# 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 an MRI-based diagnostic pathway with donation of tissue, blood and urine for biomarker analyses.

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The role of multiparametric MRI (mpMRI) in the prostate cancer diagnostic pathway is now well established. [1-3] Follwing high quality MR imaging, a significant proportion of men at low risk of harbouring cancer can safely avoid biopsy and some studies have shown that in those with a higher clinical suspicion, it 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 MR-directed sampling. When targeted histology data is inputted, disease risk may be exaggerated and lead to unnecessary, or premature, intervention. Further, incorporation of the more accurate tumour sampling from such a pathway, might lead to improved 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. Existing biomarkers have an opportunity for robust validation against the presence of clinically significant cancer on biopsy (primarily defined as any Gleason 7 or greater 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 healthcare records (linkage through NHS Digital, Public Health England and other relevant bodies) with time to metastasis and prostate cancer related death forming the primary outcomes but additional diagnostics, local therapy, and systemic therapies also being collected. Oncological 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 PSA (≤ 20ug/L) or abnormal prostate examination who subsequently had a suspicious mpMRI (Likert /PIRADSv2.1 score ≥ 3) staged T3bN0M0 or less. 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 biopsy. Blood, urine, fresh prostate tissue, radiomic 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 due to the COVID-19 pandemic. However, recruitment recommenced with an acceptance rate running high at 65% of eligible patients agreeing to participate. A mean of 36.5ml (SD+/-10.0), 12.9ml (SD+/-3.7) and 2.8ml (SD+/-0.7) urine, plasma and serum has been donated for research, respectively.

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 which 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 ones 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 and before we could not. Modern day MRI detects almost twice as many clinically significant cancers as traditional, non-targeted sampling and it is this precision which ReIMAGINE seeks to exploit. [(4)] ReIMAGINE Risk represents the first efforts to define prostate cancer risk using the full spectrum of emerging diagnostics. The outputs will provide image-based datasets that will replace and correct our historical (and flawed)

tissue archives, risk calculators and mechanistic insights. Beyond this, we will work towards ReIMAGINE databanks becoming a globally available resource that will provide research opportunity well into the future.


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