [a]

Year	Disease	Cut-off F3	AUROC for F3	Sens	Spec	Cut-off F4	AUROC for F4	Sens	Spec	Reference
ARFI										
2012	All	1.34	0.87	79.0	85.0	1.80	0.93	92	86	[141]
2015	NAFLD	-	0.90	80.2	85.2	-	-	-	-	[142]

2.8.1 Indirect biomarkers of liver fibrosis

In the context of progressive liver dysfunction and fibrosis, biochemical abnormalities in aminotransferases, alkaline phosphatase, bilirubin, albumin, clotting and platelets can be found. Combining these tests, often with clinical parameters with varying degrees of complexity can improve sensitivity and specificity to identify significant liver disease. Several such "indirect" markers of liver fibrosis have been validated. The vast majority are non-patented serum biomarkers (Table 2.6).

The NAFLD fibrosis score combines age, BMI, platelets, albumin, AST/ ALT ratio and glucose. It has been validated in patients with NAFLD with AUROC 0.82 (sensitivity 77%, specificity 71%) for advanced fibrosis [119]. FIB-4 is calculable from age, platelets, ALT and AST and was first validated in patients with hepatitis C and HIV coinfection with AUROC 0.765 for advanced fibrosis [113]. FIB-4 has been validated in hepatitis C [114] and hepatitis B [115] and has been extensively evaluated in NAFLD [105, 112, 116] (summarised in Table 6.1, Chapter 6). The AST to platelet ratio index (APRI) has been validated in viral hepatitis C with AUROC 0.82 (sensitivity 94%, specificity 22%) [102]. A meta-analysis of 8739 patients revealed an AUROC of 0.80 and 0.83 for detection of advanced fibrosis and cirrhosis respectively [106].

In general, indirect markers of liver fibrosis have the advantage that the individual components are well established routinely applied tests which allows them to be readily available and easier to commission. Inevitably, given that

indirect markers are employed as proxy markers of fibrosis, their performance characteristics including sensitivity and specificity can be less reliable as compared to “direct” or mixed indirect and direct markers.

2.8.2 Direct and mixed markers of liver fibrosis

The process of liver fibrogenesis involves alterations to the extracellular matrix (ECM). Direct markers of liver fibrosis measure these changes.

One important component of the ECM is Hyaluronic acid (HA) which is a glycosaminoglycan and is found in the liver, where it is produced by stellate cells, as well as other tissues, including joints. HA levels have been shown to correspond well with the severity of fibrosis in ARLD [143] and viral hepatitis C [144, 145]. For example, Guechot and colleagues demonstrated an HA level of 0.86 had 75% sensitivity and 85% specificity for advanced fibrosis in patients with viral hepatitis C [145].

A number of collagen components of the fibrogenesis process can be quantified. Amino-Terminal peptide of type III procollagen (PIIINP) is an extension peptide that is cleaved from Type III collagen in normal physiological conditions. PIIINP can be derived from the synthesis of new collagen or existing type III collagen fibrils. During a state of fibrogenesis, increased collagen deposition and cleavage results in an increase in degradation products such as PIIINP. Elevated PIIINP levels have been found to be elevated in fibrotic disease related to viral hepatitis C, ARLD and NAFLD [121,

145, 146]. Using a PIIINP cut-off of 0.69 for advanced fibrosis, sensitivity and specificity was 70% and 63% respectively in patients with HCV [145].

Matrix metalloproteases (MMP) are a family of proteinase enzymes involved in collagen degradation and tissue remodelling that under normal physiological conditions are tightly regulated. A loss of this control activity can lead to a number of disease states including fibrosis, arthritis and atherosclerosis [147]. Tissue inhibitors of Metalloprotease (TIMP) are an important group of inhibitors which aide regulation of MMP activity. TIMP levels correlate well with fibrosis, and a sensitivity of 94% and specificity of 57% was shown for advanced fibrosis in patients with HCV [148].

There are several commercially available direct biomarkers which utilise the above fibrogenesis by-products. The majority are patented (Table 2.7).

The Enhanced Liver Fibrosis (ELF) test is a direct biomarker which is commercially available throughout the world, although is awaiting Food and Drug Administration (FDA) approval in the USA. First validated in 2004, it is calculated using a logarithmic algorithm incorporating markers of the ECM, namely HA, TIMP-1 and PIIINP [121]. The manufacturer has validated the following thresholds [121, 149]:

- ELF < 7.7. - no to mild fibrosis (equivalent Brunt F0/ F1)
- ELF ≥7.7 to <9.8 – moderate fibrosis (F2)
- ELF ≥ 9.8 – advanced fibrosis (≥F3)

- ELF≥ 11.3 – cirrhosis

The ELF test was originally derived and then validated in a cohort of 1,021 patients who underwent liver biopsy for evaluation of chronic liver disease of mixed aetiologies [121]. ELF has subsequently been validated in patients with HBV, HCV, AIH, PBC, PSC, ARLD, NAFLD and cystic fibrosis [128, 150, 151].

The ELF test has been extensively evaluated in patients with NAFLD and is summarised in Table 6.2, Chapter 6 [122, 125-127, 152-155]. In a study of 196 patients, Guha and colleagues demonstrated ELF had an AUROC of 0.90 for distinguishing severe fibrosis, 0.82 for moderate fibrosis and 0.76 for an absence of fibrosis [122]. The same study estimated that 82% of liver biopsies could be avoided for the diagnosis of severe fibrosis using an ELF test. A systematic review encompassing over 5000 patients revealed an AUROC for detecting advanced liver fibrosis of 0.83 [128]. At a lower threshold of 7.7, sensitivity and specificity were quoted at 0.93 and 0.34 respectively. Using the manufacturer's recommended cut-off of 9.8, a sensitivity and specificity of 0.86 and 0.65 respectively were calculated, whilst increasing the ELF threshold to > 10.51 changed the sensitivity and specificity to 0.51 and 0.93 respectively [128].

The ELF test has been demonstrated to predict clinical outcomes in patients with chronic liver disease. In a study of 457 patients, Parkes and colleagues [156] demonstrated ELF test to predict liver related morbidity and mortality, with hazard ratios compared to ELF <8.34 of 75 (ELF 12.52- 16.67), 20 (10.426

– 12.51) and 5 (8.34 – 10.424). In a study of 921 patients, Day and colleagues showed that compared to patients with ELF score < 7.7, the hazard ratio for a liver related outcome after 5 years was 21 (ELF 9.8 – 11.3) and 71.04 (>11.3) [157]. Another study of 312 patients demonstrated an ELF score ≥ 9.8 predicted liver related events (19.2% compared to <1% if ELF < 9.8) [158].

Fibrotest is an example of a mixed biomarker which was first developed in 2001 and incorporates indirect markers including age, gender and GGT with direct markers of fibrosis, namely α2 macroglobulin, apolipoproteinA1 and haptoglobin [131]. It has been validated in a variety of aetiologies of chronic liver disease including NAFLD, with an AUROC 0.81, sensitivity of 92% and specificity of 71% for advanced fibrosis[159]. A systematic review of 1679 patients demonstrated AUROC 0.81 to identify Brunt ≥F2 disease in hepatitis C [133].

2.8.3 Elastography

Ultrasound elastography techniques have become established in clinical practice. They utilize the mechanical properties of the liver tissue and evaluate the speed of wave propagating through the liver to estimate the stiffness, which can be used as a surrogate for fibrosis. Transient elastography (TE), which is commercially available as Fibroscan (Echosens) uses mechanical waves whilst acoustic radiation force impulse (ARFI) and shear wave elastography (SWE) use sound waves.

For TE, the machine uses a modified ultrasound probe which transduces a moderate amplitude, low frequency mechanical wave through the liver. The machine measures the velocity of this mechanical wave through the liver, producing a liver stiffness measurement (LSM), although no ultrasonographic images of the liver are obtained [160]. TE has been extensively validated (Table 2.8) [137], although there is little consensus over thresholds that can be used for fibrosis staging, either within aetiology and less so between different aetiologies. Rather, a number of different thresholds are validated depending on disease aetiology, and within aetiologies different studies have recommended differing thresholds for the detection of advanced fibrosis and cirrhosis. In a cohort of patients with mixed aetiology chronic liver disease, Wong and colleagues recommended consideration of a liver biopsy with a cut off of 7.9KPa for advanced fibrosis, with a sensitivity 91.1%, specificity 75.3%, PPV of 52% and NPV 97% [139]. The optimal cut-off for advanced fibrosis was 8.7 kPa (sensitivity 83.9%, specificity 83.2%, PPV 59.5%, NPV 94.6%) and 10.3 kPa for cirrhosis (sensitivity 92%, specificity 87.8, PPV 46%, NPV 99%). Fibroscan can be technically challenging, particularly in patients with obesity. In a study of over 13,300 fibroscan examinations, LSM failure (no recordable readings) occurred in 3.1% and unreliable examinations in 15.8% (defined as fewer than 10 valid readings, interquartile range > 30%, success rate < 60%) [161]. Additionally, inflammation, steatosis and meal consumption prior to examination have been shown to influence TE readings [160].

ARFI technology is incorporated into a conventional ultrasound machine, allowing for traditional two-dimensional B mode ultrasound images to be obtained. A transducer produces low-frequency pulses which simultaneously displaces tissue and shear waves, with measurement of the shear wave allowing assessment of tissue stiffness. Shear wave is similar in its mode of action, with formation of the shear wave by internal radiation forces. Further elastography based techniques have emerged with time including magnetic resonance elastography (MRE) and are likely to be the focus of research in the future.

2.8.4 Thresholds for diagnostic tests

The progression from a normal liver (physiological fibrosis) to a cirrhotic liver is a continuous and linear process. Histological staging by liver biopsy, as described in section 2.3.2, converts this continuous scale into an ordinal categorical scale with no quantitative relationship between stages. This conversion introduces artificial distinctions between closely matched states of disease. Combined with diagnostic error rates of 25% by pathologists staging fibrosis by biopsy [162-164], liver biopsy suffers significant disadvantages in diagnostic accuracy. Non-invasive liver fibrosis markers have the potential to overcome these shortcomings as they assess liver fibrosis on a continuous scale ranging from normal to the diseased state, more closely reflecting the underlying biological processes.

Nevertheless, validation of non-invasive liver fibrosis tests has typically been against liver biopsy as a reference standard. Therefore, validation studies have compared the 'continuous scale' results of NITs to the categorical scale of liver biopsy, for example from normal (Brunt F0) to cirrhosis (Brunt F4). This has been achieved by determining the presence or absence of the diseased state by choosing a cut-off to predict a binary categorisation of liver fibrosis, for example presence of F3/F4 fibrosis vs. absence of F3/F4 fibrosis. An optimal threshold is usually identified for the condition of interest. A 'low' threshold will be considered to have stronger sensitivity and negative predictive value to rule out disease as determined by liver biopsy, whilst a higher threshold will have stronger specificity and positive predictive value to rule in disease as determined by liver biopsy.

The validation of non-invasive liver fibrosis tests in this manner has led to their use in clinical practice to be in a categorical manner. For example, the NAFLD fibrosis score and FIB-4 employ a low cut-off with a strong negative predictive value to identify patients with no or minimal fibrosis, and a high cut-off with a strong positive predictive value to identify patients with advanced fibrosis or cirrhosis. Between the two values, an indeterminate range exists in which the test is neither sensitive or specific enough to rule in or rule out the condition of interest. However, this conversion into categories can be considered disadvantageous and diminishes the potential applicability of the test. Using a continuous scale, there is opportunity for NITs to permit longitudinal assessment to observe disease progression and monitor the impact of

interventions such as antiviral therapy, abstinence from alcohol and weight loss. Whilst future research is needed in this field, early data is supportive of such an approach. Martinez and colleagues demonstrated in 340 patients with HCV that ELF decreased significantly in patients with sustained virological response (SVR) but not in non-responders [165]. Similar observations have been reported in studies using fibroscan [166].

2.8.5 Combining non-invasive tests

Combining different non-invasive tests can offer the opportunity of maximising their individual sensitivity and specificity characteristics.

Indirect markers of liver fibrosis are readily available or calculable, and therefore cheaper and more cost-effective than direct or mixed markers for use in large populations. However, their performance can be heavily influenced by factors not directly related to fibrosis, such as age or hepatic inflammation. As discussed in section 2.8.4 above, performance is optimised by using a lower and upper cut-off, leaving an indeterminate range. Direct and mixed biomarkers are less readily available in routine clinic practice at present. The laboratory equipment is less commonplace in healthcare laboratories and the tests are usually patented, thus increasing the charges for the tests. However, the direct tests tend to have better diagnostic performance compared to indirect markers. Similarly, elastography tends to perform better than indirect biomarkers in the detection of liver fibrosis.

As patient pathways are developed, there is an enthusiasm to combine use of indirect markers, with their advantages including applicability, scalability and low-cost, with direct markers which tend to be more sensitive and specific but more costly. These tests can be combined either in parallel or sequence[84].

In parallel testing, the tests are both performed and interpreted for the whole target group. The test can be interpreted in two ways; firstly, using the “OR” Boolean operator whereby a positive result in either test results in a positive diagnosis and a negative diagnosis if both tests are negative. Secondly, results can be interpreted using the “AND” Boolean operator whereby a positive diagnosis is achieved only if both tests are positive, and a negative diagnosis concluded if either test is negative [84]. The sensitivity of the algorithm is stronger using the OR operator, although specificity is less than either test in isolation. In the AND operator scenario, the specificity is stronger, but the sensitivity is less than would arise from applying either test in isolation.

In serial testing, the results of the first-tier test determine the need for the second-tier test. Once again, the results can be interpreted according to AND or OR operators. In the OR scenario, if the first test is positive, the second test is not required. If the first test is negative (or indeterminate), the second test is performed. If the second test is positive, the diagnosis is positive. In the AND scenario, when the first test is negative, a second test is not required, and the diagnosis is negative. If the first test is positive, the second test is performed and if the second test is positive, the diagnosis is positive. Once again,

sensitivity of the algorithm is stronger when using the OR operator, although specificity is less than either test in isolation. In the AND operator scenario, the specificity is stronger, but the sensitivity is less than either test in isolation.

Serial testing has the benefit of avoiding unnecessary tests, although does potentially increase the time required for the diagnostic process. Serial testing can be considered cost efficient, in particular if the second test is expensive or has restricted access.

2.9 The earlier identification of chronic liver disease

2.9.1 Barriers to timely disease identification

Regardless of the aetiology of the liver disease, a toxic insult to hepatocytes instigates a common pathway of hepatic inflammation and fibrosis which can progress to liver cirrhosis and its complications of HCC, portal hypertension, liver failure and death [167]. Cirrhosis develops over many decades creating opportunities for interventions that may modify disease course. Liver disease develops silently, with patients asymptomatic until the complications of cirrhosis develop, a point at which interventions are associated with poorer outcomes and increased costs. In an US based population study, between 1999 and 2010, where cirrhosis was determined by the presence of an aminotransferase-to-platelet ratio (APRI) of >2 and abnormal liver function, it was estimated 633,323 U.S. adults had chronic liver disease, of which 69% were unaware of having the condition [33]. In another study of 4929 consecutive autopsies performed during a period of 4 years, 222 patients

(4.5%) were identified to have liver cirrhosis, of whom 149/222 (67.1%) were known to have the condition but 73/222 (32.9%) had undiagnosed cirrhosis [31]. On further interrogation, 53 of the 73 silent undiagnosed cases appeared to have no clinical signs of liver cirrhosis. Interestingly, 16 percent of patients in the undiagnosed group died from hepatic complications. Not surprisingly, this was higher (70%) in the known cirrhotics. At autopsy, the presence of ascites (41% known cirrhotics vs. 8% undiagnosed cirrhotics), oesophageal varices (44% vs. 10%), splenomegaly (52% vs. 29%) was noted. The prevalence of hepatocellular carcinoma did not differ significantly in the two groups (12% vs. 8%). Another barrier to accurate fibrosis assessment is a reliance on standard LFT's, which are poor discriminators of significant liver fibrosis [88, 168, 169].

2.9.2 Advanced fibrosis and cirrhosis as a threshold target.

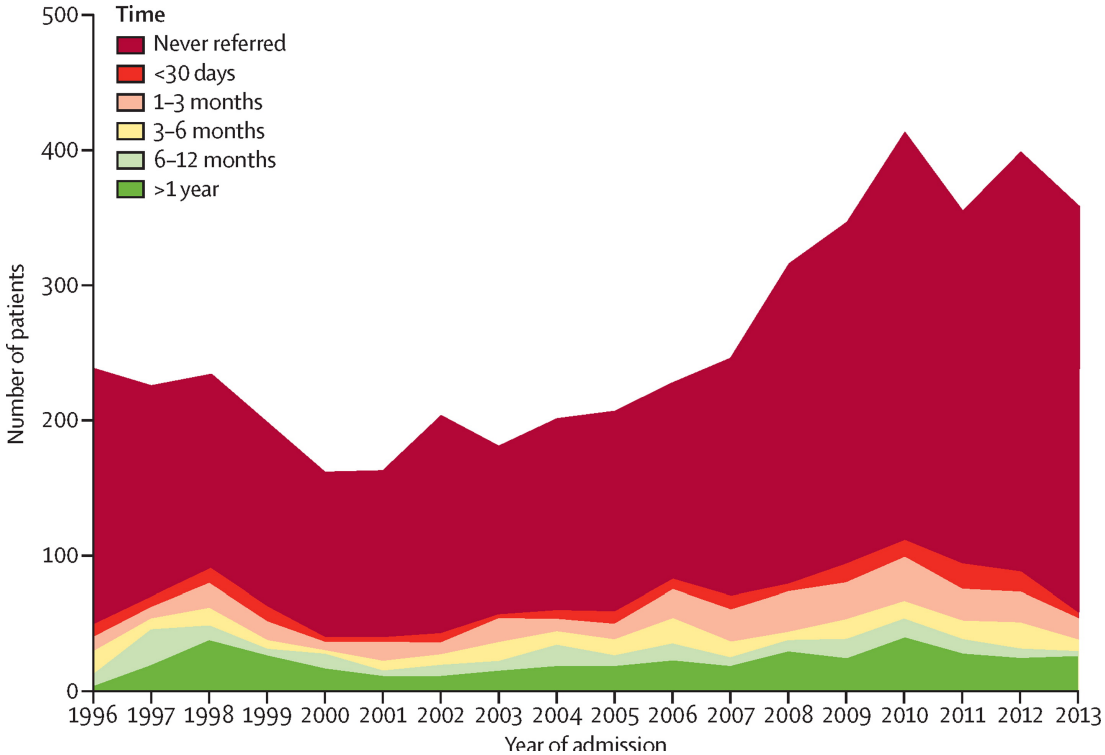
Whilst management of chronic liver disease differs by aetiology, a growing body of evidence indicates that liver fibrosis is the key factor that influences liver related outcomes. In particular, advanced fibrosis and cirrhosis (Brunt ≥F3) is associated with poorer outcomes, as detailed in section 2.5.4. A systematic review concluded that liver related mortality increases exponentially with increasing fibrosis stage. This analysis included over 1495 patients with 17,452 patient years follow up. Calculating fibrosis stage specific mortality rate ratios (MRR), liver related mortality increased by stage of fibrosis

compared to F0, with MRR 1.41, 9.57, 16.69 and 42.30 for F1, F2, F3 and F4 respectively [170].

2.9.3 The case for change

Large retrospective NHS database studies have revealed that patients with chronic liver disease are frequently diagnosed at a late stage, reflecting delays in recognition of their medical condition. Patients admitted with a first diagnosis of cirrhosis at University Hospitals Southampton, UK were analysed between 1996 and 2012 (Figure 2.7) [6]. The analysis of 4313 patients demonstrated that 73% of all newly diagnosed cirrhotics had not been referred to a hepatology clinic prior to their index presentation with end-stage liver disease necessitating admission with complications including jaundice, hepatic encephalopathy, bleeding varices and symptomatic hepatocellular carcinoma [6]. Furthermore, only 12% of patients had been known to specialist services for over a year before their first admission to hospital, suggesting that diagnosis of cirrhosis was delayed in the overwhelming majority of cases [6].

Figure 2.7 Time between referral to a liver clinic and first admission with liver cirrhosis. Reproduced with permission from Williams et al [6]



This delay in diagnosis and presentation of disease at the advanced stages inevitably impacts treatment options and prognosis. Another large retrospective UK database study spanning 20 years including over 5000 incident cases of cirrhosis demonstrated average survival probabilities at 1 and 5 years of 0.84 and 0.66 for patients identified with cirrhosis in the outpatient setting, as compared to 0.55 and 0.31 for patients presenting as an emergency with decompensated disease [171]. Focusing on hepatocellular carcinoma, Wong and colleagues [51] estimated a fifth of all patients presenting with HCC were staged with end stage (stage D) incurable disease where treatment

options were limited to symptomatic support and median survival less than 3 months. Only 30 percent were staged with curable disease (stage 0 and 1), where 5-year survival is quoted as between 40% and 70%. The remaining fifty percent (stage B and C) of patients did have treatment options but were incurable with median survival between 11 and 20 months.

The case for the earlier identification of patients with advanced fibrosis or cirrhosis appears compelling. However, some may argue that in view of the lack of effective liver-specific pharmacological and limited effect of non-pharmacological treatments in patients with NAFLD, the benefits of such an approach are potentially negligible. The current focus of treatment for patients with NAFLD is to aggressively optimize any underlying metabolic conditions such as diabetes and hypercholesterolaemia, and to promote weight loss. These interventions are the mainstay of treatment, regardless of the stage of liver fibrosis and so it could be reasoned that fibrosis stratification in primary care does not change management. Secondly, lifestyle interventions tend to have a low response rate due to poor uptake. Therefore, it could be rationalised that offering lifestyle interventions to all patients with NAFLD, regardless of fibrosis stage, will maximise benefit at a societal level, rather than focusing on patients with advanced fibrosis or cirrhosis. However, given that liver fibrosis is the key determinator of liver related morbidity and mortality, if disease progression from advanced fibrosis to cirrhosis is to be achieved through changes in lifestyle, and for interventions in cirrhosis to have optimal benefit, then there is a need to be able to firstly diagnose all cases of patients

with advanced fibrosis and secondly diagnose cirrhosis when it is asymptomatic. The earlier identification of patients with cirrhosis will allow the implementation of pathways of care which improve outcomes through targeted screening and treatment for portal hypertension [46] and hepatocellular carcinoma (HCC) [47].

2.9.4 Integrating non-invasive liver fibrosis tests into patient pathways

The premise of this thesis centres on the hypothesis that the earlier detection of significant liver disease (equivalent to Brunt ≥ F3) in primary care with serum biomarkers or elastography will improve patient outcomes including morbidity and mortality related to chronic liver disease. In summary, existing liver disease and fibrosis assessment is dependent on clinical assessment, serum liver function tests and ultrasonography in the primary care setting. However, these are poor surrogates for the presence of liver fibrosis [88, 168, 169]. Given that prognosis from chronic liver disease is dictated primarily by fibrosis severity, the challenge facing primary care physicians is the identification of patients with significant liver disease amongst those identified as being “at risk.” Patients with cirrhosis (Brunt F4) remain the most important group to identify so that evidence-based treatment and screening measures can be implemented. Patients with advanced fibrosis (Brunt F3) are a key target group as extensive liver damage has occurred and are at risk of liver cirrhosis. In the absence of disease modifying drugs, patients with mild fibrosis (Brunt F1) and

moderate fibrosis (Brunt F2) may not require specialist input if they are monitored in primary care for disease progression and steps are taken to help these people avert progression of their liver disease through changes in lifestyle. In addition, these individuals should be screened for other comorbidities that frequently accompany liver fibrosis such as diabetes, cardiovascular disease, and cancers. Suboptimal fibrosis assessment in primary care not only delays referral of patients with advanced liver disease but results in the referral of patients with mild disease who require aggressive management in the community but not specialist care. Inappropriate referral of these patients with no or early liver fibrosis represents service inefficiency and places unnecessary burdens on the patients and the healthcare services. For patients with NAFLD and non-significant fibrosis (Brunt ≤F2 disease), the appropriate preventative interventions are weight loss and exercise [172, 173] and these can be ably delivered in primary care [174] obviating the need for referral for specialist care.

The discovery, evolution and validation of non-invasive liver fibrosis tests [175] permits innovation of new patient pathways to allow more appropriate assessment and triage in primary care. Non-invasive tests have been validated for almost all aetiologies of CLD, including ARLD [125, 176, 177], NAFLD [178, 179] and viral hepatitis [180, 181], Collectively, they have strong NPVs so they perform well in excluding the presence of significant disease, whilst having acceptable PPVs. The use of non-invasive tests in hospital practice is increasingly established, both informally at the discretion of individual

clinicians and formally as part of care pathways for HBV [182] and the NHS England Hepatitis C treatment programme [183]. With an ever-increasing burden of risk for chronic liver disease in the general population including a rising incidence of excess alcohol consumption, obesity and diabetes, the need for improved risk stratification in the community is heightened.

The integration of non-invasive liver fibrosis tests in primary care pathways is attractive for these reasons. This may permit improved triage in the primary care setting, allowing identification of patients with advanced liver fibrosis and cirrhosis for specialist referral. Simultaneously, confidently excluding advanced fibrosis or cirrhosis would allow GPs to manage patients with non-significant fibrosis without referral to a specialist.

Given the increasing healthcare burden, societal impact and financial costs associated with patients with chronic liver disease, the case for change is compelling [6]. The introduction of non-invasive liver fibrosis markers in primary care to permit earlier detection of significant liver disease has been identified as a key strategy to combat the increasing burden of CLD [6, 98] and I will investigate this hypothesis in this thesis.

CHAPTER 3 SYSTEMATIC REVIEW: THE CLINICAL UTILITY OF NON-INVASIVE LIVER FIBROSIS TESTS IN COMMUNITY SETTINGS

3.1 Introduction

Over the past decade, the use of non-invasive liver fibrosis markers in clinical practice has become established in secondary and tertiary care. Both serum markers and elastography based methods form an important component of liver disease assessment by a specialist. In a patient with abnormal liver function tests or risk factors for chronic liver disease, the specialist can assess the presence or absence of advanced liver fibrosis using non-invasive liver fibrosis tests, which may influence decisions regarding further investigation and treatment as well as informing prognosis.

The use of non-invasive liver fibrosis tests (NIT) in primary care is less well established. In patients with chronic liver disease, the consequent liver fibrosis is usually asymptomatic in the early stages, but the severity of liver fibrosis is the key prognostic indicator of long-term liver related events and mortality [76, 184]. Thus, there is a clear role for the use of NIT in the early diagnosis of serious liver disease in the community. Standard care in primary care for diagnosis of chronic liver disease currently comprises clinical assessment, liver function tests and ultrasonography to assess the presence of clinically relevant fibrosis. This strategy can under- or over- estimate the stage of liver fibrosis as discussed in Chapter 2. There is a significant body of evidence that the current standard care contributes to delayed diagnosis. For example, over half of the patients newly diagnosed with liver cirrhosis in the United Kingdom

had decompensated cirrhosis manifest as variceal haemorrhage, ascites or hepatocellular carcinoma [5, 6] at their index presentation with cirrhosis.

The use of non-invasive tests for liver fibrosis can afford an opportunity to improve fibrosis detection and assessment in primary care and facilitate referral to a specialist in a timely manner. This chapter describes a systematic review performed to evaluate the existing literature on pathways of care using non-invasive liver fibrosis tests in community settings, with the aim of informing future research approaches.

3.2 Aims

To conduct a systematic review of the current literature to identify, appraise and summarise studies that have evaluated the performance of patient care pathways using non-invasive liver fibrosis tests in community settings to identify people with liver fibrosis amongst those at risk of liver disease.

3.3 Methods

3.3.1 Literature Search

This systematic review investigated studies conducted in patients suspected to have liver disease in the community (the “population”) that evaluated the performance of pathways using non-invasive liver fibrosis tests as an “intervention”, compared to standard care (the “comparator” group), to detect advanced fibrosis and cirrhosis (the “outcome”) as a proportion of patients referred to secondary care. The hierarchy of evidence for this type of study was determined to be that for interventions and so placed systematic reviews and meta-analyses of randomised controlled trials at the top, followed by

randomised controlled trials, before and after studies and case-control studies. This approach was considered preferable to conducting a systematic review of the diagnostic performance of NIT.

A systematic review was conducted in accordance with accepted published PRISMA and Cochrane Collaboration guidelines [185-187]. The following literature databases were interrogated:

- Electronic databases: 1940 – March 2016: MEDLINE (Pubmed), EMBASE, Science Citation Index Expanded, Web of Science (BIOSIS), The Cochrane Central Register of Controlled Trials in The Cochrane Library, LILACS methodology database
- Relevant websites: NICE guidelines, Clinical.trials.gov, UKCRN.

A sensitive search strategy was developed using both free-text words (for example “diagnostics”, “sensitivity”, “liver disease”, “elastography”) and Medical Subject Headings (MeSH) terms. A search strategy for MEDLINE (Pubmed) is described in Appendix 2 and this was modified for use for the other databases. The reference lists of identified studies and review articles were individually reviewed to increase the sensitivity of the search.

3.3.2 Inclusion Criteria

Studies reported in peer-reviewed journals and conference abstracts were included if they satisfied the following criteria and there were no exclusions;

1. Study population based in the community, including but not restricted to those in primary care settings managed by general practitioners or drug and alcohol services.
2. Study intervention involved use of a liver fibrosis test (including but not restricted to FIB-4, NFS, ELF test, Fibroscan, Fibrotest and liver biopsy).
3. The purpose of the study was to identify patients at risk of chronic liver disease (CLD) by targeting those at risk or the untargeted population.
4. Study outcome included but not restricted to identification of significant liver disease, referral rates to secondary care and mortality.

3.3.3 Exclusion criteria

Studies were excluded if any of the following criteria were satisfied:

1. Duplicate publications of a primary study that contained all or some of the original data.
2. Narrative reviews, letters, editorials, commentaries, lectures and addresses, books and chapters.
3. Cost-effectiveness studies without primary data.
4. Abstracts that had insufficient information to appraise the methods or results.
5. Studies using fibrosis tests in the secondary care setting.
6. Non-English articles.

3.3.4 Study selection

All titles and abstracts identified by the search were screened against the inclusion and exclusion criteria by two reviewers (AS and WMR). Duplicate records were removed by Endnote. The full text of published manuscripts was obtained to allow further evaluation. All full papers and abstracts published in the English Language, and studies published as abstracts or conference proceedings were included if sufficient details were presented to allow appraisal of the methods and results.

3.3.5 Data extraction

Information about the design, conduct and results of studies were obtained from the published literature. Published trial protocols were sought where available. A data collection tool was developed to capture:

- Patient demographics
- Study characteristics
- Disease or patient population targeted,
- Criteria for participant inclusion and exclusion,
- Non-invasive liver fibrosis tests used,
- Methods for handling indeterminate or missing data,
- Outcomes measured and intervention performance characteristics if available.

Data extraction was conducted by one reviewer (AS) from the primary studies and was independently checked by a second reviewer (JP). In the case of

disagreement, consensus was sought initially through discussion between the two reviewers, and where necessary with input from a third reviewer (WMR).

3.3.6 Data analysis and synthesis

The primary outcome was the effectiveness of the stratification pathway in detecting patients with cirrhosis or advanced fibrosis as an outcome determined as either:

- A liver biopsy or
- Composite clinical judgement (which included clinical, radiological and other methods including fibroscan).

Given a lack of validated reference standard in the community setting, flexibility was exercised.

Data are presented in tables summarizing the results extracted from the included studies. Data assessing the identification of patients with clinically insignificant (≤F2 fibrosis) and advanced fibrosis (F3 fibrosis) or cirrhosis (F4 fibrosis) were extracted from the studies. If sufficient, the post-test probability of cirrhosis after use of the pathway was calculated, as were the true positive and false positive rates for the pathway if validation against a reference standard was available. Pre-study scoping suggested that the review analysis would be restricted to a narrative approach because of the lack of primary care studies evaluating non-invasive liver fibrosis markers compared to a suitable comparator group or reference standard. In such a context where the scope to

perform a meta-analysis is limited, narrative analysis is an effective method to express and synthesize the results of studies [188].

3.3.7 Quality assessment of primary studies

The methodological quality of the identified studies was evaluated using the Cochrane Collaborations Tool for Assessing Risk of Bias for reviews of the effects of interventions [186]. Studies were assessed for quality against seven specific domains, namely

- Sequence generation
    - Assessing for selection bias - exploring systematic variations between baseline characteristics of the different groups that are compared, and the adequacy of the recruitment method for generalisability to the target population.
- Allocation concealment
    - Assessing for selection bias - exploring systematic variations between baseline characteristics of the different groups that are compared.
- Blinding of participants and personnel
    - Assessing performance bias – exploring systematic variations between groups in the care that is provided, or factors other than the intervention.
- Blinding of outcome assessment
    - Assessing detection bias – exploring systematic variations within or between groups in determining outcomes.

- Incomplete outcome data
    - Assessing attrition bias – exploring systematic variations within or between groups in withdrawals from the study
- Selective outcome reporting
    - Assessing reporting bias – exploring systematic variations within or between groups regarding reported and unreported data.
- 'Other' issues.

For each identified study, these domains were evaluated using a two-step approach [189]. The first step of the process was to collate the relevant reported data from the manuscript. The second step was to ascribe a risk of bias status – namely "low risk of bias", "high risk of bias", or "unclear risk of bias" as per the assessment tool [186]. One reviewer (AS) assessed the quality of the identified studies and his judgement was independently checked by a second reviewer (JP). In the case of disagreement, consensus was sought initially through discussion between the two reviewers, and where necessary with input from a third reviewer (WMR).

Domains were ascribed a "high risk of bias" when plausible bias was identified that seriously weakens confidence in the results. A "low risk of bias" was determined if no plausible bias that seriously weakens confidence in the results was identified [186]. Thereafter, an assessment of the risk of bias for an individual study was made in line with the guidance provided by the Cochrane Collaboration (2011) [186]. The review adopted the Cochrane recommendation that a study is deemed to be at "high risk of bias" if one or

more domain is determined to be “high risk”, whereas a study would be at “low risk of bias” if all the domains were determined to be “low risk”.

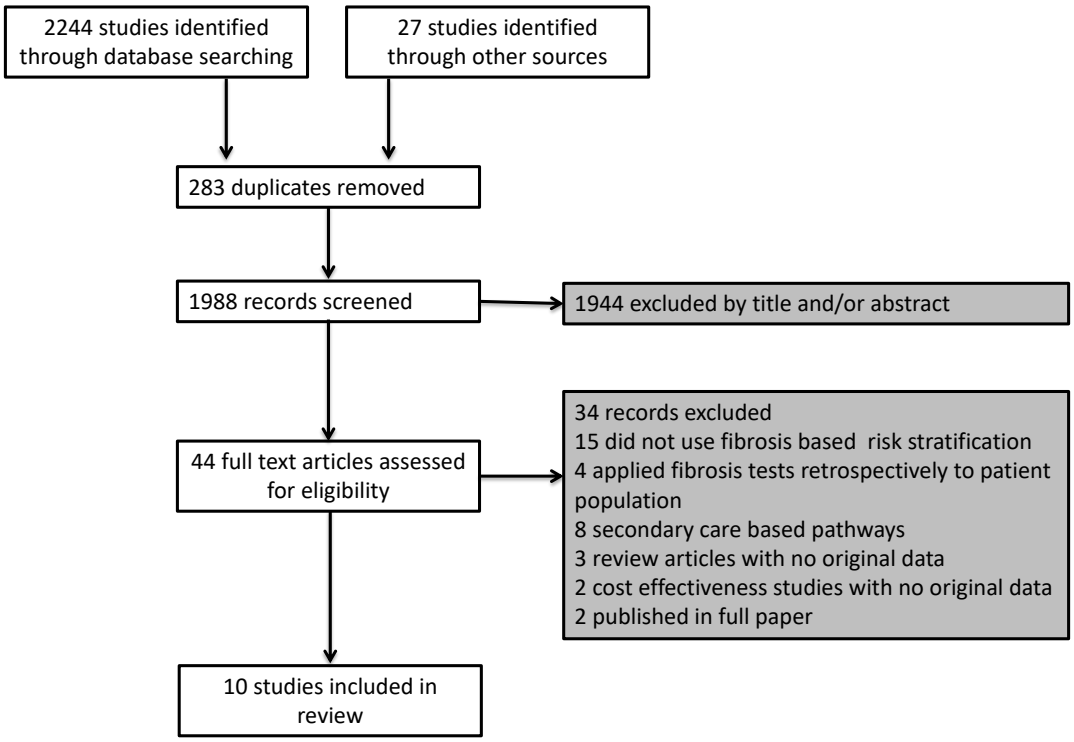
3.4 Results

3.4.1 Search results

The search strategy of electronic databases identified 2,271 references. The outcomes of selection of articles are summarised below and in Figure 3.1. After screening the titles and abstracts of all the identified references, 283 duplicates were identified, and a further 1,944 excluded after screening against the inclusion and exclusion criteria. Forty-four full papers were retrieved and reviewed, of which 34 studies were excluded leaving 10 studies to be included in the final review. The reasons for excluding studies at the final stage included:

- Risk assessment in primary care was not based on fibrosis (usually alcohol consumption risk stratification) (n=15)
- Fibrosis assessment based in secondary care (n=8)
- Retrospective fibrosis assessment with no prospective patient management (n=4)
- Review article with no original data (n=3)
- Duplicate publications of a primary study that contained all or some of the original data (n=2)
- Cost effectiveness studies with no primary data (n=2)

Figure 3.1 Flow diagram of search results and study selection for systematic review



3.4.2 Study Characteristics

Characteristics of the ten identified studies are summarized in Table 3.1. All identified studies were conducted between 2010 and 2016. No systematic reviews or meta-analyses were identified. The majority (n=9) were cross-sectional studies, and one was a 'before and after' cohort study design. One study did randomly select patients for recruitment using unspecified computer software [190] whilst in the remainder, consecutive patient recruitment (n=6), postal invitation (n=2) and local newspaper advertisement (n=1) methods were employed.

In the ten included studies, the median age of participants was 47.2 years (range 37 -59.7 years), 61.5% were male (range 41-74%), whilst median and

mean study size were 450 (range 100 – 7463) and 1262.9 participants respectively.

Table 3.1 Characteristics of studies identified in systematic review evaluating use of non-invasive liver fibrosis tests in community setting.

ETOH: Alcohol, HCV: Hepatitis C, MRE: Magnetic Resonance Elastography, NILT: non-invasive liver fibrosis test, N/R: Not recorded STL: Southampton Traffic Light test, T2DM: Type 2 diabetes

***when reported**

Author, year published, Country, number of centres*, study dates*	Total no patient	Study design and setting	Patient selection	Age Mean (years)	% male	Intervention (Noninvasive test)	Comparator/ reference standard
Moussalli [191] 2010 France 1 centre 2002 – 2004	337	Before and after study in drug addiction centre.	Patient with HCV Consecutive prospective patient recruitment.	37 (pre-intervention) 40 (post)	N/R	Fibrotest	Standard care – referral to hospital for specialist management.
Poynard [192] 2010 France 2 centres 2006 – 2008	7463	Prospective cross-sectional study in social security health centres.	Healthy adults > 40 yrs. Consecutive prospective patient recruitment.	N/R	N/R	Fibrotest	Secondary care reinvestigation for patients with advanced fibrosis.
Moessner [193] 2011 Denmark Multi-centre (Study date not specified)	450	Prospective cross-sectional study in all regional treatment centres	Registrants at drug treatment centres. Consecutive prospective patient recruitment.	42	74%	Fibroscan	Liver biopsy for patients with TE ≥12KPa

Author, year published, Country, number of centres*, study dates*	Total no patient	Study design and setting	Patient selection	Age Mean (years)	% male	Intervention (Noninvasive test)	Comparator/ reference standard
Roulot [194] 2011 France 1 centre 2005 – 2008	1358	Prospective cross sectional study in a social security centre.	Healthy adults >45 yrs. Consecutive patient recruitment.	57.8	59.2%	Fibroscan	Liver biopsy to be considered for patients with TE > 8.0 KPa.
Fabrellas [190] 2013 Spain Multi-centre. (Study date not specified)	502	Randomized prospective cross sectional study in local healthcare region.	Healthy adults (18-70 yrs.) Random identification from state health registry.	47.2	41%	Fibroscan	N/R
Grattagliano [195] 2013 Italy (Study date not specified)	259	Prospective cross-sectional study in primary care.	NAFLD (18-65 yrs.) Consecutive patient recruitment.	51	59.2%	Fibrotest	N/R
Sheron [196] 2013 UK 9 centres (Study date not specified)	393	Prospective cross-sectional study in primary care.	Alcohol excess (25-54 yrs. AUDIT≥8). Recruited via postal invitation.	N/R	N/R	Southampton Traffic Light (STL)	N/R

Author, year published, Country, number of centres*, study dates*	Total no patient	Study design and setting	Patient selection	Age Mean (years)	% male	Intervention (Noninvasive test)	Comparator/ reference standard
Harman [87] 2015 UK 2 centres (Study date not specified)	504	Prospective cross-sectional study in primary care.	Alcohol excess or T2DM or ↑ALT. Recruited via postal invitation	N/R	69.8%	ETOH – AST: ALT T2DM or ↑ALT – BARD. Fibroscan if raised.	TE >8.0 => community hepatology review. Liver biopsy if uncertainty.
Doycheva [197] 2016 USA (Study date not specified)	100	Prospective cross-sectional study in local district area.	T2DM. Recruited via local advertisement	59.7	53%	MRE	N/R
Koehler [198] 2016 Holland 2011 – 2013	3439	Prospective cross-sectional study in local district area	Healthy adults > 45 yrs. Consecutive prospective patient recruitment.	66.0	45%	Fibroscan	N/R

Heterogeneity in the target population, fibrosis tests used and study outcomes amongst the identified studies precluded meta-analysis or pooling of results. The lack of consistent reference standard or pathway diagnostic evaluation (calculation of sensitivity or specificity) prevented formulation of forest plots. In view of these barriers, a narrative summary was composed. Table 3.2. summarises the outcomes of the identified studies.

The primary care risk stratification strategies targeted a number of different populations; namely population-based screening of 'healthy adult' populations (n=4), substance users attending drug treatment units (n=1), substance users with confirmed HCV attending drug treatment units (n=1), diabetics (n=1), alcohol excess (n=1), multiple risk factors (n=1) and patients diagnosed with NAFLD (n=1).

Fibroscan was the most extensively investigated non-invasive liver fibrosis test (n=5) with studies from France, Denmark, Spain, Holland, and the UK exploring its utility in the community setting, whilst one study investigated the role of Magnetic Resonance Elastography (MRE) in detecting advanced fibrosis in patients with NAFLD diagnosed by their GP. The remaining 4 studies explored serum-based testing strategies using Fibrotest (n=3) and the Southampton Traffic Light (STL) tests in primary care, a calculation based on hyaluronic acid (HA), procollagen III N-peptide (P3NP) and platelets (n=1).

Identification of advanced liver fibrosis or cirrhosis was the primary outcome in the majority of studies (n=7, 70%). No study used the reference standard, namely liver biopsy, in all participants i.e., patients deemed to be at "low-risk" and "high-risk" of advanced fibrosis or cirrhosis. Only one study attempted to

assess the performance of the intervention on identifying advanced fibrosis against a reference standard or comparator group in a consistent manner. Poynard and colleagues [192] developed a protocol in France whereby patients with an abnormal community fibrotest score (>0.48) would be invited for reinvestigation in secondary care. A hepatologist would review the case, repeat the fibrotest score and perform a fibroscan prior to consideration of liver biopsy. It should be noted that uptake of reinvestigation was half of the eligible population (50.3%, 105 out of 209 eligible patients). In patients re-investigated with fibroscan, 47 out of 105 patients (42.8%) had ≥7.1 kPa (considered "fibrosis confirmed" by the authors), 27 patients (25.7%) had fibroscan readings between 5 kPa and 7 kPa (considered "fibrosis still suspected") and 28 patients (26.6%) <5 kPa (considered "fibrosis indeterminate". Only 4 patients (4%) accepted liver biopsy, of whom 3 were considered "fibrosis confirmed", although sub-analysis of the liver biopsy group was not described in detail. In a subpopulation of 'normal' fibrotest patients, fibroscan was performed to calculate a false negative rate (3 out of 766 patients, 0.4%).

A further 3 studies [87, 193, 194] used a reference test in a sub-group of patients – usually those identified as 'high-risk' of advanced fibrosis or cirrhosis. In a Nottingham (United Kingdom) based study [87], all patients with an abnormal community fibrosis test were eligible for review by a visiting hepatologist in the community for consideration of further evaluation including liver biopsy. All 98 eligible patients attended community review according to the authors. Further evaluation, where appropriate, would include ultrasonography and liver biopsy. Cirrhosis was definitely diagnosed based on established clinical, radiological, fibroscan and histological parameters.

Twenty-five out of 98 patients (25.5%) had liver biopsy, of whom 20 patients had hepatic fibrosis. Moessner et al [193] evaluated fibroscan in drug users. All patients with fibroscan ≥ 8.0 kPa were referred to a local hospital. Whilst all patients ≥12 kPa were recommended for liver biopsy, 19 out of 45 patients (42%) declined further investigation. Roulot et al [194] evaluated fibroscan in the general population. Liver biopsy was considered in all patients with fibroscan ≥ 8.0 kPa and recommended in all patients with ≥13 kPa. All 9 patients with fibroscan ≥13 kPa accepted liver biopsy, and all had liver cirrhosis histologically. Sixty-six out of 80 patients with fibroscan between 8kPa and 13kPa accepted re-evaluation, but 16 patients refused biopsy when recommended.

One study evaluated the impact of using non-invasive tests on treatment initiation in patients with viral hepatitis C [191], whilst another explored impact on alcohol behavioural change [196]. Another study had a primary outcome of detecting hepatic steatosis [197], and fibrosis assessment as a secondary outcome. Findings from these studies are described in Table 3.2.

Table 3.2 Performance of community pathways employing non-invasive liver fibrosis tests to detect clinically significant liver disease.

MRE: Magnetic Resonance Elastography, STL: Southampton Traffic Light, TE: Transient elastography/ Fibroscan

Study	Marker	Fibrosis stage targeted	Primary care stratification				Fibrosis reassessment (pathway performance)					Other comments
			≤F2	≥F3	F4	Failure	TN	FN	TP	FP	indeter minate	
Healthy population												
Poynard [192] 2010	Fibrotest	Advanced fibrosis (cut-off 0.48)	7254 (97.2%)	209 (2.8%)	25 (0.3%)	33 (0.4%)	763/766 (99.4%)	3/766 (0.4%)	50/105 (47.6%)[1]	28/105 (26.7%)	27/105 (25.7%)	After reinvestigation 9 confirmed cases of cirrhosis
Roulot [194] 2011	TE	≥F3 fibrosis (TE ≥8.0)	1101 (82.5%)	89 (6.6%)	9 (0.007 %)	145 (10.8%)	-	-	9/50 (18%)	41/50 (82%)	-	21 patients biopsied 9 confirmed cirrhosis
Fabrellas [190] 2013	TE	Significant liver fibrosis (TE ≥6.8)	467 (94.3%)	28 (5.7%)	-	7 (1.4%)	-	-	-	-	-	
Koehler [198] 2016	TE	Significant fibrosis (TE ≥8.0)	2879 (94.4%)	169 (5.6%)	19 (0.6%)	162 (4.8%)	-	-	-	-	-	
Community drug centre												
Moessner [193] 2011	TE	Significant fibrosis (TE ≥8.0)	289 (72%)	111 (28%)	45 (11%)	50 (11.1%)	-	-	15	11	-	9/20 biopsies confirmed cirrhosis
NAFLD												
Grattagliano [195] 2013	Fibrotest	≥F3 fibrosis	225 (86.9%)	34 (13.1%)	-	-	-	-	14/16 (87.5%)	2/16 (12.5%)	-	16 patients had liver biopsy
Hepatitis C (in community drug centre)												
Moussalli [191] 2010	Fibrotest	≥F3 fibrosis	147 (66%)	77 (34%)	-	-	-	-	-	-	-	Primary outcome was HCV treatment initiation rate

Study	Marker	Fibrosis stage targeted	Primary care stratification				Fibrosis reassessment (pathway performance)					Other comments
			≤F2	≥F3	F4	Failure	TN	FN	TP	FP	indeter minate	
Targeting risk factors												
Harman [87] 2015 (ETOH, T2DM, ↑ALT)	BARD/ AST:ALT / TE	Clinically significant disease (TE ≥8.0)	268 (73.2%)	98 (26.8%)	-	12 (3.1%)	-	-	20/25 (80%)[2]	5/25 (20%)	-	11 confirmed cirrhosis
Sheron [196] 2013 (ETOH)	STL	Clinically significant disease (Red/ Amber)	191 (48.6%)	202 (51.4%)	-	-	-	-	-	-	-	Primary outcome was AUDIT category change after 1 year.
Doycheva [197] 2016 (T2DM)	MRE	Clinically significant disease (TE ≥8.6)	91 (92.9%)	9 (7.1%)	-	0	-	-	-	-	-	1 case of HCC detected incidentally

1. 50/105 participants deemed to have fibrosis after reinvestigation. However, fibrosis stage not documented

2. 20/25 liver biopsies demonstrated stage 1-4 fibrosis

3.4.3 Target population

The risk stratification of unselected 'healthy population' subjects was the most common patient selection strategy (n=4). All were prospective cross-sectional studies of reasonable size, with a range of 502 to 7463 participants. Two French studies recruited from community social security centres [192, 194] whilst a Spanish study recruited directly from the local healthcare authority [190]. These approaches identified advanced fibrosis in 2.8% [192], 5.6% [198], 5.7% [190] and 7.5% [194] of healthy patients with an appreciable number of subjects determined to have underlying cirrhosis – 0.075% (all confirmed after reinvestigation) [194], 0.3% (36% confirmed after reinvestigation, with only 50.2% of high risk individuals reinvestigated) [192] and 0.6% (no reinvestigation data available) [198].

Two pathways recruited patients from community drug centres, one targeting all registrants [193] and one restricted to patients with confirmed hepatitis C virus (HCV) [191]. Moussalli and colleagues described a novel multidisciplinary approach including a hepatologist and specialist nurse who used fibrotest to risk stratify patients with HCV [191], reporting an increase in HCV treatment rates from 2% pre-intervention to 38% post-intervention. It was postulated that accurate fibrosis assessment contributed to this observation. In this before and after study, advanced fibrosis and cirrhosis was documented as 34% and 11% respectively in the post intervention group.

Targeting individuals with risk factors for CLD was a common strategy (n=3). All were prospective cross-sectional studies with reasonable participant

numbers (median 393, range 100 – 504). Harman and colleagues conducted fibrosis assessment in two primary care practices targeting patients with type two diabetes, history of alcohol excess or raised ALT. Advanced fibrosis was detected in 26.2% of participants after fibroscan [87] and these cases were referred for further hepatological investigation. An American study recruiting patients with type two diabetes from primary care for secondary care Magnetic Resonance Elastography (MRE) revealed an advanced fibrosis rate of 7.1% [197]. Another study looking at patients with alcohol excess using the Southampton Traffic Light (STL) test found 51% to be high risk of CLD but did not classify by fibrosis stage [196].

3.4.4 Non-invasive liver fibrosis testing strategy

Harman and colleagues used a two-tier approach using BARD or AST: ALT ratio (depending on aetiology) to identify high-risk patients who needed community fibroscan [87].

All other identified studies used a single-tier approach. Fibroscan (n=5) was the most extensively investigated non-invasive fibrosis test in community pathways. For the detection of advanced fibrosis, three studies used a cut-off of 8.0 KPa, whilst the remaining two used a 6.8 KPa cut-off. The ≥F3 fibrosis rates were estimated at 28% in registrants in community drug centres [193], compared to 6.78% and 5.7% in healthy individuals [190, 194] and 26.8% when targeting patients with diabetes, alcohol excess or raised ALT [87]. The median fibroscan failure rate was 7.1% (range 1.4%-11.1%). There was no

standardized re-assessment of patients referred to secondary care, with most relying on liver biopsy data when clinically indicated.

Three studies utilized fibrotest. The advanced fibrosis rate was 2.8% in the general population [192] and 13.1% in NAFLD [195]. A study investigating patients with hepatitis C in drug treatment centres revealed mean fibrosis to be 0.46 +/- 0.26 (equivalent to Brunt F1-F2).

A study using MRE in patients with type 2 diabetes detected 7.1% had advanced fibrosis or cirrhosis (≥F3 fibrosis). Interestingly, the study identified one patient with an incidental hepatocellular carcinoma.

3.4.5 Risk of bias assessment

The ten identified studies were critically evaluated using the Cochrane collaboration tool for assessing risk of bias [186, 188]. Each study was assessed against 7 domains, and the individual assessments can be found in Appendix 3. Overall results are summarised in Table 3.3.

Table 3.3 Risk of bias summary for the ten identified studies in systematic review

Identified studies were assessed according to the Cochrane collaboration tool [186]

L: low risk of bias, U: unclear risk of bias, H: High risk of bias

	Random selection generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	**OVERALL ASSESSMENT**
Moussalli [191] 2010	H	H	L	H	L	L	**H**
Poynard [192] 2010	H	H	L	H	L	L	**H**
Moessner [193] 2011	H	H	H	H	L	H	**H**
Roulot [194] 2011	H	H	H	L	L	H	**H**
Fabrellas [190] 2013	U	H	L	H	L	H	**H**
Grattagliano [195] 2013	H	H	L	L	L	H	**H**
Sheron [196] 2013	H	H	H	H	H	H	**H**
Harman [87] 2015 (2)	H	H	L	H	L	L	**H**
Doycheva [197] 2016	H	L	L	L	L	L	**H**
Koehler [198] 2016	H	L	L	L	L	L	**H**

Each study had limitations in design and implementation and had at least one domain that was susceptible to a high risk of bias. More than one domain was found to be at high risk in 80% of studies. No studies were identified with low risk of bias, suggesting results need to be interpreted with caution. Using the Cochrane GRADE approach, the quality of the evidence was low (observational studies) or very low (downgraded observational studies) [186].

3.5 Discussion

In this systematic review evaluating the effectiveness of introducing non-invasive liver fibrosis tests in community liver fibrosis risk stratification pathways, ten primary studies were identified. There was significant heterogeneity in the populations targeted, the non-invasive test used, and the study outcomes measured.

The risk stratification strategies targeted different patient populations including the untargeted screening of the 'healthy' population with fibroscan (n=3) and fibrotest (n=1). In the 'healthy' population, a median rate of detection of ≥F3 fibrosis 5.7% (range 2.8% - 7.5%) was identified.

Targeting patients with risk factors for chronic liver disease increased the yield of clinically significant liver fibrosis. An American study evaluating MRE in patients with diabetes identified ≥F3 fibrosis in 7.5% of patients [197]; whilst stratifying patients with alcohol excess, diabetes or raised transaminases using BARD score, AST:ALT ratio and elastography identified advanced fibrosis or cirrhosis in 26% of patients [87]. Furthermore, evaluating unselected attendees of community drug centres identified 28% of patients as high risk of

advanced fibrosis or cirrhosis[193] and 51.4% in patients with alcohol excess using the Southampton Traffic Light scoring system [196].

Finally, applying non-invasive fibrosis stratification in patients with existing liver disease was evaluated in two studies. Risk stratification in patients with NAFLD using fibrotest identified significant liver disease in 13.1% [195] and in 34% of patients with HCV in community drug centres [191].

It is postulated that one benefit of using non-invasive fibrosis testing in the community is the potential for large scale population screening, as compared to liver biopsy for example. The elastography-based studies were performed in single centre or a limited number of centres in medium to large sized populations ranging 502 – 3,439 participants [190, 192]. The published literature did not comment on the applicability of the method and difficulties encountered in providing fibroscan in the community setting, but no notable barriers were reported suggesting that using fibroscan outside hospital settings is feasible, provided the machine and clinic space are available and trained technicians are available to work in the community. A number of studies utilized serum fibrosis tests. The application of Fibrotest in two French Social security centres allowed Poynard et al. to screen a significantly larger number of individuals (7,463 healthy individuals over 3 years) identifying 2.8% with advanced fibrosis [192].

