Quality checkpoints in the MRI-directed prostate cancer diagnostic pathway

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Abstract

Multiparametric magnetic resonance imaging (MRI) of the prostate is now recommended as the initial diagnostic test for men presenting with suspected prostate cancer, with a negative MRI enabling safe avoidance of biopsy and a positive result enabling MRI-directed sampling of lesions. The diagnostic pathway consists of several steps, from initial patient presentation and preparation to performing and interpreting MR images, communicating the imaging findings, outlining the prostate and intra-prostatic target lesions, performing the biopsy, and assessing the cores. Each component of this pathway requires experienced clinicians, optimised equipment, good inter-disciplinary communication between specialists, and standardised workflows in order to achieve the expected outcomes. Assessment of quality and mitigation measures are essential for the success of the MRI-directed prostate cancer diagnostic pathway. Quality assurance processes including Prostate Imaging-Reporting and Data System (PI-RADS), template biopsy, and pathology guidelines help minimise variation and ensure optimisation of the diagnostic pathway. Quality control systems including the Prostate Imaging Quality (PI-QUAL) scoring system, patient-level outcomes (such as PI-RADS MRI score assignment and cancer detection rates), multidisciplinary meeting review and audits might also be used to provide consistency of outcomes and ensure that all the benefits of the MRI-directed pathway are achieved.

Key points

- Multiparametric magnetic resonance imaging (MRI) is now recommended as the initial diagnostic test for men presenting with suspected prostate cancer

- A negative MRI enables patients to safely avoid biopsy, whereas a positive MRI prompts targeted biopsy and pathologically accurate tissue sampling.

-The MRI-directed prostate cancer diagnostic pathway involves several steps including acquiring and interpreting MR images, communicating MRI findings, outlining suspicious target lesions, performing biopsy, and evaluating the cores.

- All steps in the pathway are prone to variation; assessment and mitigation of poor quality and variance are essential for a successful delivery of the MRI-directed pathway

- Quality assurance systems to minimise variation in performance and prevent poor quality include Prostate Imaging-Reporting and Data System (PI-RADS) imaging guidelines for radiologists, prostate biopsy templates, and International Society of Urological Pathology (ISUP) guidelines for histopathologists.

- Quality control measures include checking MRI compliance with PI-RADS, image quality assessment with the Prostate Imaging Quality (PI-QUAL) scoring system, radiologist certification, multidisciplinary team meeting (MDT) review and pathology re-review of images, and audits of cancer detection rates and biopsy core quality.

[H1] Introduction

Multiparametric magnetic resonance imaging (MRI) of the prostate, incorporating anatomical T2-weighted imaging (T2-WI) and the functional sequences of diffusion-weighted (DWI) and dynamic contrast-enhanced (DCE) sequences, is now recommended as the initial diagnostic test for men presenting with suspected prostate cancer [1–4] . T2 imaging provides anatomical structural information of tissues, with tumours showing a lower signal intensity than normal tissue. In DWI, the free motion of water molecules, which is typically more impeded in tumour tissue with a high density of cells, is measured. DCE involves the injection of a low-molecular-weight contrast agent and can identify neoangiogenesis within the tumour microenvironment, which has a "leaky" endothelia and hence a higher degree of contrast enhancement than normal vessels. [5,6]. Level 1 evidence supports the role of the MRI-directed pathway for prostate cancer diagnosis in western populations, with improved performance over the previous clinical standard of systematic transrectal ultrasound (TRUS) biopsy [7–10]. The role of prostate MRI is to detect only clinically significant prostate cancer, defined as a disease ≥ grade group 2 (GG2; Gleason ≥3+4), and/or tumour volume >0.5 cm^3, and/or presence of extraprostatic extension [11]. The prevalence of clinically significant prostate cancer in men referred to urology clinics is ~30%, indicating that a substantial proportion of patients might unnecessarily undergo an invasive biopsy procedure; however, a negative MRI would enable up to half of these patients to safely avoid biopsy [7–10,12] . Conversely, a positive MRI can directly target tumour lesions to provide pathologically accurate tissue sampling [13,14]. The negative predictive value (NPV) of MRI is high (~ 90%) and has little variability among centres, [15] whereas a comparatively low positive predictive value (PVV) of 17%, 46% and 75% has been reported for lesions with a Prostate Imaging-Reporting and Data System (PI-RADS) score of 3, 4, and 5, respectively[16,17]. Thus, MRI performs best as a rule-out test; however, results from studies in which MRI-detected lesions were compared with histopathology on prostatectomy specimens showed that 8–24% of GG2 prostate cancers might be MRI occult [18,19], which might be ascribed to technical limitations, presence of cribriform glands and/or a sparse pattern of tumour growth[20–22].

Results from several studies have highlighted that MRI quality varies substantially between centres and scanners and is vulnerable to patient-related artefacts; moreover, poor image quality is associated with increased uncertainty and reduced accuracy of the results[23,24]. [25]. The PI-RADS guidelines were initially developed in 2012 with subsequent updates in 2015 and 2019 to standardise the way prostate MRI is performed and reported [11,26,27]. However, compliance to these recommendations alone does not guarantee optimal quality imaging, as image sequences often require further optimisation based on the age of the scanner, quality of the surface coil, strength of the magnet and software updates [24,28,29]. Additionally, a learning curve for MRI reporting exists[30–32], as radiologists' experience level directly affects patient outcomes [33–36]. Thus, successful delivery of the MRI-directed pathway for prostate cancer diagnosis requires imaging to be performed and reported to high standards[37,38]. In 2020, 1.4 million men were diagnosed with prostate cancer worldwide [39]. Considering the high disease prevalence, imaging-acquisition as well as reporting has to be optimised in all healthcare settings. Assessment and mitigation of poor quality and variance is essential for every step of the MRI-directed prostate cancer diagnostic pathway in order to ensure optimal outcomes.

