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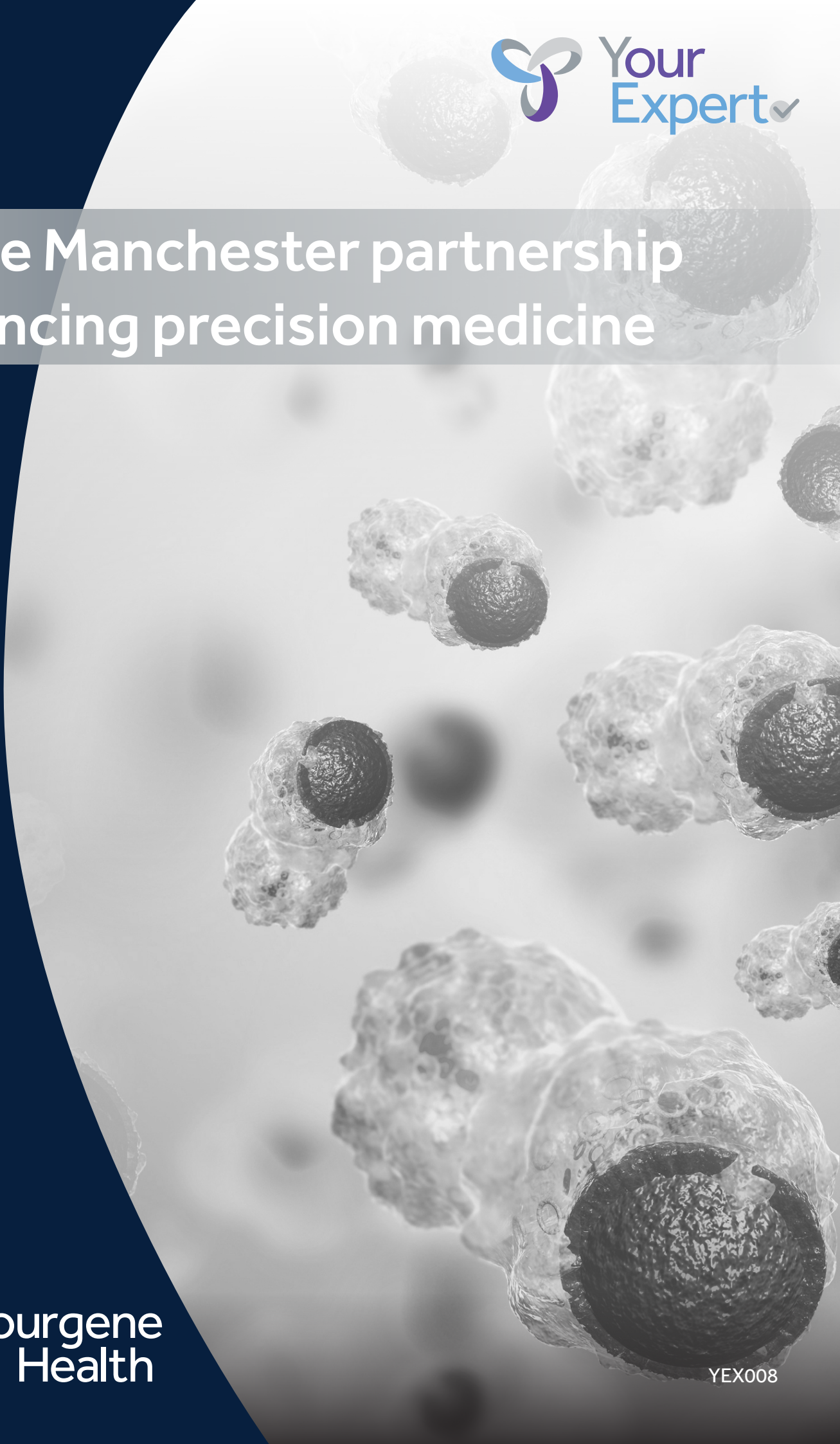
Your Expert

A true Manchester partnership advancing precision medicine



Yourgene Health

YEX008

Yourgene spoke with Joely Irlam-Jones, a Research Associate at the University of Manchester and Director and CEO of ManTRa Diagnostics, a spin-out company from the University of Manchester that is developing patient stratification solutions to personalise medicine and improve cancer treatment outcomes. The team have developed tumour-site-specific gene expression signatures which indicate the oxygen status of the tumour. ManTRa and the Yourgene Genomic Services team have a long-standing history of over 10 years working together on this development.

