

**Article:**

Iain Macpherson, et al.

Intelligent Liver Function Testing: Working Smarter to Improve Patient Outcomes in Liver Disease.

J Appl Lab Med 2020;5: 1090-1100. <https://doi.org/10.1093/jalm/jfaa109>

Guest: Dr. Jennifer Nobes is a specialty trainee in chemical pathology in NHS Tayside in Dundee, Scotland.

Randye Kaye:

Hello and welcome to this edition of JALM Talk, from *The Journal of Applied Laboratory Medicine*, a publication of the American Association for Clinical Chemistry. I'm your host, Randye Kaye.

Liver disease accounts for approximately 2 million deaths per year worldwide. However, the most common causes of liver disease such as alcohol abuse and viral hepatitis are largely preventable or curable. Early diagnosis of liver dysfunction may prevent the progression to more serious conditions of liver fibrosis and cirrhosis. However, commonly used diagnostic liver tests may be frequently abnormal and can be considered nonspecific, leading to missed opportunities to diagnose disease at an early stage.

A Special Report in the September 2020 JALM Special Collection: Value of Laboratory Testing and the Value Proposition, describes the development and piloting of the intelligent liver function testing pathway, which consists of automated algorithms of reflexive testing and clinical data to increase the diagnostic yield of liver function testing. A joint first author of the report is Dr. Jennifer Nobes. Dr. Nobes is a specialty trainee in chemical pathology in NHS Tayside in Dundee, Scotland, and she's an honorary clinical teacher for the University of Dundee. Dr. Nobes is our guest for this podcast. Welcome Dr. Nobes.

Jennifer Nobes:

Thanks very much for having me.

Randye Kaye:

What led you to develop the intelligent liver function testing pathway, or ILFT? Why is there a need for a smarter liver function testing?

Jennifer Nobes:

So liver disease is a really big issue globally. So it accounts for over 2 million deaths a year and really across the world, we have a problem with viral hepatitis. And then increasingly in more economically developed countries, we are also getting an increasing burden from non-alcoholic or metabolic-associated fatty liver disease, as I think we will soon be calling it, and also alcohol-related liver disease. So that's the problem across the world and narrowing in a bit, just looking at the UK, there was a really excellent article called "Addressing Liver Disease in the UK," which was

published in the *Lancet*. And there's a brilliant infographic that I would really recommend that people look at because it shows that in almost all major disease areas--so that's cancer, heart disease, stroke and premature mortality--so that's deaths in people under the age of 65, has been decreasing greatly between 1970 and 2010. But from liver disease, that mortality has increased by around 550% over those 40 years. So it's really the major disease area where we're just not making inroads and we're not able to identify these patients early and get them the treatment that's going to make them better.

And then even more locally than that, there was a study done over a 14-year period which was called ALFIE. So that's the abnormal liver function investigations and evaluation that was done here in Tayside, and that involved looking at 96,000 patients who had LFT, liver function test panels performed. And that found that more than one in five of them had at least one abnormality in that panel of tests and around one to two per hundred people went on to develop a chronic liver disease. So it's a very common problem that people have these abnormal liver function tests, and there's also a significant proportion of people that have chronic liver disease.

When we looked into that a bit more, even if you had an abnormal liver function test, around half of them weren't followed up in the way that guidelines would suggest that we do. And there could be lots of reasons for this. I mean, it can be that the abnormal test wasn't deemed a problem by the physician. It can be that the doctor did want to investigate it further, but the patient never turned up. It could maybe be that they explained it away by a drug or a different pathology that was causing this abnormal liver function test. But if we don't further investigate these people we can't identify which of them will go on to get chronic liver disease. And we found that even for the ones that were diagnosed, there were loads of different appointments that were required in that process and what we really want to do was streamline it so that we can identify these patients early, stop them from progressing to things like cirrhosis and hepatocellular carcinoma, and make sure that we can get them the treatment that they need early.

Randye Kaye:

Thank you. That's so important. Now, the Special Report describes that the ILFT pathway uses test results already routinely generated from biochemistry, hematology, immunology, and virology clinical testing areas, but were there any changes or additional resources required within the laboratory workflow to implement ILFT?

Jennifer Nobes:

So, we actually needed to do very little to the laboratory and I guess that was kind of the beauty of the intelligent liver function testing project.

And we're really lucky here in Dundee, we've got state-of-the-art automation. So on the track field, the automated track, we've got analyzers that do our biochemistry, hematology, and the serology for the virology testing. So really, where we needed to make changes was within the auto communications process. So we needed the requesters of the tests to be able to input some clinical details, which we wouldn't normally receive. So that's things like the body mass index of the patient and also their alcohol intake, so whether or not that's more or less than the UK guidance, which is 14 units per week as a maximum. So we needed that information to be able to go in and then for it to be able to be manipulated as data and really all the logic comes in our laboratory information management system and middleware. So that cascades the full liver screen and moves it around on the track between analyzers in real time. So as I say, the beauty of it is that we had all that automation in place and it just means that we can get all those tests done without having to interact too much with the sample.

