Prostate cancer risk prediction algorithm could help targeted testing for men at greatest risk

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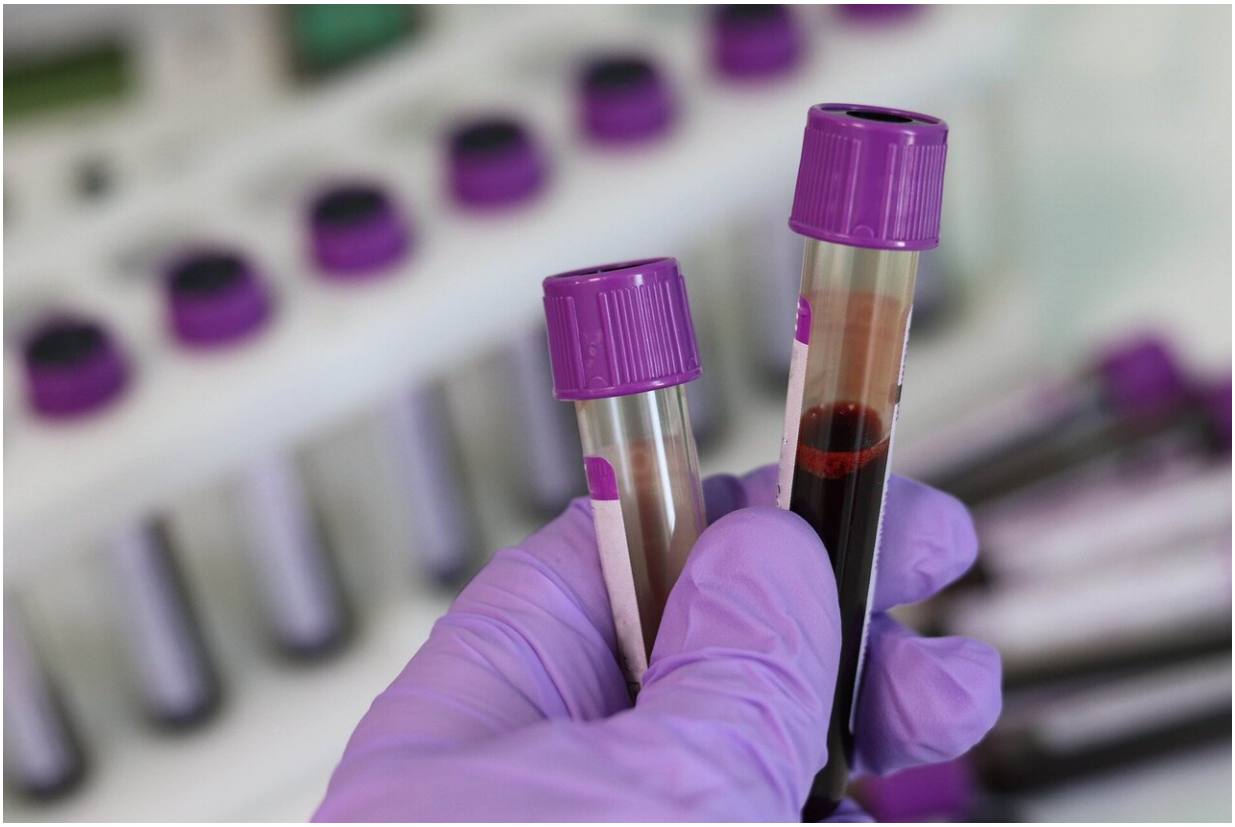

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Cambridge scientists have created a comprehensive tool for predicting an individual's risk of developing prostate cancer, which they say could

help ensure that those men at greatest risk will receive the appropriate testing while reducing unnecessary—and potentially invasive—testing for those at very low risk.

CanRisk-Prostate, developed by researchers at the University of Cambridge and The Institute of Cancer Research, London, will be incorporated into the group's CanRisk web tool, which has now recorded almost 1.2 million risk predictions. The free tool is already used by health care professionals worldwide to help predict the risk of developing breast and ovarian cancers.

Prostate cancer is the most common type of cancer in men. According to Cancer Research UK, more than 52,000 men are diagnosed with the disease each year and there are more than 12,000 deaths. Over three-quarters (78%) of men diagnosed with prostate cancer survive for over ten years, but this proportion has barely changed over the past decade in the U.K.