Of the ten studies identified, only 5 re-evaluated the outcomes of patients identified at risk of chronic liver disease. In all cases, this was in the form of re-evaluation by a specialist or a liver biopsy in those identified at risk of liver

cirrhosis. However, both the re-evaluation rates, and acceptance of liver biopsy, often restricted interpretation of the true and false positive rates in the published studies.

Only one study attempted to assess the false negative rate by re-evaluating the fibrosis stage in individuals deemed to be at low risk of clinically significant disease. Poynard and colleagues performed fibroscan in patients identified as low risk of advanced fibrosis by fibrotest (false negative rate 3 out of 766 patients, 0.4%). [192].

The heterogeneity of the study populations, tests investigated, and test cut-offs employed, coupled with the paucity of studies, limit the generalizability of the results. Additionally, it is inevitable that the prevalence of the target condition, namely advanced fibrosis or cirrhosis (≥F3 fibrosis), differed between studies. This would influence the performance of the non-invasive tests dependant on the distribution of fibrosis within a population because of spectrum bias [85]. For example, a test which has a high sensitivity across lower test scores will perform better in low prevalence populations as the negative predictive value will be higher. Direct comparisons of test diagnostic performance using area under the receiver operator curve (AUROC) between studies are therefore susceptible to error. This can be addressed using statistical correction methods including the Obuchowski measure [199] and “Difference between Advanced and Non-Advanced (DANA) fibrosis stages” [200]. However, this was not applicable in this systematic review as the diagnostic accuracy of the non-invasive tests was not evaluated, rather the

focus was on the performance of the pathways as an intervention (see section 3.3.1).

Using the Cochrane Collaboration tool for assessing risk of bias, all studies were deemed susceptible to bias. Whilst all studies were explicit about patient selection and exclusion criteria, none used an accepted reference standard to reassess patients at high risk. Therefore, caution needs to be exercised when drawing conclusions.

This systematic review has a number of strengths and limitations. It was conducted in adherence to published guidelines for systematic review [186]. Two reviewers independently assessed eligibility, whilst two reviewers were involved in the data extraction and assessment of bias, increasing the robustness of the literature review. As is common to all systematic reviews, despite this rigorous method, relevant studies may have been missed and the review remains susceptible to publication bias, with studies with negative results not published. This review was conducted in 2016, and it is inevitable that in the intervening period, new published literature is available.

This review highlighted a lack of good quality evidence in the published literature and identified a need for further studies to inform future clinical strategies. In particular, there is a lack of disease specific studies. The aim of the studies is to improve identification of patients with advanced fibrosis or cirrhosis earlier and a robust study would compare all participants to a reference standard, namely liver biopsy. This is, however, difficult to justify as community populations have a predominantly low rate of advanced fibrosis, as

opposed to carefully selected secondary care populations. Subjecting liver biopsy to these individuals in a trial setting could be considered unethical.

Despite the heterogeneity and relative paucity of published studies, the available literature supported the use of non-invasive liver fibrosis tests in asymptomatic individuals for identifying patients at risk of significant fibrosis in the order of 2.8% - 51.4%, and cirrhosis in 0.075%-11.1%.

3.6 Conclusion

This systematic review, conducted in 2016, highlighted potential regarding the utility of non-invasive liver fibrosis tests in the community setting to facilitate earlier detection of clinically significant disease. The review demonstrates the paucity of high-quality evidence that exists in the current literature base, in particular targeting specific diseases such as NAFLD. Nevertheless, the available studies provide valuable evidence of the potential of non-invasive fibrosis markers in primary care and their results should be interpreted with cautious optimism and reinforce the need for further studies in the field.

CHAPTER 4 NATIONAL SURVEY INVESTIGATING THE POTENTIAL ROLE OF NON-INVASIVE LIVER FIBROSIS TESTS IN PRIMARY AND SECONDARY CARE PATHWAYS

4.1 Introduction

A combination of rising morbidity and mortality associated with chronic liver disease (CLD) coupled with an ever-increasing burden on healthcare systems demand innovation in strategies to improve patient outcomes [6]. Patients are frequently diagnosed with liver disease at the latter stages of the condition which limits treatment options and has a negative impact on patient prognosis [6, 171, 201]. In the current standard care model, diagnostic tests used in primary care lack sufficient sensitivity and specificity to detect advanced fibrosis and cirrhosis (equivalent to Brunt ≥F3), contributing to delayed recognition of advanced liver disease. The expanding body of evidence suggests that morbidity and mortality substantially increase with the development of advanced fibrosis or liver cirrhosis [75, 76]. This combined with the evolution of non-invasive liver fibrosis markers has created the opportunity to explore the use of NIT to improve early detection of advanced liver disease in community settings.

At the time of developing an outline for this thesis, there was a limited understanding of the use of non-invasive liver fibrosis tests (NIT) in the United Kingdom, both in primary and secondary care. The systematic review described in Chapter 3 revealed a dearth of published literature regarding the utility of non-invasive liver fibrosis tests in the community setting. This chapter reports a national survey evaluating the “real-life” use of non-invasive liver

fibrosis tests in secondary care by UK specialists who manage liver disease. The objective was to assess current attitudes towards NIT and to uncover unpublished patient pathways using NIT.

4.2 Aims of study

The aim of this national survey was to determine the current attitudes and practices of secondary care specialists involved in the management of patients with liver disease in the United Kingdom, focusing on their attitudes to liver fibrosis assessment (LFA), their current knowledge and use of non-invasive liver fibrosis tests, and their use in designated patient pathways.

4.3 Methods

4.3.1 Dissemination

Opinio (ObjectPlanet Inc.) is a web-based survey tool and was used to distribute the survey to gastroenterology and hepatology specialists involved in the care of patients with CLD. Participants were identified from three sources:

(1) General Medical Council registered gastroenterologists/ hepatologists.

(2) Gastroenterologists/ Hepatologists/ speciality registrars/ physicians/ specialist nurses registered with the British Society of Gastroenterology.

(3) Gastroenterologists/ Hepatologists/ speciality registrars/ physicians/ specialist nurses registered with the British Association for the Study of the Liver.

Respondent confidentiality was maintained as responses to the survey were anonymous (unless the respondent chose to declare personal details in the comments section).

4.3.2 Survey design

This study of practice and perception of liver fibrosis assessment and the role of non-invasive liver fibrosis tests was a cross-sectional survey.

The survey was designed to explore the following themes:

(1) Respondent demographics (healthcare role, grade, location).

(2) Current practice of liver fibrosis assessment (including role of liver biopsy and non-invasive fibrosis tests).

(3) The potential of non-invasive fibrosis tests to determine liver fibrosis severity in clinical practice.

(4) The barriers to implementation of non-invasive fibrosis tests in clinical practice.

(5) The use of non-invasive fibrosis tests in clinical pathways.

The answers were either orientated (choice of different options), matrix of choices (multiple answers per row), semi-quantitative (“never”, “up to a quarter” etc.), or open-ended (unrestricted free text).

I designed and developed the survey before distributing to my educational supervisors and colleagues (WMR, ET, JP) for their review and input. The

survey underwent a validation pilot with colleagues in the UCL Institute for Liver and Digestive Health. Their feedback informed revisions resulting in a five-page survey with a total of 11 questions (Figure 4.1).

Figure 4.1 National survey investigating the attitudes of UK specialists to liver fibrosis assessment and non-invasive liver fibrosis tests (distributed October 2014 – October 2015).

Non invasive tests National Survey

Q1: What is your primary speciality?

- ◯ Hepatology
- ◯ Gastroenterology
- ◯ Primary Care
- ◯ General/ Internal Medicine
- ◯ Other (please specify)

If you have chosen "other", please specify:

Q2: What is your role?

- ◯ Consultant/ General Practitioner
- ◯ Specialist Registrar Trainee
- ◯ Nurse specialist
- ◯ Other (please specify)

If you have chosen "other", please specify:

Q3: Please name the hospital or the NHS foundation trust that you currently work for? (please leave blank if you prefer not to specify)

Q4: In what proportion of your patients with liver disease do you assess the fibrosis stage? (please select one)

- ◯ Never (0%)
- ◯ Up to a quarter of cases (1-25%)
- ◯ Up to half of cases (26-50%)
- ◯ Up to three quarters of cases (51-75%)
- ◯ Nearly all cases (76-99%)
- ◯ All cases (100%)

Q5: What are the clinical reasons for liver biopsy in your clinical practice? (please tick all that apply)

	Indication for liver biopsy
Assessment of fibrosis stage as 'standard of care'	☐
To allow prognosis assessment	☐

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To guide treatment decisions	☐
To assess response to treatment	☐
To diagnose aetiology of liver disease (acute or chronic)	☐
Other (please specify)	☐

Any additional comments:

Q6: Do you think non-invasive liver fibrosis tests are a suitable alternative to liver biopsy in the following scenarios? (please select one option per row)

	Non invasive tests a suitable alternative to biopsy	Non invasive tests useful only as an adjunct to biopsy	Non-invasive tests not useful
Assessment of fibrosis stage as 'standard of care'	○	○	○
To allow prognosis assessment	○	○	○
To guide treatment decisions	○	○	○
To assess response to treatment	○	○	○
To diagnose aetiology of liver disease (acute or chronic)	○	○	○
Other (please specify)	○	○	○

Any additional comments:

Q7: In patients with chronic liver disease, which methods to accurately stage liver fibrosis are you aware of and/ or use in clinical practice? (please select one option per row)

	Never heard of test	Not useful for liver fibrosis assessment	Useful for liver fibrosis assessment but do not use in clinical practice	Use in Clinical Practice for fibrosis assessment
Clinical Examination	○	○	○	○
Standard Liver Function Tests (LFT's)	○	○	○	○
Liver synthetic function tests (i.e. INR, albumin)	○	○	○	○
AST to Platelet Ratio (APRI)	○	○	○	○
Fibrosis 4 score (FIB-4)	○	○	○	○
NAFLD fibrosis score	○	○	○	○
Enhanced Liver Fibrosis Panel (ELF)	○	○	○	○
Fibroscan	○	○	○	○
Ultrasound Liver	○	○	○	○
Computed Tomography (i.e. CT Liver)	○	○	○	○
Magnetic Resonance Imaging (i.e. MRI Liver)	○	○	○	○

Liver Biopsy	○	○	○	○

Any additional comments including other tests of liver fibrosis that you use or are aware of:

Q8: Do you use a primary or secondary care pathway using non-invasive tests of liver fibrosis to guide management of patients with, or at risk of, liver disease?

○ Yes ○ No

If yes, please can you provide a brief description of the pathway and also provide your contact email if you are happy to be contacted to discuss further.

Q9: What are the limiting factors that prevent use of non-invasive liver fibrosis tests in your practice? (please tick all that apply)

- ☐ Not applicable - have suitable access to non-invasive liver fibrosis tests
- ☐ Availability of Test
- ☐ Cost of Test
- ☐ Diagnostic accuracy of current tests
- ☐ Lack of need of non-invasive tests in current clinical practice
- ☐ Other (please specify)

If you have chosen "other", please specify:

Q10: Which method of fibrosis assessment do you use primarily in the following liver diseases (please select one option for each row)?

	Serum fibrosis tests	Imaging fibrosis tests i.e. fibroscan	Liver Biopsy	No fibrosis assessment	Not Applicable
Hepatitis B	○	○	○	○	○
Hepatitis C	○	○	○	○	○
Alcoholic Liver Disease	○	○	○	○	○
Non alcoholic fatty liver disease	○	○	○	○	○
Haemochromatosis	○	○	○	○	○
Autoimmune Liver Disease	○	○	○	○	○
Primary Sclerosing Cholangitis	○	○	○	○	○
Primary Biliary Cirrhosis	○	○	○	○	○
Other (please specify)	○	○	○	○	○

If any additional comments, please specify:

Q11: Please document any additional comments you have regarding the use of non-invasive tests of liver fibrosis in clincal practice, including their advantages and disadvantages. Thank you.

4.3.3 Statistical analyses

Standard descriptive statistics were used to describe the data, including counts and percentages for categorical data and median and range for non-normally distributed data.

4.4 Results

4.4.1 Study participants

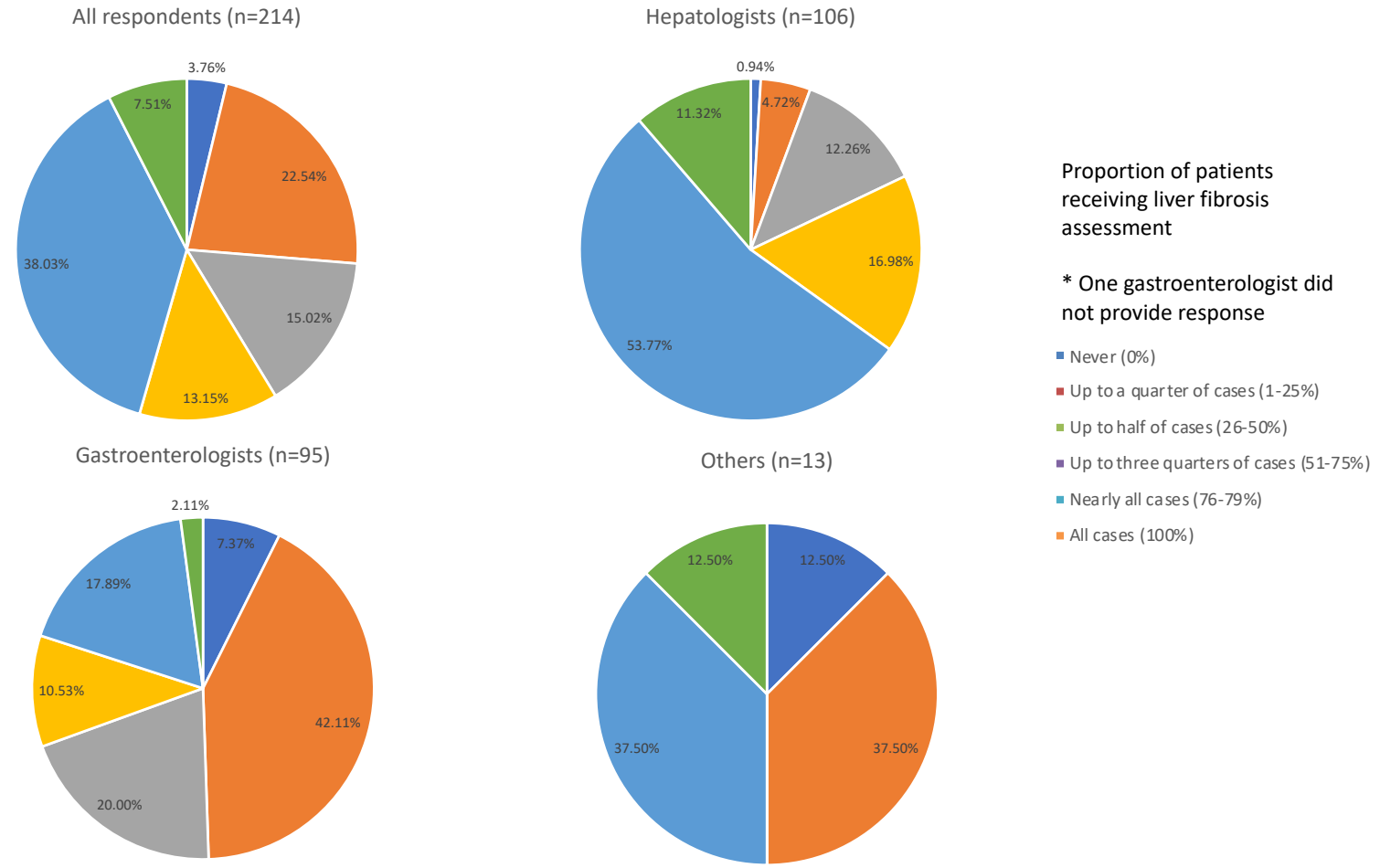
A total of 1761 invitations to the web-link for the survey were sent by email between 1st October 2014 to 1st October 2015. A total of 215 (12.2%) healthcare professionals completed the online survey. Hepatologists constituted 106 (49.5%) respondents, 96 (44.9%) were gastroenterologists and 12 (5.6%) were 'others' including internal medicine and infectious disease specialists. Approximately two-thirds (139 respondents (64.7%)) were consultants, 59 (26%) were doctors in training and 17 (2.8%) were specialist nurses. Survey responses covered 85 of 154 (55.2%) acute English NHS healthcare trusts. An additional 7 Trusts were represented from the rest of the United Kingdom (4 from Scotland, 2 from Wales, 1 from Northern Ireland).

4.4.2 The role of liver fibrosis assessment (LFA) in patients with liver disease

Two-hundred and six respondents (95.8%) performed liver fibrosis assessment (Figure 4.2) in a proportion of their liver patients. Only 9 (4.2%) respondents never conducted LFA – 7 were gastroenterologists, one public health specialist and one hepatologist. Sixteen (7.4%) assessed liver fibrosis

in all their liver patients, of whom 12 were hepatologists, 2 were gastroenterologists, 1 was an internal medicine doctor and 1 was a virologist. Eighty-one participants (37.7%) assessed fibrosis in ‘nearly all cases’ (defined as 76%-99% of liver patients), 28 (13%) in ‘up-to three quarters of cases’ (51%-75% of liver patients) and 32 (14.9%) in ‘up-to half of cases’ (26% to 50% of liver patients). Forty-eight (22.3%) performed LFA in a relative minority of patients (1%-25% of liver patients), of which 41 were gastroenterologists.

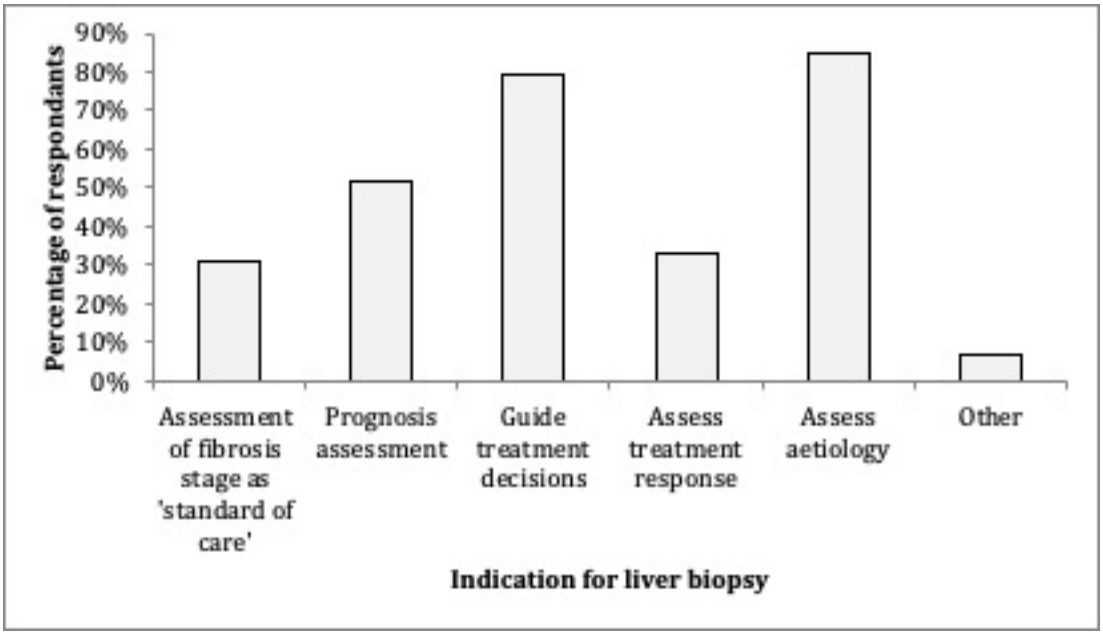
Figure 4.2 Proportion of patients in whom physicians perform liver fibrosis assessment



4.4.3 The role of liver biopsy in patients with liver disease

Liver biopsy remains an important investigative tool in the management of patients with liver disease. Whilst a third of respondents (66 respondents) used liver biopsy solely for liver fibrosis assessment, this was a relatively uncommon indication with biopsy utilized to assess aetiology, prognosis, treatment initiation and treatment response for 183 (85.1%), 111 (51.6%), 170 (79.1%) and 71 (33.0%) respondents respectively (Figure 4.3).

Figure 4.3 Indications for requesting liver biopsy in clinical practice.



Other indications volunteered by respondents included disease assessment to guide secondary care follow up, to confirm or refute a suspected diagnosis of cirrhosis based on other diagnostic modalities, as an investigation for acute cellular rejection in the post-liver transplant patient and patient selection for clinical trials. Thematic analysis of free text highlighted the important but

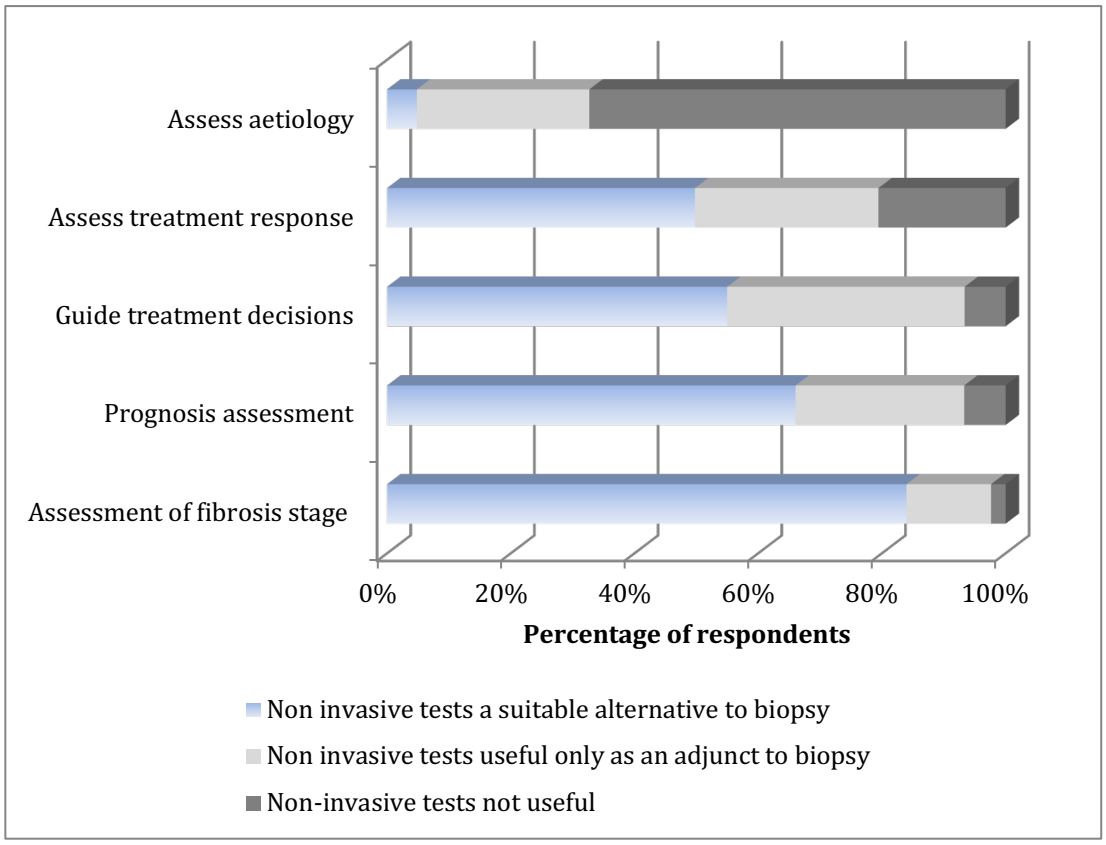
diminishing role of biopsy in the context of fibrosis assessment, with one respondent commenting,

> "Liver biopsy now second or third line for fibrosis staging and more importance in acute liver dysfunction rather than in chronic disease."

4.4.4 The potential for non-invasive liver fibrosis tests as a suitable alternative to liver biopsy

The majority of respondents (178, 84.0%) agreed non-invasive liver fibrosis tests to be a suitable alternative to liver biopsy for fibrosis assessment, whilst 29 (13.7%) saw them as a useful adjunct. Only 5 respondents (2.3%) felt non-invasive assessment had no role in clinical practice (Figure 4.4).

Figure 4.4 The potential of non-invasive liver fibrosis tests as an alternative to liver biopsy.



One-hundred and thirty-eight respondents (66.0%) agreed NIT were a suitable alternative to liver biopsy to allow assessment of prognosis in patients with liver disease. Fifty-seven respondents (27.8%) saw NIT as a useful adjunct in the assessment of patients with CLD and 14 (6.7%) felt they had little role in this respect. With regards to guiding treatment decisions, 116 respondents (55.0%) felt NIT were a suitable alternative to liver biopsy, whilst 57 (27.8%) saw them as a useful adjunct and 14 (6.7%) felt they had little role in guiding treatment. A similar opinion was expressed when asked about the role of NIT in assessing response to treatment, with 104 participants considering NIT a good alternative to biopsy whilst 62 participants felt it was a useful adjunct to liver biopsy.

For many respondents, the primary utility of non-invasive tests was to differentiate patients with little or no fibrosis (equivalent Brunt ≤F2) from patients with advanced fibrosis or cirrhosis (equivalent Brunt ≥F3). However, many considered the evidence supporting the performance of non-invasive tests as an alternative to liver biopsy to be strongest for identifying patients with liver cirrhosis (Brunt F4). Therefore, many considered liver biopsy for cases thought to have levels of fibrosis anticipated to be in the “grey” zone of histological assessment, for example Brunt fibrosis stage F2 or F3 where NIT are less reliable. In the scenario of discordance between non-invasive fibrosis tests results and the clinical picture, liver biopsy was the preferred “gold standard”. Whilst some respondents acknowledged that non-invasive tests had prognostic value, they noted that established prognostic scores including

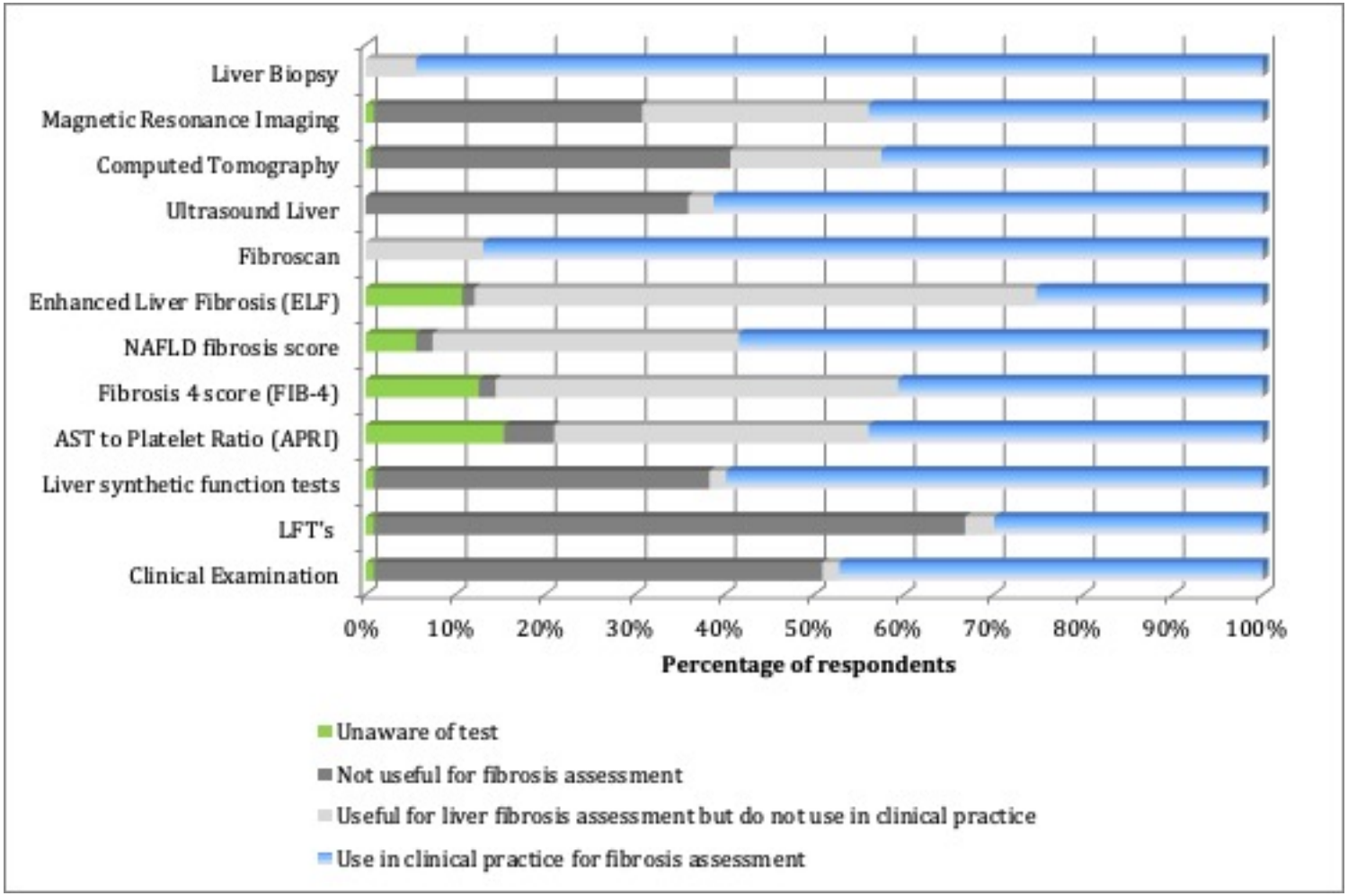
Child-Pugh, UKELD and MELD (that incorporate blood tests but are not validated to quantify fibrosis) are currently more widely used in clinical practice.

4.4.5 Clinical methods to diagnose liver fibrosis in current clinical practice

Respondents were asked to consider the methods they employ to assess a patient's liver fibrosis stage (Figure 4.5).

One hundred and one (47.2%) respondents considered clinical examination to be part of the holistic approach to patient management and disease severity assessment, whilst 107 (50%) disagreed and felt it was not useful in LFA. A common theme identified was that clinical stigmata of chronic liver disease distinguished patients with and without cirrhosis but could not differentiate earlier stages of liver fibrosis.

Figure 4.5 Evaluation of current diagnostic methods to assess liver fibrosis stage



One hundred and forty-one (65.9%) respondents believed standard liver function tests were not reliable for liver fibrosis assessment, as opposed to 64 (29.9%) who did. Markers of liver synthetic function, including albumin and pro-thrombin time, were considered to be useful by 128 (59.8%) and not useful by 80 (37.4%) respondents. One-hundred and thirty-one (61.2%) participants used abdominal ultrasound for fibrosis assessment, whilst 77 (36.0%) did not. Considering cross-sectional imaging, 91 (43.5%) and 94 (43.9%) respondents used computed tomography and magnetic resonance imaging techniques for fibrosis assessment respectively, whilst a significant proportion – 36 (16.8%) and 54 (25.2%) – recognised the value of these methods but did not currently use them for the purposes of fibrosis assessment. The remaining 86 (40.2%) and 64 (29.9%) respondents felt CT and MRI had no role in fibrosis assessment.

Respondents commented that the use of imaging techniques to detect liver fibrosis relied upon the identification of signs of portal hypertension related to cirrhosis including splenomegaly, varices and porto-systemic shunts, thus signifying the latter stages of cirrhosis. Similarly, the primary role of clinical examination, ‘simple’ blood tests and imaging was to diagnose advanced disease (cirrhosis) rather than staging earlier non-cirrhotic stages. The adequacy of this was questioned, with one respondent stating:

> “Almost all methods from clinical examination to imaging to blood work will tell you if someone has advanced cirrhosis, but nothing about the ‘grey’ cases where fibrosis assessment is so important for prognosis”

Access to liver biopsy was equitable (94.5% had access). The remainder would refer patients for specialist review and liver biopsy. Free-text analysis confirmed that the use of biopsy had significantly reduced in recent years.

With regards to the current use of non-invasive tests, there was a wide range of responses. Considering indirect serum markers, the NAFLD fibrosis score (NFS) was most widely used (58.4%), followed by AST-to-platelet-ratio (APRI) (42.9%) and FIB-4 (40.7%). A relative minority thought APRI (5.6%), FIB-4 (1.9%) and NFS (1.9%) had little role in clinical practice. Interestingly, a significant group agreed indirect markers were useful but did not use them in clinical practice. Additionally, in free-text analysis, the use of BARD was reported by 4 respondents, with 2 making reference to the Nottingham pilot liver pathway identified in the systematic review [87].

Considering direct serum markers, 54 respondents (25.2%) used ELF test in clinical practice. Whilst 134 respondents (62.6%) advocated its use, 23 (10.8%) had not heard of the test and 3 (1.4%) did not consider it clinically useful. Free-text analysis suggested one respondent used P3NP and hyaluronic acid for the purposes of fibrosis assessment. Fibrotest was not reported to be used by any of the UK respondents.

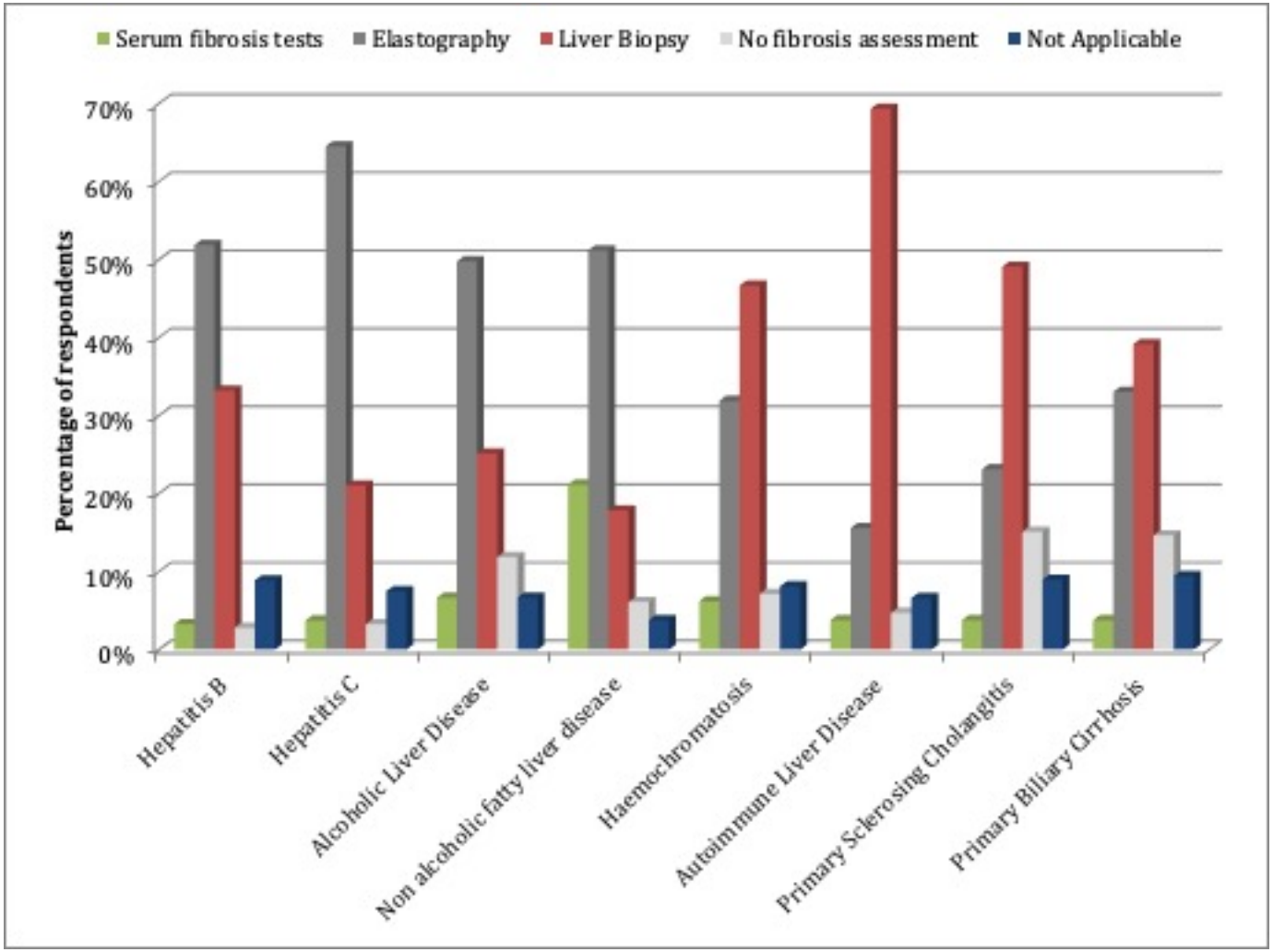
Fibroscan / transient elastography (TE) is well established in UK practice. The majority of respondents, 186 (86.9%) used fibroscan although free-text analysis confirmed that many accessed this through referral to other specialist centres. The remainder (13.1%) agreed that fibroscan had a role, but currently did not use it. Analysing the qualitative responses, Acoustic Radiation Force

Impulse (ARFI) technology has a growing body of support and practice in the UK.

The survey evaluated the influence of aetiology of liver disease on the need for fibrosis assessment. Irrespective of the aetiology, fibrosis assessment was considered an integral part of disease management in the majority of cases. However, 32 (15.1%), 31 (14.6%), 25 (11.9%), 15 (7.1%), 13 (6.1%) and 10 (5.3%) respondents did not conduct fibrosis assessment in patients with primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), alcohol related liver disease (ARLD), haemochromatosis, NAFLD and autoimmune hepatitis (AIH) respectively. Conversely, only a minority – 6 (2.8%) and 7 (3.3%) did not conduct fibrosis assessment in viral hepatitis B and C respectively. Elastography techniques including fibroscan were the preferred methods of choice in HCV, HBV, NAFLD and ARLD for 138 (64.5%), 111 (51.9%), 109 (51.2%) and 105 (49.8%) respondents respectively.

At the time of the survey (2015), the respondents thought that liver biopsy still had an established role for fibrosis assessment, mainly in HBV (71, 33,2%) and to a lesser degree in HCV (45, 21.0%), ARLD (53, 25.1%) and NAFLD (38, 17.8%) (Figure 4.6).

Figure 4.6 Primary method for fibrosis assessment used in clinical practice dependant on underlying aetiology



Non-invasive liver fibrosis testing was the primary approach used to assess fibrosis in patients with NAFLD, ARLD and viral hepatitis. For patients with NAFLD, 109 respondents (51.2%) used elastography and 45 respondents (21.1%) used serum fibrosis tests as the primary assessment tool for fibrosis assessment, compared to 38 respondents (17.8%) who used liver biopsy. A similar trend could be seen for evaluation of fibrosis in patients with ARLD; namely 105 (49.8%), 53 (25.1%) and 14 (6.6%) respondents using elastography, biopsy and serum tests respectively.

For other causes of CLD, liver biopsy predominated. For example, for patients with autoimmune hepatitis, 147 respondents (69.3%) confirmed liver biopsy was the primary assessment tool for fibrosis staging as opposed to elastography (33 respondents, 15.6%) and serum fibrosis markers (8 respondents, 3.8%). Similar responses were reported for patients with PSC, haemochromatosis and PBC (Figure 4.6). Respondents commented that for patients with AIH, PBC and PSC, the initial fibrosis assessment would frequently involve liver biopsy as it provided additional diagnostic value, but disease progression could be assessed with non-invasive fibrosis tests.

4.4.6 The use of non-invasive tests in clinical pathways

In 2015, respondents representing 21 healthcare Trusts or CCGs reported the use of non-invasive fibrosis tests in clinical pathways. There was a wide geographical distribution as illustrated in Figure 4.7. Management of NAFLD accounted for over half the pathways (13 pathways, 61.9%), 9 of which were

based in primary care. Eleven different strategies were identified and are described in Table 4.1.

Figure 4.7 Map illustrating the geographical distribution of pathways using non-invasive fibrosis tests in the United Kingdom.

Table 4.1 Clinical pathways utilising non-invasive fibrosis markers in the United Kingdom (identified by National Survey, 2015)

	Disease target	Pathway setting	Testing strategy	Fibrosis stage (Brunt)	First tier test	Second tier test
NAFLD						
A	NAFLD	Primary care	One-tier testing	F3	NAFLD Fibrosis Score < -1.455 => manage in primary care > - 1.455 => refer to specialist for investigation	
B	NAFLD	Primary care	One-tier testing	F3	ELF test < 8.4 => manage in primary care > 8.4 => refer to specialist for investigation	
C	NAFLD	Primary care	Two-tier sequential testing	F3	FIB-4 test <1.30 => manage in primary care 1.30-3.25 => indeterminate – proceed to second tier test in primary care FIB-4 > 3.25 => refer to specialist for investigation	ELF test (Primary care) < 9.5 => manage in primary care > 9.5 => refer to specialist for investigation
D	NAFLD	Primary care	Two-tier sequential testing	F3	For diabetic patients - FIB-4< -1.30 => Low risk 1.30 – 2.67 => indeterminate >2.67 => high risk For non-diabetic patients - NAFLD fibrosis score < -1.455 => Low risk -1.455 – 0.675 => indeterminate >0.675 => high risk -Low risk (remain in primary care, test CK-18 to assess steatohepatitis risk) -Indeterminate risk – proceed to second tier test High risk – refer to specialist	ELF test (Primary care) (Pathway under construction – the use of ELF as second tier test subject to confirmation) < 9.5 => manage in primary care > 9.5 => refer to specialist for investigation
E	NAFLD	Primary care	Two-tier sequential testing	F3	NAFLD Fibrosis Score < -1.455 => manage in primary care -1.455 – 0.675 => indeterminate – proceed to second tier test in secondary care >0.675 => refer to specialist for investigation	Fibroscan (one-stop secondary care clinic) Consultation with hepatology team and assessment involving review of bloods, imaging and a fibroscan. Outcome and further management determined by clinical judgment.
F	NAFLD/ negative etiology screen	Secondary care	One tier testing	F3	Fibroscan for all patients with NAFLD/ negative liver screen. Fibroscan => <7.9 kPa, discharge to primary care Fibroscan => >7.9 kPa, manage in secondary care	

G	NAFLD	Secondary care	Two test concordance strategy	F3	BARD and NFS NFS <-1.455 AND BARD < 2, => primary care and re-refer after 5 years. If NFS>-1.455 OR BARD >2, second tier test	ELF and Fibroscan ELF < 8.4 and fibroscan <8.8 (mild fibrosis) => 2 yearly hospital follow up ELF 8.4 – 9.5 OR fibroscan 8.8 – 11.7 KPa, (advanced fibrosis) => consider biopsy ELF > 9.5 or fibroscan >11.7 => cirrhosis
Alcohol						
H	ARLD	Primary Care	One tier test	F3	ELF < 9.5 => manage in primary care > 9.5 => refer to specialist for investigation	
Hepatitis C						
I	Hepatitis C	Secondary Care	One-tier	F4	Non-invasive criteria (in addition to biopsy) eligible for treatment with new direct acting antiviral agents for Hepatitis C Cirrhosis => APRI > 2.0 and AST: ALT >1 OR Fibroscan > 11.5 KPa	
Hepatitis B						
J	Hepatitis B	Secondary care	One tier	F2	Fibroscan <6KPa => treat as mild fibrosis. Consider liver biopsy in specific scenarios 6KPa – 11Kpa => consider liver biopsy >11KPa => treat as cirrhosis with anti-viral therapy	
Risk factor targeting						
K	Hazardous Drinking Type II DM Raised ALT	Primary care	Two tier	F2	BARD and AST: ALT ETOH excess => AST: ALT < 0.8 => primary care > 0.8 => second tier test Diabetes or raised ALT => BARD score < 2=> primary care ≥ 2 => second tier test	Fibroscan < 8Kpa => stay in primary care > 8Kpa => refer to hepatology clinic

Primary care NAFLD pathways

During the study period, risk stratification pathways in primary care accounted for 42.9% of 21 pathways identified. They aimed to identify patients with advanced fibrosis or cirrhosis (Brunt ≥ F3 fibrosis) for referral to specialist services, whilst managing patients with milder non-significant fibrosis (Brunt ≤F2 fibrosis) in primary care. The commonest strategy employed by 4 Trusts and CCGs (44.4% of primary care NAFLD pathways) was to use NFS to produce a binary outcome; patients with a NFS < -1.455 were stratified as low risk for advanced fibrosis and cirrhosis, whilst patients with a NFS > -1.455 were stratified as high risk for advanced fibrosis and cirrhosis and secondary care referral was recommended (pathway A, Table 4.1).

Three different Trusts and CCGs employed a pathway whereby patients were classified into low risk, indeterminate risk and high-risk groups. Patients at indeterminate risk were referred as part of a formal algorithm to a one-stop secondary care clinic where they underwent a fibroscan. Those with a normal fibroscan result were discharged back to the community (pathway E, Table 4.1).

The use of ELF was reported in the primary care setting. A one-tier primary care risk stratification pathway was identified in the Hull and East Riding of Yorkshire region [202] (pathway B, Table 4.1) using a threshold of 8.4 to identify patients at risk of ≥F3 fibrosis. The Camden and Islington NAFLD pathway [203] developed as part of work in this thesis (see Chapter 6) adopted a two-tier approach utilizing FIB-4 as a 1st tier test, stratifying patients as low

risk of ≥F3 fibrosis (FIB-4 <1.30), indeterminate (FIB-4 1.30-3.25) or high risk for ≥F3 fibrosis. Those with indeterminate scores were invited for an ELF test in primary care with a cut-off of 9.5 used to distinguish fibrosis risk and the need for referral (pathway C, Table 4.1).

Strategies targeting patients with risk factors for chronic liver disease were identified. The Nottingham research group, whose subsequent publication was identified in the systematic review described in Chapter 3 [87] have trialled a two-tier approach for patients with hazardous drinking, type II diabetes or an abnormal ALT (pathway K, Table 4.1). Patients would have an AST: ALT ratio (considered indicative of alcohol excess) or BARD score (calculated for patients with a known diagnosis of diabetics, or those with a raised ALT). Patients with normal results were managed in primary care, whilst those with abnormal results (AST: ALT > 0.8 or BARD ≥2) would be offered a fibroscan in the community. Initial results are promising, with an increase in the detection of cases with advanced fibrosis [87].

A pilot study in the Camden and Islington CCG utilizes ELF to stratify patients with harmful alcohol consumption, defined as greater than 50 units per week in males and 35 units in females for over 10 years, using a cut-off of 9.5 (pathway H, Table 4.1). This study is yet to report results.

Secondary care risk stratification pathways

The reported use of non-invasive tests in secondary care pathways of care followed established national guidance. The pathways relate to NICE guidance for hepatitis B [182] and NHS England guidance on access to direct acting

anti-viral agents for the treatment of hepatitis C [183] (pathways I and J, Table 4.1).

4.4.7 Barriers to the implementation of non-invasive liver fibrosis tests in clinical practice.

The survey explored current access to non-invasive fibrosis tests in the UK. Only 52 participants (24.9%) reported adequate access to non-invasive fibrosis tests, with the majority declaring suboptimal access. The barriers to using non-invasive fibrosis tests are summarised in Figure 4.8 with lack of local availability (123, 58.9%) and cost (65, 30.2%) the most commonly cited. Sample participant comments included

> "We have Fibroscan, but cannot use ELF on cost grounds"

> "…would like access to fibroscan but don't have one, so use bloods, ultrasound and biopsy if in doubt"

> "My practice is controlled by the lack of availability of tests that I believe are useful. This is entirely dependent on bureaucracy and intransigence of laboratories"

A significant proportion (56 respondents, 17.8%) had concerns regarding the existing non-invasive fibrosis tests with regards to reliability, diagnostic accuracy and clinical utility. Respondents conveyed concerns regarding reliability and reproducibility of non-invasive liver fibrosis tests. A key message conveyed was confidence in the ability of NIT to distinguish advanced disease from mild disease (for example identifying patients with Brunt F3 fibrosis from F2 fibrosis). However, all modalities were considered to be inaccurate in

distinguishing between F0, F1 and F2 fibrosis. Respondents' comments included

> "*non-invasive liver fibrosis tests are* not good at staging disease, but are good at excluding advanced fibrosis"

> "Major disadvantage is lack of clear prognostic information from these tests for those at early stages of the disease. Also, difficulty for many of these tests in distinguishing mild and moderate fibrosis"

> "Fibroscan can be useful though at times inconsistent and operator dependent"

Further qualitative analysis of the free text revealed a number of other themes. There were concerns regarding the practicality of elastography. The resource required for fibroscan in terms of personnel and clinic room space were perceived as barriers, with one participant stating a barrier was

> "The nurse and clinician time for fibroscanning is difficult"

A lack of access to appropriate technology, such as the Siemens Advia Centaur platform to allow ELF testing or Echosens fibroscan technology was evident, with one respondent stating

> "The fact that fibroscan gives us results immediately and can be done is an advantage. ELF test is well validated, but not marketed well"

A number of respondents admitted a lack of familiarity with NIT, their relative performance characteristics and cut-offs for specific disease aetiologies engendering anxiety about their use. A relative paucity of published literature for disease specific application of the tests, for example for their use in

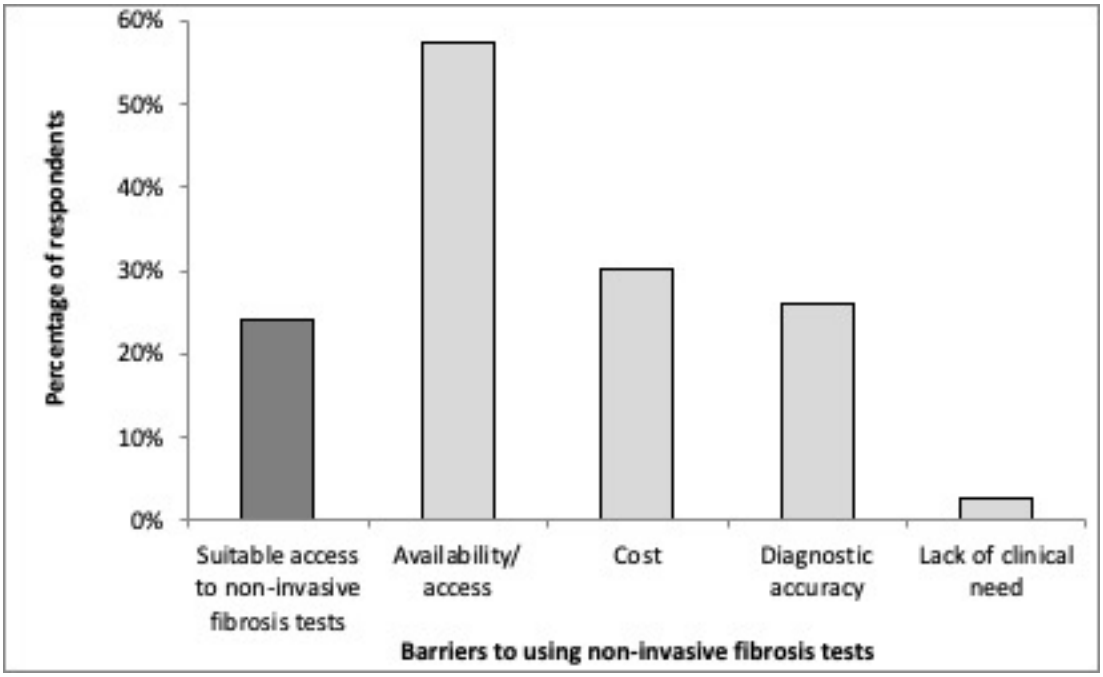
HIV/HCV co-infection, was perceived as limiting their utility. There was recognition of the known limitations to the use of fibroscan in specific patient populations, in particular clinically obese patients.

Relevant quotes included

> “Poor familiarity with tests”

> “Sounds great in theory. The non-hepatologists do not know what the options are (except fibroscan) and what the evidence is”

Figure 4.8 Barriers identified to the implementation of non-invasive liver fibrosis tests in the United Kingdom.



4.5 Discussion

This national survey conducted in 2015 demonstrated clear support for the increasing use of non-invasive liver fibrosis markers in clinical practice (supported by 97.5% of respondents). However, only a quarter of UK specialists reported having adequate access to these tests at that time. This will, in part, explain the variability in liver fibrosis assessment between clinicians and highlights an inequality in access to non-invasive liver fibrosis tests in the United Kingdom.

There was agreement amongst the participants that liver fibrosis assessment was an important part of liver disease workup. The alternative diagnostic tools including clinical assessment, simple blood tests and ultrasound were valuable

to identify advanced or end-stage liver disease but had little role in detecting or distinguishing earlier stages of liver disease. Liver biopsy remained an important part of a physician's investigative armour, but previous physician surveys on the use of liver biopsy has highlighted physician concerns remain regarding liver biopsy and just under a third of physicians did not perform liver biopsies. Concerns cited included the safety of liver biopsy, and the logistics in providing the test [204]. Another study in France suggests 55% of General Practitioners believed the main obstacle to hepatitis C treatment was patient refusal of liver biopsy [205].

There was a consensus that non-invasive liver fibrosis tests were a suitable alternative to liver biopsy. Despite recognition of the importance of non-invasive liver fibrosis markers, three quarters of respondents reported inadequate access in the United Kingdom. Fibroscan and indirect fibrosis markers such as the NAFLD fibrosis score, APRI and FIB-4 were widely used in clinical practice, whilst a quarter of respondents had access to the ELF test. However, barriers to their use were identified, including the cost of patented fibrosis tests and imaging technology, lack of local availability (of ELF or fibroscan in particular), difficulty to obtaining commissioning permissions and concern regarding performance and reliability of the available tests.

On reviewing the literature, the results of this study were comparable to results from Sebastiani and colleagues who conducted a Canadian national survey on physicians practices for diagnosing liver fibrosis in 2012-2013 [206]. In this study, fibrosis testing was identified to be important, in particular for viral hepatitis and autoimmune liver disease. Interestingly, access to fibroscan was

39.4% compared to up-to 86.9% in our study, suggesting an increase in access. Similar to our results, the Canadian study highlighted physician concerns regarding non-invasive liver fibrosis assessment centred on a lack of access or availability of tests, lack of guidelines for clinical use and the cost and lack of reimbursement. Ratziu and colleagues performed a survey of practice and perception of NAFLD in France [207]. Amongst a number of themes, they identified that whilst liver biopsy was used on occasion, fibrosis staging was dependant mainly on non-invasive liver fibrosis tests.

One of the key aims of this study was to identify existing pathways of care using non-invasive liver fibrosis markers. A total of 21 different pathways were reported. One pathway identified in the systematic review in Chapter 3 was mentioned in this survey, namely that developed by the Nottingham group that targets patients at risk of liver disease on the basis of hazardous drinking, diabetes or abnormal ALT using BARD, AST: ALT ratio and fibroscan [87]. Overall, 11 different strategies were identified and as was the case in the systematic review, there was great heterogeneity in the pathways identified (Table 4.2). The strategies employing non-invasive tests in primary care and secondary care are summarised in Table 4.3.

