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Review

Prostate biopsy: when and how to perform

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Prostate cancer, unlike other cancers, has been sampled in a non-targeted, systematic manner in the past three decades. On account of the low volume of prostate sampled despite the multiple cores acquired, systematic transrectal (TRUS) biopsy suffered from low sensitivity in picking up clinically significant prostate cancer. In addition, a significant number of cancers of the anterior, lateral peripheral zone, and the apex were missed as these areas were under-sampled or missed during this biopsy protocol. Subsequently, the number of cores acquired was increased with special focus given to targeting the previously undersampled areas. These procedures led to an increase in the complication rates as well as detection of more clinically insignificant cancers. The advent of multiparametric magnetic resonance imaging (MRI) and its high intrinsic tissue contrast enabled better detection of prostate cancer. This led to the introduction of MRI-targeted biopsies with either MRI–TRUS fusion or under direct (in-gantry) guidance. MRI-targeted biopsies increased the percentage of positive cores and detection of clinically significant prostate cancers; however, these are expensive, time-intensive, require significant capital investment and operator expertise. This article describes the indications, workflow, complications, advantages, and disadvantages of TRUS-guided biopsy followed by MRI-guided biopsies.

Introduction: the need for screening

Prostate cancer ranks among the commonest malignancies in males. As per the recent Surveillance, Epidemiology, and End Results Programme (SEER) data, it accounts for 9.6% of newly diagnosed cancers and 4.4% of cancer-related deaths in 2017. The majority of the biopsy-proven prostate cancers do not result in increased mortality; the 5-year survival rate being 98.6%.[1]

Diagnosis and screening for prostate cancer has been a matter of much debate. As per the American Cancer Society (ACS), screening is indicated in asymptomatic men above 50 years with a life expectancy of 10 years and moderate risk for prostate cancer.[2] In men at high risk, i.e., African-Americans and those with a positive family history, screening may be initiated as early as 40 years. In either case, the person must be allowed to make an informed decision with the help of his healthcare provider. Usually, screening is performed using serum prostate-specific antigen (PSA) estimation along with digital rectal examination (DRE); however, no definite consensus has been made with regard to the benefit of routine population-based screening. The Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) Screening Trial found no mortality benefit for prostate

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cancer screening at 13 years of follow-up.[3] Although the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial observed a 27% relative risk reduction in the screening arm at 13 years of follow-up, the reduction in mortality was much smaller as compared to the over-diagnosis and overtreatment associated with screening. Hence the ERSPC group recommends further studies to assess the impact of screening on quality of life before it is implemented on a routine basis.[4]

Traditionally, a serum PSA of 4 ng/ml has been used as the cut-off for performing prostate biopsy; however, the Prostate Cancer Prevention Trial (PCPT) observed that there was no "normal" PSA level that could rule high-grade cancer.[5] Hence, over the years, the cut-off for biopsy has come down at the cost of an increase in the number of unnecessary biopsies. A cut-off PSA of 2.5 ng/ml almost doubles the number of biopsies and results in increased detection of clinically insignificant cancer (defined as volume <0.5 ml and Gleason score ≤ 6).[6]

Maintaining a balance, the current Prostate Cancer Risk Management Programme (PCRMP) recommends prostate biopsy in men aged 50–69 years who have serum PSA levels >3 ng/ml and in those with abnormal DRE findings (nodules, induration or asymmetry).[7] For triaging men with PSA levels >2.5 ng/ml for biopsy, other parameters including PSA velocity (>0.75 ng/ml/year), free PSA level ($<20\%$) and PSA density (≥ 0.15) have been used.[8]

Systematic transrectal ultrasound-guided biopsy

From the time when prostate biopsies were limited to blind sampling of the palpable abnormality, we have come a long way to the era of transrectal ultrasound (TRUS)-guided systematic biopsies and MRI-guided targeted biopsies. TRUS-targeted biopsies were initially tried; however, 30–40% of prostate cancers are isoechoic to the normal prostate parenchyma on ultrasound and occult on TRUS imaging. In addition, TRUS often fails to differentiate transition zone proliferative nodules from prostate cancer. These gave way to the introduction of systematic TRUS-guided biopsy, the clear advantage of which over targeted TRUS-guided biopsy was observed first by Hodge *et al.* in 1989.[9]

In systematic TRUS-guided biopsy, the objective is in directing the needle to sample prespecified regions of the prostate gland with the hope that the tumour is sampled and localised within the gland. No attempt is made to directly visualise or specifically target the tumour. Contra-indications to TRUS-guided biopsy include acute painful conditions of the anorectum, anorectal infection or abscess, acute prostatitis, coagulopathies, severe immunosuppression, and absent rectum.

Pre-procedure instructions and antibiotic prophylaxis

TRUS-guided biopsies are frequently performed as office procedures. As the transrectal approach carries the risk of infection with Gram-negative bacteria, particularly *Escherichia coli*, antibiotic prophylaxis is provided with a single oral dose of quinolone (usually ciprofloxacin) administered a few hours before the procedure. Quinolones, in addition, have excellent tissue penetration of the prostate gland. The recommendations advise against continuing the prophylaxis beyond 24-hours after the procedure to avoid development of antibiotic-resistant strains.[10] Based on the institutional preference, additional anaerobic coverage with tinidazole or clindamycin may also be provided. A self-administered cleansing enema may be performed on the morning of the procedure.[11]

Prostate biopsies performed in patients on antiplatelet or anticoagulant therapy are not associated with increased risk of major bleeding; however, there is a one-third increase in the incidence of minor bleeding. In patients on low-dose aspirin (LDAP) who are at moderate to high risk for adverse cardiovascular or neurological events, the drug should be continued periprocedurally. Patients on dual anti-platelet drugs (LDAP and clopidogrel) should discontinue clopidogrel alone 1 week prior to the procedure. This is except in the case of post-coronary intervention patients in the critical period (up to 2 weeks after angioplasty, 6 weeks after bare-metal stent insertion, and 12 months after drug-eluting stent placement) in whom the dual anti-platelets therapies should be continued. Anticoagulants (Warfarin) should be discontinued 5 days prior and restarted 24–48 hours after the procedure. In patients at high risk of adverse thrombotic events, bridging anticoagulation with low molecular weight or unfractionated heparin should be instituted in the meantime.[12]

Procedure

After ensuring privacy and comfort, the patient is placed in the left lateral decubitus position with the knees and hips folded towards the abdomen. Per-rectal local anaesthetic (lignocaine) jelly or suppository can be provided for topical anaesthesia prior to introduction of the TRUS probe. The endocavitary phased-array probe is kept ready covered with a condom and a sterile disposable plastic needle-guide is attached. With gentle, but steadily increasing pressure, the probe is introduced into the rectum. It is preferable to hold the probe between the index finger and thumb rather than with a tight fist to allow smooth passage of the probe along the natural curvatures of the anal canal and rectum. Subsequently, the prostate is examined for the anatomy, volume, and pathology in both transverse and sagittal planes.

