Detection of ISUP≥2 Prostate Cancers Using Multiparametric MRI: Prospective Multicenter Comparison of the PI-RADS Score and an Artificial Intelligence System (CHANGE study)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-051274
Article Type:	Protocol
Date Submitted by the Author:	14-Mar-2021
Complete List of Authors:	Rouvière, Olivier; Université de Lyon, Souchon, Rémi; INSERM U1024 Lartizien, Carole; CREATIS Mansuy, Adeline; Hospices Civils de Lyon Magaud, Laurent; Service Recherche et Epidémiologie Cliniques Colom, Matthieu; Hospices Civils de Lyon Dubreuil-Chambardel, Marine; Hospices Civils de Lyon Debeer, Sabine; Hospices Civils de Lyon Jaouen, Tristan; INSERM U1032 Duran, Audrey; CREATIS Rippert, Pascal; Hospices Civils de Lyon Riche, Benjamin; Hospices Civils de Lyon, Service de Biostatistique - Bioinformatique, Pôle Santé Publique; Université de Lyon, Laboratoire de Biométrie et Biologie Évolutive CNRS UMR 5558, Équipe Biostatistiques Santé Monini, Caterina; INSERM U1032 Vlaeminck-Guillem, Virginie; Hospices Civils de Lyon Haesebaert, Julie; Hospices Civils de Lyon Rabilloud, Muriel; Hospices Civils de Lyon Crouzet, Sébastien; Hospices Civils de Lyon
Keywords:	RADIOLOGY & IMAGING, Genitourinary imaging < RADIOLOGY & IMAGING, Diagnostic radiology < RADIOLOGY & IMAGING, Magnetic resonance imaging < RADIOLOGY & IMAGING, UROLOGY, Prostate disease < UROLOGY

SCHOLARONE™
Manuscripts

Detection of ISUP≥2 Prostate Cancers Using Multiparametric MRI: Prospective Multicenter Comparison of the PI-RADS Score and an Artificial Intelligence System (CHANGE study)

Olivier Rouvière[1,2,3,4], Rémi Souchon[2,4], Carole Lartizien[2,5], Adeline Mansuy[1], Laurent Magaud[6], Matthieu Colom[7], Marine Dubreuil-Chambardel[1], Sabine Debeer[1], Tristan Jaouen[2,4], Audrey Duran[2,5], Pascal Rippert[6], Benjamin Riche[2,8], Caterina Monini[2,4], Virginie Vlaeminck-Guillem[2,9,10], Julie Haesebaert[2,6,11], Muriel Rabilloud[2,3,8], Sébastien Crouzet[2,3,4,12].

(1)　Hospices Civils de Lyon, Department of Urinary and Vascular Imaging, Hôpital Edouard Herriot, Lyon, France.

(2)　Université de Lyon ; Université Lyon 1

(3)　Faculté de médecine Lyon Est, Lyon, France.

(4)　LabTau, INSERM U1032, Lyon, France

(5)　CREATIS ; CNRS UMR5220 ; INSERM U1294 ; INSA-Lyon.

(6)　Hospices Civils de Lyon, Pôle Santé Publique, Service Recherche et Epidémiologie Cliniques, Lyon, France

(7)　Hospices Civils de Lyon, Direction de la Recherche Clinique et de l'Innovation, Lyon, France

(8)　Hospices Civils de Lyon, Pôle Santé Publique, Service de Biostatistique et Bioinformatique, Lyon, France; CNRS UMR 5558, Laboratoire de Biométrie et Biologie Évolutive, Équipe Biostatistique-Santé, F-69100, Villeurbanne, France.

(9)　Centre Léon Berard, Centre de Recherche en Cancérologie de Lyon, INSERM 1052, CNRS UMR5286, Lyon, France.

(10)　Hospices Civils de Lyon, Service de Biochimie Biologie Moléculaire Sud, Centre Hospitalier Lyon Sud, Pierre-Bénite, France.

(11)　Research on Healthcare Performance (RESHAPE), INSERM U1290, Lyon, France.

(12)　Hospices Civils de Lyon, Department of Urology, Hôpital Edouard Herriot, Lyon, France.

Corresponding author: Prof. Olivier Rouvière, Service d'imagerie, Pavillon B, Hôpital Edouard Herriot, 5 place d'Arsonval, 69437 Myon Cedex 03.

Tel: +33 (0)4 72 11 09 50; e-mail: Olivier.rouviere@netcourrier.com

Manuscript type: Protocol

Abstract

Introduction: Prostate multiparametric MRI (mpMRI) has shown good sensitivity in detecting cancers with an International Society of Urological Pathology (ISUP) grade ≥2. However, it lacks specificity, and its inter-reader reproducibility remains moderate. Biomarkers, such as the Prostate Health Index (PHI), may help select patients for prostate biopsy. Computer-aided diagnosis/detection (CAD) systems may also improve mpMRI interpretation. Different prototypes of CAD systems are currently developed under the RHU PERFUSE research program, tackling challenging issues such as robustness across imaging protocols and magnetic resonance (MR) vendors, and ability to characterize cancer aggressiveness. The study primary objective is to evaluate the non-inferiority of the receiver operating characteristic curve of the final CAD system as compared to the Prostate Imaging-Reporting and Data System version 2.1 (PI-RADSv2.1) in predicting the presence of ISUP ≥2 prostate cancer in patients undergoing prostate biopsy.

Methods: This is a prospective, multicentre, non-inferiority trial which will include 420 men with suspected prostate cancer, a prostate-specific antigen level ≤30 ng/ml and a clinical stage ≤T2c. Included men will undergo prostate mpMRI that will be interpreted using the PI-RADSv2.1 score. Then, they will undergo systematic and targeted biopsy. PHI will be assessed before biopsy. At the end of patient inclusion, MR images will be assessed by the final version of the CAD system developed under the RHU PERFUSE program. Key secondary outcomes include the prediction of ISUP ≥2 prostate cancer during a 3-year follow-up, and the number of biopsy procedures saved and ISUP ≥2 cancers missed by several diagnostic pathways combining PHI and MRI findings.

Ethics and dissemination: Ethical approval was obtained from the Comité de Protection des Personnes Nord Ouest III (ID-RCB: 2020-A02785-34). The study was registered with ClinicalTrials.gov, number NCT04732156. After publication of the results, access to MR images will be possible for testing other CAD systems.

Strengths and limitations of this study

- Prospective, multicentre, multivendor study making results more generalisable
- Design close to routine management of the patient, making results more applicable to real life clinical practice
- Constitution of a large cohort of patients with a three-year follow-up that will be made available for testing (and comparing) other CAD systems, after publication of the study results
- Ancillary study assessing PHI to determine the best diagnostic pathway combining PHI and MRI results
- Retrospective analysis of MR images by the CAD system whose results will not be used for targeted biopsy, which may underestimate the accuracy of the CAD system

Introduction

Prostate multiparametric magnetic resonance imaging (mpMRI) has shown excellent results in detecting and localizing prostate cancers with an International Society of Urological Pathology (ISUP) grade ≥2.[1-6] As a result, the European Association of Urology guidelines now recommend, in case of clinical suspicion of prostate cancer, to perform a prostate mpMRI prior to any biopsy.[7] The main strength of prostate mpMRI lies in its excellent sensitivity that was 0.91 (95% confidence interval (95%CI), 0.83 to 0.95) in a recent systematic review using template biopsy as reference standard.[5] However, mpMRI suffers from two main limitations. First, in the same systematic review, its pooled specificity was only 0.37 (95%CI, 0.29 to 0.46). This may induce useless targeted biopsy in a substantial proportion of men. Second, its inter-reader reproducibility is moderate at best, even when the Prostate Imaging-Reporting and Data system (PI-RADS) is used for interpretation.[8] Thus, the excellent results reported in large trials performed at experienced high-volume centres may not be reproduced in less-experienced institutions.

In this context, the optimal diagnostic pathway for patients with suspected prostate cancer remains unclear.[9-11] A first option would be to perform prostate biopsy systematically, regardless of mpMRI findings. Patients with positive mpMRI would undergo combined systematic and targeted biopsy; those with negative mpMRI would undergo systematic biopsy. This approach maximizes the detection of clinically significant prostate cancer (csPCa), especially in biopsy-naïve patients, but results in substantial overdetection (and potential overtreatment) of insignificant cancers and in performing useless biopsy procedures in a large proportion of men.[3-5] The opposite option would be to use mpMRI as a triage test for prostate biopsy: patients with positive mpMRI would undergo only targeted biopsy, while those with negative mpMRI would not be biopsied at all. This approach, however, is limited by mpMRI low specificity. In addition, because of mpMRI moderate inter-reader reproducibility, csPCa detection may be sub-optimal without the 'safety net' of systematic biopsy, at least in less-experienced centres.[12]

Patient selection for biopsy may be improved by combining MRI findings with simple clinical data or with other biomarkers. Among available biomarkers, the Prostate Health Index (PHI) has shown promising results in safely avoiding mpMRI and/or prostate biopsy in patients with suspected prostate cancer, at a reasonable cost.[13 14] In addition, artificial intelligence may help standardizing prostate mpMRI interpretation. Many groups have recently published good results in characterizing focal lesions seen on mpMRI with computer-aided diagnosis/detection (CAD) systems using conventional machine learning approaches or deep-learning techniques [15-25]. Some CAD systems have even been shown to improve human reading both in experienced and less-experienced readers.[26-28] Automated analysis of magnetic resonance (MR) images may therefore be the solution for improving prostate mpMRI specificity and inter-reader variability. Unfortunately, these approaches suffer from a lack of robustness across imaging protocols and MR vendors.[29-32] Of the many published CAD

systems aimed at characterizing focal MR lesions, only a few have undergone validation on cohorts from a different centre and a different vendor, with mixed results.[28] [33-35] Therefore, algorithms providing robust findings on multicentre multivendor cohorts are still lacking.

Our group is developing CAD systems aimed at detecting aggressive prostate cancer on MR images based on quantitative imaging and deep-learning techniques, under the RHU PERFUSE research program funded by the French National Research Agency (ANR-17-RHUS-0006).[25] [33] These systems are trained using a multivendor radiologic pathologic correlation database of prostate mpMRI performed before prostatectomy. The purpose of the CHANGE study is to build a large prospective multicentre multivendor cohort of patients assessed by prostate mpMRI and subsequent systematic and targeted biopsy. This cohort will be used for the final external validation of the best CAD system developed in PERFUSE, by evaluating its non-inferiority as compared to the PI-RADS version 2.1 (PI-RADSv2.1) score in predicting the presence of ISUP ≥2 prostate cancer at systematic and targeted biopsy. As an ancillary study, PHI will be measured in all patients to evaluate how this biomarker could be used to select patients who could safely avoid prostate mpMRI and/or biopsy.

Methods and analysis

Research hypothesis

The primary hypothesis of the CHANGE study is that the area under the receiver operating characteristic curve (AUC) of the tested CAD system for predicting the presence of ISUP ≥2 cancer at targeted and systematic biopsy, at patient level, will not be significantly inferior to that of the PI-RADS version 2.1 (PI-RADSv2.1) score.