In this Review, we explore quality issues at every step of the MRI-directed prostate cancer diagnostic pathway and highlight quality assurance components that can help minimise variation in practice, to help ensure consistency of outcomes.

[H1] Quality assurance and quality control

The terms quality assurance (QA) and quality control (QC), often used interchangeably, are actually distinct, although some overlap exists. QA incorporates processes put in place to ensure high quality, and includes the prevention of variability, whereas QC is used to assess whether quality standards are being met and, therefore, is about quality assessment. Several QA procedures in the MRI-guided prostate cancer diagnostic pathway are already established, and include guidelines for radiologists (PI-RADS), urologists (European Association of Urology (EAU)) and pathologists (International Society of Urological Pathology (ISUP)); conversely, agreeing on QC processes to quantify and objectively measure the quality of the prostate diagnostic pathway might be challenging (**Table 1**). Timed cancer pathways have been adopted within some healthcare systems; examples in the UK for all national health system (NHS) patients presenting with a suspected malignancy include a 28-day target to complete all diagnostic tests, and a 62-day target for patients with confirmed cancer to start treatment [40]. These pathways are important from a service delivery perspective and help reduce patient anxiety. However, expediting care does not necessarily equate to high quality or improved patient outcomes. In addition, these targets are challenging for the prostate MRI-guided diagnostic pathway, [41,42] which presents several issues: the use of a scarce resource (MRI); the number of radiologists needed to perform an MRI report (which is limited); a biopsy procedure that sometimes requires general anaesthesia; and the need to acquire multiple cores for pathological interpretation. Time pressure might lead to counter-productive measures such as performing MRI without specialist radiographers, MR image interpretation by general radiologists, omitting multidisciplinary team meeting (MDT) review (which can act as a helpful safety net) and using techniques that are not always appropriate; these techniques include fast MRI protocols omitting DCE [43–46] or resource-intensive pathways such as one-stop clinics in which MR imaging and biopsy are performed in the same session, which might not be suitable in all healthcare settings [47].

[H1] Components of the prostate cancer diagnostic pathway

The prostate cancer diagnostic pathway involves several steps: initial patient presentation, performing and interpreting MR images, communicating the findings to clinicians including uncertainties, outlining suspicious target lesions, performing the biopsy, and evaluating the cores. MRI is now recommended within international guidelines as the first-line investigation in men presenting with suspected prostate cancer, or in patients with a persistently elevated PSA level and previous negative systematic biopsies (**Table 2)** [1–4]. Other contexts in which MRI is recommended include tumour staging, follow-up monitoring during active surveillance, investigation for abscess or prostatitis, and assessment of the gland for local recurrence following cancer-treatments [1–4] . MRI is recommended to be performed with DCE, which will typically require 30–40 minutes appointment slots and will produce ~1,500 images [8,48,49]. Biparametric MRI, in which the study is performed without contrast, is only recommended by PI-RADS under specific circumstances such as patients with low-risk disease undergoing surveillance, and in instances in which quality can be assured and safety checks are in place [50]. Radiologists licensed to report medical imaging and subsequently trained in MRI interpretation will produce a report for the referring clinician in a text or pictorial format(or a combination of the two); expert radiologists should

also convey any uncertainty of interpretation, for instance owing to image quality issues. When a lesion is identified, a biopsy will typically be performed through transrectal or transperineal route; options include lesion targeting either in the MRI suite, using a freehand "cognitive" approach, or using MRI-ultrasound systems, which combine the existing MR images with a peri-procedural real time ultrasound. The latter approach requires the prostate gland to be segmented on each modality for image fusion, and the target to be outlined on the diagnostic MR images[51]. When MRI is positive (PI-RADS ≥3), systematic sampling of the background gland is recommended in addition to 2–4 target biopsies, with 12 cores typically taken through transrectal biopsy and up to 24 cores taken through transperineal approaches [2,52,53]. When target cores are negative, tumours have been shown to be localised in areas adjacent to the target, supporting the benefit of taking additional "perilesional" or "focal saturation" biopsies around the tumour-suspicious region[8,51,54,55]; thus, MRI-directed sampling could potentially limit the overall number of cores required. Pathologists will typically report the biopsy samples according to the ISUP guidelines [56].

[H1] **Variables, QA and QC in the MRI pre-biopsy diagnostic pathway**

Each step within the diagnostic pathway has several variables that can directly affect outcomes (**Table 1**) and can, in some instances, be mitigated or minimized following QA processes. Patient preparation, image acquisition and reporting are crucial issues from radiologists' perspective, whereas urologists and pathologists are involved in biopsy performance and interpretation, respectively. The expected prevalance of clinically significant cancer in a biopsy-naive population is ~30 [7–10,57]. Measuring overall cancer detection is relatively simple and might, therefore, be appealing; however, in instances in which detection rates differ from the expected prevalance, identifying the underlying cause might be difficult, and the individual components of the pathway should be assessed.

[H2]Patient-level issues

Independently of the MRI protocol used, several patient-related factors will directly affect prostate MR image quality, such as rectal spasm, bulk motion, rectal gas, the presence of hip metalwork, and any effect of previous interventions, including post-biopsy haemorrhage [58]. These artefacts will limit image interpretation and mask imaging signatures of disease, leading to false-negative results. Patient-related factors cannot be easily mitigated through QA, and the current PI-RADS guidelines do not include any detailed recommendations on patient preparation beyond advising patients to evacuate the rectum prior to scanning [11]. However, adequate rectal preparation, for example using enemas or suppositories, [58,59] and metal artefact reduction techniques [60] can be adopted to ensure quality.

