NICE advice

Paige Prostate for prostate cancer

Medtech innovation briefing
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Summary

- The **technology** described in this briefing is Paige Prostate. It is an artificial intelligence-based imaging system designed to help identify and diagnose cancer in prostate biopsies.
- The **innovative aspects** are the multiple instance learning algorithm which reports to improve accurate and timely prostate cancer detection.
- The intended **place in therapy** would be in addition to standard care, supporting the detection of prostate cancer from biopsies. It can be used in laboratories that have partial or fully digital operations.
- The **main points from the evidence** summarised in this briefing are from 5 published observational studies including a total of 3,444 biopsy slides reviewed in a pathology lab. They show that Paige Prostate may be an effective addition to standard care to increase sensitivity in detecting prostate cancer and may also help provide more efficient analysis to increase throughput and support high caseload demand in the field.

- **Key uncertainties** around the evidence are that the available studies are mainly retrospective and only 2 reported on statistical significance of using Paige Prostate compared with standard care alone. None of the studies are UK based.
- **Experts** were positive about the potential to improve both detection and efficiencies in the pathway but highlighted the current lack of prospective data showing the system benefit and cost savings in the UK. Experts highlighted the importance of training for pathologists, particularly in understanding the limitations of the technology.
- The **cost** of Paige Prostate is based on a software as a service product on a subscription basis which would depend on the laboratory's volume of biopsies but would typically start at £1 per slide. An initial one-off fee is needed for integrating into the laboratory information management system. This varies depending on the level and type of integration and typically starts at £15,000.
- The **resource impact** may be greater than standard care, needing additional investment initially however further evidence is needed to quantify the real-world cost savings and system impact of Paige Prostate.

The technology

Paige Prostate (Paige AI) is an artificial intelligence (AI)-based software system for the assessment of prostate cancer. The system is based on a deep implementation of multiple instance learning as described in Campanella et al, 2019 and is designed to detect prostate cancer from digital whole slide images of hematoxylin and eosin-stained prostate core-needle biopsies. The system was trained on digital archived data from Memorial Sloan Kettering Cancer Centre in the US (2013 to 2017) including mostly consecutive cases to represent the natural prevalence of prostate cases for diagnosis at the centre.

The AI system involves presenting results to pathologists using proprietary design features. This supports pathologists in identifying and diagnosing tumours by marking areas of suspicion, automatically grading according to Gleason scoring and measuring. Paige Prostate is used alongside a diagnostic whole slide image viewer for reviewing digital images of histopathology slides for primary diagnosis where the AI outputs are displayed to pathologists. Storage and archiving services including cloud-based GDPR-compliant platforms are optional, as requested and needed per institution. The company claim that it can increase the number of cases that can be reviewed at the same time, with greater confidence and accuracy.

Innovations

Paige Prostate is a deep learning system that is a type of machine learning software. It has learned directly from thousands of slides using clinical diagnostic reports, without the need for per-pixel annotation by using multiple instance learning. This approach has the potential to improve the accuracy and speed of detecting prostate cancer. While alternative artificial intelligence (AI)-based systems exist, the company claim that the Paige Prostate algorithm has been developed to be highly robust to variations in slide preparation from different institutions and does not need a per-site calibration using per-pixel annotations or other forms of calibration data. With Paige's FullFocus viewer pathologists can view the biopsy tissue and simultaneously access Paige Prostate results for AI-assisted diagnostic reporting.

Current care pathway

People with suspected prostate cancer are usually seen within the primary care setting and offered a blood test that looks for raised prostate specific antigen levels. If these are raised, NICE's guideline on prostate cancer recommends offering multiparametric MRI (mpMRI) as the first line investigation. Results should be reported using a radiological scoring system such as the Prostate Imaging Reporting and Data System (PI-RADS) or the 5-point Likert scale. Within the secondary care setting, urologists will consider if a biopsy is appropriate depending on the results of the mpMRI. People whose mpMRI score is 1 or 2 may opt out or opt in for a systematic prostate biopsy after discussing the risk-benefit ratio of the procedure with a healthcare professional. Individuals with a score of 3 or more should be offered a prostate biopsy.

