

Targeted prostate cancer screening could benefit men with inherited cancer syndrome

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Men who inherit an increased risk of cancer through "Lynch syndrome" could benefit from regular PSA testing from age 40 to detect early signs of prostate cancer, researchers believe.

Lynch syndrome raises the risk of several [cancer](#) types including—most famously—[bowel cancer](#), and affects 175,000 people in the UK, although only 5 percent of people with the condition know they have it.

New research found that annual PSA testing could pick up cases of [prostate](#) cancer up to eight times as often in men with genetic hallmarks of Lynch syndrome—faults in genes like MSH2 and MSH6—than in those without.

Many of the cancer cases in men with Lynch syndrome were "clinically significant," suggesting that targeted [screening](#) has the potential to save lives.

Scientists at The Institute of Cancer Research, London, believe that targeted annual screening from age 40 could lead to earlier diagnosis and treatment of prostate cancer in this high-risk group of men.

Identifying that patients have Lynch syndrome could also guide their treatment since increasing evidence suggests that immunotherapies—which harness the immune system to attack cancer—may be particularly effective in men with these mutations if they have disease recurrence.

The new research, part of the international IMPACT study, is published today (Tuesday) in *The Lancet Oncology* and was funded by Cancer Research UK, with additional support from the Ronald and Rita McAulay Foundation and the NIHR Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and the ICR.

IMPACT involves 828 men from families with Lynch syndrome at 34 centers in eight different countries, and aims to assess whether regular PSA testing is an effective way to spot prostate cancer in men who carry certain genetic alterations that increase their risk.

Out of the 828 men participating in the study, more than 600 have faults in the so-called mismatch repair genes MLH1, MSH2 or MSH6, which are associated with Lynch syndrome—an inherited condition that increases the risk of various cancers, especially bowel cancer.

PSA screening is not recommended for men in the general population because it has not been shown to be beneficial and there are concerns that it can lead to over-diagnosis and over-treatment of cases that would not have caused significant problems.

But it could carry more promise for men who are at a high inherited risk. Men in the new study were offered an annual PSA test, and those with a PSA deemed high were offered a biopsy to determine whether they had prostate cancer.

Researchers found that annual PSA tests could effectively spot prostate cancer in men who inherited a mutation in the genes MSH2 or MSH6. Out of 305 men with faults in the MSH2 gene, 13 (4.3 percent) were diagnosed with prostate cancer—while only one non-carrier out of 210 (0.5 percent) was diagnosed with prostate cancer.

For MSH6 carriers, four out of 135 men (3 percent) were diagnosed with prostate cancer, while none of 177 non-carriers had a prostate cancer diagnosis (0 percent).

Men with the MSH2 gene fault were eight times more likely to be diagnosed with prostate cancer than non-carriers, and were diagnosed at a younger age—an average of 58 years, compared with 66.

Crucially, men with the MSH2 gene fault more often had aggressive, potentially life-threatening tumors, with 85 percent showing "clinically significant" disease, compared with no non-carriers. This suggests over-diagnosis in MSH2 carriers is unlikely.

Meanwhile, MSH6 carriers were diagnosed at an average age of 62 years and 75 percent had life-threatening or "clinically significant" tumors.

Future screening rounds as part of the IMPACT study will help establish the benefits and any harms of annual screening in men carrying MLH1, MSH2 and MSH6 gene alterations, so that experts can conclude if the balance is favorable and if screening should be introduced for these groups.

The study detected no cancers in men with MLH1 mutations—another gene associated with Lynch syndrome—and longer follow-up will be needed before concluding whether these men are at an increased risk of prostate cancer and would benefit from targeted screening.

Researchers are planning another five-year follow-up to compare treatment outcomes in these men. Subsequent screening rounds and detection of cancers will also be important in determining whether the PSA threshold of 3.0ng/ml used in this study is appropriate.

Professor Ros Eeles, Professor of Oncogenetics at The Institute of Cancer Research, London and Consultant in Clinical Oncology and Oncogenetics at The Royal Marsden NHS Foundation Trust, leads the IMPACT study. She said, "Prostate cancer screening isn't recommended for the general population, but we believe it could benefit some groups of men at high inherited risk. Our new findings show that PSA testing in men with Lynch syndrome is much more likely to pick up life-threatening prostate cancer than in the general population. We think that men with the gene faults causing Lynch syndrome are likely to benefit from regular PSA testing from the age of 40.

"Targeted screening has the potential to pick out aggressive prostate cancers at an early stage in men at high inherited risk, increasing their chances of survival. And because cancers in these men are more likely to

be aggressive and potentially life-threatening, they would need to have radical treatment. I anticipate that these results, and evidence from our ongoing follow-up work, will influence future national and international screening guidelines for this group of men, with the aim of picking out prostate cancer earlier and potentially saving lives."

Professor Kristian Helin, Chief Executive of The Institute of Cancer Research, London, said, "Picking up cancers early, when they are more likely to be curable, is a vital part of our strategy to improve the lives of cancer patients. Mass screening isn't a good option in prostate cancer because of the risk of over-diagnosis, but in men who have an increased inherited risk of aggressive disease it makes more sense. This new study suggests that screening with an annual PSA test could lead to early detection of significant numbers of prostate cancer cases in men with inherited Lynch syndrome, leading to earlier treatment and increased survival. It's an exciting example of the potential of genetics research and how it can impact our lives."

Professor Charles Swanton, Cancer Research UK's Chief Clinician, said, "Overall the PSA test is not reliable enough to be used as a national screening program for prostate cancer. But this research shows it could have promise as a test for people who are at higher risk of the disease. What's needed now is research to find out how early the test can diagnose prostate cancer in this group and like any screening program, the potential harms and survival benefits would need to be investigated before it could be rolled out."

"We don't currently recommend the PSA test for high risk men who are asymptomatic, but if you're concerned about your cancer risk it's important you speak to your doctor."

Paul Cunningham, 67, from Plymouth, discovered he had Lynch Syndrome in 2016, while undergoing treatment for skin cancer. Six

weeks ago, he was diagnosed with prostate cancer. He said, "I found out I had Lynch Syndrome when I went into surgery to have my skin cancer removed, and the nurse noticed I was also undergoing treatment for bowel cancer and referred me on. My immediate reaction was doom and gloom—with so many family members dying of cancer, I'd always assumed I would too—but I talked it through with the genetic counseling team, and that was really helpful.

"Having Lynch Syndrome is a double-edged sword. No-one wants to be at higher risk of cancer, but because doctors are aware of my risk, it means I've been fast-tracked and referred where I might not have been otherwise. Four weeks ago, I was diagnosed with prostate cancer after having my annual PSA check through the IMPACT study, and I'm now waiting for a date for surgery.

"The consultant said that if I hadn't been on the study, they probably would have just kept an eye on me, but thanks to the screening, they've managed to catch my cancer early. I hope these findings will go on to help others in my position. For now, I'm just looking forward to finishing treatment and spending more time with my beautiful wife."

More information: Targeted prostate cancer screening in men with germline MSH2 and MSH6 pathogenic variants detects clinically significant disease: Initial results from the IMPACT study, *The Lancet Oncology*, DOI: [10.1016/S1470-2045\(21\)00522-2](https://doi.org/10.1016/S1470-2045(21)00522-2)

Provided by Institute of Cancer Research

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