Table 4.2 Summary of care pathways identified by national survey employing non-invasive fibrosis tests

Primary care setting	Secondary care/ Hospital setting
NAFLD Fibrosis Score for all patients with NAFLD [a] NFS < -1.455 => manage in primary care, NFS > - 1.455 => refer to specialist	Fibroscan for all patients with NAFLD/ negative liver screen [g] Fibroscan => <7.9 kPa, discharge to primary care Fibroscan => >7.9 kPa, manage in secondary care
ELF test for all patients with NAFLD [b] ELF < 8.4 => manage in primary care, ELF > 8.4 => refer to specialist	For all patients with NAFLD - BARD and NFS [h] NFS <-1.455 AND BARD < 2, => primary care and re-refer after 5 years. If NFS>-1.455 OR BARD >2, for fibroscan and ELF test ELF < 8.4 and fibroscan <8.8 (mild fibrosis) => 2 yearly hospital follow up ELF 8.4 – 9.5 OR fibroscan 8.8 – 11.7 KPa, (advanced fibrosis) => consider biopsy ELF > 9.5 or fibroscan >11.7 => cirrhosis
FIB-4 test for all patients with NAFLD [c] FIB-4 <1.30 => manage in primary care, FIB-4 > 3.25 => refer to specialist FIB-4 1.30-3.25 => indeterminate – proceed to ELF test in primary care ELF < 9.5 => manage in primary care, ELF > 9.5 => refer to specialist	For all patients with Hepatitis C, non-invasive criteria (in addition to biopsy) eligible for treatment with new direct acting antiviral agents for Hepatitis C [i] Cirrhosis => APRI > 2.0 and AST: ALT >1 OR Fibroscan > 11.5 KPa
NAFLD Fibrosis Score for all patients with NAFLD [d] NFS < -1.455 => manage in primary care, NFS >0.675 => refer to specialist NFS -1.455 – 0.675 => indeterminate –one-stop specialist fibroscan clinic	For all patients with Hepatitis B, suggest fibroscan [i] < 6 kPa – treat as mild fibrosis 6kPa – 11 kPa – consider liver biopsy >11 kPa - treat as cirrhosis and start anti-viral therapy
For all patients with NAFLD [e] Diabetic patients - FIB-4< -1.30 => Low risk, 1.30 – 2.67 => indeterminate, >2.67 => high risk For non-diabetic patients - NFS < -1.455 => Low risk, -1.455 – 0.675 => indeterminate, >0.675 => high risk Low risk (remain in primary care, test CK-18 to assess steatohepatitis risk) Indeterminate risk – proceed to ELF test (pathway under construction) High risk – refer to specialist	
ELF test for all patients at risk of alcohol related liver disease [c] < 9.5 => manage in primary care > 9.5 => refer to specialist for investigation	Locations of pathway; A – Newcastle, B – Hull, C – Camden and Islington, London, D – Portsmouth E- Norfolk and Norwich, F- Nottingham, G – South and West Devon H – Leeds, I – mentioned in survey and reflects national guidance
ETOH excess => AST: ALT < 0.8 => primary care > 0.8 => fibroscan [f] Diabetes or raised ALT => BARD score < 2=> primary care, ≥ 2 => fibroscan	Key: Green = NAFLD, orange = alcohol related liver disease, blue – viral hepatitis, purple – risk factor targeting

Table 4.3 Grid summarising non-invasive strategies in primary and secondary care pathways identified by National survey.

Setting	Primary Care	Secondary Care
Tests		
Blood based	NFS only ELF only FIB-4 ±ELF FIB-4±NFS	
Transient Elastography		TE
Both	BARD or AST:ALT ± TE	BARD+NFS ± ELF+TE

Seven out of eleven strategies focussed on NAFLD with five based in primary care. These pathways used NAFLD fibrosis score and FIB-4 either alone or in combination with ELF or fibroscan performed in a secondary care setting to identify patients at significant risk of liver fibrosis. The cut-offs used in the pathways were different, with one pathway using FIB-4 > 2.67 to identify patients at risk of advanced fibrosis, whilst others used FIB-4 > 3.25. Similarly, ELF cut-off of >8.4 or > 9.5 and fibroscan > 7.9KPa and > 8.8KPa were identified in the pathways to identify advanced fibrosis.

This study had strengths and limitations. An important strength of this study was that over 50 percent of all acute English NHS trusts were represented by the participants. There was variety in the responders, ranging from general gastroenterologists to hepatologists, and the respondents included specialist nurses and trainees. The survey gathered real-world observations and empirical data that have not been researched before in the United Kingdom.

Despite a comprehensive approach to achieve a high response rate, only a tenth of invitees responded. This relatively low response rate can bias the results as non-responders may hold different views to those who have responded. Online surveys, such as the one employed in this chapter are typically associated with low response rates. Alternative options include postal surveys, telephone interviews or personal interviews. Compared to online surveys, postal surveys are more time consuming and costly, whilst they are also susceptible to low response rates. Telephone or personal interviews are time and resource intensive, and whilst tend to result in improved response rates, the overall number of participants is usually more restricted and less

diverse. To maximise both the response rate and information gathered from the survey, there was extensive planning in the development stages of the survey. A research goal was defined, whilst direct, clear and concise questions were developed. A validation pilot was performed which allowed previously unconsidered difficulties to be identified prior to the distribution of the survey, after which changes are very hard to implement. These measures aimed to optimise the user-acceptability of the survey, and to this end, no specific comments regarding difficulty in completing the survey were received from the respondents. Another potential weakness of this survey was that the subject area surveyed has several contentious areas including the populations to target and the non-invasive test of choice. Expanding on these areas was limited with online survey used due to the rigidity in the questions, with personal interviews potentially better to explore these themes. While the invitation to enter free-text responses can address this, response rates are frequently low. Finally, online surveys capture a snapshot of opinions at a single point of time, and therefore do not measure trends. The opinion of the respondents may change as the evidence base develops, and this can only be captured with a follow-up survey.

4.6 Conclusion

In conclusion, this national survey captured the increasing appetite of UK physicians to incorporate non-invasive liver fibrosis tests into clinical practice but identified barriers to access which inevitably limited their widespread use. There is evidence of the implementation of non-invasive liver fibrosis tests into patient pathways throughout pockets of the United Kingdom. However, there

is great heterogeneity in the pathways and evaluation of these pathways will inform future research strategies and service innovation.

CHAPTER 5 BASELINE ASSESSMENT OF CURRENT PRACTICE OF REFERRAL OF PATIENTS WITH NAFLD FROM PRIMARY CARE TO SECONDARY CARE

5.1 Introduction

Non-alcoholic fatty liver disease (NAFLD) is the liver manifestation of the metabolic syndrome. NAFLD is one of the commonest causes of abnormal liver function tests [39] and chronic liver disease [69, 208, 209], and has an estimated prevalence of 20-30% in the Western population. The rising number of people with risk factors for NAFLD, namely obesity and diabetes, suggest this healthcare epidemic will increase exponentially [6]. Given the shear burden of the condition in the general population, the fact that most people with NAFLD do not have liver damage [74], and the impracticality of managing each patient in a specialist centre, it is inevitable that a significant majority of patients with NAFLD will be managed in primary care.

The spectrum of NAFLD ranges from simple steatosis, where liver related outcomes are similar to the general population, to steatohepatitis (inflammation) and progressive fibrosis. Only a relative minority of those with NAFLD (5 - 15%) will progress to advanced fibrosis or cirrhosis [40, 210]. Given that liver related events and morbidity are dictated primarily by fibrosis stage, the challenge facing primary care physicians is the correct identification of patients with advanced fibrosis or cirrhosis. At the time this study was conducted (2012-2013), standard care assessment for patients with NAFLD was dependent on clinical history and examination, serum liver function tests

and ultrasonography. Accurate assessment is hindered by the asymptomatic nature of liver disease until the latter stages of the condition and the unreliability of diagnostic tests available in primary care to accurately stage liver fibrosis. Liver biopsy, the reference standard test for fibrosis assessment, is not practicable for use in primary care given the resource required, the invasive nature of the procedure with associated risks and the size of the population requiring fibrosis assessment.

In this study, we evaluated referrals of patients with suspected NAFLD from primary care to three London Hospitals to determine the number of patients referred with advanced fibrosis and cirrhosis.

5.2 Aims of study

To assess the performance of “standard care” methods employed in primary care to identify patients with NAFLD with advanced liver fibrosis or cirrhosis (Brunt ≥F3).

5.3 Methods

5.3.1 Study design and setting

A retrospective cross-sectional audit of referrals to secondary care between 1st March 2012 and 28th February 2013 was performed to determine the diagnostic accuracy of the standard care pathway to identify patients with advanced fibrosis or cirrhosis. Referrals were audited in three London teaching hospitals that provided the majority of hepatology specialist services for the

London Boroughs of Camden and Islington – namely The Royal Free London NHS Foundation Trust (RFL), University College London Hospital NHS Foundation Trust (UCLH) and the Whittington Hospital.

The paper and electronic patient records (EPR) of patients referred by their GP with NAFLD were interrogated to identify data related to demographics, secondary care management and outcomes. Fibrosis-4 (FIB-4) scores were calculated retrospectively and used as a surrogate non-invasive marker of liver fibrosis in this population.

Patient Selection

Clinic attendance lists for all new patients referred to the Hepatology service (RFL & UCLH) and Gastroenterology and Hepatology service (Whittington Hospital) during the study period were obtained from the Trust Data and Analytics departments. The case records, including referral letter and hospital letter, were screened to identify those patients referred from primary care for further evaluation of NAFLD.

Inclusion criteria included:

1. Clinical diagnosis of NAFLD made in primary or secondary care
2. Referral from primary care (any locality – not restricted to Camden and Islington)

Exclusion criteria included:

1. Exclusion of alternative hepatological diagnosis including but not restricted to:
    - Alcohol excess (defined as >21 units/ week of alcohol in males, >14 units/ week in females),
    - Viral hepatitis,
    - Autoimmune hepatitis,
    - Haemochromatosis
    - Wilsons disease
    - Alpha-1 antitrypsin deficiency
    - Biliary liver disease (i.e., primary biliary cholangitis, primary sclerosing cholangitis)
2. Referral from another secondary care provider for specialist management
3. Known diagnosis of liver cirrhosis.
4. Age < 18 years

5.3.2 Data collection

Patient records, both paper and electronic as required, were reviewed against the inclusion and exclusion criteria. Data were extracted, where available, on the following themes:

1. Referral characteristics: referring clinical commissioning group (CCG), reason for referral, GP laboratory test results and ultrasound results.

2. Patient demographics: age, metabolic risk factors, alcohol intake, relevant concomitant medications, height, weight, body mass index (BMI) and waist circumference.
3. Laboratory results: including full blood count, liver function tests, HBA1C and cholesterol.
4. Relevant imaging results: including ultrasound, CT scan and MRI scan
5. Relevant liver fibrosis assessment when available: (including liver biopsy, fibroscan and serum markers).
6. Retrospective calculation of non-invasive liver fibrosis markers (FIB-4, AST: ALT ratio, NAFLD fibrosis score, APRI).
7. Composite clinical fibrosis assessment: based on liver histology, imaging, fibroscan, blood test results and clinical judgment but described as a binary outcome: “Advanced fibrosis/Cirrhosis” or “lesser degree/no fibrosis”.
8. Confirmed evidence of liver cirrhosis: (definitively diagnosed on clinical, radiological (including fibroscan) and/or histological assessment)/
9. Secondary care management: dietician review, cirrhosis surveillance programs, discharge rates to primary care.
10. Morbidity: focusing on liver related complications, liver transplantation and vascular events.
11. Mortality

The diagnostic performance of ‘standard care’ in detecting cases of advanced fibrosis and cirrhosis was assessed against a reference standard; namely a composite clinical fibrosis assessment performed by expert hepatologists, as described above.

In a sub-analysis, FIB-4 scores were calculated where possible and patients with FIB-4 <1.30 were deemed to have no evidence of advanced liver fibrosis

and thus were classed as having been referred inappropriately. Referrals originating from primary care practices within the Camden and Islington CCGs were analysed separately from those referred from other CCGs.

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.

5.3.3 Outcomes

The primary outcome of the study was the number of cases and proportion of those referred who did not have evidence of advanced fibrosis or cirrhosis (equivalent to Brunt ≤F2) 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 (Brunt F3) and cirrhosis after assessment by a liver specialist.
- The number and proportion of cases identified as having evidence of not having advanced fibrosis or cirrhosis using FIB-4, an indirect fibrosis marker (FIB ≤ 1.30).
- The number and proportion of cases identified as having evidence of advanced fibrosis or cirrhosis using FIB-4 (FIB-4 ≥ 3.25).

5.3.4 Statistical analyses

Statistical analyses were performed using SPSS (version 22, SPSS Inc. Chicago, IL, USA). Categorical data were presented as frequencies and percentages. Normally distributed continuous data were presented as mean (±SD) whilst medians (IQR and range) were used for non-parametric data. Demographic, biochemical and non-invasive testing results were compared between patients deemed to have advanced fibrosis or cirrhosis (≥F3 fibrosis) to patients with lesser degrees of fibrosis (≤F2 fibrosis) using two sample t-test for parametric variables, Mann-Whitney test for non-parametric and X^2 or Fisher's Exact for categorical variables.

5.3.5 Ethical approval

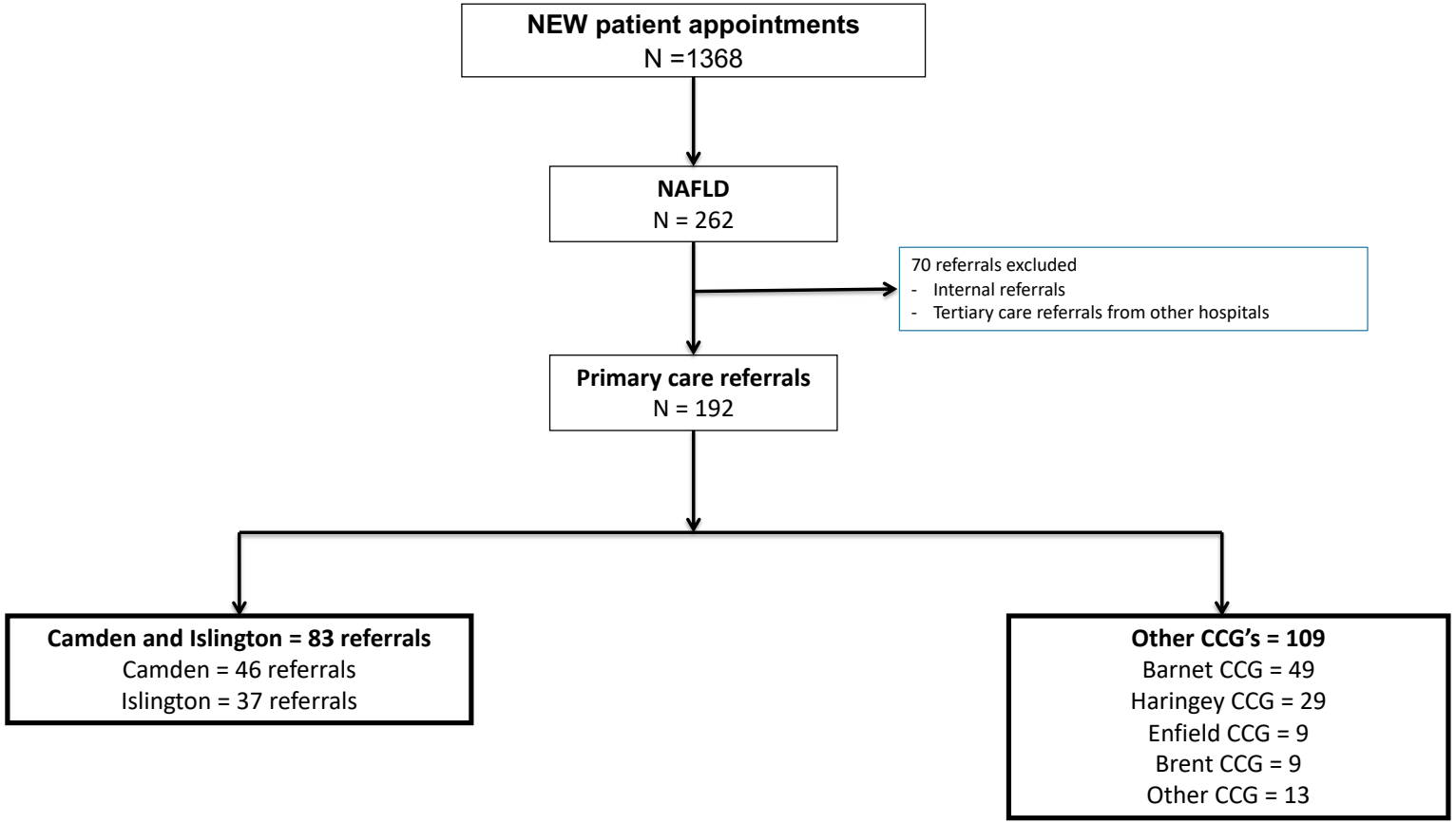
The Royal Free London NHS Foundation Trust Research and Development Department judged this study to be an evaluation of a service improvement innovation. Therefore, this study was registered for audit (EDGE ID:122031) but not subject to review by an independent ethics committee, and individual patient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

5.4 Results

5.4.1 Study population

Between 1st March 2012 and 28th February 2013, 1368 new patient referrals to the hepatology departments at RFL, UCLH and Whittington Hospital (excluding gastroenterology) were seen in outpatients from all CCG localities. After specialist review, 262 (19.2%) patients had a final diagnosis of NAFLD. Seventy (26.7%) were excluded as they were internal or external hospital referrals and not from primary care (Figure 5.1).

Figure 5.1 Total number of hepatology referrals to three London teaching hospitals between 1.3.12 and 28.2.13



A total of 192 referrals for patients with NAFLD from all CCGs were made during the study period. Eighty three of the 192 referrals (43.2%) originated from Camden and Islington CCG. The average age of patients referred was 51.1 ± 13.1 years and just over half of patients (111 patients, 56.6%) were male. The presence of metabolic risk factors, namely type II diabetes, hypertension and hypercholesterolemia were found in 25.6%, 42.1% and 60% respectively, whilst mean BMI was 31.6 ± 5.6.

5.4.2 Specialist reassessment

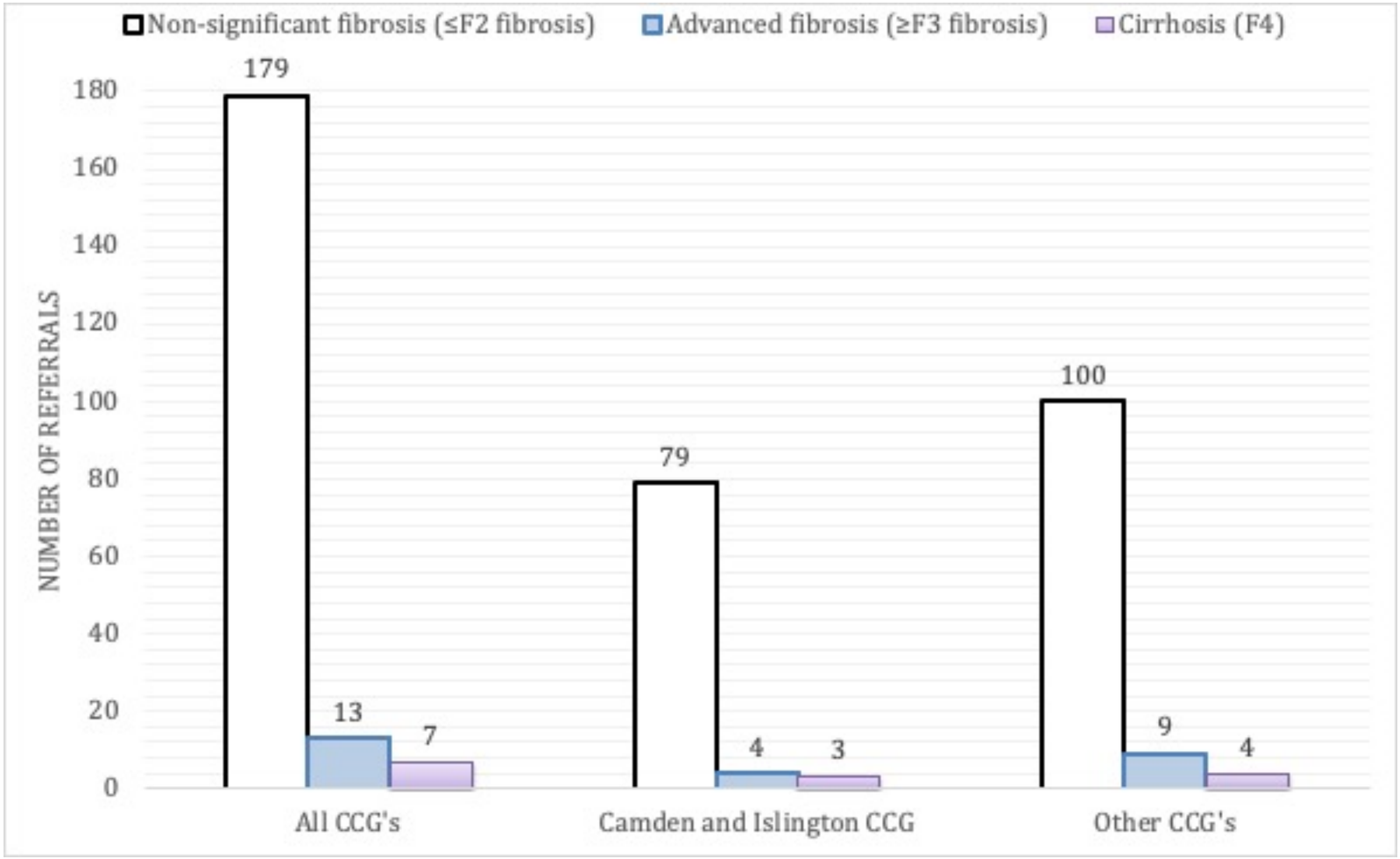
Patients referred for evaluation of NAFLD were re-assessed by a specialist. Hepatologists diagnosed non-significant (Brunt ≤F2) fibrosis in 179 out of 192 patients (93.2%). Cirrhosis was diagnosed in 7 out of 192 patients (3.6%) and confirmed on histology in five patients. A further six patients were identified as having advanced fibrosis (F3 fibrosis) (3 biopsy proven, 3 based on fibroscan). In total, 13/192 (6.8%) patients were diagnosed with advanced fibrosis or cirrhosis (Table 5.1).

Table 5.1 Clinical estimates of liver fibrosis for patients referred for evaluation of NAFLD using standard of care (2012 – 2013)

	C&I	Other CCGs	All CCG
n=	83	109	192
<F3	79	100	179
<F3 %	***95.2%***	***91.7%***	***93.2%***
F3 & F4	4	9	13
F3&F4 %	***4.8%***	***8.3%***	***6.8%***
F4	3	4	7
F4 %	***3.6%***	***3.7%***	***3.6%***

Focussing on Camden and Islington referrals only, 79 out of 83 (95.2%) had non-significant fibrosis and 4 out of 83 (4.8%) had advanced fibrosis or cirrhosis (Figure 5.2).

Figure 5.2 Evaluation of patients referred to secondary care from primary care using standard care (2012-2013).



Compared to patients with non-significant fibrosis, patients identified to have advanced fibrosis or cirrhosis were older (58.38±8.24 v. 50.48±13.29, p=0.020) and more likely to have obesity (BMI 36.79±10.56 v. 31.15±4.82, p=0.003) and type II diabetes (68.8% v. 21.9%, p<0.001). Complications of cirrhosis including varices, portal hypertensive gastropathy (PHG) and abnormal liver nodules were detected in 4 patients, all of whom had liver cirrhosis. After two years of follow up, there was one death in the ≥F3 fibrosis group (5.0%) compared to two deaths (1.1%) in the ≤F2 group, although this did not reach statistical difference (p=0.111).

5.4.3 Retrospective application of simple indirect biomarkers of liver fibrosis

Using the available laboratory results, simple indirect non-invasive liver fibrosis markers were calculated retrospectively when possible. Comparing patients with non-significant fibrosis to patients with advanced fibrosis or cirrhosis, unsurprisingly, statistical differences between the two groups were identified for FIB-4 (1.04±0.59 v. 2.51±0.88 P<0.001), AST: ALT ratio (0.68±0.24 v. 0.97±0.53 P<0.001), NFS (-2.33±1.29 v. 0.41±2.15 P<0.001) and APRI (0.48±0.41 v. 1.04±0.69 p<0.001). There was no statistical difference in the liver stiffness measurements in the two groups using fibroscan (4.76±2.35 v. 8.87±9.00 p =0.054) but the sample size with valid fibroscan readings was small with valid measurements obtained from 26 patients in the ‘low-risk’ group and 3 ‘high’ risk patients compromising the validity of this finding.

A detailed retrospective analysis of FIB-4 was performed. Due to insufficient blood parameters (AST, ALT or platelets), a valid FIB-4 was incalculable in 41 patients (21.4%). Of the 151 cases with a valid FIB-4 score, 103 patients (68.2%) had FIB-4 < 1.30 consistent with a low risk of advanced liver disease, whilst 4 patients (2.7%) had high FIB-4. FIB-4 was indeterminate (1.30-3.25) in 44 patients (29.1%). Comparison of 'high- and indeterminate- risk' patients to 'low-risk of advanced liver fibrosis' patients (Table 5.2) revealed that the high-risk patients were older and more likely to have high cholesterol, obesity, hypertension and type II diabetes. There was no statistical difference in the public health Index of Multiple Deprivation (IMD) (2010).

For 41 patients (21.0%), the application of non-invasive liver fibrosis markers would be inappropriate as 22 patients had abnormal ultrasound findings, including 4 patients with incidental findings of cirrhosis that necessitated specialist review. A further 12 patients had significant abdominal symptoms in addition to NAFLD, whilst the remaining 7 patients had a variety of reasons including abnormalities in liver screen (n=3), significantly deranged LFT's (n=1) and patient requested a specialist review (n=1).

Twenty-six patients (13.5%) had a liver biopsy. Eight patients (7.8%) had a FIB-4 < 1.30 and histology confirmed fibrosis stage of ≤ F2 fibrosis. This group of patients could have avoided both referral and biopsy through judicious application of non-invasive liver fibrosis tests. Of 8 patients (4.1%) with confirmed cirrhosis or advanced fibrosis on biopsy, one had FIB-4 >3.25, six

had indeterminate FIB-4 scores between 1.30 and 3.25 and 1 patient had no calculated score (due to a lack of AST).

Table 5.2 Retrospective application of FIB-4 to all referrals to secondary care for evaluation of NAFLD

Parameter	Total – All CCG's	FIB-4 not calculated		Low risk FIB-4<1.30	Indeterminate FIB-4 1.30–3.25	High risk FIB-4 > 3.25	P-value (High/indeterminate v. low)
N	192	44 (22.6%)		103 (52.8%)	44 (22.6%)	4 (2.0%)	n/a
Demographics							
Age (yrs)	51.1 ± 13.1	54.1 ±12.5		42.9 ± 10.8	57.9 ± 12.1	56.5 ± 13.2	**<0.001**
Male n (%)	111(56.9%)	20 (45.5%)		63 (61.2%)	25 (56.8%)	3 (75%)	0.110
Practice IMD	26.5 ± 9.8	32.5 ± 9.0		25.2 ± 9.0	22.9 ± 9.7	32.3 ± 10.2	0.391
BMI (n)	31.6 ± 5.6 (115)	34.0 ± 6.0 (6)		30.4 ± 4.3 (77)	32.0 ± 5.5 (31)	58.1 ± 0 (1)	**0.013**
Weight kg (n)	90.0 ± 18.0 (170)	92.8 ± 18.7 (27)		88.8 ± 17.1 (98)	89.3 ± 17.9 (43)	127.4 ± 30.3 (2)	0.508
Walst circumfernece cm (n)	103 ± 17.5 (5)	N/A		102 ±28.3 (2)	103.7 ± 14.6 (3)	N/A	0.934
Total Cholesterol mmol/l (n)	5.1 ± 1.3 (138)	5.1 ± 1.7 (19)		5.3 ± 1.2 (80)	4.7 ± 1.2 (37)	4.8 ± 0.7 (2)	**0.022**
Hypertension n (%)	82 (42.7%)	18 (40.9%)		33 (32.0%)	29 (65.9%)	2 (50%)	**<0.001**
Type II Diabetes n (%)	50 (26.0%)	12 (27.3%)		17 (16.5%)	19 (43.2%)	2 (50%)	**0.001**
HBA_1C mmol/l (n)	44.4 ± 23.4 (85)	42.6 ± 29.4 (12)		41.7 ± 20.8 (47)	48.4 ± 23.9 (25)	91 ± 0 (1)	0.131
Cardiovascular events n (%)	10 (5.2%)	4 (9.1%)		4 (3.9%)	2 (4.5%)	0	0.995

Parameter	Total – All CCG's	FIB-4 not calculated		Low risk FIB-4<1.30	Indeterminate FIB-4 1.30–3.25	High risk FIB-4 > 3.25	P-value (High/indeterminate v. low)
Secondary care investigation and fibrosis assessment							
Platelet x10^9/L (n)	250.9 ± 71.0 (187)	279.4 ± 97.8 (36)		270.5 ± 57.9 (75)	221.7 ± 52.3 (72)	156.0 ± 37.6 (4)	**<0.001**
ALT mmol/l (n)	64.3 ±43.5 (189)	44.5 ± 28.9 (38)		63.1 ±35.2 (103)	81.1 ±56.5 (44)	95.8 ±86.7 (4)	**0.014**
AST mmol/l (n)	43.9 ± 33.8 (152)	26 ± 0 (1)		32.3 ± 11.3 (75)	51.9 ± 36.6 (72)	122.0 ± 96.9 (4)	**<0.001**
AST:ALT (n)	0.70 ±0.29 (152)	0.70±0 (1)		0.64 ± 0.25 (103)	0.78 ± 0.21 (44)	1.60 ± 0.57 (4)	**<0.001**
APRI (n)	0.53 ± 0.47 (151)	N/A		0.37 ± 0.16 (103)	0.79 ± 0.49 (44)	1.98 ± 0.47 (4)	**<0.001**
NFS (n)	- 2.1 ± 1.6 (109)	N/A		- 2.7 ± 1.1 (77)	-0.8 ± 1.3 (31)	5.34± 0 (1)	**<0.001**
Fibroscan KPa (n)	5.2 ± 3.51 (29)	N/A		4.4 ± 2.0 (18)	6.5 ±4.9 (11)	N/A	0.117
Liver biopsy n (%)	26 (13.5%)	2 (4.5%)		8 (7.8%)	15 (34.1%)	1 (25%)	**<0.001**
Liver biopsy histological fibrosis stage	F0 6 F1 8 F2 4 F3 3 F4 5	F0 1 F1 0 F2 0 F3 0 F4 1		F0 3 F1 4 F2 1 F3 0 F4 0	F0 2 F1 4 F2 3 F3 2 F4 4	F0 0 F1 0 F2 0 F3 1 F4 0	

Parameter	Total – All CCG's	FIB-4 not calculated		Low risk FIB-4<1.30	Indeterminate FIB-4 1.30–3.25	High risk FIB-4 > 3.25	P-value (High/indeterminate v. low)
Secondary care outcomes							
Classified as low risk	179 (93.2%)	41 (93.2%)		103 (100%)	33 (75%)	1 (25%)	**<0.001**
Classfifed as high risk	13 (6.8%)	2 (4.5%)		0	11 (25%)	3 (25%)	**<0.001**
Complications of cirrhosis	4	0		0	3 (1 PHG, 1 Varcies, 1 suspicous liver nodule)	1 (1 varices)	**0.032**
Discharged	134 (68.7%)	36 (81.8%)		74 (71.8%)	23 (52.3%)	1 (25%)	**0.020**
Mortality	3 (1.5%)	1 (2.3%)		0 (0%)	1 (2.3%)	1 (25%)	0.091

5.5 Discussion

This study evaluated the efficacy of standard care to identify significant liver disease in patients with NAFLD found that the vast majority of patients were deemed to have non-significant fibrosis after specialist review. Referral could have been avoided in over 90% of cases. Reducing the unnecessary referral of patients to secondary care could deliver a range of benefits. Firstly, patients with mild disease, who are best served in primary care, could avoid incurring the time, inconvenience, anxiety and costs associated with secondary care referral. Secondly, the specialist services could focus on a referral population comprising a smaller number of patients with a higher prevalence of advanced fibrosis.

The retrospective application of FIB-4 revealed that using this simple indirect marker of liver fibrosis alone, over two thirds of patients had a FIB-4 score associated with a low risk of advanced fibrosis and these patients could have avoided referral. Thirty percent of patients had an indeterminate FIB-4 score (1.30 - 3.25), of whom a quarter of patients were later judged to have advanced liver fibrosis following specialist assessment. The optimal strategy of managing these FIB-4 indeterminant patients remains to be determined but prevalence of advanced fibrosis in one in four suggests that patients with indeterminate scores warrant further evaluation rather than watchful monitoring alone.

At the time of writing, no published studies could be identified that have evaluated the fibrosis status of patients with NAFLD referred for a specialist

opinion. The study outcomes therefore add a different perspective to the increasing body of evidence that suggests that standard care approaches are ineffective in stratifying patients with non-alcoholic fatty liver disease, or any form of liver disease for that matter, for referral from primary care to secondary care. A number of studies have concluded that liver disease is detected at the latter stages of the condition. A review of 4,313 first admissions with decompensated liver disease to a large university teaching hospital between 1996 and 2012 revealed that 73% of patients had previously not been referred to a liver clinic [6]. The same study demonstrated only 12% of patients were referred to outpatients more than one year prior to their index presentation of end-stage liver disease with jaundice, hepatic encephalopathy, bleeding varices and advanced hepatocellular carcinoma, strongly implying patients were being referred too late to secondary care. Another large UK retrospective database study of the Clinical Practice Research Datalink (CPRD), which holds data for over ten million patients, demonstrated 47.3% of patients diagnosed with cirrhosis were diagnosed after emergency presentation with a decompensating event [171] as opposed to a primary diagnosis of cirrhotic liver disease in the outpatient setting. Late diagnosis of chronic liver disease at the time of an acute decompensation had an adverse impact on outcomes, with average survival probabilities at 1 and 5 years of 0.55 and 0.31 for patients presenting as an emergency with decompensated disease compared to 0.84 and 0.66 for patients identified with cirrhosis in the outpatient setting [171].

The pattern of referrals identified in this study is likely to be common across industrialised countries. In NAFLD, for patients with non-significant disease, the appropriate preventative interventions are weight loss and exercise [172, 173] and these can be delivered effectively in primary care [174] obviating the need for referral for specialist care. Reducing inappropriate referrals represents an opportunity to reduce unnecessary clinic appointments, investigations, inconvenience and even harm for patients, and reduce pressure on secondary care services. Conversely, in patients with cirrhosis, high quality evidence supports the use of treatments for portal hypertension [46] and the early detection of HCC through targeted screening [47] as well as changes in lifestyle, particularly abstinence from alcohol [48] and weight loss [49] to reduce morbidity and mortality associated with chronic liver disease. The earlier identification of patients with advanced fibrosis or cirrhosis has the potential to reduce the global cost of managing chronic liver disease as the majority of healthcare costs are incurred for the management of patients with decompensated end stage liver disease.

This study had a number of limitations, The re-assessment of patients referred to a hospital for a specialist opinion lacked a validated outcome measure such as liver biopsy in all patients. Instead, the study used a composite clinical judgement comprising of clinical judgement, bloods tests, fibroscan and liver biopsy where available. Inevitably, patients undergoing liver biopsy in this retrospective audit had a degree of selection bias characteristic of real-world practice. Composite clinical judgement has not been validated as an outcome

measure in the literature and therefore could introduce detection bias. The use of re-investigation and composite judgement has been used by another study as identified in the systematic review (Chapter 3). Poynard and colleagues [192] did use specialist reinvestigation as their reference standard, designating a fibrosis stage to patients identified as high risk for advanced fibrosis or cirrhosis - they used a categorical, unvalidated system of 'fibrosis confirmed', fibrosis still suspected' and 'indeterminate'.

Given the retrospective nature of the study, not all patients had all the relevant parameters to calculate a FIB-4 score. A valid FIB-4 was incalculable in 21.4% of patients, usually due to a lack of AST measurement, and this could potentially be another source of bias.

This study adds weight to the case for changes in the management strategies for early diagnosis and treatment of chronic liver disease in NAFLD, advancing the case for testing the incorporation of new diagnostic tests for the detection of liver fibrosis in pathways of care with the aim of identifying patients with chronic liver disease at an earlier stage. Standard care assessment in primary care is usually based on a composite of clinical history and examination, standard liver function tests and an ultrasound. This study demonstrated the positive predictive value of this strategy at identifying patients with advanced fibrosis (F3) or cirrhosis (F4) was less than ten percent. Implementing the use of non-invasive liver fibrosis tests in primary care pathways may improve performance of primary care pathways. The aim of such strategies would be

to reduce the number of referral of patients with mild disease and the earlier detection of patients with advanced liver disease in primary care. Accordingly, such strategies have been identified as key in the approaches to combat the increasing burden of chronic liver disease [6, 98].

5.6 Conclusion

This study has provided evidence that the assessment of patients with NAFLD in primary care using ‘standard care’ is ineffective. The vast majority of referrals made using this approach had non-significant fibrosis and could have avoided referral. The implementation of non-invasive liver fibrosis tests in primary care represents an important strategy for better stratification of patients to identify those with advanced liver disease who need specialist input.

CHAPTER 6 PROSPECTIVE EVALUATION OF A PRIMARY CARE REFERRAL PATHWAY FOR PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE

6.1 Introduction

In this thesis thus far, a systematic review (Chapter 3) has highlighted a dearth of published evidence supporting the application of non-invasive liver fibrosis tests in community settings. Canvassing the opinions of gastroenterologists and hepatologists in the UK via a national survey (Chapter 4) revealed an increasing appetite amongst specialists to use emerging non-invasive tests for liver fibrosis in clinical services. Utilizing these tests in primary care was considered a key strategy to reduce referrals of patients with non-significant fibrosis (Brunt $\leq$F2) and promote earlier detection of significant liver disease (Brunt $\geq$F3). In Chapter 5, a retrospective audit of primary care referrals for patients with non-alcoholic fatty liver disease to secondary care revealed the current 'standard care' to be ineffective with over ninety percent of referrals deemed to have non-significant liver fibrosis who could have avoided referral. Inevitably, patients with advanced fibrosis and cirrhosis remain undetected in primary care, progressing silently until presenting at a later stage with end stage liver disease.

In this chapter, I describe the design of a novel primary care pathway for patients with NAFLD employing non-invasive liver fibrosis tests and a prospective longitudinal cohort evaluation. A large primary care cohort of patients with NAFLD in the London boroughs of Camden and Islington was followed for a total of 3 years to test the hypothesis that using non-invasive

liver fibrosis tests in primary care pathways improves the efficiency of referrals by reducing referral of patients with non-significant fibrosis (Brunt ≤F2) and increasing the detection of advanced fibrosis and cirrhosis, compared to standard care.

NAFLD was an appealing patient population to target. NAFLD is the commonest cause of deranged liver blood tests in primary care [39] and has an estimated prevalence of 25-30% in the Western adult population [40]. The majority of patients have non-significant fibrosis whilst only a minority, approximately 5% to 10%, develop clinically significant liver disease [40]. However, given the shear burden of disease, NAFLD is predicted to be the leading indication for liver transplantation within a decade [64]. The severity of liver fibrosis is the key determinant of liver-related morbidity and mortality in patients with NAFLD [75, 76, 170]. Identifying patients with significant liver disease, including cirrhosis, for timely specialist referral is an important component of patient management but remains highly challenging. The majority of patients with NAFLD are identified, assessed and managed by general practitioners (GPs). Clinical assessment including history-taking and examination is a poor discriminator of liver fibrosis until the development of liver cirrhosis and portal hypertension result in obvious clinical signs of liver damage. Accurate fibrosis assessment in the vast majority of primary care practices is currently reliant on liver blood tests and ultrasonography, both of which correlate poorly with liver fibrosis [88, 168]. Use and access to non-invasive liver fibrosis tests is limited and not well established in primary care. Therefore, the current 'standard care' model in primary care is inefficient in

stratifying patients for specialist referral. Patients with mild disease (Brunt ≤F2) are inadvertently referred to a specialist when the appropriate management including optimization of diabetic control and weight are effectively delivered in the community [172, 173]. Conversely, patients with advanced fibrosis (Brunt F3) or cirrhosis (Brunt F4) can remain undiagnosed and progress silently in the community until they present with complications of end-stage liver disease. Such patients, if identified earlier, would benefit from established cirrhosis surveillance protocols and specialist interventions as well as being offered access to clinical trials of investigational agents. This ineffective risk stratification in primary care contributes to late detection of significant liver disease and the poor outcomes associated with chronic liver disease.

The development of non-invasive fibrosis tests over the last few decades and their integration into hospital specialist assessment affords an opportunity to extend their use into primary care pathways with the aim to promote earlier identification of patients with chronic liver disease [6].

In this study, a pathway for patients with NAFLD in primary care was developed using non-invasive fibrosis tests (FIB-4 and ELF) to stratify patients for referral to specialist care. In this chapter, results from a prospective evaluation of this pathway are presented.

6.2 Aims of study

To evaluate the impact of introducing non-invasive liver fibrosis tests in primary care to identify patients with advanced fibrosis or cirrhosis (Brunt ≥F3).

6.3 Camden and Islington NAFLD pathway

6.3.1 The Camden and Islington Liver Working group

In April 2013, the clinical commissioning groups representing the London boroughs of Camden and Islington convened a liver working group comprising representatives from the Royal Free London NHS Foundation trust, local primary care groups and University College London to address the local burden of chronic liver disease (CLD). The working group brought together general practitioners, hepatologists, strategy leads for the commissioners, public health professionals, health economists and public and patient involvement (PPI) representatives to develop new pathways of care to improve outcomes. The boroughs of Camden and Islington serves a population of 430,000 inhabitants and this drive was in part a response to the Public Health England report 'Longer Lives' [211] which ranked Camden and Islington 20th and 21st in premature liver mortality in the UK and 2nd and 3rd highest in London. Between 2010 and 2012, the 'under 75 mortality rate from liver disease' was 26.4 per 100,000 population (95% CI 21.7 – 31.9) in Islington and 27.2 per 100,000 (21.8 – 33.6) population in Camden compared to the London average of 18.9/ 100,000 and the national average of 18.0/ 100,000 [211]. Interrogating the data from the inception of the database in 2001, this trend was consistently observed since the first dataset covering the 2001 – 2003 timeframe. The report stressed that a significant majority of these deaths were preventable where 'preventable mortality' was defined as 'deaths in people under 75 years that are considered preventable through early interventions or changes to modifiable risk factors'. Between 2010-2012, there

were 81 ‘preventable’ deaths secondary to liver disease in Islington, and 99 in Camden, equating to 23.3/ 100,000 (18.3 – 29.2) and 23.7/ 100,000 (19.1 – 29.0) ‘preventable’ deaths in Islington and Camden respectively, compared to the London average of 16.6/ 100,000 and national average of 15.8/ 100,000.

The liver working group met regularly (every 6 to 12 weeks). The remit was to address the increasing burden of CLD with the aim to review the available evidence and develop new pathways of care to improve liver disease detection and improve liver related morbidity and mortality.

6.3.2 Non-alcoholic fatty liver disease in Camden and Islington

The Camden and Islington (C&I) liver working group identified NAFLD as a key contributor to the growing burden of CLD locally. In addition to well documented national and international trends, there were CCG level data highlighting an increased prevalence of obesity in the local population. In 2012, local population obesity estimates were 19% for Islington [212] and 21% for Camden [213]. Taking Islington for example, with an estimated population of 200,000 people, this equates to 42,300 overweight adults, 25,000 obese adults and 2,900 morbidly obese adults [212]. Inevitably, this suggested the burden of NAFLD in the local population was high. Unpublished local public health data estimated hospital admissions and premature mortality related to NAFLD in 2012 - 2013 to be 2.8/ 100,000 (95% CI 1.0 – 6.1) and 0.80/ 100,000 (95% CI 0.26-1.87) respectively in Islington, and 2.6/ 100,000 (1.0 - 5.7) and 0.61/ 100,000 (0.17 – 1.57) respectively in Camden.

6.3.3 Development of the NAFLD pathway

In recognition of the increasing burden of NAFLD, the impracticality of specialist review for all patients with the condition and the inability of standard care to distinguish significant liver fibrosis (equivalent to Brunt ≥F3) from non-significant stages of liver fibrosis, the liver working group reasoned that developing a risk stratification pathway for patients with NAFLD using non-invasive fibrosis tests was a priority.

To inform pathway design, the Royal Free London Public Health and CCG Strategy Leads conducted a formal appraisal of the available evidence in conjunction with colleagues leading an NIHR systematic review of evidence, which was subsequently published in 2015 [125]. Performance characteristics of FIB-4 (Table 6.1) and ELF (Table 6.2) for patients with NAFLD are summarized from the available literature below.

Table 6.1 Summary of studies evaluating the performance of FIB-4 in NAFLD

FIB-4 cut off	Severity	Sensitivity	Specificity	PPV	NPV	N	Reference
3.25	≥F3	26	98	75	85	145	McPherson [105]
3.25	≥F3	21	97	56	87	152	Xun [214]
3.25	≥F3	48	95	53	94	576	Sumida [215]
3.25	≥F3	56	89	31	94	243	Perez [216]
2.67	≥F3	63	88	51	93	1102	Yoneda [217]
2.67	≥F3	38	96	64	89	152	Xun [214]
2.67	≥F3	33	98	80	83	541	Shah [218]
1.659	≥F3	90	71	37	97	1102	Yoneda [217]
1.54	≥F3	74	87	61	92	242	Adams [219]
1.51	≥F3	73	78	-	-	56	Dvorak [153]
1.45	≥F3	90	64	24	98	576	Sumida [215]
1.30	≥F3	85	65	36	95	145	McPherson [105]
1.30	≥F3	67	67	28	92	152	Xun [214]
1.30	≥F3	74	71	43	90	541	Shah [218]
1.24	≥F3	78	72	-	-	56	Dvorak [153]

Table 6.2 Summary of ELF single thresholds used in NAFLD population studies

ELF cut off	Severity	Sensitivity	Specificity	PPV	NPV	N	Reference
≥10.51	≥F3	100	98	90	100	112	Nobili [220]
≥10.36	≥F3	80	90	71	94	192	Guha [122]
≥9.8	≥F3	74	92	75	92	329	Fagan [221]
≥10.18	≥F2	94	93	70	99	112	Nobili [220]
≥ 9.92	≥F2	100	90	-	-	54	Karlas [222]

Modelling work conducted by the University College London liver fibrosis research group, led by Professor Rosenberg, on patient cohorts with paired liver biopsies revealed sequential use of FIB-4 and ELF had the optimal performance characteristics compared to NFS, FIB-4 and ELF alone or in combination. In this cohort of 177 biopsy staged patients with NAFLD, FIB-4 followed by ELF in the indeterminate group (64 required ELF test), the calculated NPV, PPV, AUC and diagnostic accuracy were 92%, 80%, 0.85 and 91% respectively [223].

A summary of existing liver fibrosis tests from the NIHR systematic review of evidence is described in Table 6.3 [125].

Table 6.3 Summary of non-invasive liver fibrosis tests characteristics in patients with non-alcoholic fatty liver disease

Estimated prevalence of advanced fibrosis is 5%. Indeterminate and high risk calculated for 100 patients. Adapted from Crossan (2015) [125].

Test	No. of studies	Cut-off	Sensitivity	Specificity	NPV	Indeterminate	High (refer)
NFS	10	-1.455, 0.676	80	66	98.4	31	5
FIB-4	4	1.30, 3.25	84	74	98.5	24	5
BARD	7	>2	84	61	98.6	-	41
ELF	1	10.3	80	90	98.8	-	14
Fibrotest	3	0.3, 0.7	88	73	99.1	24	6
Fibroscan	8	8.7- 9.8	82	84	98.9	-	19

The NAFLD pathway was incorporated into a wider abnormal liver blood test pathway which was developed as part of this project. The initial focus of this pathway aims to guide appropriate investigation of abnormal liver blood tests by the general practitioner (Figure 6.1).

Patients aged 18 and over are eligible to enter the pathway if they have abnormal liver function. This guides primary care investigation depending on the pattern of abnormality, namely cholestatic, hepatitic enzyme elevations or isolated raised bilirubin. Red flags for underlying malignancy are highlighted, in which case the two-week wait cancer pathway is more appropriate. In the presence of significant inflammation (ALT > 300) or evidence of decompensated liver disease (including jaundice, ascites or encephalopathy), an urgent specialist referral is recommended. Initial evaluation of a patient with abnormal liver function test focusses on history-taking, reviewing the medication history and eliciting risk factors for chronic liver disease including history of alcohol consumption and the presence of metabolic risk factors. Thereafter, investigations include an ultrasound of the liver and a liver blood screen to evaluate for viral hepatitis B and C, autoimmune hepatitis, haemochromatosis, Wilson disease and alpha one anti-trypsin deficiency. A negative liver panel, in combination with a negative alcohol history (>21 units/ week in males and > 14 units/ week in females) would suggest the abnormal liver function tests were attributable to NAFLD. The presence of hepatic steatosis on the ultrasound would be supportive of the diagnosis, although is not essential. Patients deemed to have NAFLD are then eligible to enter the NAFLD risk stratification pathway (Figure 6.2).

Figure 6.1 Camden and Islington abnormal liver blood test pathway.

Patients with abnormal liver blood tests were recommended to undergo a comprehensive liver screen to evaluate for potential causes. Pathway was created in December 2013

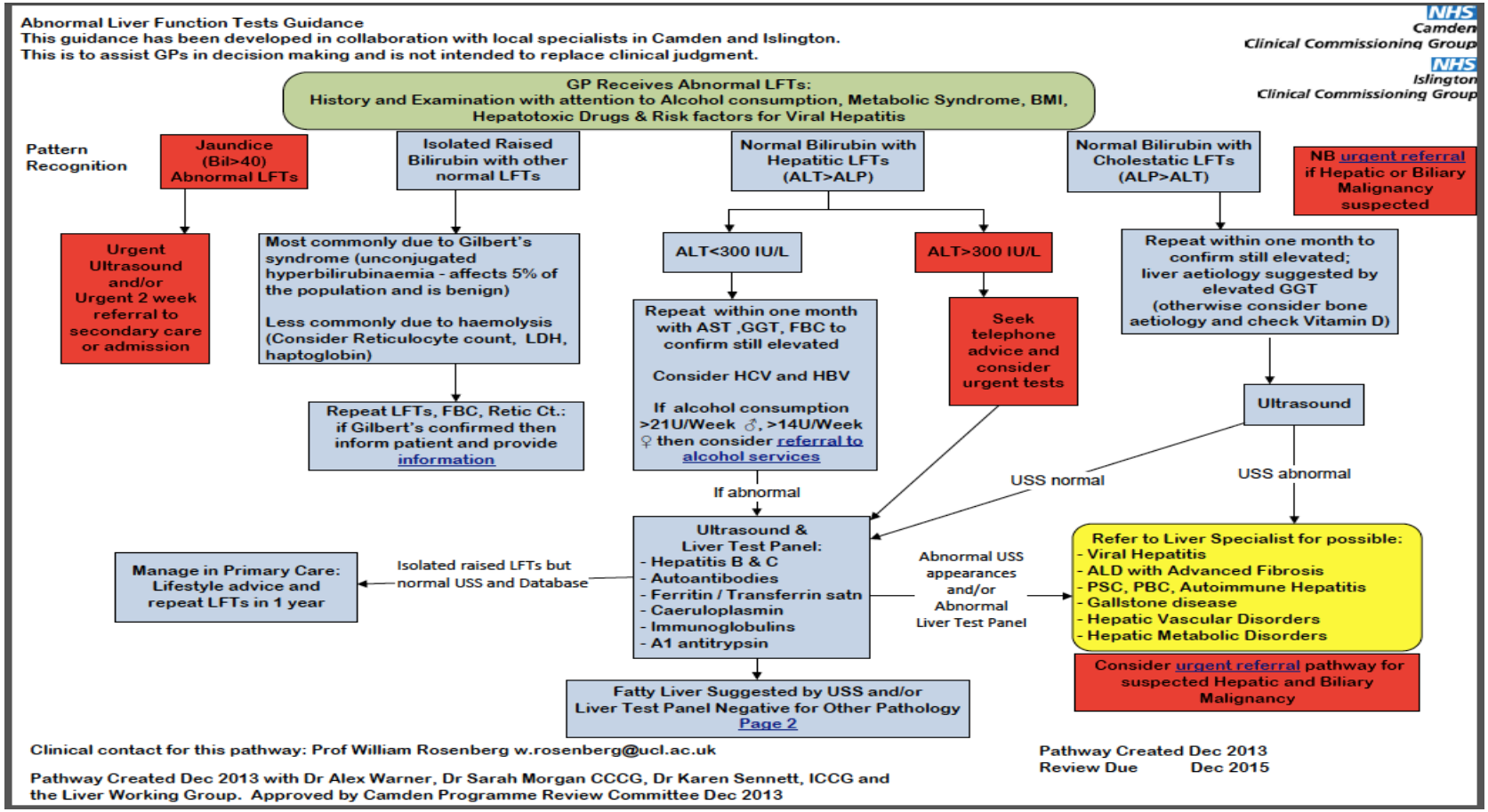
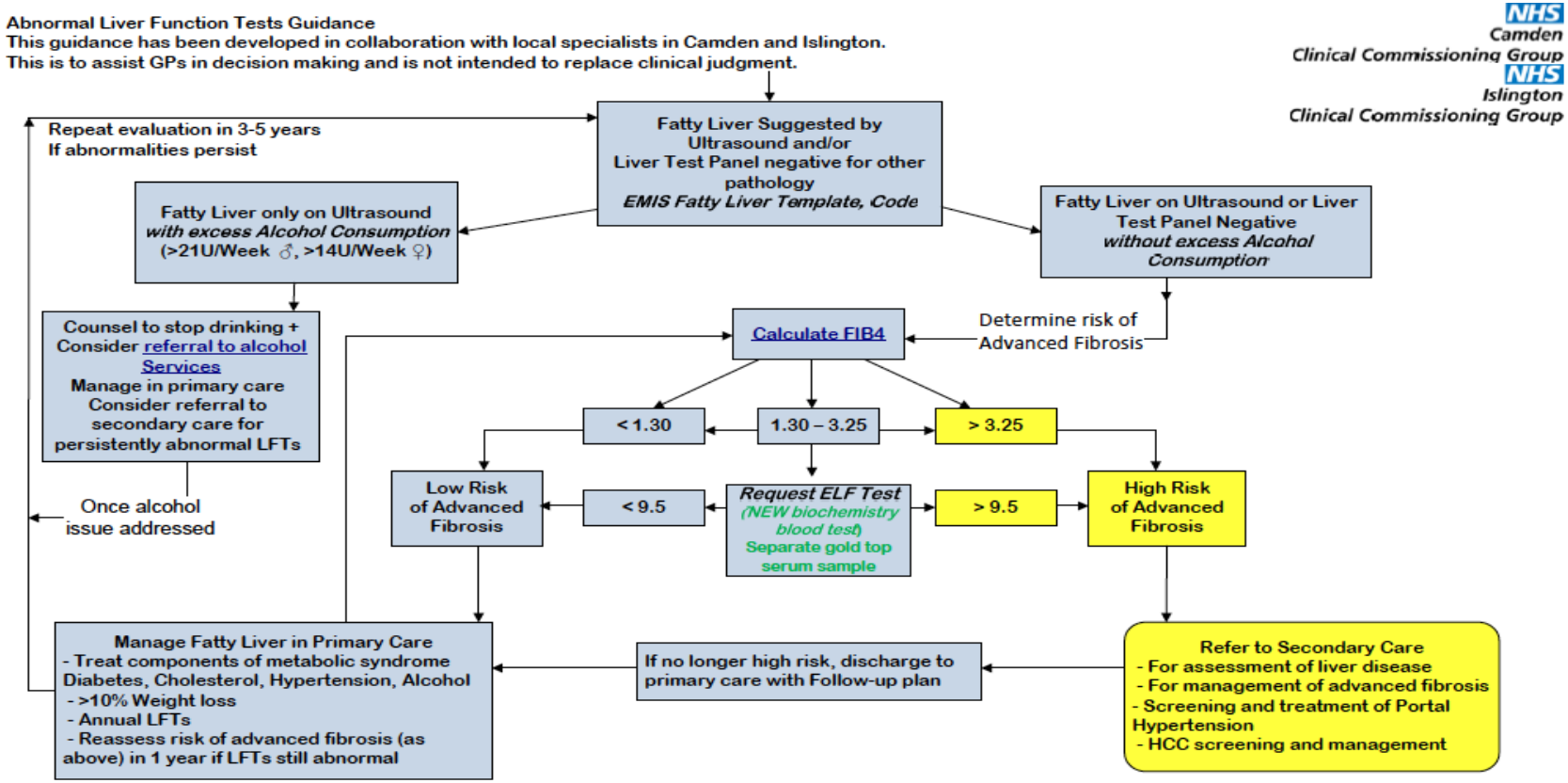


Figure 6.2 Camden and Islington NAFLD pathway

Patients diagnosed with NAFLD after a negative liver screen and negative alcohol history will undergo risk stratification for the presence of significant liver fibrosis in primary care. All patients will have a FIB-4 test. Patients with a low FIB-4 (<1.30) will be managed in primary care, whilst patients with a high FIB-4 (>3.25) will be referred for specialist assessment. Patients with an indeterminate FIB-4 (1.30 – 3.25) will have second tier testing with an ELF test. Patients with a score > 9.5 were recommended for referral. The pathway was initiated on the 1st March 2014.