Local anaesthesia is indicated for pain reduction and discomfort during the procedure and induces a significant difference in the visual analogue score in comparison to procedures without anaesthesia.[13] A long (20 cm), 22 G Chiba needle is used to administer the local anaesthetic. Usually, a total of 10 ml of 1% lignocaine without adrenalin is instilled in four aliquots of 2.5 ml into the Denonvillier's fascia at the base and apex bilaterally.[14] At the base of the gland, the local anaesthetic is administered into the echogenic fat triangle at the junction of the seminal vesicle and the posterior margin of the gland on the axial image,

targeting the area around the periprostatic nerve plexus (Fig 1a). Care must be taken not to introduce air, which may subsequently obscure the gland. During each administration, the needle must be gently withdrawn and advanced to assure infiltration of all the tissue planes. Direct intraprostatic injection is not beneficial. Any effort to move the probe without retracting the needle should be avoided, otherwise rectal mucosal tear may result.[15]

Sampling approach and number of cores

Systematic TRUS-guided biopsies are targeted at procuring cores from all prostatic zones with the hope that the tumour is also included in the sample; however, the initially used six-core systematic biopsies sampled only about 1% of the gland volume, and carried the risk of missing small tumours in large-volume glands and those in the anterolateral peripheral zone, anterior transition zone, and apex.[16] the peripheral zone accounts for up to 75% of the cancers and the standard sextant biopsy misses up to 30% of the clinically significant cancers.[17] For this reason, the number of cores was subsequently increased to 8, 12, and 14 with resultant improvement in cancer detection (Fig 1b). These 12 and 14-core biopsies, in addition to sampling more volume of the gland, also specifically target the anterolateral peripheral zone using additional cores that are directed and angulated more laterally. The extended biopsy schemes have a detection rate of up to 40% in comparison to the 25% for sextant biopsies.[18] Any further increase in the number of cores would increase the incidence of complications and is not advisable except when the clinical suspicion of malignancy remains high despite a previous negative biopsy (persistent or rising PSA levels, high PSA velocity). In such cases, a saturation biopsy is used, wherein multiple cores (usually >20 and up to 40–80 cores) are taken at regular intervals in an effort to sample as much of the gland as possible; however, saturation biopsies are associated with increased patient discomfort, pain, complications, and cost.

In the event of the repeat biopsy being negative, data have shown that the risk of harbouring a clinically significant cancer is extremely low and no further biopsy is advised. In a large observational study, the detection rate fell progressively for each of the subsequent biopsies.[19,20] Repeat biopsies are also advised in patients who have been detected to have atypical small acinar neoplasia (ASAN) and multifocal high-grade prostatic intraepithelial

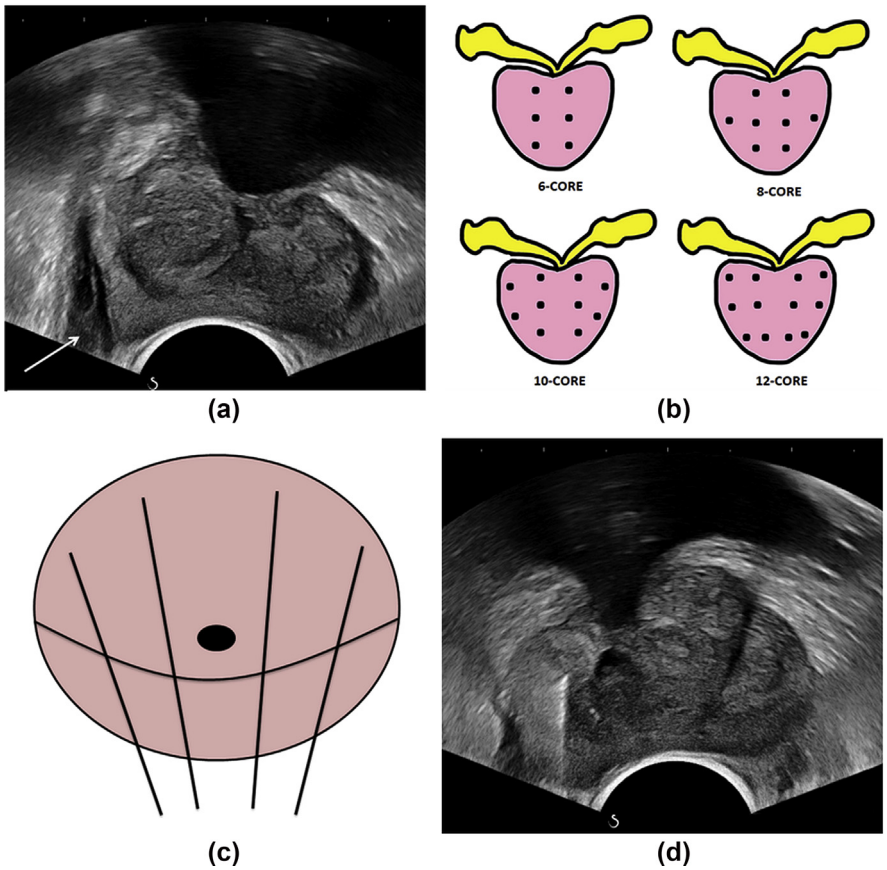

Figure 1 TRUS-guided biopsy procedure. (a) Local anaesthetic being delivered at the echogenic fat triangle along the posterolateral nerve bundle. The fluid bleb (arrow) and the needle tip are visible. (b) Schematic diagram of the coronal image of the prostate showing the commonly used biopsy schemes (6–12 cores). In the sextant biopsy scheme, the prostate is divided into base, mid-gland, and apex; and biopsies are taken from each of these sections bilaterally. In the 12-core biopsy scheme, medial and lateral cores are taken from each of these sections bilaterally. (c) Representative diagram of the axial section at the base of prostate showing the anterolateral angulation required for the needles to sample as much of the peripheral zone as possible. (d) Biopsy pass being taken through the right lateral segment of the prostate base.

neoplasia (HGPIN).[21] One study also observed that 38% of the tumours that had a Gleason score of ≥7 in the final radical prostatectomy specimen had a score of ≤6 in the initial TRUS biopsy specimen. This suggests that TRUS-guided biopsies could under-grade and miss clinically significant cancer.[22]

At the time of biopsy, the needle must be directed laterally, so that the anterolateral peripheral and transition zones are adequately sampled (Fig 1c). TRUS-biopsies are generally obtained with an 18 G, 26 cm automatic, spring-loaded biopsy gun with 20 mm throw (Fig 1d).

