The Liverpool Diagnostic Infrared Wand (LDIR wand): Imaging and Cancer Prognosis from the Same Technology

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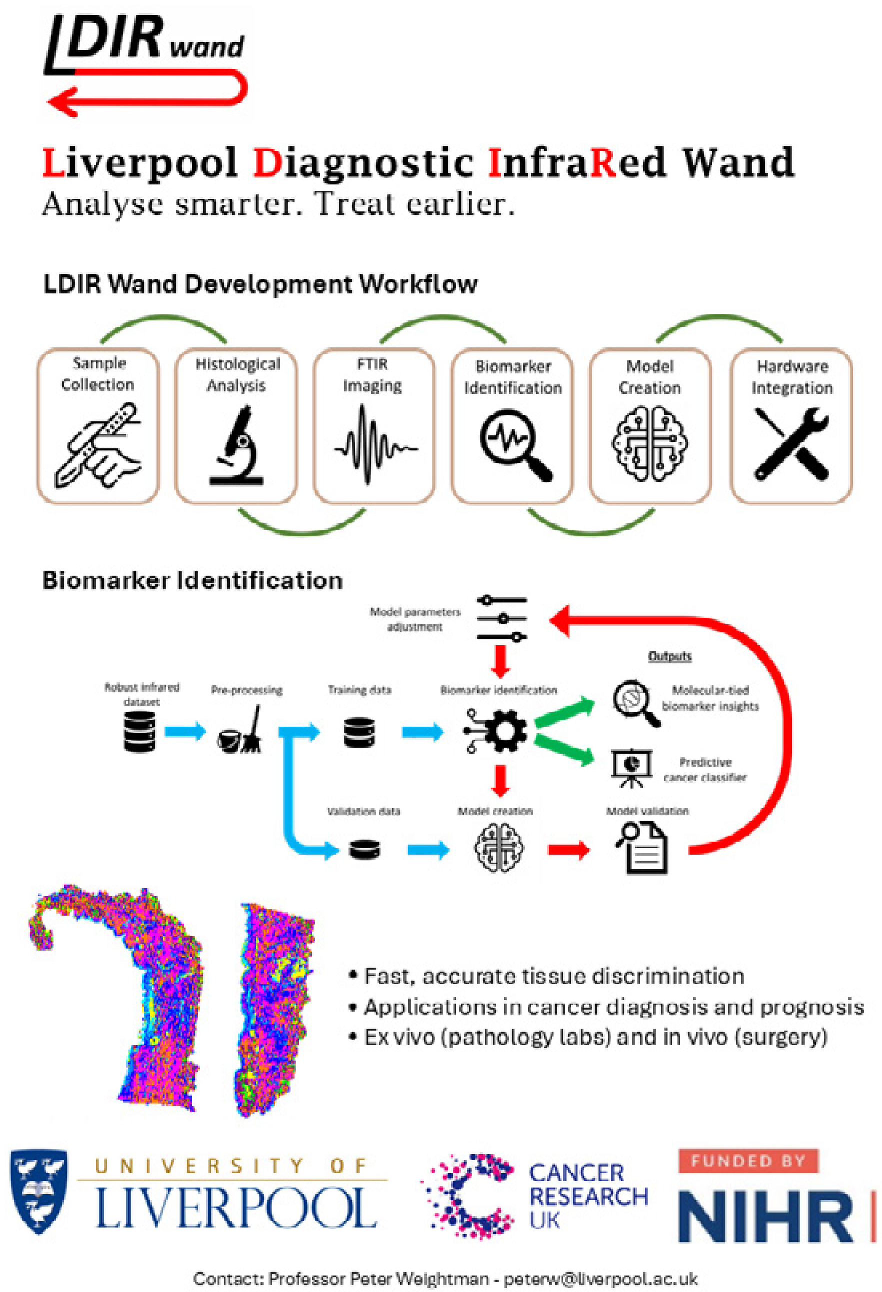
We are moving into a new era in microscopy technology development in which the microscopy technologies, in addition to the imaging function they have always provided, increasingly provide us with additional predictive and prognostic information which would be impossible to derive by any other method.

