Editorial: can urine-based metabolomics improve diagnosis of advanced fibrosis in NAFLD? Authors' reply

We are pleased by the enthusiasm with which our paper on machine learning GMLVQ analysis of the urinary steroid metabolome has been received, and the recognition of its potential as a novel, non-invasive test to accurately stage NAFLD fibrosis. In addition, with developing pharmacotherapies, the reliable tracking of fibrosis progression or regression will be critical, and the development of non-invasive tools to be able to achieve this is a clinical priority.

We do recognise that in our cohort, the FIB-4 test was highly predictive of advanced fibrosis and this almost certainly is a reflection of the high prevalence of advanced disease in our secondary care cohort. However, within our analysis, we also tested the ability of the urinary steroid metabolome to identify advanced NAFLD fibrosis from healthy control subjects, who are perhaps more representative of a primary care population. In this context, the GMLVQ analysis performed very well (AUC ROC = 0.98 [0.98-0.99]) and therefore we would anticipate that this test may have significant clinical potential to identify advanced NAFLD in the community.

Whilst we accept that the analysis of the urine sample requires specialist equipment and expertise, the methodology that we describe is widely used, and in that respect, it is no different from a serum-based assay. In addition, the use of liquid chromatography tandem mass spectrometry is also becoming more common. As a simple urine test, there is even the potential for it to be collected in the patients’ own home; it requires no specialist equipment, no expertise in collection and no complex storage conditions. Indeed, with suitable containerisation, it could even be mailed directly, by the patient, to the analysing laboratory.

A further important consideration is that whilst the FIB-4 test may be perceived as a ‘cheap’ test as it incorporates routine blood tests (ALT, AST, platelets), cost estimates from the UK are in excess of £60 (~$75) per sample. This takes into account, not only the physical measurement of the analytes, but also the personnel, time, equipment and processing prior to sample analysis. We have already proposed moving to a liquid chromatography tandem mass spectrometry platform that has the benefit of not only dramatically increasing throughput, but in parallel, significantly reducing costs to the level of (or below) that for the routine FIB-4 analysis. We believe that this, combined with the very high degree of patient acceptability and ease of sampling, makes the urine steroid metabolome analysis a highly attractive proposition both for the accurate staging of NAFLD fibrosis as well as potentially screening for advanced disease in primary and secondary care.

There is still a great deal of work to be done and we certainly agree that the future development and direction for this test will be reliant upon a detailed validation and confirmation of findings in a larger cohort of patients with biopsy-proven NAFLD as well as healthy controls. In addition, it will also be important to examine the ability of the test to track changes in liver histology and crucially also to predict meaningful clinical outcomes.

ACKNOWLEDGEMENT
The authors’ declarations of personal and financial interests are unchanged from those in the original article.
Editorial: management of exocrine pancreatic insufficiency remains a challenge—can we do better?

The prevalence of exocrine pancreatic insufficiency (EPI) is 60%-90% in advanced chronic pancreatitis (CP) and 50%-90% in pancreatic cancer (PC).\(^1\) Untreated, EPI results in fat and protein malnutrition, muscle wasting, metabolic bone disease, reduced quality of life and even mortality.\(^2\) Based on various clinicopathological parameters, the diagnosis of PC is usually accurate. CP is characterised by recurrent episodes of abdominal pain and pancreatic insufficiency with fat malabsorption and diabetes. Diagnosis is usually confirmed by abdominal CT scanning and magnetic resonance cholangiopancreatography demonstrating pancreatic calcification and ductal changes.\(^3\) The diagnosis of early stage CP is often difficult since cross-sectional imaging or even ERCP and EUS may not be diagnostic.\(^4\) Steatorrhoea develops once 90% of pancreatic function is lost although many PC and CP patients exhibit subclinical EPI on pancreatic function testing. The gold standard, but difficult to perform, three-day faecal fat test has now largely been replaced by spot faecal elastase assays. In EPI subjects, pancreatic enzyme replacement therapy (PERT) improves steatorrhoea, nutritional parameters, quality of life and mortality.\(^5,6\) Two European observational studies in PC and CP reported under-utilisation of pancreatic function testing and inadequate PERT dosing.\(^7,8\)

Forsmark et al\(^9\) assessed the use and dosing of PERT in insured US patients with CP or PC from a national administrative database of over 48 million individuals between 2001 and 2013. At least one CP claim was made for 37,061 individuals. Only 6.5% had any EPI testing (faecal fat, elastase or chymotrypsin) while 30.4% filled a PERT prescription. Adequate PERT replacement was defined as taking over 120 000 USP lipase units daily. Just 8.5% received adequate PERT (Table 1). Similarly, of 32,461 PC subjects only 1.9% had EPI testing. A PERT prescription was filled by 21.9%, while 5.5% were prescribed adequate PERT (Table 1). Having EPI testing or seeing a GI physician strongly predicted PERT use in both groups. Similarly, cystic fibrosis or operated PC subjects predicted higher PERT use implying specialist follow-up is relevant.

It is likely in the Forsmark et al study, that most PC diagnoses were accurate and subjects should usually receive PERT. A limitation however was that administrative databases may incorrectly classify diagnoses; in particular, early stage CP may be over-estimated. This was partly addressed by assessing patients with over one CP claim six months apart. PERT use increased to 55.7% in this subgroup of 9,541 although adequate dosing remained low at 36.9%. Second, although the prevalence of alcohol use in CP cohorts is 44%-68%,\(^10\) the authors reported alcoholism in just 20%. This could reflect under-reporting of alcohol consumption, but also implies over-estimation of CP diagnosis thereby offsetting the PERT requirement. Finally, EPI testing details were unavailable precluding comparisons between confirmed exocrine insufficiency and the appropriate use and dosing of PERT.

This study\(^9\) emphasises that EPI is not investigated in most PC and CP patients. Furthermore, only a minority of patients received