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Platinum Opinion

An update from the ReIMAGINE Prostate Cancer Risk Study (NCT04060589): A prospective cohort study in men with a suspicion of prostate cancer who are referred onto a magnetic resonance imaging–based diagnostic pathway with donation of tissue, blood, and urine for biomarker analyses

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The role of multiparametric magnetic resonance imaging (mpMRI) in the diagnostic pathway for prostate cancer is now well established [1–3]. Following high-quality MR imaging , a significant proportion of men at low risk of harbouring prostate cancer can safely avoid biopsy, and some studies have shown that in those with a higher clinical suspicion, MRI detects more cases of clinically significant cancer than systematic biopsies alone [4]. Importantly, following pre-biopsy mpMRI, needle deployment can be directed to specific regions of interest, leading to a potential characterisation of the cancer as a result of more representative tissue sampling.

Despite improved baseline diagnostics, the risk of overtreatment persists. Current risk calculators are derived from historical tissue archives collected when systematic biopsy was standard of care. Such models fail to reflect the additional information derived from contemporary MRI-directed sampling. When targeted histology data are input, disease risk may be exaggerated, which can lead to unnecessary or premature intervention. Incorporation of more accurate tumour sampling from an MRI pathway might lead to better treatment allocation and improved prognostic risk models that might incorporate tissue-based biomarkers that better represent the cancer.

The multidisciplinary ReIMAGINE consortium was conceived to develop or refine prostate cancer risk models to reflect this contemporary diagnostic strategy. The consortium is a collaboration between four expert academic centres and a number of leading industry partners. So far there are 15 commercial partners spanning imaging (~ 9 radiomics, artificial intelligence/machine learning), fluidic (~ 3 blood-based and ~2 urine-based) and tissue-based (~1) biomarkers.

The ReIMAGINE Prostate Cancer Risk study, the main work strand of the consortium, will deeply phenotype novel and measurable MRI disease cohorts by characterising the clinicopathological, radiomic, and molecular features of each group. Baseline features will be correlated with standard-of-care histology to permit the discovery and calibration of novel disease biomarkers. There will be an opportunity for robust validation of existing biomarkers against the presence of clinically significant cancer on biopsy (primarily defined as any Gleason $\geq$7, but which could be set at any acceptable target condition). ReIMAGINE Risk will include a longitudinal component to collect long-term health outcomes from national health care records (linkage through NHS Digital, Public Health England, and other relevant bodies), with time to metastasis and prostate cancer–related death representing the primary outcomes, but additional data on diagnostics, local therapy, and systemic therapies will also be collected. Oncological

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outcomes will be correlated with baseline disease phenotypes to inform prognostic risk models.

ReIMAGINE Risk will recruit 1000 treatment-naive men undergoing an mpMRI due to an elevated prostate-specific antigen level ($\leq$20 μg/l) or abnormal prostate examination who subsequently had suspicious mpMRI findings (Likert/PI-RADS v2.1 score $\geq$3) staged as $\leq$ T3bN0M0. Consenting patients will donate blood, urine, and additional prostate tissue cores. Two targeted cores from radiological areas of interest and one non-targeted core from an area of apparently normal tissue will be collected at the time of standard-of-care biopsy. Blood, urine, fresh prostate tissue, radiomics data, and digital pathology will be processed and stored at study-affiliated laboratories ahead of transfer to consortium partners for analysis.

Recruitment began at two London centres in September 2019 (n = 533). A first site opened in September 2019 (n = 296), a second in November 2019 (n = 210), and a third in December 2020 (n = 27). Recruitment was briefly halted between March and April 2020 because of the COVID-19 pandemic. Recruitment recommenced with the acceptance rate running high with 65% of eligible patients agreeing to participate. Mean ($\pm$ standard deviation) volumes of 36.5 $\pm$ 10.0 ml of urine, 12.9 $\pm$ 3.7 ml of plasma, and 2.8 $\pm$ 0.7 ml of serum have been donated for research.

ReIMAGINE will create the world's first image-based, deeply phenotyped cohort of men undergoing investigation for prostate cancer. This will allow us to create prostate cancer risk models that reflect the full range of novel prostate cancer diagnostics (both commercial and academic), collect tissue truly representative of underlying tumour heterogeneity, calibrate novel biomarkers, validate existing biomarkers, and assess the molecular determinants of progression and cancer risk (informed by the longitudinal study arm). The molecular profiling of advanced cancers undertaken by other groups will provide a comparator for deeply phenotyped tumours within ReIMAGINE [5].

Prostate cancer risk stratification is undergoing its most dramatic and important change since the advent of Gleason grading in the 1960s. The driving force is the simple fact that we can now see the tumour, whereas before we could not. Modern MRI detects almost twice as many clinically significant cancers as traditional, non-targeted sampling and it is this precision that ReIMAGINE seeks to exploit [4]. ReIMAGINE represents the first efforts to define prostate cancer risk using the full spectrum of emerging diagnostics. The outputs will provide image-based data sets that will replace and correct our historical (and flawed) tissue archives, risk calculators, and mechanistic insights. Beyond this, we will work towards making ReIMAGINE databanks a globally available resource that will provide research opportunities well into the future.

Conflicts of interest: Hashim U. Ahmed receives grant funding from Sonacare Inc., Sophiris Biocorp, and Boston, and has received insitutional research funds from the UK Medical Research Council, Cancer Research UK, the Wellcome Trust, the British Medical Association, the Urology Foundation, Prostate Cancer UK, and Imperial Health. Mark Emberton serves as a consultant/educator/trainer for Sonacare Inc., Exact Imaging, Angiodynamics, Inc., and Profound Medical, and receives research support from the UK National Institute of Health Research UCLH/UCL Biomedical Research Centre. Teresa Marsden has nothing to disclose.

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Ethics statement: The study received regulatory approval from the Regional Ethics Committee (London, Stanmore 19/LO/1128).

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