Rectal loading can induce susceptibility artefacts on DWI owing to rectal wall motion when excessive air is present [61]. Removal of rectal air, or the use of prone imaging might overcome susceptibility artefacts moving air away from the prostatic interface; however, this issue needs to be identified by the technician, and the extra scanning time needed might not be accommodated owing to scheduling constraints [62]. The use of anti-spasmodics such as hyoscine butylbromide or glucagon can reduce rectal motion, improving image quality (particularly T2-WI imaging) [63,64], and should be given as late as possible to ensure imaging takes place during the window of biological activity of spasmodics. Several

techniques to ensure rectal emptying have been evaluated, including cleansing enemas, deflatus catheters, and dietary restrictions [59,65–67]. Mixed results came from these studies, and no clear benefit for any of these interventions has currently been shown; for example, enemas tend to introduce air [67], which can offset the advantage of removing stool [59]. In patients with pelvic metalwork, acquisition techniques combining fast-spin echo with radial sampling of k-space, such as periodically rotated overlapping parallel lines with enhanced reconstruction (PROPELLER) can be used (other acronyms used by manufacturers for sequences analogous include BLADE and Multivane). These sequences are based on a radial "blade-like" acquisition with over-sampling of the central portion of k-space, which enables bulk motion artefacts to be corrected in the reconstruction process [60]; this approach can help overcome motion artefacts visualised on standard turbo-spin echo T2 sequences, or can reduce metalwork-related susceptibility artefacts on echo-planar imaging acquired through DWI [60,68,69]. Vendor-driven advances in artificial intelligence (AI) have been made to improve image quality, taking the raw data and using deep-learning(DL)-based reconstruction algorithms to remove image noise and ringing[70]. These algorithms can provide faster image acquisition times (to reduce motion artefact) and/or increased signal-to-noise-ratio (SNR) and image sharpness than images taken with the same parameter settings and processed with other approaches (**Figure 1**). In a small retrospective study involving 30 patients, improved T2 quality at reduced scan times was shown using DL algorithms; in this study, T2-DL images were scored by readers as of higher quality than standard imaging, leading to improved lesion detectability [71]. In another study, a convolutional neural network (CNN) with three layers was used to remove the noise from diffusion-weighted images; in this study, DWI with DL showed higher SNR and contrast-to-noise ratio than DWI without DL, improving the overall image quality of diffusion-weighted MRI [72].

Other patient-related variables potentially affecting PPV and NPV of MRI are the prevalence of disease in the population assessed, for instance clinic-referred patients versus screened cohorts, [73,74]and the biopsy status, for example biopsy-naive patients versus patients who have already had a negative biopsy, for whom prevalence is expected to be reduced.

[H2] Image quality

MR image quality is the first, crucial step in the diagnostic pathway, which will heavily influence all downstream events. All diagnostic imaging facilities in which MRI is performed must meet country-specific requirements from the local regulatory body and licensing authorities, and undertake regular vendor-defined QC calibration tests to ensure image quality. In the USA, the American College of Radiology (ACR) have established a pathway for centres to become "designated" centres for prostate MRI, which can be applied to obtain ACR accreditation in body MRI [75]. Designation is obtained at the unit and facility level, and indicates that each MR scanner and the protocols adopted have been evaluated; centres submit images from two patients for review to ensure that minimum technical and quality standards are met. Concurrently, the personnel performing and interpreting prostate MRI are also assessed to ensure that radiologists interpreted 150 independent prostate MRI studies in the prior 36 months [75]. The ACR aims to launch the Prostate Cancer MRI Center designation programme in 2022; no ACR equivalent processes are currently available in other countries.

Achieving the image quality necessary to meet optimal PI-RADS requirements will primarily depend on the magnet strength, gradient strength, scanner age, and available software updates. Evidence from a review of the benefits of DCE contrast highlighted that published studies often include a selection bias, for example excluding patients with substantial artefacts or with hip metalwork, and, therefore, the incidence of poor image quality might be underestimated in the literature[76]. The Prostate MR imaging study (PROMIS) was a prospective, multi-centre, paired-cohort, confirmatory study in which the benefit of MRI was assessed in 576 men across 576 centres who had never had a prostate biopsy [9]. Results from this study showed that MRI was more sensitive (93%) than the clinical reference test of TRUS biopsy (48%), and that 29% of men could potential avoid invasive biopsy performing prostate MRI before biopsy. Notably, central quality control MRI checks were required from all centres, and any study that was deemed of insufficient quality was repeated[9], which might be impractical outside of a trial setting with dedicated resources and a finite timeline.

PI-RADS provides useful reference standards for MRI technical specifications including slice thickness, gap, orientation and echo times for each sequence performed; however, this guideline is not explicitly designed to address quality, but is based on the predicted effect of the imaging on patient care [77]. The first version of PI-RADS provided separate "minimal" and "optimal" acquisition protocols[26], which differed for the included indications for staging or lesion detection; however, in the subsequent and current version of PI-RADS (v2.1) , a single acquisition protocol is proposed, which can be performed at 1.5T or higher magnet strength (3T) [11,78]. Compliance to PI-RADS guidelines generally results in acceptable image quality, but not in all instances [28,29,62] ; thus, acquisition parameters might require further optimization, for example increasing slice thickness to compensate for low signal, increasing temporal resolution of DCE to improve spatial resolution, or using synthetic DWI to generate high b-value sequences without the inherent noise from acquired imaging. Indeed, optimisation of MRI acquisition by experienced uroradiologists and MRI physicists have been shown to substantially improve prostate MR image quality [79]. Lastly, scanner age, particularly for 1.5T magnets and at a cut-off time of >7 years, correlates with reduced image quality [24].

PI-RADS guidelines highlight several disadvantages of the routine use of endorectal coils including cost, patient tolerance and deformity of the gland, but acknowledge that these tools enable to achieve a high SNR and might, therefore, be indispensable for obtaining diagnostic imaging with old 1.5T scanners [11]. However, whether centres would have the access, time, drive, or experience to routinely use endorectal coils is debatable. DCE has also been shown to be more robust for achieving high-quality images[24] than DWI, which is typically more prone to susceptibility artefacts owing to echo-planar imaging acquisition; thus, DCE can be a safety net for overall study quality improvement as well as for lesion detection.