There are several ways biopsies can be done, which include transrectal ultrasound-guided biopsy and transperineal template biopsies. The transrectal biopsy is usually done using local anaesthetic and takes 5 to 10 minutes. A needle is inserted through the wall of the back passage to obtain 10 to 12 small pieces of tissue from different areas of the prostate. The transperineal biopsy is done under local or general anaesthetic and the approach is through the skin of the perineum. The samples are then processed and stained, before its morphology is studied under a microscope by a histopathologist. Biopsy review might include conventional microscopy (using a standard microscope) and digital pathology (a computer-based viewing of the whole slide digital image of a glass slide), and experts advise it is becoming more common these methods are used in parallel. The tissue may be examined using a digital system and computer monitor instead of a standard microscope. If cancer is detected, it is graded according to the Gleason grading system (and the Grade

Group category) and additional quantitative information, such as the numbers of biopsy cores with cancer and the maximum length of the cancer (in mm), is normally provided as part of the report, to further inform the management. Cases may be processed with one viewing, but in some instance other opinions from colleagues may be warranted as well as further staining (immunohistochemistry) or deeper sections may be requested. Cases may also be reviewed at cancer centres as part of multidisciplinary team meetings to guide disease management decisions such as active surveillance or radical treatment.

The NHS rapid diagnostic and research pathways handbook for implementing a timed prostate cancer diagnostic pathway set out that, if appropriate, a prostate biopsy should be done within 9 days from GP referral and a target of 5 days turnaround for reported pathology should be agreed as a minimum standard. This is a 14-day turnaround from GP referral to prostate biopsy result. Many services adhere to the The Royal College of Pathology (RCP) key assurance indicators for laboratories. According to Prostate Cancer UK, the diagnostic pathway can take up to 28 days before a definitive diagnosis is made. There is an acknowledged capacity challenge in the area with an increasing complexity and volume of pathology requests but with a lack of pathologists (RCP workforce census, 2018).

The following publications have been identified as relevant to this care pathway:

- NICE's guideline on prostate cancer: diagnosis and management
- NICE's guideline on suspected cancer: recognition and referral
- NHS England's handbook on implementing a timed prostate cancer diagnostic pathway.

Population, setting and intended user

Paige Prostate is intended to be used in addition to current methods of assessing, detecting and characterising prostate cancer. There are reportedly over 40,000 new cases of prostate cancer a year in the UK (NPCA, 2017). If a person has signs and symptoms which suggest prostate cancer, a referral is made to a urology specialist. Diagnosing prostate cancer begins in a secondary care setting using biopsies. Paige Prostate is for use in cellular pathology departments by the pathologists to assist in the analysis of biopsies for the detection and characterisation of prostate cancer.

The company provide initial in person or remote training on Paige Prostate to all users as part of the standard subscription fees, which usually takes less than half a day to do. Additional advanced application or specific feature training can be provided upon request. Training materials including tutorial videos are also provided.

Costs

Technology costs

The company state that the final cost per case pricing model for Paige Prostate is in development and will include the acquisition or purchase of the software as a service (SaaS) product on a subscription basis. Prices typically start at £1 per slide but can increase depending on the laboratory's volume of prostate biopsies; the number of biopsies per slide; the number of slides per case; and usage of cloud storage and archiving services. This fee includes both detection and grading and quantification modalities with all outputs displayed within the CE-IVD Paige FullFocus clinical viewer. No hardware purchase or installation is needed for a cloud-based system. There are one-time fees associated with integrating Paige Prostate into the laboratory information management system which allows for an optimised, integrated workflow and automatic analysis of prostate cases. This cost depends on the level and type of integration and the laboratory information management system provider with the fee typically starting at £15,000.

Costs of standard care

According to the national schedule of NHS reference cost 2018/2019 a transrectal ultrasound-guided biopsy of prostate (LB76Z) costs £686 and a transperineal template biopsy of prostate (LB77Z) costs £1,582. The primary costs include the pathologist's time to report the biopsies and using ancillary tests. This may include laboratory preparation of further sections and using ancillary tests (immunohistochemistry) and associated pathologists' time to review these additional sections and stains and for further opinions. Using ancillary tests vary across laboratories and pathologists.

Resource consequences

Following on from being awarded Artificial Intelligence in Health and Care Award, the technology is understood to be in the process of being deployed for prospective clinical

use at 3 NHS trusts.

Paige Prostate can be used by cellular pathology laboratories that have partial or fully digital operations. Those with partial digital operations might need a clinical grade scanner to use this technology, depending on what types of digital pathology slide scanner(s) are already available. The NHS long term plan identified digital transformation as a priority area across the NHS. The number of laboratories with digital pathology within the NHS is increasing through several different initiatives, such as the AI Centres of Excellence and Upscaling AI centres programme including the work of the PathLAKE and PathLake Plus consortium. The benefits of digital pathology in enabling remote analysis and supporting high demand have been seen during the Covid-19 pandemic and the Royal College of Pathologists provided guidance for the remote reporting of digital pathology slides during exceptional service pressure. Digital pathology offers greater potential for collaborative work and learning as well as health and safety benefits with no physical movement of slides, avoiding potential for damage or infection transmission. The work process does involve an additional task of glass slide scanning into the workflow.