Study design

This is a prospective multicentre non-inferiority trial. Participants will be recruited in outpatient clinics by local urologists among patients referred for clinical suspicion of prostate cancer. Included patients will undergo prostate mpMRI and combined targeted and systematic biopsy. A blood sample will be taken before prostate biopsy for PHI assessment. When available (i.e., at the end of the RHU PERFUSE program), the final version of the CAD will be used to retrospectively assess the risk that the prostate harbours ISUP ≥2 cancer. CAD and biopsy findings will be compared at patient (primary objective), lobe and lesion levels. In addition, included patients will be followed for three years and any prostate cancer diagnosed during the follow-up period will be noted.

Study setting and population

Seventeen French academic or private centres with expertise in prostate mpMRI and targeted biopsy were invited to participate in this study. Patients referred for suspicion of prostate cancer, aged between 18 and 80 years, with a prostate specific antigen (PSA) level ≤30 ng/mL, a clinical stage

≤T2c and affiliated to the French Social Security will be eligible. Exclusion criteria include history of prostate cancer, history of prostate biopsy performed less than 12 months before inclusion, history of pelvic radiotherapy (regardless of its cause), history of androgen deprivation therapy, history of hip prosthesis, contraindication to MRI or prostate biopsy, participation to another research with an ongoing exclusion period, and incomprehension of the French language. Patients under guardianship or curatorship will also be excluded. One of the local investigators will introduce the trial to eligible patients who will receive verbal and written information before signing the Ethics Committee-approved consent form. Patients will be informed that their participation in the study is voluntary, that refusal to participate will not influence their future management and that they can withdraw from the study at any moment, without justification. To avoid any selection bias, patients will be included before undergoing prostate mpMRI and included patients will undergo prostate biopsy regardless of the mpMRI results.

Procedures

Prostate mpMRI will be performed in compliance with the PI-RADSv2.1 guidelines (https://www.acr.org/-/media/ACR/Files/RADS/Pi-RADS/PIRADS-V2-1.pdf?la=en) and will include at least axial T2-weighted imaging, axial diffusion-weighted imaging with a maximal b-value ≥1400 s/mm², and axial dynamic contrast-enhanced (DCE) imaging after intravenous injection of a bolus of gadolinium chelates (0.1 mmol/kg) with a temporal resolution ≤15 seconds. MR examinations will be interpreted by a local senior radiologist, using PI-RADSv2.1 criteria.[36] Focal lesions with a PI-RADSv2.1 score ≥2 will be noted on a standardized prostate diagram. For each lesion, the radiologist will assess its size and location (peripheral zone, transition zone or central zone), T2, diffusion and DCE categories using PI-RADSv2.1 criteria, the overall PI-RADSv2.1 score, and the likelihood of extracapsular extension (5-level Likert score). The radiologist will also outline each lesion on T2-weighted, diffusion-weighted and DCE images. For each pulse sequence, delineation will be performed only on the section level considered the most representative of the lesion. The prostate lobes will be assigned the PI-RADSv2.1 score corresponding to the highest score of the lesion they contain. The patients will be assigned the highest PI-RADSv2.1 score of the two lobes. MR images and lesion outlines will be anonymized and transferred to the coordinating centre (Hospices Civils de Lyon).

A blood sample will be taken from included patients at least three weeks after any digital rectal examination or prostate manipulation, and less than three months before prostate biopsy. Samples will be centrifuged at the local laboratory and the serum will be stored at -20°C within one hour. If this is not possible, samples will be kept at +4°C and centrifuged and stored at -20°C, but no longer than 3 hours after blood sampling, as recommended.[37 38] The delay between blood sampling and storage at -20°C will be noted for each patient. Then, samples will be sent at -20°C to the coordinating centre where they will be processed for PHI assessment. PHI will be calculated from the serum

concentrations of total PSA, free PSA (fPSA) and [-2]proPSA using the following formula: $PHI = \frac{[-2]\text{proPSAx}\sqrt{PSA}}{\text{fPSA}}$. PHI results will not be available to local investigators at the time of biopsy, to avoid bias. At the end of the study, the remaining blood samples will be destroyed. No biological collection is planned.

Prostate biopsy will be performed by a senior radiologist or a senior urologist under transrectal ultrasound (TRUS) guidance, no longer than 3 months after prostate mpMRI and blood sampling for PHI determination. All lesions with a PI-RADSv2.1 score ≥3 will be targeted at biopsy. Targeted biopsy will be obtained according to the centre's routine technique, using cognitive guidance, software-assisted registration, or direct targeting under high-frequency ultrasound guidance. The guidance technique for each patient will be documented. At least three biopsy cores will be taken from each targeted lesion to ensure proper sampling.[39 40] In addition, 12 systematic biopsies will be taken; however, for patient comfort, the biopsy operator will be free not to obtain systematic biopsy from prostate areas already sampled by targeted biopsy. Patients without any lesions with a PI-RADSv2.1 score ≥3 will undergo 12-core systematic biopsy. The total number of systematic and targeted cores will be noted for each patient. Prostate biopsy cores will be analysed by a local senior pathologist on a core-by-core basis. For each core, the presence of cancer and the core length will be noted. In addition, the ISUP grade group and the length of cancer invasion will be noted for each core containing cancer.

The evaluated CAD system will be the final CAD system developed under the RHU PERFUSE research program. Its output will be, for each slice level, a parametric map providing a probability score that each pixel corresponds to ISUP ≥2 cancer. Parametric maps will be analysed at the end of the program, and therefore, their results will not be known at the time of biopsy. The analysis of the CAD parametric maps will be performed by two radiologists from the coordinating centre, working in consensus, and who will be blinded to the biopsy and follow-up results. First, they will copy onto the CAD parametric maps the lesions' outlines drawn by the local radiologist on MR images. The mean CAD score of the pixels located within each lesion outline will correspond to the lesion's CAD score, for per-lesion analysis. Then, the two radiologists will define the CAD score of each lobe. It will correspond to the highest score of any lesion ≥6 mm located in the lobe, whether it was seen by the local radiologist or not. Lesions of the transition zone with a complete peripheral capsule will be excluded from analysis regardless of their CAD score, since encapsulation is a definitive sign of benignity.[36] For per-patient analysis (primary analysis), the CAD score will be the highest score of both lobes.

Included patients will be followed at least 3 years by local investigators. The date of any diagnosis of prostate cancer made during this follow-up period (whether by another prostate biopsy or by transurethral prostate resection) will be collected.

Standard of reference

The results of the combined targeted and systematic biopsy performed within 3 months of the prostate mpMRI will be considered the histological standard of reference for per-patient and per-lobe analysis. For per-lesion analysis, only the results of targeted biopsy will be taken into consideration. csPCa will be defined as ISUP ≥2 cancer throughout the analysis.

Primary and secondary objectives

The primary objective will be the assessment of the non-inferiority of the AUC of the CAD score as compared to that of the PI-RADSv2.1 score for predicting the presence of csPCa at subsequent targeted and systematic biopsy, at patient level.

Secondary objectives include : i) the comparison of the sensitivity and specificity of the CAD and PI-RADSv2.1 scores for predicting the presence of csPCa at subsequent targeted and systematic biopsy, at lesion, lobe and patient levels, ii) the comparison of the AUC, sensitivity and specificity of the CAD and PI-RADSv2.1 scores for predicting the diagnosis of csPCa within the three years of follow-up, at patient level, iii) the assessment of the influence of the biopsy setting (biopsy naïve vs history of prior negative biopsy), magnetic field strength (1.5T vs 3T), experience (years) of the radiologist assessing the PI-RADSv2.1 score, guidance method (cognitive vs software-assisted registration) for targeted biopsy, and prostate volume (ml) on the AUC of the CAD and PI-RADSv2.1 scores for predicting the presence of csPCa at subsequent targeted and systematic biopsy, at patient level, iv) the comparison of the AUC of PHI, the CAD score and the PI-RADSv2.1 score for predicting the presence of csPCa at subsequent targeted and systematic biopsy, at patient level, and v) the estimation of the number of avoided mpMRI and prostate biopsies and of the number of missed csPCa in various diagnostic pathways combining the use of PHI and mpMRI as triage tests (Fig 1).

Data collection and assessment points

Patient recruitment will start in the first trimester of 2021 and is expected to last 24 months. Table 1 summarizes enrolment and interventions time points.

Data management, access and sharing

Only the data necessary to complete the protocol and the scientific publication will be collected, using an electronic case report form (eCRF). The eCRF will be developed by a data manager at the Hospices Civils de Lyon, using the Ennov Clinical 7.5.720 software that is compliant with the United States Food and Drug Administration (FDA) guidelines on clinical trial management (Guidance for Computerized Systems Used in Clinical Trial - FDA-2004-D-0039) and on electronic signature (FDA 21CRF part 11). The data set will be computerized in a coded way, in accordance with the Law for Data Protection and Freedom of Information. The study patients will be identified by a unique inclusion number and by the first initials of their surname and given name. The patient identification log will be kept in the investigator file. Data will be entered, as soon as they are collected, by the authorized persons

using their own login names according to the Law for Data Protection and Freedom of Information. The investigator is responsible for the accuracy, quality, and pertinence of all the data entered. As a result, each eCRF page will be electronically dated and signed by the investigator. On receipt of the data, the coordinating centre will check the eCRF and query all missing, implausible and inconsistent data.

This study falls within the framework of the "Reference Methodology" (MR-001) under the provisions of Article 54, Paragraph 5 of modified French Law 78-17 from January 6, 1978, related to Information Technology, Files and Liberties. This alteration has been approved by the decision made on January 5, 2006 and modified on July 21, 2016. The Hospices Civils de Lyon, sponsor of the study, have signed a commitment of compliance to this "Reference Methodology".

A Trial Steering Committee, presided by the study coordinator and composed of the scientists, biologists, methodologists, biostatisticians, and coordinators involved in defining the study design and protocol will oversee the final version of the protocol, the conduct of the trial, and the redaction of the publication. It will also validate and justify any change in the study protocol or statistical analysis plan.

Sample size

The calculation of the sample size was performed according to the method described by Zhou et al.[41] The AUC of the PI-RADSv2.1 score at patient level is expected to be 0.85.[42] Under the hypothesis of equality of the AUC of the CAD and PI-RADSv2.1 scores, for a non-inferiority margin of -5%, a bilateral alpha risk of 5% (one-sided significance level of 2.5%), an expected prevalence of csPCa of 30%,[3-5] and a correlation of 0.3 between the CAD and PI-RADSv2.1 scores in patients with csPCa and in those without csPCa, the inclusion of 385 patients will allow to assess the non-inferiority of the CAD score with a statistical power of 80%. To account for 10% of excluded patients, the trial will include 420 patients.

Statistical analysis

Analysis will be performed by a professional statistician from the Department of Biostatistics of the Hospices Civils de Lyon. A statistical analysis plan will be written before the database lock. It will consider any unexpected event or change in protocol with impact on data analysis. Any change in the statistical analysis plan occurring after the database lock will be documented and justified.

