Institution: University of Nottingham

Unit of Assessment: UoA1

Title of case study: Improving Chronic Liver Disease Diagnosis and Prevention: Implementing Novel, Non-Invasive Tests and Pathways in England, Scotland and India

Period when the underpinning research was undertaken: 2008 to 2018

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Professor Neil Guha	**Professor of Hepatology**	(NUHT/UoN: 2009 to present)
Professor Guruprasad Aithal	**Professor of Hepatology**	(NUHT/UoN: 2001 to present)

Period when the claimed impact occurred: 2015 onwards

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact

Chronic liver disease is the third most common cause of premature mortality in working age people in the UK. Research conducted at the University of Nottingham by Professors Neil Guha and Guru Aithal has transformed the care of patients with chronic liver disease in the community. Their prize-winning Scarred Liver Project delivers an innovative pathway that integrates primary and secondary care. The ELF ™ test (Enhanced Liver Fibrosis) is a blood test that detects liver scarring without the need for invasive liver biopsies. Together these have provided earlier detection, improved diagnostic accuracy and increased cost effectiveness. The Scarred Liver Project has been commissioned by the NHS and has shaped national and international pathways of care. ELF™ has been recommended by NICE, has been commissioned by the NHS and is estimated to save GBP406,000,000 across the UK. Commercial impact has been realised through sales of ELF™ in the UK generating revenue of over GBP3,000,000, and sales of ELF™ internationally.

2. Underpinning research

Chronic liver disease (CLD) is problematic to diagnose, the third most common cause of premature mortality in working age people in the UK and the only major killer without a national strategy. The Chief Medical Officers Report 2011 highlighted the need for earlier detection of CLD, when interventions can still effectively treat or reverse CLD. Detecting CLD is problematic as itis usually asymptomatic (silent) until it's reached advanced stages, resulting in substantially poorer outcomes for patients. Advanced stage symptoms can result in emergency admission to hospital following a decompensating event, with a 3-fold higher risk of death than ambulatory patients. Alongside this, current diagnostic tests in primary care, liver enzyme tests, lack precision. They are poorly sensitive, failing to detect patients with early stage CLD. They are poorly specific, being unable to distinguish between liver disease and other types of liver damage, resulting in unnecessary referrals to secondary care for a liver biopsy. Liver biopsies, although considered the gold standard for diagnosing CLD, are invasive, painful and have risks of complications including death. Professors Guha and Aithal were committed to improving outcomes for patients through earlier detection and improved diagnosis of CLD, whilst reducing the need for invasive tests. This has been achieved through the ELF™ and the Scarred Liver Project (SLP).

ELF™: A New Standard of Non-Invasive Liver Fibrosis Assessment

The ELF™ panel is a non-invasive blood test that can be used to diagnose and stage CLD in both primary and secondary care to the same standard as a liver biopsy. The ELF™ combines three serum biomarkers to assess the severity of a patient's liver fibrosis, indicating the extent of their CLD. In **2008 (1)** Professors Guha and Aithal worked collaboratively with academics from the University of Southampton and University of Newcastle. Professors Guha and Aithal **undertook the key diagnostic study in non-alcoholic fatty liver that established that the ELF™ had excellent performance in detecting significant and advanced fibrosis, compared to liver biopsies**. Professors Guha and Aithal's key diagnostic study showed that by using ELF™ **liver biopsies could be avoided in 80% of cases**. Professors Guha and Aithal's pivotal, collaborative research and

validation study **(1)** provided the critical clinical evidence for the CE marking (2011) and subsequent NICE recommendation **(2016)** of the ELF™.

The Scarred Liver Project: A Novel, Non-Invasive Pathway

The Scarred Liver Project (SLP) is an innovative new CLD diagnostic pathway that integrates primary and community care, reducing demands on secondary care. Patients are screened and stratified for CLD with Fibroscan, which uses non-invasive transient elastography (TE) and provides a liver stiffness measurement (LSM). The LSM indicates the extent of CLD. Referrals for screening are made directly from primary care. Screening is carried out by nurses in a community setting, rather than hepatology specialists in a secondary setting, reducing demand on secondary care. Alongside this, choice for screening of patients in primary care targets known risk factors for CLD.