Adopting the technology is likely to cost more than standard care, but the company claim it has greater benefits which may lead to releasing resources and producing cost savings overall. Cost savings may be produced because of improved productivity, where there is published evidence to support these claims, as well as improved patient outcomes, eliminating the costs of unnecessary treatment or progression of a disease and its related costs. There are no published studies on prospective use of this technology to improve patient outcomes or optimise treatment. The investment in scanning infrastructure may affect multiple other workflow improvements and AI applications across all areas of cancer and non-cancer diagnostics in the NHS.

Regulatory information

Paige Prostate and FullFocus whole slide image Viewer are classified as General in vitro diagnostic devices in the US, UK and EU. Both are currently registered with the USFDA as Class II IVD devices and the Dutch authority as General IVDs (self-certified). Paige has an active project in place to transition to IVDR (2017/746), where both FullFocus and Paige Prostate will be classified as Class C devices. Paige Prostate has recently been granted market authorisation from the USFDA (September 2021).

Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Paige Prostate is intended for people that are being screened for prostate cancer by prostate needle core biopsy. Older people and people with an African-Caribbean and African family background are at higher risk of developing prostate cancer. Some people may not identify as men but have a prostate. Disability, age, race and gender reassignment are protected characteristics under the Equality Act (2010).

Paige reports they have unpublished data that examined performance across ethnicities and concluded no performance differences.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the interim process and methods statement. This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

Published evidence

In total, 5 observational studies are summarised in this briefing including a total of 2,844 slides for analysis. These include 3 full text articles and 2 abstracts. One abstract (Kannan et al. 2020) reports on work later published in full text (Da Silva et al. 2021). The clinical evidence and its strengths and limitations is summarised in the overall assessment of the evidence.

Overall assessment of the evidence

The evidence base for the technology is of low to moderate methodological quality. None of the studies are based in the UK and performance may vary across different populations. The studies reported on suggest that the device may increase diagnostic performance

and productivity to current standard care. However further evidence would benefit from sufficiently powered sample sizes across multiple pathology lab assessments within the UK system to show statistically significant clinical benefit compared with standard care.

Da Silva et al. (2021)

Study size, design and location

Diagnostic accuracy study of 600 previously diagnosed unique transrectal ultrasound-guided prostate biopsies in 100 consecutive people in Brazil.

Intervention and comparator(s)

Paige Prostate 1.0

Key outcomes

Aimed to assess the true diagnostic performance of the AI system in whole slide images and TRUS prostate biopsies, assessing sensitivity, specificity, positive predictive values and negative predictive values (NPV) Paige Prostate displayed a favourable sensitivity (0.99; confidence interval (CI) 0.96 to 1.0) and NPV (1.0; CI 0.98 to 1.0) and specificity (0.93; CI 0.90 to 0.96). at the part-specimen level. At the patient level, it produced optimal sensitivity of (1.0; CI 0.93 to 1.0) and NPV (1.0; CI 0.91 to 1.0) at a specificity of 0.78 (CI 0.64 to 0.89). Paige Prostate results were generated for 661 whole slide images from 579 prostate needle core biopsy parts. Of the 682 slides initially assessed, 5 were excluded because they could not be retrieved, and 41 discordant part-specimen results were seen which upon re review with IHC were reduced to 29 discordant results. Using Paige Prostate resulted in identifying 4 additional patients whose diagnoses were changed from benign to malignant. The study collected the median time spent per glass slide and calculated that where only whole slide images from parts classified as suspicious were assessed by the pathologists (200/579), Paige Prostate could result in a 65.5% reduction in the diagnostic time taken for the full 579 whole slide images assessment. Findings conclude that Paige Prostate could accurately identify the parts containing cancer as suspicious, without flagging a disproportionately high number of parts as suspicious.

Strengths and limitations

Eleven out of the 21 study authors are employed by Paige Inc and have equity in the

company. One author is a co-founder and equity holder, and 2 authors are consultants for Paige Inc.

Perincheri et al. (2021)

Study size, design and location

Retrospective analysis of 1876 biopsies from 118 consecutive patients at a single pathology department in the US.