The Camden and Islington NAFLD pathway consists of a two-step non-invasive fibrosis assessment. All patients have a FIB-4 score calculated in primary care. Patients with FIB-4 score <1.30 are classified as low risk of advanced fibrosis or cirrhosis (Brunt ≤F2) and remain in primary care [105] with management focussing on optimising cardiovascular risk and diabetic control, with a recommendation of annual liver blood tests and re-assessment of liver fibrosis after three to five years. Patients with FIB-4 score > 3.25 are classified as high risk of advanced fibrosis or cirrhosis (Brunt ≥F3) and referral for specialist assessment is advised. Patients with indeterminate FIB-4 scores between the lower and higher thresholds (≥1.30 and <3.25) will have second tier testing with an ELF test. Patients with ELF scores <9.5 are classified as low risk of advanced fibrosis or cirrhosis and remain in primary care. Patients with an ELF score ≥9.5 are classified as high risk of advanced fibrosis or cirrhosis and are recommended for referral to secondary care [121, 122, 149].

The working group attempted to accommodate the competing preferences of the group. Serum tests of liver fibrosis were preferred to elastography after an independent appraisal of non-invasive tests for liver fibrosis conducted by the local public health consultants. A local NHS hospital (North Middlesex Hospital, Edmonton, London) was commissioned by Camden and Islington CCG to perform the ELF test as they had procured a Siemens analyser. The use of transient elastography in general practice clinics was deemed impractical given the desire to establish a pathway which was entirely based in the community. The project budget would not accommodate the required investment and maintenance of fibroscan technology and associated costs

including technician employment and training and acquisition of clinic space in the community.

Compared to the ELF thresholds published in the literature (Table 6.2) or recommended by the manufacturer [149], a lower ELF cut-off of 9.5 was adopted for the detection of advanced fibrosis or cirrhosis. The liver working group recognized that at the time of conception of the pathway (2013), use of non-invasive liver fibrosis tests in primary care was not established in the United Kingdom. Pathway design was predicated on reducing referrals of patients with non-significant fibrosis and, arguably more importantly, on reducing the rate of missed cases of advanced fibrosis or cirrhosis in the community (false negative rate). By using a lower ELF cut-off, we improved the specificity of the pathway, thereby reducing the false negative rate and improving the negative predictive value. All non-invasive liver fibrosis tests have been derived and validated in specialist tertiary care populations, where the prevalence of the population of interest (patients with ≥F3 fibrosis) is higher than the general population due to inherent selection bias involved in those studies. In our study, the use of non-invasive liver fibrosis tests was in a relatively unselected primary care cohort of patients with NAFLD, where the prevalence of advanced fibrosis or cirrhosis (≥F3 fibrosis) would be lower. This equates to a lower pre-test probability in identifying patients with significant fibrosis or cirrhosis and therefore strengthened the negative predictive value of the pathway, therefore reducing the risk of missing cases (a lower false negative rate).

The NAFLD pathway was circulated for external peer review by expert colleagues at the University of Birmingham and University of Newcastle. The pathway was formally introduced on the 1st March 2014.

6.3.4 Camden and Islington NAFLD pathway evaluation

The Camden and Islington NAFLD pathway was commissioned by the clinical commissioning groups (CCG) of both boroughs as a service improvement innovation. As part of the commissioning process, both the Camden CCG and Islington CCG Boards authorised funding and adoption of the pathway with the recommendation that a full-service evaluation should be performed to evaluate impact of the intervention. This evaluation was funded by the CCGs and supported by the Local Authority, UCL Research Department of Primary Care and Population Health, the UCL Institute of Liver and Digestive Health, and the departments of Hepatology and Public Health at the Royal Free London NHS Foundation Trust.

6.4 Methods

6.4.1 Donabedian model for evaluation of health services

The Donabedian Model for the evaluation of Health services [224] provided the framework to evaluate the Camden and Islington NAFLD pathway. An outline is summarized in Table 6.4. The evaluation framework assesses the effectiveness of an intervention using a three-component paradigm – structure, process and outcomes. The outputs of these measurement domains align with the NHS vision of quality, which includes patient safety and service efficiency. The model is based on the premise that the structure measures

have an effect on process measures, which in turn influence outcome measures. Structure measures incorporate the impact of an intervention on infrastructure, staffing and equipment. It reflects the characteristics of the individual provider organizations and the baseline equipment available. Process measures relate to the delivery of care and include numbers of patients entered onto the pathway, numbers of tests performed, time taken to move through the pathway and adherence to the pathway protocol. Outcome measures attempts to assess the impact of the intervention on patient health, patient and provider experience and focuses on the number of correct diagnoses, numbers of patients referred to secondary care, proportion of patients seen in secondary care who have significant disease and the impact on hospital clinic outcomes.

Table 6.4 Structure of Camden and Islington NAFLD pathway evaluation

The Donabedian model of health evaluation [224] describes three components in the evaluation of a new healthcare intervention. This provided the framework for the Camden and Islington NAFLD pathway evaluation.

	Indicator	Rationale	Data source
1. Service Structure			
1A	Change in staffing, funding, equipment and other resources as a result of implementing the pathway	It is important to note any additional costs that arise aside from those accounted for in the business plan (cost of increased number of tests) such as additional costs due to changes in referral patterns.	Primary care Electronic Patient Records (EPR) – via Local Authority Health Intelligence Teams.
2. Process Monitoring			
2A	Number of primary care consultations (new and follow up) for patients with a diagnosis of NAFLD	The introduction of the pathway will increase awareness of NAFLD, and therefore coding of liver disease as part of a consultation should increase amongst those with abnormal LFTs.	Primary care Electronic Patient Records (EPR) – coding for NAFLD via Local Authority Health Intelligence Teams.
2B	Number of patients receiving a FIB-4 test	It is important to monitor the numbers of patients entered onto the pathway to assess uptake and applicability. The measure of FIB-4 (with a newly developed electronic code) will be a proxy measure for patients being entered onto the pathway.	Primary care Electronic Patient Records (EPR) search via Local Authority Health Intelligence Teams.
2C	Proportion of patients consulting for NAFLD receiving a FIB-4 test	It is important to monitor the usuage of the pathway as a proportion of the number of patients consulting for the condition. This would provide an indicator of pathway uptake.	Primary care Electronic Patient Records (EPR) search via Local Authority Health Intelligence Teams.
2D	Number of patients receiving an ELF test.	It is important to monitor the number of patients receiving ELF test and to determine if the request is appropriate (for indeterminate patients)	Primary care Electronic Patient Records (EPR) search via Local Authority Health Intelligence Teams.

	Indicator	Rationale	Data source
2E	Number of patients referred to specialist for management of NAFLD through - C&I NAFLD pathway - C&I Standard Care - C&I Total - Other CCGs (Standard care) - Standard Care Total (C&I and other) - Total referrals (all)	It is important to monitor the impact of the pathway on referrals after correct management as per the pathway (C&I NAFLD pathway) compared to standard care from both C&I and other CCG's This will inform future service planning and pathway refinement.	Secondary care Electronic Patient Records (EPR) search/ pathway evaluation
2F	Proportion of patients referred to specialist for management of NAFLD who have consulted GP.	It is important to determine proportion of patients being referred who consult GP, to assess impact of the pathway on total referrals.	Primary care Electronic Patient Records (EPR) search via Local Authority Health Intelligence Teams. Secondary care Electronic Patient Records (EPR) search/ pathway evaluation
2G	Proportion of patients referred to specialist for management of NAFLD who have been referred because of the pathway.	It is important to determine proportion of patients being referred because of the pathway as a proportion of the total number of patients referred. It can be speculated that this would increase with time.	Secondary care Electronic Patient Records (EPR) search/ pathway evaluation
2H	Proportion of patients referred to specialist for management of NAFLD who have - Had ultrasound abdomen/ liver in primary care - Were eligible for pathway - Had appropriate FIB-4 and ELF testing in primary care	It is important to document adherence to the pathway, with attention focussing on the correct use of screening tests (ultrasound), correct selection of patients for pathway and appropriate use and intepretation of FIB-4 and ELF.	Secondary care Electronic Patient Records (EPR) search/ pathway evaluation

	Indicator	Rationale	Data source
2I	Proportion of patients referred to secondary care from pathway who fulfilled referral criteria.	It is important to assess adherence to the pathway protocol.	Secondary care Electronic Patient Records (EPR) search/ pathway evaluation
2J	Waiting time to see a hepatologist	It is important to assess the impact of the pathway on waiting times to see a hepatologist.	Secondary care Electronic Patient Records (EPR) search/ pathway evaluation
2K	Number and proportion of liver biopsies performed by specialist	It is important to document the impact of the pathway on the requesting of liver biopsy by a specialist. It maybe speculated that the pathway reduces liver biopsies due to primary care risk stratificaiton, or alternatively increases biopsy requests as identifying patients at risk of significant disease at a pre-symptomatic stage.	Secondary care Electronic Patient Records (EPR) search/ pathway evaluation
3. Outcome measures			
3A	Proportion of patients stratified by pathway in primary care as Low risk of significantfibrosis High risk of significant fibrosis	It is important to document the primary care risk stratification of patients	Primary care Electronic Patient Records (EPR) search via Local Authority Health Intelligence Teams.
3B	Number and Proportion of those referred to secondary care that have ≥F3 fibrosis: - C&I NAFLD pathway - C&I Standard Care - C&I Total - Other CCGs (Standard care) - Standard Care Total (C&I and other)	It is important to document the impact of the pathway on detection of advanced fibrosis and cirrhosis. It could be speculated that the pathway should increase detection of advanced fibrosis/cirrhosis as a result of the use of non-invasive tests. The definition of advanced fibrosis/cirrhosis will be a composite specialist judgement.	Secondary care Electronic Patient Records (EPR) search/ pathway evaluation
3C	Number and Proportion of those referred to secondary care that have cirrhosis:	It is important to document the impact of the pathway on detection of cirrhosis. It could be speculated that the	Secondary care Electronic Patient Records (EPR) search/ pathway evaluation

	Indicator	Rationale	Data source
	- C&I NAFLD pathway - C&I Standard Care - C&I Total - Other CCGs (Standard care) - Standard Care Total (C&I and other)	pathway should increase detection of cirrhosis as a result of the risk stratification. The definition of cirrhosis will be a composite specialist judgement.	
3D	Number and Proportion of those referred to secondary care that have ≤F2 fibrosis: - C&I NAFLD pathway - C&I Standard Care - C&I Total - Other CCGs (Standard care) - Standard Care Total (C&I and other)	It is important to document the impact of the pathway on the referral of patients with non-significant fibrosis (≤F2 fibrosis). It could be speculated that the pathway should decrease referral of patients with ≤F2 fibrosis as a result of primary care risk stratification. The definition of non-significant fibrosis will be a composite specialist judgement.	Secondary care Electronic Patient Records (EPR) search/ pathway evaluation
3E	Mortality (all cause and liver-related)	It is important to document the impact of the pathway on liver related mortality, liver related premature mortality and all-cause mortality. It can be speculated that this will be evident in the long term rather than short term. It should be noted that due to the relatively small population targetted by the pathway, any statistically significant impact on these outcomes may take at least 10 years.	Secondary care Electronic Patient Records (EPR) search/ pathway evaluation
3F	Secondary liver-related events e.g. number of admissions for decompensated liver disease, variceal bleeds etc.	It is important to document the impact of the pathway on liver related events. It can be speculated that this will be evident in the long term rather than short term. It should be noted that due to the relatively small population targetted by the pathway, any statistically significant impact on these outcomes may take at least 10 years.	Secondary care Electronic Patient Records (EPR) search/ pathway evaluation

	Indicator	Rationale	Data source
3G	Enrolment in therapeutic clinical trials	One the proposed benefits of detecting F3 disease (as well as F4 disease) is enrolment to therapeutic clinical trials.	Secondary care Electronic Patient Records (EPR) search/ pathway evaluation
3H	Patients qualitative experience	It is expected that the implementation of the pathway should lead to improved quality of life for patients with significant liver disease that they would have otherwise had. It should be noted that as many of the patients seen on the pathway will be asymptomatic, it is less likely that quality of life will improve compared to their current situation.	Patient interviews (beyond remit of this thesis)
3I	GP experience	Feedback on the pathway from users is crucial to inform future improvements and pathway re-design	GP interviews (beyond remit of this thesis)
3J	Economic evaluation	As part of evaluation, it would be beneficial to explicitly consider a health economics approach to determine the cost-benefits of the pathway.	Health economic study

6.4.2 Study design and setting

To evaluate the impact of the NAFLD pathway, a prospective longitudinal cohort study was designed. Analyses were performed before and after the intervention using the baseline data from Chapter 5, and comparisons were made to unexposed controls (those cases referred from Camden and Islington without using the pathway and those referred from boroughs not using the pathway) during the study period.

The NAFLD pathway was introduced as a service innovation on 1st March 2014. The analysis was performed between 1st March 2014 and 31st May 2016 to evaluate the impact of the pathway in reducing unnecessary referrals and improving the detection of patients with advanced fibrosis or cirrhosis. The pathway was introduced into Camden and Islington CCGs, which represented two out of twenty-five (8%) of CCGs making referrals to liver specialist services at The Royal Free London NHS Foundation Trust, The Whittington Hospital NHS Trust and University College London Hospitals NHS Foundation Trust during the study period. Camden and Islington accounted for 43% of the referrals to the aforementioned hospitals in 2012–13. All practices in Camden and Islington implemented the pathway as part of the service innovation, but individual general practitioners were not mandated to use it nor were GPs required to use the pathway for every case of suspected NAFLD. Therefore, GPs could employ either standard care or the NAFLD pathway for their patients prior to referral as they wished. A longitudinal evaluation was performed, in which Camden and Islington represented the CCGs exposed to

the intervention (NAFLD pathway) and the remaining 23 CCGs represented the control CCGs (unexposed to the intervention/ NAFLD pathway).

6.4.3 Comparator groups

Outcomes of patients managed on the NAFLD pathway were compared to

- Pre-pathway (baseline) outcomes described in Chapter 5 (2012 - 2013)
- Patients referred using 'standard care' during the evaluation period (2014 – 2016).

Evaluation of standard care 2012–2013 prior to pathway introduction

To determine the performance of standard care to identify patients with advanced fibrosis or cirrhosis prior to the introduction of the NAFLD pathway, an audit of referrals by GPs was undertaken between 01/03/2012 and 28/02/2013. A detailed report is described in Chapter 5. All patients referred with a diagnosis of NAFLD to The Royal Free London NHS Foundation Trust, The Whittington Hospital NHS Trust and University College London Hospitals NHS Foundation Trust were reviewed and evaluated for evidence of advanced fibrosis or cirrhosis (Brunt ≥ F3) based on a composite of history, physical examination, blood tests, imaging, Fibroscan, and liver histology when available. Where possible, FIB-4 scores were calculated and patients with FIB-4 <1.30 were deemed to have low risk of advanced fibrosis or cirrhosis, thus referred inappropriately. Patients referred from practices in Camden and Islington were analysed separately from those referred from other CCGs.

6.4.4 Pathway evaluation

The NAFLD pathway was introduced in Camden and Islington on 1st March 2014. Outcome data were collected for patients referred with a diagnosis of NAFLD to the three hospital sites for a specialist opinion. Referrals were differentiated by the CCG of the referral origin and use of standard care or the NAFLD pathway. The diagnostic performance of the Camden and Islington NAFLD pathway in detecting cases of advanced fibrosis or cirrhosis was evaluated against a reference standard. This was a composite clinical assessment, as described above, conducted by specialists blinded to the use of the NAFLD pathway. This evaluation included a fibroscan performed independently of the use of the pathway in the majority of cases. A subgroup of patients underwent liver biopsy following clinical assessment, with samples analysed for aetiology, inflammation and fibrosis stage.

The study team (led by AS and WMR) reviewed all outcomes and any differences of opinion between the experts and the study team (<10% of cases) were resolved through discussion within the wider committee.

6.4.5 Outcomes

The primary outcome measure was the proportion of patients with NAFLD referred to secondary care who had non-significant liver fibrosis (Brunt ≤F2) (false positive rate).

Secondary outcomes included:

- The proportion of those referred who were deemed to have advanced fibrosis or cirrhosis (true positive rate).
- Proportion of patients diagnosed with NAFLD avoiding referral after primary care stratification.

Sensitivity analyses were performed to evaluate the impact of using age-specific cut-offs for FIB-4 to stratify patients with NAFLD. Alternative ELF thresholds for detection of significant fibrosis were evaluated including the manufacturer's recommendation for advanced fibrosis (ELF = 9.8) [149] and the cut-off for referral endorsed in the NICE guidance on NAFLD (ELF = 10.51) [225].

To evaluate the effectiveness of the pathway, patients referred using the Camden and Islington NAFLD pathway were compared to patients referred from Camden and Islington prior to introduction of the pathway; and to patients referred using standard care from either Camden and Islington, or from other CCGs not employing the pathway during the evaluation period. To evaluate the effectiveness of the introduction of the NAFLD pathway to all general practices across Camden and Islington, outcomes for all patients referred from

Camden and Islington, irrespective of the use of the NAFLD pathway, were compared to patients referred from all other CCGs.

6.4.6 Primary care data collection

The electronic patient records in Camden and Islington stored on EMISWeb (Egton Medical Information Systems), were interrogated centrally to obtain pseudonymised patient-level data on individuals diagnosed with NAFLD. Data on demographics, co-morbidities, investigations and use of the pathway were collected using Read codes in primary care.

Data acquisition was facilitated by the Camden & Islington CCG Informatics Teams to cover the 72 GP practices in Camden and Islington. Search terms to identify patients with newly coded NAFLD across all practices between 01/03/2014 and 29/02/2016 were captured. An EMISweb search algorithm was developed after liaison between CCG data analysts and myself (appendix 4) to capture the required data.

A database with patient level data, which was inaccessible to the research team, was downloaded from EMISweb in a CCG data safe-haven. The database was stripped of all patient identifiers including NHS number and assigned a pseudonym. The pseudonymised database was accessible to the research team. In the event of an identifiable clinical risk, the patient could be identified using the pseudonym and their GP or secondary care clinician contacted as necessary through linkage performed by the CCG data safe-haven staff.

The search term ‘FIB-4 score’ was used as a surrogate for pathway entry as neither the code, nor the test, were in use prior to the launch of the pathway. Values attached to FIB-4 scores were used to generate four patient groups:

- FIB-4 <1.3 Low risk of advanced fibrosis or cirrhosis.
- FIB-4 1.3 – 3.25 Intermediate risk of advanced fibrosis or cirrhosis.
- FIB-4 >3.25 High risk of advanced fibrosis or cirrhosis.
- NAFLD not risk stratified.

Patient identifiable data were not obtained as this would require consent from all residents in the CCGs. In the context of this work, the principles of data confidentiality and data protection stipulated that all individuals have the legal right to consent or object to the use of their personal data for research. Camden and Islington have a combined population of over 400,000 residents, in which there are vulnerable patients, patients who do not speak English, patients with cognitive impairment and patients who do not want their personal details shared with researchers. Therefore, individual consent would have been required to obtain patient level data. This was not practicable and therefore a pseudonymised dataset was made available to the research team.

6.4.7 Secondary care data collection

All patients aged 18 and over referred by their GP to the Royal Free London, University College London Hospitals and Whittington Hospitals with a final diagnosis of NAFLD were included in the hospital outcome analysis. Data were collected between 1st March 2014 and 31st May 2016 – an additional 3 months data were collected in addition to the two year period to reflect the time-lag

from entering the pathway in primary care to specialist review. Secondary care outcomes were collected as described in Chapter 5. Patient paper files and electronic records were interrogated to extract data related to patient demographics, secondary care management, clinical outcomes and fibrosis staging against a pre-defined reference standard (see section 6.4.8).

6.4.8 Reference standard (specialist reinvestigation)

The reference standard was the "specialist fibrosis assessment" - a binary outcome: advanced fibrosis/ cirrhosis (equivalent to Brunt ≥F3) vs. lesser degree/no fibrosis (equivalent to Brunt ≤F2) based on a composite of liver histology (when available), imaging, fibroscan, bloods and clinical judgment.

6.4.9 Statistical Analyses

Statistical analyses were performed using SPSS (version 22, SPSS Inc., Chicago, IL, USA). Categorical data are presented as numbers (frequencies and percentages). Normally distributed continuous data were presented as mean (±SD) whilst medians (IQR and range) were used for non-parametric data. Demographic, biochemical and non-invasive testing results were compared between patients deemed to have advanced fibrosis or cirrhosis (Brunt ≥F3 fibrosis) compared to patients deemed to have non-significant disease (Brunt ≤F2 fibrosis) using two sample t-test for parametric variables and Mann-Whitney test for non-parametric variables and x^2 or Fisher's exact test for categorical variables. The odds ratios (ORs) 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).

6.4.10 Ethical approval

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

6.5 Results

6.5.1 Donabedian model of health evaluation results summary

The Donabedian model of health evaluation [224] provided the framework for the Camden and Islington NAFLD pathway service evaluation. Detailed results are described in this section, with a summary of the evaluation described in Table 6.5.

Table 6.5 Summary of Camden and Islington NAFLD pathway outcomes

The Donabedian model of health evaluation [224] describes three components in the evaluation of a new healthcare intervention. An outline summary of the results of the Camden and Islington NAFLD pathway evaluation are described in this table.

	Indicator	Baseline (2012 – 2013)	Year 1 (2014 – 2015)	Year 2 (2015 – 2016)	Intepretation/ Comments	Detailed section
1. Service Structure						
1A	Change in staffing, funding, equipment and other resources as a result of implementing the pathway	FIB-4 – N/A ELF – N/A	FIB-4 – no additional cost ELF - 160 x £40 = £6400	FIB-4 – no additional cost ELF – 227 x £40 = £9080	Informal GP survey – no evidence of increased resources, staffing, funding, or equipment required at a practice level. One comment that patients had to make more phlebotomy trips.	-
2. Process Monitoring						

	Indicator	Baseline (2012 – 2013)	Year 1 (2014 – 2015)	Year 2 (2015 – 2016)	Intepretation/ Comments	Detailed section
2A	Number of primary care consultations (new and follow up) for patients with a diagnosis of NAFLD NOTE: New codes of NAFLD used as a surrogate.	New codes of NAFLD – 601 patients	New codes of NAFLD – 1437 patients (2.37 fold increase compared to baseline)	New codes of NAFLD – 1575 patients (2.62 fold increase compared to baseline, 1.09 fold increase compared to year 1)	Data regarding primary care appointments for NAFLD were unavailable. The practice of coding is heterogenous amongst practices and therefore searching for 'consultations for NAFLD' would be of 'low quality' negating meaningful intepretation. The number of new codes for NAFLD will be influenced by confounding factors including increased awareness of the condition.	Table 6.6
2B	Number of patients receiving a FIB-4 test	0	416	1036 (2.49 fold increase compared to year 1)	FIB-4 use used as a surrogate for pathway use.	Section 6.5.3

	Indicator	Baseline (2012 – 2013)	Year 1 (2014 – 2015)	Year 2 (2015 – 2016)	Intepretation/ Comments	Detailed section
2C	Proportion of patients consulting for NAFLD receiving a FIB-4 test	0	416/1437 (28.9%)	1036 / 1575 (64.8%)	The true denomintor is likely to be higher than reported, as denominator only considers new NAFLD registrations and pathway likely to have been used on patiens already known to have NAFLD.	Section 6.5.3
2D	Number of patients receiving an ELF test.	0	160	227 (1.41 fold increase compared to year 1)		Figure 6.3
2E	Number of patients referred to specialist for management of NAFLD through C&I NAFLD pathway C&I Standard Care C&I Total Other CCG Standard care total Standard Care Total (C&I and other) Total referrals (all)	C&I NAFLD pathway N/A C&I Standard Care 83 C&I Total 83 Other CCG Standard Care Total 109 Standard Care Total (C&I and other) 192 Total referrals (all) 192	C&I NAFLD pathway 56 C&I Standard Care 81 C&I Total 137 Other CCG Standard Care Total 120 Standard Care Total (C&I and other) 201 Total referrals (all) 257	C&I NAFLD pathway 96 C&I Standard Care 96 C&I Total 192 Other CCG Standard Care Total 173 Standard Care Total (C&I and other) 269 Total referrals (all) 365		Table 6.8 Figure 6.8

	Indicator	Baseline (2012 – 2013)	Year 1 (2014 – 2015)	Year 2 (2015 – 2016)	Intepretation/ Comments	Detailed section
2F	Proportion of patients referred to specialist for management of NAFLD who have consulted GP (Camden and Islington).	83/601 (13.8%)	137/1437 (9.5%)	192/1575 (12.1%)		Section 6.5.5
2G	Proportion of patients referred to specialist for management of NAFLD who have been referred because of the pathway (Camden and Islington)	N/A	56/137 (40.8%)	96/192 (50%)		Section 6.5.5
2H	Proportion of patients referred to specialist for management of NAFLD who have Had ultrasound abdomen/ liver in primary care (all) Had ultrasound abdomen/ liver in primary care (C&I pathway)) Had appropriate FIB-4 and ELF testing in primary care	138/ 192 (71.9%) N/A N/A	198/257 (77.0%) 41/56 (73.2%) 100%	313/365 (85.8%) 81/96 (84.3%) 100%	No inappropriate referrals of patients with FIB-4 < 1.30 or ELF < 9.5	-
2I	Proportion of patients referred to secondary care from pathway who fulfilled criteria.	N/A	2014 – 2016 152/275 (55.3%)		C&I pathway was a service innovation, so protocol adherement could be expected to be sub-optimal	-Figure 6.9

	Indicator	Baseline (2012 – 2013)	Year 1 (2014 – 2015)	Year 2 (2015 – 2016)	Intepretation/ Comments	Detailed section
2J	Waiting time to see a hepatologist	Mean 5.76 weeks Median 4 weeks Range (1 wk – 20 weeks)	Mean 5.30 weeks Median 4 weeks (2 wks – 16 wks)	Mean 5.87 weeks Median 5 weeks (2wk – 16 wks)	Pathway did not alter waiting times	-
2K	Number and proportion of liver biopsies performed by specialist all referrals pathway patients	26 (13.3%) N/A	35/257 (13.6%) 16/56 (28.6%)	46/365 (12.6%) 19/96 (19.7%)	More biopsies are performed in patients referred by the pathway. However, overall biopsy rate remained unchanged, suggesting targetted biopsies guided by non-invasive tests.	Section 6.5.11
			3. Outcome measures			
3A	Proportion of patient stratified by pathway as Low risk of significant fibrosis High risk of advacned fibrosis	N/A	2014 - 2016 Low risk of significant fibrosis 1177/1452 (81.1%) High risk of advanced fibrosis or cirrhosis 275/1452 (18.9%)			Section 6.5.4

	Indicator	Baseline (2012 – 2013)	Year 1 (2014 – 2015)	Year 2 (2015 – 2016)	Intepretation/ Comments	Detailed section
3B	Number and Proportion of those referred to secondary care that have ≥F3 fibrosis: C&I NAFLD pathway C&I Standard Care C&I Total Other CCG Standard Care Total Standard Care Total (C&I and other) Total referrals (all)	C&I NAFLD pathway N/A C&I Standard Care 4/83 (4.8%) C&I Total 4/83 (4.8%) Other CCG Standard Care Total 9/109 (8.3%) Standard Care Total (C&I and other) 13/192 (6.8%) Total referrals (all) 13/192 (6.8%)	C&I NAFLD pathway 21/56 (37.5%) C&I Standard Care 6/81 (7.4%) C&I Total 27/137 (19.7%) Other CCG Standard Care Total 12/120 (10.0%) Standard Care Total (C&I and other) 18/201 (8.9%) Total referrals (all) 39/257 (15.2%)	C&I NAFLD pathway 24/96 (25.0%) C&I Standard Care 8/96 (8.3%) C&I Total 32/192 (16.6%) Other CCG Standard Care Total 10/173 (5.8%) Standard Care Total (C&I and other) 18/269 (6.7%) Total referrals (all) 42/365 (11.5%)		Section 6.5.6

	Indicator	Baseline (2012 – 2013)	Year 1 (2014 – 2015)	Year 2 (2015 – 2016)	Intepretation/ Comments	Detailed section
3C	Number and Proportion of those referred to secondary care that have cirrhosis: C&I NAFLD pathway C&I Standard Care C&I Total Other CCG Total Standard Care Total (C&I and other) Total referrals (all)	C&I NAFLD pathway N/A C&I Standard Care 3/83 (3.6%) C&I Total 3/83 (3.6%) Other CCG Standard Care Total 4/109 (3.7%) Standard Care Total (C&I and other) 7 192 (6.8%) Total referrals (all) 13/192 (6.8%)	C&I NAFLD pathway 9/56 (16.1%) C&I Standard Care 4/81 (4.9%) C&I Total 13/137 (9.4%) Other CCG Standard Care Total 8/120 (6.7%) Standard Care Total (C&I and other) 12/201 (6.0%) Total referrals (all) 21/257 (8.2%)	C&I NAFLD pathway 13/96 (13.5%) C&I Standard Care 6/96 (6.3%) C&I Total 19/192 (9.9%) Other CCG Standard Care Total 7/173 (4.0%) Standard Care Total (C&I and other) 13/269 (4.8%) Total referrals (all) 26/365 (7.1%)		Section 6.5.6

	Indicator	Baseline (2012 – 2013)	Year 1 (2014 – 2015)	Year 2 (2015 – 2016)	Intepretation/ Comments	Detailed section
3D	Number and Proportion of those referred to secondary care that have ≤F2 fibrosis: C&I NAFLD pathway C&I Standard Care C&I Total Other CCG Total Standard Care Total (C&I and other) Total referrals (all)	C&I NAFLD pathway N/A C&I Standard Care 79/83 (95.2%) C&I Total 79/83 (95.2%) Other CCG Standard Care Total 100/109 (91.7%) Standard Care Total (C&I and other) 179/192 (93.2%) Total referrals (all) 179/192 (93.2%)	C&I NAFLD pathway 35/56 (62.5%) C&I Standard Care 75/81 (92.6%) C&I Total 110/137 (80.3%) Other CCG Standard Care Total 108/120 (90.0%) Standard Care Total (C&I and other) 183/201 (91.1%) Total referrals (all) 218/257 (84.8%)	C&I NAFLD pathway 72/96 (75.0%) C&I Standard Care 88/96 (91.7%) C&I Total 160/192 (83.3%) Other CCG Standard Care Total 163/173 (94.2%) Standard Care Total (C&I and other) 251/269 (93.3%) Total referrals (all) 323/365 (88.5%)		Section 6.5.6
3E	Mortality (all cause and liver-related)	Standard care 3/192 (1.5%)	Standard care 3/201 (1.5%) Pathway 1/56 (1.8%)	Standard care 2/269 (0.7%) Pathway 0/96 (0%)		Section 6.5.12
3F	Secondary liver-related events	Standard care 4 (30.8%)	Standard care 10 (27.8%) Pathway 1 (2.2%)			Section 6.5.12
3G	Enrolment in therapeutic clinical trials	0	0	0		

	Indicator	Baseline (2012 – 2013)	Year 1 (2014 – 2015)	Year 2 (2015 – 2016)	Intepretation/ Comments	Detailed section
3H	Patients qualitative experience	Beyond remit of this thesis				
3I	GP experience	Beyond remit of this thesis				
3J	Economic evaluation	See Chapter 7				Chapter 7

6.5.2 Burden of NAFLD in primary care

Patients coded for NAFLD in Camden and Islington CCGs has increased yearly since 2012 (Table 6.6). Between 2012–13 and 2014–16, the number of patients assigned Read codes for NAFLD in the EMISweb database increased from 601/year to 1,506/year, representing a 2.5-fold increase.

Table 6.6 Annual primary care Read codes for a diagnosis of NAFLD by general practitioners in Camden and Islington between 2012 – 2016

	New GP codes of NAFLD			
Year	Camden	Islington	Total	% change on previous year
Mar 12 – Mar 13	306	295	601	
Mar 13 – Mar 14	455	382	837	39.3%
Mar 14- Mar 15	891	546	1437	71.7%
Mar 15 – Mar 16	933	642	1575	9.6%

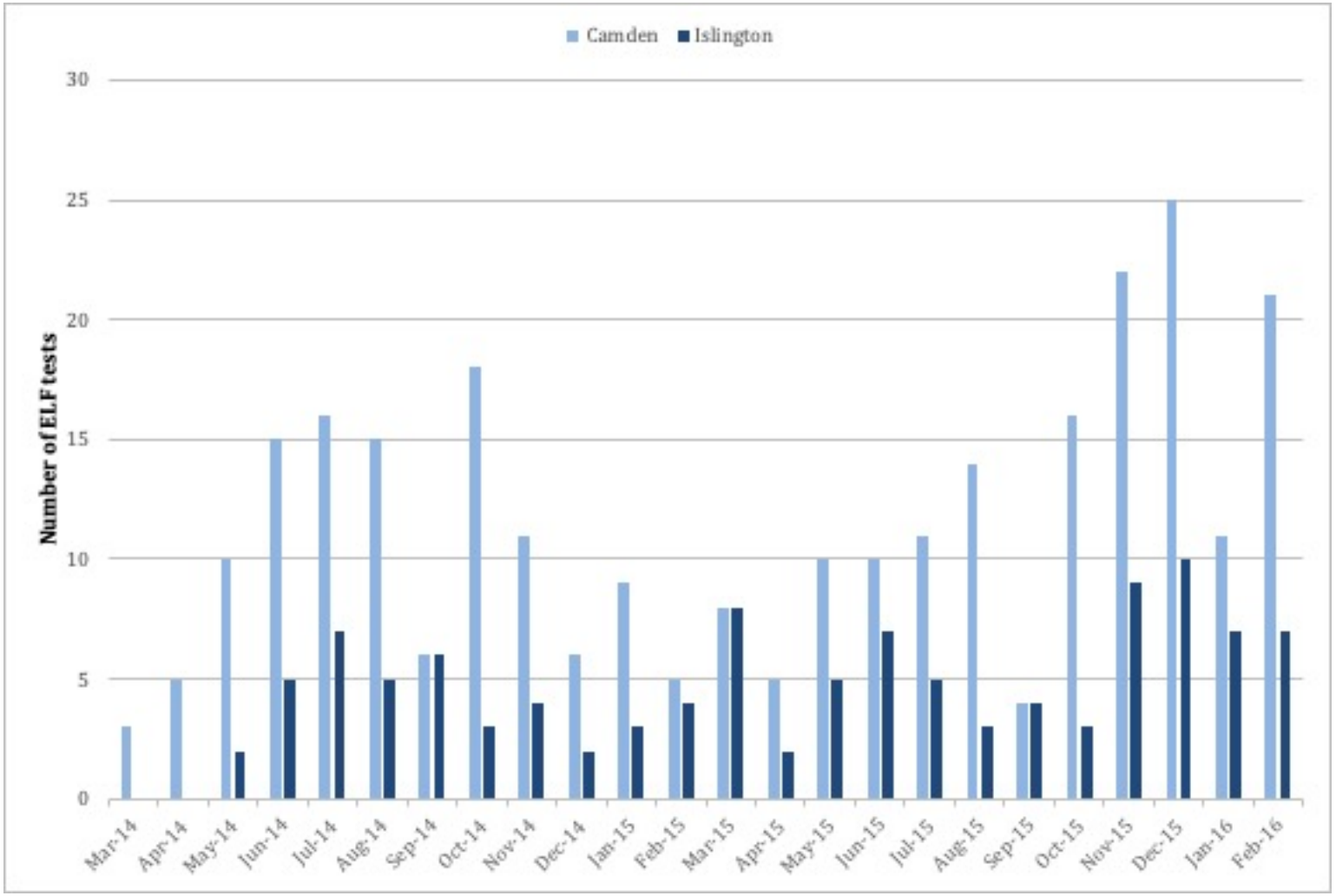
6.5.3 Camden and Islington NAFLD pathway uptake

During the evaluation period between March 2014 and March 2016, 3012 patients were coded with NAFLD in Camden and Islington. During this period, 1452/3012 patients with NAFLD (47.6%) were risk stratified using the pathway. The remaining 1560 Camden and Islington patients were managed according to standard care.

Practice-level analysis revealed 52 out of 72 (72%) eligible Camden and Islington GP practices used the NAFLD pathway to manage at least a proportion of their patients (at least 1 patient). The first FIB-4 was registered

in a Camden practice 6 days after pathway launch (6th March 2014). In the first month (March 2014) a total of 6 ELF tests were requested in Camden, whilst the first ELF test in Islington was requested after three months (May 2014). Pathway uptake increased with time – for example a 133% increase in ELF requests was observed between month 24 (Feb 2016, 28 ELF requests) and month 3 (May 2014, 12 ELF requests) (Figure 6.3). Monthly ELF test requesting patterns did not reveal seasonal variations during the two year follow up period.

Figure 6.3 Monthly ELF testing by borough as a surrogate for pathway use



Baseline characteristics of patients stratified by the pathway are described in Table 6.7. Patients stratified by the NAFLD pathway were older (54.4 years vs. 51.5, p <0.001), had a higher prevalence of hypertension (41.7% vs. 33.0%, p <0.001) and treated type 2 diabetes (27.6% vs. 21.0%, p <0.001) than patients managed by standard care. There were less patients with dyslipidaemia (13.5% vs. 14.6%, p <0.001) on the pathway. No statistical difference was seen between the two groups in aminotransferases, platelet count, Q-Risk2 score, glycated haemoglobin or high-density lipoprotein.

FIB-4 scores were calculable in 695 standard care cases. The distribution of FIB-4 between patients managed using the NAFLD pathway and those managed using standard care was very similar; NAFLD pathway FIB-4 <1.30: 1022/1452 (71.3%); 1.30–3.25: 387/1452 (25.7%); >3.25: 43/1452 (3.0%) compared to standard care FIB-4 <1.30: 513/695 (73.8%); 1.30–3.25:162/695 (23.3%); >3.25: 20/695 (2.9%).

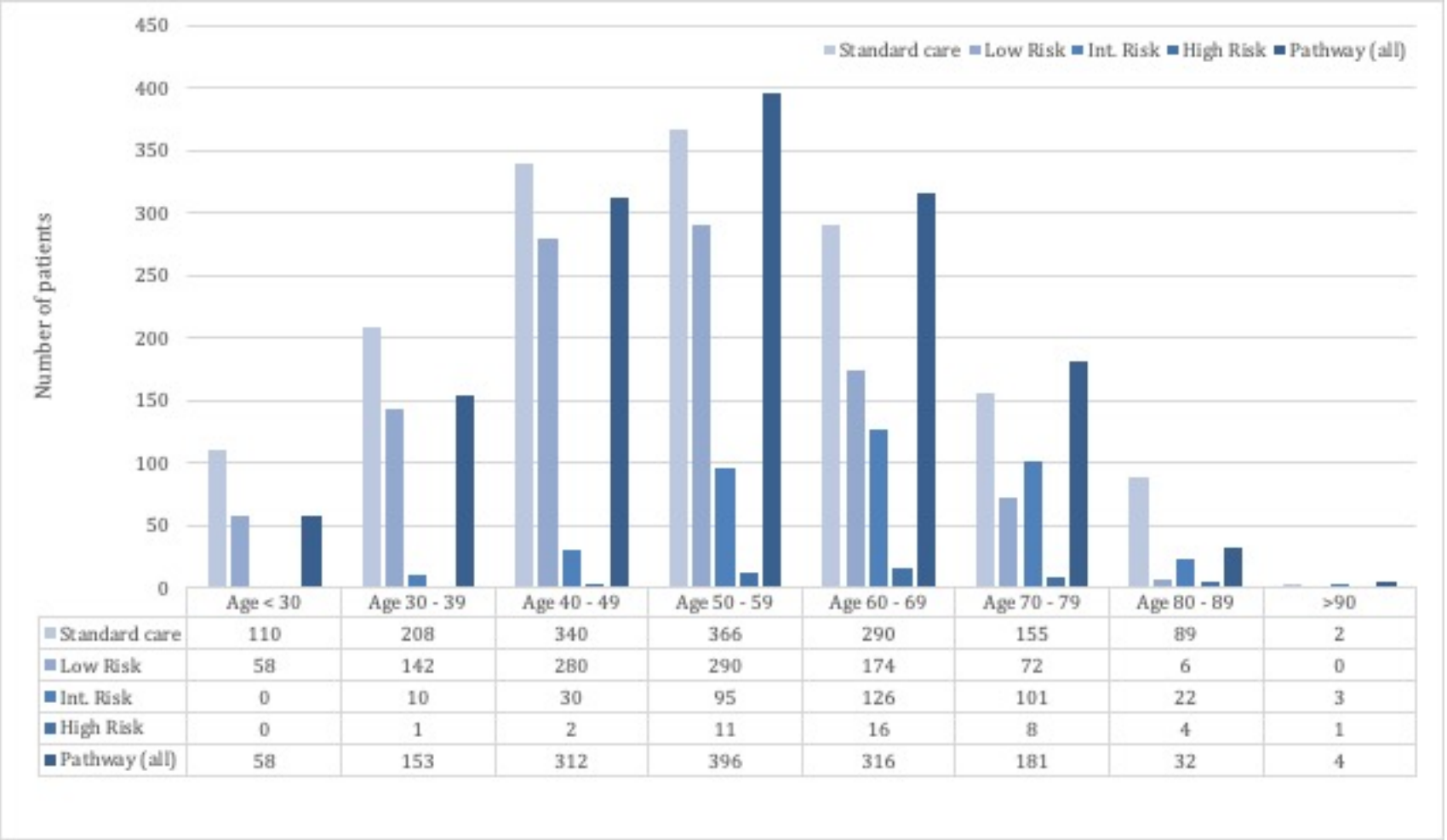
Table 6.7 Baseline characteristics of patients managed in Camden and Islington for NAFLD between 2014 and 2016

				Camden and Islington Pathway Split by FIB4		
	Standard Care	**Pathway Patients**	**p value**	**FIB-4 < 1.30**	**FIB-4 1.30 – 3.25**	**FIB-4 > 3.25**
	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 – 15.61
Age, years	51.5 ± 14.1	54.4 ± 13.7	<0.001	50.5 ± 12.8	63.4 ± 11.2	64.21 ± 11.9
Male, n (%)	570 (50.5%)	788 (54.3%)	N.S.	560 (54.7%)	204 (71.1%)	24 (55.8%)
BMI 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
T2DM, n (%)	237/1126 (21.0%)	344/1245 (27.63)	<0.001	190/846 (22.5%)	141/364 (38.7%)	13/35 (37.1%)
HBA1c (mean ± S.D)	42.2 ± 12.8 (585)	42.5 ± 13.35 (1059)	N.S.	42.3 ± 13.6 (769)	43.4 ± 13.4 (267)	41.4 ± 15.2 (23)
Hypertension, n (%)	371/ 1124 (33.0%)	521/1248 (41.7%)	<0.001	266/ 849 (31.3%)	234/364 (64.2%)	21/35 (60.0%)
Hyperlipidaemia, n (%)	95/650 (14.6%)	168/1248 (13.5%)	<0.001	96/ 849 (11.3%)	64/364 (7.5%)	8/35 (22.8%)
Total Cholesterol (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)
HDL (mean ± S.D)	1.3 ± 0.4 (602)	1.3 ± 0.4 (1084)	N.S.	1.3 ± 0.4 (792)	1.4 ± 0.4 (267)	1.3 ± 0.4 (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%)
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)
ALT (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
AST (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
Platelets (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

The distribution of the age of patients managed according to the pathway and standard care in Camden and Islington during the study period (2014-2016) is shown in Figure 6.4. In the NAFLD pathway, risk stratification with FIB-4 did occur at the extremes of age, as per the protocol. For patients stratified by the NAFLD pathway, a total of 211 patients (14.5%) were aged less than 40 years old compared to 318 patients (20.3%) managed in the standard care group. Fifty-eight NAFLD pathway patients were aged less than 30 years old and all were deemed low risk of advanced fibrosis or cirrhosis (FIB-4 < 1.30). In the 153 patients aged between 30 and 40 years old, 142 patients were classified as low risk, 10 patients as indeterminate and 1 patient as high risk of advanced fibrosis or cirrhosis.

A total of 217 patients (14.9%) aged 70 years and over were risk stratified by the NAFLD pathway, of whom three were aged 90 and above – 2 had indeterminate FIB-4 results, whilst one patient was determined as high risk.

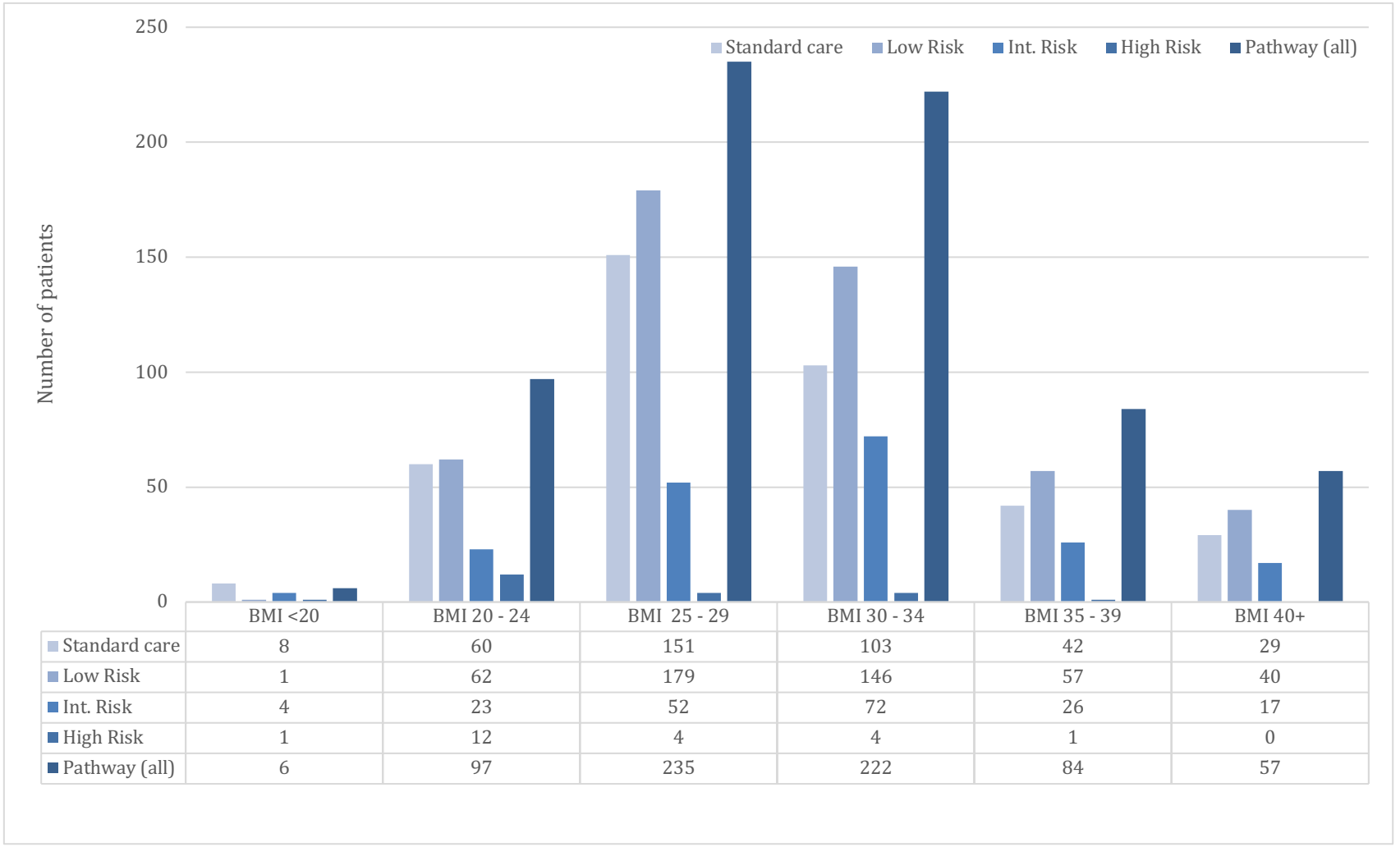
Figure 6.4 Age distribution of patients with NAFLD in Camden and Islington 2014-2016 managed by standard care and NAFLD pathway



	Age < 30	Age 30 - 39	Age 40 - 49	Age 50 - 59	Age 60 - 69	Age 70 - 79	Age 80 - 89	>90
Standard care	110	208	340	366	290	155	89	2
Low Risk	58	142	280	290	174	72	6	0
Int. Risk	0	10	30	95	126	101	22	3
High Risk	0	1	2	11	16	8	4	1
Pathway (all)	58	153	312	396	316	181	32	4

The distribution of BMI (where data was available) amongst patients managed according to the pathway and standard care in Camden and Islington during the study period (2014-2016) is shown in Figure 6.5. One hundred and three patients on the pathway (14.7% of 701 available readings) had a BMI less than 25. Further evaluation of patients on the pathway revealed 235 patients (33.5%) were overweight (BMI 25-30) and 222 patients (31.6%) were obese (BMI 30-35).

Figure 6.5 Distribution of BMI of patients with NAFLD in Camden and Islington 2014-2016 managed by standard care and NAFLD pathway



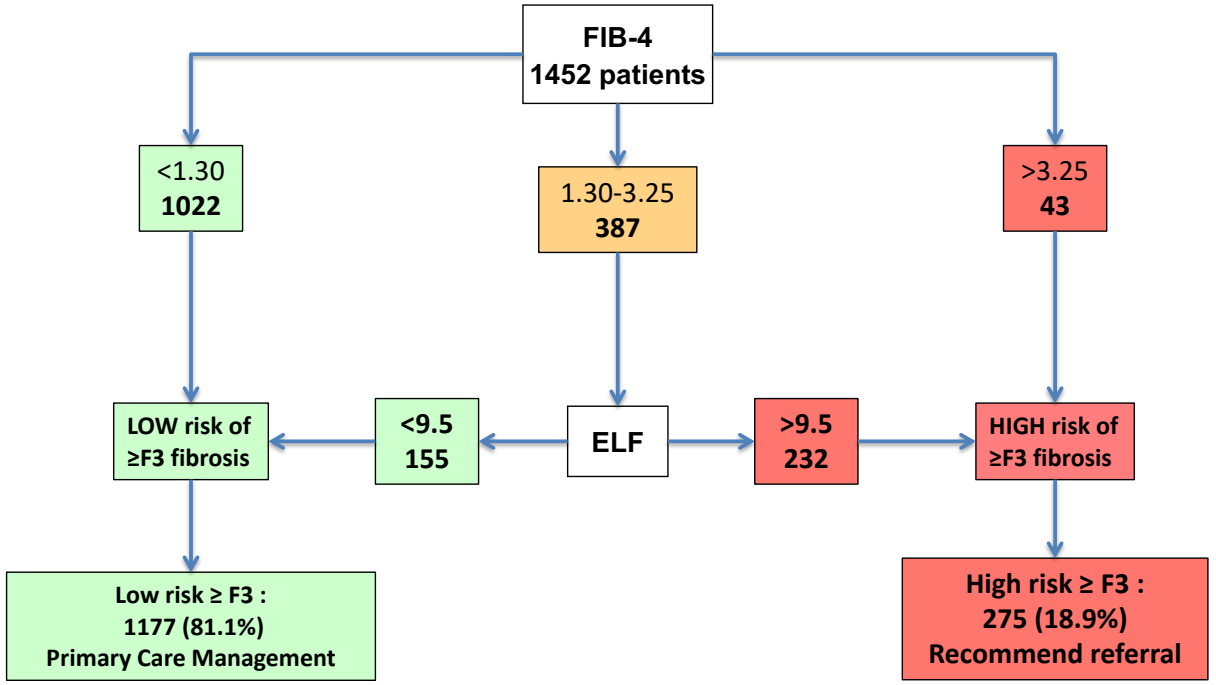
	BMI <20	BMI 20 - 24	BMI 25 - 29	BMI 30 - 34	BMI 35 - 39	BMI 40+
Standard care	8	60	151	103	42	29
Low Risk	1	62	179	146	57	40
Int. Risk	4	23	52	72	26	17
High Risk	1	12	4	4	1	0
Pathway (all)	6	97	235	222	84	57

6.5.4 Risk stratification in primary care

Over the two-year evaluation period, 1452 patients were risk stratified by the Camden and Islington NAFLD pathway for the presence of advanced fibrosis or cirrhosis (Figure 6.6). FIB-4 score <1.30 consistent with low probability of advanced fibrosis or cirrhosis was calculated in 1022 patients (71.3%), whilst 43 patients (3.0%) had FIB-4 > 3.25 consistent with a high probability of advanced fibrosis or cirrhosis. The remaining 387 patients had an indeterminate FIB-4 score (1.30 -3.25) and proceeded to a second-tier ELF test; 155 patients (40.0%) had ELF score < 9.5 consistent with low risk of advanced fibrosis or cirrhosis and 232 patients (60.0%) had ELF score > 9.5 consistent with high risk of advanced fibrosis or cirrhosis. Overall, 1177 patients (81.1%) were assessed as low risk of advanced fibrosis or cirrhosis and remained in primary care for follow-up of their condition. The remaining 275 patients (18.9%) were stratified as high risk of advanced fibrosis or cirrhosis and were recommended for referral to a hospital specialist.

Figure 6.6 Flow chart of primary care risk stratification

A total of 1452 patients entered the pathway and had a FIB-4 test. 387 patients (25.7%) had an indeterminate FIB-4 and required ELF test as a second-tier test. Overall, 1177 (81.1%) of patients were stratified as low risk of ≥F3 fibrosis, and 275 patients were stratified as high risk of ≥F3 fibrosis and recommended for referral



6.5.5 Impact of NAFLD pathway on total referrals

The total number of referrals for patients with NAFLD received from GPs in Camden and Islington increased from 83 referrals in 2012–13 to 164.5 referrals per year in the study period (2014–16). However, relative to the increased coding of patients with NAFLD as described in section 6.5.2, the proportion of patients with NAFLD referred for a specialist opinion reduced from 13.8% (83/601) prior to pathway launch (2012-2013) to 10.9% (165/1,506) post pathway implementation (2014-2016).

Evaluating referral patterns in the standard care group, one year after pathway initiation, there was a 2% decrease in referrals from the Camden and Islington standard care group (year 0 -83 referrals, year 1 -81) compared to a 10% increase in the other CCGs control group not exposed to the pathway (year 0 – 109, year 1 – 120) (Table 6.8). In year two, compared to baseline, a 15.7% increase in Camden and Islington standard care referrals (year 0- 83, year 2- 96) was observed, compared to a 58.7% increase in 'Other CCGs Standard Care' (year 0- 109, year 2- 173). Monthly referral patterns from Camden and Islington to the three London hospitals is shown in Figure 6.7, and culminative referrals over the study period are shown in Figure 6.8. Over the 27 months, there were a total of 152 referrals resulting from the pathway compared to 177 by standard care in Camden and Islington. Comparing monthly referral patterns, there was a no statistically significant difference between the groups as determined by one-way ANOVA ($F(1,52) = 0.9782$, $p=0.32$).

Table 6.8 Total number of specialist referrals to for patients with NAFLD.