Two types of transrectal probes are available depending on the orientation of the probe tip. In the side-firing probes, the tip is oriented longitudinally. This directs the biopsy trajectory in a craniocaudal axis and causes difficulty in sampling the gland in the transverse axis. Significant torque is required to adequately sample the lateral peripheral zone and the apex. Hence the learning curve is steep for these probes. On the other hand, the curved tip of the end-firing probes enables easy visualisation in the transverse plane and has been shown to have significantly better cancer detection rate in comparison to side-firing probes.[17]

During sampling, care must be taken not to move the probe once the biopsy needle is placed across the rectal mucosa otherwise mucosal tear may result. After sampling, all the cores are sent for histopathology analysis in separately labelled bottles, which help to localise the cancer detected.

Complications

Minor complications such as transient haematuria and haematochezia are frequent after TRUS-guided biopsy and are usually managed with patient reassurance alone. Major complications requiring hospitalisation are rare. There is no significant increase in the incidence of complications with increase in the number of cores up to 12 or 14; however, the occurrence increases proportionately with any further increase in the number of cores and in case of saturation biopsies. The ProtecT (Prostate Testing for Cancer and Treatment) study observed that at 35 days after the biopsy, the prevalence of minor complications were 92.6% for haemoejaculate, 65.8% for haematuria, 43.6% for pain, 36.8% for haematochezia, and 17.5% for fever. At 7 days after the biopsy, 19.6% of the men considered that any further biopsy would be a moderate or major problem.[23]

Transient haematospermia and haematuria are the most frequent complications and require only reassurance.[24] Mild haematochezia often occurs due to injury of a rectal vein and usually resolves within 48 hours. Compression with the probe or a rectal balloon helps in arresting the bleed. Major bleeding can occur in patients with coagulopathy and arterial injury, the latter requiring proctoscopy-guided clipping or cauterisation.

There is a small risk of acute urinary retention (up to 6%; due to glandular oedema) and a higher incidence in the worsening of lower urinary tract symptoms (up to 25%) after transrectal biopsy. The incidence of urinary retention is higher with transperineal biopsy; however, most cases do not need invasive treatment more than transient placement of a urethral catheter. The risk of retention is higher with repeated saturation biopsies and in large-volume prostates, whereas the association with the number of cores and type of anaesthesia is controversial. Prophylactic alpha blockers are useful in reducing symptoms in patients with large-volume prostates and in those with severe prior lower urinary tract symptoms.[24]

Local infection and sepsis are unusual when antibiotic prophylaxis is given.[25] When this happens, it is imperative to consider quinolone-resistance and administer intravenous third-generation cephalosporins or aminoglycosides.[26] Vasovagal syncope and erectile dysfunction may also occur after prostate biopsy. Administration of local anaesthetic may itself cause complications such as temporary urinary incontinence (due to paralysis of the external sphincter), infection, bleeding, erectile dysfunction, drug toxicity, and allergy.[14]

In summary, local anaesthesia and antibiotic prophylaxis along with the relative ease of the procedure has made transrectal biopsy the most common route preferred for office biopsy of the prostate; however, as highlighted earlier, there are significant concerns regarding the risk of under-diagnosis and safety with the transrectal approach. There is an inherent risk of local infections as well as urosepsis, considering that the site of biopsy is already contaminated (class III surgical wound). Of late, the rise of quinolone-resistant strains have increased the incidence of such complications in spite of the antibiotic prophylaxis.[27] Some practitioners advise routine testing of the rectal swab for drug sensitivity; however, this procedure is cumbersome and rather impractical in most centres.

Transperineal approach

The transperineal approach has come up as a good alternative to transrectal biopsy. The procedure is performed with the patient in the dorsal lithotomy position and the needles are inserted through the perineum, which is cleaned and prepared in advance. The transperineal route provides unrestricted access to the prostate, particularly of the anterior transition zone and the apex, which are inaccessible via the transrectal approach. One meta-analysis observed a higher cancer detection rate for transperineal biopsy in comparison to transrectal saturation biopsy (36.8% vs. 30%) although the difference was not statistically significant.[28] Transperineal biopsy can be performed in patients with absent rectum. In comparison to the rectum, perineal wounds are clean-contaminated (class II surgical wounds) and can be prepared, resulting in a lower incidence of minor infections as well as sepsis.[29,30]

As the perineum is more pain sensitive than the rectal mucosa and transperineal approach involves piercing several muscles, the procedure is generally performed under spinal or general anaesthesia; however, recently, several local anaesthetic approaches have been described and found to be simpler, effective, and tolerable. These include the subcutaneous perineal nerve block, periprostatic nerve

block, prostatic apex block, pudendal nerve block, and periapical triangle block.[31]

For transperineal biopsies, side-firing biplane probes (which provide both transverse and sagittal images of the gland) are used. The biopsies can be performed with a freehand technique (more commonly used) or using a template grid (prostate mapping) protocol. In the freehand technique, the probe is inserted into the rectum and sagittal images are used to guide the needle into the prostate. The probe can be rotated to demonstrate the lateral aspects of the gland. Following this, at least two cores are taken from each of the medial and lateral portions of the anterior, mid, and posterior sectors on both sides (Ginsburg protocol). A relatively large number of cores (usually 24–40) are generally obtained.[32]

In the template grid technique, a brachytherapy grid having several holes spaced 5 mm apart is used as the needle guide. The grid and endocavitary probe are mounted onto a stepper–stabiliser assembly, which is attached to the table or floor stand. The stepper enables mechanically stabilised forward as well as rotatory motion of the probe using knobs and extensions. The template grid holes are then overlaid over the transverse image of the prostate to guide the initial precise placement of the needle into the desired region. Then the operator switches onto the sagittal image for real-time visualisation at the time of firing. Apart from transperineal biopsies, the same grid can also be used for guiding fiducial marker placement and focal therapy (cryo and brachytherapy).