In **2012**, Guha and Aithal undertook a study **(2)** which confirmed previous findings that '*LSM correlates with liver biopsy for the detection of cirrhosis and significant fibrosis*'. It evidenced nurses achieved results comparable with physician operators in secondary care thus establishing the foundations of a nurse led service in community care. They then performed a clinical study in **2013 (3)** comparing TE against clinical acumen and routine tests for detecting CLD. It found TE was equivalent for the detection of cirrhosis, and crucially, superior for the detection of significant fibrosis, compared to clinical acumen. This provided the rationale of how and why non-invasive tests should be deployed in a community rather than a secondary setting. In **2015 (4)** they completed a study using TE in a primary care setting. Screening of patients for CLD targeted multiple risk factors (type two diabetes and alcohol use) and found a **140% increase in detection of liver cirrhosis**. 67% of the new cirrhosis cases had normal liver enzymes, which current tests would have failed to identify, further demonstrating the superiority of TE compared to current tests. In **2018 (5)** a further study identified obesity as an additional risk factor for CLD and found risk of cirrhosis was far higher for patients with multiple risk factors.

Alongside their clinical research, to innovate their new pathway, in **2017 (6)** they conducted a health economic analysis that demonstrated the pathway was cost effective, showing an ICER of 2138 per QUALY gained. The pathway is prizewinning, has been CCG commissioned and has received national acclaim.

3. References to the research

Underpinning research:

1. **Guha IN... Aithal GP...** 2008. Noninvasive markers of fibrosis in nonalcoholic fatty liver disease: Validating the European Liver Fibrosis Panel and exploring simple markers. *Hepatology* 47(2), 455-460. DOI: 10.1002/hep.21984

2. ...**Aithal GP**. 2012. Development and evaluation of a nurse-led transient elastography service for the staging of hepatic fibrosis in patients with suspected chronic liver disease. QJM 105(8), 749-54. DOI: 10.1093/qjmed/hcs043

3. ...**Aithal GP**, **Guha IN**. 2013. The performance of transient elastography compared to clinical acumen and routine tests - what is the incremental diagnostic value? *Liver International* 33(2), 172-9. DOI: 10.1111/liv.12017

4. ...**Aithal GP**, **Guha IN**. 2015. Direct targeting of risk factors significantly increases the detection of liver cirrhosis in primary care: a cross-sectional diagnostic study utilising transient elastography. *BMJ Open* 5(4), e007516. DOI: 10.1136/bmjopen-2014-007516

5. ...**Aithal GP**, **Guha IN**. 2018. Obesity and type 2 diabetes are important risk factors underlying previously undiagnosed cirrhosis in general practice: a cross-sectional study using transient elastography. *Alimentary Pharmacology and Therapeutics* 47(4), 504-515. DOI: 10.1111/apt.14463

6. ...**Aithal GP... Guha IN...** 2017. Economic evaluation of a community-based diagnostic pathway to stratify adults for non-alcoholic fatty liver disease: a Markov model informed by a feasibility study. *BMJ Open* 7(6), e015659. DOI: 10.1136/bmjopen-2016-015659

Underpinning grant:

G1 2014-2020 Awarded to: Professor Neil Guha. 'Adoption and Spread of Innovation' grant for the Scarred Liver Project. Sponsor: East Midlands Academic Health Science Network. GBP910,170.44

4. Details of the impact

Chronic liver disease (CLD) is problematic to diagnose and the third most common cause of premature mortality in working age people in the UK. Research by Professors Guha and Aithal has improved the outcomes for patients through earlier detection and improved diagnosis of CLD, whilst reducing the need for invasive tests. This has been achieved through the ELF™ and the Scarred Liver Project (SLP). The results have been improvements to clinical standards, reductions in healthcare costs and commercial impact.