Personalised medicine and getting the right treatment into the right patient for maximum benefit has really taken off in recent years, where did the idea come from that tumours may have different levels of oxygenation and that those levels could impact responses to treatment?

In the past, everyone with the same type of cancer used to get the same treatment called a one-size-fits-all-approach. We now know the approach doesn't work for everyone. Precision (or personalised) medicine is a new way to treat cancer. The approach uses tests to choose the best treatment for each patient based on their likely response. The tests help to tailor medical decisions to the individual patient to increase cures and reduce side effects.

A hypoxic tumour microenvironment is a feature of solid tumours. Many tumour types contain high fractions of hypoxic tissue, such as those of the brain, head and neck, lung, breast, prostate, pancreas and cervix. The relationship between high levels of tumour hypoxia and a poor patient outcome (prognosis) is firmly established. Patients with the most hypoxic tumours have the worst prognosis and the tumours are more likely to spread to other sites in the body (metastasise). The most hypoxic tumours are also more likely to recur following surgical removal and hypoxia leads to resistance to many treatments including radiotherapy, chemotherapy and immunotherapy.

If these tumours could be identified prior to treatment commencing, these patients can be put on the most appropriate treatment pathway. For example, for a patient with a hypoxic tumour, who therefore would be unlikely to respond to a chemotherapeutic agent such as 5-FU should not be given that particular treatment as they could experience the associated side effects and toxicities, with no beneficial response in their cancer, in effect making them more unwell than offering no treatment. On the flip side, if a patient's tumour is not hypoxic, they are more likely to respond well to treatment, which again can be beneficial for the clinician to know. Our research has shown that bladder cancer patients whose tumours were identified as hypoxic by our test and were given hypoxia targeted treatment had a 30% increase in overall survival. Clearly demonstrating that by identifying patients with hypoxic tumours, who are then given a targeted therapy, boosts their response to treatment and improves their outcome.

How were these gene expression signatures developed and what has the role of the Yourgene Genomic Services team been in that process?

We can measure hypoxia by the expression (whether a gene is being made into a protein) of a number of genes – a signature. We made signatures for different cancers (head and neck, prostate, bladder, sarcoma). The signatures, each made up of 24-28 genes, can be measured together in a single test (pan-cancer panel). The signatures were derived by looking at the co-expression of known hypoxia seed genes and genes differentially expressed under hypoxic conditions.

The signatures were validated using multiple patient cohorts and took over a decade to complete. This required processing of samples for DNA extraction, micro-array and more recently NGS. We have worked with Yourgene Health in its various iterations for approximately 12 years; I used to deliver patient blood samples to their Wythenshawe site and when our group suffered a fire the team helped us rescue and store precious patient samples. This long working history has resulted in a trusted relationship. This is a story of Manchester research science and a Manchester commercial company working together to bring benefit to patients.

How are tumours identified as being hypoxic to then enable the decision to be made as to what the appropriate treatment for that particular patient is?

We can measure hypoxia by the expression (whether a gene is being made into a protein) of a number of specially selected genes – a signature. We made signatures for different cancers (head and neck, prostate, bladder, sarcoma). The signatures, are each made up of 24-28 genes, can be measured together in a single test (pan-cancer NGS panel). By measuring this differential gene expression, we are able to use an algorithm to generate a hypoxia score. We now need to get our test into the clinic so it can help patients.

To get the test into the clinic we set up a company – ManTRa Diagnostics. Over the past 2 years our company has worked closely with Yourgene Health to take our test forward using the latest technology for measuring gene expression - next generation sequencing (NGS). NGS is fast, accurate, widely available and getting cheaper all the time. NGS has helped start the move to precision medicine in cancer. We made a single NGS test for all our signatures – Pan-cancer panel.

Are there particular types of cancer and tumours that are more prone to being hypoxic and that are likely to benefit the most from this testing?

Approximately 50% of solid tumours are hypoxic. Head and neck, prostate, bladder, and soft-tissue cancers are highly impacted by hypoxic microenvironments, and this reduces survival rates. Identification of patients for potential treatment with hypoxia targeted therapies could increase cancer survival rates by 30% in some patient populations with hypoxia scoring required to make informed patient-specific treatment decisions. The use of precision medicine (treatment according to hypoxic-status) would reduce the need for trial-and-error approaches, improve patient outcomes, reduce the risk of exposure to cancer therapy complications while also improving cost-efficiency and patient quality-of-life.