Despite the anaesthesia, transperineal biopsies are associated with greater post-procedure pain and discomfort. As a relatively larger number of cores are obtained in comparison to the transrectal approach, the incidence of post-procedure urinary retention is higher and can be reduced with the avoidance of peri-urethral tissue sampling and usage of indwelling catheter. In addition, the procedure is time-intensive and has a longer learning curve.[33] The basic differences between the two approaches is demonstrated in Fig 2.

Advances in targeted TRUS-guided biopsy

Colour Doppler, contrast-enhanced ultrasound (CEUS) and elastography have been used to guide targeted biopsy of prostate cancer. These techniques increase the conspicuity of prostate cancer, which otherwise is unapparent on grey-scale imaging. On colour and power Doppler, prostate usually has minimal, symmetric flow although significant periurethral and periprostatic vascularity is normally seen. Prostate cancer results in asymmetric flow, which can be used to target the biopsy[34,35]; however, this finding is non-specific as prostatitis can also cause increased flow.[14] CEUS qualitatively highlights the enhancing prostate cancer. In addition, parametric CEUS perfusion provides quantitative data (bolus arrival time, time to peak enhancement, wash-in and wash-out kinetics) which can be plotted on a colour overlay map. Among the parameters, time to peak enhancement was observed to be the most useful parameter in one study[36]; however, all CEUS-targeted biopsies require information from prior MRI in identifying the tumour as only a small portion of the prostate can be assessed per pass of the contrast and only a limited number of injections (passes) are possible at the time of biopsy. Several studies have shown the advantage of contrast-enhanced colour Doppler in detecting more clinically significant cancers that systematic biopsy.[37,38] Recently, shear-wave elastography with real-time depiction of tissue stiffness (Young's modulus) has been found useful in identifying malignant tissue and targeting it for biopsy.[39,40]

MRI-guided biopsies

Multiparametric MRI (mp-MRI) has high intrinsic tissue contrast and is the technique of choice for localising prostate cancer. Its utility comes in men who have had previous negative biopsies but continue to carry a high suspicion for prostate cancer. A large meta-analysis observed that although MRI-guided biopsies did not significantly differ

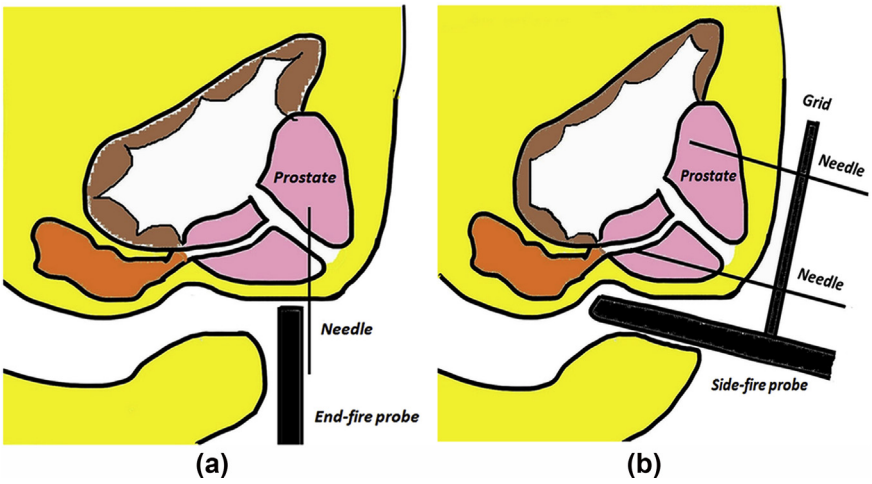

Figure 2 Line art showing the major differences between the (a) transrectal and (b) transperineal approaches to prostate biopsy. In the transrectal approach, an end-fire endorectal probe is used and the needle is directed through the rectal mucosa. On the other hand, the transperineal approach uses a side-fire endorectal probe and the needle is directed through the skin of the perineum using a brachytherapy grid.

from TRUS-guided biopsies in the overall detection of prostate cancer, they detected significantly more (91% sensitivity) clinically significant cancers and increase the percentage of positive cores.[41] Other studies have reproduced similar observations.[42–44] The consensus statement of the American Urological Association (AUA) and Society of Abdominal Radiology (SAR) recommend high-quality MRI followed by MRI-targeted biopsy in men who have persistently high suspicion for cancer despite a previous negative biopsy.[45] The statement suggests procuring at least two cores from the suspicious area in addition to the systematic 12-core biopsy.

MRI has also challenged the need for routine TRUS-guided biopsies in screening positive patients. Kasivisvanathan *et al.* observed that prior risk assessment with upfront mp-MRI followed by MRI-targeted biopsy (if required) reduced the number of men requiring biopsy.[43] According to the Prostate MR Imaging Study (PROMIS), a negative MRI (PI-RADS score <3) is reassuring and has high negative predictive value for clinically significant cancer.[46] Most urologists, at present, prefer to avoid TRUS-guided biopsy if the MRI is not suspicious. The latest UK National Institute for Health and Care Excellence (NICE) guidelines recommend upfront mp-MRI in biopsy-naive men who are clinically suspected of having localised prostate cancer.[47] MRI-targeted biopsy can be done using cognitive fusion, MRI–TRUS fusion, or the direct (in-gantry or in-bore) technique. The techniques are described below.