ELF™: A New Clinical Standard for diagnosing Chronic Liver Disease

In the most recent NICE guidelines (**2016**) on the assessment and management of Non-alcoholic fatty liver disease, the **ELF™ was the recommended test for diagnosis and ongoing monitoring of Liver Disease (A(a), p. 15-6).** In the UK, the National Institute for Health and Care Excellence (NICE) provides national evidence-based guidance and advice to improve health and social care and are considered when planning and delivering services. **When compared with up to 17 diagnostic strategies for CLD, including liver biopsy, the ELF™ was found to be '*the most clinically and cost-effectiveness option*' (A(a), p. 123), consistently ranking first compared to other diagnostic strategies (A(a), p. 115-6, p. 120)**. The ELF™ was considered the most '*practical*' **(A(a), p. 138)** and '*appropriate*' **(A(a), p. 125)** test for advanced fibrosis in adults. The NICE guidelines also identified that rather than using ELF in combination with other tests, such as FIB-4, '*using ELF alone requires only a single blood test, and therefore does not require people to return to the surgery for an additional appointment and additional blood test*' **(A(a), p. 124)**. The **ELF™ was also recommended in the British Society of Gastroenterology (BSG) Guidelines (2018) on the management of abnormal liver blood tests (A(b), p. 6)**.

ELF™: Implementation of a New Clinical Standard

The clinical study carried out in 2008 by Professors Guha and Aithal **(1)** was fundamental to the success of ELF™, which is manufactured by Siemen's. As the Clinical Marketing Manager Chemistry & Immunoassay at Siemen's explains '***(1)** made a critical contribution to the subsequent commercialisation of the ELF™ test in the UK and Europe and contributed to the NICE approval for ELF™ in 2016'* **(B(a), p. 1)**. To 11th September 2020 CLD care has improved across the UK as the ELF™ has been implemented in the following:

- **Pathways: Camden CCG and Islington CCG (C, p. 372)**, covering Camden and Islington, **NHS Scotland Tayside Health Board's award-winning iLFT Pathway (B(b))**, covering Angus, Dundee, Perth and Kinross
- **Hospitals: Southampton University Hospitals (B(a), p. 2)** covering the whole of Hampshire, Dorset, Oxfordshire and parts of Somerset**, University of the North Midlands (B(a), p. 2)**, covering Staffordshire & North Midlands CCGs, **Leeds Teaching Hospitals Liver Unit (B(a), p. 2)**, covering referral work from West Yorkshire, Humberside and Lancashire
- **Services: HSL Pathology** (UCLH, Royal Free and The Doctor's Laboratory Pathology Partnership) **(B(a), p. 1)**, covering North London, North Home Counties and many private hospitals in London, **NHS Black Country Pathology Services** (Sandwell and West Birmingham NHS Trust, The Dudley Group NHS Foundation Trust, The Royal Wolverhampton NHS Trust and Walsall Healthcare NHS Trust) **(B(b))**, covering Dudley, Sandwell, Walsall and Wolverhampton

Camden and Islington CCG's performed an evaluation of the effect between March 2014 and May 2016 of introducing a referral pathway based on the BSG Guidelines, using the ELF™ as the second line screening test following the FIB-4 score. **The pathway was highly successful, detecting 5 times more cases of advanced fibrosis and cirrhosis than standard care and reducing unnecessary referrals from primary to secondary care by 81% (C, p. 374)**. Of the 1,452 patients, just over a quarter (387, 27%) needed an ELF™ test due to an indeterminate FIB-4 score, with 60% subsequently identified as high risk of advanced fibrosis **(C, p. 373)**. Of the 275 patients referred to secondary care, 45 patients were identified with advanced fibrosis or cirrhosis. **Of these 45 patients, only 7 were referred due to FIB-4 alone, with 38, more than 5 times as many, being referred from the combination of FIB-4 and ELF™ (C, p. 374).** This clearly demonstrates the importance

of the ELF™ in the increased detection and reduced referrals achieved by this pathway. The economic impact of this approach has been highlighted showing that across the UK a saving of GBP406,000,000 in 1 year (a decrease of 23% in expenditure and the greatest cost saving) could be made by managing NAFLD using this 2-tier strategy **(D, p. 11, Table 5)**.