Randye Kaye:

Now, it's been two years since the ILFT pathway was incorporated into your hospital and region of Scotland. How's it gone so far and what impacts have you seen it have on patient care?

Jennifer Nobes:

So, almost 6,000 patients have gone through the pathway over the last two years just at the start of August there. That was when we passed the two-year mark. We're finding that our most common diagnoses, as you would expect in our local area, are nonalcoholic fatty liver disease or nonalcoholic steatohepatitis. So that's about one in three of our diagnoses that we're generating from this intelligent pathway and about one in five of the diagnoses we generate are alcohol-related liver disease. But we've also identified some rarities and some things that are really good pickups using the pathway. So we've got quite a few cases of primary biliary cholangitis that we've picked up, some autoimmune hepatitis. We've had more than 30 patients with hemochromatosis, and more than 30 patients with hepatitis C, and handful of patients too with hepatitis B. And I think it's important to remember that these are probably patients who wouldn't be going through a lot of the screening programs that are in place for viral hepatitis because they would be deemed low-risk. So it's really valuable that we're picking them up through this alternate pathway. We've also found a few alpha-1 antitrypsin deficiencies as well, which might have impacts not only for them but also for the future generations in their family.

Randye Kaye: All right, thank you, very interesting. So how about issues or unanticipated setbacks, anything like that happen that required you to make updates or changes along the way?

Jennifer Nobes: I think as it with the case with any new test or pathway we've have to adapt and take on some feedback especially from our users because they're the people that were really making this for. And the majority of this has been sort of GP-backed to make the test requesting as straightforward as possible. The primary care physicians, or GPs as we call them here, are very time stretched. So it's very useful to have an easy procedure for them to follow just a few clicks on the screen in order to be able to request this pathway. We also identified some recurrent errors, so parts of their requesting process that were being easily missed such as forgetting to put in the body mass index. And we've changed the interface that they're using so that we minimize all of these errors. The biggest change that we've introduced recently has been the enhanced liver fibrosis score. So that's a direct assay, which is actually measuring markers of collagen or extracellular matrix turnover in the liver. Before then, we've been using calculated fibrosis markers and by introducing this direct marker as well, we can further stratify the risk of fibrosis or scarring of the liver in the patients that we're seeing in the pathway. And that helps us to know which of them really need to be seen in a specialist liver patient clinic in the hospital sooner and can help us work out which patients need to be referred.

Randye Kaye: So, what's next? Will the ILFT pathway be implemented in other regions, more regions? Does your team have any other plans in the pipeline?

Jennifer Nobes: So we're currently helping with rollout in other areas. So we've actually got a meeting next week to start implementation in one of our neighboring health boards. And so that's very exciting to see how we're going to be able to replicate this pathway in a different laboratory setup. We've got ongoing work that's really always happening in the background to help optimize the algorithms. And something that we're focusing on at the moment is optimizing the diagnosis of non-alcoholic or metabolic associated fatty liver disease, and are going to try to incorporate some of the other criteria for metabolic syndrome to help primary care physicians be able to confidently let us know whether or not someone has features of the metabolic syndrome. We continue to review the referral practices post intelligent liver function testing pathway results. So when we issue the diagnosis and management report with the results, sometimes we advise that the patient is seen in the liver clinic.

And what we need to do is go back and see how many of those patients did get referred to the liver clinic. And then once they were seen by a specialist, what the clinical outcome was. This data collection has been ongoing the whole time. We've had the project running but obviously with the changing clinical priorities that we've faced with the COVID-19 pandemic, there's been a little bit of a delay in getting these patients through the system. So I think that's work that will continue to happen over the next 6 or 12 months and then we'll be delighted to share some of our data from that.

And then finally we're kind of thinking about different disease areas now that we can apply this intelligence approach to. So how we could use algorithms like this that combine clinical details and laboratory investigations to generate automatic management plans or diagnoses. And I think that interface between clinical and laboratory medicine provides a really exciting opportunity for the future which may help to overcome some of the financial time and staffing pressures that certainly our health system in the UK faces, and I'm sure can be seen in other health systems across the world.

Randye Kaye: All right. Very important information. Thank you so much for joining the podcast today.

Jennifer Nobes: It's been a pleasure.

Randye Kaye: That was Dr. Jennifer Nobes from NHS Tayside in Dundee, Scotland, describing the JALM Special Report, "Intelligent Liver Function Testing: Working Smarter to Improve Patient Outcomes in Liver Disease." Thanks for tuning in to this episode of JALM Talk. See you next time and don't forget to submit something for us to talk about.