Cognitive fusion biopsy

The traditional technique of cognitive fusion, wherein the operator targets the lesion on real-time TRUS using fiducials and landmarks identified on the MRI images, is cheap and simple. Extrapolating the MRI findings onto real-time TRUS images requires specialised expertise in reading and interpreting the MRI, performing TRUS as well as identifying and utilising anatomic fiducials as aids in targeting the tumour. The most common limitation of cognitive fusion is the possible misregistration resulting from incorrect judgment of location of the lesion. This is particularly true with operator inexperience and when the operator has not himself assessed the MRI images and rather relies on the report to help localise the lesion. In comparison with cognitive fusion biopsies, software-aided fusion used by the MRI–TRUS fusion biopsy platforms is more accurate and reliable. In a study by Cool *et al.*, cognitive fusion missed >50% of the clinically significant cancers, whereas software-aided fusion detected all the cancers[48]; however, the AUA-SAR consensus statement supports the adequacy of cognitive biopsies in resource-poor settings when skilled operators are available. In such cases, MRI–TRUS fusion biopsies may be reserved for small and difficult-to-access tumours (apical and anterior lesions).[45]

MRI–TRUS fusion biopsy

MRI–TRUS fusion combines the advantages of MRI (in localising the tumour) and ultrasound (real-time assessment, portability and ergonomics). It is used in three scenarios: (a) detection of cancer in patients with previous negative biopsies who have persistently high suspicion; (b) detection of cancer in the voluminous prostate where the utility of systematic biopsy is low; and (c) active surveillance of patients who are detected to have low-risk prostate cancer.[49]

The currently available platforms for MRI–TRUS fusion biopsy (Table 1) include Artemis (Eigen, USA), BioJet (D&K Technologies, Germany), BiopSee (Pi Medical, Greece), iSR'obot Mona Lisa (Biobot Surgical, Singapore), Logiq 9 (GE Healthcare, UK), MIM Symphony Bx (MIM Software, USA), Navigo (UC-Care, Israel), RVS (Hitachi, Japan), UroNav (Invivo, USA), Urostation and Trinity (Koelis, France), and Virtual Navigator (Esaote, Italy).[50] These platforms differ in (a) software interface (b) volumetric-USG acquisition technique; (c) needle tracking method; (d) image fusion algorithm; and (e) biopsy route. The routine workflow described below involves four steps (Fig 3).

Step 1. Prostate and tumour segmentation on mp-MRI

First, the MRI images are transferred onto a dedicated image analysis and processing software specific to the vendor. Some of the examples include DynaCAD (Invivo), ProFuse (Eigen), McDraw (Koelis), and UroFusion (Biobot Surgical). These software enable retrieval and export of digital imaging and communications in medicine

Table 1
The currently available magnetic resonance imaging (MRI)–transrectal ultrasound (TRUS) fusion biopsy platforms and the key operational differences between them.

Platform	TRUS probe manipulation	Mode of fusion	Probe tracking and navigation	Biopsy route
Artemis	Mechanically stabilised rotation	Elastic	Encoders	Both
BioJet	Mechanically stabilised rotation	Elastic	Encoders	Both
BiopSee	Motorised craniocaudal translation	Rigid	Encoders	Both
iSR'obot Mona Lisa	Motorised translation	Elastic	Robotic arm	Transperineal
Logiq 9	Freehand sweep	Rigid	Electromagnetic	Transrectal
MIM Symphony Bx	Motorised translation	Rigid	Encoders	Transperineal
NaviGo	Freehand sweep	Rigid	Electromagnetic	Transrectal
RVS	Freehand sweep	Rigid	Electromagnetic	Both
UroNav	Freehand sweep	Elastic	Electromagnetic	Both
Urostation	3D ultrasound probe freehand sweep	Elastic	Ultrasound image to image fusion	Both
Virtual Navigator	Freehand sweep	Rigid	Electromagnetic	Transrectal

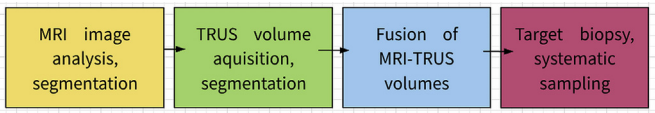

Figure 3 Flowchart showing the key steps in MRI–TRUS fusion biopsy.

(DICOM) files from and to portable storage devices, cloud as well as picture archiving and communication system (PACS).

The radiologist first carefully analyses the images in accordance with the PI-RADS v2 guidelines. The diffusion-weighted images (DWI) are primarily used to assess peripheral zone tumours and the T2-weighted images are used for transition zone tumours. The peripheral zone lesions, which are indeterminate on DWI, are further characterised on dynamic contrast-enhanced (DCE) images. The identified lesions are assigned a PI-RADS score and labelled on the prostate sector map. The radiologist then segments the contour of the prostate as well as that of the suspicious area on the MRI images. Subsequently, a three-dimensional (3D) image of the prostate gland and the segmented tumour is generated by the software, which can then be uploaded onto the biopsy system (Fig 4).

Step 2. TRUS acquisition and segmentation

Just prior to the biopsy, a volumetric USG image is acquired on a TRUS system attached to the biopsy device and is subsequently co-registered and fused with the MRI image for real-time guidance. In majority of the platforms, the 2D TRUS images acquired undergo 3D volumetric reconstruction with the exception of Urostation where a dedicated 3D probe is used. The 2D-TRUS image acquisition is done using a freehand sweep in case of UroNav and a motorised craniocaudal translation for iSR'obot Mona Lisa and MIM Symphony Bx. Artemis on the other hand, uses an articulated arm, which enables a mechanically stabilised motion of the probe (Fig 5a and b). For reconstruction of artefact-free 3D images, the entire gland must be acquired in one slow, smooth, steady sweep from the base to the apex. Subsequently, the operator manually outlines the contour of the prostate gland on the ultrasound images and the system semi-automatically creates the 3D ultrasound volume (Fig 5c).

Step 3. MRI–TRUS fusion

The key step in the entire workflow is fusion itself and any error in this step can drastically affect the accuracy of sampling. The MRI images and the volumetric USG images are fused, and the suspicious area labelled on the MRI is mapped onto the 3D TRUS images. The most important challenge to accurate fusion is the difference in the geometry and orientation of the prostate between the USG and MRI images, which results from the difference in position and time at which they are performed. MRI is acquired in the supine position whereas TRUS is performed in lateral recumbent position. In these positions, there are rotational and translational differences in the orientation of prostate as well as altered geometry resulting from differing directions of the compressive and tensile forces on the gland. In addition, the pressure exerted by the TRUS probe and the differences in the degree of bladder distention at the time of the scan also contributes to the distortion of gland geometry.

Depending on the type of correction applied, software fusion can be rigid or non-rigid (elastic). Rigid fusion used with RVS and Virtual Navigator is a shape-preserving transformation model and compensates for only the differences in the rotational and translational orientation of the gland between the ultrasound and MRI volumes. On the other hand, the technologically superior non-rigid fusion used with Artemis and Urostation can correct for the differences in the geometry of the gland between the two techniques.