The joint European Society of Urogenital Radiology and EAU Section of Urological Imaging (ESUR/ESUI) consensus document on multi-parametric MRI for the detection of clinically significant prostate cancer recommends that image quality should be reported for all prostate MRI studies [37]; the publication of the Prostate Imaging Quality (PI-QUAL) scoring system is the first attempt to standardise this approach [80]. The PI-QUAL score is built on a Likert-scale in which the quality of each MR sequence (T2-WI, DWI and DCE) is evaluated

against a set of objective criteria (defined by PI-RADS guidelines), and also through subjective assessment of image quality, for instance the ability to clearly see anatomical structures (**Table 3**). The publication in which PI-QUAL score was presented incorporates a dedicated scoring sheet that includes technical parameters and visual evaluation criteria that should be considered for each MR sequence before assigning the PI-QUAL score[80]. This scoring sheet should be used to assess prostate MR quality in a standardised and robust manner [81]. A PI-QUAL score of 1 or 2 means that all MR sequences fall below the minimum standard of diagnostic quality, and, therefore, clinically significant prostate cancer cannot be ruled in or ruled out, implicating that MRI should ideally be repeated taking measures to improve quality. An exception might be the presence of a large clearly visible lesion (**Figure 2**), in which instance a targeted biopsy is clearly needed, and repeating imaging would not change the management choice. A PI-QUAL score of 3 means that the scan is of sufficient diagnostic quality to rule in but not to rule out clinically significant prostate cancer, and a PI-QUAL score of 4 or 5 entails that all three sequences are of optimal diagnostic quality and, therefore, enables to both rule in and rule out the presence of clinically significant prostate cancer..

To date, many institutions have reported on prostate MRI quality based on internal subjective scoring systems, incorporating differing Likert scales. In a review of studies published within the past 5 years in which prostate MRI quality was reported, poor inter-reader agreement (measured with the Cohen's kappa agreement) was observed when institution-specific criteria were used to assess image quality, with DWI being the diagnostic sequence with the highest variability [82]. Conversely, preliminary data from a study in which the inter-reader variability of the PI-QUAL score was assessed in 103 patients enrolled in the NeuroSAFE PROOF trial [83] suggest good reproducibility of the PI-QUAL score; in this study, the agreement between two expert radiologists in assessing the PIQUAL score was strong both for individual PI-QUAL scores (kappa = 0.85) and when scans were clustered into three groups (PI-QUAL score 1–2 versus PI-QUAL 3 versus PI-QUAL 4–5 (kappa = 0.82)). The agreement between the two experts on diagnostic quality was highest for T2-WI (89%), followed by DCE (88%) and DWI (78%) sequences. Different groups are already applying this scoring system in patient cohorts [84–86]; however, PI-QUAL version 1 is only the starting point for the standardisation of image quality. Future iterations of PI-QUAL criteria are likely to include elements of lesion detection and quantification of the effect of PI-QUAL scores in clinical practice; the revision of PI-QUAL scores might create the basis of future QC processes to assess image quality [87,88]. AI might have a role to support the process of image quality assessment; results from a feasibility study showed that CNNs could be used to provide a binary classification of prostate MR images as high-quality or low-quality on an individual-slice basis with high accuracy (79.8–96.6%) and at a sequence level with almost perfect accuracy (92.3– 100%) [89]. Automation of this process and calibration to PI-QUAL scoring would make central review of image quality a realistic goal and could be used at a centre level to identify poor image quality on a cases-by-case basis, to indicate whether repeating sequences is necessary.

[H2] *Radiologist interpretation*

A consensus that only uro-radiologists or radiologists specialized in prostate cancer imaging should report prostate MRI has been reached [37,38,75,90]. Other specialists such as MR radiographers, oncologists, or urologists should be familiar with expected normal and

abnormal MRI appearances within their scope of practice [90,91].

A learning curve for prostate MRI reporting exists, with re-reviews of MRI reporting by experienced readers and specialists resulting in improved outcomes [32,92]. Inter-observer agreement for overall PI-RADS scoring is moderate (kappa = 0.41–60), and has been shown to be better in the peripheral zone (PZ) than the transitional zone (TZ); moreover, a substantial inter-observer agreement is reported between expert readers (kappa = 0.61–80) in the identification of PI-RADS ≥4 lesions [93–96]. High MRI reporting experience reduces diagnostic uncertainty and can increase the rate of biopsy avoidance, with a resultant 25–57% decrease in the over-detection of insignificant cancers[37,38,90,91].

A debate exists in the community about how many prostate MRI reads are necessary to overcome the learning curve; the general consensus is that 100 is the minimum threshold level of reads required for independent reporting [37,38,90,91,97]. The ESUR/ESUI consensus document defines a radiologist who reads a minimum of 400 studies as a "beginner" and a specialist who reads > 1,000 studies as an "expert" [37]. Notably, reading studies alone is insufficient for QA, and knowledge can be supplemented by accruing continuing professional development (CPD) credits attending training workshops and MDT [37,38,90]. Certification in prostate MRI is a potential QC measure for radiologists, and should incorporate minimum reporting numbers, mandatory feedback for MRI reports (for example through audit of biopsy results or MDT attendance), requirements to obtain prostate-specific CPD credits, and, potentially, an exam [98]. Qualifications aimed at improving quality already exist for mammography, cardiac CT, and CT colonography screening. For example, the USA federal government enacted the Mammography Quality Standards Act (MQSA) in 1994 to ensure high-quality mammography for early breast cancer detection[99]. [100,101]. MDT in which MR images and histopathology reports are re-reviewed by radiologists and histopathologist, respectively, can be used as a safety check, provide QC, and might both help the local T-staging of the gland by combining radiology and pathology, and support the selection of management options considering clinical information[38,90,102].