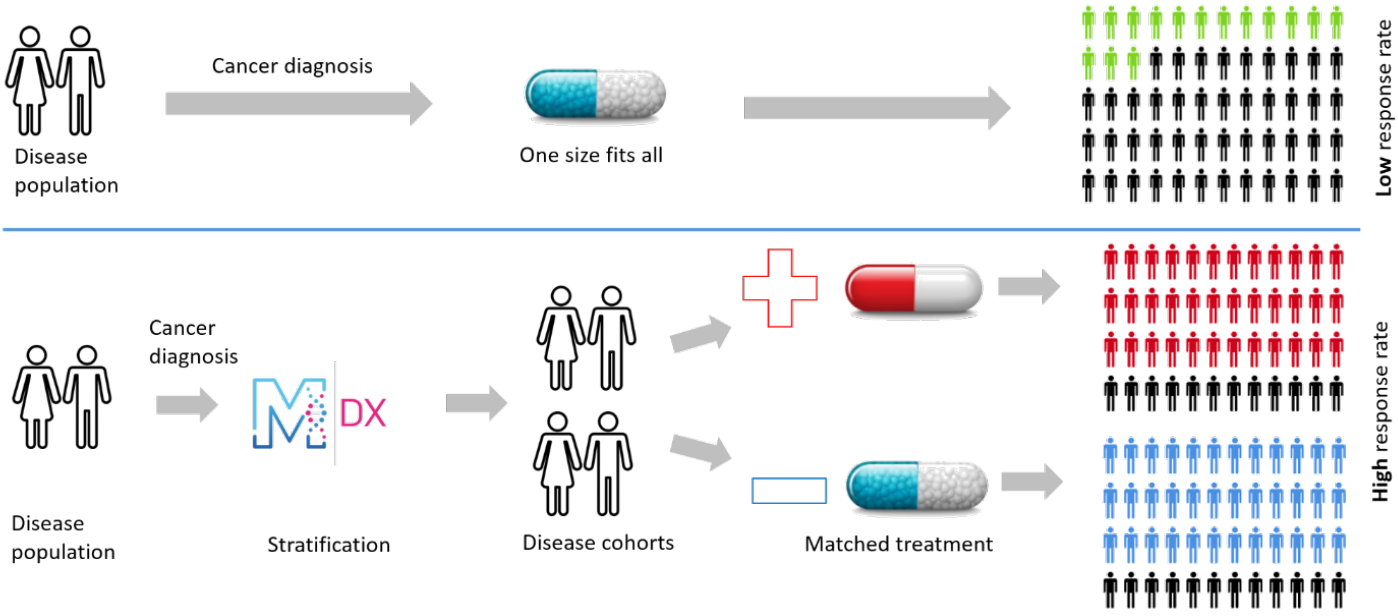
How do you envision this testing fitting into current cancer treatment pathways?

The test will be taken from the original diagnostic biopsy and will help clinicians in their treatment decisions at the start of the cancer care pathway. The value of our test is to enable clinicians to make informed decisions on patient-specific precision treatment pathways according to tumour hypoxia-status. Using a hypoxia score to predict the benefit of applying targeted hypoxia-modifying therapy to a patient's radiotherapy and the suitability of specific drug classes to enhance an individual patient's treatment.

What do you see as the next steps for the implementation of this testing?

In the short term we aim to engage with large pharmaceutical companies to demonstrate our test's ability to stratify clinical trial cohorts according to hypoxia score giving improved trial success. Hypoxia's negative impact on treatment efficacy reduces trial success rates. For example, when trialling a drug negatively impacted by hypoxia, assessors can refine cohorts to low-hypoxia patients who are more likely to benefit from the drug. This is more likely to reveal the benefits of the drug and therefore facilitate progression to market.

In the medium term we will try and integrate our test into the North West Genomics Laboratory Hub (GLH) for delivery in to the NHS for radiotherapy patients in the first instance. GLHs were set up to exploit cutting-edge genomics technologies within the NHS to deliver national genomic testing.



About YOURGENE HEALTH

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