Step 4. Probe tracking, biopsy route, and technique

To enable real-time navigation and identification of the lesion in the USG images, probe tracking is performed (Fig 5d). UroNav, Virtual Navigator, and RVS use a small electromagnetic generator (a box 1 ft wide, generating 0.1 T) positioned above the pelvis of the patient and a sensor attached to the probe. This sensor can identify any change in the probe position relative to the generator and thereby the prostate gland. Some vendors use angle-sensing position encoders to track the movement of a mechanised arm (Artemis) or stepper (BiopSee, BioJet). Urostation, on the other hand, uses entirely software-based elastic registration between the initially acquired volumetric TRUS image and the real-time USG imaging used at the time of the biopsy. This can compensate for potential errors resulting from patient motion during the procedure.[51]

In most devices, both transrectal and transperineal approaches can be used. A standard 26 cm, 18 G coaxial biopsy gun is used to obtain the cores (Fig 5e and f). In addition to the routine systematic biopsy, at least two spatially distributed cores are sampled from the target area. Targeted cores may miss up to 23% of the clinically significant prostate cancer detected by systematic biopsies. Hence, it is not advisable to defer concurrent systematic biopsy until sufficient expertise, accuracy, and supporting evidence has been obtained with targeted biopsies in the individual practice.[45] There is also a conflict regarding the optimal number of targeted cores to be obtained. Kenigsberg *et al.* observed that the first two targeted cores detected almost 90% first clinically significant cancer; however, the remaining 10% benefited from additional cores.[52] The AUA-SAR consensus statement recommends at least two targeted cores. Additional cores may be considered based on the lesion size and location, operator preferences, and confidence in accurate targeting.[45] After sampling, the biopsy tracks can be recorded and later used to guide focal therapy (Fig 5G). The targeted and systematic biopsy cores must be labelled separately before being dispatched for histopathological analysis.

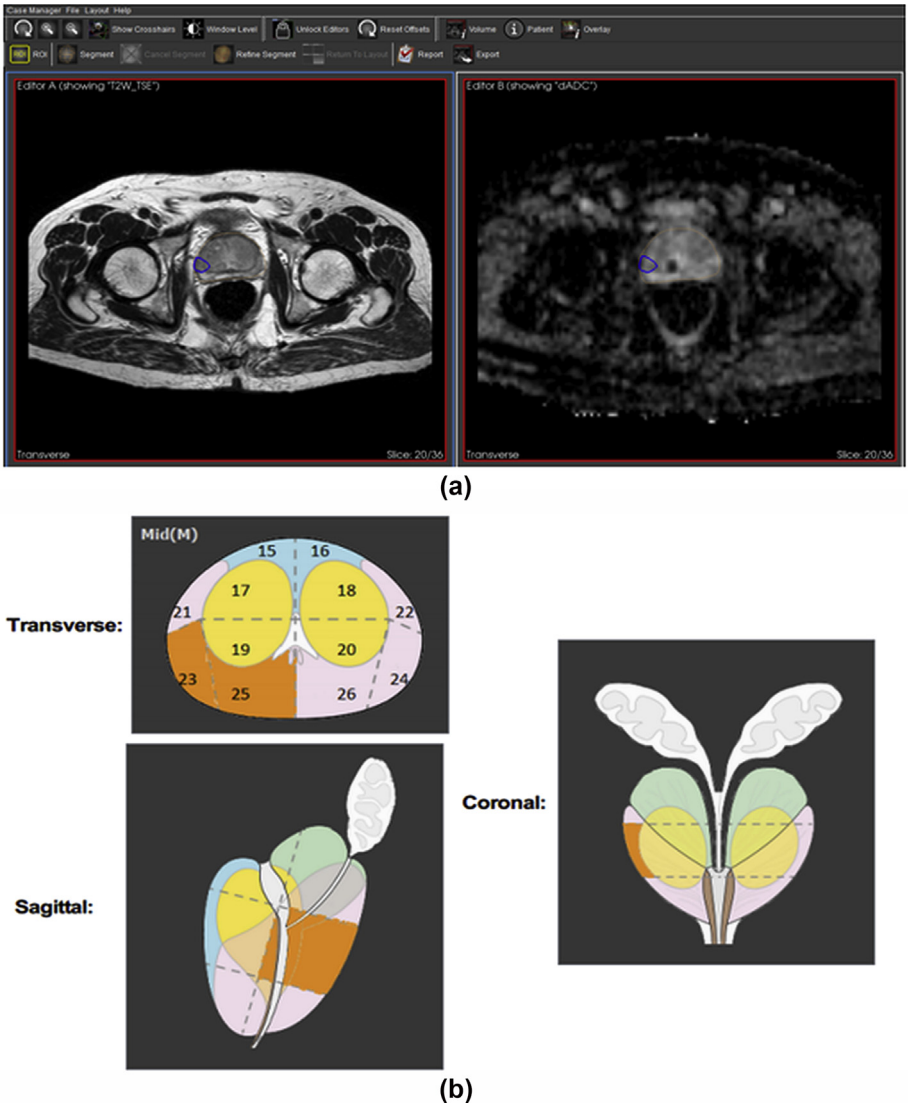

Figure 4 Multiparametric prostate MRI of a 62-year-old patient who presented with lower urinary tract symptoms. The serum PSA level was 14 ng/ml. (a) The T2-weighted (left panel) and ADC map (right panel) images of the patient are displayed on the graphical user interface (GUI) of the ProFuse software (Eigen, USA). The prostate gland (yellow outline) and the suspicious area (blue outline) have been segmented. (b) The software provides an option for labelling the suspicious area on the PI-RADS v2 prostate sector map.

MRI–TRUS fusion biopsies involve high cost and capital investment apart from the steep learning curve required for the operators. Increase in the experience of the operator has been shown to improve the detection rate for prostate cancer.[53–55] Fusion biopsy demands meticulous attention to detail at the time of image interpretation and fusion as targeting is entirely dependent on accurate registration of the suspicious area on the real-time USG images. Any error in the four key steps takes away the advantage of using fusion biopsy.