DCE has been shown to benefit low-experienced readers [103] and improves performance of intermediate-level readers to that of experienced reporters [104], potentially because DCE highlights lesions not readily identified on T2 and DWI, acting as a "safety net". Additionally, DCE can increase reader confidence and, based on the application of the PI-RADS scoring system, leads to a reduced number of indeterminate PI-RADS 3 MRI calls in the peripheral zone, which can be up-scored to 4 when DCE is positive [43,46,105]. Indeed, the overall frequency of indeterminate PI-RADS 3 lesions might be used for QC purposes, as indeterminate lesions are particularly dependent on both MRI quality and radiologist experience [98]. PI-RADS 3 lesions are problematic, as the decision to perform biopsy is equivocal, considering that the detection rate of clinically significant cancer in these instances is only 17% [96]. The PI-RADS 3 call rate in four crucial prospective studies including biopsy-naive patients[7–10] ranged from 6% in the three-centre 4M study, in which a 3T scanner was used and MRI were reported by expert radiologists [8], to 29% in the PROMIS study, in which a 1.5T scanner was used in multiple centres and healthcare settings[9]. Re-review of MR imaging by expert radiologists has been shown to reduce incidence of PI-RADS 3 images by ~10% [34,36], and the use of DCE can further reduce PI-RADS 3 call rate by 2–8%, depending on reader experience [43,104]. Establishing optimal PI-RADS 3 call rates is a priority,

and could mirror the expected "recall-rate" range used for mammography, which has been informed by large datasets acquired from established screening programmes [98,106]. In this scenario, a frequency of PI-RADS 3 calls higher than expected could be a surrogate marker to help highlight issues with either MRI quality or reader experience (**Figures 3, 4**).

[H2] *Data processing*
MRI targets are not always defined at the time of reporting and might be outlined by a different radiologist in a second stage; thus, lesion localisation is subject to inter-reader variability [107]. In some centres, the biopsy operator might be responsible for outlining the lesion; in these instances, an adequate communication of lesion locations between the operator and the reporting radiologist is vital. The best scenario is the one in which the radiologist reporting the study concurrently outlines the lesion in communication with the biopsy operator, assigning a PI-RADS lesion probability score and using a reporting template [108,109].

According to PI-RADS guidelines, the axial plane can be acquired either in an axial-oblique plane matching the long axis of the prostate, or an oblique plane matching the posterior surface of the prostate or the anterior rectal wall, which closely approximates the transrectal ultrasound probe position [11,110]. The axial imaging plane selected might affect the anatomical division of the prostate (**Figure 5.**), and subtle translocational shifts in prostate position might also occur based on the patient position (supine for MR image acquisition and lateral decubitus position for performing transrectal biopsy) [111].

A linear relationship connects the different components of the radiological pathway, as each step affects the subsequent one, but further inter-relations among the various steps exist (**Figure 6.**). MRI-quality will affect the ability of radiologists to interpret images; however, radiologists' knowledge of expected MRI performance and protocol optimisation can directly lead to improved image quality. Image quality might also influence data processing in instances in which anatomical distortion or displacement is observed. Moreover, patient factors such as biopsy history or PSA density might affect the initial MRI interpretation, particularly if a Likert-based interpretation system is used, as this system enables the incorporation of clinical information, differently from the purely images-based PI-RADS scoring system [112–114]; patient factors such as patient performance status might also influence the decision to perform biopsy following MDT review. Moreover, patient factors might affect the accuracy of MRI-ultrasound image-fusion, for example in cases of substantial motion on MR images, or when no rectal access is available owing to prior surgery [115].

[H1] Variables, QA and QC in prostate biopsy

Performing systematic transrectal ultrasound guided biopsies (TRUSGB) alone is no longer recommended within guidelines as the initial diagnostic test in men with suspected prostate cancer , owing to the over-detection of indolent lesions and concurrent under-detection of clinically significant tumours [1–4]. Upfront prostate MRI facilitates subsequent MRI-targeted biopsy (MRTB) of suspicious regions of interest (ROI) in order to improve risk stratification of patients. The MRI-directed approach has multiple benefits [7,9,15] : reduce the number of men

who need biopsy; reduce the diagnoses of indolent cancers that are unlikely to cause harm, in turn decreasing patient over-treatment and related complications; improve detection of clinically significant prostate cancer, particularly for patients with a prior negative systematic biopsy; and improve risk stratification of patients based on the diagnosed cancers.

MRTB is recommended in clinical guidelines[1,2,4], but the MRTB technique, the number of cores, the experience of the operator, and the biopsy route are still matters of debate, and can influence the quality of the prostate cancer pathway [2,55]. MRTB techniques can be grouped into three different approaches, which all involve the combination of pre-biopsy MRI with real-time imaging, and can all be performed using a transrectal or transperineal approach: TRUS/MRI fusion MRTB (MRTB-fus), cognitive registration (MRTB-cog), or direct in-bore MRI-guidance. In MRTB-fus techniques, the target ROI previously identified though MR is fused with real-time ultrasound imaging with a dedicated software[52]. During cognitive biopsy, MRI is reviewed by the operator before biopsy, and knowledge of the MRI-identified lesion is used as a guidance for visual estimation under TRUS [116]. During in-bore MRTB, direct MRI visualization is used to guide the biopsy needle towards the ROI [117]. Which biopsy technique offers the best cancer detection rate is still debated. In clinical practice, in-bore MRTB (if available) can be chosen for small and difficult-to-reach lesions; however, limited capacity of MRI resources as opposed to the increasing demand, high implementation costs and inability to obtain systematic cores might contribute to the low uptake of this technique. In the hands of an experienced operator, MRTB-cog can be a practical and low-cost option to detect large lesions[12]. In the FUTURE trial, a multicenter, randomized-controlled study, 665 men with prior negative biopsy and a suspicious prostate cancer lesion at MRI were randomised to undergo MRTB-fus, MRTB-cog, or in-bore MRTB; in this study, no significant differences in the detection rate of clinically significant prostate cancer were observed among the three groups (MRTB-fus: 34%, MRTB-cog: 33%, and in-bore MRITB: 33%, $p>0.9$) [118]. Additionally, no significant differences were reported between cognitive fusion and TRUS/MRI fusion techniques in other two trials (PICTURE ($p = 0.53$) and SmartTarget ($p = 0.5$)); these results were also supported by a subsequent meta-analysis including 9 studies and 1,714 patients [119–121].

