NICE advice

Prolaris gene expression assay for assessing long-term risk of prostate cancer progression

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Summary

The Prolaris test is a multi-gene assay designed to predict the aggressiveness (growth and spread) of prostate cancer. Most of the relevant evidence is on clinical validity, and evidence for the prognostic value of Prolaris is based only on the retrospective analyses of archived material. No studies examined the prospective use of Prolaris on patient outcomes. Two studies examined whether Prolaris results affected clinicians' treatment decisions. In 1 study, 65% of clinicians changed their treatment recommendation based on Prolaris results. In the second study results caused a change in treatment in 47.8% of patients. Limited economic evidence was identified. The list price for Prolaris is £1,800, excluding VAT.

Product summary and likely place in therapy	Effectiveness and safety
• Prolaris is an in vitro diagnostic test that measures gene expression levels to generate a Prolaris score, a measure of the aggressiveness (growth and spread) of prostate cancer. The Prolaris score is combined with patient and tumour information to generate either the 10-year prostate cancer-specific mortality risk (from biopsy samples) or the 10-year risk of biochemical recurrence (from prostatectomy specimens), which may indicate the need for further treatment. • The Prolaris score would be used in addition to existing risk stratification information and is likely to be used in place of available nomograms, where these are used.	• The published evidence summarised in this briefing comes from 9 studies including 4,548 patients. No studies examined the prospective use of Prolaris on clinical outcomes. • Two retrospective UK-based studies (n=747 and n=349) demonstrated that the Prolaris score was associated with biochemical recurrence or cancer-related mortality. Another retrospective UK study (n=761) found the Prolaris score predicted the 10-year risk of cancer-related mortality, both independently and in combination with standard clinical variables. • One retrospective study (n=582) with 3 cohorts (2 in the US and 1 in Germany) found that the Prolaris score was a statistically significant predictor of biochemical recurrence. • Another retrospective study (n=141) based in the US found that the Prolaris score was a statistically significant predictor of biochemical recurrence and mortality.

	• Two studies (n=331 and n=1,206) examined the effect of the Prolaris score on clinicians' treatment decisions. The studies found that clinicians would change their treatment plan based on the Prolaris test results in at least 47% of cases. • One study (n=413) validated the Prolaris score against the cancer of the prostate risk assessment post-surgical score that is used to predict biochemical recurrence and cancer-related mortality. The study found that the scores were weakly but significantly correlated (r=0.21, p<0.001). • One analytical validation study (n=18 samples) examined the reproducibility and precision of the Prolaris gene signature, the quantity and stability of extracted RNA and the linear and dynamic range of the Prolaris score. The study found that the score is reproducible and robust.

Technical and patient factors	Cost and resource use
• The Prolaris test measures the expression profiles of 31 cell cycle progression genes in prostate biopsy samples. • The patient's 10-year prostate cancer-specific mortality risk and 10-year biochemical recurrence risk is estimated based on the addition of the Prolaris score to other scores which combine prostate-specific antigen levels, Gleason score and other tumour characteristics. • The tissue samples must be prepared by a hospital pathology department using detailed standard operating procedures before being sent to a Myriad Genetics laboratory in Germany for logging and processing. The total turnaround time, from the date the sample is shipped to the laboratory until the report is sent back to the referring clinician (via secure email), is 14 days.	• Each Prolaris test costs £1,800, excluding VAT. • Two economic studies showed that the use of Prolaris reduced costs per patient in a hypothetical US-based cohort and was cost effective in a study based in France.

Introduction

Prostate cancer is diagnosed through a range of tests. These include measuring serum prostate-specific antigen (PSA) levels, digital rectal examination, rectal ultrasound, imaging tests such as MRI or CT scans and prostate biopsy. Biopsy specimens are scored based on the appearance of the prostate cells under a microscope. This is a form of tumour grading which gives an indication of the abnormality of the prostate cells. The most common system used is the Gleason score. This is used to help predict disease outcome; cancers with higher Gleason scores are more aggressive and are associated with worse prognoses. Tumours are also staged to determine how far the cancer has spread, most commonly using the TNM (tumour, node, metastasis) system.

Based on the results of these tests, people with prostate cancer are categorised into 1 of 3 risk groups (often called D'Amico risk classification). The criteria for the different risk

groups are outlined in NICE's guideline on prostate cancer: diagnosis and treatment, and the classification is used to help guide treatment decisions. The groups are as follows:

- Low risk: PSA score of less than 10 ng/ml, and small size tumour confined within the prostate (T1–T2a), and biopsy result showing a Gleason score of less than 6.
- Intermediate risk: PSA score of 10–20 ng/ml, or tumour confined to the prostate involving more than 50% of 1 lobe (T2b), or biopsy results showing a Gleason score of 7.
- High risk: PSA score of more than 20 ng/ml, or tumour confined to the prostate involving both lobes (T2c and above), or biopsy results showing a Gleason score of 8–10.

Clinicians can also use nomograms (mathematical models) to help make decisions about treatment. A nomogram predicts long-term outcomes in people with prostate cancer. Nomograms can use various factors including TNM, PSA level and Gleason score to estimate the risk of the cancer spreading to other parts of the body or recurrence after treatment (surgery or radiotherapy).

Depending on their risk group, people with prostate cancer may be offered the following options:

- Watchful waiting, where no treatment is given, but patients are monitored for signs of change. If symptoms of progressive disease are found, treatment aims to control the cancer rather than cure it.
- Active surveillance, where no treatment is given, but patients are closely monitored for signs of change. If any changes are found, treatment aims to cure the cancer.
- Radical prostatectomy (surgical removal of the prostate) with or without removal of lymph nodes.
- External beam radiotherapy with or without brachytherapy (internal radiotherapy).
- Brachytherapy alone.
- Hormonal therapy.

For many people prostate cancer can be cured with surgery or radiotherapy, but in around 1 in 3 cases the cancer comes back some time after treatment. PSA levels are used to

monitor this. An increase in the levels of PSA is called biochemical recurrence and may indicate that further treatment is needed (Cancer Research UK 2014d).

Despite the routine use of risk classification and nomograms to categorise prostate cancer, these tools have some limitations. These include the lack of patient specificity, which may lead to misclassifications and to over- or under-treatment. A more personalised approach for assigning risk categories to people diagnosed with prostate cancer may improve accuracy and, therefore, appropriateness of treatment.

Technology overview

This briefing describes the regulated use of the technology for the indication specified, in the setting described, and with any other specific equipment referred to. It is the responsibility of healthcare professionals to check the regulatory status of any intended use of the technology in other indications and settings.

About the technology

CE marking

Myriad Genetic Laboratories received CE marking for the specimen collection set for Prolaris on 27 March 2015 and for the entire test (all processes, consumables, equipment and software) on 30 November 2015. In Europe, Prolaris is regulated as an in vitro diagnostic medical device (within the scope of Directive 98/79/EC).