Oral cancer is one of the fastest developing cancers in the UK, with over 12,000 new cases a year. It is often preceded by oral lesions with approximately 1 in 8 progressing to cancer. In order to optimise therapy, it is crucial to identify those lesions that will progress to cancer. The current best practice is to take tissue biopsies which are then examined by an histopathologist. However, histopathological assessments are labour-intensive, complex, have poor inter-observer reliability, do not completely reflect the risk of long-term malignant transformation and correctly predict cancer progression in only ~40% of cases. Many patients require repeated biopsies which are painful and delay surgery. There is a need to be able to predict with accuracy which patients are going to progress and which are not.

The Liverpool Diagnostic Infrared Wand (LDIR Wand) is based on a patented machine learning algorithm that makes it possible to identify key infrared biomarkers that discriminate between different tissue types (Ingham et al, 2019a). The power of the algorithm was demonstrated by the early work on oral cancer where it identified two IR biomarkers, 1252 cm^{-1} and 1285 cm^{-1}, which yielded intensity ratios that discriminated between metastatic oral cancer and lymphoid tissue with sensitivities and specificities of 98.8 ± 0.1% and 99.89 ± 0.01% respectively (Ellis et al, 2021). This research has recently been confirmed by a larger study on 46 tissue cores (Al Jedani et al, 2023) that also provided insight into the chemical composition of this cancer (Al Jedani et al, 2024). When applied to the prognosis of oral cancer lesions, accuracies of ~80% can be achieved – a significant advance on current histopathological techniques (Ellis et al, 2022; Ingham et al, 2022).

In addition to oral cancer, similar problems are present across a range of other cancer types. For example, it is difficult to predict which cases of ductal carcinoma in situ of the breast are going to progress. If these patients can be identified with confidence, treatment can be stratified on the basis of the prediction of progression and many patients could be spared surgery.

Ductal carcinoma-in-situ (DCIS) is the in-situ precursor lesion of invasive breast carcinoma. Preliminary research on a small cohort of specimens supports the hypothesis that the methodology outlined above will identify IR biomarkers which will predict which cases of DCIS will progress or recur. In a study of six DCIS biopsies we have identified eight biomarkers that predict the prognosis with



sensitivities of ~80% and specificities of ~75%, a considerable improvement on current approaches.

A Receiver Operating Characteristic curve (ROC curve) is a graph of the True Positive Rate (Sensitivity) plotted against the False Positive Rate (1 - Specificity) at various decision thresholds. It is one of the most commonly used and accepted methods for assessing the performance of a classification model. In preliminary research on invasive breast cancer, a study on a cohort of biopsies from 10 patients achieved sensitivities and specificities of 83% and 81% respectively, and an area under the ROC curve of 0.9, in identifying those patients who do not benefit from neoadjuvant therapy. It may also be possible to use this technology to measure the receptor status of breast tumours rapidly.

The LDIR Wand was born out of pioneering technology developed on the ALICE accelerator facility, the UK's only 4th generation light source, at Daresbury Laboratory well over a decade ago. The University of Liverpool physics group developed a scanning near-field optical microscope (SNOM) on the ALICE infrared (IR) free electron laser and led a collaboration with colleagues from four universities and three hospitals in applying a range of techniques in studies of oesophageal, cervical and prostate cancers (Ellis et al 2021Smith et al, 2013; Haliwell et al, 2016; Inghan et al, 2019b; Al-Jedani et al, 2024).

It was recognised that while IR spectral images are able to distinguish between tissue types, and have been studied for decades, scientific instruments did not represent this information in a way that could be translated into clinic. Furthermore, analytical methods could not summarise the information that was undoubtably present in the spectral images in a way that captured the essential differences between types of tissue. If the information content of the spectra could be captured in a small number of the several thousand wavelengths measured in an IR spectrum, then it would be possible to radically simplify the instrumentation. This observation led to a focus on the development of algorithms that discriminated between spectral images. The identification of a few key IR wavelengths led to the development of the LDIR Wand and a related device for use in histopathology, the Liverpool University Cancer Imaging Device (LUCID).

The algorithm is able to extract a small number of key IR biomarkers that discriminate between tissue types. Intriguingly, these lie not within the spectral peaks where most researchers have been looking, but often between the peaks. Having a small number of IR biomarkers makes it possible to use a small number of IR lasers in the construction of LUCID and the hand-held LDIR Wand probe. These are compact devices that are simple to use and do not require any training in spectroscopic techniques.