Data will be analysed according to the intention-to-treat principle (i.e., all patients who underwent both mpMRI and prostate biopsy will be included). In case of major protocol deviations, an additional per-protocol analysis will be performed after exclusion of the patients with major deviations. The list of major deviations will be established after review of the data and specified in the statistical analysis plan.

For the primary objective, the AUC of the CAD and PI-RADSv2.1 scores will be estimated at patient level, using the binormal method, along with their 95% confidence intervals. The difference between the AUC of the CAD and PI-RADSv2.1 scores will be estimated with its 95% confidence

interval. Non-inferiority will be established if the lower limit of the 95% confidence interval of the AUC difference is superior to -5%.

For secondary objectives, the specificity and sensitivity of the PI-RADSv2.1 score at patient, lobe and lesion level will be estimated using a positivity threshold of ≥3. For the CAD score, they will be estimated using the threshold yielding a sensitivity of 90% in the training database. The Wilson method will be used to calculate the 95% confidence intervals for sensitivities and specificities. Sensitivities and specificities of the CAD and PI-RADSv2.1 scores will be compared using the McNemar test. Positive and negative likelihood ratios and their 95% confidence intervals will also be estimated for both tests. The effect of biopsy setting, magnetic field strength, reader's experience, guidance method for targeted biopsy and prostate volume on the AUC of the final CAD and the PI-RADSv2.1 scores will be quantified by modelling the ROC curve using a probit regression model.[43]

The AUC of PHI will be estimated and compared to the AUC of the CAD score and the PI-RADSv2.1 score respectively using the binormal method. The following PHI positivity cut-offs will be used to assess different diagnostic pathways (Fig 1): 25 when PHI is used as an upfront diagnostic test (pathways a and b) or in combination with MRI (pathways f and g), and 50 when PHI is used in as a second-line test after mpMRI (pathways c-e). The different diagnostic pathways will be applied to the studied population to predict the number of avoided mpMRI, avoided biopsies or missed csPCa. These numbers will be given with a predicted interval taking into account the uncertainty on the estimate of the diagnostic performance of the tests.

Patient and public involvement

Patient and public were not involved in the design of this study.

Ethics and dissemination

Ethical approval was obtained from the Comité de Protection des Personnes Nord Ouest III (ID-RCB: 2020-A02785-34) on January 22, 2021. The study was registered with ClinicalTrials.gov, number NCT04732156. The Hospices Civils de Lyon is the responsible institution for this trial. The study coordinator will coordinate dissemination of the trial data through scientific conferences and publications in peer-reviewed international journals. Data reporting will follow the Standards for the Reporting of Diagnostic Accuracy Studies guideline.[44]

After publication of the results of the trial, the CHANGE cohort will be made partially accessible to other investigators wishing to test a CAD system aimed at detecting/localizing prostate cancer on MR images while respecting patient information. Request for access to pseudonymized data will be reviewed by the Trial Steering Committee that will grant access or not. To gain access, requestors will need to sign a data access agreement. Of note, investigators will have access only to the MR images and not to the histological findings. After analysis of the CHANGE MR images by

their CAD system, investigators will be requested to send the results to the Hospices Civils de Lyon. The comparison between the CAD findings and the targeted and systematic biopsy findings will be made by the Hospices Civils de Lyon that will then inform the investigator of the CAD diagnostic performance.

Discussion

The CHANGE study is aimed at constituting a prospective multicentre multivendor cohort of patients with suspected prostate cancer who underwent prostate mpMRI and subsequent targeted and systematic biopsy. This cohort will be used for external validation of the final CAD system developed under the RHU PERFUSE research program. For this study, we made four main methodological choices.

First, we did not plan to study patients with scheduled prostatectomy, although this would have allowed comparing CAD findings to a solid histological ground truth. Indeed, patients treated by prostatectomy constitute a biased population with a 100% prevalence of prostate cancer. Instead, we chose to study the real target population of any CAD aimed at diagnosing csPCa on MR images: patients with clinical suspicion of prostate cancer referred for prostate biopsy. We did not include patients under active surveillance. Thus, our results may not be applicable to this population.

Second, we decided to use the results of targeted and systematic biopsy as standard of reference, although it may miss some csPCa. Using a more sensitive biopsy technique such as transperineal template saturation biopsy would have improved the detection of csPCa. However, template saturation biopsy is not obtained routinely in France. In addition, the clinical significance of ISUP ≥2 detected by such sensitive an approach remains debated. Therefore, we chose to use as standard of reference the biopsy technique that is recommended for prostate cancer diagnosis in daily routine.[7]

Third, patient recruitment will start before the CAD is finalized, and thus, the CAD will not be used to trigger targeted biopsy. This results from a pragmatic choice. Setting a prospective study in which the CAD is used to trigger targeted biopsy would need a CAD system that has good and stable results on its training databases, is embedded in an easy-to-install, user-friendly interface, and has gone through all legal and regulatory requirements for clinical use. It was unrealistic to develop such a CAD system and then perform a multicentre validation study within the duration of the RHU PERFUSE program funding. Instead, we preferred recruiting a multicentre prospective cohort while the CAD was being developed. We acknowledge that comparing the accuracy of the CAD and the PI-RADS2.1 scores in this cohort will be to the disadvantage of the CAD score. Indeed, the CAD system may show some cancer foci missed by human reading and subsequent biopsy and that will be erroneously considered as CAD false positive findings at per-lobe and per-patient analysis. To mitigate this, we included a 3-year follow-up for patients with negative biopsy. Of note, because no

particular CAD system will be used to trigger targeted biopsy, our cohort may be used as a reference cohort for evaluating other CAD systems. Therefore, our data sharing policy stipulates that the cohort will be made accessible to other research groups, as a test cohort, once our own CAD system has been evaluated. We hope that this will allow rapid comparisons between artificial intelligence solutions in a challenging multicentre multivendor setting.

Fourth, PHI will be measured in all patients. This ancillary study is independent to the evaluation of the CAD system. However, we took advantage of constituting a prospective multicentre cohort to also assess whether PHI could be used, as a stand alone or in combination with mpMRI, to select patients who could safely avoid mpMRI and/or prostate biopsy, thereby reducing both patient discomfort and the cost of prostate cancer diagnostic pathway.

Captions for figures

Figure 1: Possible diagnostic pathways using PHI, prostate MRI or the combination of both as triage tests

References

1. Ahmed HU, El-Shater Bosaily A, Brown LC, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. *Lancet* 2017;389(10071):815-22.

2. Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. *N Engl J Med* 2018;378(19):1767-77.

3. Rouviere O, Puech P, Renard-Penna R, et al. Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naive patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. *Lancet Oncol* 2019;20(1):100-09.

4. van der Leest M, Cornel E, Israel B, et al. Head-to-head Comparison of Transrectal Ultrasound-guided Prostate Biopsy Versus Multiparametric Prostate Resonance Imaging with Subsequent Magnetic Resonance-guided Biopsy in Biopsy-naive Men with Elevated Prostate-specific Antigen: A Large Prospective Multicenter Clinical Study. *Eur Urol* 2019;75(4):570-78.

5. Drost FH, Osses DF, Nieboer D, et al. Prostate MRI, with or without MRI-targeted biopsy, and systematic biopsy for detecting prostate cancer. *Cochrane Database Syst Rev* 2019;4:CD012663.

6. Klotz L, Chin J, Black PC, et al. Comparison of Multiparametric Magnetic Resonance Imaging-Targeted Biopsy With Systematic Transrectal Ultrasonography Biopsy for Biopsy-Naive Men at Risk for Prostate Cancer: A Phase 3 Randomized Clinical Trial. *JAMA Oncol* 2021 doi: 10.1001/jamaoncol.2020.7589 [published Online First: 2021/02/05]

7. Mottet N, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer-2020 Update. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *Eur Urol* 2021;79(2):243-62.

8. Richenberg J, Logager V, Panebianco V, et al. The primacy of multiparametric MRI in men with suspected prostate cancer. *Eur Radiol* 2019;29(12):6940-52.

9. Padhani AR, Weinreb J, Rosenkrantz AB, et al. Prostate Imaging-Reporting and Data System Steering Committee: PI-RADS v2 Status Update and Future Directions. *Eur Urol* 2019;75(3):385-96.

10. Schoots IG, Padhani AR, Rouviere O, et al. Analysis of Magnetic Resonance Imaging-directed Biopsy Strategies for Changing the Paradigm of Prostate Cancer Diagnosis. *Eur Urol Oncol* 2020;3(1):32-41.

11. Donato P, Morton A, Yaxley J, et al. Improved detection and reduced biopsies: the effect of a multiparametric magnetic resonance imaging-based triage prostate cancer pathway in a public teaching hospital. *World J Urol* 2020;38(2):371-79.

12. Rouviere O. Choosing the Right Diagnostic Pathway in Biopsy-Naive Patients With Suspected Prostate Cancer. *JAMA Oncol* 2021 doi: 10.1001/jamaoncol.2020.7578 [published Online First: 2021/02/05]

13. Kim L, Boxall N, George A, et al. Clinical utility and cost modelling of the phi test to triage referrals into image-based diagnostic services for suspected prostate cancer: the PRIM (Phi to RefIne Mri) study. *BMC medicine* 2020;18(1):95.

14. Ferro M, De Cobelli O, Lucarelli G, et al. Beyond PSA: The Role of Prostate Health Index (phi). *Int J Mol Sci* 2020;21(4):1184

15. Lemaitre G, Marti R, Freixenet J, et al. Computer-Aided Detection and diagnosis for prostate cancer based on mono and multi-parametric MRI: a review. *Comput Biol Med* 2015;60:8-31.

16. Goldenberg SL, Nir G, Salcudean SE. A new era: artificial intelligence and machine learning in prostate cancer. *Nat Rev Urol* 2019;16(7):391-403.

17. Cuocolo R, Cipullo MB, Stanzione A, et al. Machine learning applications in prostate cancer magnetic resonance imaging. *Eur Radiol Exp* 2019;3(1):35.

18. Liu L, Tian Z, Zhang Z, et al. Computer-aided Detection of Prostate Cancer with MRI: Technology and Applications. *Acad Radiol* 2016;23(8):1024-46.

19. Schelb P, Kohl S, Radtke JP, et al. Classification of Cancer at Prostate MRI: Deep Learning versus Clinical PI-RADS Assessment. *Radiology* 2019;293(3):607-17.

20. Hoang Dinh A, Melodelima C, Souchon R, et al. Quantitative Analysis of Prostate Multiparametric MR Images for Detection of Aggressive Prostate Cancer in the Peripheral Zone: A Multiple Imager Study. *Radiology* 2016;280(1):117-27.

21. Dinh AH, Melodelima C, Souchon R, et al. Characterization of Prostate Cancer with Gleason Score of at Least 7 by Using Quantitative Multiparametric MR Imaging: Validation of a

Computer-aided Diagnosis System in Patients Referred for Prostate Biopsy. *Radiology* 2018;287(2):525-33.

22. Abraham B, Nair MS. Computer-aided classification of prostate cancer grade groups from MRI images using texture features and stacked sparse autoencoder. *Comput Med Imaging Graph* 2018;69:60-68.