Description

Prolaris is an in vitro diagnostic test which measures gene expression levels in RNA extracted from formalin-fixed, paraffin-embedded (FFPE) prostate tumour samples, taken from needle biopsies or prostatectomy specimens. The test measures the expression levels of 31 cell cycle genes (involved in cell division and duplication) and 15 control or reference genes (those involved in the normal functioning of the cell; Cuzick et al. 2011). From this information, it generates a Prolaris score (also known as the cell cycle progression or CCP score), which is designed to predict either the patient's 10-year risk of mortality using prostate biopsy samples or the 10-year risk of biochemical recurrence using prostatectomy specimens.

FFPE samples (either blocks or slides) are prepared in the local hospital laboratory using the Prolaris specimen collection kit and are sent to the Myriad Genetics laboratory in Germany for processing. Each collection kit is intended for the shipment of specimen(s) for 1 patient only. A Prolaris test request form with the patient's clinical and tumour pathology information must be sent to the laboratory with the sample. One or more samples can be sent per patient. Where multiple samples are sent, a pathologist at Myriad will select the most appropriate sample according to a predefined process. The total turnaround time for the Prolaris results, from the date the sample is shipped to Myriad's laboratory until the report is sent back to the referring clinician (by secure email), is 14 days.

The company provides comprehensive and detailed instructions for sample preparation including the shipment of haematoxylin and eosin-stained slides to aid sample processing.

Previously, the Prolaris score was reported on a scale of −3 to +7, but this has recently been changed to a scale from 0 to 10. In both systems, a higher score indicates a more aggressive cancer and each 1-unit increase in the score represents a doubling in risk.

The Prolaris test report includes both the Prolaris score and a D'Amico risk analysis, which shows how the patient's score compares to that of patients within the same D'Amico risk category (low or intermediate; the test is not intended for high-risk prostate cancer). This allows differentiation between patients with the same D'Amico risk profiles and, consequently, refinement of level of risk.

According to the new Prolaris scoring system, for patients in the D'Amico low risk category, a Prolaris score below 2.7 indicates that the cancer is less aggressive than the average cancer in this risk category. A Prolaris score above 3.7 indicates a more aggressive cancer. Similarly, for the D'Amico intermediate risk category, Prolaris scores below 3.0 and above 4.0 indicate that the cancer is less aggressive and more aggressive respectively than the average cancer in this risk category.

This analysis is based on Prolaris test results from a population in the US, which may limit its generalisability to the UK.

In clinical practice, the Prolaris score is designed to be used in combination with other clinical and pathological information obtained as part of the normal diagnostic pathway. For example:

- The patient's 10-year prostate cancer-specific mortality risk may be estimated based on the combined Prolaris score (from biopsy samples) and CAPRA score (combining the PSA level, Gleason score, patient age, percentage of positive biopsy cores and clinical tumour stage). This mortality risk is also known as the combined clinical-cell-cycle-risk (CCR) score.
- The patient's 10-year biochemical recurrence risk may be estimated based on the combined Prolaris score (from prostatectomy specimens) and CAPRA-S score (combining the PSA level before surgery, Gleason score, patient information and tumour characteristics including lymph node involvement).

Setting and intended use

Prolaris is intended for use in people with low or intermediate-risk localised prostate cancer who have not had hormonal therapy or radiation therapy before biopsy or surgery. Prolaris is not intended for use in people with high-risk prostate cancer.

Prolaris is intended for use in secondary care settings. The test is requested by either oncologists or urologists, who complete a Prolaris test request form and send it to their local pathology department. The samples are prepared by medical laboratory assistants and sent to the Myriad Genetics laboratory in a pre-paid shipping package provided by the manufacturer. No additional specialist training on sample preparation is needed for staff in the pathology department.

The manufacturer recommends that the Prolaris results be used in addition to other clinical and pathological information that is obtained as part of the normal diagnostic pathway.

Current NHS options

NICE's guideline on prostate cancer: diagnosis and treatment recommends the use of PSA testing, Gleason score and tumour stage to predict low, intermediate, or high risk of tumour growth and spread, which is in line with the D'Amico risk classifications. The guideline also states that clinicians can use nomograms as a decision support tool to help predict tumour progression and risk of treatment failure. Although the guideline does not recommend specific nomograms, a number of them are readily accessible online including:

- Memorial Sloan Kettering Cancer Center (MSKCC) calculator (USA; Memorial Sloan Kettering Cancer Center 2016)

- the European prostate risk indicator (SWOP-PRI; Europe; Kranse et al. 2008)
- North American Prostate Cancer Prevention Trial Risk Calculator (PCPT-CRC; USA; Thompson et al. 2006).

These nomograms were validated in different populations and require different types of clinical data.

NICE is aware of the following CE-marked test that appears to fulfil a similar function to Prolaris:

- Oncotype DX Prostate (Genomic Health).

Costs and use of the technology

The list price for Prolaris is £1,800 per test, excluding VAT. Because the samples are processed remotely, each test kit is for 1 patient sample and includes a test request form (including patient, clinical and pathological information), instructions for use, specimen and shipping containers, and pre-paid shipping envelopes. One or more samples can be included per test request. Where multiple samples are sent, a pathologist at Myriad will select the most appropriate sample for testing. There is no increase in costs for this additional step. No charge is made for samples that are not tested (for example, due to insufficient tumour sample or incorrect tumour type). The requesting hospital or clinic will receive an invoice for the test after the Myriad Genetics laboratory has generated a result. No additional equipment needs to be purchased and therefore no maintenance or training is needed.

Online nomograms including those listed above are all free of charge.

Likely place in therapy

Prolaris would be used to help make decisions about treatment for low or intermediate-risk localised prostate cancer in people who are being considered for active surveillance or radical treatment, to estimate the risk of mortality before surgery or the risk of biochemical recurrence after prostatectomy. It would be used in addition to existing risk stratification information.

Specialist commentator comments

In terms of current care pathways for prostate cancer, 1 specialist commentator noted that multiple clinical parameters have been investigated as methods of predicting the risk of prostate cancer. Nomograms have also been developed for this purpose. The commentator observed that nomograms could be used as decision support tools to help predict tumour progression and risk of treatment failure, but they suggested that nomograms have shortcomings despite being effective and available for free. Another commentator agreed that nomograms have limitations that make it difficult to use them to accurately predict the risk of prostate cancer, comorbidity or general life expectancy. The commentator stated that nomograms are rarely used in UK practice. The same commentator noted that in patients with low or intermediate risk prostate cancer, tumours may be missed because of their small size. Problems accessing the tumour may arise in some patients with larger tumours that are in front of, above or very close to the prostate apex. In addition, the commentator highlighted that small tumours can be difficult to grade, leading to a significant number of cancers being staged incorrectly compared with results from histology or biopsy. The specialist commentator noted that current measures to improve the accuracy of grading include functional MRI scans before biopsy, systematic biopsies (where multiple biopsies are taken from different regions of the prostate), template biopsies (where 50 to 60 needle biopsies are taken through a grid template with holes spaced 5 mm apart to thoroughly sample the entire prostate) and targeted biopsies guided by MRI.