In September 2020 the Clinical Marketing Manager at Siemen's reported: '*ELF™ has now been incorporated into the award winning iLFT Pathway and used to clear Fibroscan waiting lists, which have built up during the COVID19 pandemic. iLFT is seen as best practise by NHS Scotland, consequently it is being rolled out across Scotland*' **(B(b), q. 1).**

ELF™: Commercial Impact

Between 1st August 2013 to 31st July 2020 there has been an increase of **9 times the UK sales of ELF™ tests** (exact sales figures not provided) **(B(b), q. 2)**, with **UK revenue of over GBP3,000,000 (B(b), q. 3)**. This has created new jobs as '*Manufacturing capacity for immunoassays of which ELF™ is part have expanded in both the USA and China*' **(B(b), q. 4)**. The ELF™ test is also sold into Japan '*the biggest user, on a par with the UK*' and Europe (Spain, Czech Republic and Austria) **(B(b), q. 5)**.

SLP: Award Winning, with National Influence and Acclaim

- **NICE**: in 2018 the SLP featured on the NICE website as an exemplar of how a pathway should adopt NICE guidelines **(E(a)),** in 2019 the SLP was a runner up in the NICE Shared Learning Awards **(E(b))** and in June 2020 SLP research **(4, 6)** contributed half of the evidence in a NICE Medical Technology Innovation briefing **(E(c), pp. 5-8, 2 of 4 papers)**
- **Healthcare providers and leaders:** in 2018 the SLP was selected by The Royal College of General Practitioners to feature in their 'Liver Disease Toolkit' as an example of 'Innovation and Best Practice in Primary Care' **(E(d))**, in 2019 the SLP received the 'Improving the Value of Diagnostic Services' Award **(E(e))** from the Health Services Journal, a journal directed towards commissioners of health
- **NHS England innovation:** in 2018 the SLP and Professor's Guha and Aithal featured in a Kings Fund report **(E(f), p. 33-5)** commissioned by the NHS **(E(f), p. 2)** to contribute to facilitating faster adoption of innovation in the NHS **(E(f), p. 4)**, in 2018 the SLP was also highlighted in a NHS Innovation Accelerator Evaluation Final Report, where Professor Guha featured as a fellow **(E(g), p. 12)**

SLP: Impact on Clinical Practice

The SLP pathway was CCG commissioned in 2016 and currently covers a population of 700,000 and 4 CCGs (encompassing 100 GPs) in Nottinghamshire **(F, p. 87, G(a))**. An evaluation was completed of the first 12 months following implementation of the pathway (between 1st September 2016 and 30th August 2017) compared to current BSG guidelines **(F, p. 87)**. 968 patients were reviewed through this pathway, 23% had significant liver disease and 39% of this group would have been missed using current guidelines **(F, p. 88 - 89)**.

The SLP is a cost-effective pathway **(5)** and a 2019 Lancet Commission final report referred to it as an exemplar proven model of care **(H, p. 10)**. The report highlighted '*the prizewinning Scarred Liver Project...need to be rolled out more widely in an effective context across the country*' **(H, p. 10)**. The paper also reported the pathway led to a '*reduction in unnecessary referrals to hospital-based consultant clinics with consequent cost savings*' **(H, p. 10)**. Excitingly, the risk factors for screening can be adapted to meet local needs. Nottingham are key partners in a GBP2,500,000 Innovate UK grant which is focussed on adopting a community liver pathway in Manchester **(I)**. Despite the challenges with adoption of innovation highlighted in the NHS commissioned Kings Fund Report **(E(f))** this new community liver pathway in Manchester, based on the concepts of the SLP, began in September 2020. The expectations are that 800 patients per year will travel through this pathway.

