Dr Lars Henrik Jensen explains how his research into screening for Lynch syndrome at a molecular level across Denmark has the potential to allay health concerns and save many lives.

Could you briefly outline your research into molecular screening for Lynch syndrome in colorectal cancer patients? What are the objectives of this investigation?

The question that almost every cancer patient will ask themselves is whether their disease is hereditary and if their relatives are at risk. As doctors, we are obliged to take this question seriously and give patients the best possible answer. Primarily, we do this by exploring their family history. However, as a supplement to this, the molecular revolution over the last few decades now allows us to identify a subgroup of patients who are likely to have familial cancer. Our project explores molecular screening for Lynch syndrome and our objective is to ensure that every new colorectal cancer patient with this hereditary syndrome is identified.

Why is it important to diagnose Lynch syndrome early?

Patients with Lynch syndrome have a very high risk of developing other types of cancer, especially new colorectal or endometrial forms of cancer, as are half of their closest relatives. It is possible to detect both types of cancer in their early stages by colonoscopy or ultrasound, thus preventing life-threatening development. Of course, it is also very important to diagnose Lynch syndrome early at an individual level. For example, I remember treating a patient with end-stage cancer some years ago. I found out that she had another cancer several years earlier – a cancer that screening for Lynch syndrome would have identified. If she had been given some simple examinations, her new and lethal cancer could have been prevented.

How does your research into molecular marker screening improve on present techniques?

Much of our research aims to validate the molecular markers and improve screening methods. A popular saying is ‘from bench to bedside’ – and it refers to bringing knowledge and new methods from the laboratory bench to the patient’s bedside. In addition, our previous research has shown the clinical benefits of using immunohistochemical staining instead of more complicated DNA methods. Some of our research is now focused on attempts to validate new staining for a protein, BRAF, as a routine that can be more easily performed than MLH1 methylation analysis.

How did you validate your screening strategy? How were the patients in the study selected?

Our strategy evolved through asking a series of questions. First, what is the basic biology and methodology? Second, which strategy would work best in daily clinics? Third, how can the strategy be performed best in a retrospective cohort of patients with a long follow-up? Fourth, do the hypotheses stand the test of real life? Finally, how can we make screening a national requirement in a way that ensures every patient benefits? Right now, we are between questions four and five.

Can you summarise the major challenges faced in population-based screening for Lynch syndrome? How can these challenges be overcome in daily clinics?

Lynch syndrome is not common and many doctors are not aware of the consequences of its diagnosis. Therefore, most of the screening should be done automatically. Staining of every new colorectal tumour followed by methylation analysis should be a standard procedure. Importantly, the interpretation of the molecular analysis is best performed by the gastrointestinal pathologist because they specialise in both the diseases and the methods. The written pathology report should include both the results and a suggestion for referral to a clinical geneticist if Lynch syndrome is likely.

What are your hopes for your future research?

I hope that our research will help make a difference to cancer patients in real life. Thousands of publications covering every aspect of molecular biology in medicine have been published but, regrettably, only a few of these studies have had any real-life clinical impact. My hope is that the molecular revolution will give us the tools we need to prevent and cure more and more types of cancers. However, in the meantime, it is important we remain focused on implementing a molecular screening strategy that will make a huge difference to the lives of patients with Lynch syndrome.
Investigating Lynch syndrome

A team of collaborative researchers in the Departments of Pathology and Genetics in Denmark are conducting innovative research into molecular screening for one of the most common forms of hereditary cancer in the world.

Colorectal cancer is one of the leading causes of cancer death worldwide, and it affects approximately one in every 20 individuals in Western countries. While most tumours are of sporadic origin and have some unspecific familial clustering, it is estimated that between 2-4 per cent of all newly-diagnosed colorectal cancers are caused by certain hereditary mutations.

Lynch syndrome is the name commonly assigned to this hereditary form of cancer; in fact, each patient has on average three relatives who also have the syndrome. In addition to this, Lynch syndrome patients have a much higher risk of developing colorectal cancer and multiple types of other cancers, especially endometrial cancer. This means that although the overall percentage of sufferers is low, the total number of those who have the syndrome is extremely relevant to the healthcare system at large.

Dr Lars Henrik Jensen, based at the Department of Oncology in Vejle Hospital in Denmark, is conducting important research into molecular screening for Lynch syndrome in colorectal cancer patients. He believes that systematic screening, the consequent genetic counselling and relevant follow-up services are vital and will prevent many deaths from new colon and endometrial cancers among patients and their relatives.

Successful screening

Microsatellite instability caused by mutations in certain genes – MLH1, MSH2, MSH6 and PMS2 – is the hallmark of Lynch syndrome. The genes are involved in the repair of mistakes that happen when DNA is copied in preparation for cell division, and mutations in any of these genes prevent the proper repair of DNA replication mistakes. As the abnormal cells continue to divide, the accumulated mistakes can lead to uncontrolled cell growth and possibly cancer. Similarly, mutations in the EPCAM gene also lead to impaired DNA repair, although the gene itself is not involved in this process.

Jensen and his team have demonstrated that it is possible to identify Lynch syndrome in a subset of colorectal cancer patients through a robust and inexpensive molecular screening strategy across two distinct steps. The first step consists of screening patients’ molecular markers for mismatch-repair (MMR) deficiency in the proteins of interest. Approximately four in five patients with MMR deficiency are sporadic – and genetic counselling to all of these patients would be a huge drain on resources. Therefore, in order to eliminate these individuals with sporadic tumours, the second step involves the analysis of BRAF V600E mutation and/or the testing of the MLH1 gene for promoter hypermethylation.