All 4 specialist commentators identified potential benefits from using Prolaris. One noted that the test could be used to estimate mortality and inform treatment for low or intermediate-risk localised prostate cancer without requiring changes in the organisation, delivery of current services or additional facilities or technology. The same commentator referred to an economic evaluation conducted in the US, which found that using the CCP (Prolaris) score over 10 years reduced patient costs by approximately £1,938 (Crawford et al. 2015). However, a different commentator cautioned that non-UK cost studies cannot be generalised to the NHS. Another commentator anticipated that Prolaris may be helpful before treatment to reduce anxiety in lower-risk patients who are recommended for active surveillance but might prefer active intervention. A third commentator considered that Prolaris was a promising test in an area where no others are available for routine diagnostic use but noted that more evidence was needed. The fourth specialist commentator stated that the rationale for using Prolaris to differentiate between patients with the same D'Amico risk profile is very good and that the link shown between the Prolaris score, biochemical recurrence and cancer-related mortality is clinically relevant

and indicates that the test has practical use. The commentator added that Prolaris could be a useful addition to daily practice for guiding shared decision-making. The commentator felt it would be useful to gauge what the uptake of Prolaris would be in the UK, suggesting that a questionnaire to urologists may clarify this. The same commentator felt that a treatment decision change of 47.8% (taken from the Shore et al. [2016] study) was impressive, but was unsure how this would transfer to general prostate cancer clinics. The commentator also noted that clinician preference is a large factor in treatment decisions and that an objective test such as Prolaris would help provide standardisation.

In terms of the limitations of the Prolaris test, 2 commentators noted that the test was expensive considering the current financial burden on the NHS, with 1 commentator stating that it would be very challenging to show that Prolaris is cost effective in the NHS. The second commentator noted that the use of Prolaris, involving preparation and shipping, leads to considerable extra work for clinicians. A third commentator agreed that some pathology laboratories may not have the resources for this extra work and, in these cases, additional funding will be needed. One commentator referred to the Cuzick et al. (2012) study and noted that patients with lower grade prostate cancer had CCP scores greater than 2, so the score was not predictive of the outcome in this clinical subgroup. The commentator speculated whether this would place doubt on the utility of Prolaris in a low-risk population for deciding on immediate or deferred treatment.

All 4 specialist commentators mentioned evidence limitations for Prolaris. One commentator suggested that the strength of evidence was low to moderate and would benefit from additional studies. Three commentators highlighted that the retrospective nature of most of the studies limited their value. One commentator suggested the best evidence would be derived from a large-scale prospective randomised UK radiotherapy trial. Another commentator noted that although there were a relatively low number of studies, the overall cohort size across the studies was good. Overlapping cohorts and the lack of power calculations were also noted as potential limitations by 1 commentator.

Two specialist commentators mentioned that new imaging techniques such as multiparametric MRI (MPMRI) have the potential to identify the most aggressive areas of prostate cancer and allow targeted biopsies or template biopsies for molecular determinants of biologic aggressiveness. One of these commentators suggested that with limited funding and the lack of MPMRI facilities in UK hospitals, money may be better spent on this technology rather than Prolaris. The other commentator suggested that other molecular tests are emerging (based on general features of malignancy such as proliferation indices, or on more specific features for prostate cancer), making it a

challenge to predict which would have the best comparative clinical relevance and cost effectiveness. They suggested that head-to-head comparisons across multiple patient cohorts with specifically designed clinically relevant end points should be done.

Equality considerations

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relationships between people with particular characteristics and others. In producing guidance, NICE aims to comply fully with all legal obligations to:

- promote race and disability equality and equality of opportunity between men and women
- eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, marriage and civil partnership, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief (these are protected characteristics under the Equality Act 2010).

Black people of African or Caribbean family origin and people aged over 50 years have a higher risk of prostate cancer (Cancer Research UK 2014b). Gender, race and age are protected characteristics as defined in the Equality Act 2010.

Evidence review

Clinical and technical evidence

Regulatory bodies

A search of the Medicines and Healthcare Products Regulatory Agency website revealed no manufacturer Field Safety Notices or Medical Device Alerts for this device. No reports of adverse events were identified from a search of the US Food and Drug Administration (FDA) database: Manufacturer and User Device Facility Experience (MAUDE).

Clinical evidence

Of the 19 relevant papers identified, 10 were excluded because they were abstracts, based

on intention or examined overlapping populations. Consequently, 9 studies are included in this briefing. Of these, 6 were prognostic value studies, 2 studied clinical utility (the effect of Prolaris results on clinicians' treatment decisions) and 1 was an analytical validation study. In these studies, the Prolaris score is referred to as the cell cycle progression (CCP) score and the previous scoring system is used (scoring range −3 to +7). According to this system, for patients in the D'Amico low risk category, a CCP score below −0.7 indicates that the cancer is less aggressive than the average cancer in this risk category. A CCP score above 0.3 indicates a more aggressive cancer. Similarly, for the D'Amico intermediate risk category, CCP scores below −0.9 and above 0.1 indicate that the cancer is less aggressive and more aggressive respectively than the average cancer in this risk category.

Prognostic value

Bishoff et al. (2014) studied the prognostic utility of CCP scores generated from tissue samples in 582 men who had had radical prostatectomies in 3 patient cohorts (2 in the US and 1 in Germany). The score was derived from a diagnostic or simulated biopsy (taken randomly from a post-operative, FFPE tumour block) that was analysed at Myriad Genetics. Time to biochemical recurrence (BCR) and time to metastasis were measured. Combined analysis of all patients showed that the CCP score was a strong predictor of biochemical recurrence; the hazard ratio was 1.60 (95% confidence interval [CI] 1.35 to 1.90; $p=2.4\times10^{-7}$) by univariate analysis and 1.47 (95% CI 1.23 to 1.76, $p=4.7\times10^{-5}$) by multivariate analysis. Similarly, a combined analysis in 12 men with metastatic prostate cancer showed that the CCP score was predictive of metastatic disease. The hazard ratio was 3.35 (95% CI 2.89 to 9.92; $p=2.1\times10^{-8}$) by univariate analysis.