23. Cao R, Mohammadian Bajgiran A, Afshari Mirak S, et al. Joint Prostate Cancer Detection and Gleason Score Prediction in mp-MRI via FocalNet. *IEEE Trans Med Imag* 2019;38(11):2496-506.

24. Vente C, Vos P, Hosseinzadeh M, et al. Deep Learning Regression for Prostate Cancer Detection and Grading in Bi-Parametric MRI. *IEEE Trans Biomed Eng* 2021;68(2):374-83.

25. Duran A, Jodoin P, Lartizien C. Prostate Cancer Semantic Segmentation by Gleason Score Group in bi-parametric MRI with Self Attention Model on the Peripheral Zone. Third Conference on Medical Imaging with Deep Learning, in Proceedings Machine Learning Research (PMLR), 2020;121:193-204.

26. Hambrock T, Vos PC, Hulsbergen-van de Kaa CA, et al. Prostate cancer: computer-aided diagnosis with multiparametric 3-T MR imaging--effect on observer performance. *Radiology* 2013;266(2):521-30.

27. Niaf E, Lartizien C, Bratan F, et al. Prostate focal peripheral zone lesions: characterization at multiparametric MR imaging--influence of a computer-aided diagnosis system. *Radiology* 2014;271(3):761-9.

28. Gaur S, Lay N, Harmon SA, et al. Can computer-aided diagnosis assist in the identification of prostate cancer on prostate MRI? a multi-center, multi-reader investigation. *Oncotarget* 2018;9(73):33804-17.

29. Fedeli L, Belli G, Ciccarone A, et al. Dependence of apparent diffusion coefficient measurement on diffusion gradient direction and spatial position - A quality assurance intercomparison study of forty-four scanners for quantitative diffusion-weighted imaging. *Phys Med* 2018;55:135-41.

30. Kim H. Variability in Quantitative DCE-MRI: Sources and Solutions. *J Nat Sci* 2018;4(1):e484

31. Schlett CL, Hendel T, Hirsch J, et al. Quantitative, Organ-Specific Interscanner and Intrascanner Variability for 3 T Whole-Body Magnetic Resonance Imaging in a Multicenter, Multivendor Study. *Invest Radiol* 2016;51(4):255-65.

32. Shukla-Dave A, Obuchowski NA, Chenevert TL, et al. Quantitative imaging biomarkers alliance (QIBA) recommendations for improved precision of DWI and DCE-MRI derived biomarkers in multicenter oncology trials. *J Magn Reson Imaging* 2019;49(7):e101-e21.

33. Transin S, Souchon R, Gonindard-Melodelima C, et al. Computer-aided diagnosis system for characterizing ISUP grade >= 2 prostate cancers at multiparametric MRI: A cross-vendor evaluation. *Diag Interv Imaging* 2019;100(12):801-11.

34. Peng Y, Jiang Y, Antic T, et al. Validation of quantitative analysis of multiparametric prostate MR images for prostate cancer detection and aggressiveness assessment: a cross-imager study. *Radiology* 2014;271(2):461-71.

35. Castillo TJ, Starmans MPA, Arif M, et al. A Multi-Center, Multi-Vendor Study to Evaluate the Generalizability of a Radiomics Model for Classifying Prostate cancer: High Grade vs. Low Grade. *Diagnostics* 2021;11(2):369

36. Turkbey B, Rosenkrantz AB, Haider MA, et al. Prostate Imaging Reporting and Data System Version 2.1: 2019 Update of Prostate Imaging Reporting and Data System Version 2. *Eur Urol* 2019;76(3):340-51.

37. Igawa T, Takehara K, Onita T, et al. Stability of [-2]Pro-PSA in whole blood and serum: analysis for optimal measurement conditions. *J Clin Lab Anal* 2014;28(4):315-9.

38. Semjonow A, Kopke T, Eltze E, et al. Pre-analytical in-vitro stability of [-2]proPSA in blood and serum. *Clin Biochem* 2010;43(10-11):926-8.

39. Zhang M, Milot L, Khalvati F, et al. Value of Increasing Biopsy Cores per Target with Cognitive MRI-targeted Transrectal US Prostate Biopsy. *Radiology* 2019;291(1):83-89.

40. Lu AJ, Syed JS, Ghabili K, et al. Role of Core Number and Location in Targeted Magnetic Resonance Imaging-Ultrasound Fusion Prostate Biopsy. *Eur Urol* 2019;76(1):14-17.

41. Zhou XH, Obuchowski NA, McClish DK. Statistical Methods in Diagnostic Medicine. Hoboken: John Wiley & Sons 2011:203-17.

42. Stabile A, Giganti F, Kasivisvanathan V, et al. Factors Influencing Variability in the Performance of Multiparametric Magnetic Resonance Imaging in Detecting Clinically Significant Prostate Cancer: A Systematic Literature Review. *Eur Urol Oncol* 2020;3(2):145-67.

43. Alonzo TA, Pepe MS. Distribution-free ROC analysis using binary regression techniques. *Biostatistics* 2002;3(3):421-32.

44. Bossuyt PM, Reitsma JB, Bruns DE, et al. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. *BMJ* 2015;351:h5527.

Author's Contributions

All authors have cooperated to the design of the study and to the formulation of the protocol. OR is the principal investigator for this trial and has initiated and planned this trial project with SC. SC is the medical coordinator of the RHU PERFUSE Research program and CM is the scientific project manager coordinating the different work packages of the program. RS, CL, TJ, and AD are developing and testing different approaches for the CAD systems as senior scientists (RS, CL) or PhD students (TJ, AD). RS is also responsible of the quality control of the MR examinations performed in the participating centres. JH oversaw the study design. MR and BR are biostatisticians. MR played a

central role in the sample size calculation and the statistical analysis plan. AM, LM, MC, MDC and SD drafted the protocol and will play a central role in study coordination, data management and in providing support to the participating centres. PR designed the electronic case report form. VV participated to the design of the ancillary study and is responsible for supervising the management of blood samples and the dosage of PHI.
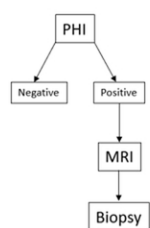
Funding

Competing interests statement

None

	Enrolment (Month 0)	Visit 1 (Month 0)	Visit 2 (Month 0-3)	Visit 3 / End of study (Month 36±2)
Informed consent and enrolment	X			
Assessment of patient history, clinical stage, and PSA level	X			
Blood test (PHI)		X		
Multiparametric MRI		X		
Targeted biopsy based on human reading of MR images (PI-RADSv2.1)			X	
Systematic biopsy			X	
Assessment of adverse events		X	X	X
Assessment of 3-year follow-up				X

Table 1: Time points of enrolment and interventions

Possible diagnostic pathways using PHI, prostate MRI or the combination of both as triage tests

72x105mm (300 x 300 DPI)

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	Abstract (AUC)
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	Yes
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	Yes
	4	Study objectives and hypotheses	Yes
METHODS			
Study design	5	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	Yes
Participants	6	Eligibility criteria	Yes
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	Yes
	8	Where and when potentially eligible participants were identified (setting, location and dates)	Yes
	9	Whether participants formed a consecutive, random or convenience series	Yes
Test methods	10a	Index test, in sufficient detail to allow replication	Yes
	10b	Reference standard, in sufficient detail to allow replication	Yes
	11	Rationale for choosing the reference standard (if alternatives exist)	Yes (see discussion)
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	Yes
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	Yes
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	Yes
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	Yes
Analysis	14	Methods for estimating or comparing measures of diagnostic accuracy	Yes
	15	How indeterminate index test or reference standard results were handled	No – will be defined in the SAP at database lock
	16	How missing data on the index test and reference standard were handled	No - will be defined in the SAP at database lock
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	Yes
	18	Intended sample size and how it was determined	Yes
RESULTS			
Participants	19	Flow of participants, using a diagram	N/A (protocol); but will be provided when the study is done
	20	Baseline demographic and clinical characteristics of participants	N/A (protocol); but will be provided when the study is done
	21a	Distribution of severity of disease in those with the target condition	N/A (protocol); but will be provided when the study is done
	21b	Distribution of alternative diagnoses in those without the target condition	N/A (protocol); but will be provided when the study is done

		22	Time interval and any clinical interventions between index test and reference standard	N/A (protocol); but will be provided when the study is done
Test results		23	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	N/A (protocol); but will be provided when the study is done
		24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	N/A (protocol); but will be provided when the study is done
		25	Any adverse events from performing the index test or the reference standard	N/A (protocol); but will be provided when the study is done
DISCUSSION				
		26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	Yes
		27	Implications for practice, including the intended use and clinical role of the index test	N/A – it will depend on the study results
OTHER INFORMATION				
		28	Registration number and name of registry	Yes
		29	Where the full study protocol can be accessed	N/A
		30	Sources of funding and other support; role of funders	Yes

STARD 2015

AIM

STARD stands for "Standards for Reporting Diagnostic accuracy studies". This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or "2x2" table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.

Detection of ISUP≥2 Prostate Cancers Using Multiparametric MRI: Prospective Multicenter Assessment of the non-inferiority of an Artificial Intelligence System as compared to the PI-RADS Version 2.1 Score (CHANGE study)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-051274.R1
Article Type:	Protocol
Date Submitted by the Author:	11-Oct-2021
Complete List of Authors:	Rouvière, Olivier; Université de Lyon, Université Lyon 1; Hospices Civils de Lyon, Department of Urinary and Vascular Imaging, Hôpital Edouard Herriot Souchon, Rémi; INSERM U1032, LabTau Lartizien, Carole; INSERM U1294, CREATIS Mansuy, Adeline; Hospices Civils de Lyon Magaud, Laurent; Service Recherche et Epidémiologie Cliniques Colom, Matthieu; Hospices Civils de Lyon Dubreuil-Chambardel, Marine; Hospices Civils de Lyon Debeer, Sabine; Hospices Civils de Lyon Jaouen, Tristan; INSERM U1032, LabTau Duran, Audrey; INSERM U1294, CREATIS Rippert, Pascal; Hospices Civils de Lyon Riche, Benjamin; Hospices Civils de Lyon, Service de Biostatistique - Bioinformatique, Pôle Santé Publique; Université de Lyon, Laboratoire de Biométrie et Biologie Évolutive CNRS UMR 5558, Équipe Biostatistiques Santé Monini, Caterina; INSERM U1032 Vlaeminck-Guillem, Virginie; Hospices Civils de Lyon Haesebaert, Julie; Hospices Civils de Lyon Rabilloud, Muriel; Hospices Civils de Lyon Crouzet, Sébastien; Hospices Civils de Lyon, Deaprtment of Urology, Hôpital Edouard Herriot
Primary Subject Heading:	Radiology and imaging
Secondary Subject Heading:	Urology, Diagnostics
Keywords:	RADIOLOGY & IMAGING, Genitourinary imaging < RADIOLOGY & IMAGING, Diagnostic radiology < RADIOLOGY & IMAGING, Magnetic resonance imaging < RADIOLOGY & IMAGING, UROLOGY, Prostate disease < UROLOGY

SCHOLARONE™
Manuscripts

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Detection of ISUP≥2 Prostate Cancers Using Multiparametric MRI: Prospective Multicenter Assessment of the non-inferiority of an Artificial Intelligence System as compared to the PI-RADS Version 2.1 Score (CHANGE study)

Olivier Rouvière[1,2,3,4], Rémi Souchon[2,4], Carole Lartizien[2,5], Adeline Mansuy[1], Laurent Magaud[6], Matthieu Colom[7], Marine Dubreuil-Chambardel[1], Sabine Debeer[1], Tristan Jaouen[2,4], Audrey Duran[2,5], Pascal Rippert[6], Benjamin Riche[2,8], Caterina Monini[2,4], Virginie Vlaeminck-Guillem[2,9,10], Julie Haesebaert[2,6,11], Muriel Rabilloud[2,3,8], Sébastien Crouzet[2,3,4,12].