Intervention and comparator(s)

Paige Prostate

Key outcomes

This study investigated 2 uses for Paige Prostate in both its utility as a pre-screening tool to identify negative cores not needing manual review by a pathologist and its utility as a second read tool to identify cancer foci not identified by the pathologist. In this study, the performance of Paige Prostate was reported to be similar to that of pathologists in a highly specialised setting in which prostatic biopsies are typically reviewed by a genitourinary pathologist more than once. Paige Prostate categorised at least 1 core as suspicious of malignancy in 84 of the 86 patients with adenocarcinoma while no cores were identified as suspicious of malignancy in 26 of the 32 without carcinoma or glandular atypia. There was an apparent discrepancy between final diagnosis and Paige Prostate diagnosis in 80 cores, which upon blinded re review reduced to only 21 discordant cores. Issues were reported in 37 slides because of absent tissue or bad scans. From these results the study suggested that using Paige Prostate as a pre-screening tool would reduce the number needed for review by the pathologist to 589 of 1,876 core biopsies, increasing productivity. In the absence of any additional quality review this would also mean that 14 cores with adenocarcinoma would be missed, as well as 6 cores with glandular atypia.

Strengths and limitations

The study was funded by Paige.ai. Two authors are employees and equity holders in Paige. One author serves on the advisor board for Paige and is a founder and equity holder in PixelGear.

Raciti et al. (2020)

Study size, design and location

Retrospective analysis of 304 prostate needle core biopsy whole slide images in the US.

Intervention and comparator(s)

Paige Prostate Alpha

Paige Prostate Alpha has some operational improvements from Paige Prostate 1.0 to computational efficiency, memory management and improved handling of slides in the iSyntax format and slides of abnormal scan resolutions.

Key outcomes

Pathologists assessed 304 anonymised prostate needle core biopsies and repeated the review 4 weeks later using Paige Prostate Alpha (phase 2). In the analysis, the dataset consisted of 232 anonymised whole slide images of hematoxylin and eosin-stained prostate needle core biopsies. With Paige Prostate Alpha, the average sensitivity for pathologists significantly increased to 90% (from 74%) with no statistically significant change in specificity. The aggregate number of whole slide images classified incorrectly (false negative or false positive) by pathologists without Paige Prostate Alpha was 87. In phase 2, 61 of those slides were correctly classified, while 26 remained incorrect. Pathologists were reported to classify smaller, lower grade tumours more often correctly with Paige Prostate Alpha. Pathologists were also reported to be significantly faster (21%) with Paige Prostate Alpha ($p<0.001$) taking an average of 63 (+/-39) seconds per slide, compared with 55 (+/-43) seconds with Paige Prostate Alpha. A survey given to the participating pathologists reported that they would consider digitally reviewing whole slide images for primary diagnosis if such a system included Paige Prostate Alpha.

Strengths and limitations

The study was sufficiently powered which allowed appropriate statistical analysis to be done. The authors reported that the pathologists had similar background experience and further studies with users across the pathology community would inform the general useability. The study did not consider using additional inputs that also inform pathologists, including immunohistochemical stains or consultation. Seven authors are employees and

equity holders at Paige.

Dogdas et al. (2020)

Study size, design and location

Performance of Paige Prostate at identifying treated prostatic tumour on 64 hematoxylin and eosin-stained slides in the US.

Intervention and comparator(s)

Paige Prostate 1.0

Key outcomes

Evaluating the performance of Paige Prostate 1.0 at identifying treated prostatic tumour on 64 hematoxylin and eosin-stained slides. These cases were of neoadjuvant treated prostate tissue from needle core biopsies and radical prostatectomies (post-treatment), as an investigative exercise and is not what the Paige Prostate was designed for. Analysis of the receiver operating characteristic curve showed an area under the curve of 0.96. Using the Paige Prostate 1.0 operating point, it achieved a sensitivity of 91% and a specificity of 94%, corresponding to correctly identifying challenging treated morphology in 59 of 64 slides using expert pathologists as the reference. False negative cases were typically represented by atypical small acinar proliferation that needed expert pathological consensus confirmation. This showed tumour identification despite treatment effects and proposes it as a complementary pathological assessment.

Strengths and limitations

Limited in detail because it is an abstract.

Kanan et al. (2020)

Study size, design and location

Retrospective analysis of 600 digitised hemotoxylin-and-eosin (H&E) stained diagnostic prostate core needle biopsy slides from 100 consecutive patients in the US.

