Genetic testing could help Irish doctors solve mystery cancers

BY GARY FINNEGAN

A new project aims to develop Ireland's first Molecular Tumour Board to accelerate diagnosis and treatment of patients with Cancers of Unknown Primary (CUP)

A cancer diagnosis can be devastating news. Patients need information on therapies and on likely outcomes; they want clarity for themselves and their loved ones. Answering the key question **'Will I be okay?'** is rarely straightforward.

However, patients with Cancer of Unknown Primary (CUP) face particularly high levels of uncertainty and anxiety about their prognosis. Most cancers are named and managed based on where the first tumour is found. But those with CUP present with cancer in more than one site and the origin of their disease is a mystery.

This can come with profound consequences in a patient population presenting with advanced metastatic cancer. Knowing where the cancer began is far from academic. There are clear pathways for patients with colon cancer or breast cancer. People with CUP, and their clinicians, are in the dark.

Information is power

Hospital pathologists play a key role in guiding treatment based on the characteristics of tumours down the microscope. However, Dr Maura Cotter, Consultant Pathologist at St Vincent's University Hospital in Dublin who has reviewed how CUP is managed in Ireland, says **'more cancers are now also being subclassified by their molecular characteristics and increased tumour sequencing could reduce the number of cases of unknown origin'.**

'Our aim is to broadly classify and subtype the cancer, and where possible, to confirm the likely primary site as this information best predicts patient outcome and guides treatment,' she says. **'However, 10-15% of patients present with metastatic disease from the outset rather than with a primary tumour, and in one third of those, the origin is never found. CUP is therefore a common and challenging clinical problem and good communication between all clinicians involved is key.'**

While multidisciplinary teams (MDT) regularly discuss patients' treatment, these meetings usually group patients together based on the location of their initial tumour. CUP patients are clinically homeless, often taken in by the first oncologist they are referred to rather than working with a consultant specialising in the kind of cancer they are living with.

That's where molecular tumour boards come in. Modelled on MDTs, they bring together pathologists, oncologists, radiologists, radiation oncologists, clinical nurse specialists and bioinformatics experts to discuss cases of CUP. Rather than looking primarily at patients' symptoms or at the site of a tumour, their focus is on the tumour. Does it have genes that could be targeted by existing treatments? How does a tissue sample respond to a battery of histopathology and immunohistochemistry tests?

Next generation sequencing (NGS) has opened up new possibilities to learn about tumours. Pathologists can look for faulty genes associated with specific cancers. To go further, whole genome sequencing (WGS) offers a complete picture of the tumour's genetic makeup. This is more expensive and not suitable in all cases, but for CUP, it may provide vital clues about the origin of the problem.

Building momentum

The idea of molecular tumour boards is relatively new. It reflects growing momentum behind the shift towards treating cancer based on genomic information. The task now is to translate scientific advances into clinical practice, including the CUPISCO trial, in which Prof John Crown is participating, and the Cancer Genome Atlas.

A team at St Vincent's is in the process of establishing Ireland's first molecular tumour board, with funding from the Sarah Jennifer Knott Foundation. Over a two-year period, they will recruit 10 patients with CUP and perform a range of tests which can include MSI status, single gene testing, panel testing and whole genome testing.

Along the way, they hope to generate awareness and interest among scientists and clinicians, ultimately developing a critical mass of experts to expand the use of state-of-the-art pathology and bioinformatics insights. The group is also exploring how it could develop a CUP biobank within the UCD Clinical Research Centre. The initiative kicked off with a virtual CUP symposium in January 2021 which heard from leading international experts in the field.

'In addition to gene sequencing work, we are looking at how to integrate that into the clinical pathway,' says Dr Bruce Moran, Clinical Bioinformatician at St. Vincent's. **'As part of the study, we will see if selected patients benefit from this approach and determine whether a larger study could be of value.'**

Tanya Knott, Director of the Sarah Jennifer Knott Foundation said the aim of the SJK Research Award is to encourage research into cancer of unknown primary and genomic profiling. **'The SJK CUP study is exactly the type of research we want to fund,'** she said. **'By enabling patient access to WGS and the chance to find an actionable mutation, WGS will also help the researchers to understand more about cancer of unknown primary.'**

Ms Knott added that the value of funding studies like this is that through the research, CUP patients will benefit from the bigger focus on cancer of unknown primary which has led the SVUH/UCD group (Prof K Sheahan, Prof D Brennan, Prof J Crown, Dr B Moran and Dr M Cotter) to collaborate with the international CUP study in the US. **'The CUP virtual symposium helped to highlight nationally and internationally the unmet diagnostic and treatment needs of patients with cancer of unknown primary,'** she said.

Wanted: national genomics strategy

The project is a step forward for Ireland which has been a slow starter in tackling CUP, at least compared to near neighbours in the UK where the publication of 2010 NICE Guidelines on CUP and the establishment of Genomics England have helped accelerate the use of whole genome sequencing.

'It has been very piecemeal,' says Dr Moran. **'There is no central strategy for genomics in Ireland so it comes down to collaboration between individuals in hospitals, our participation in international clinical trials, and small projects like this one to set up a molecular tumour board.'**

Prof Kieran Sheahan, Consultant Pathologist at St Vincent's and UCD, said that the field has been moving quickly in recent years, requiring investment in technology and expertise. **'We are late adopters of next generation sequencing,'** he says. **'This has slowed us down compared to some peer countries, but this may come with some advantages: if we step up our capacity now, we'll benefit from the latest technologies.'**

Raising CUP awareness

The establishment of molecular tumour boards and medical education events are helping to spread the word about CUP among clinicians and scientists. Crucially, as new genes and therapeutic targets are identified, CUP could become more treatable. This may attract stronger interest from funding bodies, hospitals and health professionals keen to be at the forefront of a fast-moving story.

To help raise the public profile of CUP, the Sarah Jennifer Knott Foundation is working with advocacy groups Cancer of Unknown Primary Foundation - Jo's friends in the UK and Missie Tumour Onkebend in the Netherlands on a world CUP Awareness Week. The initiative includes daily webinars with leading world CUP experts that will connect patients and scientists with the latest information on CUP. The aim of the website is to connect CUP researchers around the world, to share ideas and to promote collaboration on future research projects.

'Through sharing best practices in the care of all patients we need to ensure Ireland is providing the most up to date diagnostics and treatment pathways for not only CUP patients but all cancer patients ultimately,' Ms Knott said.

Cancer of Unknown Primary
WORLD AWARENESS WEEK

www.worldcupawareness.org