Direct (in-gantry or in-bore) MRI-guided biopsy

In the direct technique, biopsy is done while the patient is lying prone within the gantry and the operator directly visualises the positioning of the needle in steps. This enables the assessment of the final position of the needle within the target and verification of the accuracy of the targeted biopsy. The most common platform used for in-bore biopsy is DynaTRIM (Invivo), which is compatible with all MRI systems (all vendors, both 1.5 and 3 T). The biopsy system consists of a baseplate, which rests on the MRI table and supports a clamp stand to which a needle sleeve is attached (Fig 6A). The needle sleeve acts as the fiducial for targeting biopsy as well as the guide for advancing the needle.

The procedure is performed through the transrectal route with the patient in the prone position. First, the previously acquired mp-MRI images are analysed and the suspicious lesion is identified (Fig 6b and c). Then after a digital rectal examination, the needle sleeve is introduced into the rectum. Multiplanar T2-weighted fast spin-echo MRI images are acquired to locate the position of the needle sleeve within the rectum (Fig 6d), determine its relation

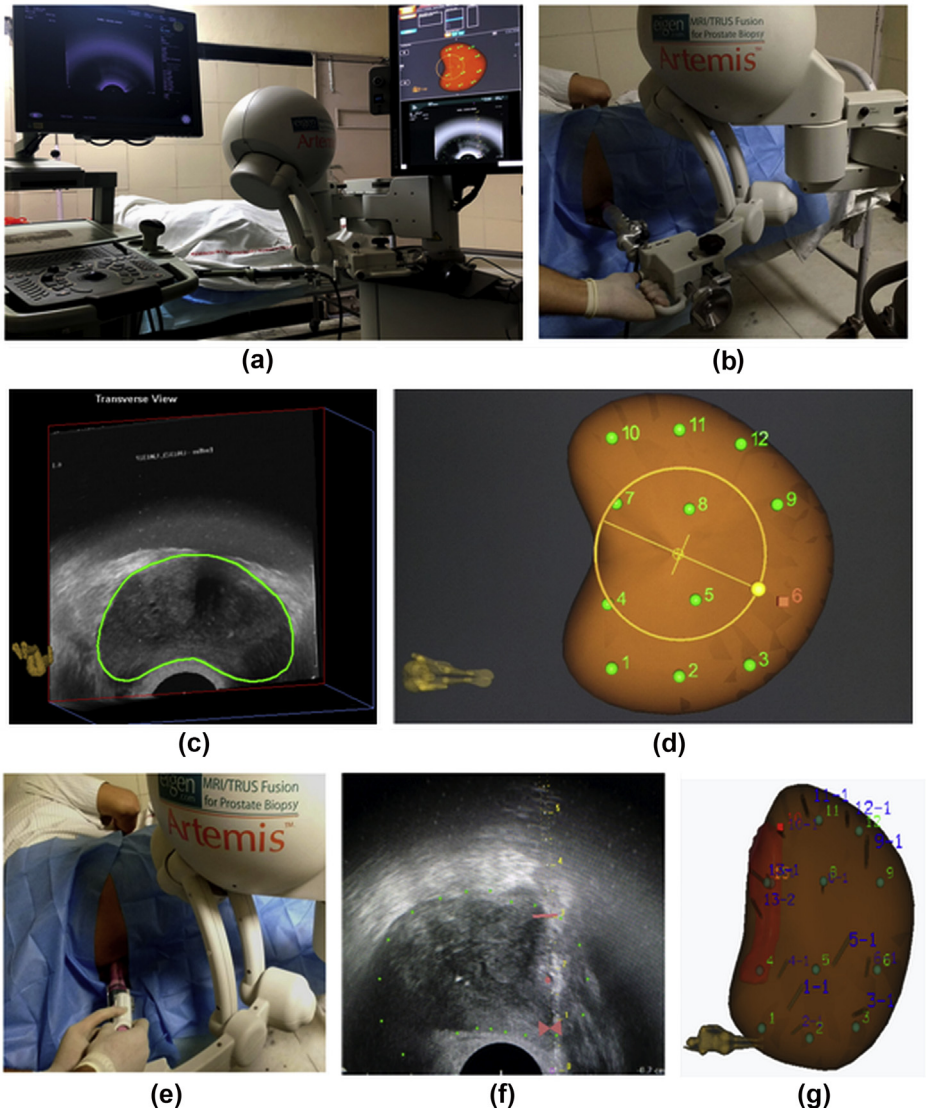

Figure 5 (a) The Artemis MRI–TRUS fusion biopsy system (Eigen, USA). (b) The TRUS probe is fixed to the articulated arm of the device and the 2D USG images are acquired with a mechanically stabilised motion of the probe. (c) The 3D prostate volume is generated semi-automatically after the gland is outlined. (d) With the help of navigation, the articulated arm and the probe attached to it are moved towards the indented segment/target area for the purpose of sampling. (e) Biopsy cores are obtained using an 18 G, 26 cm automatic spring-loaded gun after (f) estimating the depth of penetration for the needle prior to firing (red bow-tie). (g) 3D-surface view of prostate showing all the sites where biopsy was performed.

to the gland and the target lesion. The images are transferred onto the special intervention planning software (DynaCAD) provided by the vendor. The software calculates the coordinates of the target lesion using the needle sleeve as the fiducial.

The position of the needle sleeve can be adjusted using the knobs provided on the stand, which enables the sleeve to be moved longitudinally in the craniocaudal direction or in an arc along the anteroposterior and left-to-right directions. Once the position is verified, the needle is introduced and biopsy is performed (Fig 6e). Check images may be obtained at the time of the biopsy to ensure correct sampling. Typically only a few targeted cores are taken and no systematic biopsy is obtained with the in-bore approach.

