

Institution: University of Dundee		
Unit of Assessment: UoA 1 Clinical Medicine		
Title of case study: Intelligent liver function testing		
Period when the underpinning research was undertaken: 2015-2017		
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 John Dillon	Professor of Hepatology and Gastroenterology	2006 to date
Period when the claimed impact occurred: 2018 to date		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Professor **Dillon**'s team has created new, highly cost-effective automated pathways for the investigation of abnormal liver function tests. This has led to improved patient outcomes and quality of care through the earlier diagnosis and treatment of liver disease, thus helping to prevent progression to cirrhosis and liver failure. The "intelligent Liver Function Test" has been adopted as standard NHS care in Tayside and is being rolled out in other regions across the UK. Since 2018 over 7,000 patients have benefitted from this approach, which has informed Scottish national health policy and contributed to the effective elimination of hepatitis C in Tayside.

2. Underpinning research

Liver disease is a leading cause of death in individuals <65 years of age in England, especially in the 35–49 year age group, and deaths from hepatocellular carcinoma have tripled since 1997. The Scottish Public Health Observatory estimates that liver disease accounted for 16.3 deaths per 100,000 population in Scotland in 2018.

Each year, approximately 23.5 million LFTs are carried out by GPs in the UK to detect liver disease or as a measure of general wellness; **Dillon**'s research, however, has demonstrated frequent failure to follow up properly on the results of such testing.

In a retrospective study published in 2003, **Dillon**'s team integrated electronic health record data for residents of Tayside between 1980-1999 and identified abnormal LFT findings in >21,000 individuals (~5%; 72,871 abnormal results); however, few of these were further investigated, leading to the diagnosis of a specific liver disease in only 1770 cases [**R1**]. This research both demonstrated the scale of abnormal LFTs and highlighted shortcomings in follow-up. Investigation of abnormal results was inefficient, often leading to delays in treatment and subsequent adverse effects on health because of late diagnosis.

These findings led **Dillon** to initiate the Abnormal Liver Function Investigation Evaluation (ALFIE) study, a population-based historical cohort study initiated in 2007 which addressed the population of Tayside between 1989-2003. The ALFIE study examined how follow-up of some 96,000 patients with abnormal LFT findings was managed in general practice, revealing that abnormal results occurred in >20% of tests, but more than half of these were not investigated further [**R2**]. Of the patients who were investigated, 3% had liver disease with the potential to progress to life-limiting complications, highlighting the importance of timely investigation and intervention [**R3**].

A subsequent systematic review identified non-alcohol-related fatty liver disease, alcoholic liver damage and viral infections as the commonest aetiologies associated with abnormal LFTs [R4]. Each of these can be prevented, mitigated or cured if diagnosed early enough.

In further research, **Dillon** developed minimum diagnostic criteria for liver disease based on clinical information, LFT results and possible causes [R5]. Existing biomarkers, originally developed to diagnose cirrhosis, were repurposed to exclude fibrotic liver disease. This made it possible to identify patients with low risk of liver complications, facilitating effective triage of liver abnormalities and their subsequent management through referral or GP management.

These elements have now been integrated to create a system for automated diagnosis using tracked multi-analyser platforms which are widely available in clinical laboratories. Laboratory information management systems were programmed to redirect samples and integrate the resulting clinical data using an intelligent liver function testing (iLFT) algorithm which generates one of 32 possible diagnostic outcomes and associated management plans.

The key to ensuring adoption of the iLFT approach was making the tool automatic and easier than standard of care. A single sample can provide results which would previously have required up to six separate bloods, thus obviating the need for repeated GP appointments and reducing infection risks from repeated blood sampling.

A step-wedge randomised control trial of the system [R6] demonstrated a 43% increase in the diagnosis of liver disease compared with standard protocols and diagnostic accuracy >90%. Additional benefits were a reduction in GP workload compared to current ideal investigation and savings to the NHS of £3,216 per patient lifetime.