		C&I NAFLD Pathway		C&I Standard Care		Other CCG's Standard Care	
Total patients		1452		1560		Unknown	
Year	Time frame	Number of referrals	Compared to previous year	Number of referrals	Compared to previous year	Number of referrals	Compared to previous year
Baseline	Mar 12- Feb 13	-	-	83	-	109	-
Year 1	Jun 14– May 15	56	-	81	-2 (-2.4%)	120	+11 (+10.0%)
Year 2	Jun 15– May 16	96	+40 (+71.4%)	96	+15 (+18.5%)	173	+ 53 (+44.2%)

Figure 6.7 Number of referrals for management of NAFLD after introduction of NAFLD pathway

Total number of referrals for specialist management of NAFLD after stratification by the C&I NAFLD pathway or management with standard care

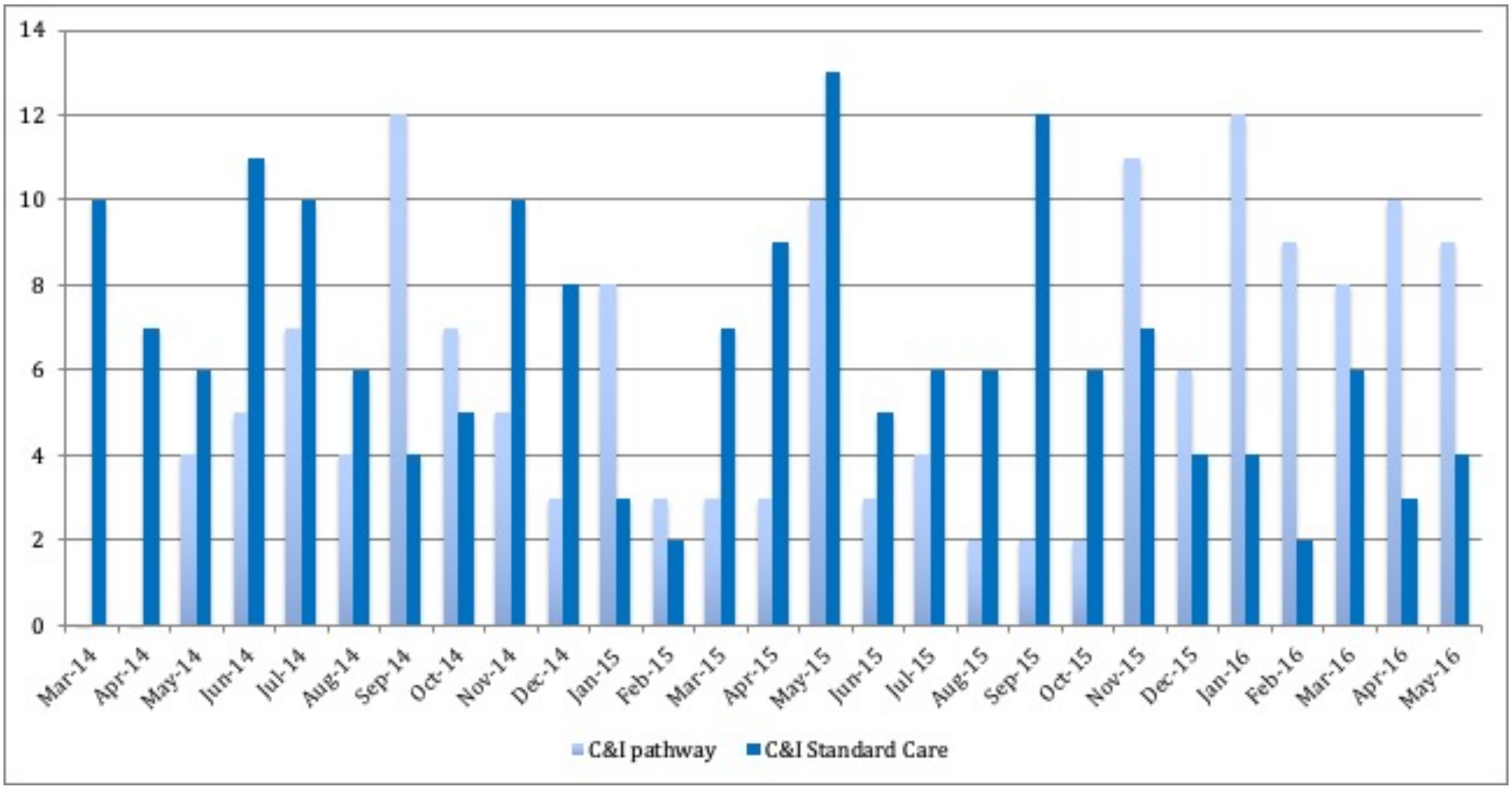
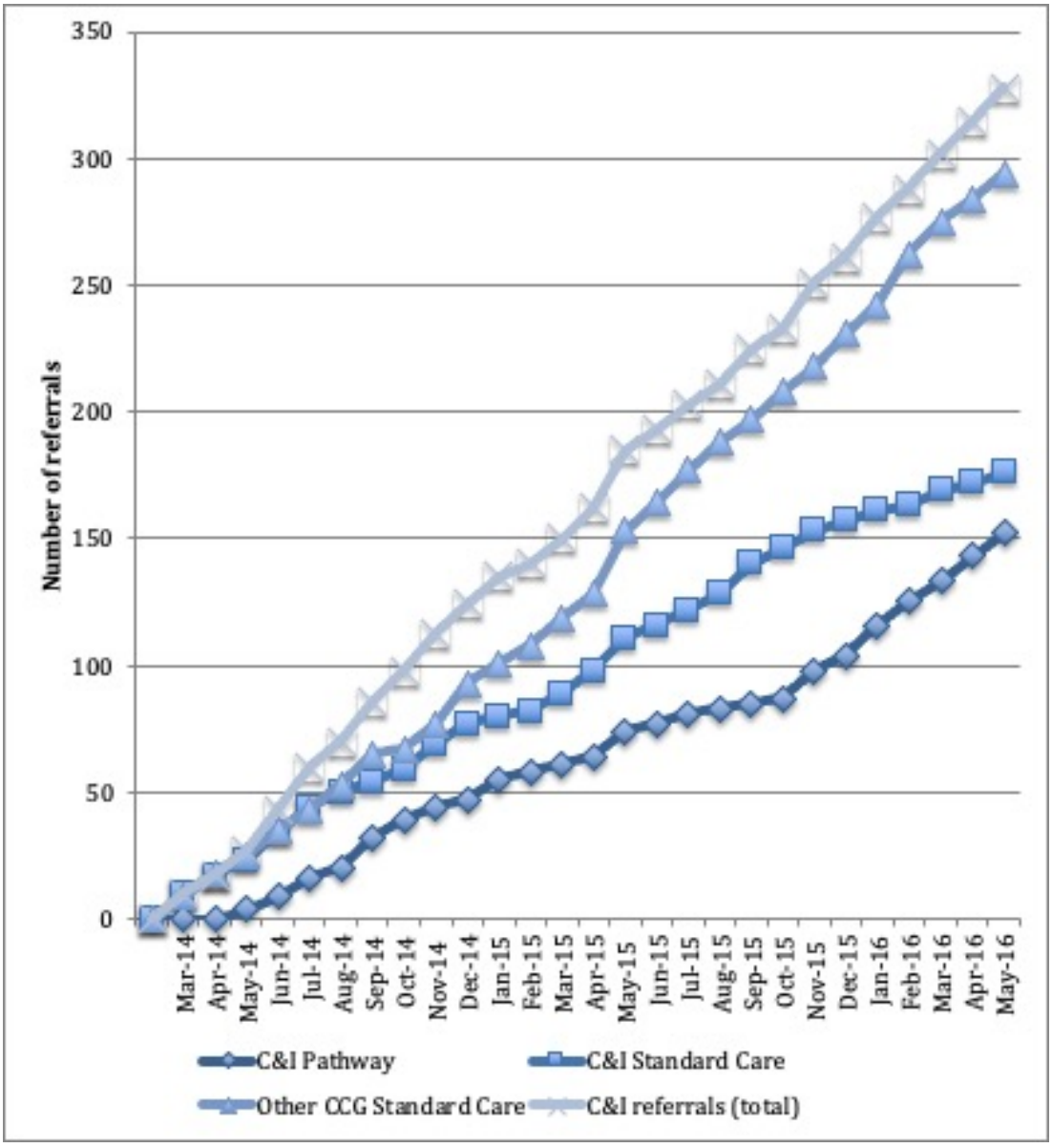


Figure 6.8 Cumulative number of referrals to specialist for management of NAFLD over follow up period.



The NAFLD pathway identified 275 patients for referral. The first patient to be reviewed by a specialist was seen 74 days after launch of the pathway in the Royal Free London hospital. This reflected the time required to complete the pathway journey, a process which includes initial primary care review and follow up, bloods tests including liver screen and FIB-4, then referral to a specialist and subsequent wait for an outpatient specialist appointment. This, in part, justified the extension of the follow-up period to record hospital outcomes from patients on the pathway by 3 months so secondary care data were collected until 31st May 2014.

6.5.6 Detection of advanced fibrosis and cirrhosis by NAFLD pathway

A total of 275 patients were stratified as being at high-risk for advanced fibrosis or cirrhosis and recommended for referral to a specialist. A total of 152 patients (55.3%) had referral and specialist reinvestigation with a hepatologist within the follow up period (Figure 6.9). The baseline characteristics for patients referred for evaluation of NAFLD in the study period is described in Table 6.9, and a summary of investigations and outcomes from re-investigation described in Table 6.10.

After specialist investigation, 45 out of 152 referrals (29.6%) were judged to have advanced fibrosis or cirrhosis. Of the 45 patients with advanced fibrosis or cirrhosis, thirty-eight patients were referred after indeterminate FIB-4 and high ELF, whilst seven patients were referred due to a high FIB-4 score, of whom 6 were cirrhotic. Advanced fibrosis or cirrhosis was confirmed by liver

biopsy (n = 14, 31.1%), Fibroscan (n = 25, 55.6%) or radiological features of cirrhosis (n = 6, 13.3%).

Figure 6.9 Specialist re-investigation of referrals for patients with NAFLD to secondary care in evaluation period (2014-2016)

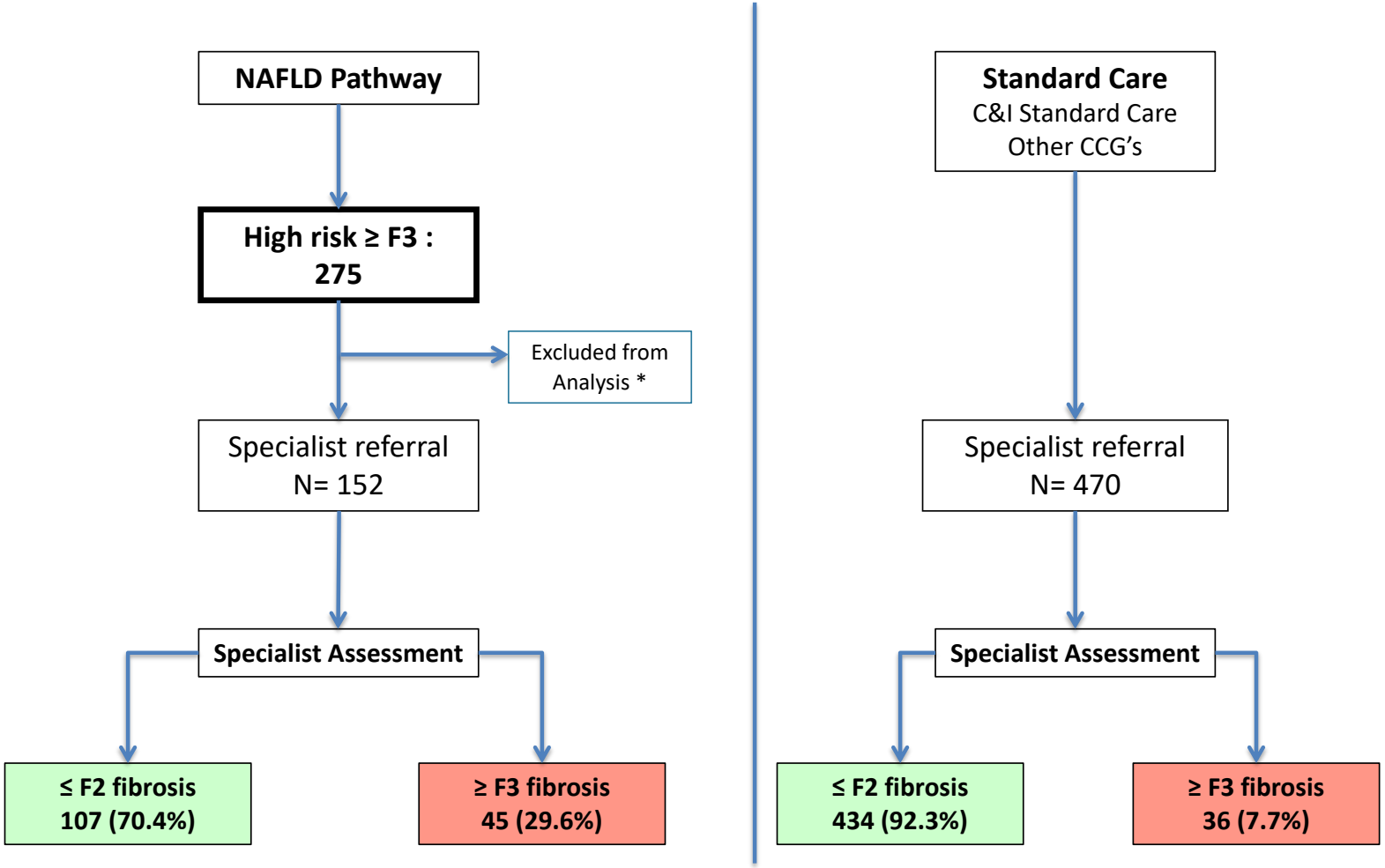


Table 6.9 Baseline characteristics of all patients reviewed in a specialist management for further evaluation of NAFLD between 2014-2016

	Camden and Islington Pathway (2014- 2016)				Standard Care (2014 – 2016)		
Parameter	≤ F2 fibrosis	≥ F3 fibrosis	P-value		≤ F2 fibrosis	≥ F3 fibrosis	P-value
N	107 (70.4%)	45 (29.6%)			434 (9.3%)	36 (7.7%)	
Age (yrs)	66.3 ± 10.5	67.7 ±8.7	0.17		49.8 ± 13.6	62.2 ± 11.9	<0.001
Male n (%)	50 (50.5%)	30 (66.6%)	0.11		235 (54.1%)	19 (52.8%)	0.95
Practice IMD	27.0 ± 6.6	29.3 ± 7.8	0.06		26.3 ± 9.6	25.3 ± 9.6	0.39
Hypertension n (%)	69 (69.7%)	32 (71.1%)	0.09		153 (35.3%)	28 (77.7%)	<0.001
Hypercholesterolaemia n (%)	63 (63.6%)	26 (57.7%)	0.54		182 (41.9%)	24 (66.6%)	0.02
Type II Diabetes n (%)	41 (41.4%)	25 (55.6%)	0.54		106 (24.4%)	24 (66.6%)	<0.001
CVS events n (%)	13 (13.1%)	12 (26.6%)	0.03		20 (4.6%)	8 (22.2%)	<0.001
BMI (kg/m2)	31.5 ± 5.2	31.5 ± 8.6	0.99		30.6 ± 7.4	33.6 ± 7.7	0.01
Walst circumfernece cm	110.0 ± 12.4	114.4 ± 14.1	0.14		101.8 ±14.1	111.6 ± 19.3	0.93
Total Cholesterol mmol/l	5.2 ± 3.8	4.3 ± 1.0	0.08		5.1 ± 1.2	4.7 ± 1.20	0.09

	Camden and Islington Pathway (2014- 2016)				Standard Care (2014 – 2016)		
Triglyceride mmol/l	1.6 ± 0.6	1.8 ± 0.8	0.20		2.0 ± 1.2	2.1 ± 1.2	0.98
HDL mmol/l	1.3 ± 0.3	1.7 ± 2.3	0.14		1.3 ± 0.5	1.3 ± 0.5	0.70
HBA1c	45.3 ± 12.7	46.1 ± 17.6	0.43		43.9 ± 13.6	56.5 ± 17.4	<0.001

Table 6.10 Investigation and outcomes for all patients referred for specialist management of NAFLD between 2014 – 2016

Parameter	Camden and Islington Pathway (2014- 2016)				Standard of Care (2014 – 2016)		
	≤ F2 fibrosis (n=107)	≥ F3 fibrosis (n=45)	P-value		≤ F2 fibrosis (n=434)	≥ F3 fibrosis (n=36)	P-value
Platelet	229.7 ± 60.4	197.3 ± 59.4	0.003		261.2 ± 66.7	183.2 ± 74.3	<0.001
INR	1.03 ± 0.39	1.04 ± 0.19	0.89		0.97 ± 0.9	1.1 ± 0.2	<0.001
ALT mmol/l	42.1 ± 30.4	48.3 ± 24.6	0.24		63.9 ± 49.4	63.4 ± 55.0	0.95
AST mmol/l	34.0 ± 18.3	43.3 ± 21.3	0.09		39.3 ± 27.8	51.7 ± 30.6	0.013
GGT mmol/l	59.5 ± 57.8	148.9 ± 31.9	<0.001		104.5 ± 148.7	166.0 ± 162.2	0.04
Bilirubin mmol/l	9.27 ± 5.5	10.4 ± 6.5	0.27		9.1 ± 8.2	10.4 ± 6.9	0.33
Albumin mmol/l	44.9 ± 2.5	44.5 ± 3.9	0.48		46.1 ± 2.5	43.4 ± 4.5	<0.001
Ferritin mmol/l	189.4 ± 167.1	321.5 ± 349.4	<0.001		222.2 ± 208.6	246.7 ± 258.1	0.55
Creatinine mmol/l	78.9 ± 22.5	85.1 ± 31.9	0.20		74.3 ± 18.3	73.1 ± 20.6	0.71
AFP mmol/l	2.93 ± 1.36	2.82 ± 1.22	0.76		3.3 ± 1.19	598.9 ± 3145.7	0.01

Parameter	Camden and Islington Pathway (2014- 2016)				Standard of Care (2014 – 2016)		
	≤ F2 fibrosis (n=107)	≥ F3 fibrosis (n=45)	P-value		≤ F2 fibrosis (n=434)	≥ F3 fibrosis (n=36)	P-value
FIB-4	1.65 ± 0.67	2.49 ± 1.89	<0.001		1.02 ± 0.59	3.0 ± 2.7	<0.001
NFS	-1.00 ± 1.11	-0.24 ± 1.38	<0.001		-2.4 ± 1.3	0.3 ± 1.7	<0.001
APRI	0.43 ± 0.32	0.66 ± 0.49	0.002		0.4 ± 0.3	1.0 ± 0.8	<0.001
AST:ALT ratio	0.95 ± 0.36	0.97 ± 0.39	0.73		0.69 ± 0.3	1.0 ± 0.5	<0.001
ELF (n)	10.19 ± 0.56 (95)	10.76 ± 0.9 (36)	<0.001		N/A	N/A	
FLI (n)	32.6 ± 22.8 (70)	148.65 ± 279.8 (9)	0.035		19.7 ± 57.4 (43)	42.6 ± 67.3 (6)	0.37
Fibroscan KPa (n) Fibroscan KPa (range) < 5.8 5.8 – 7.8 7.9 – 10.3 10.3 – 12.5 > 12.5	5.83 ± 2.82 (70) 3.0 - 21.0 46 17 4 0 3	11.62 ± 8.89 (26) 4.7 – 47.2 3 4 7 3 9	<0.001		5.6 ± 3.4 (229) 2.8 – 40.3 161 48 9 5 6	16.0 ± 10.6 (70) 3.8 – 49.7 2 0 2 6 11	<0.001
Liver Biopsy n (%) F0 F1 F2 F3 F4	24 (24.2%) 8 12 4 0 0	16 (35.6%) 0 0 0 9 7	0.23		32 (7.3%) 15 11 5 0 0	9 (25.0%) 0 0 0 2 7	<0.001

Parameter	Camden and Islington Pathway (2014- 2016)				Standard of Care (2014 – 2016)		
	≤ F2 fibrosis (n=107)	≥ F3 fibrosis (n=45)	P-value		≤ F2 fibrosis (n=434)	≥ F3 fibrosis (n=36)	P-value
Weight loss/ 6 months (Kg)	1.1 ± 5.25	0.02 ± 2.32	0.193		1.54 ± 8.09	0.85 ± 2.42	0.682
Complications of CLD n Variceal bleed Varices (surveillence) Ascites PVT HCC Suspicious nodules	0 0 0 0 0 0 0	1 (0.6%) 0 1 0 0 0 0			0 0 0 0 0 0 0	10 (27.8%) 0 3 4 1 2 0	
Discharged (after 2 nd appointment)	196 (45.2%)	0 (0%)	<0.001		48 (48.5%)	0 (0%)	<0.001
Mortality (all-cause, within 1 year)	0	1 (2.2%)	0.30		4 (0.9%)	1 (2.7%)	0.24

Process evaluation revealed that 37/152 (24.3%) referrals had normal LFTs, and therefore should not have been on the pathway. A total of 123 out of 275 patients (44.7%) eligible for referral were not seen by a specialist during the evaluation period. A subgroup analysis was performed in three surgeries that were audited to further investigate reasons for non-referral. In this subgroup which included 32/123 (26.0%) of the non-referrals, non-referral occurred for the following reasons: patient already managed by a hepatologist (n = 4), inappropriate for pathway due to excess alcohol consumption (n = 2), comorbidity precluding need for specialist review (n = 1), ongoing management/ monitoring in primary care (n = 3) awaiting outpatient specialist appointment at time of evaluation (n = 2) and lost to follow-up (n = 2). No recorded decision or reasons was found in 18 patients.

6.5.7 Referrals made using the NAFLD pathway compared to standard care during evaluation period

The NAFLD pathway increased detection of advanced fibrosis and cirrhosis fivefold compared to patients referred by GPs using standard care during the evaluation period (2014-2016). Compared to standard care referrals from Camden and Islington only, the NAFLD pathway improved detection of advanced fibrosis and cirrhosis 4.9-fold (OR 4.90; 95% CI 2.56–9.36; p <0.0001) whilst compared to referrals made by GPs outside Camden and Islington using standard care, the NAFLD pathway improved detection 5.2-fold (OR 5.18; 95% CI 2.97–9.04; p <0.0001).

Compared to standard care, the use of the NAFLD pathway resulted in an 81% reduction in referrals of patients from primary care with non-significant liver fibrosis (Brunt ≤ F2 fibrosis) (OR 0.193; 95% CI 0.111–0.337; p <0.0001) (Table 6.11).

Table 6.11 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 SC	All C&I	Other CCG SC	All SC	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
F4 %	***3.6%***	***3.7%***	***3.6%***	***14.5%***	***5.6%***	***9.7%***	***5.1%***	***5.3%***	***7.5%***	***19.4%***

The introduction of the NAFLD pathway resulted in nearly a 3-fold increase in the detection of patients with cirrhosis (OR 2.83; 95% CI 1.29–6.18; p = 0.009). compared to patients referred by Camden and Islington GPs using standard care (22/152 [14.5%] compared to 10/177 [5.6%]). Employing the Camden and Islington NAFLD pathway, the number of referrals required to detect 1 case of advanced fibrosis was 3.4 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 in standard care used by GPs within Camden and Islington (Table 6.12). The baseline characteristics of patients diagnosed with advanced fibrosis or cirrhosis by the NAFLD pathway or standard care during the evaluation period are compared in Table 6.13.

Table 6.12 Impact of implementation of the Camden and Islington NAFLD Pathway

C&IP = Camden and Islington pathway, C&I SC = Camden and Islington standard care

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

Table 6.13 Characteristics comparing patients diagnosed with advanced fibrosis stratified by pathway use

	Standard care	Pathway	
	≥ F3 fibrosis (n=36)	≥ F3 fibrosis (n=45)	P-value
Age (yrs)	62.2 ± 11.9	67.7 ±8.7	0.03
Male n (%)	19 (52.8%)	30 (66.6%)	0.28
Practice IMD	25.3 ± 9.6	29.3 ± 7.8	0.04
Hypertension n (%)	28 (77.7%)	32 (71.1%)	0.70
Hypercholesterolaemia n (%)	24 (66.6%)	26 (57.7%)	0.56
Type II Diabetes n (%)	24 (66.6%)	25 (55.6%)	0.31
Cardiovascular events n (%)	8 (22.2%)	12 (26.6%)	0.69
BMI (kg/m2)	33.6 ± 7.7	31.5 ± 8.6	0.37
Walst circumfernece cm	111.6 ± 19.3	114.4 ± 14.1	0.65
Total Cholesterol mmol/l	4.7 ± 1.20	4.3 ± 1.0	0.22
Triglyceride mmol/l	2.1 ± 1.2	1.8 ± 0.8	0.13
HDL mmol/l	1.3 ± 0.5	1.7 ± 2.3	0.34
HBA1c	56.5 ± 17.4	46.1 ± 17.6	<0.04

	Standard care	Pathway	
Platelet	183.2 ± 74.3	197.3 ± 59.4	0.41
INR	1.1 ± 0.2	1.04 ± 0.19	0.32
ALT mmol/l	63.4 ± 55.0	48.3 ± 24.6	0.11
AST mmol/l	51.7 ± 30.6	43.3 ± 21.3	0.14
GGT mmol/l	166.0 ± 162.2	148.9 ± 31.9	0.70
Bilirubin mmol/l	10.4 ± 6.9	10.4 ± 6.5	0.96
Albumin mmol/l	43.4 ± 4.5	44.5 ± 3.9	0.17
Ferritin mmol/l	246.7 ± 258.1	321.5 ± 349.4	0.35
Creatinine mmol/l	73.1 ± 20.6	85.1 ± 31.9	0.05
AFP mmol/l	598.9 ± 3145.7	2.82 ± 1.22	0.39
FIB-4	3.0 ± 2.7	2.49 ± 1.89	0.26
NFS	0.3 ± 1.7	-0.24 ± 1.38	0.19
APRI	1.0 ± 0.8	0.66 ± 0.49	0.06
AST:ALT ratio	1.0 ± 0.5	0.97 ± 0.39	0.69
ELF (n)	N/A	10.76 ± 0.9 (36)	
FLI (n)	42.6 ± 67.3 (6)	148.65 ± 279.8 (9)	0.39
Fibroscan KPa (n) Fibroscan KPa (range) < 5.8 5.8 – 7.8 7.9 – 10.3	16.0 ± 10.6 (70) 3.8 – 49.7 2 0 2	11.62 ± 8.89 (26) 4.7 – 47.2 3 4 7	0.17

	Standard care	Pathway	
10.3 – 12.5 > 12.5	6 11	3 9	
Liver Biopsy n (%) F0 F1 F2 F3 F4	9 (25.0%) 0 0 0 2 7	16 (35.6%) 0 0 0 9 7	0.22
Weight loss/ 6 months (Kg)	0.85 ± 2.42	0.02 ± 2.32	0.37
Complications of CLD n (%) Variceal bleed Varices (surveillence) Ascites PVT HCC Suspicious nodules	10 (27.8%) 0 3 4 1 2 0	1 (2.2%) 0 1 0 0 0 0	<0.001
Discharged	0 (0%)	0 (0%)	0.96
Mortality	1 (2.7%)	1 (2.2%)	0.97

6.5.8 Referrals made from Camden and Islington before and after introduction of the NAFLD pathway

Given the increased awareness of NAFLD during the pathway evaluation period (2014–16) compared to pre-pathway baseline (2012–13), referral rates to hospital specialists 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 introduction of the NAFLD pathway, 79 out of 83 (95.2%) referrals in 2012-2013 made to secondary care were deemed to have non-significant fibrosis (Brunt ≤F2). The introduction of the NAFLD pathway over a period of 2 years resulted in an 88% reduction of referrals of patients with non-significant fibrosis (OR 0.12; 95% CI 0.042–0.349; p <0.0001), with the number of unnecessary referrals falling to 107/152 (70.4%) (see Table 6.11 and Table 6.12). The improved selection of cases of significant 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).

Comparing the distribution of FIB-4 scores of patients referred for NAFLD by Camden and Islington GPs before and after the introduction of the NAFLD pathway revealed no evidence of bias in patient selection (Table 6.14). Statistically significant differences in the outcomes for patients managed using standard care before or after introduction of the pathway were not seen, suggesting an absence of a Hawthorne or bystander effect [226] from diffusion of the benefits of the pathway to patients managed using standard care.

Table 6.14 FIB-4 stratification of patients in primary care before and after introduction of the Camden and Islington NAFLD Pathway

	FIB-4 = 1.30-3.25		FIB-4 >3.25	
	Before *2012-2013*	After *2014-2016*	Before *2012-2013*	After *2014-2016*
Total	43	136	4	16
<F3 (%)	33 (77)	102 (75)	1 (25)	5 (31)
F3/F4 (%)	10 (23)	34 (25)	3 (75)	11 (69)

6.5.9 The impact of using age-adjusted FIB-4 thresholds

The influence of age on FIB-4 has been investigated in recent years after the introduction of the Camden and Islington pathway. Recent recommendations have advocated an adjustment to the threshold of FIB-4 score in patients over the age of 65 [227]. Adopting a higher FIB-4 cut-off of < 2.0 rather than < 1.30 to rule out advanced fibrosis or cirrhosis reduced the referrals of patient with non-significant fibrosis (Brunt ≤F2) by 29 referrals from 122 to 93 (23% reduction), but at the expense of missing 12 cases with advanced fibrosis, of whom 4 patients had cirrhosis (Table 6.11).

6.5.10 Modelling of the impact of other ELF thresholds

The ELF threshold to rule-in or rule-out advanced fibrosis or cirrhosis employed in the Camden and Islington NAFLD pathway (9.5) was lower than recommended by the manufacturers of ELF (9.8) [149] and in the NICE

guidelines for patients with NAFLD (10.51) [225]. Using an ELF threshold of 9.8 would have resulted in 11 (7.2%) fewer referrals of patients with non-significant fibrosis (Brunt ≤F2), but with a concomitant loss of 3 (6.7%) cases of advanced fibrosis. Raising the ELF threshold further to 10.51 would reduce the number of patients referred with non-significant fibrosis by 34 (22%), at the expense of missing 10 cases of advanced fibrosis (22%), comprising 7 cases of F3 fibrosis and 3 cases of cirrhosis (Table 6.15).

Table 6.15 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*

6.5.11 Pathway cohort undergoing liver biopsy

Of the 152 patients reinvestigated by a specialist after referral using the NAFLD pathway, 35 patients (23.2%) underwent liver biopsy as part of their routine clinical care. Patient-level liver biopsy data are presented in Table 6.16. Using liver biopsy as a reference standard, the diagnostic performance of the NAFLD pathway to identify advanced fibrosis or cirrhosis was calculated. ELF thresholds were tested with a cut-off of 9.5 (used in the pathway), 9.8 (recommended by the manufacturer) and 10.51 (NICE guidance) (Table 6.17).

Employing an ELF threshold of ≥9.5 to detect advanced fibrosis or cirrhosis, liver histology was concordant in 14 out of 35 cases (PPV=40%), with a false positive rate of 60% (21/35). In all 14 cases of advanced fibrosis and cirrhosis on liver biopsy, the ELF score was concordant (sensitivity=100%).

Increasing the ELF threshold in line with the manufacturers recommendation (ELF ≥ 9.8 for advanced fibrosis or cirrhosis) resulted in an increase in histological concordance (overall =19/35, true positive = 14, true negative = 5) Performance characteristics of the NAFLD pathway with ELF threshold ≥ 9.8 was: sensitivity=100%; Specificity=24%; PPV = 47%; NPV=100%.

Increasing the ELF threshold further in line with NICE recommendations (ELF ≥10.51 for advanced fibrosis or cirrhosis) resulted in an increase in histological concordance (overall 25/35, true positive 10, true negative = 15). Performance characteristics of the NAFLD pathway with ELF threshold ≥ 10.51 was: sensitivity=71%; Specificity=71%; PPV = 63%; NPV=79%.

Table 6.16 Clinical and histological data for patients referred from Camden and Islington using the Camden and Islington NAFLD pathway who underwent liver biopsy.

TP – True positive FP – false positive

Patient number	ID	C&IP Performance	Age	Platelet	INR	ALT	Imaging suggestive of cirrhosis	FIB-4	ELF	TE	Biopsy: Fibrosis	Biopsy: inflammation
1	P016	TP	51	177	1.0	36	No	1.47	10.9	17.3	F4	Mild
2	P027	TP	57	172	1.0	34	No	1.93	10.2	-	F4	Mild
3	P028	TP	79	284	1.0	34	No	1.95	10.7	-	F4	Mild
4	P001	TP	63	179	1.0	41	No	1.98	9.8	47.2	F4	Mild
5	P019	TP	75	201	0.9	78	No	2.20	11.9	17.5	F4	Mild
6	P037	TP	62	183	1.0	62	No	2.45	12.0	-	F4	Mild
7	P038	TP	66	150	1.0	39	Yes: Irregular liver	3.24	12.8	12.4	F4	Mild
8	P033	TP	44	189	1.0	101	No	1.30	11.8	13.9	F3	Moderate

Patient number	ID	C&IP Performance	Age	Platelet	INR	ALT	Imaging suggestive of cirrhosis	FIB-4	ELF	TE	Biopsy: Fibrosis	Biopsy: inflammation
9	P032	TP	60	204	1.0	22	No	1.37	11.3	-	F3	Mild
10	P021	TP	59	149	1.2	26	Yes: Splenomegaly	1.63	9.8	-	F3	Mild
11	P023	TP	76	239	1.0	41	No	1.74	10.0	-	F3	Mild
12	P045	TP	64	202	1.0	40	No	1.75	10.8	11.7	F3	Mild
13	P031	TP	60	222	1.0	53	No	1.90	11.2	17.5	F3	Mild
14	P015	TP	63	280	1.0	136	No	2.35	10.7	23.6	F3	Moderate
15	P099	FP	41	268	1.0	90	No	1.31	10.5	9.3	F2	Moderate
16	P050	FP	68	209	0.9	45	Yes: Irregular liver	2.18	9.5	14.3	F2	Mild
17	P097	FP	56	188	1.0	39	No	2.24	10.5	-	F2	Moderate
18	P060	FP	57	264	1.0	41	No	1.30	10.3	3.8	F1	Mild
19	P081	FP	63	241	1.0	43	No	1.36	9.8	-	F1	Mild

Patient number	ID	C&IP Performance	Age	Platelet	INR	ALT	Imaging suggestive of cirrhosis	FIB-4	ELF	TE	Biopsy: Fibrosis	Biopsy: inflammation
20	P075	FP	46	177	1.0	108	No	1.43	9.6	-	F1	Nil
21	P085	FP	66	208	1.0	23	No	1.52	10.0	-	F1	Mild
22	P065	FP	71	247	0.9	26	No	1.69	11.1	8.7	F1	Moderate
23	P062	FP	57	210	0.9	90	Yes: Irregular liver	1.70	10.7	-	F1	Mild
24	P066	FP	70	215	0.9	55	No	1.76	11.3	-	F1	Mild
25	P104	FP	71	178	1.0	74	No	2.36	10.8	7.7	F1	Mild
26	P051	FP	65	191	1.0	88	No	2.39	9.5	-	F1	Mild
27	P089	FP	71	151	0.9	50	No	2.73	10.2	7.0	F1	Mild
28	P114	FP	71	107	0.9	34	No	2.84	10.1	-	F1	Mild
29	P048	FP	55	141	1.0	217	Yes: Splenomegaly	3.76	-	5.4	F1	Mild
30	P073	FP	55	274	0.9	28	No	1.36	9.5	-	F0	Nil

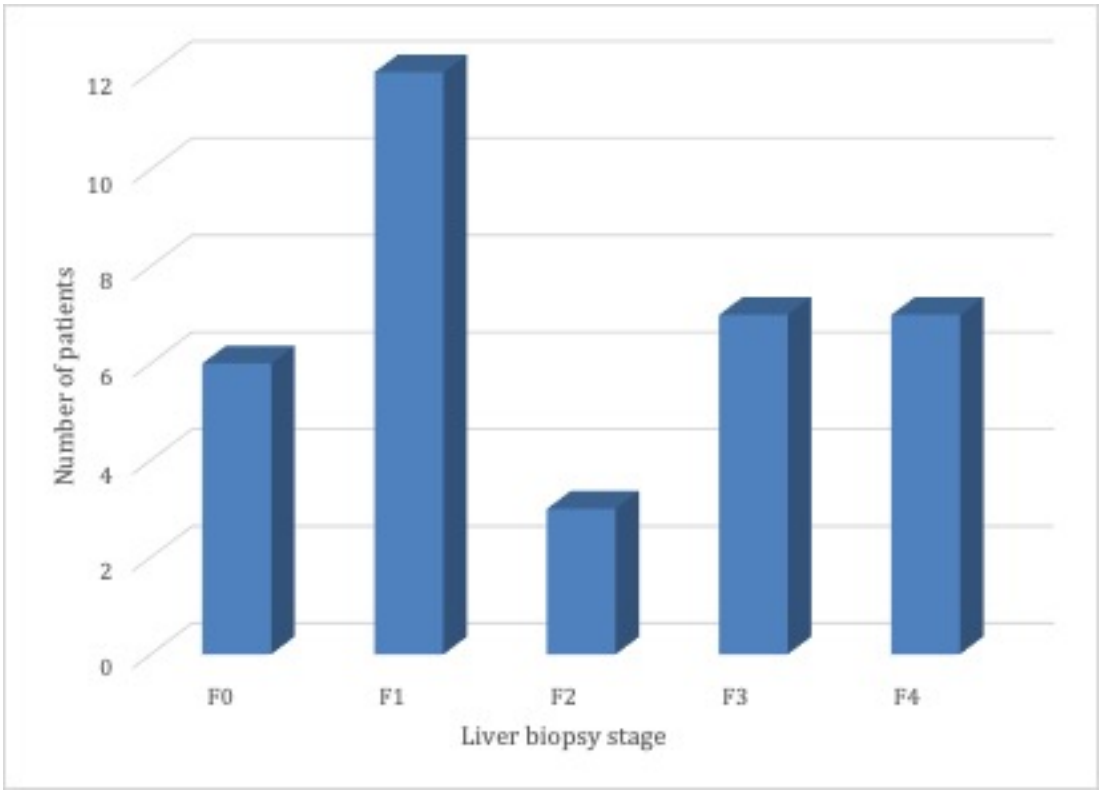
Patient number	ID	C&IP Performance	Age	Platelet	INR	ALT	Imaging suggestive of cirrhosis	FIB-4	ELF	TE	Biopsy: Fibrosis	Biopsy: inflammation
31	P093	FP	72	217	1.0	65	No	1.36	10.3	-	F0	Mild
32	P084	FP	70	235	1.0	15	No	1.54	10.0	-	F0	Nil
33	P063	FP	67	186	0.8	26	No	1.55	10.8	-	F0	Nil
34	P136	FP	58	240	0.9	27	No	1.57	10.3	4.0	F0	Nil
35	P125	FP	74	255	1.0	29	No	2.26	9.5	-	F0	Nil

Table 6.17 NAFLD pathway diagnostic characteristics for patients undergoing liver biopsy.

NAFLD pathway ELF threshold	True positive	False positive	True negative	False negative	Sensitivity	Specificity	PPV	NPV	Pathway/ histological concordance
≥9.5	14	21	NA	NA	100%	NA	40%	NA	14/35
≥9.8	14	16	5	0	100%	24%	47%	100%	19/35
≥10.51	10	6	15	4	71%	71%	63%	79%	25/35

Only five liver biopsies (14.3%) demonstrated an absence of fibrosis or inflammation. Twenty-nine patients (78.3%) had at least some degree of fibrosis (≥F1 fibrosis) (Figure 6.10).

Figure 6.10 Distribution of liver fibrosis as staged by biopsy for patients on NAFLD pathway

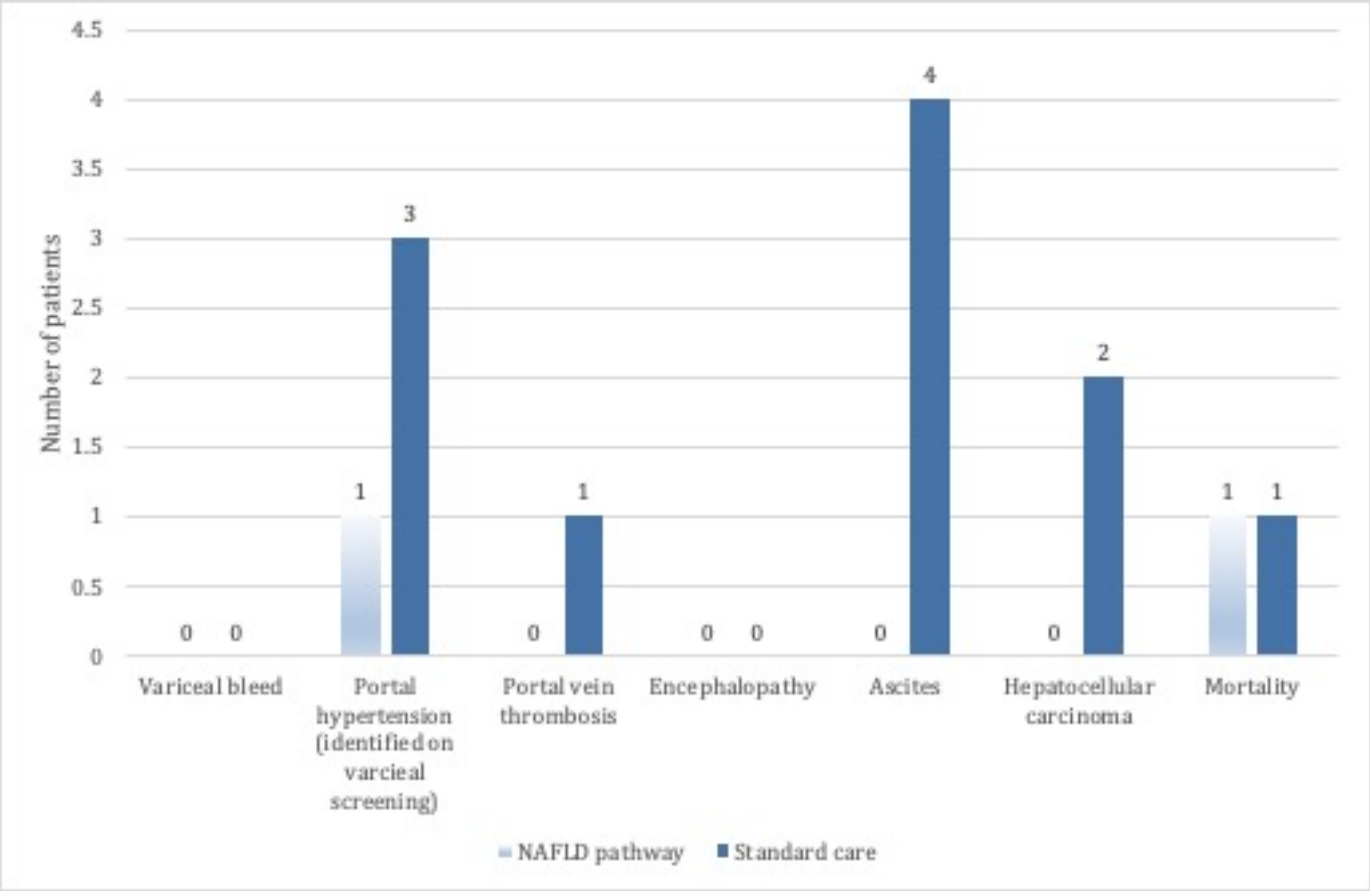


6.5.12 Severity of Chronic Liver Disease

Comparing patients diagnosed with liver cirrhosis on the NAFLD pathway to standard care, no statistical difference was found in baseline liver severity scores; namely UKELD (45.47 ± 3.04 vs. 45.72±9.05, p=0.51), MELD (12.26 ± 2.82 vs. 12.13 ± 2.88, p = 0.25) and Child Pugh Score (5.00±0.00 vs. 5.31 ± 0.86, p = 0.24).

During the study follow up period (2014-2016), a total of 11 liver-related complications were recorded (Figure 6.11) in patients diagnosed with cirrhosis. One patient (9.1% of liver related complications) was referred on the NAFLD pathway and identified to have oesophageal varices on screening endoscopy. The remaining 10 complications of liver cirrhosis (90.9% of liver related complications) occurred in the standard care group; 3 patients were identified to have oesophageal varices on screening endoscopy, one patient developed portal vein thrombosis and 4 patients developed ascites during the study period. There were two cases of hepatocellular carcinoma in the standard care group. One patient with an established diagnosis of NAFLD managed in primary care was investigated for increasingly deranged liver function tests. A community ultrasound demonstrated a mass lesion suspicious for hepatocellular carcinoma precipitating referral. Subsequent imaging confirmed HCC outside established treatment criteria. The patient was palliated and died. Another patient was referred by their GP for investigation of worsening LFT's in the context of NAFLD and a community ultrasound suggestive of cirrhosis. After initial review, a surveillance ultrasound after 6 months demonstrated multi-lobar HCC, and an elevated AFP of 16,000. The tumour was outside transplant criteria. The patient underwent first cycle of TACE in July 2016. There was no statistical difference in mortality between the groups (1/21 C&I pathway, 1/25 standard care, p=0.97).

Figure 6.11 Complications of chronic liver disease for all patients referred between 2014 - 2016



6.6 Discussion

In this study, we evaluated a prospective, pragmatic, real-world pathway to risk-stratify patients with NAFLD in primary care based on their risk of advanced fibrosis or cirrhosis. To the best of my knowledge, this study represents the largest published cohort of patients with NAFLD in primary care to date. Additionally, this study adds to the evidence base, which is sparse as my literature review described in Chapter 3 with only one other published study using non-invasive tests in the community for patients with NAFLD identified [195].

The use of FIB-4 and ELF to risk-stratify patients on the Camden and Islington NAFLD pathway reduced the proportion of referrals of patients with non-significant fibrosis (Brunt $\leq$ F2) whilst increasing the detection of advanced fibrosis (F3) and cirrhosis (F4). The NAFLD pathway resulted in an 81% decrease in referrals of patients with non-significant fibrosis, and a 5-fold increase in the referral of patients with advanced fibrosis or cirrhosis, and a 3-fold increase in the referral of patients with cirrhosis.

An audit of the performance of standard care to identify patients with advanced fibrosis or cirrhosis prior to the implementation of the pathway found that the majority of referrals made to hospital specialists had non-significant fibrosis and could have avoided referral altogether and been managed in primary care. This pattern of referral for patients with NAFLD is likely to be replicated nationally and beyond. Implementing innovations which reduce referrals of patients deriving little benefit from specialist review represents an opportunity

to reduce inconvenience and even harm for patients, unnecessary investigations and potentially relieve pressure on over-stretched secondary care services and healthcare budgets.

The Camden and Islington NAFLD pathway stratified 1,452 patients over the two years demonstrating that the pathway can function at scale, which is important given the increasing prevalence of NAFLD worldwide. The decision to employ serum blood tests, rather than transient elastography that has been used in other successful pathways [87], aided large-scale implementation. Both FIB-4 and ELF have the advantage that they are easily incorporated into routine primary care investigations and do not require specialist technology, training or clinic space. Additionally, serum tests have a lower diagnostic failure rate compared to elastography-based methods, with failure rates documented between 5–15%, especially in NAFLD [161]. The use of a ‘‘simple” and inexpensive non-invasive first tier test, FIB-4, allowed over two thirds of patients to avoid referral to a specialist as they did not have evidence of advanced fibrosis or cirrhosis. It is important to highlight that this large group of patients with NAFLD (70.1% of total cohort) could be managed in primary care without specialist review and reassured with the use of readily available inexpensive tests.

However, using FIB-4 alone only identified 3.0% of NAFLD cases for referral to secondary care with high probability of advanced fibrosis or cirrhosis. Using the ‘‘direct biomarker” ELF test for FIB-4 indeterminate cases was only required in 26.7% of cases. However, the use of ELF avoided inappropriate referral for 40.1% of those with indeterminate FIB-4 results and allowed for a

further 15.9% of the overall cohort to be selected for specialist referral due to an increased risk of advanced fibrosis and cirrhosis. Overall, the NAFLD pathway selected only 19% of patients with NAFLD diagnosed in primary care for referral to secondary care due to high risk of advanced fibrosis or cirrhosis. The remaining 81% of patients were recommended for management in primary care due to low risk of advanced fibrosis or cirrhosis.

The benefits of the pathway were restricted to cases that followed the NAFLD pathway. Despite improved awareness of NAFLD, suggested by increased coding of NAFLD, in the evaluation period, there was no improvement in case detection of advanced fibrosis or cirrhosis or reduction in referrals of patients with non-significant fibrosis when standard care was followed rather than the NAFLD pathway. This reinforces the merits of the NAFLD pathway but also demonstrates a lack of diffusion of the pathway benefits to patients managed with standard care or any significant change in ‘‘standard” practice due to emerging awareness of NAFLD and the NAFLD pathway during the evaluation period.

The success of an innovation is dependent on engagement from healthcare professionals. Over the two-year evaluation period, just under a half (48%) of referrals from Camden and Islington for patients with NAFLD were made using the NAFLD pathway. Despite this, the implementation of the NAFLD pathway resulted in significant improvements in referral practice for patients with NAFLD in Camden and Islington, even when referrals made using standard care were included in the analysis. This reinforces the success of the service innovation which was delivered in the context of routine clinical care and

moderate adoption, suggesting the results reported in this study are generalizable. Increased adoption of the NAFLD pathway by GPs in Camden and Islington would likely produce even more notable changes in efficiency and the detection of cases of advanced fibrosis or cirrhosis. To achieve this, a more regular and extensive programme to disseminate information about the pathway in primary care maybe helpful. Additionally, employing stricter referral triage systems and an insistence that FIB-4 and ELF if required are performed as a minimum requirement for all NAFLD referrals may improve pathway adherence.

Sensitivity analyses revealed that the application of a validated age-adjusted FIB-4 cut-off or of a higher ELF threshold in line with the manufacturer's or NICE recommendations increased the positive predictive value of the NAFLD pathway for detection of advanced fibrosis and cirrhosis, but at the expense of an increased number of false negative cases. The employment of these other thresholds may not be justified for some healthcare providers, as in this context the reduction in referral numbers carries significant risks of missing cases that would benefit from specialist care. In line with most healthcare screening strategies, future recommendations would need to balance the detection of advanced fibrosis and cirrhosis and long-term cost effectiveness over shorter-term cost savings associated with avoiding referral of patients with non-significant fibrosis.

Prior to introduction and evaluation of the NAFLD pathway, commissioners from Camden and Islington raised concerns that the introduction of a formal NAFLD pathway may cause a significant increase in referrals for patients with

NAFLD to secondary care resulting in higher costs. In the context of an increase in the diagnosis of patients with NAFLD in Camden and Islington between 2012–2016, use of the NAFLD pathway allowed a 3% reduction in the proportion of NAFLD cases referred for a specialist opinion.

This study was a prospective, pragmatic and novel study evaluating an important research question and had a number of strengths and weaknesses. 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 and implementation. Over the two-year evaluation period, 1452 patients underwent risk stratification in the community, which was significantly more than the only other published study using non-invasive tests in primary care for patients with NAFLD, where 259 patients in Italy were evaluated with Fibrotest [195]. The study also offered patients stratified at high risk of advanced fibrosis and cirrhosis (≥ F3 fibrosis) re-investigation and specialist re-assessment of their fibrosis stage in a logical and consistent manner which increased the reliability of the results. Re-investigation of high-risk patients was poorly documented in the studies identified in the literature review (Chapter 3).

In this longitudinal cohort study, the performance of the NAFLD pathway could be compared to two groups, pre-pathway and standard care during the evaluation period.

The study was a real-life evaluation of a new service improvement initiative, which will increase the generalizability and applicability of the results to other health systems.

The limitations of this study mostly stem from the nature of the implementation in which an evaluation of a health service innovation was designed. It was considered not possible to perform a randomized controlled trial because of the commitment to adopt the pathway once it was discussed with GPs and public health clinicians who concluded that there was already sufficient evidence to support implementation of the pathway for the local population without a trial. This view was subsequently endorsed by NICE in the NAFLD Guidance [225]. The re-investigation of patients referred for specialist opinion lacked a validated outcome measure of liver biopsy in all patients and rather used the composite clinical judgement of an expert clinician blinded to the pathway use. Only a limited number of studies have attempted reinvestigation on a consistent basis. Poynard and colleagues [192] did use specialist reinvestigation as their reference standard, and are the only study that attempted to systematically ascribe a fibrosis stage to patients identified as high risk for advanced fibrosis or cirrhosis - they used a categorical, unvalidated system of 'fibrosis confirmed', fibrosis still suspected' and 'indeterminate'. Patients undergoing liver biopsy had a degree of selection bias reflecting real-world practice.

The lack of formal evaluation of the prevalence of fibrosis amongst patients allocated to remain in primary care prevented assessment of the "true negative' and ''false negative" rate. The working group, including PPI, has

deemed it unethical to perform liver biopsies on patients stratified to primary care management by the pathway on the basis of diagnosis of minimal fibrosis.

6.7 Conclusion

The Camden and Islington NAFLD pathway increased the referral of patients with advanced fibrosis or cirrhosis to secondary care, whilst reducing the referral of patients with non-significant fibrosis. This facilitates early detection of significant liver disease, efficient use of healthcare resources and cost savings. The subject area is topical for the NHS. Obesity is an increasing epidemic contributing to diabetes, cardiovascular disease, cancer and liver disease [4]. It is predicted that NAFLD will become the leading indication for liver transplant within the next decade [22]. At present there is no widely accepted approach to case identification and risk stratification for patients with NAFLD in primary care [14]. A more efficient referral system to secondary care will help reduce the strain on healthcare services that are confronting a rising prevalence of obesity and NAFLD as well as improving patient experiences by avoiding unnecessary clinic appointments and investigations. 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 in the long-term.

6.8 Publication

The contents of this chapter have been published after peer-review [203]. The citation is:

Srivastava *et al*: Prospective evaluation of a primary care referral pathway for patients with non-alcoholic fatty liver disease. *Journal of hepatology* 2019, 71(2):371-378.

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CHAPTER 7 COST COMPARISON ANALYSIS OF FIB-4, ELF AND FIBROSCAN IN COMMUNITY PATHWAYS FOR NON-ALCOHOLIC FATTY LIVER DISEASE

7.1 Introduction

The impact of chronic liver disease (CLD) is substantial and can be measured in health, societal and economic terms [1, 3]. CLD is a leading cause of premature mortality in the Westernized world [4], and with an increasing prevalence of risk factors such as obesity, diabetes and excess alcohol consumption, this trend is likely to continue in the future.

Non-alcoholic fatty liver disease (NAFLD) is the commonest cause of deranged liver blood tests in the primary care setting [39]. However, the vast majority of patients do not have liver related consequences, with only a relatively small proportion (10%) progressing to clinically significant liver disease [40]. The evidence base has increasingly highlighted that the key predictor of liver related morbidity and mortality is the severity of liver fibrosis [75, 76]. Therefore, the principle aim for general practitioners (GPs) in their initial assessment of a patient with NAFLD in the community is to identify patients at risk of significant liver fibrosis (equivalent to Brunt ≥F3). In the current 'standard care' (SC) model, the GP assesses the presence or absence of significant liver disease and need for specialist referral based on a composite of history, examination, blood tests including liver blood tests and ultrasound. This assessment is hindered by a reliance on investigations that are poor discriminators of liver fibrosis including liver blood tests [88]. Patients assessed to have a high risk of advanced fibrosis or cirrhosis are referred to a

hospital specialist as they may benefit from active management including enrolment into clinical trials for emerging therapies for NAFLD and fibrosis [3, 52] or into surveillance pathways for patients with liver cirrhosis. This includes the targeted screening and treatment for complications of cirrhosis including portal hypertension [46] and hepatocellular carcinoma (HCC) [47].

Current standard care approaches in primary care result in the referral of patients that do not have significant liver fibrosis (Brunt ≤F2). This was exemplified in Chapter 5 where a retrospective audit revealed 93% of referrals to secondary care over one year had non-significant fibrosis. This inefficiency places a burden on hospital services, incurring unwarranted costs and engendering significant inconvenience and anxiety for patients. Furthermore, the primary care assessment misses an important number of patients with advanced fibrosis or cirrhosis who are not referred to secondary care. These patients are falsely reassured and may silently progress before presenting with decompensated liver disease or hepatocellular carcinoma.

The evolution of non-invasive liver fibrosis tests (NIT) [175] may afford improved fibrosis risk stratification in the community setting [6, 228]. In Chapter 6, I described an evaluation of a primary care pathway for patients with NAFLD ("Camden and Islington NAFLD pathway") employing FIB-4 and ELF which yielded a fivefold increase in the detection of patients with advanced fibrosis or cirrhosis and reduced referrals of patients with non-significant fibrosis (≤ F2 fibrosis) by 81%.

The Camden and Islington Liver Working Group, which is described in detail in section 6.3.1 and comprised of primary care physicians, secondary care liver specialists, commissioners, public health practitioners and patient representatives, recommended a health economic analysis of the Camden and Islington NAFLD pathway as part of the evaluation process. In this chapter, I developed a probabilistic decision analytical model to investigate the clinical and cost impact of primary care risk stratification pathways for patients with NAFLD.

7.2 Aims

To assess the clinical and cost utility of introducing competing pathways employing non-invasive liver fibrosis tests in primary care to identify patients with NAFLD and advanced fibrosis or cirrhosis (Brunt ≥F3).