Cooperberg et al. (2013) aimed to validate the use of the CCP score to predict radical prostatectomy outcomes in 413 men in the US. The study assessed the CCP score for prognostic utility and generated prediction models based on CCP only, the CAPRA-S score, and the combined CCP and CAPRA-S score. The hazard ratio of the CCP score was 2.1 (95% CI 1.6 to 2.9, p<0.001) and after combination with the CAPRA-S score it was 1.7 (95% CI 1.3 to 2.3, p<0.001). The CCP score correlated weakly but significantly with the CAPRA-S score (r=0.21, p<0.001). When the CCP score and CAPRA-S variables were combined (to provide the patient's 10-year biochemical recurrence risk), a decision curve analysis demonstrated that the combined model was more predictive than CAPRA-S alone.

Cuzick et al. (2011) assessed the prognostic value of the CCP score in 2 cohorts (1 from the US and 1 from the UK) of patients with prostate cancer. Patients from the US cohort

had had radical prostatectomies (n=410). The UK cohort were patients with clinically localised prostate cancer diagnosed following transurethral resection of the prostate (TURP) and managed by watchful waiting, randomly selected from 6 registries (n=337). Patients who had radical prostatectomies were evaluated for time to biochemical recurrence and patients who had TURP were evaluated for time to death. Median follow-up time was 9.4 years for the radical prostatectomy group and 9.8 years for TURP group. Hazard ratios showed that the CCP score was predictive of outcomes in both cohorts. After radical prostatectomy, the CCP score alone was useful for predicting biochemical recurrence as assessed by the univariate analysis, and in combination with tumour and patient data, as assessed by multivariate analysis. The hazard ratios were 1.89 (95% CI 1.54 to 2.31; $p=5.6\times10^{-9}$) and 1.77 (95% CI 1.40 to 2.22; $p=4.3\times10^{-6}$) respectively. In the TURP cohort, the CCP score was the most important variable for prediction of time to death from prostate cancer in both univariate analysis (hazard ratio 2.92, 95% CI 2.38 to 3.57, $p=6.1\times10^{-22}$) and multivariate analysis (hazard ratio 2.57, 95% CI 1.93 to 3.43; $p=8{\cdot}2\times10^{-11}$).

Cuzick et al. (2012) examined the prognostic value of the CCP score compared with other variables, including the Gleason score, PSA level and clinical stage, in a cohort of 349 patients who had conservatively treated localised prostate cancer which had been diagnosed by needle biopsy. The median CCP score was 1.03 (interquartile range from 0.41 to 1.74) and was associated with a 2.02-fold increase in risk of cancer-related mortality in the univariate analysis ($\chi^2=37.6$, 95% CI 1.62 to 2.53, $p=8.6\times10^{-10}$). The risk of death from prostate cancer at 10 years after diagnosis was associated with an increased CCP score. For example, for a CCP score of less than 0, the estimated rate of death from prostate cancer was 19.3%. For a CCP score greater than 3, the estimate was 74.9%. The CCP score was a stronger prognostic factor than the Gleason score or PSA level. Multivariate analysis hazard ratio for CCP score was 1.65 (95% CI 1.31 to 2.09, $p=2.6\times10^{-5}$).

Cuzick et al. (2015) assessed the prognostic value of the CCP score in predicting the 10-year risk of cancer-related mortality, both independently and in combination with standard clinical variables used to determine the CAPRA score (such as Gleason score, PSA level and clinical stage). A cohort of patients (n=761) with clinically localised prostate cancer diagnosed by needle biopsy was selected from 3 UK registries. Using univariate analysis, a 1-unit increase in CCP score was associated with a hazard ratio of 2.08 (95% CI 1.76 to 2.46; $p=6.0\text{x}10^{-14}$). Using multivariate analysis, the CCP score hazard ratio was 1.76 (95% CI 1.44 to 2.14; $p=4.2\text{x}10^{-8}$), whereas the CAPRA score hazard ratio was 1.29 (95% CI 1.18 to 1.42; $p=4.6\text{x}10^{-9}$). The CCR score (combination of CCP and CAPRA scores) was most predictive of cancer related mortality, with a hazard ratio of

2.17 (95% CI 1.83 to 2.57; $p=4.1x10^{-21}$).

Freedland et al. (2013) evaluated the prognostic utility of the CCP score in patients with prostate cancer who had external beam radiation therapy less than 2 years after biopsy. The authors analysed time to biochemical recurrence in a US-based population (n=141). The median CCP score was 0.12 and the hazard ratio for biochemical recurrence was 2.55 (95% CI 1.43 to 4.55) for a 1-unit increase in CCP score (p=0.0017). The multivariate analysis had similar results. Freedland et al. (2013) concluded that CCP was a statistically significant predictor of outcome for patients who had external beam radiation therapy and that the test provided greater prognostic information than other clinical parameters.

Clinical utility

Crawford et al. (2014) studied how the CCP score affected clinicians' treatment recommendations for 331 patients diagnosed with prostate cancer after biopsy in the US. The main evaluations were:

- change in treatments recommended before and after the test (that is, the change between interventional and non-interventional therapy options)
- the overall direction of change (to a more aggressive or less aggressive treatment).

Most patients had cancers classified as being low (43.5%) or intermediate risk (44.1%) for 10-year cancer related mortality. The average CCP score was −0.69±0.82 with an average risk of 10-year mortality with conservative management of 3.5%. Overall, 65% of clinicians changed their treatment recommendation based on the results of the CCP score. There was a reduction in therapeutic burden in 40% of cases (122/305) and an increase in 24.9% of cases (76/305). The authors concluded that the study demonstrates high clinical utility for CCP scoring among clinicians.

In a prospective registry study, Shore et al. (2016) evaluated how CCP score affected shared treatment decision-making for 1,206 patients with newly diagnosed prostate cancer. Four sequential surveys tracked changes to the initial therapy: before the initial CCP (Prolaris) test; after clinical review of the CCP score; after shared clinician/patient review of the test results; and after at least 3 months of clinical follow-up (actual treatment). There was a significant reduction in the treatment burden recorded at each successive evaluation (p<0.0001). The mean number of treatments per patient decreased from 1.72 before the CCP score was determined to 1.16 in clinical follow-up. The CCP score resulted in a change in treatment in 47.8% of patients. Of these changes, 72.1% were

reductions and 26.9% were increases in treatment burden, measured as the total number of treatment options recommended or administered per patient. For each clinical risk category there was a significant change in treatment modality (intervention versus non-intervention) before the CCP test compared with after CCP testing (p=0.0002). The authors concluded that the CCP score had a significant impact in helping clinicians and patients to reach shared treatment decisions.