3. References to the research

[R1] **Steinke**, D. T., Weston, T. L., Morris, A. D., MacDonald, T. M. & **Dillon**, J. F. (2003) The epidemiology of liver disease in Tayside database: a population-based record-linkage study. *Journal of Biomedical Informatics*, 35 (3), pp. 186-193; DOI: [10.1016/s1532-0464\(02\)00526-9](https://doi.org/10.1016/s1532-0464(02)00526-9).

[R2] **Donnan**, P. T., McLernon, D., **Dillon**, J. F., Ryder, S., Roderick, P., Sullivan, F. & Rosenberg, W. (2009) Development of a decision support tool for primary care management of patients with abnormal liver function tests without clinically apparent liver disease: a record-linkage population cohort study and decision analysis (ALFIE). *Health Technology Assessment*, 13 (25), pp. iii-iv, ix-xi, 1-134; DOI: [10.3310/hta13250](https://doi.org/10.3310/hta13250).

[R3] **McLernon**, D. J., **Dillon**, J. F., Sullivan, F. M., Roderick, P., Rosenberg, W. M., Ryder, S. D. & **Donnan**, P. T. (2012) The utility of liver function tests for mortality prediction within one year in primary care using the algorithm for liver function investigations (ALFI). *PLoS One*, 7 (12), e50965; DOI: [10.1371/journal.pone.0050965](https://doi.org/10.1371/journal.pone.0050965).

[R4] Radcke, S., **Dillon**, J. F. & Murray, A. L. (2015) A systematic review of the prevalence of mildly abnormal liver function tests and associated health outcomes. *European Journal of Gastroenterology and Hepatology*, 27 (1), pp. 1-7; DOI: [10.1097/meg.000000000000233](https://doi.org/10.1097/meg.000000000000233).

[R5] **Miller**, M. H., Fraser, A., Leggett, G., MacGilchrist, A., Gibson, G., Orr, J., Forrest, E. H., Dow, E., Bartlett, W., Weatherburn, C., Laurell, A., Grant, K., Scott, K., Neville, R. & **Dillon**, J. F. (2018) Development and validation of diagnostic triage criteria for liver disease from a minimum data set enabling the 'intelligent LFT' pathway for the automated assessment of deranged liver enzymes. *Frontline Gastroenterology*, 9, pp. 175-182; DOI: [10.1136/flgastro-2017-100909](https://doi.org/10.1136/flgastro-2017-100909).

[R6] **Dillon**, J. F., Miller, M. H., Robinson, E. M., Hapca, A., Rezaiehemami, M., Weatherburn, C., McIntyre, P. G., Bartlett, B., **Donnan**, P. T., Boyd, K. A. & Dow, E. (2019) Intelligent liver function testing (iLFT): A trial of automated diagnosis and staging of liver disease in primary care. *Journal of Hepatology*, 71 (4), pp. 699-706; DOI: [10.1016/j.jhep.2019.05.033](https://doi.org/10.1016/j.jhep.2019.05.033).

Funding:

British Liver Trust (1999-2001): "Epidemiology of liver disease in Tayside", 7/jfd3898, £106,076
John **Dillon**

NIHR HTA (2005-2009): "Development of a decision support tool to facilitate primary care management of patients with abnormal liver function tests without clinically apparent liver disease", 03/38/02, £177,000 plus £53,588 Peter **Donnan** and John **Dillon**

CSO (2015-2017): "A pilot evaluation of an intelligent liver diagnostic pathway: making sense of LFTs for patients, GPs and the NHS in Scotland" CZH/4/1090, £222,249 John **Dillon**

4. Details of the impact

The iLFT approach provides a rapid, reliable means of identifying abnormal LFTs which require specialist follow-up, thus improving patient outcomes through timely intervention and NHS infrastructure through the exploitation and adaptation of existing clinical tools and processes. By identifying the highest priority patients it facilitates workload management in hepatology specialist services and builds the confidence of GPs in handling a previously complex and unwieldy diagnostic pathway. This has contributed to better diagnosis of liver disease, often at an early stage when lifestyle interventions are effective, with minimal workload implications for GPs and inconvenience to patients.