After performing the molecular screening, Jensen suggests three main criteria for deciding whom to refer for further tests: patients with a positive family history; patients with tumours defective in MSH2, MSH6 or isolated loss of PMS2; and patients with MLH1-deficient tumours not shown to harbour the BRAF V600E mutation or the MLH1-promoter hypermethylation. As a result of this two-stage molecular screening coupled with these three criteria, approximately 4 per cent of patients will be referred to a genetic counsellor for suspected Lynch syndrome, which is a manageable number.

Jensen enthuses that after being referred, it is important that patients are given the necessary follow-up services. He believes that systematic screening, the consequent genetic counselling and relevant follow-up services are vital and will prevent many deaths from new colon and endometrial cancers among patients and their relatives.

COLORECTAL CANCER IS

SUCCESSFUL SCREENING

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INTERNATIONAL INNOVATION
necessary support and advice to enable them to reach an informed decision for further diagnostic procedures, such as DNA analysis and personalised follow-up. The hope is that they would perceive these measures as highly beneficial, in turn raising the likelihood of them successfully reaching out to their relatives who may also have the disease.

MOLECULAR MARKERS

While multiple molecular markers have been proposed and tested with the promise of improving cancer care, very few have been validated and even fewer have been implemented in real-life clinics. In view of this, Jensen and his team executed important clinical trials with the aim of validating the molecular markers for Lynch syndrome.

The comprehensive study comprised every possible colorectal cancer patient diagnosed between October 2010 and September 2012 in southern Denmark. The two-stage molecular screening was carried out on these patients in order to pinpoint those who were at risk. Patients were included in the study irrespective of their stage, post-mortem diagnosis, surgery or other treatment. Jensen and his team also checked the national pathology database for missing data every three to six months and feedback was given to clinicians to ensure the enrolment of all colorectal cancer patients. Some 2,120 patients were diagnosed with colorectal cancer from a total population of 1,200,000 and, at the time of analysis, the researchers had access to informative data for 1,932 of the patients. Overall, molecular screening for hereditary MMR deficiency was found to be positive in 54 of 1,932 patients (some 2.8 per cent), and these patients were offered further genetic counselling and testing.

LEARNING LESSONS

This study demonstrated that screening for Lynch syndrome is feasible in a geographically defined area that has several clinical departments. Importantly, the implementation of molecular markers in cancer care can be optimised by support from national databases and good-quality formal feedback to the clinicians. In addition, the study showed successful screening requires a high level of conversation and collaboration between medical centres and laboratories, as well as the implementation of solid infrastructure for sending samples and receiving answers as quickly as possible.

INTERNATIONAL IMPLICATIONS

The fact that it is possible to successfully screen patients for Lynch syndrome is something that holds enormous benefits for individuals and families all over the world. With many people at risk from hereditary cancer, the wider implementation of this screening procedure has the potential to prevent unnecessary suffering and save many lives.

Jensen points out that Denmark has proved to be an ideal place to test and establish population-based screening: "Every person in Denmark is registered so we know the exact population and the denominator of the fraction," he explains. "The healthcare system is public and free, and it is mandatory to report every diagnosis and treatment to national databases." As an added bonus, researchers in Denmark have relatively easy access to these health databases, and the multidisciplinary approaches to diagnosing and treating cancer patients mean there are high levels of collaboration between researchers and healthcare professionals.

Yet the results of Jensen’s national screening strategy can be applied to countries other than Denmark. Jensen reports that preliminary discussions with international colleagues about the screening procedure have yielded great interest and highly positive feedback. However, the successful implementation of the procedure requires high levels of support from the national healthcare systems within different countries, as well as a greater degree of political awareness and endorsement from patient organisations. For molecular screening to have a tangible impact on individuals with Lynch syndrome, Jensen emphasises the necessity of forging close international collaborations with other researchers and urgent national governments and policy makers to take action.

INTRODUCTION

MOLECULAR SCREENING FOR LYNCH SYNDROME

OBJECTIVES

To ensure every colorectal cancer patient with Lynch syndrome in Denmark is identified. Relying on national databases and strict quality control, strategies are now being implemented to facilitate immunohistochemistry and methylation analyses, allowing pathologists to offer valuable clinical interpretations of the molecular profile.

KEY COLLABORATORS

Departments of Clinical Genetics:
Aarhus University • Vejle University • Odense University • Aalborg University

Departments of Pathology:
Aalborg University • University of Aarhus • Aalborg University – Esbjerg • Herlev University Hospital • University College of Northern Denmark • VIA University College Holstebro • Copenhagen University Hospital Hvidovre • University of Southern Denmark • Roskilde University

PARTNERS

Danish Colorectal Cancer Group (DCCG) • Hereditary non-polyposis colorectal cancer (HNPPC) Registry

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LARS HENRIK JENSEN graduated from the University of Aarhus, Denmark, in 2001 and earned his PhD in 2007 from the University of Southern California, Los Angeles. His primary interest involves gastrointestinal cancers, especially improving the treatment of biliary tract cancer and colorectal cancer through clinical trials.