SLP: Improved Patient Care and Wellbeing

The 2019 Lancet Commission final report identified that '*Screening for early liver disease with transient elastography by general practitioners is worthwhile for detection of previously*

undiagnosed cases of cirrhosis at a stage when treatment measures can be effective' **(H, p. 1)**. Since inception of the pathway, between September 2016 and July 2020, 4,187 patients have been stratified by this pathway and received interventions to address their underlying risk factors **(G(a)).** Patients having been identified with CLD through the SLP are engaging with lifestyle changes to prevent progression of CLD **(J).** As 1 patient explains: *'the doctor looked us straight in the face and said another week and she would be dead. And that's where I reached out to the pathway and I have never looked back because they've educated me and they have helped me to be so aware of my body'* **(J, Clare's video, 0:58 to 1:13)**. 1 patient also commented '*...and they diagnosed that I had liver cirrhosis. I've always considered cirrhosis being a drink related problem and I haven't drunk for thirty-odd years*' **(J, Malcolm's video, 0:59 to 1:12)**.

SLP: International developments

In Trivandrum, the capital of Kerala (India) with a population of 400,000, 2 programmes have taken place based on the SLP. Between December 2017 and December 2019, 12,433 people have had TE in the community, based on their risk factors for chronic liver disease. Of these, 24% had high liver stiffness and 421 (3.39%) of patients had liver stiffness associated with cirrhosis. **These patients are now receiving specialist care (K)**. The SLP has been incorporated into the development of the 'Preventive Hepatology' project. As the President of Anad Grama Panchayat (Local Self Government in Kerala) explains '*the innovation and lessons from the 'Scarred Liver Project' has shaped health care related to chronic liver disease in our community*' **(K)**. The SLP was also selected as 1 of only 10 Impact case stories from Europe and Central Asia for the World Evidence Healthcare Day in 2020 **(G(a), G(b) Europe & Central Asia)**.

5. Sources to corroborate the impact

A(a) NICE Guideline: Non-alcoholic fatty liver disease (NAFLD): assessment and management (2016) (weblink, last accessed 7th January 2021), **A(b)** British Society of Gastroenterology Guideline: Guidelines on the management of abnormal liver blood tests (2018), DOI: 10.1136/gutjnl-2017-314924
B(a) Siemens letter of support, **B(b)** Siemen's supplementary email, with attachment
C Prospective evaluation of a primary care referral pathway for patients with non-alcoholic fatty liver disease (2019), DOI: 10.1016/j.jhep.2019.03.033
D Cost-comparison analysis of FIB-4, ELF and fibroscan in community pathways for non-alcoholic fatty liver disease (2019), DOI: 10.1186/s12876-019-1039-4
E(a) NICE Shared learning database (weblink, last accessed 7th January 2021), **E(b)** NICE Shared learning award winners and finalists 2019 (weblink, last accessed 7th January 2021), **E(c)** NICE Medical Technology Innovation briefing 2020 (weblink, last accessed 6th January 2021) **E(d)** Royal College of General Practitioners 'Liver Disease Toolkit', 'Innovation and best practice in primary care' tab, (weblink, last accessed 8th January 2021), **E(e)** HSJ Value Awards 2019: Improving the value of diagnostic services award (weblink, last accessed 7th January 2021), **E(f)** Kings Fund report: Adoption and spread of innovation in the NHS 2018 (weblink, last accessed 8th January 2021)**, E(g)** NHS Innovation Accelerator Evaluation 2018 (weblink, last accessed 8th January 2021)
F Development and implementation of a commissioned pathway for the identification and stratification of liver disease in the community (2019), DOI: 10.1136/flgastro-2019-101177
G(a) World Evidence-Based Healthcare Day 2020 case study (weblink, last accessed 7th January 2021), **G(b)** World Evidence-Based Healthcare Day 2020 map of impact, 'Europe and Central Asia' (weblink, last accessed 8th January 2021)
H Unacceptable failures: the final report of the Lancet Commission into liver disease in the UK (2019), DOI: 10.1016/S0140-6736(19)32908-3
I University of Manchester Article (2020): Multimillion pound scheme could make early diagnosis of liver disease a reality (weblink, last accessed 7th January 2021)
J Scarred Liver Project website (weblink, last accessed 6th January 2021)
K Letter of support from the president of Local Self Government in Kerala