In-bore MRI-guided biopsies accurately sample the target and enable precise documentation of the biopsy site. They detect 81–93% of the clinically significant cancers and on account of precise targeting, require a lesser number of cores than systematic biopsies.[56] As in-gantry biopsies involve the same technique in visualising and targeting the tumour, they are free from the errors of misregistration which occur with fusion biopsies; however, no studies have found a significant difference in the detection of clinically significant prostate cancer when the in-bore technique was compared head-to-head with MRI–TRUS fusion biopsy.[57–59]

Despite the advantage of precision targeting, in-bore biopsies are not free from operator-induced errors in interpretation and targeting. In-bore biopsies are

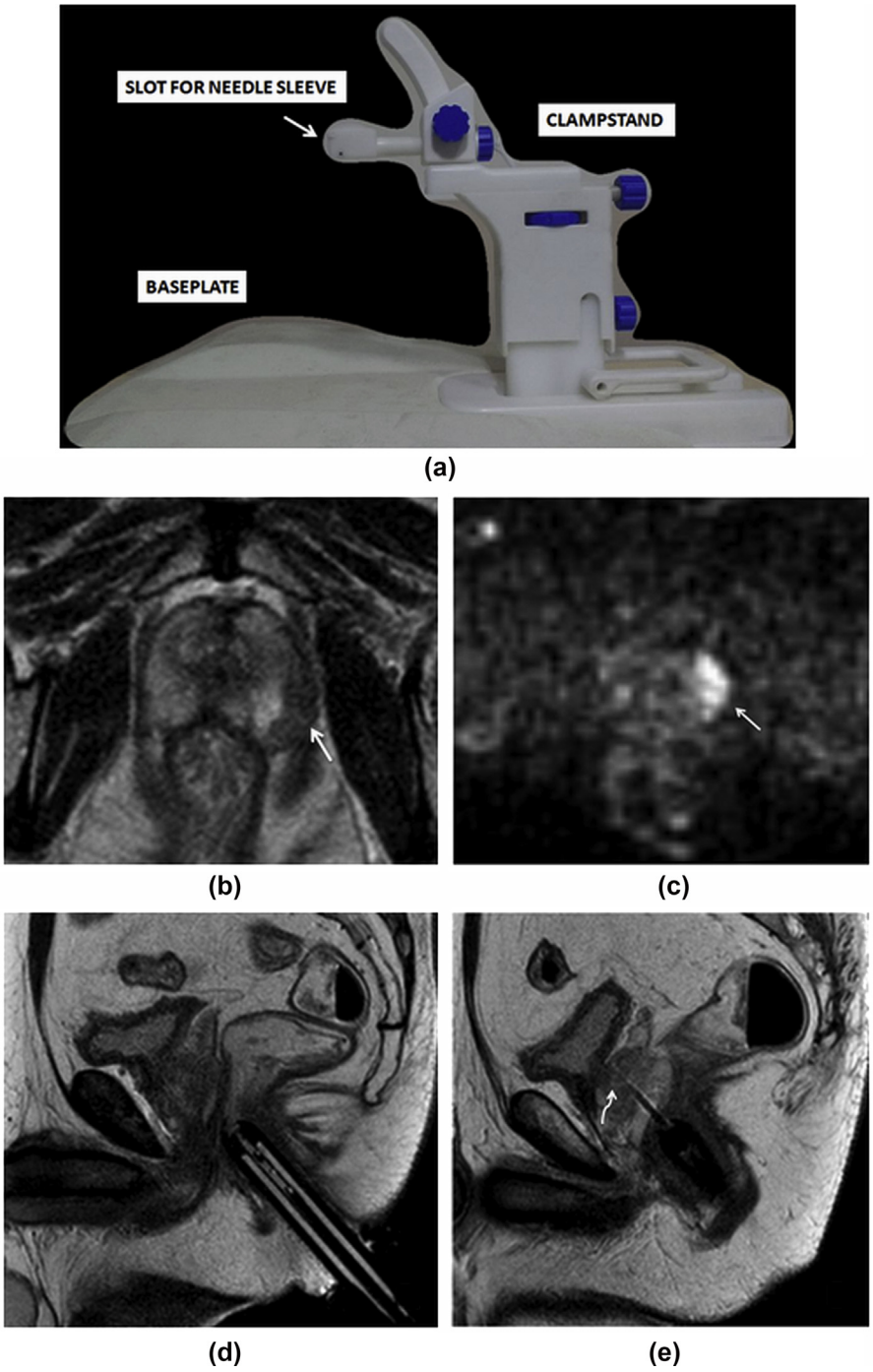

Figure 6 (a) The DynaTRIM in-bore prostate biopsy device. (b) Axial T2-weighted and (c) DWI images of a 75-year-old patient who presented with a PSA of 17 ng/ml and had a negative TRUS-guided biopsy. A PIRADS 5 lesion (T2 hypointense, intense diffusion restriction) is seen in the left lateral mid-gland (arrows). (d) The gadolinium-filled needle sleeve is positioned in the rectum. (e) The needle tip (curved arrow) is directed towards the lesion before biopsy is performed.

uncomfortable for the patient, who needs to be positioned prone for the entire length of the procedure. The procedure demands significance experience from the side of the operator, who is required to interpret and orient himself to the MRI anatomy, pathology, and at the same time work within the tight space of the MRI suite. In addition, the procedure is expensive and time-consuming. This takes away valuable gantry time, which can be used for routine diagnostic services.

Most recently, an MR Safe Robot (MrBot) has been FDA-approved for robotic-assisted MRI-targeted biopsy.[60] This has been mainly used for research purposes and is available for both transrectal and transperineal approaches. In this system, the needle is steered remotely from outside the

gantry room. The lack of operator interference within the MRI suite reduces the procedure time and increases accuracy; however, the challenges include safety, ergonomics, and compatibility with the many different scanner types available.[61]

Summary

Even in the present era, TRUS-guided biopsy is the investigation of choice for detection and localisation of prostate cancer in most centres because of its relative simplicity, ergonomics, and cost-effectiveness of the procedure; however, TRUS-guided biopsy is limited by the unacceptably low detection of clinically significant cancer, which remains an important challenge. The advent of mp-MRI and its clear advantage in delineating small prostate cancers have reduced the number of patients requiring biopsy. MRI-guided biopsies (cognitive, MRI–TRUS fusion and in-bore techniques) provide a high detection rate for clinically significant cancer and increase the percentage of positive cores. In future, with increase in operator expertise and reduced costs, more widespread use of MRI-guided biopsies in general is expected. With several new studies and guidelines supporting upfront use of mp-MRI and MRI-guided biopsies in biopsy-naive men, these biopsies may ultimately replace TRUS as the technique-of-choice for the diagnosis and sampling of prostate cancers; however, several issues still remain unresolved including the most optimal technique of MRI-guided biopsy, approach (transperineal versus transrectal), number of biopsy cores, and the need for additional systematic biopsy (with fusion biopsies). As increasing evidence becomes available, many of these issues are expected to be resolved in the near uture.

Conflict of interest

The authors declare no conflict of interest.

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