(1) Hospices Civils de Lyon, Department of Urinary and Vascular Imaging, Hôpital Edouard Herriot, Lyon, France.
(2) Université de Lyon ; Université Lyon 1
(3) Faculté de médecine Lyon Est, Lyon, France.
(4) LabTau, INSERM U1032, Lyon, France
(5) CREATIS ; CNRS UMR5220 ; INSERM U1294 ; INSA-Lyon.
(6) Hospices Civils de Lyon, Pôle Santé Publique, Service Recherche et Epidémiologie Cliniques, Lyon, France
(7) Hospices Civils de Lyon, Direction de la Recherche Clinique et de l'Innovation, Lyon, France
(8) Hospices Civils de Lyon, Pôle Santé Publique, Service de Biostatistique et Bioinformatique, Lyon, France; CNRS UMR 5558, Laboratoire de Biométrie et Biologie Évolutive, Équipe Biostatistique-Santé, F-69100, Villeurbanne, France.
(9) Centre Léon Berard, Centre de Recherche en Cancérologie de Lyon, INSERM 1052, CNRS UMR5286, Lyon, France.
(10) Hospices Civils de Lyon, Service de Biochimie Biologie Moléculaire Sud, Centre Hospitalier Lyon Sud, Pierre-Bénite, France.
(11) Research on Healthcare Performance (RESHAPE), INSERM U1290, Lyon, France.
(12) Hospices Civils de Lyon, Department of Urology, Hôpital Edouard Herriot, Lyon, France.

Corresponding author: Prof. Olivier Rouvière, Service d'imagerie, Pavillon B, Hôpital Edouard Herriot, 5 place d'Arsonval, 69437 Myon Cedex 03.

Tel: +33 (0)4 72 11 09 50; e-mail: Olivier.rouviere@netcourrier.com

Manuscript type: Protocol

Abstract

Introduction: Prostate multiparametric MRI (mpMRI) has shown good sensitivity in detecting cancers with an International Society of Urological Pathology (ISUP) grade ≥2. However, it lacks specificity, and its inter-reader reproducibility remains moderate. Biomarkers, such as the Prostate Health Index (PHI), may help select patients for prostate biopsy. Computer-aided diagnosis/detection (CAD) systems may also improve mpMRI interpretation. Different prototypes of CAD systems are currently developed under the RHU PERFUSE research program, tackling challenging issues such as robustness across imaging protocols and magnetic resonance (MR) vendors, and ability to characterize cancer aggressiveness. The study primary objective is to evaluate the non-inferiority of the area under the receiver operating characteristic curve of the final CAD system as compared to the Prostate Imaging-Reporting and Data System version 2.1 (PI-RADSv2.1) in predicting the presence of ISUP ≥2 prostate cancer in patients undergoing prostate biopsy.

Methods: This prospective, multicentre, non-inferiority trial will include 420 men with suspected prostate cancer, a prostate-specific antigen level ≤30 ng/ml and a clinical stage ≤T2c. Included men will undergo prostate mpMRI that will be interpreted using the PI-RADSv2.1 score. Then, they will undergo systematic and targeted biopsy. PHI will be assessed before biopsy. At the end of patient inclusion, MR images will be assessed by the final version of the CAD system developed under the RHU PERFUSE program. Key secondary outcomes include the prediction of ISUP ≥2 prostate cancer during a 3-year follow-up, and the number of biopsy procedures saved and ISUP ≥2 cancers missed by several diagnostic pathways combining PHI and MRI findings.

Ethics and dissemination: Ethical approval was obtained from the Comité de Protection des Personnes Nord Ouest III (ID-RCB: 2020-A02785-34). The study was registered with ClinicalTrials.gov, number NCT04732156. After publication of the results, access to MR images will be possible for testing other CAD systems.

Strengths and limitations of this study

- Prospective, multicentre, multivendor study making results more generalisable
- Design close to routine management of the patient, making results more applicable to real life clinical practice
- Constitution of a large cohort of patients with a three-year follow-up that will be made available for testing (and comparing) other CAD systems, after publication of the study results
- Ancillary study assessing PHI to determine the best diagnostic pathway combining PHI and MRI results
- The CHANGE study is limited by the retrospective analysis of MR images by the CAD system whose results will not be used for targeted biopsy; this may underestimate the accuracy of the CAD system

Introduction

Prostate multiparametric magnetic resonance imaging (mpMRI) has shown excellent results in detecting and localizing prostate cancers with an International Society of Urological Pathology (ISUP) grade ≥2.[1-6] As a result, the European Association of Urology guidelines now recommend, in case of clinical suspicion of prostate cancer, to perform a prostate mpMRI prior to any biopsy.[7] The main strength of prostate mpMRI lies in its excellent sensitivity that was 0.91 (95% confidence interval (95%CI), 0.83 to 0.95) in a recent systematic review using template biopsy as reference standard.[5] However, mpMRI suffers from two main limitations. First, in the same systematic review, its pooled specificity was only 0.37 (95%CI, 0.29 to 0.46). This may induce useless targeted biopsy in a substantial proportion of men. Second, its inter-reader reproducibility is moderate at best, even when the Prostate Imaging-Reporting and Data system (PI-RADS) is used for interpretation.[8] Thus, the excellent results reported in large trials performed at experienced high-volume centres may not be reproduced in less-experienced institutions.

In this context, the optimal diagnostic pathway for patients with suspected prostate cancer remains unclear.[9-11] A first option would be to perform prostate biopsy systematically, regardless of mpMRI findings. Patients with positive mpMRI would undergo combined systematic and targeted biopsy; those with negative mpMRI would undergo systematic biopsy. This approach maximizes the detection of clinically significant prostate cancer (csPCa), especially in biopsy-naïve patients, but results in substantial overdetection (and potential overtreatment) of insignificant cancers and in performing useless biopsy procedures in a large proportion of men.[3-5] The opposite option would be to use mpMRI as a triage test for prostate biopsy: patients with positive mpMRI would undergo only targeted biopsy, while those with negative mpMRI would not be biopsied at all. This approach, however, is limited by mpMRI low specificity. In addition, because of mpMRI moderate inter-reader reproducibility, csPCa detection may be sub-optimal without the 'safety net' of systematic biopsy, at least in less-experienced centres.[12]

Patient selection for biopsy may be improved by combining MRI findings with simple clinical data or with other biomarkers. Among available biomarkers, the Prostate Health Index (PHI) has shown promising results in safely avoiding mpMRI and/or prostate biopsy in patients with suspected prostate cancer, at a reasonable cost.[13 14] In addition, artificial intelligence may help standardizing prostate mpMRI interpretation. Many groups have recently published good results in characterizing focal lesions seen on mpMRI with computer-aided diagnosis/detection (CAD) systems using conventional machine learning approaches or deep-learning techniques [15-25]. These CAD systems can either help characterizing lesions outlined by the radiologist (computer-aided diagnosis systems, or CADx systems) or provide parametric maps highlighting regions of cancer that may correspond to cancers or aggressive cancers (computer-aided detection systems, or CADe systems). Some CAD

systems have even been shown to improve human reading both in experienced and less-experienced readers, but mostly in single-institution studies which makes it hard to extrapolate the results to other centres or MRI machines.[26-28] Indeed, these approaches suffer from a lack of robustness across imaging protocols and MR vendors.[29-32] Of the many published CAD systems aimed at characterizing focal MR lesions, only a few have undergone validation on cohorts from a different centre and a different vendor, with mixed results.[28 33-35] Therefore, algorithms providing robust findings on multicentre multivendor cohorts are still lacking.

Our group is developing CADe systems aimed at detecting aggressive prostate cancer on MR images based on quantitative imaging and deep-learning techniques, under the RHU PERFUSE research program funded by the French National Research Agency (ANR-17-RHUS-0006).[25 33] These systems are trained using a multivendor radiologic pathologic correlation database of prostate mpMRI performed before prostatectomy. The purpose of the CHANGE study is to build a large prospective multicentre multivendor cohort of patients assessed by prostate mpMRI and subsequent systematic and targeted biopsy. This cohort will be used for the final external validation of the best CAD system developed in PERFUSE, by evaluating its non-inferiority as compared to the PI-RADS version 2.1 (PI-RADSv2.1) score in predicting the presence of ISUP ≥2 prostate cancer at systematic and targeted biopsy. As an ancillary study, PHI will be measured in all patients to evaluate how this biomarker could be used to select patients who could safely avoid prostate mpMRI and/or biopsy.

Methods and analysis

Research hypotheses

The primary hypothesis of the CHANGE study is that the area under the receiver operating characteristic curve (AUC) of the tested CAD system for predicting the presence of ISUP ≥2 cancer at targeted and systematic biopsy, at patient level, will not be significantly inferior to that of the PI-RADS version 2.1 (PI-RADSv2.1) score.

As a secondary hypothesis, we also hypothesized that combining PHI and mpMRI findings would improve the selection of patients referred to prostate biopsy.

Study design

This is a prospective multicentre non-inferiority trial. Participants will be recruited in outpatient clinics by local urologists among patients referred for clinical suspicion of prostate cancer. Included patients will undergo prostate mpMRI and combined targeted and systematic biopsy. A blood sample will be taken before prostate biopsy for PHI assessment. When available (i.e., at the end of the RHU PERFUSE program), the final version of the CAD will be used to retrospectively assess the risk that the prostate harbours ISUP ≥2 cancer. CAD and biopsy findings will be compared at patient

(primary objective), lobe and lesion levels. In addition, included patients will be followed for three years and any prostate cancer diagnosed during the follow-up period will be noted.

Study setting and population

Seventeen French academic or private centres with expertise in prostate mpMRI and targeted biopsy were invited to participate in this study. Patients referred for suspicion of prostate cancer, aged between 18 and 80 years, with a prostate specific antigen (PSA) level ≤30 ng/mL, a clinical stage ≤T2c and affiliated to the French Social Security will be eligible. Exclusion criteria include history of prostate cancer, history of prostate biopsy performed less than 12 months before inclusion, history of pelvic radiotherapy (regardless of its indication), history of androgen deprivation therapy, history of hip prosthesis, contraindication to MRI or prostate biopsy, participation to another research with an ongoing exclusion period, and incomprehension of the French language. Patients under guardianship or curatorship will also be excluded. One of the local investigators will introduce the trial to eligible patients who will receive verbal and written information before signing the Ethics Committee-approved consent form. Patients will be informed that their participation in the study is voluntary, that refusal to participate will not influence their future management and that they can withdraw from the study at any moment, without justification. To avoid any selection bias, patients will be included before undergoing prostate mpMRI and included patients will undergo prostate biopsy regardless of the mpMRI results.