MRTB-fus is becoming increasingly popular owing to ease of use as an outpatient procedure and relatively low cost compared with in-bore biopsies [122]. Fusion software should undergo regular manufacturer-specific QC assessment, which might include phantom studies [123]. The commercially available MRTB-fus systems can be divided into two main groups: rigid and elastic image fusion [51]. The rigid systems use anatomical landmarks to fuse the prostate contour from MRI with real-time ultrasound images [51] . Elastic fusion systems use contours from both MRI and ultrasound images, and the software subsequently uses both contours to correct for deformation and movement of the prostate during the biopsy procedure [124]. During MRTB-fus, the registration of MRI and ultrasound images might result in fusion mismatch errors, for example owing to deformity of the prostate gland by the probe, patient motion, or differences in the degree of rectal loading; however, accuracy does not seem to differ between the two registration systems [125].

With regards to the biopsy route, the transperineal route benefits from reduced or no antibiotic prophylaxis and, therefore, has gained popularity owing to concerns on the

transrectal route regarding sepsis [126–128]. Transperineal biopsy favours an improved sampling of the anterior part of the prostate [129], and can also be implemented in an outpatient setting under local anaesthesia [130]. Thus, transperineal biopsy is gaining momentum, considering that the transperineal and the transrectal approaches offer equal cancer detection rates [131]. QA for systematic biopsy is achieved by obtaining cores according to a standardised template such as the modified MD Anderson (MDA) template (for the transrectal route), in which the gland is divided into apex, mid and base, and right and left, or the Ginsburg or Barzell templates (for transperineal biopsy). In the Ginsburg technique, two core biopsies are acquired medially and laterally from each of 12 sectors from the right and left sides of the gland, which is further divided into anterior, mid and posterior [132] ; with the Barzell template, samples are taken every 5 mm throughout the volume of the prostate using a brachytherapy grid [133,52].

Targeted biopsy improves detection of clinically significant cancer over systematic biopsy alone[7,8], but the combination of the two techniques improves overall detection[134,135]. At least two target cores from a suspicious ROI are acquired to help minimize the risk of sampling error [132,136,137]; however, for high probability MRI lesions (PI-RADS score 4–5), systematic cores are often positive around the index lesion even when target cores are negative, suggesting the existence of targeting error rather than radiological overcalling. [138]. Up to 22% of clinically significant prostate cancers might be missed with a 4-core targeted biopsy, and higher grade prostate cancer is detected with perilesional biopsies than targeted biopsy in 8% of patients, supporting the use of 'focal saturation biopsies' or 'region-targeted biopsies', with 3-5 cores taken within and around the ROI, depending on lesion size [135,139–141] .

The learning curve for operators should also be considered for all biopsy techniques. Equivocal data are available in the literature about the number of biopsies to be performed during the learning curve (ranging from 100 to 1,500 biopsies) [142,143]. In the first 100 biopsies, an operator might need to acquire an increased number of targeted cores, as an improved detection of clinical significant cancer is achieved by taking 4 or 5 cores during this period[143].

The rate of concordance in biopsy outcomes between different targeted biopsy techniques or routes (transperineal versus transrectal) and the radical prostatectomy histopathology might be used as a QC metric for sampling accuracy. Evidence from a study in which grade groups from preoperative biopsies (performed with different techniques) were compared with histopathology from radical prostatectomy showed a lower incidence of grade-group upgrading with MR in-bore biopsies than with fusion biopsies, suggesting improved sampling accuracy with the in-bore technique [144]; however, further work is required to use this information in defining specific QC criteria.
QC for the operator could be assessed by audits of complications rates, core quality and length, and overall cancer detection rates, as well as comparing biopsy pathology to final histopathology derived from prostatectomy specimens. Overall, biopsy is a highly operator-dependent technique, and precautions should be taken when biopsy results are discordant with MRI findings. In this scenario, three points should be assessed: the quality of MRI examination; the quality of MRI interpretation; the quality of the biopsy procedure. Reviewing samples from these patients in MDT is essential to understand whether the

observed results can be ascribed to radiologists' overcalls, to the presence of benign pathologies (such as chronic inflammation), or whether the initial procedure can be deemed suboptimal and, therefore, the targeted biopsy needs to be repeated

[H2] *Pathology*

The Gleason score obtained by biopsy is the most important prognostic marker for men with prostate cancer, and has a crucial role in treatment decision making. Patients with low-grade cancer (GG1 and, in some instances, GG2) can be treated with active surveillance, whereas patients with high–grade cancer (GG3; Gleason ≥4+3=7) generally require active treatment [4,145]. Several international pathology guidelines including the International Collaboration on Cancer Reporting (ICCR) datasets and the widely applied ISUP reporting guidelines provide pathologists with rules for assessing tumour Gleason grade , and standardize the way of reporting results, and, therefore, can be used for QA purposes [56,146]. However, the Gleason scoring system is hampered by substantial inter-observer and intra-observer variability and depends on pathologist's experience, tissue volume, and quality of the sampled tissue [147–151]. Gleason score takes into account the two most common cell subtypes rather than the worst pattern, which can lead to underestimation of the aggressiveness of the tumour. Additionally, different rules exist for reporting Gleason scores in biopsy specimens, which can lead to undergrading the tumour compared with radical prostatectomy biopsy [152–154]. Gleason score is further categorized into one of five prognostic ISUP groups, ranging from 1 (low risk) to 5 (high risk) [56], with group 1, 2, 3, 4 and 5 tumours corresponding to Gleason scores ≤3+3, 3+4, 4+3, 4+4, and ≥4+5, respectively [56] . The categorisation of borderline grades (GG2 versus GG3), for which reader variability is the highest, can have a substantial effect on treatment strategies for individual patients [155,156]. Several attempts to improve the inter-observer variability and standardize the grading systems have been made, including online educational material. One example is the "pathology imagebase" initiative, a public image library with examples of prostate cancer biopsies, which was subsequently validated by a panel of 24 international expert uropathologists[157]. The average kappa coefficient measuring the agreement among the 24 independent readers for ISUP grades was 0.67, with the lowest reproducibility observed for tumours with ISUP grade 3, for which consensus was reached for only 56% of samples [157].