Benefits to patients and population health

In August 2018, NHS Tayside adopted iLFT as standard care accessible to all its GP practices. During its first year, iLFT generated >2000 diagnoses from 1824 samples with an abnormality in their initial LFTs **[E1]**. Compared with current real-world practice it did not increase overall GP workload; indeed, 21/23 GPs involved in the trial felt that iLFT reduced their workload. Since July 2020, NHS Tayside has performed Enhanced Liver Fibrosis testing, a further refinement of iLFT, on >500 patients; of these, 44% had a score which showed they could safely be managed in the community, thus reducing pressure on in-patient services **[E2]**.

By testing all samples for viral hepatitis, iLFT made it possible to identify unsuspected carriers of hepatitis C and target them for treatment, preventing wider community transmission and contributing to the elimination of hepatitis C in Tayside by the end of 2019. Having become the first region in the world to effectively eradicate the virus, Tayside has already met the WHO target of eliminating hepatitis C as a public health threat by 2030 **[E3]**.

National adoption in Scotland and the wider UK

Following the success of iLFT in Tayside the Scottish Access Collaborative (part of the Scottish Government's Directorate for Health Performance and Delivery) recommended national roll-out **[E4]**. Implementation groups have been established in NHS Greater Glasgow and Clyde, Fife, Lothian and Lanarkshire; when roll-out is complete the service will be available to 1.6 million people. The Clinical Lead for the introduction of iLFTs in the Modern Patient Pathways Programme writes **[E5]**:

The introduction of iLFTs in Tayside resulted in the correct patients being seen by the correct staff, in the correct setting, at the correct time.....The Scottish Government has adopted this as being an area where there is not only the potential for better patient management but also for significant financial benefit to the NHS.

The Lancet Commission for Liver Disease has recommended iLFT for implementation to reduce the burden of liver disease **[E6]** and it is now being adopted across the UK. North Cumbria Integrated Care NHS Foundation was the first to have a working system **[E7]** and iLFT is under consideration by the Wales Liver Disease Delivery Plan **[E8]**.

Global recognition

In 2019 the **Dillon** team's achievements in integrated clinical care were rewarded with the UNIVANTS Healthcare Excellence Award; this award recognises teams who collaborate across disciplines to transform healthcare delivery and patient lives, and involves a rigorous selection process conducted by seven leading international healthcare organizations including The International Federation of Clinical Chemistry and Laboratory Medicine [E9]. The iFLT has also won accolades for innovation from the British Society of Gastroenterology and the Royal Colleges of Physicians and Pathologists.

Benefit to GPs

One reason for the low follow-up rate for abnormal LFTs is that many GPs lack confidence in interpreting these findings and using them to inform referral decisions, partly because of the lack of a quantitative relationship between abnormal LFT findings and severity of disease: very high serum enzyme levels may resolve spontaneously whereas lower levels often persist and can lead to chronic liver disease. Referring everybody with an abnormal LFT is unnecessary and would overwhelm specialist hepatology services; by providing a rapid and reliable triage process, iLFT ensures that only those individuals requiring specialist services are referred. Following roll-out of iLFT in Tayside, **Dillon** surveyed the views of 100 GPs, over a third of the workforce [E10]. The opinions expressed were overwhelmingly positive (Table 1).

Target group: all GPs in Tayside	Yes	No
Responded to survey	100	-
Have used iLFT	97	3
Liked iLFT	96	1
Would recommend iLFT to a colleague	95	2
Found iLFT outcomes helpful or very helpful	95	2

Table 1: Outcomes of a survey of GP opinion on iLFT

The features most liked by respondents were the automatic calculation of fibrosis scores and information around referral criteria (80 respondents) and the reduction in number of consultations required before arriving at a diagnosis (77 respondents).