Procedures

Prostate mpMRI will be performed in compliance with the PI-RADSv2.1 guidelines (https://www.acr.org/-/media/ACR/Files/RADS/Pi-RADS/PIRADS-V2-1.pdf?la=en) and will include at least axial T2-weighted imaging, axial diffusion-weighted imaging with a maximal b-value ≥1400 s/mm², and axial dynamic contrast-enhanced (DCE) imaging after intravenous injection of a bolus of gadolinium chelates (0.1 mmol/kg) with a temporal resolution ≤15 seconds. MR examinations will be interpreted by a local senior radiologist, using PI-RADSv2.1 criteria.[36] Focal lesions with a PI-RADSv2.1 score ≥2 will be noted on a standardized prostate diagram. For each lesion, the radiologist will assess its size and location (peripheral zone, transition zone or central zone), T2, diffusion and DCE categories using PI-RADSv2.1 criteria, the overall PI-RADSv2.1 score, and the likelihood of extracapsular extension (5-level Likert score). The radiologist will also outline each lesion on T2-weighted, diffusion-weighted and DCE images. For each pulse sequence, delineation will be performed only on the section level considered the most representative of the lesion. The prostate lobes will be assigned the PI-RADSv2.1 score corresponding to the highest score of the lesion they contain. The patients will be assigned the highest PI-RADSv2.1 score of the two lobes. MR images and lesion outlines will be anonymized and transferred to the coordinating centre (Hospices Civils de Lyon).

A blood sample will be taken from included patients at least three weeks after any digital rectal examination or prostate manipulation, and less than three months before prostate biopsy. Samples will be centrifuged at the local laboratory and the serum will be stored at -20°C within one hour. If this is not possible, samples will be kept at +4°C and centrifuged and stored at -20°C, but no longer than 3 hours after blood sampling, as recommended.[37 38] The delay between blood sampling and storage at -20°C will be noted for each patient. Then, samples will be sent at -20°C to the coordinating centre where they will be processed for PHI assessment. PHI will be calculated from the serum concentrations of total PSA, free PSA (fPSA) and [-2]proPSA using the following formula: $PHI = \frac{[-2]\text{proPSAx}\sqrt{PSA}}{\text{fPSA}}$. PHI results will not be available to local investigators at the time of biopsy, to avoid bias. At the end of the study, the remaining blood samples will be destroyed. No biological collection is planned.

Prostate biopsy will be performed by a senior radiologist or a senior urologist under transrectal ultrasound (TRUS) guidance, no longer than 3 months after prostate mpMRI and blood sampling for PHI determination. All lesions with a PI-RADSv2.1 score ≥3 will be targeted at biopsy. Targeted biopsy will be obtained according to the centre's routine technique, using cognitive guidance, software-assisted registration, or direct targeting under high-frequency ultrasound guidance. The guidance technique for each patient will be documented. At least three biopsy cores will be taken from each targeted lesion to ensure proper sampling.[39 40] In addition, 12 systematic biopsies will be taken; however, for patient comfort, the biopsy operator will be free not to obtain systematic biopsy from prostate areas already sampled by targeted biopsy. Patients without any lesions with a PI-RADSv2.1 score ≥3 will undergo 12-core systematic biopsy. The total number of systematic and targeted cores will be noted for each patient. Prostate biopsy cores will be analysed by a local senior pathologist on a core-by-core basis. For each core, the presence of cancer and the core length will be noted. In addition, the ISUP grade group and the length of cancer invasion will be noted for each core containing cancer.

The evaluated CAD system will be the final CAD system developed under the RHU PERFUSE research program. Its output will be, for each slice level, a parametric map providing a probability score that each pixel corresponds to ISUP ≥2 cancer. Parametric maps will be analysed at the end of the program, and therefore, their results will not be known at the time of biopsy. The analysis of the CAD parametric maps will be performed by two radiologists from the coordinating centre, working in consensus, and who will be blinded to the biopsy and follow-up results. First, they will copy onto the CAD parametric maps the lesions' outlines drawn by the local radiologist on MR images. The mean CAD score of the pixels located within each lesion outline will correspond to the lesion's CAD score, for per-lesion analysis. Then, the two radiologists will define the CAD score of each lobe. It will correspond to the highest score of any lesion ≥6 mm located in the lobe, whether it was seen by the local radiologist or not. [36]For per-patient analysis (primary analysis), the CAD score will be the highest score of both lobes.

Included patients will be followed at least 3 years by local investigators. The date and type of treatment will be recorded for all patients treated by active therapy for prostate cancer (prostatectomy, radiotherapy, brachytherapy, high-intensity focused ultrasound, hormone therapy, etc…) after the study biopsy. For patients with negative biopsy findings and for those managed by active surveillance, the date and results of any additional histological examination of prostate tissue (after additional prostate biopsy or transurethral prostate resection) will be recorded. Follow-up data will be collected from medical records or after a telephone interview with the patients.

Standard of reference

The results of the combined targeted and systematic biopsy performed within 3 months of the prostate mpMRI will be considered the histological standard of reference for per-patient and per-lobe analysis. For per-lesion analysis, only the results of targeted biopsy will be taken into consideration. csPCa will be defined as ISUP ≥2 cancer throughout the analysis.

Primary and secondary objectives

The primary objective will be the assessment of the non-inferiority of the AUC of the CAD score as compared to that of the PI-RADSv2.1 score for predicting the presence of csPCa at subsequent targeted and systematic biopsy, at patient level.

Secondary objectives include : i) the comparison of the sensitivity and specificity of the CAD and PI-RADSv2.1 scores for predicting the presence of csPCa at subsequent targeted and systematic biopsy, at lesion, lobe and patient levels, ii) the comparison of the AUC, sensitivity and specificity of the CAD and PI-RADSv2.1 scores for predicting the diagnosis of csPCa within the three years of follow-up, at patient level, iii) the assessment of the influence of the biopsy setting (biopsy naïve vs history of prior negative biopsy), magnetic field strength (1.5T vs 3T), experience (years) of the radiologist assessing the PI-RADSv2.1 score, guidance method (cognitive vs software-assisted registration) for targeted biopsy, and prostate volume (ml) on the AUC of the CAD and PI-RADSv2.1 scores for predicting the presence of csPCa at subsequent targeted and systematic biopsy, at patient level, iv) the comparison of the AUC of PHI, the CAD score and the PI-RADSv2.1 score for predicting the presence of csPCa at subsequent targeted and systematic biopsy, at patient level, and v) the estimation of the number of avoided mpMRI and prostate biopsies and of the number of missed csPCa in various diagnostic pathways combining the use of PHI and mpMRI as triage tests (Fig 1).

Data collection and assessment points

Patient recruitment will start in the first trimester of 2021 and is expected to last 24 months. Table 1 summarizes enrolment and interventions time points.

Data management, access and sharing

Only the data necessary to complete the protocol and the scientific publication will be collected, using an electronic case report form (eCRF). The eCRF will be developed by a data manager at the Hospices Civils de Lyon, using the Ennov Clinical 7.5.720 software that is compliant with the United States Food and Drug Administration (FDA) guidelines on clinical trial management (Guidance for Computerized Systems Used in Clinical Trial - FDA-2004-D-0039) and on electronic signature (FDA 21CRF part 11). The data set will be computerized in a coded way, in accordance with the Law for Data Protection and Freedom of Information. The study patients will be identified by a unique inclusion number and by the first initials of their surname and given name. The patient identification log will be kept in the investigator file. Data will be entered, as soon as they are collected, by the authorized persons using their own login names according to the Law for Data Protection and Freedom of Information. The investigator is responsible for the accuracy, quality, and pertinence of all the data entered. As a result, each eCRF page will be electronically dated and signed by the investigator. On receipt of the data, the coordinating centre will check the eCRF and query all missing, implausible and inconsistent data.

This study falls within the framework of the "Reference Methodology" (MR-001) under the provisions of Article 54, Paragraph 5 of modified French Law 78-17 from January 6, 1978, related to Information Technology, Files and Liberties. This alteration has been approved by the decision made on January 5, 2006 and modified on July 21, 2016. The Hospices Civils de Lyon, sponsor of the study, have signed a commitment of compliance to this "Reference Methodology".

A Trial Steering Committee, presided by the study coordinator and composed of the scientists, biologists, methodologists, biostatisticians, and coordinators involved in defining the study design and protocol will oversee the final version of the protocol, the conduct of the trial, and the redaction of the publication. It will also validate and justify any change in the study protocol or statistical analysis plan.

Sample size

The calculation of the sample size was performed according to the method described by Zhou et al.[41] The AUC of the PI-RADSv2.1 score at patient level is expected to be 0.85.[42] Under the hypothesis of equality of the AUC of the CAD and PI-RADSv2.1 scores, for a non-inferiority margin of -5%, a bilateral alpha risk of 5% (one-sided significance level of 2.5%), an expected prevalence of csPCa of 30%,[3-5] and a correlation of 0.3 between the CAD and PI-RADSv2.1 scores in patients with csPCa and in those without csPCa, the inclusion of 385 patients will allow to assess the non-inferiority of the CAD score with a statistical power of 80%. To account for 10% of excluded patients, the trial will include 420 patients.

Statistical analysis

Analysis will be performed by a professional statistician from the Department of Biostatistics of the Hospices Civils de Lyon. A statistical analysis plan will be written before the database lock. It

will consider any unexpected event or change in protocol with impact on data analysis. Any change in the statistical analysis plan occurring after the database lock will be documented and justified.

Data will be analysed according to the intention-to-treat principle (i.e., all patients who underwent both mpMRI and prostate biopsy will be included). In case of major protocol deviations, an additional per-protocol analysis will be performed after exclusion of the patients with major deviations. The list of major deviations will be established after review of the data and specified in the statistical analysis plan.

For the primary objective, the AUC of the CAD and PI-RADSv2.1 scores will be estimated at patient level, using the binormal method, along with their 95% confidence intervals. The difference between the AUC of the CAD and PI-RADSv2.1 scores will be estimated with its 95% confidence interval. Non-inferiority will be established if the lower limit of the 95% confidence interval of the AUC difference is superior to -5%.