7.3 Methods

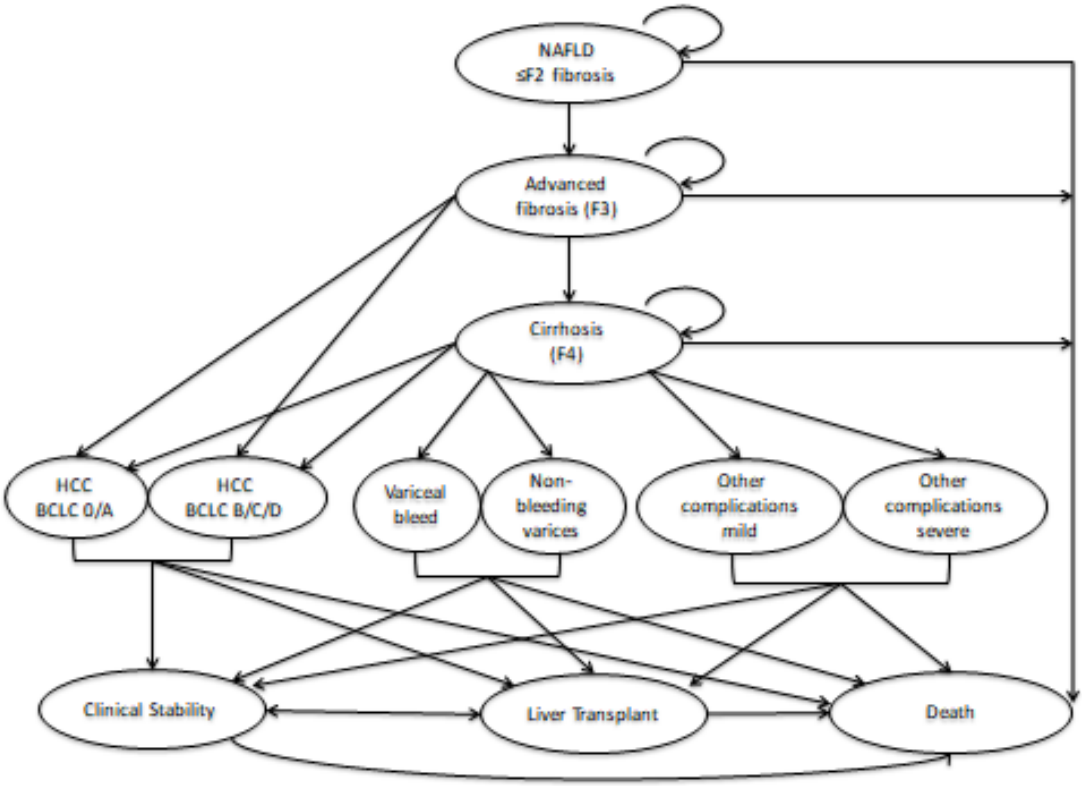
7.3.1 Probabilistic decision model

A probabilistic decision analytical simulation model was created using Microsoft Excel Software (version 16.23, 2019). The model piloted competing primary care strategies employing non-invasive liver fibrosis tests for 1000 patients with a confirmed diagnosis of NAFLD (Figure 7.1). The average patient was 50 years old with elevated transaminases. The time horizon for the base-case was 1 year to assess short-term benefits, likely to relate to resource utilisation. This was extended to a 5- year timeframe in a separate analysis to assess the longer-term implications.

The Camden and Islington liver working group favoured the selection of patients with deranged liver function tests (LFT) in line with the Camden and Islington NAFLD pathway, even though it was recognised that this would miss cases of patients with significant liver fibrosis who have normal LFTs. Following an independent review of the literature by colleagues in Public Health, the Liver Working Group preferred restricting the pathway to patients with abnormal LFTS on the basis that they perceived a lack of evidence from studies based in primary care to recommend including patients with NAFLD and normal ALT. Whilst the hepatologists favoured including patients with NAFLD and normal LFTs on the basis that studies based in secondary care have found that up to 25% of patients with cirrhosis may have normal LFTs, the consensus of the Liver Working Group was to restrict the study to patients with abnormal LFTs.

Figure 7.1 Decision tree presenting overview of transition of a patient with NAFLD through the model

In the model, a patient with NAFLD and ≤ F2 fibrosis could remain well, progress to F3 fibrosis or die. A patient with F3 fibrosis could remain well, progress to compensated cirrhosis, develop hepatocellular carcinoma (HCC) or die. Patients with compensated cirrhosis could remain stable, develop a complication of cirrhosis, undergo liver transplantation, or die. The model differentiated early-stage complications (non-bleeding varices detected by surveillance endoscopy, Barcelona Clinic Liver Cancer (BCLC) stage 0/A HCC and mild/moderate 'other' complication including ascites, jaundice and hepatic encephalopathy managed as outpatient), from late-stage complications (bleeding varices, BCLC stage B-D HCC and severe 'other' CLD complications necessitating inpatient admission).



7.3.2 Clinical data inputs

The model parameters were informed by a comprehensive literature search. The model inputs were critically ratified to ensure suitability for this study and were supplemented by expert opinion when the literature base was unsatisfactory. In particular, the diagnostic accuracy and performance of standard care is poorly described in the published literature, but estimates were extrapolated from available studies and the Camden and Islington data described in Chapter 5 and Chapter 6 [5, 203].

An intention-to-diagnose strategy was assumed by the model. All patients were managed in accordance to the pathway. The prevalence of advanced fibrosis or cirrhosis (Brunt ≥F3 fibrosis) was set at 7.5% [39]. The model used published sensitivities and specificities of FIB-4 [105, 125], ELF [122, 125] and fibroscan [125, 139] to estimate the rates of patients deemed to be low risk of significant fibrosis and high risk of significant fibrosis (Table 7.1 and Figure 7.2. Clinical estimates of disease progression in patients with NAFLD were obtained from the published literature to inform the model (Table 7.2).

Table 7.1 Test performance and disease prevalence estimates.

Published test characteristics of non-invasive liver fibrosis tests to detected significant fibrosis (Brunt ≥F3) in patients with non-alcoholic fatty liver disease

Test characteristics	Sensitivity	Specificity	Reference
Standard of care	0.35	0.65	Expert Opinion [171, 229]
FIB-4 (cut off 1.30)	0.84	0.74	[105, 125]
FIB-4 (cut off 3.25)	0.38	0.97	[105, 125]
ELF	0.80	0.90	[122, 125]
Fibroscan	0.82	0.84	[125, 139]
Population and disease characteristics	Transition probability		
Prevalence of significant fibrosis in the general population	0.075		[39]

Figure 7.2 Predicted patient referral patterns and pathway performance in scenarios employing non-invasive liver fibrosis markers.

Published test performances allowed prediction of true and false positive and negative rates for the detection of ≥F3 fibrosis

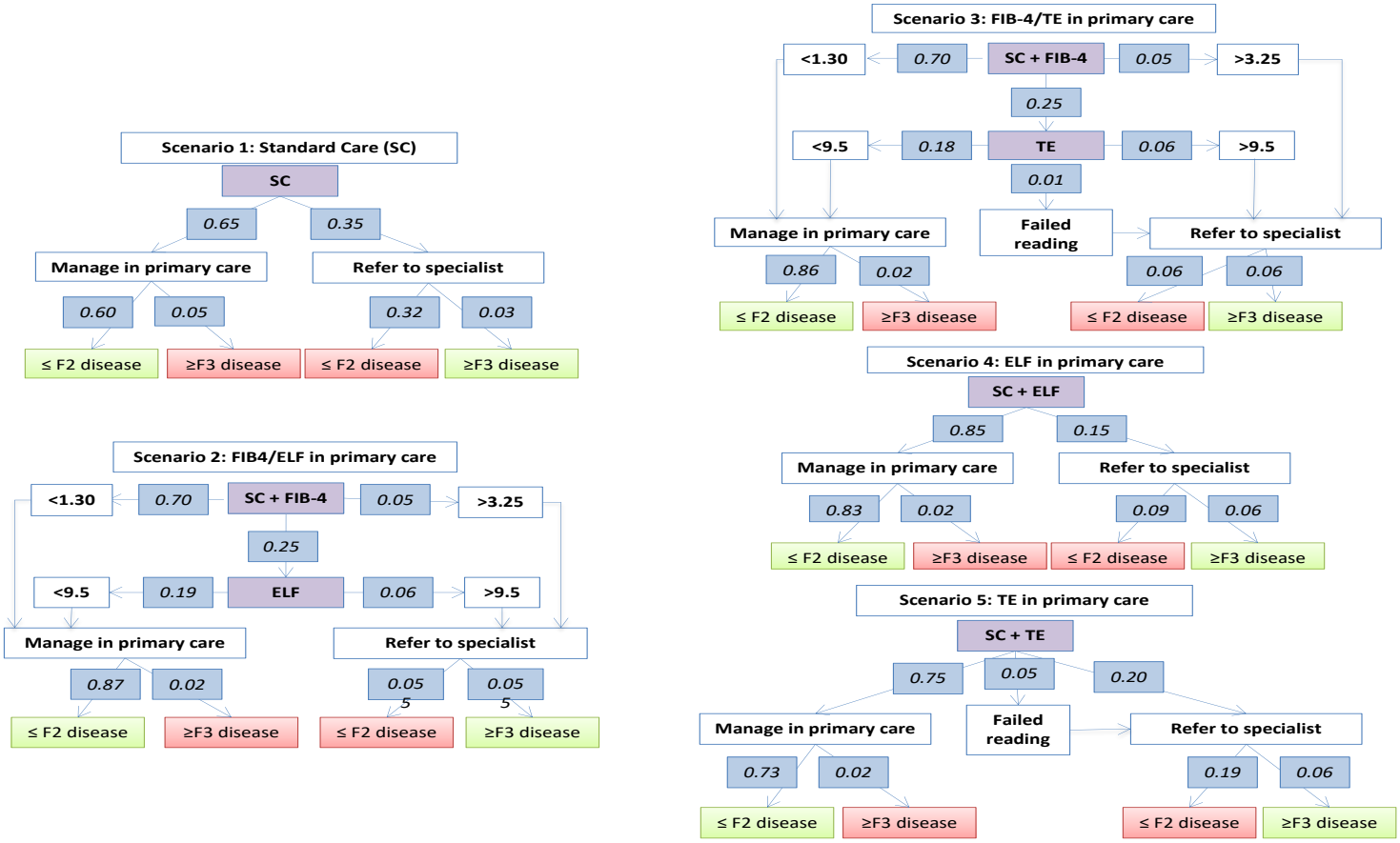


Table 7.2 Transitional probability estimates used to populate the probabilistic analytical model for the base case (annual progression rates)

Parameter/ Health state	Transition probability	References
Population and disease characteristics		
Prevalence of significant fibrosis in the general population	0.075	[39]
Reduction in fibrosis progression after GP management	0.01	[230], Author assumption
Reduction in fibrosis progression after specialist review	0.025	[230]
Mild/ No fibrosis (F0, F1, F2)		
Remain healthy	0.99	[62, 231-235]
Develop F3 disease	0.001	[62, 231-233]
Mortality (all cause)	0.005	[233-235]
Discharge from specialist services	0.7	Unpublished audit
Advanced fibrosis (F3)		
Remain healthy	0.95	[61, 233, 236]
Develop F4 disease/ cirrhosis	0.04	[61, 233, 236]
Develop HCC (without cirrhosis)	0.004	[236]
Mortality (all cause)	0.005	[236]
Compensated cirrhosis (F4)		
Remain compensated	0.93	Calculated from other variables
Develop varices	0.03	[237-239]
Develop HCC	0.03	[238, 240-243]
Develop other complications (inc. jaundice, ascites, HE)	0.02	[236-238]
Mortality (all-cause)	0.02	[237-239, 244, 245], expert opinion

Parameter/ Health state	Transition probability		References
BCLC Stage 0 and A HCC			
Cure (liver transplant)	0.36		[246]
Cure (non-transplant)	0.39		[246]
Mortality (all-cause)	0.25		[246]
BCLC stage B – D HCC			
Clinical stability (post TACE, RFA etc)	0.24		[247]
Mortality (all-cause)	0.76		[241]
Varices detection in surveillance programme			
Clinical stability	0.92		[248]
Liver transplant	0.01		Expert opinion
Mortality (all-cause)	0.07		[239]
Detection of varices after emergency presentation			
Clinical stability	0.73		[249]
Liver transplant	0.02		[248]
Mortality (all-cause)	0.25		[250]
Mild/ Moderate 'other' complication			
Clinical stability	0.74		[171]
Liver transplant	0.10		[248]
Mortality (all-cause)	0.16		[171]
Severe 'other' complication			
Clinical stability	0.45		[171]
Liver transplant	0.10		[248]
Mortality (all-cause)	0.45		[171]
Severity of CLD Complication	No screening	Screening	
Probability of BCLC stage 0 + A HCC	0.299	0.709	[251]
Probability of BCLC stage B - D HCC	0.701	0.291	[251]

Parameter/ Health state	Transition probability		References
Detecting varices in surveillance programme	0.0	0.60	[248]
Detecting varices after emergency presentation	100.0	0.40	[248]
Mild/ moderate CLD 'other' complication	0.527	0.622	[171, 252]
Severe CLD 'other' complication	0.473	0.378	[171, 252]

7.3.3 Cost data inputs

For the purposes of this model, a healthcare payer perspective was adopted. Published resources and local costing tariffs obtained from the Royal Free London NHS trust (census date for the study, February 2015) informed the model of healthcare costs (Table 7.3). A 3.5% discount rate was applied.

Direct healthcare costs were accounted for and included primary care consultations with GPs and subsequent investigations including blood tests and ultrasound scans. FIB-4 was costed at zero pounds (£0.00) as ALT, AST and platelet count were incorporated in the 'routine blood tests' tariff. The Camden and Islington CCG was charged £42 per ELF test for the NAFLD pathway, and so was used at this rate in the model, whilst fibroscan was priced at £43 [125]. For secondary care costings, the costs incurred related to consultations with a hospital specialist and subsequent investigations including further blood tests, imaging, and liver biopsy. The cost of HCC surveillance (6 monthly AFP and ultrasound) and variceal surveillance (2 - 3 yearly endoscopy) for patients with cirrhosis was incorporated into the model. The costs associated with the management of complications of CLD, including the cost of inpatient and outpatient episodes, pharmacological treatments and surgical procedures including liver resection and transplant were obtained from the Royal Free London NHS Foundation Trust finance department.

Table 7.3 Health care costs for patients with NAFLD/ NASH (£, 2014-2015)

Resource Use	Unit Cost	Reference
Primary Care		
GP consultation (per patient contact lasting 11.7 minutes)	£45.00	[253]
Secondary care		
Hepatology Consultant appointment (new)	£148.34	Royal Free, February 2015
Hepatology Consultant follow up appt	£98.63	Royal Free, February 2015
Dietician review	£57.00	Royal Free, February 2015
Investigations		
Routine blood tests (inc. FBC, LFT's, INR)	£68.06	Royal Free, February 2015
Liver aetiology panel	£147.98	Royal Free, February 2015
FIB-4 (AST/ALT/ platelets included in 'routine blood tests')	£0.00	Royal Free, February 2015
ELF	£42.00	North Middlesex Hospital, February 2015,
Ultrasound Liver	£63.67	Royal Free, February 2015
CT Abdomen/ Liver	£80.78	Royal Free, February 2015
MRI Abdomen/ Liver	£101.00	Royal Free, February 2015
Fibroscan	£43.00	Royal Free, February 2015
Liver biopsy	£642.75	Royal Free, February 2015
Endoscopy	£264.00	Royal Free, February 2015
Surgical procedures		
Liver resection	£7,000	[254]
Liver transplant (1st year)	£70,000	[125, 254, 255], Royal Free, February 2015

7.3.4 Standard care modelling

The current standard care (SC) was modelled based on the UK National Health Service (NHS) (scenario 1) (Figure 7.3). The standard care scenario involved consultations with a GP which would include a clinical history and physical examination followed by investigation including liver blood tests and tests for viral, immune, and metabolic causes of liver disease, as well as an ultrasound scan. The GP would use the information generated by these processes to assess the risk of advanced liver fibrosis or cirrhosis. This assessment was a binary outcome with cases deemed to be at 'high risk' of significant liver disease necessitating referral to a specialist, and cases deemed to be at 'low risk' appropriate for management in primary care. After consultation within the Camden and Islington Liver Working Group, this assessment process was deemed to need three primary care consultations, three routine bloods tests and one ultrasound scan for the typical patient.

The diagnostic performance of the primary care assessment for the presence of significant liver disease (Brunt ≥F3) has four outcomes (see Figure 7.3)

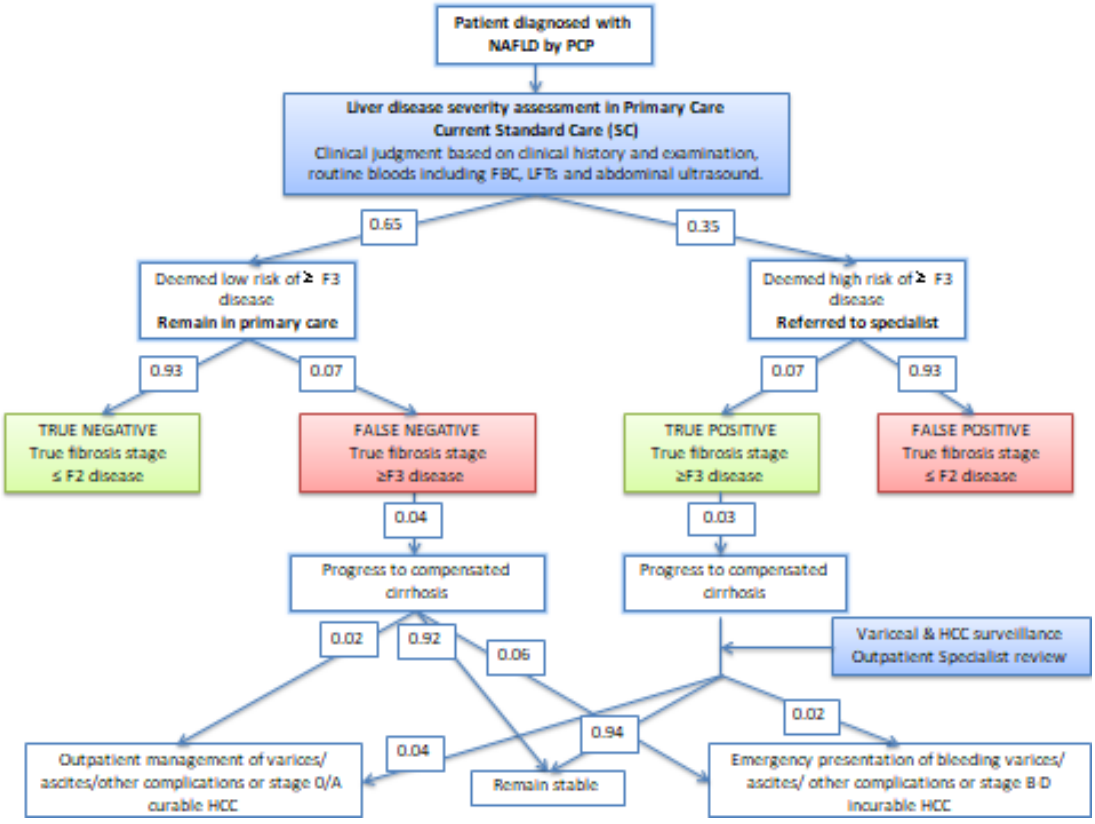
1. 'True positive'; Patients deemed to be at high risk for advanced fibrosis or cirrhosis (Brunt ≥F3 fibrosis) subsequently confirmed as having advanced fibrosis or cirrhosis after specialist assessment. Patients will be actively managed in secondary care (including consideration for clinical trials). Patients with cirrhosis will be enrolled in pathways of care that improve outcomes through targeted screening and treatment for portal hypertension and hepatocellular carcinoma (HCC).

2. ‘True negative’; Patients deemed to be at low risk for advanced fibrosis or cirrhosis (Brunt ≤ F2) found to have non-significant fibrosis. These patients are unlikely to suffer morbidity from their liver disease. Management in primary care should be focussed on managing reversible metabolic disorders.
3. ‘False positive’; Patients deemed to be at high risk for advanced fibrosis or cirrhosis in primary care but found to have non-significant fibrosis after specialist assessment. The referral can be considered inappropriate for this group of patients, whom can be managed effectively in primary care with weight loss and exercise.
4. ‘False negative’; Patients deemed to be at low risk for advanced fibrosis or cirrhosis who have advanced fibrosis or cirrhosis. This cohort of patients have been falsely reassured and represent a failure of the pathway as they remain in primary care unless they present with complications of CLD if their disease progresses, at which point interventions are increasingly limited.

Figure 7.3 Schematic simulating current 'standard care' journey of patient with NAFLD

Simplified simulated journey of a patient with NAFLD through the healthcare system after primary care assessment using standard care over a 1-year timeframe (see Table 7.1 and Table 7.2 for references)

Key: FBC – full blood count, HCC – hepatocellular cancer, LFT – liver function tests, PCP – primary care physician, SC: standard care



Patients deemed to be at high-risk of advanced fibrosis or cirrhosis were recommended for referral to a hospital specialist. Specialist re-assessment included further blood tests, fibroscan and further imaging including US scan (50% of cases, informed by local audit), CT scan (5% of cases, informed by local audit), MRI Liver (5%, informed by local audit) and liver biopsy (15% of cases, informed by local audit). After re-assessment, patients deemed to have an absence of advanced fibrosis or cirrhosis (false positive) would be discharged to primary care with lifestyle advice, whilst patients confirmed to have advanced fibrosis or cirrhosis would enter established surveillance pathways for complications of portal hypertension and HCC if indicated.

7.3.5 Competing strategies in the model and analyses

The model compared standard care (scenario 1) to scenarios employing non-invasive liver fibrosis tests. In scenario 2, FIB-4 and ELF was used in a two-tier stratification approach to replicate the Camden and Islington NAFLD pathway[203], as described in Chapter 6. Fibroscan is increasingly common-place in the hospital setting, and therefore in Scenario 3, FIB-4 and Fibroscan were used in a two-tier stratification approach. One-tier primary care strategies were tested by the model with standard care supported by ELF (scenario 4) or fibroscan alone (Scenario 5).

In all scenarios, standard care was delivered by GPs as described above. In scenarios 2 and 3, standard care assessment of liver fibrosis was supported by the calculation of a FIB-4 score in all patients to improve the identification of patients at risk of advanced fibrosis or cirrhosis (Brunt ≥ F3). Patients with

a FIB-4 score <1.30 were considered low risk of significant fibrosis and were managed in primary care whilst patients with a FIB-4 score > 3.25 were considered high risk for advanced fibrosis or cirrhosis and were recommended for referral to a hospital specialist. Patients with indeterminate FIB-4 scores between 1.30 and 3.25 required an ELF test (Scenario 2) or a community fibroscan (Scenario 3). Published cut-offs were used to identify cases at increased risk of advanced fibrosis or cirrhosis (≥10.51 for ELF and ≥7.9kPa for Fibroscan). A failure rate of 5% was incorporated into the model for patients undergoing fibroscan [161]. For patients managed in Scenarios 4 and 5, standard care was followed by ELF test for all patients or fibroscan for all patients respectively.

7.3.6 Study outcomes

The primary outcome measure was cost per case of advanced fibrosis or cirrhosis detected - a surrogate for cost utility.

Secondary outcomes included:

- Rates of unnecessary referral of patients with non-significant disease (Brunt ≤ F2 fibrosis),
- The severity of CLD complications,
- Rates of liver transplantation,
- Mortality rates.

7.4 Results

7.4.1 Clinical outcomes

The base case analysis (scenario 1, standard care) for 1000 patients with NAFLD over a 1-year timeframe revealed that 650 patients (65%) were identified as being at low risk of advanced fibrosis or cirrhosis and were triaged to remain in primary care. The model predicted 49 patients (8%) of the low-risk group had advanced fibrosis or cirrhosis but remained in primary care inappropriately (false negative rate). The remaining 350 patients (35%) were triaged as high risk of advanced fibrosis or cirrhosis and were referred to a specialist. After specialist reinvestigation, 93% (324 patients) of patients were determined to be at low risk (false positive rate) and discharged whilst 26 patients (7%) were confirmed to have advanced fibrosis or cirrhosis (true positive) and were managed long term in secondary care.

The impact of introducing non-invasive tests into primary care pathways using FIB-4, ELF and fibroscan, either in combination or alone was assessed. In Scenario 2, patients were risk stratified employing FIB-4 and ELF, whilst FIB-4 and TE was used in scenario 3, as compared to ELF alone in scenario 4 and TE alone in scenario 5 (see Table 7.4 and Figure 7.4). Compared to standard care, over the 1-year time-horizon, all the strategies employing non-invasive tests reduced the relative referral rate from primary care to a specialist by 70%, 67%, 56% and 43% for scenarios 2, 3, 4 and 5 respectively, equating to 245, 223, 198 and 150 fewer referrals annually per 1000 patients. Unsurprisingly, this had an onward impact on secondary care services, with a reduction in hospital investigations. For example, the number of patients requiring imaging

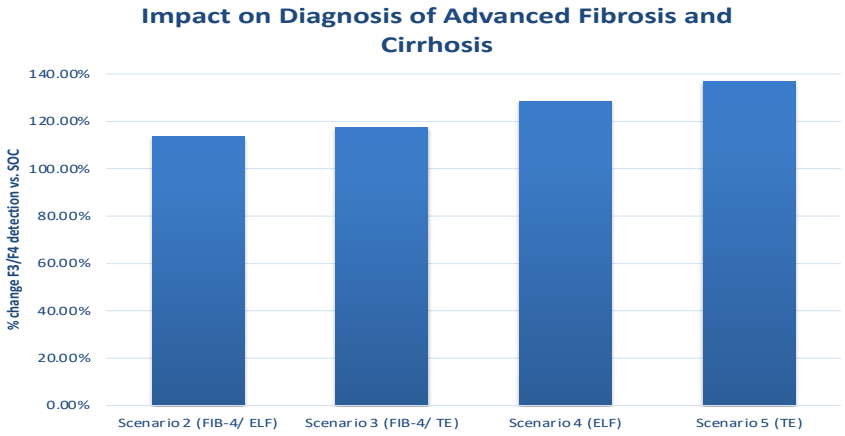
in secondary care reduced by 147, 134, 118 and 60 scans in scenarios 2, 3, 4, and 5 respectively, whilst the number of endoscopies performed was reduced by 25, 22, 20 and 10 procedures per 1000 patients after one year. The need for liver biopsy, a procedure associated with both risk and cost, was reduced by 37, 33, 30 and 15 patients in scenarios 2, 3, 4 and 5 respectively. Overall, there were significant cost savings related to secondary care investigation in the order of £165,530.04, £150,184.67, £133,505.60 and £68,256.85 for scenarios 2, 3, 4 and 5 respectively in the first year per 1000 patients with NAFLD.

All scenarios employing non-invasive liver fibrosis tests resulted in a reduction in the referral of patients with non-significant liver fibrosis (deemed “unnecessary” referrals) by 85%, 78%, 71% and 42% (absolute reduction) in scenarios 2, 3, 4, and 5 respectively compared to scenario 1, corresponding to 275, 253, 231 and 137 reduction in inappropriate referrals from 324 patients in scenario 1 over the 1-year time horizon.

Figure 7.4 Clinical impact of risk stratification in primary care

Impact of risk stratification pathways on detection of advanced fibrosis and cirrhosis (graph A), hospital referrals (graph B) and overall healthcare spend (graph C), for 1000 patients with NAFLD over 1 year compared to standard care.

A



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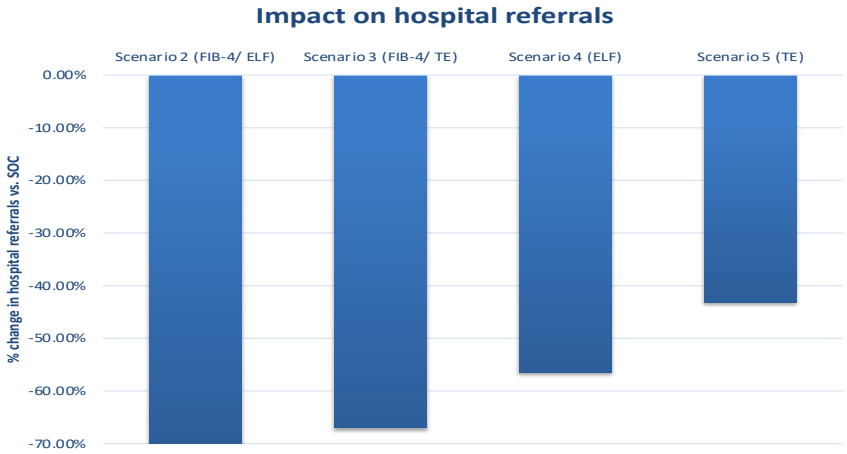

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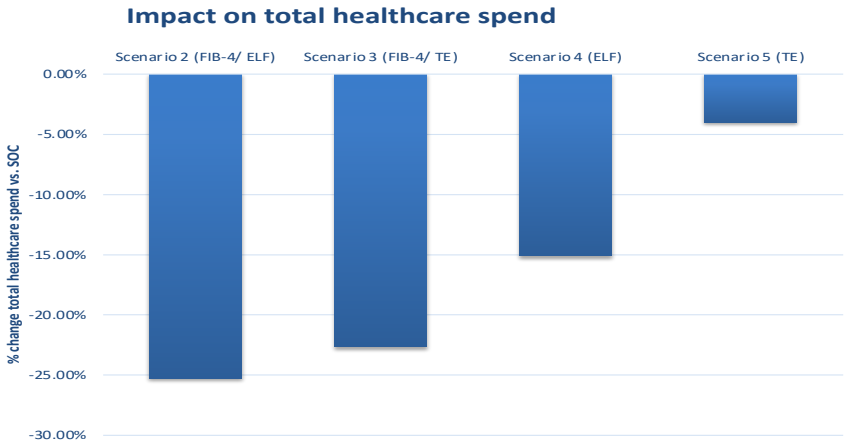


Table 7.4 Base case analysis of introducing non-invasive liver fibrosis markers in primary care pathways compared to standard care.

Tabulated analysis of the impact of non-invasive liver fibrosis tests for the management of patients with NAFLD (scenarios 2 – 5) compared to the standard care (scenario 1) in the primary care setting (scenario 1) after one year for 1000 patients with NAFLD.

	SCENARIO 2 - FIB-4/ELF	SCENARIO 3 - FIB-4/ TE	SCENARIO 4 - SC + ELF	SCENARIO 5 - SC + TE
PATHWAY PERFORMANCE: PATIENTS REFERRED TO SPECIALIST (SECONDARY CARE)				
Number of decreased referrals (stratified as ≥F3 fibrosis) vs SC (% decrease vs SC)	245 (70%)	222 (67%)	198 (56%)	101 (25%)
Number of increased True positive (≥F3 disease) correctly referred	30 (53%)	31 (45%)	34 (39%)	36 (25%)
Number of decreased False positive (≤F2 disease) incorrectly referred	275 (85%)	253 (78%)	231 (71%)	137 (42%)
Number of increased cirrhotics referred	1.16 (113%)	1.20 (116%)	1.31 (128%)	1.40 (136%)
PATHWAY PERFORMANCE: PATIENTS REMAIN UNDER PRIMARY CARE MANAGEMENT				
Number of patient stratified as ≤F2 fibrosis (Primary care management)	245 (38%)	222 (34%)	198 (30%)	101 (15%)
Number of patients correctly identified as ≤F2	274 (46%)	253 (42%)	231 (38%)	137 (23%)
Decrease in number of patients incorrectly identified as ≤F2	30 (61%)	31 (63%)	34 (69%)	36 (74%)
OVERALL PERFORMANCE OF PATHWAYS FOR DETECTION OF ADVANCED FIBROSIS AND CIRRHOSIS (≥F3 fibrosis)				
Sensitivity	0.75	0.76	0.80	0.83
Specificity	0.95	0.92	0.90	0.80
Positive Predictive Value	0.53	0.45	0.39	0.25
Negative Predictive Value	0.98	0.98	0.98	0.98
Positive Likelihood Ratio	14.11	9.96	8.00	4.10
Negative Likelihood ratio	0.27	0.26	0.22	0.21
IMPACT ON END STAGE LIVER DISEASE				
BCLC Stage 0/A curable HCC detected (% of all HCC)	0.06 (36%)	0.06 (38%)	0.07 (41%)	0.08 (44%)

	SCENARIO 2 - FIB-4/ELF	**SCENARIO 3 - FIB-4/ TE**	**SCENARIO 4 - SC + ELF**	**SCENARIO 5 - SC + TE**
BCLC Stage B-D incurable HCC detected (% of all HCC)	-0.06 (-29%)	-0.07 (-30%)	-0.07 (-33%)	-0.08 (-35%)
Varices detected via surveillance programme (% of all new varices)	0.02 (113%)	0.02 (117%)	0.02 (128%)	0.03 (136%)
Emergency presentation of varices (% of all new varices)	-0.02 (-30%)	-0.02 (-31%)	-0.02 (-34%)	-0.03 (-36%)
Mild/Moderate 'other' complications	<0.01 (6%)	<0.01 (6%)	<0.01 (7%)	<0.01 (7%)
Severe 'other' complication	<0.01 (-9%)	<0.01 (-9%)	<0.01 (-10%)	<0.01 (-10%)
Number of liver transplants (% of all cirrhotics known to specialist)	0.02 (32%)	0.02 (33%)	0.03 (36%)	0.03 (39%)
OUTCOMES				
Mortality / 1000 NAFLD patients	-0.03 (-0.34%)	-0.03 (-0.35%)	-0.04 (-0.39%)	-0.04 (-0.41%)

All scenarios were more effective compared to standard care to detect patients with advanced fibrosis or cirrhosis (Brunt ≥F3 fibrosis, true positive rate). Employing fibroscan alone in Scenario 5 proved to be the most effective strategy. Introducing non-invasive fibrosis tests improved the detection of patients with advanced fibrosis or cirrhosis by 30, 31, 34 and 36 patients per 1000 patients over 1 year in scenarios 2, 3, 4 and 5 respectively, equating to an 114%, 118%, 129% and 137% improvement.

Employing the use of non-invasive liver fibrosis tests in each scenario increased detection of patients with cirrhosis (Brunt F4) by 1 patient per 1000 population compared to standard care. To be more exact, an extra 1.2 (113%), 1.2 (116%), 1.3 (128%) and 1.4 (136%) cirrhotic patients per 1000 population were detected in scenarios 2, 3, 4 and 5 respectively over one year compared to SC.

The impact of diagnosing patients with advanced fibrosis or cirrhosis earlier on disease trajectory and subsequent development of complications related to chronic liver disease was evaluated (Table 7.4). Patients with liver cirrhosis known to healthcare services routinely undergo regular surveillance for complications including HCC and varices to identify them at earlier stages. The introduction of non-invasive fibrosis markers in the scenarios resulted in an increase in the number of patients presenting with curable HCC (Stage O/A) from a base case rate of 0.17 patients per 1000 population (standard care) by 0.06 patients per 1000 population in scenarios 2 and 3 and by 0.07 and 0.08 patients per 1000 population in scenarios 4 and 5 respectively. Crucially, over one year, the number of patients presenting with incurable HCC (stage B-D),

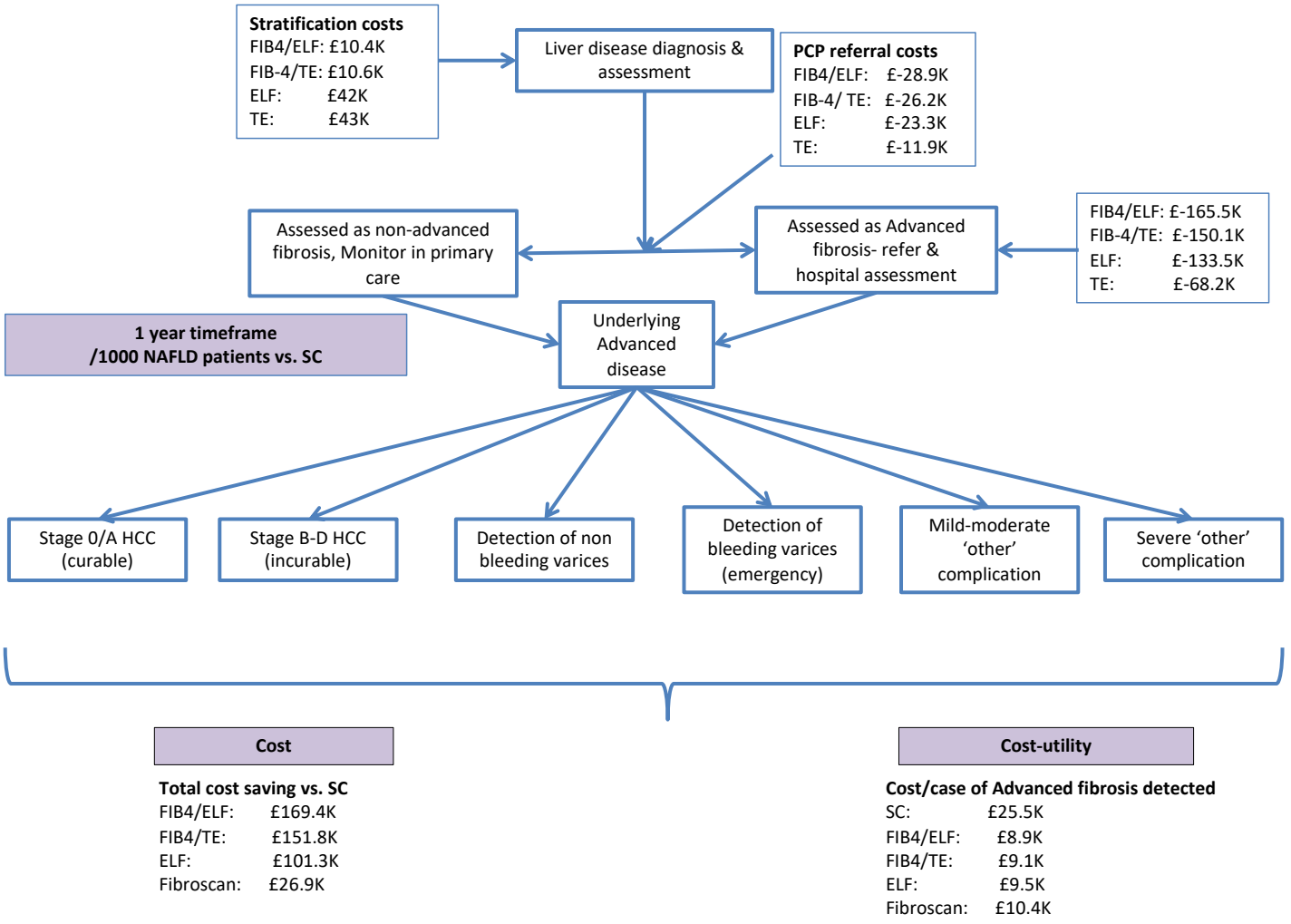
decreased from 0.22 patients per 1000 population in the standard care scenario by 29%, 30%, 33% and 35% for scenarios 2, 3,4 and 5 respectively. Similarly, the number of patients presenting with variceal haemorrhage reduced by 0.02 patients per 1000 population in scenarios 2, 3 and 4, and by 0.03 patients per 1000 population in scenario 5, compared to standard care (0.07 patients per 1000 population). Variceal detection facilitated by endoscopic surveillance prior to a haemorrhagic event increased from 0.02 patients per 1000 in scenario one by 0.02 patients per 1000 in scenarios 2, 3, 4 and 0.03 patients per 1000 in scenario 5. Earlier identification of varices permitted the commencement of primary prophylaxis of variceal haemorrhage [250]. The model also suggested that earlier detection of significant liver disease and earlier specialist involvement achieved a reduction in episodes of hospitalization due to other complications of CLD including jaundice, ascites and hepatic encephalopathy from 0.03 patients per 1000 in standard care by 0.01 patients per 1000 in all scenarios over one year.

The earlier detection of patients with liver cirrhosis allows implementation of surveillance strategies which aim to improve patient outcome. The model predicted that introducing non-invasive fibrosis markers in primary care pathways would result in an increase in the rates of liver transplantation by 0.02 patients per 1000 in scenarios 2 and 3 and 0.03 patients per 1000 in scenarios 4 and 5 compared to standard care (0.07 patients per 1000) over 1 year. Overall, all-cause mortality was lowered by 0.03 patients per 1000 in scenarios 2 and 3 and 0.04 patients per 1000 in scenarios 4 and 5 over 1 year compared to standard care (9.87 patients per 1000).

7.4.2 Cost outcomes

The cost to healthcare systems for employing standard care or the competing strategies employing non-invasive tests for 1000 patients with NAFLD are described in Figure 7.5 using a 1-year horizon. The costs directly associated with non-invasive liver fibrosis tests for 1000 patients with NAFLD were £10,385 in Scenario 2 (FIB-4 +/- ELF), £10,632 in scenario 3 (FIB-4 +/- fibroscan), £42,000 in scenario 4 (ELF) and £43,000 in scenario 5 (fibroscan). These estimates incorporated costs related to additional GP appointments, blood tests including ELF test and fibroscan.

Figure 7.5 Cost impact of risk stratification strategies in primary care compared to standard care (SC) over one year for 1000 patients.



The model estimated that costs attributable to the care of 1000 undifferentiated patients with NAFLD in the current standard care (scenario 1) was £670,504 over 1 year. The introduction of non-invasive fibrosis markers in patient pathways resulted in reductions in healthcare spending with £169,000, £152,000, £101,000, and £27,000 cost reductions per 1000 patients in 1 year in scenarios 2, 3, 4 and 5 respectively, which equated to reductions of 25%, 23%, 15% and 4%. Using cost-per-case of significant fibrosis as a surrogate for cost utility, all scenarios were favourable compared to standard care (£25,543.02), with the model predicting cost-per-case of significant fibrosis at £8.932.19, £9,083.78, £9,487.26, and £10,351.67 in scenarios 2, 3, 4 and 5 respectively over the 1-year timeframe.

A major contributor to the immediate cost saving observed was a reduction in secondary care referrals due to improved primary care triage. Compared to scenario 1 (£41,300 per 1000 patients over 1 year), cost-savings directly related to less referrals to secondary care were £28,895, £26,216, £23,305 and £11,915 in scenarios 2, 3, 4 and 5 respectively, equating to 70%, 63%, 56% and 29% reductions.

Table 7.5 summarises the impact of introducing non-invasive liver fibrosis tests in primary care for the base case.

Table 7.5 Summary of outcomes resulting from introducing non-invasive liver fibrosis tests in primary care (per 1000 NAFLD patients over 1 years)

	Scenario 1 Standard Care	Scenario 2 FIB 4 +/- ELF	Scenario 3 FIB 4 +/- TE	Scenario 4 ELF	Scenario 5 TE
Total Referrals avoided (vs. SC)	-	245	234	198	150
Cases F3/F4 detected	26.3	56.1	57.1	60.0	62.2
Cases Cirrhosis detected	5.3	11.0	11.2	11.8	12.3
Cases Cirrhosis missed	11.3	5.5	5.3	4.7	4.2
Cost saving (vs. SC)	-	- £169,408	- £151,816	- £101,268	- £26,889
Cost per ≥ F3 detected	£25,543	£8,932	£9,083	£9,487	£10,351

To evaluate the impact of introducing the interventions (non-invasive liver fibrosis tests in primary care pathways) nationally in the UK NHS system, a budget impact analysis was performed and is detailed in Table 7.6. Assuming a UK population of 60 million people with a prevalence of NAFLD of 20% (12 million people with NAFLD), and a 5-year cycle of disease assessment, 2.4 million people would be risk stratified annually nationwide. The incremental direct cost to the budget holder of introducing non-invasive fibrosis markers on a national scale would be £24.9M, £25.5M, £100.8M and £103.2M in scenarios 2, 3, 4 and 5 respectively. However, due to improved patient triage and earlier detection of significant liver disease, total healthcare budget savings equating to 23%, 21%, 14% and 4% were observed in scenarios 2, 3, 4 and 5 respectively.

Table 7.6 Budget impact analysis of introducing FIB-4, ELF and fibroscan into primary care risk stratification pathways compared to standard care for a population of 60 million patients on a 5-year cycle

	SCENARIO 2 - FIB-4/ELF	SCENARIO 3 - FIB-4/ TE	SCENARIO 4 - SC + ELF	SCENARIO 5 - SC + TE
PATHWAY PERFORMANCE:				
Number of decreased referrals (stratified as ≥F3 fibrosis) vs SC (% decrease vs SC)	587,700 (70%)	533,217 (67%)	474,000 (56%)	242,340 (25%)
Number of increased True positive (≥F3 disease) correctly referred	71,640 (53%)	74,041 (45%)	81,000 (39%)	86,220 (25%)
Number of decreased False positive (≤F2 disease) incorrectly referred	659,340 (85%)	607,258 (78%)	555,021 (71%)	328,560 (42%)
Number of increased cirrhotics referred	2,786 (113%)	2,880 (116%)	3,153 (128%)	3,359 (136%)
Number of decreased patients incorrectly identified as ≤F2 (false negatives)	71,640 (61%)	74,041 (63%)	81,000 (69%)	86,220 (74%)
IMPACT ON END STAGE LIVER DISEASE				
BCLC Stage 0/A curable HCC identified (% of all HCC)	121 (36%)	125 (38%)	137 (41%)	146 (44%)
BCLC Stage B-D incurable HCC (% of all HCC) identified	-121 (-29%)	-125 (-30%)	-137 (-33%)	-146 (-35%)
Varices detected via surveillance programme (% of all new varices)	50 (113%)	51 (117%)	57 (128%)	60 (136%)
Emergency presentation of varices (% of all new varices)	-50 (-30%)	-51 (-31%)	-57 (-34%)	-60 (-36%)
Mild/Moderate 'other' complications	5 (6%)	5 (6%)	6 (7%)	<6 (7%)
Severe 'other' complication requiring hospital admission	-5 (-9%)	-5 (-9%)	-6 (-10%)	-6 (-10%)
OUTCOMES				
Mortality reduction / 1000 NAFLD patients	67 (0.34%)	69 (0.35%)	76 (0.39%)	81 (0.41%)
BUDGET				
Cost of tests	£24.9M	£25.5M	£100.8M	£103.2M
Budget savings	£406M (23%)	£364M (21%)	£243M (14%)	£65M (4%)

7.4.3 Projected outcomes over a 5-year timeframe

To evaluate the longer-term impact of introducing non-invasive liver fibrosis tests in patient pathways, further analyses were performed with the timeframe extended to a five-year horizon (Table 7.7)

The model demonstrated ongoing clinical benefit five years after the introduction of non-invasive liver fibrosis tests. The detection of patients with liver cirrhosis increased by 107%, 111%, 123% and 132% in scenarios 2, 3, 4 and 5 respectively, which equated to an extra 5.69, 5.90, 6.48 and 6.95 cases per 1000 patients tested per year.

Applying a discount rate of 3.5%, over 5 years, incremental savings of £168,449.80, £142,752.51, £86.604.60, and £20,769.62 were made in scenarios 2, 3, 4, and 5 respectively per 1000 patients with NAFLD compared to standard care.

Table 7.7 Projected clinical outcomes and costs of the scenarios projected over 1 year and 5 years

	SCENARIO 1- SC		SCENARIO 2 - FIB-4/ELF		SCENARIO 3 - FIB-4/ TE		SCENARIO 4 - SC + ELF		SCENARIO 5 - SC + TE	
	1 year	5 years	1 year	5 years	1 year	5 years	1 Year	5 years	1 year	5 years
Total number of cirrhotics entered into specialist services (out of all cirrhotics)	1.03 (34%)	5.28 (32%)	2.19 (74%)	10.97 (66%)	2.23 (75%)	11.17 (68%)	2.34 (79%)	11.75 (71%)	2.43 (82%)	12.23 (74%)
Total number of cirrhotics not known to specialist services (out of all cirrhotics)	1.96 (66%)	11.278 (68%)	0.78 (26%)	5.53 (34%)	0.74 (25%)	5.41 (32%)	0.63 (21%)	4.73 (29%)	0.54 (18%)	4.24 (26%)
Early-stage complication (stage 0/A HCC, non-bleeding varices, mild ascites etc) (% of all complications) Cost	0.22 (42%) £3.0K	3.52 (39%) £31.1K	0.31 (57%) £4.1K	4.62 (52%) £41.2K	0.31 (58%) £4.1K	4.66 (52%) £41.5K	0.32 (60%) £4.3K	4.77 (54%) £42.6K	0.33 (61%) £4.3K	4.87 (55%) £43.4K
Late-stage complication (stage B-D HCC, bleeding varices, severe ascites etc) (% of all complications) Cost	0.32 (58%) £12.9K	5.44 (61%) £141K	0.23 (43%) £9.2K	4.3 (48%) £108K	0.23 (42%) 9.1K	4.26 (48%) £107K	0.22 (40%) £8.8K	4.14 (46%) £103K	0.21 (39%) £8.4K	4.05 (45%) £101K
Liver transplant Cost	0.07 £5.9K	1.05 £89.5K	0.10 £7.9K	1.16 £98.9K	0.10 £8.0K	1.16 £99.3K	0.10 £8.2K	1.17 100.2K	0.10 £8.3K	1.18 £101K
Mortality (%)	9.87 0.99%	28.56 2.86%	9.84 0.98%	28.18 2.82%	9.83 0.98%	28.17 2.82%	9.83 0.98%	28.13 2.81%	9.83 0.98%	28.10 2.81%
Total cost/1000 NAFLD patients	638K	1.1M	502K	946K	522K	971K	570K	1.0M	647K	1.1M
Cost/significant fibrotic detected	25.7K	49.9K	9.0K	19.4K	9.1K	19.4K	9.5K	19.5K	10.4K	20.5K

7.4.4 One way sensitivity analyses

One-way sensitivity analysis on the base-case scenario using a timeframe of 1 year were performed.

A pathway uptake sensitivity analysis was performed to test the impact of differing proportions of patients entering the pathway (0-100%) and confirmed a linear benefit proportional to pathway uptake. The analyses reinforced that any utilisation of the pathway (i.e. >0%) would deliver some benefit in all scenarios over the 1-year timeframe.

In the base-case model, the specificity of standard care was given a value of 0.65 (65% specificity for the detection of significant fibrosis). To counter the influence of this assumption, around which sparse data are published, a clinical effectiveness sensitivity analysis was performed by varying the specificity of standard care for the detection of significant fibrosis. The specificity was varied from 0.00 to 1.00, which had a significant influence on cost-benefit. The analyses demonstrated that the cost-benefit was only negated when the specificity of standard care for the detection of significant fibrosis exceeded 0.88, 0.86, 0.80 and 0.68 in scenarios 2, 3, 4 and 5 respectively.

7.5 Discussion

The cost consequence analyses described in this study indicate that the use of non-invasive liver fibrosis markers to stratify patients with NAFLD in primary care is both clinically effective and cost saving. Using fibroscan alone was most clinically effective in detecting patients with advanced fibrosis or cirrhosis, whilst employing FIB-4 with ELF for indeterminate cases, as per the Camden and Islington NAFLD pathway described in Chapter 6, delivered the greatest cost saving.

The introduction of non-invasive tests in primary care permitted the earlier identification of advanced fibrosis or cirrhosis in all the scenarios compared to standard care. This allows opportunities to modify fibrosis progression [172] and to enter patients into surveillance and treatment programmes for varices and hepatocellular cancer. The modelling indicated significant benefits could accrue from the detection of curable early-stage HCC (stage 0/ A) and non-bleeding varices that can be treated with beta-blockers and band ligation to avert emergency presentations with bleeding varices. A modest reduction in hospital admissions for other complications of CLD including jaundice, ascites and hepatic encephalopathy was demonstrated. It should be noted that overall, there was a relatively limited impact of the pathways on mortality. The reasons for this are likely to be multi-factorial. There were still cases of missed or late diagnosis of advanced fibrosis or cirrhosis, whilst the lack of impact on mortality highlights the urgent need for new approaches to diagnose NAFLD and steatohepatitis, and to identify therapeutic agents to modify NAFLD

disease trajectory and progression to a cirrhosis state and subsequent liver decompensation.

The introduction of non-invasive liver fibrosis tests in primary care pathways affords the opportunity to reduce the total number of referrals made to secondary care, and in particular the unnecessary referral of patients who have non-significant fibrosis. This is of particular interest to commissioners and those involved in managing over-stretched outpatient clinics. Over a 1-year horizon, there was a reduction in total referrals of 70%, 63%, 56% and 29% in scenarios 2, 3, 4 and 5 respectively, with an 85%, 78%, 71% and 42% reduction in referrals of patients with non-significant liver fibrosis. Real-world data from my pre-pathway study, described in Chapter 5, revealed that 66% of referred patients to specialist services for evaluation of NAFLD had a baseline FIB-4 score <1.30. This suggests that these patients had a low risk of significant fibrosis and could have avoided referral to a specialist [203]. Such cohorts of patients represents an inefficient use of resources, adding pressure to overstretched outpatient specialist services and healthcare budgets [256]. The use of non-invasive liver fibrosis markers in primary care pathways would deliver immediate reductions in referrals of patients with non-significant fibrosis, with associated reduction in expenditure, although the true cost-benefits associated with improved patient outcomes attributable to earlier diagnosis tend to accrue much later. Interestingly given its universal adoption in secondary care, fibroscan delivered the least benefit in terms of reduction of patients referred with non-significant fibrosis despite using a conservative failure rate.

The use of non-invasive liver fibrosis tests in all scenarios were cost saving. The cost of detecting a case of advanced fibrosis or cirrhosis using standard care was £49,917.83 in scenario 1. This compared to £19,360.75 in scenario 2, £19,448.49 in scenario 3, £19,487.75 in scenario 4 and £20,451.35 in scenario 5. There were reductions by 17%, 15%, 11% and 3% in total healthcare budget spends in scenarios 2, 3, 4 and 5 respectively. Much of this was attributable to a reduction in costs related to managing patients with end stage liver disease and more efficient resource utilisation. In the fibroscan only cohort (scenario 5), the decrease in healthcare spend was more modest as it was assumed all patients who failed fibroscan (5% of cohort) were referred to specialists.

The cost-utility analyses evaluated the Camden and Islington pathway described in Chapter 6 by exploring the impact of introducing FIB-4 and ELF for FIB-4 indeterminate cases in primary care. This combination of tests has previously been demonstrated as optimal for the stratification of patients in a hospital based population [223].

There are limitations to the model employed in this study. Whilst the model was populated with the best available published evidence, there is a dearth of high-quality data for several of the data inputs. This was remedied by using expert opinion but remains an inherent weakness. The diagnostic performance of the non-invasive liver fibrosis tests, namely FIB-4, ELF and fibroscan, were drawn from validation studies in hospital cohorts. These estimates may be inaccurate for a primary care population, where the prevalence of advanced fibrosis and cirrhosis is likely to be lower [257, 258]. Additionally, the model

assumes that the sequential use of ELF and fibroscan as second-tier tests has the same performance characteristics as when there are employed as a first-tier test. This may under-estimate their performance in the two-tier pathways and hence the overall performance of the pathway as using FIB-4 as a first-tier test is likely to enrich the 'indeterminate' population with patients with advanced fibrosis or cirrhosis and so improve diagnostic performance. This may explain why the performance of ELF in scenario 2 was 'better' than those reported in similar studies [128]. The model evaluated three non-invasive tests (FIB-4, ELF and fibroscan). The Liver Working Group outlined the practical need for simplicity in the tests used in primary care, giving FIB-4 an advantage over the NAFLD fibrosis score (NFS), which the primary care physicians consider to be more challenging to calculate accurately as it requires the inclusion of variables such as BMI, whilst there is continued variability in diagnosing diabetes amongst general practitioners. The model examines fibrosis, but not steatohepatitis, and so may underestimate disease progression in a sub-group of the cohort. Other sources of error include analytical performance. We assumed a 5% failure rate for fibroscan but higher rates have been reported [161], whilst serum tests including ELF test can be influenced by comorbidities. An inherent issue in modelling as described in this study is the use of liver biopsy as a reference test for liver fibrosis. Given the inaccuracies associated with liver biopsy [94], the use of liver biopsy as a reference standard can under-estimated the performance of non-invasive tests. The cost estimate of liver biopsy incorporated procedural elements but not those associated with complications of the procedure and so is likely to have underestimated the true cost associated with liver biopsy.