The benefits of iLFT to healthcare providers are succinctly summarized by North Cumbria Integrated Care NHS Foundation Trust [E7]:

The journey to date has been truly transformational, empowering primary care to have the confidence in managing low risk liver disease, expediting care for those with significant liver disease who truly need secondary care input and undoubtedly shortening the timescales in the assessment and management of liver disease across the health economy.

5. Sources to corroborate the impact

[E1] Macpherson, I., Nobes, J. H., Dow, E., Furrie, E., Miller, M. H., Robinson, E. M. & Dillon, J. F. (2020) Intelligent Liver Function Testing: Working smarter to improve patient outcomes in liver disease. *Journal of Applied Laboratory Medicine*, 5 (5), pp. 1090-1100; DOI: [10.1093/jalm/jfaa109](https://doi.org/10.1093/jalm/jfaa109).

[E2] Chief Executive, NHS Tayside 2021. Covid-19: Chief Executive Weekly Brief 15 January 2021. The iLFT is discussed on pages 4-5.

[E3] NHS Tayside. (2020) *NHS Tayside first region in the world to eliminate hepatitis C* [Online]. Available: https://www.nhstayside.scot.nhs.uk/News/Article/index.htm?article=PROD_339892 [Accessed 31st December 2020]

[E4] NHS Scotland (2019) Demand Optimisation in Laboratory Medicine: Phase II Report. Available at: <https://www.gov.scot/publications/demand-optimisation-laboratory-medicine-phase-ii-report/> [Accessed 12th February 2021]. Section 6.1.1 (pages 28-29) discusses the NHS Tayside iFLT pathway study.

[E5] Clinical Lead for iLFTs, Modern Patient Pathways Programme 2020. Rollout of iLFT by Modern Patient Pathways Programme. Letter of Support, 2nd November 2020.

[E6] Williams, R., Alexander, G., Aspinall, R., Batterham, R., Bhala, N., Bosanquet, N., Severi, K., Burton, A., Burton, R., Cramp, M. E., Day, N., Dhawan, A., **Dillon**, J., Drummond, C., Dyson, J., Ferguson, J., Foster, G. R., Gilmore, I., Greenberg, J., Henn, C., Hudson, M., Jarvis, H., Kelly, D., Mann, J., McDougall, N., McKee, M., Moriarty, K., Morling, J., Newsome, P., O'Grady, J., Rolfe, L., Rice, P., Rutter, H., Sheron, N., Thorburn, D., Verne, J., Vohra, J., Wass, J. & Yeoman, A. (2018) Gathering momentum for the way ahead: Fifth report of the Lancet Standing Commission on Liver Disease in the UK. *Lancet*, 392 (10162), pp. 2398-2412; DOI: [10.1016/s0140-6736\(18\)32561-3](https://doi.org/10.1016/s0140-6736(18)32561-3). Intelligent liver function testing is mentioned in the text (pages 2405-2406) and the Table on p2406.

[E7] North Cumbria Integrated Care NHS Foundation Trust. 2020. The Impact of iLFT Research and Practice. Letter of Support, 26th October 2020.

[E8] Clinical Lead for the Wales Liver Disease Delivery Plan. 2020. Intelligent Liver Function Tests. Letter of Support, 21st October 2020.

[E9] UNIVANTS of Healthcare Excellence. (2019) *2019 Global Winners* [Online]. Available: <https://www.univantshce.com/int/en/2019-winners> [Accessed 8th January 2021]. "Intelligent liver function testing (iFLT): A cost-effective way to increase early diagnosis of liver disease" is the first prize winner mentioned and is described in detail on pages 6-7 of the pdf.

[E10] **Dillon**, J. 2020. Survey of General Practitioner opinion on Intelligent Liver Function Testing (Unpublished data).