For secondary objectives, the specificity and sensitivity of the PI-RADSv2.1 score at patient, lobe and lesion level will be estimated using a positivity threshold of ≥3. For the CAD score, they will be estimated using the threshold yielding a sensitivity of 90% in the training database. The Wilson method will be used to calculate the 95% confidence intervals for sensitivities and specificities. Sensitivities and specificities of the CAD and PI-RADSv2.1 scores will be compared using the McNemar test. Positive and negative likelihood ratios and their 95% confidence intervals will also be estimated for both tests. The effect of biopsy setting, magnetic field strength, reader's experience, guidance method for targeted biopsy and prostate volume on the AUC of the final CAD and the PI-RADSv2.1 scores will be quantified by modelling the ROC curve using a probit regression model.[43]

The AUC of PHI will be estimated and compared to the AUC of the CAD score and the PI-RADSv2.1 score respectively using the binormal method. The following PHI positivity cut-offs will be used to assess different diagnostic pathways (Fig 1): 25 when PHI is used as an upfront diagnostic test (pathways a and b) or in combination with MRI (pathways f and g), and 50 when PHI is used in as a second-line test after mpMRI (pathways c-e). The different diagnostic pathways will be applied to the studied population to predict the number of avoided mpMRI, avoided biopsies or missed csPCa. These numbers will be given with a predicted interval taking into account the uncertainty on the estimate of the diagnostic performance of the tests.

Patient and public involvement

Patient and public were not involved in the design of this study.

Discussion

The CHANGE study is aimed at constituting a prospective multicentre multivendor cohort of patients with suspected prostate cancer who underwent prostate mpMRI and subsequent targeted and systematic biopsy. This cohort will be used for external validation of the final CAD system developed under the RHU PERFUSE research program. For this study, we made four main methodological choices.

First, we chose not to include patients with scheduled prostatectomy, although this would have allowed comparing CAD findings to a solid histological ground truth. Indeed, patients treated by prostatectomy constitute a biased population with a 100% prevalence of prostate cancer. Instead, we chose to study the real target population of any CAD aimed at diagnosing csPCa on MR images: patients with clinical suspicion of prostate cancer referred for prostate biopsy. We did not include patients under active surveillance. Thus, our results may not be applicable to this population.

Second, we decided to use the results of targeted and systematic biopsy as standard of reference, although it may miss some csPCa. Using a more sensitive biopsy technique such as transperineal template saturation biopsy would have improved the detection of csPCa. However, template saturation biopsy is not obtained routinely in France. In addition, the clinical significance of ISUP ≥2 detected by such sensitive an approach remains debated. Therefore, we chose to use as standard of reference the biopsy technique that is recommended for prostate cancer diagnosis in daily routine.[7]

Third, patient recruitment will start before the CAD is finalized, and thus, the CAD will not be used to trigger targeted biopsy. This results from a pragmatic choice. Setting a prospective study in which the CAD is used to trigger targeted biopsy would need a CAD system that has good and stable results on its training databases, is embedded in an easy-to-install, user-friendly interface, and has gone through all legal and regulatory requirements for clinical use. It was unrealistic to develop such a CAD system and then perform a multicentre validation study within the duration of the RHU PERFUSE program. Instead, we preferred recruiting a multicentre prospective cohort while the CAD was being developed. We acknowledge that comparing the accuracy of the CAD and the PI-RADS2.1 scores in this cohort will be to the disadvantage of the CAD score. Indeed, the CAD system may show some cancer foci missed by human reading and subsequent biopsy and that will be erroneously considered as CAD false positive findings at per-lobe and per-patient analysis. To mitigate this, we included a 3-year follow-up for patients with negative biopsy. Nonetheless, such a design also has advantages. Because no particular CAD system will be used to trigger targeted biopsy, our cohort may be used as a reference cohort for evaluating other CAD systems. Therefore, our data sharing policy stipulates that the cohort will be made accessible to other research groups, as a test cohort, once our own CAD system has been evaluated. We hope that this will allow rapid comparisons between artificial intelligence solutions in a challenging multicentre multivendor setting. Furthermore, although the CHANGE cohort is primarily designed for testing algorithms developed on mpMRI datasets, it is also suitable for testing CADs aimed at assessing bi-parametric MRIs. In such case, the DCE datasets

will be removed from the cohort and the lesions' PI-RADS scores will be calculated without considering the DCE category, as detailed in the PI-RADS v2.1 guidelines. Finally, the definition of csPCa is currently highly controversial [44]. Our primary objective will be assessed using the definition currently used in most studies (ISUP grade group ≥2). Nonetheless, because we collected the ISUP grade group and the length of cancer invasion on a core-by-core basis, alternate definitions for csPCa could be easily used.

Our fourth methodological choice was to measure PHI in all patients. This ancillary study is independent to the evaluation of the CAD system. However, we took advantage of constituting a prospective multicentre cohort to also assess whether PHI could be used, as a stand alone or in combination with mpMRI, to select patients who could safely avoid mpMRI and/or prostate biopsy, thereby reducing both patient discomfort and the cost of prostate cancer diagnostic pathway. Other simple biomarkers such as PSA density or PHI density can also be easily calculated from the database. Including them in combination with PHI and MRI would have resulted in too many possible diagnostic pathways. A large body of literature is available on PSA density although the way it should be combined with MRI and the optimal diagnostic threshold remain unclear [45 46]. Nonetheless, there may be guidelines for the use of PSA density when the inclusions are completed. Similarly, whether PHI density is useful is currently unclear [14], but this may be clarified by the end of the inclusions. If this is the case, the statistical analysis plan, written at the end of the inclusions but before the database can be accessed, may include PSA density and/or PHI density in the tested diagnostic pathways.

Ethics and dissemination

Ethical approval was obtained from the Comité de Protection des Personnes Nord Ouest III (ID-RCB: 2020-A02785-34) on January 22, 2021. The study was registered with ClinicalTrials.gov, number NCT04732156. The Hospices Civils de Lyon is the responsible institution for this trial. The study coordinator will coordinate dissemination of the trial data through scientific conferences and publications in peer-reviewed international journals. Data reporting will follow the Standards for the Reporting of Diagnostic Accuracy Studies guideline.[47]

As specified in the informed consent form signed by the patients, the CHANGE cohort will be made partially accessible to other investigators wishing to test a CAD system aimed at detecting/localizing prostate cancer on MR images, once the results of the trial have been published. Request for access to pseudonymized data will be reviewed by the Trial Steering Committee that will grant access or not. To gain access, requestors will need to sign a data access agreement. Of note, investigators will have access only to the MR images and not to the histological findings. After analysis of the CHANGE MR images by their CAD system, investigators will be requested to send the results to the Hospices Civils de Lyon. The comparison between the CAD findings and the targeted

and systematic biopsy findings will be made by the Hospices Civils de Lyon that will then inform the

investigator of the CAD diagnostic performance.

Captions for figures

Figure 1: Possible diagnostic pathways using PHI, prostate MRI or the combination of both as triage tests

References

1. Ahmed HU, El-Shater Bosaily A, Brown LC, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. *Lancet* 2017;389(10071):815-22.

2. Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. *N Engl J Med* 2018;378(19):1767-77.

3. Rouviere O, Puech P, Renard-Penna R, et al. Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naive patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. *Lancet Oncol* 2019;20(1):100-09.

4. van der Leest M, Cornel E, Israel B, et al. Head-to-head Comparison of Transrectal Ultrasound-guided Prostate Biopsy Versus Multiparametric Prostate Resonance Imaging with Subsequent Magnetic Resonance-guided Biopsy in Biopsy-naive Men with Elevated Prostate-specific Antigen: A Large Prospective Multicenter Clinical Study. *Eur Urol* 2019;75(4):570-78.

5. Drost FH, Osses DF, Nieboer D, et al. Prostate MRI, with or without MRI-targeted biopsy, and systematic biopsy for detecting prostate cancer. *Cochrane Database Syst Rev* 2019;4:CD012663.

6. Klotz L, Chin J, Black PC, et al. Comparison of Multiparametric Magnetic Resonance Imaging-Targeted Biopsy With Systematic Transrectal Ultrasonography Biopsy for Biopsy-Naive Men at Risk for Prostate Cancer: A Phase 3 Randomized Clinical Trial. *JAMA Oncol* 2021 doi: 10.1001/jamaoncol.2020.7589 [published Online First: 2021/02/05]

7. Mottet N, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer-2020 Update. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *Eur Urol* 2021;79(2):243-62.

8. Richenberg J, Logager V, Panebianco V, et al. The primacy of multiparametric MRI in men with suspected prostate cancer. *Eur Radiol* 2019;29(12):6940-52.

9. Padhani AR, Weinreb J, Rosenkrantz AB, et al. Prostate Imaging-Reporting and Data System Steering Committee: PI-RADS v2 Status Update and Future Directions. *Eur Urol* 2019;75(3):385-96.

10. Schoots IG, Padhani AR, Rouviere O, et al. Analysis of Magnetic Resonance Imaging-directed Biopsy Strategies for Changing the Paradigm of Prostate Cancer Diagnosis. *Eur Urol Oncol* 2020;3(1):32-41.

11. Donato P, Morton A, Yaxley J, et al. Improved detection and reduced biopsies: the effect of a multiparametric magnetic resonance imaging-based triage prostate cancer pathway in a public teaching hospital. *World J Urol* 2020;38(2):371-79.

12. Rouviere O. Choosing the Right Diagnostic Pathway in Biopsy-Naive Patients With Suspected Prostate Cancer. *JAMA Oncol* 2021 doi: 10.1001/jamaoncol.2020.7578 [published Online First: 2021/02/05]

13. Kim L, Boxall N, George A, et al. Clinical utility and cost modelling of the phi test to triage referrals into image-based diagnostic services for suspected prostate cancer: the PRIM (Phi to RefIne Mri) study. *BMC medicine* 2020;18(1):95.

14. Ferro M, De Cobelli O, Lucarelli G, et al. Beyond PSA: The Role of Prostate Health Index (phi). *Int J Mol Sci* 2020;21(4):1184-97.

15. Lemaitre G, Marti R, Freixenet J, et al. Computer-Aided Detection and diagnosis for prostate cancer based on mono and multi-parametric MRI: a review. *Comput Biol Med* 2015;60:8-31.

16. Goldenberg SL, Nir G, Salcudean SE. A new era: artificial intelligence and machine learning in prostate cancer. *Nat Rev Urol* 2019;16(7):391-403.

17. Cuocolo R, Cipullo MB, Stanzione A, et al. Machine learning applications in prostate cancer magnetic resonance imaging. *Eur Radiol Exp* 2019;3(1):35.

18. Liu L, Tian Z, Zhang Z, et al. Computer-aided Detection of Prostate Cancer with MRI: Technology and Applications. *Acad Radiol* 2016;23(8):1024-46.

19. Schelb P, Kohl S, Radtke JP, et al. Classification of Cancer at Prostate MRI: Deep Learning versus Clinical PI-RADS Assessment. *Radiology* 2019;293(3):607-17.

20. Hoang Dinh A, Melodelima C, Souchon R, et al. Quantitative Analysis of Prostate Multiparametric MR Images for Detection of Aggressive Prostate Cancer in the Peripheral Zone: A Multiple Imager Study. *Radiology* 2016;280(1):117-27.

21. Dinh AH, Melodelima C, Souchon R, et al. Characterization of Prostate Cancer with Gleason Score of at Least 7 by Using Quantitative Multiparametric MR Imaging: Validation of a Computer-aided Diagnosis System in Patients Referred for Prostate Biopsy. *Radiology* 2018;287(2):525-33.