External quality assessment (EQA) is used to compare a laboratory's testing to a source outside the laboratory. The Cellular Pathology National Quality Assurance Advisory Panel (NQAAP) oversees the running of histopathology and cytopathology EQA schemes and provides a QC system for objectively assessing the technical work of laboratories and the quality of microscope slides interpretation by pathologists [158]. AI systems based on deep learning are starting to be developed, and show promise for improving pathologists' interpretation and reducing inter-reader variability [159–161].

[H1] **Conclusions**

Prostate MRI demand is increasing owing to the incorporation of pre-biopsy MRI into international guidelines, and will continue to rise, mirroring trends in the incidence of prostate cancer. The MRI-guided prostate cancer diagnostic pathway involves several steps: performing and interpreting MR images, communicating the findings to clinicians, outlining suspicious targets, performing the biopsy, and evaluating biopsy cores. Variables that influence outcomes of this pathway include patient-related artefacts, MRI scanners' age and software updates, and experience of reporting radiologists, biopsy operators, and histopathologists. Quality assurance systems including PI-RADS imaging guidelines, prostate biopsy templates, and ISUP pathology guidelines all help minimise variation and ensure optimisation of radiology, biopsy and histopathology processes. Quality control measures for this pathway include checking MRI compliance with PI-RADS acquisition parameters, assessing image quality with PI-QUAL score, obtain certification for reporting radiologists, MDT re-review of imaging and pathology data, and audits of cancer detection rates, biopsy core quality and complications. Assessment and mitigation of poor quality and variability of performance is essential at every step of MRI-directed prostate cancer pathway in order to ensure optimal diagnostic outcomes.

Link box

Pathology imagebase: www.isupweb.org

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Toc Blurb

In this Review, the authors analyse all the steps of the multiparametric magnetic resonance imaging (MRI)-guided prostate cancer diagnostic pathway, focusing on quality assurance systems to minimise variation in performance and discussing quality control measures to assess and mitigate poor quality throughout the process.

Author contributions

T.B.,M.D.R., F.G. and C.A. researched data for the article. All authors contributed substantially to discussion of the content. T.B.,M.D.R. and F.G. wrote the article. All authors reviewed and edited the manuscript before submission.

Competing interests

The authors declare no competing interests.

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Figure legends

Figure 1. Improved image quality using deep learning reconstruction algorithms.
MRI from a 77 year old biopsy-naive patient; PSA 9.61 ng/ml. a: Motion artefact on standard T2. b: Deep learning (DL) reconstruction of T2 sequence. DL reconstruction provides quicker scan time than the standard approach, with reduced motion artefact, improved signal-to-noise ratio and image sharpness, as well as clear demarcation of benign prostate hyperplasia nodules within the transitional zone, in which T2 is the dominant assessment sequence. No lesions were shown on the MRI study and no biopsy was performed owing to low PSA density.

Figure 2. Possibility to rule in the presence of clinically significant prostate cancer despite poor MRI image quality.
MRI from a 79 year old biopsy-naive patient, PSA 10.13 ng/ml. Motion artefact considerably affects the quality of T2 (a); the DWI sequence (b,c) is substantially affected by susceptibility and aliasing artefacts. The DCE (d) sequence is relatively unaffected by motion artefact and a clear 17×13 mm area in the right mid/apex transitional zone (arrow) is visible, which can be then retrospectively identified on T2 (PI-RADS score ≥3). Although only 1 of 3 sequences in considered diagnostic (PI-QUAL score =3), the clinical effect of this poor quality study is minimised, as the ability to rule in the presence of lesions is preserved. Target biopsy: Gleason 3+4=7 (10% grade 4) in 2 of 3 cores.

Figure 3. Inadequate DWI technique results in PI-RADS 3 lesion assessment .
Biparametric MRI from a 61 year old biopsy-naive patient, PSA 8.29 ng/ml. a) A 15x8 mm

wedge-shaped area of low T2 is observed in the left mid-peripheral zone, with T2-WI PI-RADS score 2 (arrow), which has a marked low signal on apparent diffusion coefficient (ADC) maps (b, arrow), and only a mildly high signal on diffusion-weighted imaging (DWI) performed with a b-value of b-1,000 s/mm^{2,} (c). In this instance, without further image post-processing, the biparametric MRI score would be PI-RADS 3. However, a marked high signal intensity is observed in the same area on DWI performed with a synthetic high b-value of 2,500 s/mm^2 calculated by post-processing (d); with these parameters, a PI-RADS score of 5 is assigned to this area (based on size and possible early extracapsular extension). Synthetic b-values can be used if the acquired b-value imaging is not high enough. After targeted biopsy, 4 of 4 cores were Gleason 3+4, with a maximum tumour length of 9 mm.

Figure 4. Improved quality T2 with repeated acquisition.
Biparametric MRI from a 62 year old biopsy-naive patient, PSA 4.5 ng/ml. a) MRI with standard T2 imaging shows a blurred outline of the prostate, secondary to rectal spasm, with a geographical low signal area located in the right apex peripheral zone (PZ, arrow), PI-RADS score 2. b) MRI with PROPELLER-T2 shows a sharper margination of the prostate lesion than the one observed with the standard T2 image, and the right apex PZ is now appreciated as a focal lesion (PI-RADS score 4). Mild restricted diffusion is shown on b-1000 imaging (c) and apparent diffusion coefficient map (d), resulting in overall PI-RADS score 3. T2 imaging cannot affect the overall PI-RADS score, but the improved quality of the T2-PROPELLER should increase reader confidence in identifying a focal lesion. After targeted biopsy, 3 of 3 cores have Gleason score 3+4=7, with a maximum tumour length of 14 mm and the presence of perineural invasion.