Testing for prostate cancer involves a blood test that looks for a protein known as a prostate-specific antigen (PSA) that is made only by the prostate gland; however, it is not always accurate. According to the NHS website, around three in four men with a raised PSA level will not have cancer. Further tests, such as tissue biopsies or MRI scans, are therefore required to confirm a diagnosis.

Professor Antonis Antoniou from the Department of Public Health and Primary Care at the University of Cambridge said, "Prostate cancer is the most common cancer in men in the U.K., but population-wide screening based on PSA isn't an option: these tests are often falsely positive, which means that many men would then be biopsied unnecessarily. Also, many prostate tumors identified by PSA tests are slow-growing and would not have been life-threatening. The treatment of these tumors may do more harm than good.

"What we need is a way of identifying those men who are at greatest risk, allowing us to target screening and diagnostic tests where they are most needed, while also reducing the harms for those men who have low risk of the disease. This is what CanRisk-Prostate aims to do. For the first time, it combines information on the genetic makeup and prostate cancer family history, the main risk factors for the disease, to provide personalized cancer risks."

Prostate cancer is one of the most genetically determined of common cancers. Inherited faulty versions of the BRCA2, HOXB13 and possibly BRCA1 genes are associated with moderate-to-high risk of prostate cancer, though such faults are rare in the population. In addition, there are several hundred more common genetic variants that each confer a lower risk, but in aggregate they act like "volume control" that moderate or increase the prostate cancer risk.

Writing in the *Journal of Clinical Oncology*, the researchers—supported by Cancer Research UK—describe the development of the first comprehensive prostate cancer model using genetic and cancer family history data from almost 17,000 families affected by prostate cancer. It uses data on rare genetic faults in moderate-to-high-risk genes and a risk score based on 268 common low-risk variants, together with detailed cancer family history, to predict the future risks.

One in six men (16%) will develop prostate cancer by the time they are 85 years old. Using the model, the team found that the predicted risk was higher for men who had a father diagnosed with prostate cancer—27% if the father was diagnosed at an older age (80 years) but as high as 42% if the father was diagnosed at a young age (50 years).

The risks were considerably higher for men with genetic faults. For example, 54% of men who carry an alteration in the BRCA2 gene would develop prostate cancer—however, among men with BRCA2 gene

faults, the risks were substantially lower if they also had a small number of the low-risk variants, but much higher if they also had a large number of the low-risk variants.

In practice, say the researchers, clinicians will be able to use any combination of cancer family history, rare and common genetic variants to provide a personalized risk.

To validate their model, the team ran the risk model on an independent cohort of over 170,000 men recruited to UK Biobank, a biomedical database and research resource containing anonymized genetic, lifestyle and health information from half a million U.K. participants. All of these men were free from prostate cancer when they were recruited to the study, but more than 7,600 developed prostate cancer within the subsequent ten years.

When validating their model, the researchers found that 86% of the UK Biobank participants who developed cancer were in the half of men with the highest predicted risks, which suggests that it may be possible to target screening and diagnostic tests to the subgroup of the population at highest risk, among whom the majority of the cancers will occur.

Dr. Tommy Nyberg from the MRC Biostatistics Unit at Cambridge said, "We've created the most comprehensive tool to date for predicting a man's risk of developing prostate cancer. We hope this will help clinicians and genetic counselors assess their clients' risk and provide the appropriate follow-up.

"Over the next 12 months, we aim to build this tool into the widely used CanRisk tool, which will facilitate the risk-based clinical management of men seen in family cancer clinics and enable risk-adapted early detection approaches to the population at large."

Professor Ros Eeles from The Institute of Cancer Research, London and co-author on the study said, "This is an important step forward as it will enable clinicians to have conversations with men about their individual risk of prostate cancer based on the most accurate computer model to date. This will help them in making decisions about screening."

So far, the data used to develop CanRisk-Prostate has been from men of European ancestry. The team hope to be able to include data from men of other ethnicities as further research is undertaken.

The University of Cambridge recently launched the Early Cancer Institute with the aim of detecting cancer early enough to cure it. It is the first physical institute in the U.K. dedicated to early cancer. A new Cambridge Cancer Research Hospital is also planned for the near future, bringing together clinical and research expertise in a new, world-class hospital, designed in partnership with patients.

There is also an Early Detection and Diagnosis center at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust where a prostate risk clinic has been established to translate these findings into targeted screening programs.

More information: CanRisk-Prostate: a comprehensive, externally validated risk model for the prediction of future prostate cancer, *Journal of Clinical Oncology* (2022). DOI: 10.1200/JCO.22.01453

Provided by University of Cambridge

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