Simple, cheap urine test can detect urothelial cancers in Lynch Syndrome patients

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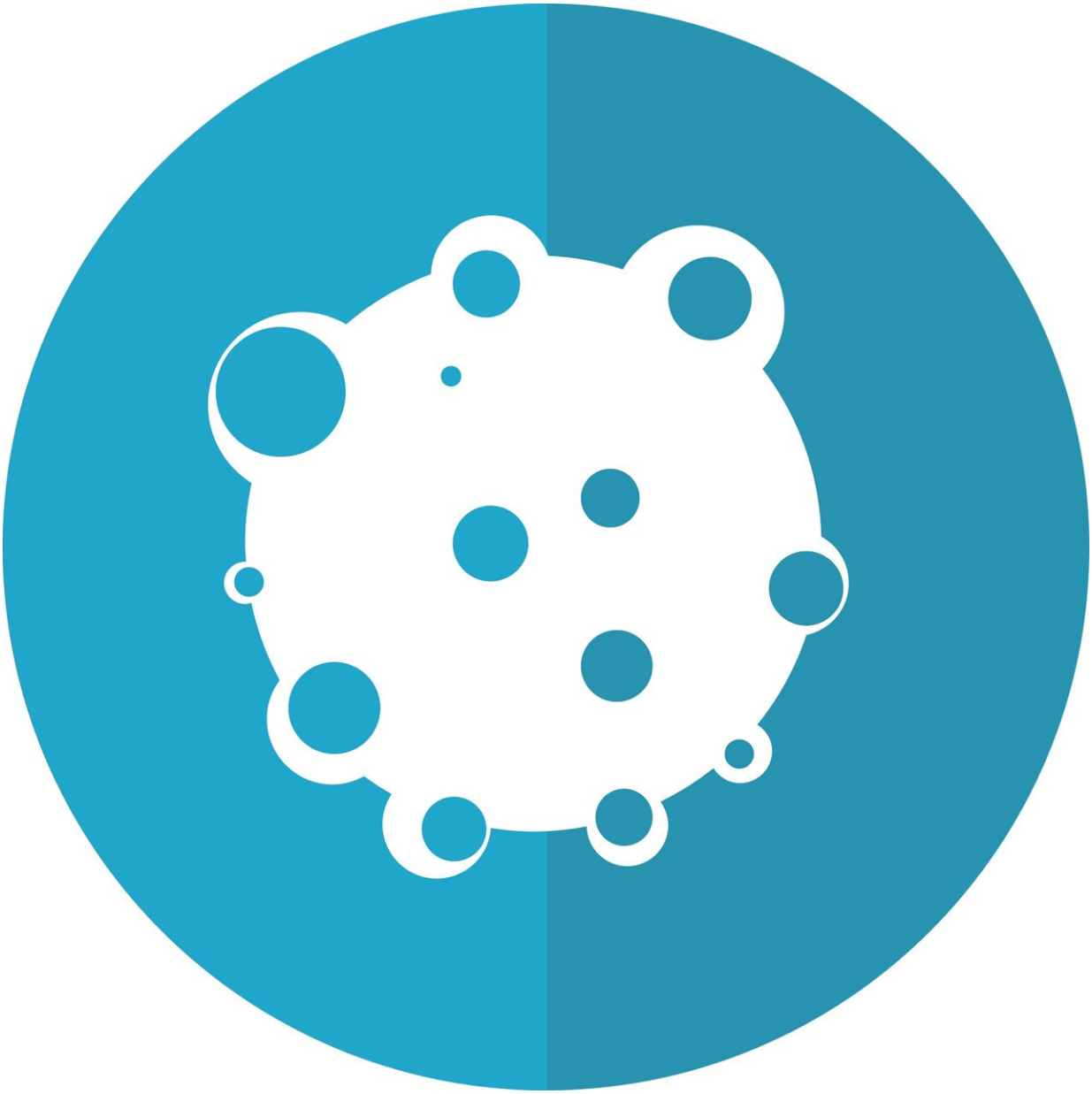

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Researchers have shown for the first time that it is possible to detect signs of urothelial cancer using a simple, postal, urine test in Lynch Syndrome (LS) patients who are at high risk of developing tumours.

The findings, presented at the NCRI Festival, offer the potential to develop a cheap, easy and non-invasive way of screening LS patients for cancers of the bladder, kidney and ureter (the tube connecting the bladder with the kidneys).