Figure 5. Effect of axial orientation on prostate anatomical division.
a) Sagittal T2-weighted MRI images; reference lines indicate planes of images potentially acquired axial to the patient (yellow dashed line) or axial to the posterior surface of the prostate (red dashed line). The corresponding anatomical division of the prostate in apex, mid, and base is highlighted (solid lines). b) Differences in anatomical division (apex/mid/base) between planes (axial to the patients or to the rectum) are shown, with green and orange areas indicating concordance and discordance, respectively.

Figure 6. Inter-relationships between different steps of the MRI-directed prostate biopsy pathway.
Linear relationship between the four components of the MRI-directed prostate biopsy pathway (dashed arrow) and further inter-relations among the different steps (solid arrows) are shown. MDT = multidisciplinary team meeting, PSA = prostate-specific antigen, DICOM = digital imaging and communications in medicine image format.

Tables

Factor	Speciality	Variables	QA	QC
Patient-level issues	General practice, urology and radiology (MRI physicists, radiographers)	Disease prevalence Patients with suspicion of prostate cancer or screened populations Biopsy history Artefacts (motion, susceptibility, and/or metal)	Anti-spasmodics Bowel preparation Metal-reduction techniques Motion-reduction techniques	Cancer detection rates
Image quality	Radiology (radiologists, MRI physicists, radiographers)	Age of scanner Magnet field strength Magnet gradient strength Receiver coils (endorectal or surface) Software iteration Contrast medium usage	PI-RADS v2.1 Software updates AI solutions	Scanner-level QC PI-QUAL PI-RADS 3 call rates
Radiologist interpretation	Radiology (radiologists)	Expertise of the reporter Inter-reader variability	PI-RADS v2.1 Image interpretation workshops CPD points	Certification MDT review External peer-review PI-RADS 3 call rates
Biopsy	Radiology and urology	Threshold for biopsy decision Outlining (contouring) of targets Segmentation of prostate gland	Modified MDA template(TR) Ginsburg template(TP) Barzell template (TP)	Phantom work Audit of complication rates Audit of positive predictive value for cancer detection

				Comparison with radical prostatectomy histologic analysis MDT review
Pathology	Urology (or radiology) and histopathology	Biopsy route (TP or TR approach) MRTB technique (cognitive versus MRI/US fusion versus in-bore) Rigid or elastic fusion Biopsy plan (targeted versus targeted plus systematic; core distribution) Experience of the operator	ISUP guidelines ICCR datasets	Uropathology EQA scheme to audit core quality MDT review

Table 1. Prostate diagnostic pathway— quality assurance and quality control issues, and variables affecting the pathway . *CPD* = continuing professional development, EQA = external quality assessment, ICCR = International Collaboration on Cancer Reporting, ISUP = International Society of Urological Pathology, MDA = MD Anderson, MDT = multidisciplinary team meeting, PI-QUAL = Prostate Imaging Quality, PI-RADS = Prostate Imaging–Reporting and Data System, TR = transrectal, TP *= transperineal MRI = magnetic resonance imaging, US = ultrasound, MRTB MRI-targeted biopsy*

Organisation	Prior negative biopsy	No prior biopsy	Can biopsy be avoided in case of MRI negative result?
AUA and SAR [1]	Recommend MRI	Recommend MRI	Other ancillary tests (such as PSA, PSA density, PSA velocity) might be useful to identify patients for whom a systematic biopsy is needed. Further data is needed
EAU [2]	Strong evidence	Strong evidence	If clinical suspicion of prostate cancer is low (PSA density < 0.15 ng/m), biopsy can be omitted based on shared decision-making with the patient
NICE [4]	Consider MRI	Offer MRI	Consider omitting biopsy, but only after discussing the risks and benefits with the patient and reaching a shared decision
NCCN [3]	Strongly consider MRI	Consider MRI	Biomarkers and/or PSA density should be considered when deciding whether biopsy can be avoided

Table 2. International multiparametric MRI guidelines for prostate cancer detection

ACR = American College of Radiology, AUA = American Urological Association, EAU = European Association of Urology, NICE = National Institute for Health and Care Excellence, NCCN = National Comprehensive Cancer Network, PSA = prostate specific antigen, SAR = Society of Abdominal Radiology, TRUS = transrectal ultrasound.

PI-QUAL score	Criteria	Clinical implications
1	All mpMRI sequences are below the minimum standard for diagnostic quality	Not possible to rule in all clinically significant lesions * Not possible to rule out all clinically significant lesions *
2	Only one mpMRI sequence is of acceptable diagnostic quality	Not possible to rule in all clinically significant lesions * Not possible to rule out all clinically significant lesions *
3	At least two mpMRI sequences taken together are of diagnostic quality	Possibility to rule in all clinically significant lesions Not possible to rule out all clinically significant lesions
4	Two or more mpMRI sequences are independently of diagnostic quality	Possibility to rule in all clinically significant lesions Possibility to rule out all clinically significant lesions
5	All mpMRI sequences are of optimal diagnostic quality	Possibility to rule in all clinically significant lesions Possibility to rule out all clinically significant lesions

Table 3. Assessment of the diagnostic quality of multiparametric MRI scans using the PI- QUAL score. PI-QUAL: prostate imaging quality; mpMRI: multiparametric magnetic resonance imaging; PI-RADS: prostate imaging reporting and data system. * reports should not include PI-RADS or Likert scores. *Adapted from Ref [80]: Giganti F, et al. Prostate Imaging Quality (PI-QUAL): A New Quality Control. Eur Urol Oncol. 2020; 3(5):615-619. Copyright (2020).*