The outcomes predicted by the model for all the scenarios employing non-invasive liver fibrosis tests were highly favourable in terms of clinical- and cost-efficiency but may not reflect real-life outcomes. Not all patients with NAFLD consult their primary care provider, and pathway uptake by health professionals is variable and will not be 100 percent. The base case is a 50-year-old man with abnormal transaminases, reflecting the screening approach recommended by the Camden and Islington Liver Working Group as practical in real-life community practice. However, such a strategy will miss cases of patients with NAFLD and normal liver blood tests but have advanced fibrosis or cirrhosis. A screen-all strategy for all patients with NAFLD could be considered clinically optimal, as patients with NAFLD and normal transaminases are at risk of significant fibrosis but was beyond the scope of this study. The costing in the model is comprehensive, assuming full adherence to all guidelines and protocols and thereby potentially overestimating the cost of care. Adherence to cirrhosis surveillance programmes for variceal and hepatocellular carcinoma screening was assumed to be one hundred percent, which will not reflect real-life practice. Therefore, the clinical benefits of introducing the interventions are likely to be overstated.

The use of a probabilistic decision model could be justified as the main economic focus of this work was on the payer perspective. Focussing on a population health perspective may have made an alternative cost-effectiveness approach using quality of life data and Markov simulations desirable. Additionally, the absence of both beta or triangular distributions and

true probability sensitivity analysis limits the model. The lack of cost per quality adjusted life year (QALY) data meant that the model relies on descriptive measures including cost per case of significant fibrosis detected. These outcome measures have no standard comparator limiting the current model.

NAFLD is considered the hepatic manifestation of a multisystem metabolic disorder associated with morbidity beyond the liver including complications related to cardiovascular disease, diabetes, hyperlipidaemia, and cancer. The model we employed focussed on the liver related complications and accommodating all NAFLD associated morbidities, their evaluation and management was beyond the scope of this study.

The model used in this study has several strengths. The data used for clinical parameters, transition rates and costs resulted from a comprehensive literature review. The study adds to the current body of evidence and the conclusions are like those from other health economic analyses [125, 128, 259-263]. A Health Technology Assessment undertaken for the National Institute for Health Research [125] concluded that use of NIT was more cost-effective than liver biopsy in detecting cases of significant fibrosis. Tapper and colleagues [263] showed that introducing the NAFLD fibrosis score and fibroscan in primary care yielded cost-effective results. Robust data are lacking regarding the performance of GPs in the identification of patients with significant liver disease. Harman et al [87] have demonstrated the use of fibroscan in patients with risk factors for CLD, including diabetes, obesity and alcohol excess can increase detection of cirrhosis by 140%, like the modelling

results in scenario 5 (132%). Our group has evaluated the pathway employing FIB-4 and ELF (Scenario 2) as described in Chapter 6.

7.6 Conclusion

This cost comparison analysis study showed that the introduction of non-invasive liver fibrosis tests in primary care increased the detection of cases of NAFLD with advanced fibrosis or cirrhosis, whilst reducing unnecessary referrals to secondary care of patients at low risk of liver disease and to deliver immediate and sustained cost savings. Given the similarity between the effectiveness modelled in this study and the real-world effectiveness reported in our evaluation of the Camden and Islington NAFLD pathway (Chapter 6), we conclude that the cost-effectiveness modelled in this work is likely to be replicated through clinical application of the pathway.

The model provides compelling evidence for clinicians, commissioners, and policy makers to consider the formal introduction of non-invasive liver fibrosis testing in primary care, in line with other central policy statements [6, 225, 264].

7.7 Publication

The contents of this chapter have been published after peer-review [265]. The citation is:

Srivastava A, Jong S, Gola A, Gailer R, Morgan S, Sennett K, Tanwar S, Pizzo E, O'Beirne J, Tsochatzis E *et al*: **Cost-comparison analysis of FIB-4, ELF and fibroscan in community pathways for non-alcoholic fatty liver disease**. *BMC Gastroenterol* 2019, **19**(1):122.

CHAPTER 8 DISCUSSION

8.1 Overview

The burden that chronic liver disease imposes on society and the healthcare system is increasing exponentially. Better patient outcomes are likely to arise from the development and validation of primary care pathways employing non-invasive liver fibrosis markers with the potential to identify significant liver disease at earlier stages. The aim of this thesis was to establish evidence of the need for these primary care pathways and to develop and evaluate a novel primary care NAFLD pathway delivered in North Central London. In this chapter, I will summarise the main findings of my work, outline a case for change in clinical practice and discuss future research directions.

8.2 Statement of key findings

8.2.1 Review of the current evidence base

In Chapter 3, a review of the literature revealed a limited number of published studies evaluating the performance of non-invasive liver fibrosis tests in the primary care setting. In total, ten relevant studies were identified. They were heterogeneous in the populations they targeted, the non-invasive tests used and the study outcomes measured, limiting generalisability to daily clinical practice. The employed strategies ranged from the untargeted screening of the 'healthy' population using fibroscan or fibrotest to screening for fibrosis in patients with risk factors for chronic liver disease. Examples included using MRE in patients with diabetes [197] or using BARD score, AST:ALT ratio and elastography in patients with alcohol excess, diabetes or raised

aminotransferases [87]. The literature review identified only one study in patients with NAFLD – where the use of fibrotest identified significant liver disease in 13.1% of the patients [195]. The identified studies were not free of bias, but despite the paucity and heterogeneity of published studies, thematic analysis did highlight early promise regarding the benefits of using non-invasive fibrosis tests in the community to promote early detection of patients with significant liver fibrosis.

8.2.2 Exploring the opinions and practices of UK clinicians

The dearth of published evidence contrasted with a growing consensus amongst clinicians and experts that use of non-invasive liver fibrosis tests in the community had an important role in future strategies to improve outcomes associated with chronic liver disease. To address and assess this inconsistency, I conducted a national survey of clinicians in the UK to explore current attitudes to liver fibrosis assessment (LFA) and the use of, and access to, non-invasive liver fibrosis tests. Conducted in 2015 and described in Chapter 4, the national survey identified themes pertinent to the core of this thesis. Liver fibrosis assessment was considered an integral component of the evaluation of a patient with liver disease. Importantly, there was a recognition that clinical assessment, liver blood tests and ultrasound, which form the backbone of current standard care fibrosis assessment, were valuable to identify decompensated cirrhosis, but had little role in detecting earlier stages of significant liver disease or in distinguishing between fibrosis stages. Only a quarter of UK specialists reported having adequate access to non-invasive liver fibrosis tests at the time of the survey. Common barriers included difficulty

in engaging commissioners, difficulty in accessing and commissioning technology (especially for ELF and fibroscan) and the cost of patented technology. Despite this, the study identified twenty-one pathways and eleven different strategies employing non-invasive liver fibrosis tests. Seven strategies were community based, of which five focussed on patients with NAFLD. The strategies could be broadly grouped into a three-by-three matrix with pathways using blood-based or physical tests of liver fibrosis or both, in primary care, secondary care or both (see Table 4.3, Chapter 4).

This national survey captured the increasing recognition amongst decision-makers that the use of non-invasive liver fibrosis tests in primary care pathways was a critical intervention to promote earlier detection of advanced liver disease and to improve patient outcomes.

8.2.3 Exploring the performance of standard care to identify patients with advanced fibrosis or cirrhosis in primary care

To further consolidate the case for change, I evaluated the efficacy of standard care pathways used in primary care to identify advanced fibrosis or cirrhosis in patients with NAFLD. Described in Chapter 5, this retrospective study of primary care referrals conducted in 2012-2013 demonstrated that over ninety percent of those patients referred to hospital had non- significant fibrosis (Brunt ≤ F2) when reassessed by liver specialists. This group of patients could have avoided referral to hospital, and therefore were unnecessarily burdened in terms of wasted time, anxiety generated and potential harm from investigations. This ineffective triage of patients for referral represents

noteworthy inefficiency in the use of overstretched healthcare resources. The unnecessary referrals are costly for national health systems, both in terms of the cost of appointments and investigations, but also the cost in terms of the distraction from focus on patients with advanced fibrosis or cirrhosis. Patients with significant liver fibrosis were falsely reassured and progressed silently in the community, until they present with complications of chronic liver disease.

To investigate the potential role of non-invasive liver fibrosis tests to improve patient selection for referral, I retrospectively applied FIB-4 to this cohort of patients. The analysis revealed over two thirds of patients referred had a low-risk FIB-4 score (<1.30) and could have avoided referral using this simple, effective and cheap indirect marker of liver fibrosis alone. A quarter of patients with indeterminate FIB-4 (1.30 – 3.25) had significant liver fibrosis suggesting patients in this subgroup warrant further evaluation to identify those with advanced liver disease rather than watchful monitoring alone.

This study provided strong evidence that standard care triage in primary care was inefficient in identifying patients with significant liver disease. Additionally, the sub-analyses clearly demonstrated that non-invasive liver fibrosis tests could serve to improve patient identification for referral.

8.2.4 Evaluating a primary care pathway for patients with NAFLD using non-invasive liver fibrosis tests

After establishing a strong case for change in primary care triage for patients with NAFLD, I evaluated the Camden and Islington NAFLD pathway – a novel

pathway introduced in 2013 for patients with NAFLD that uses FIB-4 and ELF to identify patients with advanced fibrosis or cirrhosis (Brunt≥ F3 fibrosis).

Described in Chapter 6, the Camden and Islington NAFLD pathway processed nearly 1500 patients over two years. Service evaluation demonstrated a reduction in the proportion of patients with NAFLD being referred to secondary care, highlighting the ability of the pathway to function at scale and manage the rising prevalence of NAFLD. The NAFLD pathway, when compared to standard care, resulted in a 5-fold increase in the referral of patients with advanced fibrosis (Brunt F3) and a three-fold increase in the detection of patients with liver cirrhosis (Brunt F4). There was an 81 percent decrease in referrals of patients with milder degrees of liver fibrosis (Brunt ≤ F2).

This service evaluation of the NAFLD pathway provided strong evidence that the introduction of non-invasive liver fibrosis tests in a primary care pathway improved the selection of patients with advanced fibrosis or cirrhosis for referral to secondary care, and reduced referrals of patients with milder disease.

8.2.5 Cost comparison analysis of non-invasive tests in community patient pathways

Building on the outcomes from the Camden and Islington NAFLD pathway evaluation, working with health economists, I developed a probabilistic decision analytical model to assess the clinical utility and cost utility of introducing competing pathways employing non-invasive liver fibrosis markers in primary care for patients with NAFLD (Chapter 7). The model evaluated FIB-

4, ELF and fibroscan, either alone or in combination, and the cost utility of the Camden and Islington NAFLD pathway was explored. The cost consequence analyses demonstrated that the use of non-invasive liver fibrosis markers to stratify patients with NAFLD in primary care was both clinically effective and cost saving. Utilizing fibroscan alone was most effective in detecting patients with advanced fibrosis, whilst employing FIB-4 and ELF, as per the Camden and Islington NAFLD pathway, delivered the greatest cost saving. All the scenarios facilitated the earlier detection of patients with advanced fibrosis or cirrhosis, allowing opportunities to modify fibrosis progression and enter surveillance programmes [172, 230]. The model reinforced the likelihood that significant benefits could be obtained from the detection of early-stage curable HCC and detection of non-bleeding varices. The model also demonstrated all scenarios were cost saving compared to standard care.

8.3 Strengths and limitations of thesis

8.3.1 Strengths

The major strength of this thesis is the systematic approach taken to the evaluation of the use of non-invasive liver fibrosis markers in primary care patient pathways to promote earlier detection of significant liver disease. The thesis was carefully structured to evaluate the existing literature, establish a case for change, and then to evaluate a novel primary care pathway employing non-invasive tests designed by an expert working group after a thorough review of the alternatives. After a systematic review of the literature revealed a lack of published evidence, the initial emphasis was to build a ‘case for change’. A far-reaching national survey of UK specialists aimed to gather the

opinions of frontline UK physicians regarding this topic. It reinforced the view that non-invasive liver fibrosis markers had an important role in future initiatives to improve detection of significant liver disease. It revealed a widespread recognition of the need for better strategies for detecting liver disease, identified barriers to change and a wide diversity of opinion about the optimal strategy, with respect to both location and method of stratification,

To further consolidate the ‘case for change’, I explored the performance of standard care in stratifying patients for significant liver fibrosis. The existing evidence base provides evidence of the late detection of liver disease and includes retrospective reviews of national databases which have shown patients present late in their disease course [5]. I designed a study specifically evaluating the efficacy of primary care referrals to identify patients with significant liver fibrosis. No similar studies could be identified through an extensive literature search and discussion with experts in the field.

The design, implementation and evaluation of a novel primary care pathway employing FIB-4 and ELF for patients with NAFLD in the London boroughs of Camden and Islington provided the backbone of the thesis. The formation of a multidisciplinary liver working group and collaboration between appropriate stakeholders including patient representatives, general practitioners, hepatologists, commissioners, and public health specialists ensured wide representation and contribution to the pathway. A strong desire to improve the poor outcomes associated with liver disease in the London Boroughs of Camden and Islington [211] motivated the group to embrace newer innovations as well as established interventions. The willingness to embrace

local clinical expertise through the regional liver unit (Royal Free London) and local academic expertise through University College London permitted a structured and scientific approach. A readiness to involve public health specialists, statisticians, quantitative researchers, and health economists strengthened the scientific integrity of the liver working group. A robust scientific critique of the literature, in conjunction with consultation with patients and peer-review by national experts, led to the design of the Camden and Islington NAFLD pathway and ensured incorporation of the perspectives of patients and the public. The engagement, cooperation and commitment of the hospital and CCG data analytic departments to provide reliable, reproducible, and secure data were critical to the evaluation. The result of this multi-disciplinary effort was the prospective evaluation of over 3000 patients with NAFLD based in primary care; a cohort I believe to be the largest of its kind in the published literature. The design of the study, a before- and after- cohort, was comprehensive and has delivered outcomes that have influenced clinical practice and clinical guidelines (described in section 8.4 below).

8.3.2 Limitations

There are limitations to the work that has been presented in this thesis.

With regard to the national survey, despite extensive efforts made to achieve a high response rate, such as using national society circulation lists, only a tenth of invitees responded. This relatively low response rate can bias the results as non-responders may hold views that differ from those who have responded.

When considering the baseline assessment of standard care, and evaluation of the Camden and Islington NAFLD pathway, the limitations mostly stem from the nature of the methodology used, namely the evaluation of a health service innovation. It was not possible to conduct a randomized controlled trial once the GPs and public health professionals had formally expressed 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 [225]. The evaluation lacked a hard validated outcome measure of liver fibrosis. Liver biopsy was deemed impractical and unethical in the context of evaluating patients outside of a formal clinical trial. An alternative surrogate - a composite clinical judgement – was developed and used instead but remains to be validated. Given the study was a service evaluation, the outcomes reflect real-world practice, and there was an inevitable degree of selection bias in the patients undergoing liver biopsy.

Similarly, the true and false negative rates for the pathway could not be determined without evaluation of the prevalence of fibrosis amongst patients deemed to be low risk of advanced fibrosis who were not referred or assessed in secondary care.

The cost comparison model developed in this thesis was comprehensive. Whilst it was populated with data from the published literature, a lack of high-quality data for several of the data inputs remained an inherent weakness. The diagnostic performance of the non-invasive liver fibrosis tests was derived from validation studies performed in secondary care settings. Using these performance estimates for a primary care population, where the prevalence of

advanced fibrosis and cirrhosis is likely to be lower [257, 258] may lead to inaccuracies. The outcomes predicted by the model for all the scenarios employing non-invasive liver fibrosis tests were highly favourable in terms of clinical- and cost- efficiency but may not reflect real-life outcomes. The model assumed one hundred percent uptake of the pathway by both the GP and subsequently by the patients. Not all patients consulting their GP will be managed by the pathway. For example, in the Camden and Islington pathway evaluation (Chapter 6), over 2 years, 46.2% (152/329) of the referrals from Camden and Islington CCG GPs were for patients on the pathway, whilst the remaining referrals did not adhere to the pathway and were referred via standard care. In future it is likely that GPs will not use the pathway for all NAFLD referrals, despite measures instituted to encourage them to do so, such as declining referrals that do not follow the pathway and workshops and publications to disseminate the pathway. Furthermore, not all patients entered into the pathway by their GP will continue through to full diagnosis. In the pathway evaluation, only 55.3% (152/275) of patients deemed to be high risk of advanced fibrosis or cirrhosis attended specialist review. This means that the clinical and cost benefits of the pathway are likely to be overstated. It was beyond the remit of the model to explore non-compliance from clinicians and patients, but this could be considered for a future piece of work.

8.4 Implications for practice

I believe the work presented in this thesis has contributed to the field of the study of the role of non-invasive liver fibrosis test in primary care, particularly in NAFLD. There is a clear consensus amongst healthcare professionals that

promoting earlier detection of significant liver disease (equivalent to Brunt ≥F3) is a key strategy to improve outcomes. The work in this thesis has demonstrated and concluded that the current standard care is inefficient, resulting in unnecessary referrals of patients with non-significant disease and non-referral of patients with advanced fibrosis or cirrhosis. An evaluation of a novel NAFLD pathway, and a probabilistic health utility model, have both shown that that the introduction of non-invasive liver fibrosis tests in primary care has the potential to increase the detection of cases of NAFLD with advanced fibrosis or cirrhosis, reduce unnecessary referrals to of patients with non-significant fibrosis and deliver immediate and sustained significant cost savings.

In parallel to the work described in this thesis, a number of guidelines have been published that advocate the use of non-invasive tests for fibrosis stratification, including the NICE NAFLD guidelines [225], the NICE Cirrhosis assessment guidelines [266], the British Society of Gastroenterology guidelines on the management of abnormal liver function tests [264] and the EASL guidelines on non-invasive fibrosis tests [98]. A member of the Camden and Islington liver working group, Dr Karen Sennet (GP), was a member of the BSG committee which developed the abnormal liver blood test guidelines [264]. These guidelines, which had early access to unpublished data from the Camden and Islington NAFLD pathway, recommended the routine fibrosis assessment of patients with NAFLD in primary care using combinations of FIB-4, NFS, ELF and fibroscan depending on local resources.

8.5 Future work and research

The work presented in this thesis forms part of an increasing programme of work evaluating the utility of non-invasive markers in patient pathways. In this section, I describe future work, not only related to ongoing research into the biomarkers of disease but also work to translate the findings of this research into clinical practice.

There is a growing consensus that strategies evaluated in this thesis form an important role in improving outcomes for patients with liver disease. We evaluated a pathway employing FIB-4 and ELF. However, a number of other technologies and pathways are being considered. Whilst the number of evidence-based effective interventions currently available for patients with chronic liver disease is limited, many more are emerging. There is also considerable interest in repurposing licensed drugs (such as treatments available for diabetes), behavioural interventions (such as brief advice) and public health measures (such as minimum unit pricing of alcohol and “sugar taxation”). These approaches to the treatment and prevention of CLD strengthen the already strong case for earlier detection of liver fibrosis. The critical questions that remain to be answered can be considered in the context of the PICO format.

Patients and populations

Who should be tested in order to detect liver fibrosis earlier? The national survey of practice in Chapter 4 revealed two different approaches to early detection of liver fibrosis; namely targeting patients with abnormal

aminotransferase results or targeting people at risk of CLD due to their behaviour or phenotype. Although there is abundant evidence to show that abnormal aminotransferase results are neither sensitive nor specific for liver fibrosis, their use as a first marker of liver disease is so widespread and entrenched in clinical practice that there is a requirement for pathways to handle patients found to have “abnormal LFTs.” Strategies based on testing for liver fibrosis require research to determine their effectiveness and cost-effectiveness. Research is needed to compare these two approaches to early detection of liver fibrosis.

What methods for diagnosis should be used for early detection of liver fibrosis?

Although this thesis has presented abundant evidence about the performance of diagnostic tests for liver fibrosis in the primary care setting, there remains a lack of evidence about the comparative effectiveness and cost-effectiveness of blood based and elastography-based methods for detecting liver fibrosis. Furthermore, the optimal combination of non-invasive tests and the setting in which they are applied remains uncertain. Blood-based tests have considerable advantages over physical fibrosis tests in that they can be combined, automated and standardised. Physical methods deliver instant results, providing the opportunity to engage patients in behaviour change. Research is needed to determine the optimum combination of NIT in the primary care setting.

What outcome is required?

One of the key challenges to determining the optimal strategy for early detection of liver fibrosis is the outcome measure or reference standard against which to judge the interventions. It would be desirable to assess interventions against the delivery of improvements in clinical endpoints including reductions in morbidity and mortality. However, given the nature of CLD, it often takes many years and even decades before these endpoints are reached and thus cannot be captured within the span of most funded studies. An alternative approach is to define the development of cirrhosis as a surrogate endpoint for clinical outcomes. However, determining the presence of cirrhosis is not straightforward. The use of liver biopsy, the established "reference standard" test for the diagnosis of cirrhosis, would not be acceptable in a primary care based diagnostic evaluation of non-invasive liver fibrosis tests, where both test-positive and test-negative participants would need to be assessed with the reference test. An alternative approach is to use surrogate markers of cirrhosis as outcome measures or to use composite clinical judgement in order to identify participants with or without cirrhosis. The latter approach is gaining increasing acceptance and was used in the Camden and Islington NAFLD pathway evaluation presented in Chapter 6.

Adoption and diffusion:

It is apparent that there are now a number of non-invasive tests of liver fibrosis in widespread use and there is a reasonable evidence base for their effectiveness and cost effectiveness. Their use is recommended in guidelines

and yet the work presented in the national survey (Chapter 4) reveals that they are not in widespread use. Undoubtedly there has been a failure of adoption and diffusion representing a need for research into the barriers to effective use of the existing tests.

A quantitative multi-centre evaluation of the uptake, clinical impact and resource use of different pathways nationally is attractive. Data collection focussing on pathway uptake (patients entering a pathway as a proportion of all those eligible), healthcare activity (secondary care referrals), detection of advanced fibrosis or cirrhosis, detection of clinically important disease (hepatocellular cancer, varices), healthcare provider experience (general practitioners and hospital specialists) and patient experience (health related quality of life measures) would help inform future strategies both nationally and internationally. Such an approach would permit the development of a national cohort of patients with NAFLD. This would allow longer term follow up and assessment of the impact on liver related morbidity and all-cause mortality, potentially using a central NHS database. The long-term follow up of a NAFLD cohort which has undergone fibrosis stratification is of considerable importance to determine the true disease burden, natural history and outcomes associated with the pathways and their interventions. This will permit evaluation of the impact of specific pathways on the incidence of liver related events and provide further definitive assessment of the clinical effectiveness of the pathways. Furthermore, such an approach would allow to compare the incidence of liver related events and extrahepatic complications of NAFLD and assess the impact of the pathways in influencing long term morbidity and

mortality. Ultimately, comparing different pathways will allow synthesis of the available evidence and recommendations on case identification strategies in the community.

Beyond patients with NAFLD, an important group of patients who are at risk of chronic liver disease are those who drink alcohol to excess. Extending the work performed in this thesis to patients in this category will form an important part of any future strategies to improve outcomes for patients with chronic liver disease.

One important aspect of any strategy is improving patient awareness of liver disease and its causes. There is limited awareness of liver disease in the general public, and limited awareness of risk beyond excessive alcohol consumption. The risk of liver disease related to diabetes and obesity is under-appreciated by the general public. Given the increasing incidence of these risk factors, and the likely continued increase prevalence of chronic liver disease, it is important to improve public knowledge and to reduce the stigma attached to liver disease. This will improve awareness amongst patients with NAFLD, who can then seek appropriate review in primary care and disease assessment and fibrosis risk stratification.

8.6 Concluding remarks

Chronic liver disease is the fifth commonest cause of death in the UK and the only one that is rising in incidence. Approximately a third of the population is at risk of chronic liver disease and a significant proportion present with end stage liver disease, when outcomes are poorer. Earlier detection of significant

liver disease is a key strategy to improve patient outcomes. Liver biopsy has been considered the ‘reference standard’ for fibrosis assessment, but is impractical at large scale, whilst standard liver blood tests are ineffective to identify significant liver disease reliably.

The work in this thesis has demonstrated that using non-invasive liver fibrosis markers in primary care is both clinically effective and cost efficient. This strategy permits the earlier detection of patients with clinically significant disease and reduces the number of referrals of patients with non-significant fibrosis. The data from this thesis provides compelling evidence for clinicians, commissioners and policy makers to consider the formal introduction of non-invasive liver fibrosis testing in primary care, in line with other central policy statements [6, 225, 264].

APPENDICES

Appendix 1 Publications from this thesis

Chapter 6

Srivastava A, Gailer R, Morgan S, Sennet K, Warner A, Tanwar S, Trembling P, Hogan B, Parkes J, O'Beirne J, Patch D, Thorburn D, Tsochatzis E, Rosenberg W. Prospective evaluation of a primary care referral pathway for patients with non-alcoholic fatty liver disease. Journal of Hepatology 2019, 71: 371 – 378

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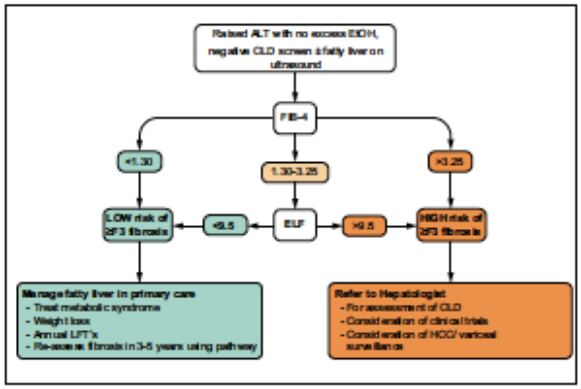
Research Article
Genetic and Metabolic Diseases

JOURNAL
OF HEPATOLOGY

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

Graphical abstract



Highlights

- Established blood tests can be used in primary care to stratify patients with fatty liver disease.
- A 2-step pathway (FIB-4 followed by ELF™ if required) reduced unnecessary referrals by 80%.
- This pathway also improved the detection of cases of advanced fibrosis 5-fold and cirrhosis 3-fold.
- This pathway can be used in primary care to identify patients who might benefit from referral to liver specialists.
- This should reduce unnecessary referrals while at the same time improving the detection of cirrhosis.

Authors

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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, leading to a reduction in unnecessary referrals by 80% and greatly improving the detection of cases of advanced fibrosis and cirrhosis.

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

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Background & Aims: The development of non-invasive liver fibrosis tests may enable earlier identification of patients with non-alcoholic fatty liver disease (NAFLD) requiring referral to secondary care. We developed and evaluated a pathway for the management of patients with NAFLD, aimed at improving the detection of cases of advanced fibrosis and cirrhosis, and avoiding unnecessary referrals.

Methods: This was a prospective longitudinal cohort study, with analyses performed before and after introduction of the pathway, and comparisons made to unexposed controls. We used a 2-step algorithm combining the use of Fibrosis-4 score 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 (odds ratio [OR] 5.18; 95% CI 2.97–9.04; p <0.0001), while reducing unnecessary referrals from primary care to secondary care by 81% (OR 0.193; 95% CI 0.111–0.337; p <0.0001). Although it was used for only 48% of referrals, significant benefits were observed in practices exposed to the pathway compared to those which were not, with unnecessary referrals falling by 77% (OR 0.23; 95% CI 0.658–0.082; p = 0.006) and a 4-fold improvement in detection of cases of advanced fibrosis and cirrhosis (OR 4.32; 95% CI 1.52–12.25; p = 0.006). Compared to referrals made before the 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 0.042–0.349; p <0.0001).

Conclusions: The use of non-invasive blood tests for liver fibrosis improves the detection of advanced fibrosis and cirrhosis, while reducing unnecessary referrals in patients with NAFLD. 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, leading to a reduction in unnecessary referrals by 80% and greatly improving the detection of cases of advanced fibrosis and cirrhosis.

Keywords: FIB-4; ELF; Steatohepatitis; Non-invasive fibrosis test; Cirrhosis; Cost effectiveness; Clinical management; NAFLD.
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Introduction

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] with 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 interven-

tions 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 complications of cirrhosis, 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 chronic liver disease.[12]

Whilst there is little evidence supporting the application of non-invasive tests in community settings, with only 1 study focusing on patients with NAFLD,[13] guidelines recommend a 2-tier approach to detect the presence of advanced fibrosis in NAFLD using either Fibrosis-4 (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, enhanced liver fibrosis (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 2 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 (CCGs) of the London boroughs of Camden and Islington (C&I), between April 2013 and March 2014, before being 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 supplementary information. 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 2 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 2 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 individuals aged 18 and over attending their GP with a new or established diagnosis of NAFLD were eligible for entry. For purposes of the pathway, 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 2-step non-invasive test assessment, starting with the calculation of the FIB-4 score (Fig. 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.

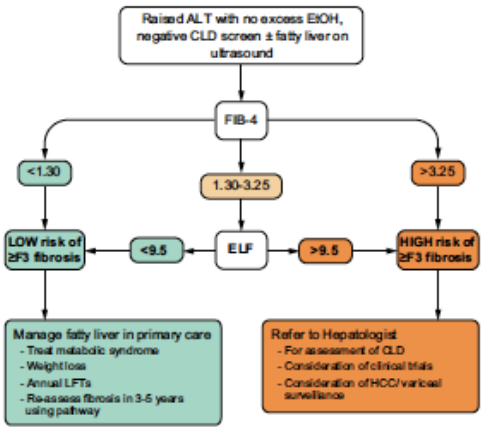

Fig. 1. The Camden and Islington NAFLD pathway. CLD, chronic liver disease; ELF, enhanced liver fibrosis; EtOH, ethanol; FIB-4, Fibrosis-4; HCC, hepatocellular carcinoma; LFTs, liver function tests; NAFLD, non-alcoholic fatty liver disease. (This figure appears in colour on the web.)

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 blinded 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, performed independently of the use of the pathway. A subset of 35/152 patients, referred from C&I and 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 (Table S1).

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 2 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 (ORs) for differences in outcomes for patients managed in accordance with the pathway and those managed using standard care were calculated, along with 95% CIs 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 study 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 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) than patients managed by standard care. There were no significant differences in Q-Risk2 score, glycated haemoglobin, aminotransferases, platelet counts or high-density lipoprotein. 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 patients with NAFLD 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, considering 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% (165/1,506).

Comparison of the distribution of FIB-4 scores of patients referred for NAFLD by C&I GPs before and after the introduction of the NAFLD pathway revealed no evidence of bias in patient selection (Table S2).

Over 2 years, 1,452 patients were risk-stratified for the presence of advanced fibrosis using FIB-4 (Fig. 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.

Table 1. Patient demographics.

	Standard care	Pathway patients	p value	Camden and Islington pathway split by FIB-4			p value (<1.30 vs. >1.30)
				FIB-4 <1.30	FIB-4 1.30–3.25	FIB-4 >3.25	
	n = 1,560	n = 1,452		1,022 (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 ± SD (n)	30.5 ± 7.1 (1,082)	30.4 ± 5.9 (1,238)	n.s.	30.4 ± 5.6	30.7 ± 6.3	27.3 ± 5.7	n.s.
T2DM, n(%)	237/1,126 (21.0%)	344/1245 (27.6%)	<0.001	190/846 (22.5%)	141/364 (38.7%)	13/35 (37.1%)	<0.001
HbA1c, mmol/mol (mean ± SD)	42 12.8 (585)	42.5 ± 13.35 (1,059)	n.s.	42.3 ± 13.6 (769)	43.4 ± 13.4 (267)	41.4 ± 15.2 (23)	n.s.
Hypertension, n(%)	371/ 1,124 (33.0%)	521/1,248 (41.7%)	<0.001	256/ 849 (31.3%)	234/364 (64.2%)	21/35 (60.0%)	<0.001
Hyperlipidaemia, n(%)	95/650 (14.6%)	168/1,248 (13.5%)	<0.001	96/ 849 (11.3%)	64/364 (7.5%)	8/35 (22.8%)	<0.001
Total cholesterol, mmol/L (mean ± SD)	4.9 ± 1.1 (602)	4.8 ± 1.1 (1,084)	0.03	4.8 ± 1.1 (792)	4.6 ± 1.2 (267)	4.8 ± 1.1 (25)	0.02
HDL, mmol/L (mean ± SD)	1.3 ± 0.4 (602)	1.3 ± 0.4 (1,084)	n.s.	1.3 ± 0.4 (792)	1.4 ± 0.4 (267)	1.3 ± 0.4 (25)	0.006
IHD, n(%)	49/1,127 (3.9%)	84/1,248 (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 ± SD)	43.0 ± 36.5 (1,096)	45.1 ± 36.5 (1,254)	n.s.	45.3 ± 29.5	42.8 ± 27.4	59.5 ± 39.2	n.s.
AST, IU/L (mean ± SD)	33.7 ± 22.1 (704)	33.7 ± 22.6 (1,206)	n.s.	29.4 ± 17.3	37.8 ± 23.9	70.2 ± 52.1	<0.001
Bilirubin, mmol/L (mean ± SD)	8.9 ± 5.9 (1,094)	8.9 ± 5.7 (1,250)	n.s.	8.6 ± 5.2	9.2 ± 5.1	14.2 ± 13.3	0.02
Albumin, g/L (mean ± SD)	45.3 ± 5.9 (1,101)	45.3 ± 3.1 (1,249)	n.s.	45.7 ± 2.7	44.8 ± 3.6	42.4 ± 6.4	<0.001
Ferritin, ng/ml (mean ± SD)	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 ± SD)	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 ± SD)	260.4 ± 70.1 (1,092)	255.1 ± 65.8 (1,254)	n.s.	271.4 ± 61.5	226.4 ± 56.6	159.0 ± 65.8	<0.001

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FIB-4, Fibrosis-4 score; HbA1c, glycated haemoglobin; HDL, high density lipoprotein; IHD, ischaemic heart disease; INR, international normalized ratio; T2DM, type II diabetes mellitus. p values were calculated using t-test for normally distributed variables and Chi squared tests for categorical variables.

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 (Fig. 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 LFTs, 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 whom 6 were cirrhotic) and 38 due to the combination of FIB-4 and ELF (Fig. 4).

Referrals made using the NAFLD pathway compared to standard care during the evaluation period

Comparisons were made between 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 1 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 information).

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

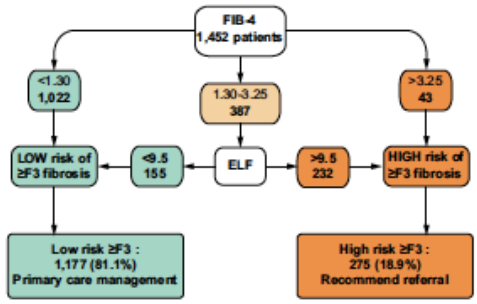

Fig. 2. Primary care risk stratification using the Camden and Islington NAFLD pathway 2014–2016. ELF, enhanced liver fibrosis; FIB-4, Fibrosis-4; NAFLD, non-alcoholic fatty liver disease. (This figure appears in colour on the web.)

NAFLD cases, rather than comparing the absolute numbers of cases referred and detected per year.

In the year prior to pathway introduction, 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 of 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 improving the 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

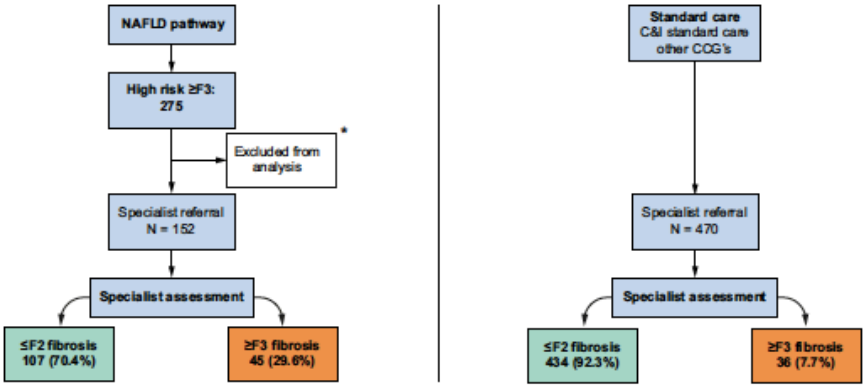

Fig. 3. Liver specialists' evaluation of referrals to secondary care of NAFLD cases in the evaluation period 2014–2016. CCG, clinical commissioning group; NAFLD, non-alcoholic fatty liver disease. (This figure appears in colour on the web.)

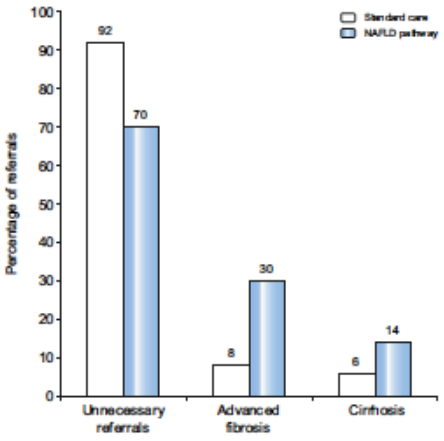

Fig. 4. Evaluation of patients referred to secondary care from Camden and Islington 2014–2016. NAFLD, non-alcoholic fatty liver disease.

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 on 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 of between 5–15%, 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

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

ELF, enhanced liver fibrosis.

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 CCGs	C&I pathway	C&I standard care	All C&I	Other CCGstandard 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
F4%	3.6	3.7	3.6	14.5	5.6	9.7	5.1	5.3	7.5	19.4

C&I, Camden and Islington; CCG, clinical commissioning group; FIB-4, Fibrosis-4 score; NAFLD, non-alcoholic fatty liver disease.

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	p value	OR	95% CI	p value	OR	95% CI	p value
C&I pathway	C&I before	88	75–96	0.0001	8.30	2.87–24.05	0.0001	4.51	1.31–15.56	0.017
C&I pathway	C&I standard care	80	61–89	<0.0001	4.90	2.56–9.36	<0.0001	2.83	1.29–6.18	0.0092
C&I pathway	Other CCGs	81	66–89	<0.0001	5.18	2.97–9.04	<0.0001	3.14	1.57–6.24	0.0011
All of C&I	Other CCGs	77	35–92	0.006	4.32	1.52–12.25	0.006	2.87	0.86–9.62	0.0871

C&I, Camden and Islington; CCG, clinical commissioning group; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio. Odds Ratios were calculated for the "Intervention" groups compared to the listed "Comparator" groups.

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 recommendations would have improved the positive predictive value of the NAFLD pathway for detection of advanced fibrosis at the expense of an 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, with only a modest increase in the total 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 C&I 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 improving patient experiences by avoiding unnecessary clinic appointments and investigations. This is the first study to incorporate the British Society for Gastroenterology guidance on the management of NAFLD and validates the recommendation to use FIB-4 and ELF for 2-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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Conflict of interest

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.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

AS data collection, study design, primary authorship; RG data collection, study design; ST study concept, critical revision of manuscript for important intellectual content; PT study concept, critical revision of manuscript for important intellectual content; JP data analysis, critical revision of manuscript for important intellectual content; AR critical revision of manuscript for important intellectual content; DS data collection;

DT study concept, critical revision of manuscript for important intellectual content; KS study concept, critical revision of manuscript for important intellectual content; SM study concept, critical revision of manuscript for important intellectual content; EAT study concept and design, critical revision of manuscript for important intellectual content; WR study concept and design, critical revision of manuscript for important intellectual content. All authors approved the final version of the manuscript before submission.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.03.033.

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Chapter 7

Srivastava A, Jong S, Gola A, Gailer R, Morgan S, Sennet K, Fenlon L, Tanwar S, Parkes J, O'Beirne J, Thorburn D, Tsochatzis E, Rosenberg W. Cost-comparison analysis of FIB-4, Enhanced Liver Fibrosis Panel and Fibroscan in the primary care risk stratification of non-alcoholic fatty liver disease. BMC Gastroenterology 2019, 19: 122

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RESEARCH ARTICLE Open Access

Cost-comparison analysis of FIB-4, ELF and fibroscan in community pathways for non-alcoholic fatty liver disease

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Abstract

Background: The identification of patients with advanced liver fibrosis secondary to non-alcoholic fatty liver disease (NAFLD) remains challenging. Using non-invasive liver fibrosis tests (NILT) in primary care may permit earlier detection of patients with clinically significant disease for specialist review, and reduce unnecessary referral of patients with mild disease. We constructed an analytical model to assess the clinical and cost differentials of such strategies.

Methods: A probabilistic decisional model simulated a cohort of 1000 NAFLD patients over 1 year from a healthcare payer perspective. Simulations compared standard care (SC) (scenario 1) to: Scenario 2: FIB-4 for all patients followed by Enhanced Liver Fibrosis (ELF) test for patients with indeterminate FIB-4 results; Scenario 3: FIB-4 followed by fibroscan for indeterminate FIB-4; Scenario 4: ELF alone; and Scenario 5: fibroscan alone. Model estimates were derived from the published literature. The primary outcome was cost per case of advanced fibrosis detected.

Results: Introduction of NILT increased detection of advanced fibrosis over 1 year by 114, 118, 129 and 137% compared to SC in scenarios 2, 3, 4 and 5 respectively with reduction in unnecessary referrals by 85, 78, 71 and 42% respectively.
The cost per case of advanced fibrosis (METAVIR ≥F3) detected was £25,543, £8932, £9083, £9487 and £10,351 in scenarios 1, 2, 3, 4 and 5 respectively. Total budget spend was reduced by 25.2, 22.7, 15.1 and 4.0% in Scenarios 2, 3, 4 and 5 compared to £670 K at baseline.

Conclusion: Our analyses suggest that the use of NILT in primary care can increases early detection of advanced liver fibrosis and reduce unnecessary referral of patients with mild disease and is cost efficient. Adopting a two-tier approach improves resource utilization.

Keywords: Enhanced Liver fibrosis (ELF), Fibroscan, |NAFLD, Cirrhosis detection, Cost savings

Background

The health, societal and economic burden of chronic liver disease (CLD) is substantial and represents a public health priority [1, 2]. CLD is the 5th commonest cause of death in the United Kingdom, and the only one in the top five that is increasing [3]. With rising prevalence of risk factors for liver disease including obesity and alcohol, pressure on healthcare resources is likely to intensify. Better and earlier detection of CLD in primary care is key to improving health outcomes and associated costs [4].

Non alcoholic fatty liver disease (NAFLD) is the commonest cause of deranged liver function tests (LFTs) in primary care [5]. Only a minority (5%) of these cases progresses to clinically significant liver disease [6] whilst evidence highlights fibrosis severity as the key determinant of liver related morbidity and mortality [7, 8]. The identification of patients with significant liver disease is a primary care challenge, where accurate fibrosis assessment is

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limited by a reliance on LFTs, which are poor discriminators of liver fibrosis [9].

In the current 'standard care' (SC), primary care physicians (PCP) assess the severity of a patient's liver disease and subsequent need for specialist referral based on history, examination, blood tests including LFTs and ultrasound.

Patients referred to secondary care deemed to have significant liver disease due to NAFLD may benefit from active management (including consideration for clinical trials of emerging therapies for NAFLD and fibrosis) [2, 10]. Patients with cirrhosis will be enrolled in pathways of care that improve outcomes through targeted screening and treatment for complications of cirrhosis including portal hypertension [11] and hepatocellular carcinoma (HCC) [12]. However, current primary care approaches result in the referral of many patients that do not have significant liver fibrosis, placing a burden on secondary care services, incurring unwarranted costs and generating unnecessary inconvenience and anxiety for patients [13]. Furthermore a significant number of patients with advanced liver fibrosis are missed and not referred to secondary care. These patients have been falsely reassured and will silently progress before presenting with end-stage liver disease or liver cancer.

The use of non-invasive liver fibrosis tests (NILT) [14] may improve PCP staging of disease [4, 15] and referral practice but there is a lack of health-economic evidence about the use of NILT in fatty liver disease to inform clinicians, commissioners and policy makers about the value of such strategies. In this study, we developed a probabilistic decision analytical model to investigate the clinical and cost impact of primary care risk stratification of patients with NAFLD.

Methods

A liver working group, comprising primary care physicians and secondary care liver specialists, commissioners, public health practitioners and patient representatives was formed in the London Boroughs of Camden and Islington to develop new pathways of care for patients with NAFLD. Part of the strategy was to establish current practice (standard care (SC)) (Fig. 1) and to establish pragmatic guidance on how to improve the identification of NAFLD cases with advanced liver disease for referral to secondary care. In the first instance, PCP favoured the selection of patients with deranged liver function tests (LFT) even though it was agreed that this would miss a minority of cases with liver fibrosis who have normal LFTs.

Probabilistic decision model

A probabilistic decision analytical simulation model was created using Microsoft Excel Software (version16.23, 2019). The model piloted competing primary care risk stratification diagnostic strategies for 1000 patients with a confirmed diagnosis of NAFLD (Fig. 2). The average patient was 50 years old with elevated transaminases. The cycle length was 1 year.

Competing Strategies in the Model and Analyses

We modelled the standard care in the UK National Health Service (NHS) (scenario 1). The use of FIB-4 and ELF in a two-tier stratification approach (scenario 2) was modelled to replicate a local pilot pathway - the Camden and Islington NAFLD pathway [13]. Following an independent evaluation of NILT public health consultants favoured the use of FIB-4 over the NAFLD Fibrosis Score, in part due to a lack of standardization in the diagnosis of diabetes. Fibroscan is increasingly established in secondary care practice, and was incorporated to assess its performance in place of ELF in a two-tier strategy (Scenario 3). One-tier approaches were also considered in which SC was supported by ELF (scenario 4), or fibroscan alone (Scenario 5).

In all scenarios SC delivered by PCPs included history, physical assessment followed by investigation of liver function, tests for viral, immune and metabolic causes of liver disease and an ultrasound scan in order to make an assessment of the risk of advanced liver fibrosis. This was classified as a binary outcome with the case deemed to be at 'high risk' of advanced liver disease necessitating referral to a specialist, or at 'low risk' and thus appropriate for management in primary care. This decision process required 3 PCP consultations, 3 routine bloods tests and 1 ultrasound scan. In scenarios 2 and 3, SC was supported by the calculation of a FIB-4 score in all patients to improve the identification of patients at risk of advanced fibrosis (METAVIR $\geq$ F3). Low risk patients (FIB-4 < 1.30) were managed in primary care whilst high-risk patients (FIB-4 > 3.25) were referred to a specialist in secondary care. Patients with indeterminate scores (FIB-4 1.30–3.25) required an ELF test (Scenario 2) or a community fibroscan (Scenario 3). Published cut-offs were used to identify cases at increased risk of advanced fibrosis ($\geq$10.3 for ELF and $\geq$ 7.9 kPa for Fibroscan). A fibroscan failure rate of 5% was assumed [47]. For patients managed in Scenario 4, SC was followed by ELF test for all patients and in Scenario 5 SC was followed by fibroscan for all patients.

Patients identified as being at high-risk of advanced fibrosis were referred to a secondary care specialist. Evaluation included further blood tests, fibroscan, imaging including US scan (50% of cases, informed by local audit), CT scan (5% of cases, informed by local audit), MRI Liver (5%, informed by local audit) and liver biopsy (15% of cases, informed by local audit). Patients deemed to not have advanced fibrosis (false positive) would be discharged to primary care, whilst those confirmed with advanced fibrosis would enter recognised surveillance pathways.

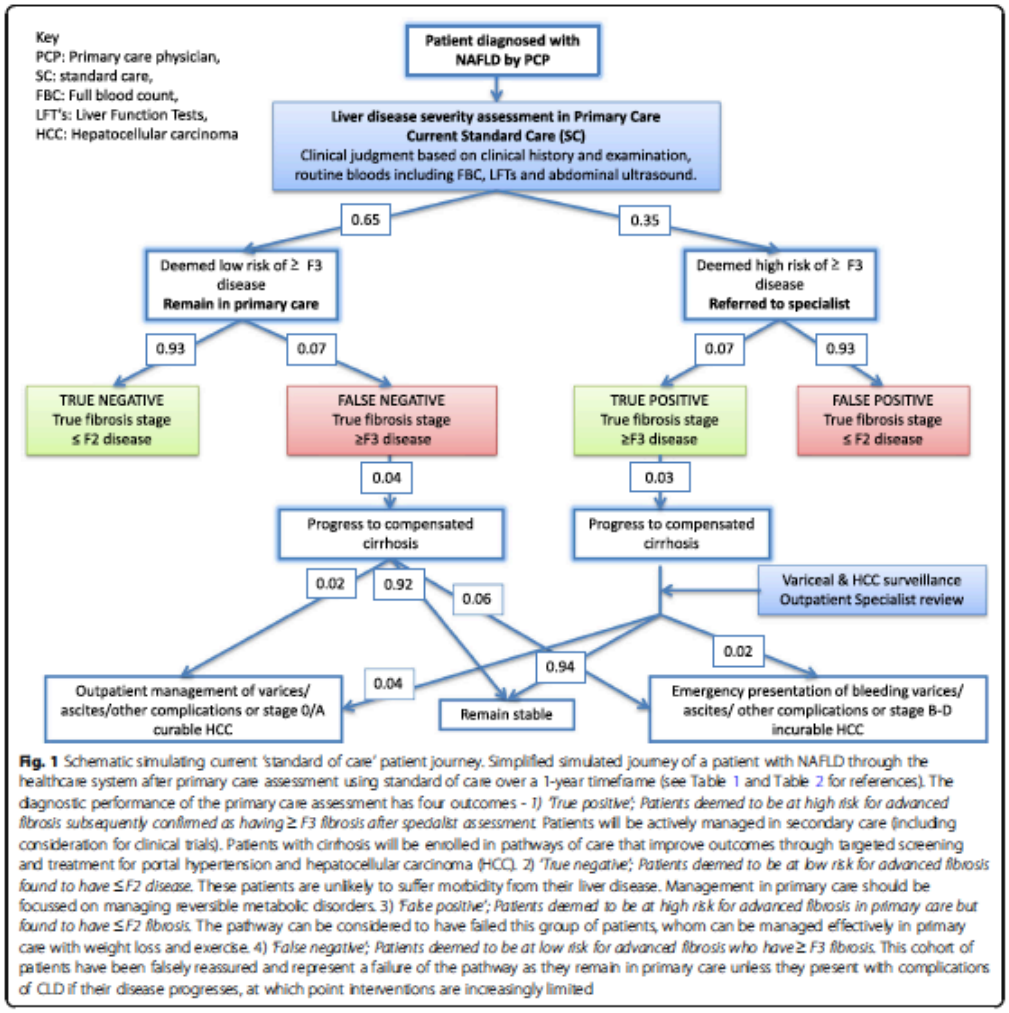

Fig. 1 Schematic simulating current 'standard of care' patient journey. Simplified simulated journey of a patient with NAFLD through the healthcare system after primary care assessment using standard of care over a 1-year timeframe (see Table 1 and Table 2 for references). The diagnostic performance of the primary care assessment has four outcomes - *1) 'True positive'; Patients deemed to be at high risk for advanced fibrosis subsequently confirmed as having ≥ F3 fibrosis after specialist assessment.* Patients will be actively managed in secondary care (including consideration for clinical trials). Patients with cirrhosis will be enrolled in pathways of care that improve outcomes through targeted screening and treatment for portal hypertension and hepatocellular carcinoma (HCC). *2) 'True negative'; Patients deemed to be at low risk for advanced fibrosis found to have ≤F2 disease.* These patients are unlikely to suffer morbidity from their liver disease. Management in primary care should be focussed on managing reversible metabolic disorders. *3) 'False positive'; Patients deemed to be at high risk for advanced fibrosis in primary care but found to have ≤F2 fibrosis.* The pathway can be considered to have failed this group of patients, whom can be managed effectively in primary care with weight loss and exercise. *4) 'False negative'; Patients deemed to be at low risk for advanced fibrosis who have ≥ F3 fibrosis.* This cohort of patients have been falsely reassured and represent a failure of the pathway as they remain in primary care unless they present with complications of CLD if their disease progresses, at which point interventions are increasingly limited

The time horizon for the base-case was 1 year to assess short-term benefits, likely to relate to resource utilisation. A 5- year timeframe was applied to assess the longer-term implications.

Clinical data inputs

A comprehensive literature search informed model parameters. The data were critically assessed to ensure suitability for this study and were supplemented by expert opinion when required.

The model assumed an intention-to-diagnose strategy. All patients would be managed according to the pathways. SC performance is poorly documented, but estimates were extrapolated from available studies [13, 16, 17]. Advanced fibrosis (≥F3 fibrosis) prevalence was set at 7.5% [5] and published sensitivities and specificities of FIB-4 [18, 19], ELF [19, 20] and fibroscan [19, 21] were used to predict stratification rates for low- and high- risk of advanced fibrosis (Table 1 and Fig. 3). Estimates of NAFLD disease progression were used to inform pathway performance (Table 2).