LS is an inherited genetic disorder that carries a high risk of cancer. More than one in 300 people have LS but most don't know it—that's more than 2,300 new cases every year in the UK. LS patients are at high risk of bowel and endometrial cancers. The risk of urothelial cancer is less well recognised, with a lifetime risk of up to 28.5%, depending on which gene is involved. This means that those LS patients who have an underlying defect in the *MSH2* gene are more than ten times as likely to get a potentially curable cancer in their urinary tract than the general population. Failure to screen for these cancers means that even after being diagnosed with the condition, one in 20 LS patients will die of urothelial cancer, often at a young age.

Sir John Burn, Professor of Clinical Genetics at Newcastle University, UK, and Chair of Newcastle Hospitals, told the NCRI Festival: "People with Lynch Syndrome can benefit from screening programmes that enable cancers to be found at an early stage when they can be cured. LS carriers are at high risk of cancers of the bowel and womb, and screening is available for these using colonoscopy for the large bowel and ultrasound for the womb. Unfortunately, the urinary tract has been ignored because there are currently no cheap, non-invasive screening

methods that can reliably detect tumours here. Cancer of the upper urinary tract is the third most common cancer associated with LS."

Sir John and his colleagues, including Ms Rachel Phelps, a research Ph.D. student in the Cancer Research UK-funded Cancer Prevention Group at Newcastle University, redesigned the Newcastle MSI-Plus Assay. This has recently become the standard test in North East England to find people with LS among those diagnosed with bowel cancer. MSI, which stands for microsatellite instability, shows that an important DNA repair system isn't working. Most LS patients are in this group. The test is being evaluated for national rollout.

"Dying cells within the human body shed small fragments of DNA into the surrounding tissues and circulation. These fragments are known as cell-free DNA and can be extracted from urine," said Sir John. "LS is caused by inherited changes that affect the cells' ability to repair DNA damage. As a result, almost all cancers that develop within individuals with LS have a characteristic pattern of errors called microsatellite instability. Microsatellites are regions of repetitive DNA that often change their length if not repaired correctly. Our test uses this 'signature' to identify DNA from tumour cells that are shedding into the urine."

To see if the test could be used for urothelial cancers as well as bowel cancer, the researchers tested blood and urine samples in a LS patient who had been diagnosed with urothelial cancer in the upper urinary tract. They tested the urine before and after surgery to remove the tumour.

"Before surgery, the test detected a clear signal for microsatellite instability in the patient's urine. After removing the tumour, we tested the patient's urine again and the signal had disappeared. Nor was it present in blood samples," said Sir John.

"A big question we need to answer now is how sensitive is our test?

What proportion of urothelial cancers in LS patients shed DNA into urine, and how early in the course of the disease can this be detected? The earlier the cancer can be detected, the more likely it is to be treated successfully."

The researchers are setting up a regional pilot study in which they will collect urine samples from LS patients between the ages of 40 and 75 who have a confirmed diagnosis of LS based on DNA testing their blood, either after they present with cancer or because they have an affected relative. Initially, the researchers will target patients with LS that is caused by a mutation in the *MSH2* gene, as this is the group of patients with the greatest risk of cancer.

Next year funding will be requested to roll out the urine screening test nationwide. To help establish the test's sensitivity, international researchers will be invited to send in urine samples from LS patients before they are treated for urothelial cancers.

LS is caused by mutations affecting *MLH1*, *MSH2*, *MSH6* or *PMS2* genes. "Men with the *MSH2* variant are at the greatest risk of developing cancer, with a higher than one in four risk of developing cancer of the kidney, ureter or bladder between the ages of 45 and 75. As we improve management of the high risk of bowel cancer, the importance of urothelial cancers rises as it accounts for 5% of all deaths in Lynch syndrome patients," said Sir John.

In a review of 10,243 urothelial cancers in England in 2018, the researchers found that only 43 patients (0.4%) had undergone testing for genetic variants that could identify whether or not they carried the variants for LS.

"We estimate that around 2% of urothelial cancers are in people with the LS genetic mutations and at least 5% should be tested to identify LS

cases, so there is an urgent need to improve screening for this disease," he concluded.

Rob Jones, Chair of the NCRI Bladder & Renal Group and Professor of Clinical Cancer Research at the University of Glasgow, UK, who was not involved in the research, said: "Early detection is key to reducing cancer deaths. This is a particular challenge in cancers of the bladder and kidney because there are no simple screening tests. However, if we know a patient has Lynch Syndrome, we know they are at high risk, so should be targeted for screening. This important discovery means that these high-risk individuals could undergo a simple, regular urine test to check if they are developing one of these cancers, in the hope that it might be caught early with a better chance of cure."

More information: 'Molecular screening of urine for Mismatch Repair deficient urothelial tumours; an under-appreciated cancer in Lynch syndrome" by Rachel Phelps et al. Short talks – Prevention and early detection session, 18.30-19.00 hrs, Thursday 11 November: conference.ncri.org.uk/program … and-early-detection/

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