Analytical validation

One study demonstrated the analytical validity of the CCP (Prolaris) score. Warf et al. (2015) examined the precision of the CCP score, the stability of stored RNA, the yield of RNA extraction (from FFPE tissue), the linearity of the score (in relation to RNA concentration), the amplification efficiency of genes within the CCP score and the dynamic range over which this gene expression signature could produce valid CCP scores in both prostatectomy and needle biopsy samples. The authors concluded that the CCP score is reproducible and robust, its linear and dynamic range exceeds the parameters utilised in the clinical setting (indicating that it is suitable for use) and it is analytically validated for use on FFPE prostate biopsy samples and radical prostatectomy specimens.

Recent and ongoing studies

Two ongoing or in-development trials using Prolaris were identified in the preparation of this briefing.

- NCT02209584 is a US-based open registry with the aim of measuring the impact of Prolaris on treatment decisions after biopsy in newly diagnosed prostate cancer patients. It is sponsored by the manufacturer and was expected to be completed in September 2015.
- NCT02454595 is a US-based open registry with the aim of measuring the impact of Prolaris in selecting first-line therapy for newly diagnosed, treatment-naive patients with early-stage localised prostate cancer. It is sponsored by the manufacturer and is estimated to be completed in November 2016.

Costs and resource consequences

Two abstracts (Crawford et al. 2015, de Pouvourville 2015) providing economic evidence

on Prolaris were identified. Crawford et al. (2015) quantified the economic impact of the CCP (Prolaris) test in the US healthcare setting using a hypothetical cohort of patients with localised prostate cancer (of all risk types) over 10 years. Management and progression assumptions were made based on published clinical data and interviews with clinicians (Crawford et al. 2015). The study found that using the CCP score over 10 years reduced per patient costs by about £1,938. The authors concluded that the savings were a result of increased use of active surveillance in low- and intermediate-risk patients with less aggressive disease, as well as reduced progression rates in high-risk patients. De Pouvourville (2015) evaluated the cost effectiveness of using the CCP score in France using a Markov model. They compared the treatment decisions based on diagnosis with and without the CCP score in patients with localised low-risk prostate cancer. Direct medical costs were calculated from public data sources. The study found that in the long term (the time period was not defined in the abstract), using the test at a hypothetical price of £1,502 was a dominant strategy, with a lower limit lifetime discounted cost of £1,284 and an incremental discounted quality-adjusted life-year gain of 0.23.

If the adoption of Prolaris led to more accurate risk stratification, it could avoid the need for chemotherapy in some patients. The use of Prolaris will not require changes in the organisation or delivery of current services, and no additional facilities or technology will be needed. Sample preparation requirements are exacting and will require pathology resources to enable the test to be used. The product is not currently used in the NHS but is used in UK private practice.

Strengths and limitations of the evidence

The evidence for clinical validity and prognostic value of Prolaris is based on the retrospective analyses of archived material, mainly from registries. The exception to this is Cooperberg et al. (2013), who collected specimens prospectively and then used retrospective blinded evaluation design for validation (Pepe et al. 2008).

Crawford et al. (2014) and Shore et al. (2016) prospectively examined clinicians' treatment decisions after receiving the CCP score for their patients. Clinical utility studies should show that changes in treatment ultimately translate to benefits for patients but clinical effectiveness outcomes to validate clinical utility results were not included in the 2 studies. Questionnaires administered after a clinical procedure may introduce the risk of recall bias, because clinicians' recollections of how they planned to manage individuals' care before receiving the test results may have been skewed by the results themselves. Crawford et al. (2014) and Shore et al. (2016) eliminated the risk of recall bias by doing a pre-test survey

to assess how the clinicians planned to manage their patients' care, as well as a post-test survey done after the clinicians saw the CCP results.

The UK cohorts in Cuzick et al. (2011, 2012 and 2015) included patients with high-risk prostate cancer who were conservatively managed, for example by watchful waiting, which is not representative of current prostate cancer treatment in the NHS.

Cuzick et al. (2012 and 2015), Bishoff et al. (2014) and Freedland et al. (2013) used biopsy samples to evaluate the CCP test. In the study by Cooperberg et al. (2013), samples were taken from the largest tumour area of prostatectomy specimens which may have limited the heterogeneity of the sampled tissue leading to biased results. None of the studies explicitly stated the number of biopsy cores assessed and therefore the effect of tumour heterogeneity cannot be discounted.

None of the studies discussed the power calculations used to justify their sample sizes. The patient cohorts were mainly based in the US. Three patient cohorts were taken from UK registries, and there was 1 German cohort. Incidence rates and standard treatment for prostate cancer vary by country, which may limit the generalisability of the results to the UK population. Most studies had relatively large sample sizes, ranging from 141 to 761 patients. In contrast, the metastasis group in the Bishoff (2014) study included only 12 patients with metastatic cases of prostate cancer. Low sample sizes can bias the power and reliability of statistical findings.

The generalisability to the NHS of the studies by de Pouvourville (2015) and Crawford et al. (2014) is limited due to their respective settings (France and the US), as well as the lack of detail about which specific costs were used in the calculations and how the models were constructed. The Crawford et al. (2014) study is inherently limited because it used a hypothetical cohort, which assumes that the likelihood of advancing to a different health state is homogeneous across the population (independent of time or past health states). Additionally, the hypothetical cost used by de Pouvourville (2015) was slightly lower than the actual cost of the Prolaris test (£1,502 compared with £1,800 respectively), which could affect the results of the cost analysis.

All of the clinical studies presented in this briefing received some or all of their funding from the manufacturer. All 9 publications included authors employed by Myriad Genetics. The manufacturer's involvement in these publications introduces the potential for bias in reporting the outcomes. The 2 economic abstracts did not mention a funding source.

Relevance to NICE guidance programmes

NICE has issued the following guidance:

Prostate cancer: diagnosis and treatment (2014) NICE guideline CG175. Date for review: to be confirmed.

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Appendix

Contents

Table 1 Overview of the Bishoff et al. (2014) study

Study component	Description
Objectives/ hypotheses	To evaluate the prognostic utility of the CPP score derived from biopsy specimens in men treated with radical prostatectomy.
Study design	Retrospective cohort study.

Setting	3 cohorts: Martini Clinic (Germany; 2005–2006), Durham Veterans Affairs (USA; 1994–2005) and Intermountain Healthcare (US; 1997–2004).
Inclusion/ exclusion criteria	Inclusion: • Men treated with radical prostatectomy. • Patients diagnosed with prostate adenocarcinoma without evidence of lymph node or bone metastases. • Formalin fixed, paraffin embedded tumour blocks containing a simulated (Martini Clinic) or diagnostic (Durham Veterans Affairs and Intermountain Healthcare) biopsy analysed at Myriad Genetics. Exclusion: • Patients with preoperative PSA >100 ng/ml. • Patients with evidence of systemic disease or insufficient remaining tumour to generate a CCP score. • Patients who received neoadjuvant hormone therapy or radiation preoperatively.
Primary outcomes	Time to biochemical recurrence or metastatic disease.
Statistical methods	Survival analysis was performed with Cox proportional hazard methods using date of surgery as the starting time and time to BCR or metastatic progression as endpoints for the 3 cohorts combined. Effect size was measured by HR per unit of CCP score or another variable of interest with the 95% CI.