Intervention and comparator(s)

Paige Prostate 1.0

Key outcomes

Evaluating the impact of Paige Prostate on biopsy review, 2 pathologists reviewed the 600 hematoxylin and eosin-stained slides. Paige Prostate's slide-level sensitivity was 98.9% and its specificity was 93.3% (100% and 78.0% at patient level). The pathologists' average slide-level sensitivity and specificity without Paige Prostate was 90.9% and 98.6%, respectively. The sensitivity with their consensus read and Paige Prostate increased by 5.7% to 96.6% with 0.8% decrease in specificity. Three new prostate cancer cases were discovered with Paige Prostate that were initially missed.

Strengths and limitations

Limited detail report in abstract format.

Sustainability

The company provided no details about sustainability.

Recent and ongoing studies

Oxford University and regional NHS partners have won the Phase 4 Artificial Intelligence in Health and Care award from the Accelerated Access Collaborative to study Paige Prostate prospectively in a real-world cancer laboratory setting.

Expert comments

Comments on this technology were invited from clinical experts working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

Two experts were familiar with the technology and had both used it in a study. Two experts had not used this specific technology before.

Level of innovation

All experts agreed that Paige Prostate is novel and is proposed as an addition to standard care. One expert highlighted that although the technology is not widely used in the NHS, this is reflective of the position of all AI technology for histopathology and cellular pathology.

Using AI to help histopathologists was highlighted in the UK Government Life Sciences Strategy and by implication in the NHS Long Term Plan as part of digitally enabled care. The aim is to help solve some of the workforce and other resource challenges. Experts acknowledged that there are other systems available in this area. One expert highlighted this technology to be the first AI product in digital pathology to receive FDA approval (see Regulatory information).

Potential patient impact

All experts reported that the system has the potential to reduce missed cancers or areas suspicious of cancer valuable for all patients. All experts also highlighted the potential to increase the efficiencies in the care pathway and as a result the speed of turnaround for patients. One expert highlighted it could reduce staff time, although there would likely be a learning curve before this was seen. One expert highlighted that there is inherent subjectivity to assessment of Gleason scoring by human observers and Paige Prostate has the potential to standardise assessments such as objective grading of the cancer. Two experts reported the technology would benefit all who have a prostate biopsy regardless of the diagnosis.

Potential system impact

Experts identified the complexities in the cost implications for the current care pathway. The balance of cost savings because of greater efficiencies in pathologists time against the cost of the technology is difficult to say. Two experts highlighted a barrier to widespread adoption in the IT infrastructure needed for the deployment in laboratories. One expert reported the deployment of digital pathology to be gaining traction through different initiatives and funding routes including groups of trusts completing successful business cases and the AI centres of excellence programme to allow such technologies across the field.

All experts also highlighted the need for pathologists training on using Paige Prostate and functionality, in particular limitations to make sure it is used correctly. One expert highlighted that those conveying the results to patients (urologists, oncologists, and specialist nurses) may also need brief training in the technology to support patient understanding around the decision making for their diagnosis and management.

General comments

One expert highlighted the studies reported are retrospective and prospective use and audits would be important to inform how valuable the technology could be in practice. One expert highlighted the theoretical possibility that AI may change pathologist reporting profiles influencing diagnostic patterns. This may involve flagging more suspicious areas as atypical small acinar proliferation, leading to more patients being followed up than discharged. However, the rate of atypical small acinar proliferation may be reduced by more diagnostic certainty afforded by AI, allowing more to be definitively categorised as benign or malignant. While these are mitigated by the pathologist having ultimate oversight of the technology the expert highlighted the importance of pathologists training and for professionals to consider and monitor the impact of AI on their reporting patterns.

Expert commentators

The following clinicians contributed to this briefing:

- Dr Uttara Karnik, consultant cellular pathologist, Royal Wolverhampton NHS Trust. No declarations of interests were declared.
- Dr Jon Oxley, consultant in cellular pathology, North Bristol NHS Trust. No declarations of interests were declared.
- Professor Clare Verrill, associate professor and honorary consultant in cellular pathology, University of Oxford and Oxford University Hospitals NHS Foundation Trust. No financial interests were declared. Reports that industry investment (digital pathology equipment and software) have been made within PathLAKE by the industry partner (Philips). Has published academic papers on AI software (not including Paige Prostate) and is the principal investigator of the current AAC funded phase 4 study evaluating Paige Prostate.

- Dr Anne Warren, consultant histopathologist, Cambridge University Hospitals NHS Foundation Trust and Associate Lecturer University of Cambridge. No declarations of interests were declared.

Development of this briefing

This briefing was developed by NICE. The interim process and methods statement sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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