22. Abraham B, Nair MS. Computer-aided classification of prostate cancer grade groups from MRI images using texture features and stacked sparse autoencoder. *Comput Med Imaging Graph* 2018;69:60-68.

23. Cao R, Mohammadian Bajgiran A, Afshari Mirak S, et al. Joint Prostate Cancer Detection and Gleason Score Prediction in mp-MRI via FocalNet. *IEEE Transactions on Medical Imaging* 2019;38(11):2496-506.

24. Vente C, Vos P, Hosseinzadeh M, et al. Deep Learning Regression for Prostate Cancer Detection and Grading in Bi-Parametric MRI. *IEEE Trans Biomed Eng* 2021;68(2):374-83.

25. Duran A, Jodoin P, Lartizien C. Prostate Cancer Semantic Segmentation by Gleason Score Group in bi-parametric MRI with Self Attention Model on the Peripheral Zone. . Third Conference on Medical Imaging with Deep Learning, in Proceedings Machine Learning Research (PMLR), 2020:193-204.

26. Hambrock T, Vos PC, Hulsbergen-van de Kaa CA, et al. Prostate cancer: computer-aided diagnosis with multiparametric 3-T MR imaging--effect on observer performance. *Radiology* 2013;266(2):521-30.

27. Niaf E, Lartizien C, Bratan F, et al. Prostate focal peripheral zone lesions: characterization at multiparametric MR imaging--influence of a computer-aided diagnosis system. *Radiology* 2014;271(3):761-9.

28. Gaur S, Lay N, Harmon SA, et al. Can computer-aided diagnosis assist in the identification of prostate cancer on prostate MRI? a multi-center, multi-reader investigation. *Oncotarget* 2018;9(73):33804-17.

29. Fedeli L, Belli G, Ciccarone A, et al. Dependence of apparent diffusion coefficient measurement on diffusion gradient direction and spatial position - A quality assurance intercomparison study of forty-four scanners for quantitative diffusion-weighted imaging. *Phys Med* 2018;55:135-41.

30. Kim H. Variability in Quantitative DCE-MRI: Sources and Solutions. *J Nat Sci* 2018;4(1):e484.

31. Schlett CL, Hendel T, Hirsch J, et al. Quantitative, Organ-Specific Interscanner and Intrascanner Variability for 3 T Whole-Body Magnetic Resonance Imaging in a Multicenter, Multivendor Study. *Invest Radiol* 2016;51(4):255-65.

32. Shukla-Dave A, Obuchowski NA, Chenevert TL, et al. Quantitative imaging biomarkers alliance (QIBA) recommendations for improved precision of DWI and DCE-MRI derived biomarkers in multicenter oncology trials. *J Magn Reson Imaging* 2019;49(7):e101-e21.

33. Transin S, Souchon R, Gonindard-Melodelima C, et al. Computer-aided diagnosis system for characterizing ISUP grade >= 2 prostate cancers at multiparametric MRI: A cross-vendor evaluation. *Diagn Interv Imaging* 2019;100(12):801-11.

34. Peng Y, Jiang Y, Antic T, et al. Validation of quantitative analysis of multiparametric prostate MR images for prostate cancer detection and aggressiveness assessment: a cross-imager study. *Radiology* 2014;271(2):461-71.

35. Castillo TJ, Starmans MPA, Arif M, et al. A Multi-Center, Multi-Vendor Study to Evaluate the Generalizability of a Radiomics Model for Classifying Prostate cancer: High Grade vs. Low Grade. *Diagnostics (Basel)* 2021;11(2):369.

36. Turkbey B, Rosenkrantz AB, Haider MA, et al. Prostate Imaging Reporting and Data System Version 2.1: 2019 Update of Prostate Imaging Reporting and Data System Version 2. *Eur Urol* 2019;76(3):340-51.

37. Igawa T, Takehara K, Onita T, et al. Stability of [-2]Pro-PSA in whole blood and serum: analysis for optimal measurement conditions. *J Clin Lab Anal* 2014;28(4):315-9.

38. Semjonow A, Kopke T, Eltze E, et al. Pre-analytical in-vitro stability of [-2]proPSA in blood and serum. *Clin Biochem* 2010;43(10-11):926-8.

39. Zhang M, Milot L, Khalvati F, et al. Value of Increasing Biopsy Cores per Target with Cognitive MRI-targeted Transrectal US Prostate Biopsy. *Radiology* 2019;291(1):83-89.

40. Lu AJ, Syed JS, Ghabili K, et al. Role of Core Number and Location in Targeted Magnetic Resonance Imaging-Ultrasound Fusion Prostate Biopsy. *Eur Urol* 2019;76(1):14-17.

41. Zhou XH, Obuchowski NA, McClish DK. Statistical Methods in Diagnostic Medicine. Hoboken: John Wiley & Sons 2011:203-17.

42. Stabile A, Giganti F, Kasivisvanathan V, et al. Factors Influencing Variability in the Performance of Multiparametric Magnetic Resonance Imaging in Detecting Clinically Significant Prostate Cancer: A Systematic Literature Review. *Eur Urol Oncol* 2020;3(2):145-67.

43. Alonzo TA, Pepe MS. Distribution-free ROC analysis using binary regression techniques. *Biostatistics* 2002;3(3):421-32.

44. Matoso A, Epstein JI. Defining clinically significant prostate cancer on the basis of pathological findings. *Histopathology* 2019;74(1):135-45.

45. Pagniez MA, Kasivisvanathan V, Puech P, et al. Predictive Factors of Missed Clinically Significant Prostate Cancers in Men with Negative Magnetic Resonance Imaging: A Systematic Review and Meta-Analysis. *J Urol* 2020;204(1):24-32.

46. Schoots IG, Padhani AR. Risk-adapted biopsy decision based on prostate magnetic resonance imaging and prostate-specific antigen density for enhanced biopsy avoidance in first prostate cancer diagnostic evaluation. *BJU Int* 2021;127(2):175-78.

47. Bossuyt PM, Reitsma JB, Bruns DE, et al. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. *BMJ* 2015;351:h5527.

Author's Contributions

All authors have contributed to the design of the study and to the formulation of the protocol. OR is the principal investigator for this trial and has initiated and planned this trial project with SC. SC is the medical coordinator of the RHU PERFUSE Research program and CM is the scientific project manager coordinating the different work packages of the program. RS, CL, TJ, and AD are developing and testing different approaches for the CAD systems as senior scientists (RS, CL) or PhD students (TJ, AD). RS is also responsible of the quality control of the MR examinations performed in the participating centres. JH oversaw the study design. MR and BR are biostatisticians. MR played a central role in the sample size calculation and the statistical analysis plan. AM, LM, MC, MDC and SD drafted the protocol and will play a central role in study coordination, data management and in providing support to the participating centres. PR designed the electronic case report form. VV

participated to the design of the ancillary study and is responsible for supervising the management of blood samples and the dosage of PHI.
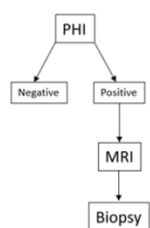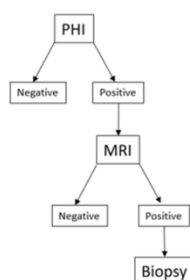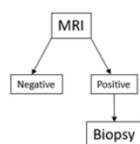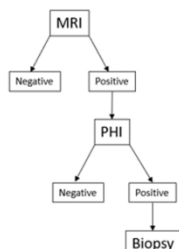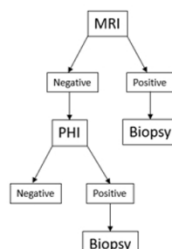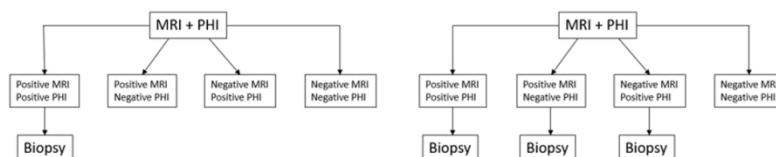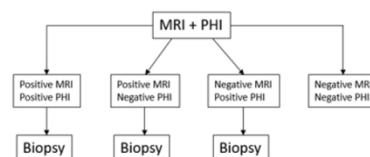
Funding

This work was supported by the RHU PERFUSE research program (ANR-17-RHUS-0006) of Université Claude Bernard Lyon 1, within the program "Investissements d'Avenir" operated by the French National Research Agency.

Competing interests statement

None

	Enrolment (Month 0)	Visit 1 (Month 0)	Visit 2 (Month 0-3)	Visit 3 / End of study (Month 36±2)
Informed consent and enrolment	X			
Assessment of patient history, clinical stage, and PSA level	X			
Blood test (PHI)		X		
Multiparametric MRI		X		
Targeted biopsy based on human reading of MR images (PI-RADSv2.1)			X	
Systematic biopsy			X	
Assessment of adverse events		X	X	X
Assessment of 3-year follow-up				X

Table 1: Time points of enrolment and interventions

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

Possible diagnostic pathways using PHI, prostate MRI or the combination of both as triage tests

73x105mm (400 x 400 DPI)

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	Abstract (AUC)
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	Yes
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	Yes
	4	Study objectives and hypotheses	Yes
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	Yes
Participants	**6**	Eligibility criteria	Yes
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	Yes
	8	Where and when potentially eligible participants were identified (setting, location and dates)	Yes
	9	Whether participants formed a consecutive, random or convenience series	Yes
Test methods	**10a**	Index test, in sufficient detail to allow replication	Yes
	10b	Reference standard, in sufficient detail to allow replication	Yes
	11	Rationale for choosing the reference standard (if alternatives exist)	Yes (see discussion)
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	Yes
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	Yes
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	Yes
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	Yes
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	Yes
	15	How indeterminate index test or reference standard results were handled	No – will be defined in the SAP at database lock
	16	How missing data on the index test and reference standard were handled	No - will be defined in the SAP at database lock
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	Yes
	18	Intended sample size and how it was determined	Yes
RESULTS			
Participants	**19**	Flow of participants, using a diagram	N/A (protocol); but will be provided when the study is done
	20	Baseline demographic and clinical characteristics of participants	N/A (protocol); but will be provided when the study is done
	21a	Distribution of severity of disease in those with the target condition	N/A (protocol); but will be provided when the study is done
	21b	Distribution of alternative diagnoses in those without the target condition	N/A (protocol); but will be provided when the study is done

		22	Time interval and any clinical interventions between index test and reference standard	N/A (protocol); but will be provided when the study is done
Test results		23	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	N/A (protocol); but will be provided when the study is done
		24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	N/A (protocol); but will be provided when the study is done
		25	Any adverse events from performing the index test or the reference standard	N/A (protocol); but will be provided when the study is done
DISCUSSION				
		26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	Yes
		27	Implications for practice, including the intended use and clinical role of the index test	N/A – it will depend on the study results
OTHER INFORMATION				
		28	Registration number and name of registry	Yes
		29	Where the full study protocol can be accessed	N/A
		30	Sources of funding and other support; role of funders	Yes

STARD 2015

AIM

STARD stands for "Standards for Reporting Diagnostic accuracy studies". This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or "2x2" table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.