Patients included	582 patients total: • Martini Clinic: n=283; median age at surgery=63 years; 44% Gleason score ≥7; 77% clinical stage T1 • Veterans Affairs: n=176; median age at surgery=62 years; 43% Gleason score ≥7; 62% clinical stage T1 • Intermountain Healthcare: n=123; median age at surgery=62 years; 37% Gleason score ≥7; 58% clinical stage T2
Results	Median CCP score: • Martini Clinic: –0.4 (IQR –0.9, 0.2) • Veterans Affairs: 0.0 (IQR –0.4, 0.6) • Intermountain Healthcare: 0.3 (IQR –0.3, 0.9) Combined analysis of all cohorts (total 582 patients) showed that CCP score was a strong predictor of biochemical recurrence on univariate analysis (HR per score unit 1.60, 95% CI 1.35 to 1.90, $p=2.4\times10^{-7}$) and multivariate analysis (HR per score unit 1.47, 95% CI 1.23–1.76, $p=4.7\times10^{-5}$). The combined cohort included 12 men with metastatic prostate cancer. Univariate analysis found that the score was predictive of metastatic disease (HR 3.35, 95% CI 2.89 to 9.92, $p=2.1\times10^{-8}$).
Conclusions	Increased CCP score derived from biopsy samples was associated with an increased risk in BCR in all 3 cohorts. CCP was also predictive of metastatic disease in univariate and multivariate analysis.
Abbreviations: BCR, biochemical recurrence; CCP, cell cycle progression; CI, confidence interval; HR, hazard ratio; IQR, interquartile range; PSA, prostate specific antigen.	

Table 2 Overview of the Cooperberg et al. (2013) study

Study component	**Description**

Objectives/ hypotheses	To validate the CCP score in predicting RP outcomes.
Study design	Prospective specimen collection, retrospective blinded evaluation design for biomarker validation.
Setting	USA, 1994–2011.
Inclusion/ exclusion criteria	Inclusion: • Patients who underwent RP without neoadjuvant or adjuvant therapy. • Patients with at least 5 years follow-up after RP. Exclusion: • Patients diagnosed prior to 1994.
Primary outcomes	The value of the CCP score. The clinical utility of the CCP score.
Statistical methods	Association between the CAPRA-S score and the CCP score was examined using scatter plots and Pearson's correlation. Kaplan–Meier survival analysis was performed and multivariable Cox regression was used to assess the utility of the score.
Patients included	n=413; median age 59 years, IQR 54-63; 58% with Gleason score ≥7
Results	82/413 (19.9%) experienced recurrence. The hazard ratio for each unit increase in CCP score was 2.1 (95% CI 1.6 to 2.9, p<0.001). Hazard ratio was 1.7 (95% CI 1.3 to 2.4, p<0.001) after adjustment by CAPRA-S score.
Conclusions	The CCP score was predictive of BCR regardless of the clinical risk group. The CCP score was weakly but significantly correlated to the CAPRA-S score (r=0.21, p<0.001). The combination of the 2 scores was more predictive than the CAPRA-S score alone.
Abbreviations: BCR, biochemical recurrence; CAPRA-S, Cancer of the Prostate Risk Assessment post-Surgical; CCP, cell cycle progression; CI, confidence interval; IQR, interquartile range; PSA, prostate specific antigen; RP, radical prostatectomy.	

Table 3 Overview of the Cuzick et al. (2011) study

Study component	Description
Objectives/ hypotheses	To assess the prognostic value of CCP in patients with prostate cancer.
Study design	Retrospective cohort.
Setting	1985–1995 Scott and White Clinic, US (RP cohort). 1990–1996 6 cancer registries in the UK (TURP cohort).

Inclusion/ exclusion criteria	RP inclusion: • Patients who had RP for prostate cancer. RP exclusion: • Patients who had been treated with neoadjuvant drugs. • Patients without clinical data and available tumour tissue. TURP inclusion: • Men with clinically localised prostate cancer treated with watchful waiting. • Diagnosed following transurethral resection of prostate. • Under 76 years old at the time of diagnosis. • Had a baseline PSA measurement recorded. TURP exclusion: • Patients treated with RP or radiation therapy within 6 months of diagnosis. • Patients who died or showed evidence of metastatic disease within 6 months of diagnosis. • Patients who had hormone therapy before the diagnostic biopsy.
Primary outcomes	Time to BCR for RP cohort; time to death for TURP cohort.
Statistical methods	Survival analysis was done with Cox proportional hazards models. The main assessment was a univariate analysis of the association between outcome and CCP score. A further predefined assessment of the added prognostic information after adjustment for the baseline variables was also done and a multivariate model was used.

Patients included	RP cohort: n=410; median follow-up time 9.4 years (IQR 6.8–10.9); median age 68 years (IQR 63–71). TURP cohort: n=337; median follow-up time 9.8 years (IQR 5.4–11.8); median age 70.3 years (IQR 66.7-73.1).
Results	RP Cohort: 148/410 (36%) had BCR by 10 years after surgery. 366 scores were judged valid for statistical analysis. The increase in hazard ratio for a 1-unit change in CCP score was 1.89 (95% CI 1.54 to 2.31; $p=5.6\times10^{-9}$). The multivariate analysis hazard ratio was 1.77 (1.40–2·22; $p=4.3\times10^{-6}$). TURP cohort: 171/337 (51%) died within 10 years of diagnosis; 68 (20%) from prostate cancer and 103 (31%) from other causes. The CCP score was the most important variable for prediction of time to death from prostate cancer in both univariate analysis (2.92, CI 95% 2.38 to 3.57, $p=6.1\times10^{-22}$) and the final multivariate analysis (2.57, 95% CI 1.93–3.43; $p=8.2\times10^{-11}$), and was stronger than all other prognostic factors, although PSA concentration also added useful information.
Conclusions	The CCP score was a good predictor of death from prostate cancer.
Abbreviations: BCR, biochemical recurrence; CCP, cell cycle progression; CI, confidence interval; IQR, interquartile range; PSA, prostate specific antigen; RP, radical prostatectomy; TURP, transurethral resection of the prostate.	

Table 4 Overview of the Cuzick et al. (2012) study

Study component	**Description**
Objectives/ hypotheses	To evaluate the clinical utility of the CCP score when generated from needle biopsies from men managed by watchful waiting.
Study design	Retrospective cohort.