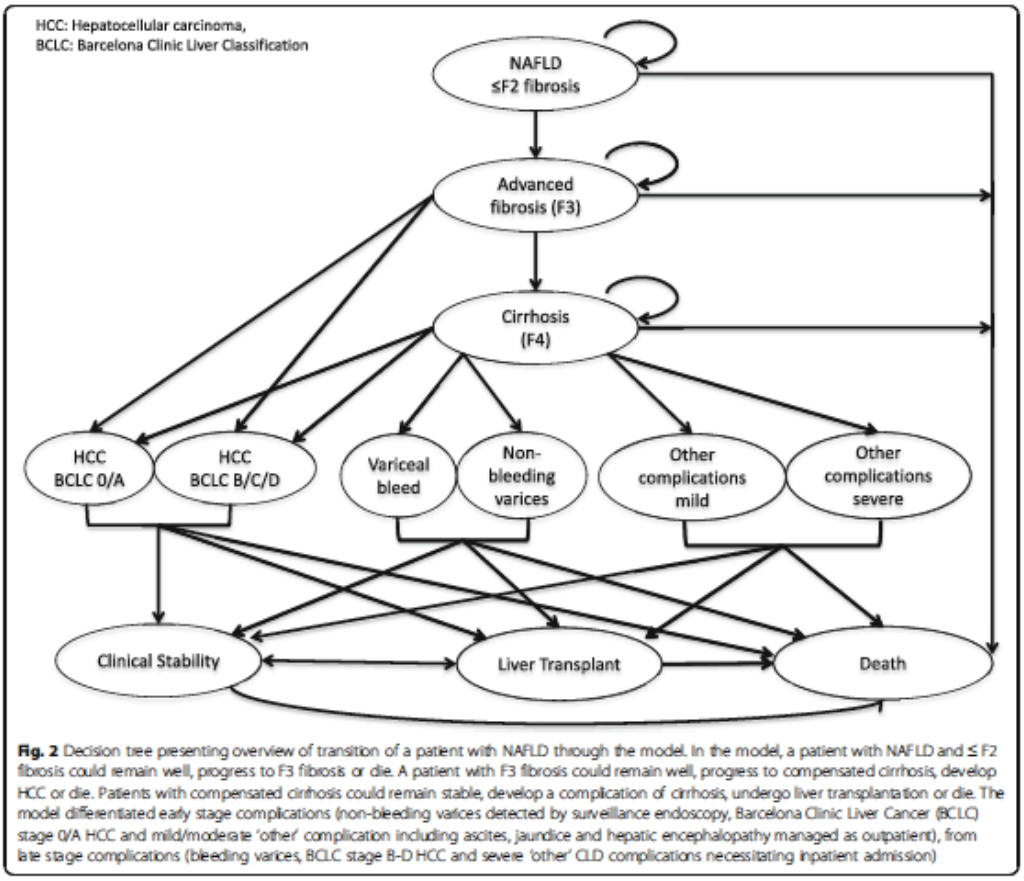

Fig. 2 Decision tree presenting overview of transition of a patient with NAFLD through the model. In the model, a patient with NAFLD and ≤ F2 fibrosis could remain well, progress to F3 fibrosis or die. A patient with F3 fibrosis could remain well, progress to compensated cirrhosis, develop HCC or die. Patients with compensated cirrhosis could remain stable, develop a complication of cirrhosis, undergo liver transplantation or die. The model differentiated early stage complications (non-bleeding varices detected by surveillance endoscopy, Barcelona Clinic Liver Cancer (BCLC) stage 0/A HCC and mild/moderate 'other' complication including ascites, jaundice and hepatic encephalopathy managed as outpatient), from late stage complications (bleeding varices, BCLC stage B-D HCC and severe 'other' CLD complications necessitating inpatient admission)

Cost data inputs

A healthcare payer perspective was adopted. Costs were derived from published resources and local costing tariffs (February 2015) (Table 3) for the UK. A 3.5% discount rate was applied. Direct healthcare costs included PCP consultations, blood tests and ultrasound scans. The cost of FIB-4 was considered to be £0, as ALT, AST and platelet tests were incorporated as 'routine blood tests'. ELF was priced at £42, the quoted rate charged to the Camden and Islington CCG in their pathway, and fibroscan was priced at £43 [19]. In secondary care, the costs incurred related to specialist consultations, investigations including liver biopsy

Table 1 Test performance and Disease prevalence estimates

Test characteristics	Sensitivity	Specificity	Reference
Standard of care	0.35	0.65	Expert Opinion [16, 17]
FIB-4 (cut off 1.30)	0.84	0.74	[18, 19]
FIB-4 (cut off 3.25)	0.38	0.97	[18, 19]
ELF	0.80	0.90	[19, 20]
Fibroscan	0.82	0.84	[19, 21]
Population and disease characteristics	Transition probability		
Prevalence of advanced fibrosis in the general population	0.075		[5]

Published test characteristics of non-invasive liver fibrosis tests to detect advanced fibrosis (METAVIR ≥F3) in patients with non-alcoholic fatty liver disease

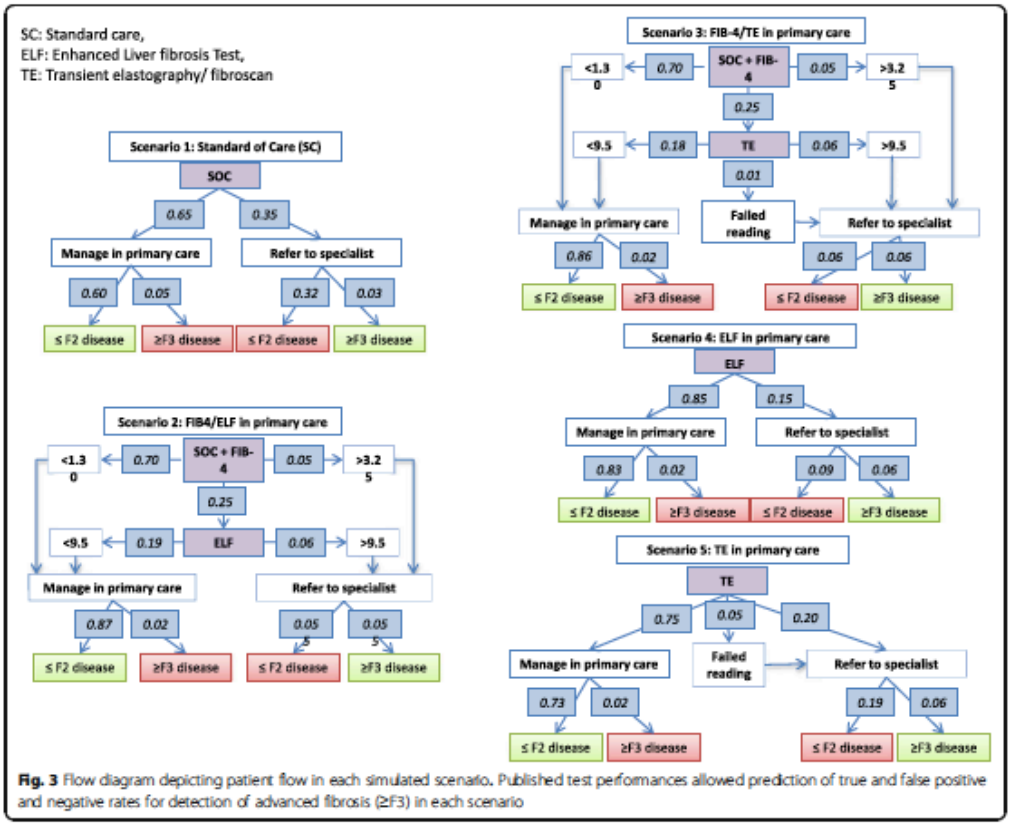

Fig. 3 Flow diagram depicting patient flow in each simulated scenario. Published test performances allowed prediction of true and false positive and negative rates for detection of advanced fibrosis (≥F3) in each scenario

and expenditure related to HCC surveillance (6 monthly AFP and ultrasound) and variceal surveillance (2–3 yearly endoscopy). Finally, costs for the management of complications of CLD, including inpatient and outpatient costs, pharmacological treatment and surgical procedures including liver resection and transplant were obtained from the Royal Free London NHS Foundation Trust finance department.

The primary outcome measure was cost per case of advanced fibrosis detected - a surrogate for cost utility.

Secondary outcomes included unnecessary referral rates of patients with non-advanced disease, the severity of CLD complications, liver transplantation and mortality rates.

Results

Clinical outcome

The base case analysis for 1000 patients with NAFLD over a 1-year timeframe demonstrated 650 patients (65%) were identified as being at low risk of advanced fibrosis and remained in primary care (scenario 1, SC). Of this group, 49 patients (8%) had advanced fibrosis but remained in primary care inappropriately (false negative rate). The remaining 350 patients (35%) were referred to a specialist. After specialist investigation, 93% (324 patients) were determined to be at low risk (false positive rate) and discharged whilst 26 patients (7%) were confirmed to have advanced fibrosis (true positive) and progressed on specialist pathways.

The impact of introducing non-invasive tests into primary care using FIB-4 and ELF (Scenario 2), FIB-4 and TE (Scenario 3), ELF alone (scenario 4) or TE alone (Scenario 5) was assessed (Fig. 4 and Table 4). Over the 1 year time-horizon, compared to SC these strategies reduced the relative referral rate from primary care to hospital by 70, 67, 56 and 43% for scenarios 2, 3, 4 and 5 respectively; corresponding to 245, 223, 198 and 150 fewer referrals over 1 year per 1000 patients. This reduced the need for investigation performed in secondary care. The number of patients requiring imaging in secondary care reduced by 147, 134, 118 and 60 in

Table 2 Transitional probability estimates used to populate the probabilistic analytical model for the base case (annual progression rates)

Parameter/ Health state	Transition probability	References
Population and disease characteristics		
Prevalence of advanced fibrosis in the general population	0.075	[5]
Reduction in fibrosis progression after GP management	0.01	[22], Author assumption
Reduction in fibrosis progression after specialist review	0.025	[22]
Mild/ No fibrosis (F0, F1, F2)		
Remain healthy	0.99	[23–26]
Develop F3 disease	0.001	[23, 24]
Mortality (all cause)	0.005	[25, 27, 28]
Discharge from specialist services	0.7	Unpublished audit
Advanced fibrosis (F3)		
Remain healthy	0.95	[25, 29, 30]
Develop F4 disease/ cirrhosis	0.04	[25, 29, 30]
Develop HCC (without cirrhosis)	0.004	[29]
Mortality (all cause)	0.005	[29]
Compensated cirrhosis (F4)		
Remain compensated	0.93	Calculated from other variables
Develop varices	0.03	[31]
Develop HCC	0.003	[32, 34–37]
Develop other complications (inc. jaundice, ascites, HE)	0.02	[29, 31, 32]
Mortality (all cause)	0.02	[31, 38, 39], expert opinion
BCLC Stage 0 and A HCC		
Cure (liver transplant)	0.36	[40]
Cure (non transplant)	0.39	[40]
Mortality (all cause)	0.25	[40]
BCLC stage B – D HCC		
Clinical stability (post TACE, RFA etc)	0.24	[41]
Mortality (all cause)	0.76	[35]
Varices detection in surveillance programme		
Clinical stability	0.92	[42]
Liver transplant	0.01	Expert opinion
Mortality (all cause)	0.07	[33]
Detection of varices after emergency presentation		
Clinical stability	0.73	[43]
Liver transplant	0.02	[42]
Mortality (all cause)	0.25	[44]
Mild/ Moderate 'other' complication		
Clinical stability	0.74	[17]
Liver transplant	0.10	[42]
Mortality (all cause)	0.16	[17]
Severe 'other' complication		
Clinical stability	0.45	[17]
Liver transplant	0.10	[42]
Mortality (all cause)	0.45	[17]

Table 2 Transitional probability estimates used to populate the probabilistic analytical model for the base case (annual progression rates) *(Continued)*

Parameter/ Health state	Transition probability		References
Severity of CLD Complication	No screening	Screening	
Probability of BCLC stage 0 + A HCC	0.299	0.709	[45]
Probability of BCLC stage B - D HCC	0.701	0.291	[45]
Detecting varices in surveillance programme	0.0	0.60	[42]
Detecting varices after emergency presentation	100.0	0.40	[42]
Mild/ moderate CLD 'other' complication	0.527	0.622	[17, 46]
Severe CLD 'other' complication	0.473	0.378	[17, 46]

scenarios 2, 3, 4, and 5 respectively, whilst 25, 22, 20 and 10 fewer patients required endoscopy after 1 year per 1000 patients referred. The requirement for liver biopsy was reduced by 37, 33, 30 and 15 patients in scenarios 2, 3, 4 and 5 respectively. This translated into cost savings in secondary care investigation in the first year per 1000 patients referred of £165,530.04, £150,184.67, £133,505.60 and £68,256.85 for scenarios 2, 3, 4 and 5 respectively.

These approaches resulted in reductions in referral of patients with non-advanced liver fibrosis (deemed "unnecessary" referrals) by 85, 78, 71 and 42% (absolute reduction) in scenarios 2, 3, 4, and 5 respectively compared to scenario 1; corresponding to 275, 253, 231 and 137 reduction in inappropriate referrals from 324 patients in scenario 1 over the 1-year time horizon.

TE alone was the most clinically effective strategy in the detection of ≥F3 fibrosis. Compared to SC, introducing NILT increased the identification of patients with advanced fibrosis (true positive rate) by 30, 31, 34 and 36 patients in scenarios 2, 3, 4 and 5 respectively equating to an 114, 118, 129 and 137% improvement..

Considering cirrhosis specifically, over the 1-year timeframe, employing each of the strategies improved detection by 1 patient per 1000 population compared to the SC,. Specifically, an extra 1.2 (113%), 1.2 (116%), 1.3 (128%) and 1.4 (136%) cirrhotic patients per 1000

Table 3 Health care costs for patients with NAFLD/ NASH (£, 2014–2015)

Resource Use	Unit Cost	Reference
Primary Care		
GP consultation (per patient contact lasting 11.7 min)	£45.00	[48]
Secondary care		
Hepatology Consultant appointment (new)	£148.34	Royal Free, February 2015
Hepatology Consultant follow up appt	£98.63	Royal Free, February 2015
Dietician review	£57.00	Royal Free, February 2015
Investigations		
Routine blood tests (inc. FBC, LFT's, INR)	£68.06	Royal Free, February 2015
Liver aetiology panel	£147.98	Royal Free, February 2015
FIB-4 (AST/ALT/ platelets included in 'routine blood tests')	£0.00	Royal Free, February 2015
ELF	£42.00	North Middlesex Hospital, February 2015,
Ultrasound Liver	£63.67	Royal Free, February 2015
CT Abdomen/ Liver	£80.78	Royal Free, February 2015
MRI Abdomen/ Liver	£101.00	Royal Free, February 2015
Fibroscan	£43.00	Royal Free, February 2015
Liver biopsy	£642.75	Royal Free, February 2015
Endoscopy	£264.00	Royal Free, February 2015
Surgical procedures		
Liver resection	£7000	[49]
Liver transplant (1st year)	£70,000	[19, 49, 50], Royal Free, February 2015

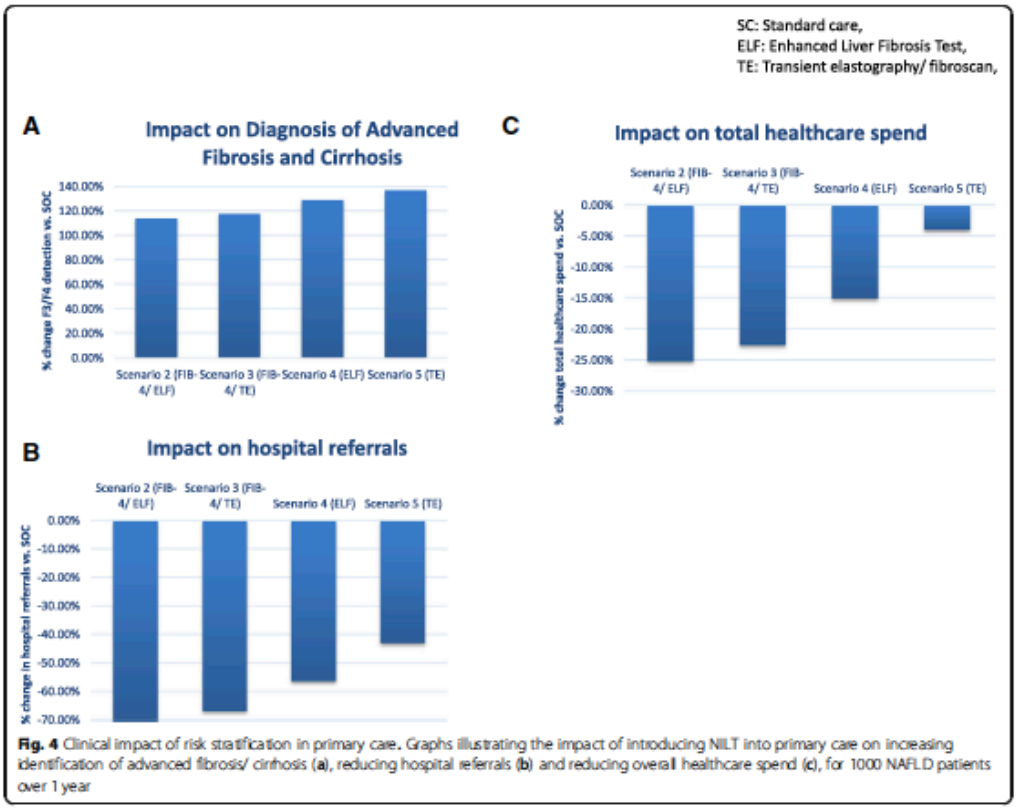

Fig. 4 Clinical impact of risk stratification in primary care. Graphs illustrating the impact of introducing NILT into primary care on increasing identification of advanced fibrosis/ cirrhosis (**a**), reducing hospital referrals (**b**) and reducing overall healthcare spend (**c**), for 1000 NAFLD patients over 1 year

population were detected in scenarios 2, 3, 4 and 5 respectively over 1 year compared to SC.

The model tested the impact of earlier detection of advanced fibrosis on complications of CLD (Table 4). Patients known to have cirrhosis routinely undergo regular surveillance. The model demonstrated that the number of patients presenting with curable HCC (Stage O/A) increased from a base case of 0.17 patients per 1000 population following SC, by 0.06 patients per 1000 population in scenarios 2 and 3 and by 0.07 and 0.08 patients per 1000 population in scenarios 4 and 5 respectively. Conversely, over 1 year, incurable HCC (stage B-D), rates decreased from a base case of 0.22 patients per 1000 population following SC the same amounts equivalent to reductions of 29, 30, 33 and 35% for scenarios 2–5 respectively. Patients presenting with variceal haemorrhage reduced by 0.02 patients per 1000 population in scenarios 2, 3 and 4, and by 0.03 patients per 1000 population in scenario 5, compared to SOC (0.07 patients per 1000 population). The model predicted that variceal detection through surveillance prior to haemorrhage increased from 0.02 patients per 1000 with SC by 0.02 patients per 1000 in scenarios 2, 3, 4 and 0.03 patients per 1000 in scenario 5, permitting the instigation of primary prophylaxis of variceal haemorrhage that is associated with reduced mortality [44]. Finally, the model demonstrated that management of cirrhosis in secondary care achieved a reduction in episodes of hospitalization due to other complications of CLD including jaundice, ascites and hepatic encephalopathy from 0.03 patients per 1000 in SC by 0.01 patients per 1000 in all scenarios.

Improvements in the detection and management of cirrhosis would permit increased rates of liver transplantation by 0.02 patients per 1000 in scenarios 2 and 3 and 0.03 patients per 1000 in scenarios 4 and 5, compared to SC (0.07 patients per 1000) over 1 year. Predicted all-cause mortality reduced by 0.03 patients per 1000 in scenarios 2 and 3 and 0.04 patients per 1000 in scenarios 4 and 5 over 1 year compared to SC (9.87 patients per 1000).

Cost outcome

The healthcare costs of the competing strategies are summarised in Fig. 5 using a 1-year horizon. For 1000

Table 4 Base case analysis of introducing FIB-4, ELF and fibroscan into primary care risk stratification pathways compared to standard of care (scenario 1) after 1 year for 1000 patients with NAFLD

	Scenario 2 - FIB-4/ELF	Scenario 3 - FIB-4/ TE	Scenario 4 - SOC + ELF	Scenario 5 - SOC + TE
Pathway performance: patients referred to specialist (secondary care)				
Incremental number of referrals (stratified as ≥F3 fibrosis) (% increase vs SOC)	−245 (− 70%)	− 222 (− 67%)	−198 (− 56%)	− 101 (25%)
Incremental number of ≥F3 disease referred	30 (53%)	31 (45%)	34 (39%)	36 (25%)
Incremental number of ≤F2 disease referred	−275 (−85%)	−253 (−78%)	− 231 (−71%)	−137 (−42%)
Incremental number of cirrhotics referred	1.16 (113%)	1.20 (116%)	1.31 (128%)	1.40 (136%)
Pathway performance: patients remain under primary care management				
Incremental number of patient stratified as ≤F2 fibrosis (Primary care management)	245 (38%)	222 (34%)	198 (30%)	101 (15%)
Incremental number of patients correctly identified as ≤F2	274 (46%)	253 (42%)	231 (38%)	137 (23%)
Incremental number of patients incorrectly identified as ≤F2	−30 (−61%)	−31 (−63%)	−34 (− 69%)	−36 (−74%)
Overall performance of pathways				
Sensitivity	0.75	0.76	0.80	0.83
Specificity	0.95	0.92	0.90	0.80
Positive Predictive Value	0.53	0.45	0.39	0.25
Negative Predictive Value	0.98	0.98	0.98	0.98
Positive Likelihood Ratio	14.11	9.96	8.00	4.10
Negative Likelihood ratio	0.27	0.26	0.22	0.21
Impact on end stage liver disease				
BCLC Stage 0/A curable HCC (% of all HCC)	0.06 (36%)	0.06 (38%)	0.07 (41%)	0.08 (44%)
BCLC Stage B-D incurable HCC (% of all HCC)	−0.06 (−29%)	−0.07 (−30%)	−0.07 (−33%)	−0.08 (−35%)
Varices detected via surveillance programme (% of all new varices)	0.02 (113%)	0.02 (117%)	0.02 (128%)	0.03 (136%)
Emergency presentation of varices (% of all new varices)	−0.02 (−30%)	− 0.02 (−31%)	−0.02 (−34%)	−0.03 (−36%)
Mild/Moderate 'other' complications	< 0.01 (6%)	< 0.01 (6%)	< 0.01 (7%)	< 0.01 (7%)
Severe 'other' complication	< 0.01 (−9%)	< 0.01 (−9%)	< 0.01 (−10%)	< 0.01 (−10%)
Number of liver transplants (of all cirrhotics known to specialist)	0.02 (32%)	0.02 (33%)	0.03 (36%)	0.03 (39%)
Outcomes				
Mortality / 1000 NAFLD patients	−0.03 (−0.34%)	− 0.03 (− 0.35%)	−0.04 (− 0.39%)	−0.04 (− 0.41%)

Tabulated analysis of the impact of non-invasive liver fibrosis tests for the management of patients with NAFLD (scenarios 2–5) compared to the standard of care (scenario 1) in the primary care setting

patients with NAFLD undergoing PCP assessment for liver disease, the costs directly associated with NILT were £10,385 in Scenario 2, £10,632 in scenario 3, £42,000 in scenario 4 and £43,000 in scenario 5 (incorporating additional PCP appointments and blood tests).

Compared to SC (scenario 1) which cost £670,504 over 1 year, the incremental reductions in healthcare spending achieved through use of NILT in each scenario were £169 K, £152 K, 101 K and 27 K per 1000 patients in 1 year in scenarios 2, 3, 4 and 5 respectively equating to reductions of 25, 23, 15 and 4%. Using cost-per-case of advanced fibrosis as a surrogate for cost utility, all scenarios were favourable to SC (£25,543.02), with the model predicting cost-per-case of advanced fibrosis at £8.932.19, £9083.78, £9487.26 and £10,351.67 in scenarios 2, 3, 4 and 5 respectively over the 1 year timeframe.

From a commissioning perspective, a significant contributor to the immediate cost saving was the reduction in secondary care referrals. Compared to scenario 1 (£41,300 per 1000 patients over 1 year), cost-savings attributable to reduced specialist referral were £28,895, £26,216, £23,305 and £11,915 in scenarios 2, 3, 4 and 5 respectively, equating to 70, 63, 56 and 29% reductions.

A budget impact analysis (Table 5) assessed the impact of introducing the interventions nationally in the UK NHS system. Assuming the prevalence of NAFLD to be 20% in the UK population of 60 million people and a 5-year cycle of disease assessment, nationally 2.4 million

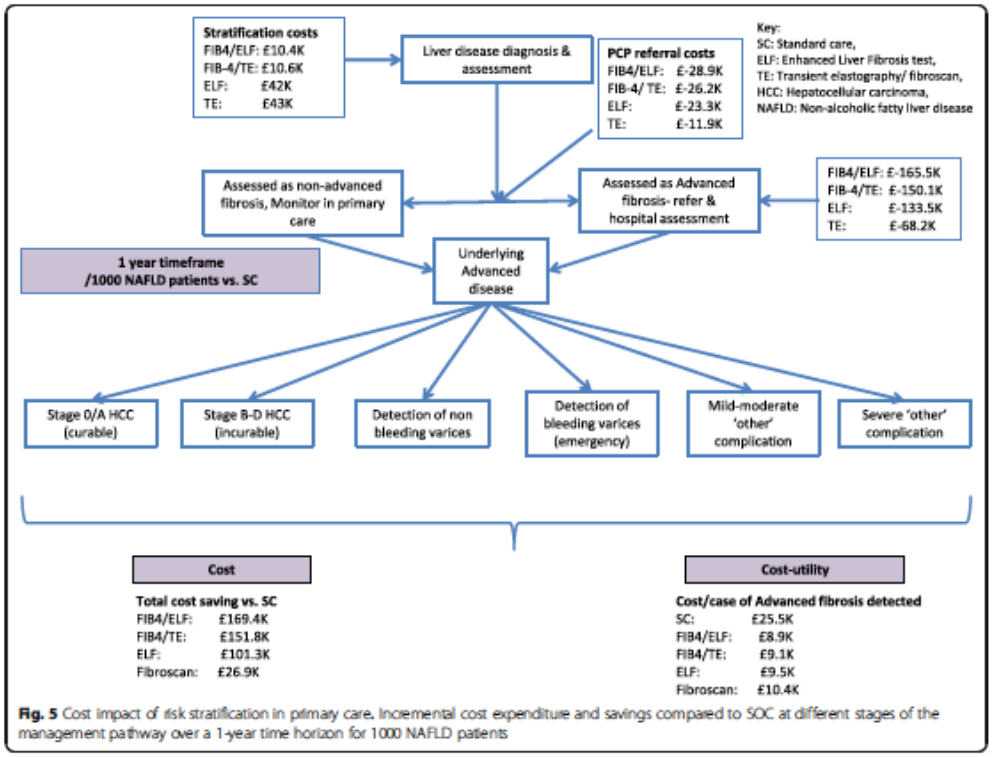

Fig. 5 Cost impact of risk stratification in primary care. Incremental cost expenditure and savings compared to SOC at different stages of the management pathway over a 1-year time horizon for 1000 NAFLD patients

people would potentially be risk stratified annually. The incremental cost to the budget holder of introducing NILT for fibrosis in NAFLD in primary care would be £24.9 M, £25.5 M, £100.8 M and £103.2 M in scenario's 2, 3, 4 and 5 respectively. However, this would deliver savings equating to 23, 21, 14 and 4% reductions in total healthcare expenditure for each of the scenarios respectively.

Table 6 summarises the outcomes of introducing non-invasive liver fibrosis tests in primary care for the base case.

Projected outcomes over a 5 year timeframe

Analyses were performed using a five-year horizon to assess the longer-term outcomes of the pathway (Table 7).

Five years after the introduction of NILT the model demonstrated clinical benefit, with increases in the detection of cirrhosis by 107, 111, 123 and 132% in scenarios 2, 3, 4 and 5 respectively equating to an extra 5.69, 5.90, 6.48 and 6.95 cases per 1000 patients tested per year.

Using a discount rate of 3.5%, compared to SC over 5 years incremental savings of £168,449.80, £142,752.51, £86,604.60 and £20,769.62 were made in scenarios 2, 3, 4, and 5 respectively.

One way sensitivity analyses

We performed a one-way sensitivity analysis on the base-case scenario using a time-frame of 1 year.

A pathway uptake sensitivity analysis tested assumptions about the proportion of patients entering the pathway (0–100%) and confirmed a linear benefit proportional to pathway uptake and reinforced that any utilisation of the pathway (i.e. > 0%) would deliver benefit in all scenarios over the 1-year timeframe.

A clinical effectiveness sensitivity analysis was performed by varying the specificity of SC for the detection of advanced fibrosis. In the base-case model, a value of 0.65 was assumed (65% specificity for the detection of advanced fibrosis). To counter the influence of this assumption, around which sparse data are published, it was varied from 0.00 to 1.00, demonstrating a significant influence on cost-effectiveness. However, the cost-benefit was only negated when the specificity of SC for

Table 5 Budget impact analysis of introducing FIB-4, ELF and fibroscan into primary care risk stratification pathways compared to standard care after 1 year for a population of 60 million patients

	Scenario 2 - FIB-4/ ELF	Scenario 3 - FIB-4/ TE	Scenario 4 - SC + ELF	Scenario 5 - SC + TE
Pathway performance:				
Incremental number of referrals (stratified as ≥F3 fibrosis) (% increase vs SOC)	− 587,700 (− 70%)	− 533,217 (− 67%)	− 474,000 (− 56%)	− 242,340 (− 25%)
Incremental number of ≥F3 disease referred	71,640 (53%)	74,041 (45%)	81,000 (39%)	86,220 (25%)
Incremental number of ≤F2 disease referred	− 659,340 (− 85%)	− 607,258 (− 78%)	− 555,021 (− 71%)	− 328,560 (− 42%)
Incremental number of cirrhotics referred	2786 (113%)	2880 (116%)	3153 (128%)	3359 (136%)
Incremental number of patients incorrectly identified as ≤F2	− 71,640 (− 61%)	− 74,041 (− 63%)	− 81,000 (− 69%)	− 86,220 (− 74%)
IMPACT ON END STAGE LIVER DISEASE				
BCLC Stage 0/A curable HCC (% of all HCC)	121 (36%)	125 (38%)	137 (41%)	146 (44%)
BCLC Stage B-D incurable HCC (% of all HCC)	− 121 (− 29%)	− 125 (− 30%)	− 137 (− 33%)	− 146 (− 35%)
Varices detected via surveillance programme (% of all new varices)	50 (113%)	51 (117%)	57 (128%)	60 (136%)
Emergency presentation of varices (% of all new varices)	− 50 (− 30%)	− 51 (− 31%)	− 57 (− 34%)	− 60 (− 36%)
Mild/Moderate 'other' complications	5 (6%)	5 (6%)	6 (7%)	< 6 (7%)
Severe 'other' complication requiring hospital admission	− 5 (− 9%)	− 5 (− 9%)	− 6 (− 10%)	− 6 (− 10%)
Outcomes				
Mortality / 1000 NAFLD patients	− 67 (− 0.34%)	− 69 (− 0.35%)	− 76 (− 0.39%)	− 81 (− 0.41%)
Budget				
Cost of tests	£24.9 M	£25.5	£100.8	£103.2 M
Total expenditure	-£406 M (− 23%)	-£364 M (− 21%)	-£243 M (− 14%)	-£65 M (− 4%)

Tabulated analysis of the impact of non-invasive liver fibrosis tests for the management of patients with NAFLD (scenarios 2–5) compared to the standard of care (scenario 1) in the primary care setting for a population of 60 million patients with 20% NAFLD prevelance risk stratified on a 5 year cycle

the detection of advanced fibrosis exceeded 0.88, 0.86, 0.80 and 0.68 in scenarios 2, 3, 4 and 5 respectively.

Discussion

Our cost consequence analyses indicate that the use of NILT to stratify patients with NAFLD in primary care is clinically effective and cost saving. Utilizing fibroscan alone was most effective in detecting patients with advanced fibrosis, whilst employing FIB-4 and ELF delivered the greatest cost saving.

All of the scenarios using NILT in primary care permitted the earlier identification of advanced fibrosis/cirrhosis, creating opportunities to modify fibrosis progression [22, 51] and to start surveillance and treatment of varices and HCC. Modelling indicated that significant benefits could accrue from the detection of early stage curable HCC (stage 0/ A) and non-bleeding varices that can be treated with beta-blockers and band ligation that can avert emergency presentations with bleeding varices. A modest reduction in hospital admissions for other complications of CLD including jaundice, ascites and hepatic encephalopathy was demonstrated. The relatively limited impact of current care pathways on mortality, largely attributable to missed or late diagnosis of advanced fibrosis,

Table 6 Summary of outcomes resulting from introducing non-invasive liver fibrosis tests in primary care (per 1000 NAFLD patients over 1 years)

	Scenario 1 Standard Care	Scenario 2 FIB 4 +/− ELF	Scenario 3 FIB 4 +/− TE	Scenario 4 ELF	Scenario 5 TE
Total Referrals avoided (vs. SOC)	–	245	234	198	150
Cases F3/F4 detected	26.3	56.1	57.1	60.0	62.2
Cases Cirrhosis detected	5.3	11.0	11.2	11.8	12.3
Cases Cirrhosis missed	11.3	5.5	5.3	4.7	4.2
Cost saving (vs. SOC)	–	- £169,408	- £151,816	- £101,268	- £26,889
Cost per ≥ F3 detected	£25,543	£8932	£9083	£9487	£10,351

Table 7 Projected clinical outcomes and costs of the scenarios projected over 1 year and 5 years

	Scenario 1 - SC		Scenario 2 - FIB-4/ ELF		Scenario 3 - FIB-4/ TE		Scenario 4 - SC + ELF		Scenario 5 - SC + TE	
	1 year	5 years	1 year	5 years	1 year	5 years	1 Year	5 years	1 year	5 years
Total number of cirrhotics entered into specialist services (out of all cirrhotics)	1.03 (34%)	5.28 (32%)	2.19 (74%)	10.97 (66%)	2.23 (75%)	11.17 (68%)	2.34 (79%)	11.75 (71%)	2.43 (82%)	12.23 (74%)
Total number of cirrhotics not known to specialist services (out of all cirrhotics)	1.96 (66%)	11.278 (68%)	0.78 (26%)	5.53 (34%)	0.74 (25%)	5.41 (32%)	0.63 (21%)	4.73 (29%)	0.54 (18%)	4.24 (26%)
Early stage complication (stage 0/A HCC, non-bleeding varices, mild ascites etc) (% of all complications) Cost	0.22 (4.2%) £3.0 K	3.52 (39%) £31.1 K	0.31 (57%) £4.1 K	4.62 (52%) £41.2 K	0.31 (58%) £4.1 K	4.66 (52%) £41.5 K	0.32 (60%) £4.3 K	4.77 (54%) £42.6 K	0.33 (61%) £4.3 K	4.87 (55%) £43.4 K
Late stage complication (stage B-D HCC, bleeding varices, severe ascites etc) (% of all complications) Cost	0.32 (58%) £12.9 K	5.44 (61%) £141 K	0.23 (43%) £9.2 K	4.3 (48%) £108 K	0.23 (42%) 9.1 K	4.26 (48%) £107 K	0.22 (40%) £8.8 K	4.14 (46%) £103 K	0.21 (39%) £8.4 K	4.05 (45%) £101 K
Liver transplant Cost	0.07 £5.9 K	1.05 £89.5 K	0.10 £7.9 K	1.16 £98.9 K	0.10 £8.0 K	1.16 £99.3 K	0.10 £8.2 K	1.17100.2 K	0.10 £8.3 K	1.18 £101 K
Mortality (%)	9.87 0.99%	28.56 2.86%	9.84 0.98%	28.18 2.82%	9.83 0.98%	28.17 2.82%	9.83 0.98%	28.13 2.81%	9.83 0.98%	28.10 2.81%
Total cost/1000 NAFLD patients	638 K	1.1 M	502 K	946 K	522 K	971 K	570 K	1.0 M	647 K	1.1 M
Cost/advanced fibrotic detected	25.7 K	49.9 K	9.0 K	19.4 K	9.1 K	19.4 K	9.5 K	19.5 K	10.4 K	20.5 K

highlights the need for new approaches to diagnosis and treatment to prevent NAFLD progression.

Of interest to commissioners, the implementation of NILT in primary care offers the potential to reduce the total number of referrals, and in particular the unnecessary referral of patients who have minimal fibrosis. Over a 1-year horizon, there was a reduction in total referrals of 70, 63, 56 and 29% in scenarios 2, 3, 4 and 5 respectively, with an 85, 78, 71 and 42% reduction in referrals of patients with non-advanced disease. Real-world data from a secondary care hepatology service found that 66% of referred patients had a baseline FIB-4 score < 1.30 indicating that these patients had a low risk of advanced fibrosis and could have avoided referral [13]. This group of patients represents an inefficient use of resources, adding pressure to overstretched outpatient specialist services and PCP healthcare budgets [52]. Introduction of the use of NILT in primary care would deliver immediate reductions in expenditure through avoidance of unnecessary referrals, unlike the cost-benefits associated with improved outcomes attributable to earlier diagnosis that accrue much later.

All scenarios were cost saving. The cost of detecting a case of advanced fibrosis using SC was £49,917.83 in scenario. This compared to £19,360.75 in scenario 2, £19,448.49 in scenario 3, £19,487.75 in scenario 4 and £20,451.35 in scenario 5. Healthcare budgets were reduced by 17, 15, 11 and 3% in scenarios 2, 3, 4 and 5 respectively, attributable to the reduction in costs associated with end stage liver disease and improved resource utilisation. The budget decrease in scenario 5 was modest as it was assumed all patients who failed fibroscan (5% of cohort) were referred to specialists.

In this analysis, we explored the impact of the use of FIB-4 and ELF to replicate a primary care pathway introduced in north London. This combination of tests was optimal for the stratification of patients in a hospital based population [53] and has subsequently been shown to be clinically effective [13] when applied in primary care where the proportion of cases of advanced fibrosis amongst cases of NAFLD is smaller.

There are limitations to the model. The model was populated with the best available published evidence. A lack of high quality data for some variables was remedied with expert opinion. The measures of performance for FIB-4, ELF and fibroscan were drawn from validations in hospital cohorts, but these estimates may be inappropriately high for primary care populations in which the prevalence of fibrosis is likely to be lower (spectrum bias) [54, 55]. The model assumes that use of ELF and fibroscan as second-tier tests has the same performance characteristics as a first-tier test. This may under-estimate the performance of the pathway. Additionally, the model was limited to FIB-4, ELF and fibroscan. Local PCP focus groups supported by consultants in Public Health, formed to aide Camden and Islington pathway development, outlined the practical need for simplicity, giving FIB-4 an advantage over the NAFLD-fibrosis score, which the PCP considered to be more challenging to obtain such as BMI, or associated with uncertainty about case definition such as diabetes. The model examines fibrosis, but not NASH, and so may underestimate disease progression. Other sources of error include analytical performance. We assumed a 5% failure rate for fibroscan but higher rates have been reported [47], whilst serum tests can be influenced by comorbidities. For the

purposes of the model, liver biopsy was considered the reference test for liver fibrosis. Given the inherent inaccuracies associated with liver biopsy [56], this may have overestimated the performance of liver biopsy. The cost estimate of liver biopsy incorporated procedural elements but not those associated with complications of the procedure. This approach may underestimate the true cost associated with liver biopsy. The clinical- and cost- efficiency of all scenarios are highly favourable, but may not reflect real-life outcomes. Not all patients with NAFLD consult their PCP, and pathway uptake by health professionals is variable. The base case is a 50-year-old man with abnormal transaminases, reflecting a screening strategy identified by the Camden and Islington steering committee as practical in real-life primary care practice. However this approach will miss cases of NAFLD with advanced fibrosis but normal LFTs. A screen-all strategy is likely to be clinically optimal, as patients with NAFLD and normal transaminases are at risk of significant fibrosis. The costing in the model is comprehensive, assuming full adherence to guidelines and protocols and thereby potentially overestimating the cost of care. We employed a probabilistic decision model as our main economic focus was on the payer perspective rather than a population health perspective, where alternative cost-effectiveness approaches using quality of life data and Markov simulations would be desirable. The lack of beta or triangular distributions and true probability sensitivity analysis limits the model. The model lacks cost/ QALY data and relies on descriptive measures including cost per case of advanced fibrosis detected. These outcome measures have no standard comparator limiting the current model. These shortcomings will be addressed in future work.

NAFLD should be considered as the hepatic manifestation of a multisystem disorder associated with widespread morbidity including cardiovascular disease, diabetes, hyperlipidaemia and cancer. While a fully comprehensive health economic model would need to take these morbidities into consideration we chose to focus on liver disease. Accommodating all NAFLD associated morbidities, their evaluation and management was beyond the scope of this study.

This study has several strengths. A comprehensive literature review was undertaken to identify estimates for clinical parameters, transition rates and costs. The study adds to the current body of evidence and our conclusions are similar to other health economic analyses [57]. A Health Technology Assessment undertaken for the National Institute for Health Research [19] concluded that use of NILT was more cost-effective than liver biopsy in detecting cases of advanced fibrosis. Tapper et al. [58] demonstrated that the use of the NAFLD fibrosis score and fibroscan in primary care yielded cost-effective results. Robust data are lacking regarding the performance of PCP's in the identification of patients with advanced liver disease. Additionally, there is no published randomised controlled trial exploring the performance of NILT in primary care. Whilst limiting the model, the information provided by the analysis may be supplemented with the results from real-life pilot studies in due course. Harman et al. [59] have demonstrated the use of fibroscan in patients with risk factors for CLD, including diabetes, obesity and alcohol excess can increase detection of cirrhosis by 140%, similar to the modelling results in scenario 5 (132%). Our group has evaluated the pathway employing FIB-4 and ELF (Scenario 2) [13].

Conclusions

This study demonstrates that the introduction of NILT in primary care has the potential to increase the detection of cases of NAFLD with advanced fibrosis and cirrhosis, reduce unnecessary referrals to secondary care of patients at low risk of liver disease and to deliver immediate and sustained significant cost savings. The model provides compelling evidence for clinicians, commissioners and policy makers to consider the formal introduction of non-invasive liver fibrosis testing in primary care, in line with other central policy statements [4, 60, 61].

Abbreviations

ALD: Alcoholic liver disease; ALT: Alanine aminotransfeaase; AST: Aspartate aminotransferase; BCLC: Barcelona Clinic Liver Cancer; CLD: Chronic liver disease; ELF: Enhanced Liver Fibrosis; FIB-4: Fibrosis-4 score; HCC: Hepatocellular carcinoma; HCV: Hepatitis C Virus; LFT: Liver function tests; NAFLD: Non-alcoholic fatty liver disease; NHS: National health system; NILT: Non-invasive liver fibrosis tests; PCP: Primary care physician; SOC: Standard of care

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Authors' contributions

AS, SJ, AG and WR were major contributors in study conception and design, acquisition of data, analysis and intepretation of data, drafting of manuscript, and critical revision. RG, SM, KS, ST, JO, ET and JP were involved in acquisition of data and critical revision of the manuscript. EP contributed to analysis and intepretation of data, and critical revision of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study does not report on animal or human data. It reports theoretical modelling data. Data used for calculating costs in the modelling work were obtained from NHS sources and published literature. Some of the clinical data were drawn from an evaluation of service improvement conducted at The Royal Free London NHS Foundation Trust. The Royal Free London NHS Foundation Trust Research and Development Department judged this work 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.

Consent for publication
Not applicable.

Competing interests
AS, JP and WR have received speaker bureau from Siemens Healthineers; AS, SJ and WR have received support for research from Siemens Healthineers; WR is a NIHR Senior Investigator and is supported by the UCLH NIHR BRC. EP is supported by the NIHR Collaboration for Leadership in Applied Health Research and Care (CLAHRC) North Thames at Bart's Health NHS Trust. The views expressed are those of the author (s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.
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Publisher's Note

Appendix 2 MEDLINE search strategy for systematic review

Search strategies were developed to identify studies published evaluating pathways of care using markers of liver fibrosis to allow earlier identification of patients with advanced liver disease and guide referral to a specialist. The following search strategy outlines the OVID MEDLINE search strategy, which was conducted on 15th March 2016 and generated 832 papers for review. This strategy was adapted for use on other databases.

	Field input	Results
1	exp Diagnostic Techniques, Digestive System/ or exp Diagnostic Self Evaluation/ or exp Diagnostic Imaging/ or exp Diagnostic Tests, Routine/ or exp Molecular Diagnostic Techniques/ or exp Reagent Kits, Diagnostic/ or exp "Diagnostic Techniques and Procedures"/ or exp Diagnostic Errors/	6024463
2	di.fs.	2146633
3	diagnos$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	2236884
4	1 or 2 or 3	7862361
5	stratification.mp.	38327
6	risk stratification.mp.	16664
7	4 or 5 or 6	7880596
8	exp Primary Health Care/	112796
9	primary health care.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	69595
10	primary adj2 (care or physician$ or healthcare or practice)) or (general adj practi$) or PHC).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	186329
11	8 or 9 or 10	237282
12	exp "Sensitivity and Specificity"/	462576

13	(sensitivity or specificity).ti,ab.	798916
14	exp "Predictive Value of Tests"/	159046
15	(predictive value* or ppc or npv).ti,ab.	82575
16	((pre test or pretest or post test) adj probability).ti,ab.	1816
17	likelihood ratio*.ti,ab.	10669
18	likelihood function/	18477
19	(roc curve* or auc).ti,ab.	55032
20	(diagnos* adj3 (accurac* or performance* or utilit* or value* or efficient* or effectiveness)).ti,ab.	87808
21	exp Research Design/	363868
22	exp Epidemiologic Methods/	4849479
23	exp "Review Literature as Topic"/	8432
24	Randomized controlled trial.pt.	409959
25	controlled clinical trial.pt.	90291
26	clinical trials.mp. or exp Clinical Trial/	970172
27	trial.ti.	147476
28	exp Case-Control Studies/	761844
29	exp Cohort Studies/	1506143
30	exp Cross-Sectional Studies/	208945
31	exp Observational Study/ or exp Observational Studies as Topic/	20253
32	((follow up or observational or uncontrolled or non randomized or epidemiological*) adj (study or studies)).ti,ab.	146450
33	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analyse* or cohort*)).ti,ab.	886542
34	exp "Costs and Cost Analysis"/	195062
35	exp Cost-Benefit Analysis/	64719
36	exp Economics, Medical/ or exp Economics, Hospital/	34472
37	(cost* adj2 (effective* or utility* or benefit* or minima* or unit* or unit* or variable*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	140898
38	(value adj2 (money or monetary)).ti,ab.	1575
39	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38	6207673
40	7 and 11 and 39	52740
41	liver disease.mp. or exp Liver Diseases/	483205

42	exp Hepatitis C/ or exp Liver Diseases/ or exp Liver Cirrhosis/ or exp Liver/ or chronic liver disease.mp.	788463
43	cirrhosis.mp. or exp Fibrosis/	160908
44	((liver or hepatic) adj (failure or decompensation)).mp.	25123
45	non alcoholic fatty liver disease.mp. or exp Fatty Liver/ or exp Non-alcoholic Fatty Liver Disease/ or exp Liver Diseases/	470093
46	exp Liver Diseases, Alcoholic/	12892
47	41 or 42 or 43 or 44 or 45 or 46	866577
48	alanine transaminase.mp. or exp Alanine Transaminase/	29767
49	liver function tests.mp. or exp Liver Function Tests/	31597
50	(fibro test* or fibro-test* or fibrometer or fibroscan or fib4 or fib-4).ti,ab.	964
51	((nafld or bard or ferritin* or fibrosis) adj4 (test* or measure* or level* or ratio or score*)).ti,ab.	13989
52	((ast-to-platelet ratio index or apri or elf or enhanced liver fibrosis or nash) adj4 (test* or measure* or level* or score*)).ti,ab.	873
53	(elastogra* or sonoelastogra* or elasticity imag* or sheer wave).ti,ab.	4474
54	48 or 49 or 50 or 51 or 52 or 53	76577
55	47 or 54	896181
56	40 and 55	832

Appendix 3 Risk of bias assessment for each identified published study in systematic review

Moussalli [191] 2010		
Entry	**Judgment**	**Support for judgment**
Random sequence generation (selection bias)	High risk.	No randomization. Sequence generated by rule based on date of registration into treatment centre.
Allocation concealment (selection bias)	High risk.	No allocation concealment. All patients entered onto intervention arm after intervention implementation
Blinding of participants and personnel (performance bias)	Low risk.	No attempt at blinding of participants, but this is unlikely to influence fibrosis staging or the primary outcome of Hepatitis treatment initiation.
Blinding of outcome assessment (detection bias)	High risk.	No attempt to blind the assessor. This is unlikely to have an impact on fibrosis assessment, but introduces bias to the primary outcome “hepatitis treatment rates’
Incomplete outcome data addressed (attrition bias)	Low risk.	No missing data is reported
Selective reporting (reporting bias)	Low risk.	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified
Other sources of bias		There is at least one other important risk of bias. There is an extended lag period between study period (2002-2004) and publication. It is not clearly stated if study is retrospective or prospective. No exclusion criteria are mentioned. No reference standard. Pre-intervention used as comparator for primary outcome of hepatitis treatment rate

Poynard [192], 2010		
Entry	**Judgment**	**Support for judgment**
Random sequence generation (selection bias)	High risk.	Quote “Consecutive subjects ……were eligible for inclusion” No randomization. Consecutive patient recruitment
Allocation concealment (selection bias)	High risk.	No allocation concealment. All patients entered onto intervention arm after intervention implementation
Blinding of participants and personnel (performance bias)	Low risk.	No attempt at blinding of participants, but this is unlikely to influence fibrosis staging.
Blinding of outcome assessment (detection bias)	High risk.	No attempt to blind the assessor. The specialist physician conducting reinvestigation was not blinded to the original fibrotest score, introducing bias in the re-assessment.
Incomplete outcome data addressed (attrition bias)	Low risk.	105/209 (50%) high risk patients accepted reinvestigation. The characteristics of the two groups are detailed in table 1 and there was no significant difference.
Selective reporting (reporting bias)	Low risk.	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified
Other sources of bias		There is at least one other important risk of bias. There is no comment on the time interval between the index and reference test. All patients did not receive the same reference test. Some patients had liver biopsy, other patients did not. Patients who were not re-investigated were not included in the analysis.

Moessner [193], 2010		
Entry	**Judgment**	**Support for judgment**
Random sequence generation (selection bias)	High risk.	All drug users affiliated with participating drug centres eligible. No randomization performed. No methodology described regarding approach of patients.
Allocation concealment (selection bias)	High risk.	No allocation concealment. No methodology described regarding the approach of patients. No assignment of patients.
Blinding of participants and personnel (performance bias)	High risk.	The fibroscan result was not blinded to participant. It is noted that 6 (out of 45) patients with a high fibroscan reading had prior history of cirrhosis and decompensation, and there is no documentation that the technician is blinded to patients past medical history.
Blinding of outcome assessment (detection bias)	High risk.	The histopathologist evaluating liver biopsy was blinded to the fibroscan result, but no information provided about the rest of the study team being blinded.
Incomplete outcome data addressed (attrition bias)	Low risk.	450/759 agreed to participate in the study. Reasonable attempt made to ensure no significant difference in patient populations between participants and non-participants. Age was the only statistically different variable.
Selective reporting (reporting bias)	High risk.	Study protocol is not available. There are no reported outcomes of patients with fibroscan 8-11.9 KPa who were referred to a specialist.
Other sources of bias		The reference standard for patients with high fibroscan score (>12 KPa) was not accepted by 42% of patients.

Roulot [194], 2011		
Entry	**Judgment**	**Support for judgment**
Random sequence generation (selection bias)	High risk.	No randomization. Consecutive patient recruitment between September 2005 - February 2008
Allocation concealment (selection bias)	High risk.	No allocation concealment. All patients entered onto intervention arm after intervention implementation.
Blinding of participants and personnel (performance bias)	High risk.	No attempt at blinding of participants. The participant was aware of the fibroscan result.
Blinding of outcome assessment (detection bias)	Low risk.	All transient elastography conducted by single technician, who was blinded to patient's clinical data.
Incomplete outcome data addressed (attrition bias)	Low risk.	Missing data accounted for and no statistical difference documented.
Selective reporting (reporting bias)	High risk.	66/80 patients with high fibroscan readings (8.0Kpa - 13Kpa) received specialist review - however data only reported on the 27 patients who accepted liver biopsy. Data was not reported for individuals who had a failed fibroscan.
Other sources of bias		Prospective study. There is no comparator arm. It was not documented the time interval between fibroscan and liver biopsy.

Fabrellas [190], 2013		
Entry	**Judgment**	**Support for judgment**
Random sequence generation (selection bias)	Unclear risk.	Quote: 'Subjects, aged 18-70 years, were identified randomly from the state health registry using specific software' There is a lack of detailed information regarding the identification of participants for the study. However, it is suggested that computer software is used and therefore the risk of bias is unclear.
Allocation concealment (selection bias)	High risk.	No allocation concealment.
Blinding of participants and personnel (performance bias)	Low risk.	No blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias)	High risk.	No attempt to blind the assessor.
Incomplete outcome data addressed (attrition bias)	Low risk.	Limited exclusion criteria, but this is appropriate for the study. There was limited information on why patients declined participation in the trial.
Selective reporting (reporting bias)	High risk.	The study protocol was not documented. The outcome of hospital fibrosis assessment is not quantified in any detail and this introduces a high risk of bias.
Other sources of bias		There is little evidence that in patients with elevated fibroscan, the diagnosis of advanced fibrosis is reconfirmed in secondary care.

Grattagliano [195], 2013		
Entry	**Judgment**	**Support for judgment**
Random sequence generation (selection bias)	High risk.	Each practitioner recruited 10 consecutive patients with NAFLD
Allocation concealment (selection bias)	High risk.	No allocation concealment.
Blinding of participants and personnel (performance bias)	Low risk.	No blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias)	Low risk.	No blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding.
Incomplete outcome data addressed (attrition bias)	Low risk.	The study reports there was no incomplete data, or participants that dropped out.
Selective reporting (reporting bias)	High risk.	16/34 patients deemed to have advanced fibrosis underwent liver biopsy after secondary care review. No information provided on the other patients regarding their secondary care review
Other sources of bias		Prospective study. Exclusion criteria are exhaustive. No reference standard.

Sheron [196], 2013		
Entry	**Judgment**	**Support for judgment**
Random sequence generation (selection bias)	High risk.	Recruitment of participants was through postal invitation. This introduces self-selection bias. There are no comprehensive inclusion or exclusion criteria. The study included patients with known fibrosis or cirrhosis
Allocation concealment (selection bias)	High risk.	No allocation concealment.
Blinding of participants and personnel (performance bias)	High risk.	No attempt at blinding participants to result of liver fibrosis test, and this may influence how they respond to subsequent patient questionnaire.
Blinding of outcome assessment (detection bias)	High risk.	No blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding.
Incomplete outcome data addressed (attrition bias)	High risk.	No detailed information provided regarding missing data or patients.
Selective reporting (reporting bias)	High risk.	No published protocol and no individual component data of STL provided. Cohort included patients with known fibrosis/ cirrhosis but this cohort is not reported on separately.
Other sources of bias		Prospective study. Lack of detailed exclusion criteria. There is a lack of reference standard. Patients who did not attend the clinic were not included in the analysis.

Harman [87], 2015		
Entry	**Judgment**	**Support for judgment**
Random sequence generation (selection bias)	High risk.	A non-random selection of patients based on electronic patient record search and willingness to participate. Self-filled questionnaire, whilst patients with type I diabetes detected by read codes
Allocation concealment (selection bias)	High risk.	No allocation concealment.
Blinding of participants and personnel (performance bias)	Low risk.	No blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias)	High risk.	No attempt to blind the assessor i.e. fibroscan technician. This could influence the primary outcome.
Incomplete outcome data addressed (attrition bias)	Low risk.	The study reports there was no incomplete data.
Selective reporting (reporting bias)	Low risk.	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified
Other sources of bias		Prospective study. Appropriate exclusion criteria. No reference standard.

Doycheva [197], 2016		
Entry	**Judgment**	**Support for judgment**
Random sequence generation (selection bias)	High risk.	Method of recruitment was via primary care and newspaper advertisement. Therefore, significant risk of self-selection bias . 100 consecutive eligible patients recruited.
Allocation concealment (selection bias)	Low risk.	No allocation concealment, however unlikely to impact outcome of study.
Blinding of participants and personnel (performance bias)	Low risk.	No blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias)	Low risk.	Quote: 'The MR examinations were …….. analysed by a single image analyst who was blinded to clinical and biochemical data.'
Incomplete outcome data addressed (attrition bias)	Low risk.	The study reports missing data on 2% of the study group.
Selective reporting (reporting bias)	Low risk.	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified
Other sources of bias		Prospective study. The authors do not explain the exclusion of patients with end-stage complications of diabetes or HIV No reference standard

Koehler [197], 2016		
Entry	**Judgment**	**Support for judgment**
Random sequence generation (selection bias)	High risk.	Method of recruitment was via primary care and newspaper advertisement. Therefore, significant risk of self-selection bias . 100 consecutive eligible patients recruited.
Allocation concealment (selection bias)	Low risk.	No allocation concealment, however unlikely to impact outcome of study.
Blinding of participants and personnel (performance bias)	Low risk.	No blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias)	Low risk.	No blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding.
Incomplete outcome data addressed (attrition bias)	Low risk.	The study reports missing data on 2% of the study group.
Selective reporting (reporting bias)	Low risk.	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified
Other sources of bias		Prospective study. No reference standard

Appendix 4 Camden and Islington EMISweb search strategy to obtain relevant primary care demographic and clinical data.

Gender
Age
FIB Score code, date value
ALT code, date, value
AST code, score, value
Bilirubin code, date, value
Albumin code, date, value
Platelets code, date, value
INR code, date, value
BMI latest code, date, value
History of Diabetes code, date

At risk of Diabetes code, date
Date referred to hepatology/gastroenterology code, date, associated text
Ultrasound performed code, date
Alcohol history code, date
History of Diab Type 1 code, date
History of Diab Type 2, code, date
History of hypertension code, date
History of Hypercholesterolemia code, date
History of IHD code, date
History of stroke code, date
History of Peripheral Disease code, date
History of Gout code, date
History of Hepatocellular carcinoma code, date
History of Ascites code, date

History of Varices code, date
History of hepatic encephalopathy code, date
History of liver biopsy code, date
History of liver transplantation code, date
History of inflammatory bowl disease code, date
History of obstructive sleep apnoea code, date
History of cancer code, date
History of smoking code, date
Weight
Height
Total cholesterol
HDL levels
Blood glucose
HBA1c

Ferritin
Gamma GT
Hepatitis neg test
Hepatitis C neg test
Autoimmune testing negative
Alpha-1 anti trypsin testing
Caeuroplasmin testing
Referred to dietician?
Evidence patient has lost weight/ cholesterol lowering agent/anti hypertensive/anti platelet therapy/bariatric surgery/is on Orlistat/previous prescriptions of steroids/Tamoxifen/amiodarone/
Calculated 10yr cardiovascular risk

Anti-diabetic medication Gliclazide/Sitagliptin/Pioglitazone hydrochloride/Metformin hydrochloride/Rosiglitazone Maleate/Glipizide/Tolbutamide/Glimepiride/
ELF Blood results code, date, value, associated text

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