The LDIR Wand technology has a number of distinct advantages. It can be automated and is simpler, cheaper and more accurate than other methods of addressing these clinical problems. Also, unlike other approaches, this approach is non-destructive to tissue, meaning that once the tissue has been tested it can then be used for other purposes. This means that the tissue section could be scanned by LUCID prior to being stained with H&E, creating a seamless integration into pathology laboratory workflows.

It is difficult to be certain precisely which chemical moieties in the cell are responsible for the discriminating IR biomarkers that are identified. It is likely that the signals are a composite of signals from DNA (both mutational and epigenetic), RNA, proteins and even potentially the metabolome. It is therefore likely that they are detecting shifts in entire cellular networks at multiple levels of organisation, making them practical, easily elicited and rapid multiomic biomarkers.

Any technology with the power to accurately predict the progression of cancer has the potential to revolutionise cancer care. The LDIR Wand has shown an unparalleled ability to predict cancer behaviour in every cancer type to which it has so far been applied. Our vision is that, like its fictional namesake in the tale of Harry Potter, it will have power and impact. The power to predict smarter, the impact of saving lives.

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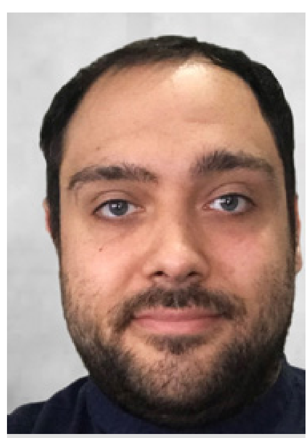
Professor Vijay Sharma

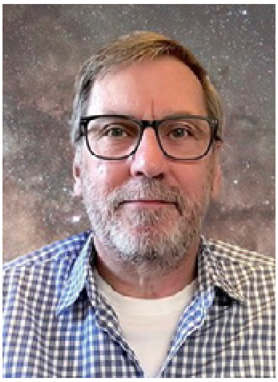
Professor Sharma is currently the Clinical Director of Cellular Pathology and a Consultant Histopathologist with a specialist interest in Breast Pathology in Liverpool, and is also a member of the Department of Molecular and Clinical Medicine and the School of Medicine in the University of Liverpool. His research interests are in the role of energy metabolism in disease, including cancer, heart disease and diabetes, in the development of new biotechnologies for predicting tumour progression and therapy responses, and also in the implementation and development of Artificial Intelligence in Digital Pathology. He is a recognised expert in Biobanking and one of the UK's leading authorities on the use of Artificial Intelligence in Histopathology.

Dr James Ingham



James Ingham is interested in the application of advanced imaging technologies, particularly infrared spectroscopy, and their integration with analytical methods and novel AI approaches to address major challenges in biology and medicine.

Dr Steve Barrett



As a Senior Research Fellow in the Department of Physics, Dr. Barrett's research interests span all aspects of imaging, image processing and image analysis. This includes medical imaging (biophysics), scanning probe microscopy of atoms and molecules (nanophysics), microscopy of earth materials (geophysics) and astrophotography.

Dr Caroline Smith

Dr Caroline Smith is a physical chemist with an interest in spectroscopy of molecules at interfaces and in developing instrumentation. She has many years' experience of research studying cancer with infrared spectroscopy.

Dr Janet Risk

Dr. Janet Risk is an Honorary Senior Lecturer in the Department of Molecular and Clinical Medicine and is a member of the Liverpool Head and Neck Centre. Dr. Risk investigates the molecular biology of aerodigestive tract cancer and has previously published on the role of tumour suppressor gene methylation in head and neck squamous cell carcinoma and the role of tumour associated fibroblasts in the aggressiveness of HPV negative oral squamous cell carcinomas. She is a key member of the team investigating the utility of infrared imaging for the early diagnosis of oral cancer.

Professor Richard Shaw

Richard Shaw is an academic head and neck cancer surgeon with translational interests in premalignancy, early diagnosis and prevention. He is chief investigator on several clinical trials and has held senior roles in the NIHR clinical research network and the International Academy of Oral Oncology.

Professor Peter Weightman

Peter Weightman has a history of developing scientific instruments and has been fortunate in collaborating with colleagues in a variety of fields. These collaborative activities have resulted in a number of awards including the Mott Medal of the UK Institute of Physics (2006) and a co-recipient of the UK Institute of Physics Rosalind Franklin Medal (2020) through his membership of the Steering Committee of the UKRI "The Physics of Life Network"