Setting	6 UK cancer registries; 1990–1996.
Inclusion/ exclusion criteria	Inclusion: • Men with clinically localised prostate cancer treated by watchful waiting. • Diagnosed using needle biopsy specimens. • Under 76 years old at the time of diagnosis. • Had a baseline PSA measurement recorded. Exclusion: • Patients treated with radical prostatectomy or radiation therapy within the first 6 months after diagnosis. • Patients who died or showed evidence of metastatic disease within 6 months of diagnosis. • Patients who had hormone therapy before the diagnostic biopsy.
Primary outcomes	Death from prostate cancer.
Statistical methods	Survival analysis was carried out using a Cox proportional hazards model (time to death from prostate cancer). All p-values were 2-sided and 95% CI and p-values were based on chi-squared statistics with 1 degree of freedom, unless otherwise indicated, obtained from partial likelihoods of proportional hazards models. A univariate analysis of the association between death from prostate cancer and CCP score was also performed.
Patients included	n=349 patients complete baseline and follow-up information; median age 70.5 years, median PSA 21.4 ng/ml, 91% Gleason score >7.

Results	Median CCP score was 1.03 with an interquartile range from 0.41 to 1.74. A 1-unit increase in CCP score was associated with a 2.02-fold increase in the hazard of dying from prostate cancer (χ^2=37.6, p=8.6×10^{-10}, 95% CI 1.62 to 2.53). The 10-year death rate from prostate cancer was: • 19.3% for CCP score <0; • 19.8% for CCP score 0-1; • 21.1% for CCP score 1-2; • 48.2% for CCP score 2-3; • 74.9% for CCP score >3. The multivariate analysis showed that extent of disease, age, clinical stage and use of hormone therapy were not statistically significant and therefore only CCP score, Gleason score and PSA level remained in the analysis. Multivariate analysis hazard ratio for CCP score was 1.65 (95% CI 1.31 to 2.09, p=2.6×10^{-5}).
Conclusions	80% of the needle biopsies provided enough material to generate a CCP score. For these patients, the CCP score was a stronger prognostic factor than either the Gleason score or PSA levels.
Abbreviations: CCP, cell cycle progression; CI, confidence interval; PSA, prostate specific antigen.	

Table 5 Overview of the Cuzick et al. (2015) study

Study component	Description
Objectives/ hypotheses	To validate the prognostic value of a CCP score independently and in a pre-specified linear combination with standard clinical variables (the clinical CCR score).
Study design	Retrospective cohort study.

Setting	3 UK cancer registries; 2000–2003.
Inclusion/ exclusion criteria	Inclusion: • Men aged under 76 years at diagnosis. • Men with clinically localised prostate cancer diagnosed by needle biopsy. Exclusion: • Men treated with radical prostatectomy or radiation therapy within 6 months of diagnosis. • Men with objective evidence of metastatic disease (for example by bone scan, X-ray, radiograph, CT scan or MRI). • Men with clinical indications of metastatic disease (including pathological fracture, soft tissue metastases or spinal compression). • Men with a PSA measurement >100 ng/ml at or within 6 months of diagnosis. • Men who had hormone therapy prior to the diagnostic biopsy. • Men who died within 6 months of diagnosis or had <6 months of follow-up.
Primary outcomes	The prognostic value of the CCP score.
Statistical methods	Survival was analysed with a Cox proportional hazards model. The primary end point was time to death from prostate cancer. A predefined combined CCR score encompassing both the CAPRA (linear) and CCP score was calculated to predict death from prostate cancer. Further exploratory analyses included testing for proportional hazards, and testing for interactions of the CCP score with individual clinical covariates.
Patients included	n=761 (median age 70.8 years, IQR 66.5-73.6).

Results	In a univariate analysis, the CCP score hazard ratio was 2.08 (95% CI 1.76 to 2.46, $p<6.0x10^{-14}$) for 1 unit change of the score. In multivariate analysis including CAPRA, the CCP score hazard ratio was 1.76 (95% CI 1.44 to 2.14), $p<4.2x10^{-7}$). The CAPRA score hazard ratio was 1.29 (95% CI 1.18 to 1.42; p<4.6x10-9). The predefined CCR score was significantly predictive of death from prostate cancer, hazard ratio 2.17 (95% CI (1.83 to 2.57), X^2=88.9, $p<4.1x10^{-21}$).
Conclusions	The CCP score provides significant pre-treatment prognostic information and can be useful for determining which patients can be safely managed conservatively, avoiding radical treatment. The combined CCR score as a linear combination of the CCP score almost completely accounted for all molecular and clinical prognostic information.
Abbreviations: CAPRA, Cancer of the Prostate Risk Assessment; CCP, Cell cycle progression; CCR, Cell cycle risk; CI, confidence interval; CT, computerised tomography; IQR, interquartile range; MRI, magnetic resonance imaging.	

Table 6 Overview of the Freedland et al. (2013) study

Study component	**Description**
Objectives/ hypotheses	To evaluate the prognostic utility of the CCP score in men with prostate cancer treated with EBRT.
Study design	Retrospective cohort.
Setting	USA; 1991–2006.

Inclusion/ exclusion criteria	Inclusion: • Patients who underwent diagnostic biopsy for prostate cancer and were treated with definitive EBRT. Exclusion: • Patients without available formalin-fixed and paraffin-embedded blocks containing original diagnostic biopsy. • PSA level >100 ng/ml. • Patients who began treatment >2 years after diagnostic biopsy. • Patients with follow-up data for <3 years who had not developed BCR within the time frame.
Primary outcomes	Time to BCR event.
Statistical methods	Survival analysis was carried out using Cox proportional hazards models to assess the association between the CCP score as a continuous variable and risk of BCR. Most of the analyses are based on 5-year censoring to address the observed time dependence of HR for CCP.
Patients included	n=141; median age 66 years, IQR 60–71; 60% clinical stage T1; 61% Gleason score ≥7.
Results	The median CCP score was 0.12 (IQR –0.43, 0.66). The HR for BCR was 2.55 (95% CI 1.43 to 4.55) for 1-unit increase in CCP score (p=0.0017). The multivariable analysis included Gleason score, PSA, percent positive biopsy cores and androgen deprivation therapy; the HR per CCP unit was 2.11 (95% CI 1.05 to 4.25, p=0.034).
Conclusions	CCP was a significant predictor of BCR in patients having EBRT.
Abbreviations: BCR, biochemical recurrence; CCP, cell cycle progression; CI, confidence interval; EBRT, external beam radiation therapy; HR, hazard ratio; IQR, interquartile range; PSA, prostate specific antigen.	

Table 7 Overview of the Crawford et al. (2014) study

Study component	Description
Objectives/ hypotheses	To evaluate the impact of the CCP report on clinician treatment recommendations for patients with prostate cancer.
Study design	Prospective cohort.
Setting	USA; July to September 2013.
Inclusion/ exclusion criteria	Inclusion: • Prostate cancer patients diagnosed by biopsy. • Patients who had CCP tests ordered by their clinician who completed both pre- and post-test report forms with intended selection of treatment. Exclusion: • Not stated.
Primary outcomes	Binary change in treatment (a change from interventional to non-interventional therapy options) and the overall direction of change (to a more or less aggressive treatment).
Statistical methods	Outcomes were calculated along with their 2-sided 95% CI. The sample size was calculated to demonstrate a change of at least 10% (lower limit of 95% CI) in the magnitude of change between pre- and post-test recommendations assuming an observation of a 15% change in the study.
Patients included	n=331 patients, 67.4±7.43 years old. 82.5% had clinical stage T1c adenocarcinoma; 91.9% had Gleason scores of 6 or 7.

Results	The average CCP score was –0.69 with an average risk of 10-year mortality with conservative management of 3.5%. Samples from 305 people were evaluable (in 26 people, the therapeutic decision was recorded as 'undecided' either pre-test or post-test). Overall, 64.9% (95% CI: 59.4 to 70.1%) showed a change between intended therapy options pre- and post-CCP test report. There was a reduction in therapeutic burden in 40% of people (122/305), no change in 35.1% of people (107/305), and an increase in 24.9% of people (76/305).[a]
Conclusions	The use of CCP testing is associated with clinical utility among clinicians based on their changes in treatment plans for patients.
Abbreviations: CCP, cell cycle progression; CI, confidence interval. [a] The therapeutic burden was defined by the following hierarchy: radical prostatectomy>radiation therapy>other therapy (brachytherapy/cryotherapy etc.)>androgen deprivation therapy>active surveillance>watchful waiting, where reduction in therapeutic burden includes both a shift from an interventional to a non-interventional therapy (from example from radical prostatectomy to active surveillance) as well as reduction in intended interventional burden (from example from radiation and radical prostatectomy to radiation only).	

Table 8 Overview of the Shore et al. (2016) study

Study component	Description
Objectives/ hypotheses	To evaluate the impact of the CCP test on shared treatment decision making for patients newly diagnosed with prostate cancer.
Study design	Prospective registry study with questionnaires.
Setting	USA; dates not specified.

Inclusion/ exclusion criteria	Inclusion: • Men with recently (<6 months) diagnosed prostate cancer. • Men with histologically proven, presumed clinically localised prostate cancer. • Men who had not received any treatment and had sufficient biopsy tissue. Exclusion: • Men with a known history of hypogonadism. • Men who had been treated with hormonal therapy.
Primary outcomes	Change in treatment.
Statistical methods	A subgroup analysis was conducted to assess change from interventional to non-interventional therapy options. Multiple logistic regression was used to determine the impact of mortality risk, as determined by the CCP test, on treatment change.
Patients included	Of the 1,596 patients enrolled in the registry 1206 were eligible for analysis. Mean age 65.9±8.36 years.
Results	There was a significant reduction in the treatment burden recorded at each successive evaluation (p <0.0001), with the mean number of treatments per patient decreasing from 1.72 before the CCP test to 1.16 in actual follow up. The CCP test caused a change in actual treatment in 47.8% of patients. Of these changes 72.1% were reductions and 26.9% were increases in treatment burden. For every 1 unit increase in mortality risk there was an associated 2.7% increase in the odds of treatment increasing (and vice versa for decrease in treatment). For each clinical risk category there was a significant change in treatment modality (intervention vs non-intervention) before compared with after CCP testing (p=0.0002).

Conclusions	The CCP test has a significant impact on shared decision making between patients and clinicians in terms of changes in treatment plans.
Abbreviations: CCP, cell cycle progression.	

Table 9 Overview of the Warf et al. (2015) study

Study component	Description
Objectives/ hypotheses	To demonstrate that the CCP score is a robust and reproducible molecular diagnostic tool that is appropriate for clinical use for the testing of either RP or needle biopsy FFPE samples.
Study design	The precision of the CCP score was assessed in a set of 6 biopsy and 12 RP samples.
Setting	All studies were performed within a CLIA-certified laboratory under established protocols.
Inclusion/ exclusion criteria	The RP samples had sufficient tissue for 3 replicates, while the biopsy samples had sufficient tissue for 4 or 6 replicates. Samples were required to have mean expression of housekeeper (reference) genes ≤24 Ct, in order to match the average expression of clinical samples.
Primary outcomes	The analytical performance of the CCP test through assessment of: • Precision of the CCP gene expression signature. • Stability of stored RNA. • Yields of RNA extracted from FFPE tissue. • Linearity of the CCP score in relation to RNA concentration. • Amplification efficiency of genes within the CCP gene expression signature. • Dynamic range of the CCP gene expression signature.

Statistical methods	The precision for the overall CCP score was defined as the standard deviation captured in the residual variation term using a linear mixed model.
Samples included	6 biopsy and 12 RP samples.
Results	• The overall SD of the signature was determined to be 0.1 CCP score units (95% CI, 0.08 to 0.13) between replicate measurements. • CCP scores were reproducible across all time points, with no trend in the scores of any of the individual samples • 100% of the RP and 99.8% of the biopsy samples produced sufficient RNA for testing • All samples had consistent CCP scores across the entire range of RNA concentrations that was assessed • None of the samples produced a CCP score at 0.06 ng/microlitre (1.5 ng of input RNA) because the CCP scores at those concentrations did not pass the quality control measures. • The linear range of the RNA concentration was from 62.5 to 0.24 ng/microlitre. This approximately 260-fold range exceeds the 20-fold range of RNA concentrations over which the signature was clinically validated and clinical samples are tested (40 to 2 ng/microlitre). • No statistical difference in the amplification efficiencies was observed when comparing housekeeper and target genes (p-value 0.39). • The observed range of the CCP scores was within recent clinical validations in prostate cancer samples (CCP scores from −2.0 to 4.1) and is well within the dynamic range of the gene expression signature.
Conclusions	The linear and dynamic range of the CCP signature exceeds the parameters utilized in clinical testing, indicating that the test is suitable for use.

Abbreviations: CCP, cell cycle progression; CI, confidence interval; Ct, cycle threshold; FFPE , formalin-fixed, paraffin-embedded; ng, nanograms, RNA, ribonucleic acid RP, radical prostatectomy; SD, standard deviation.

Table 10 Summary of the economic abstracts

Study	Country	Intervention (compared with standard treatment)	Population	Costs included	Original costs	Adjusted costs (PPP ER, inflation)
Crawford et al. (2015)	US	Prolaris	Men with localised prostate cancer (with 10 year follow up)	Costs of each unit of care that a patient might undergo (diagnostic, surgical, radiotherapy procedures and drug therapy)	$2,850 per patient, per year	£1,938

de Pouvourville (2015)	France	Prolaris	Men with localised low risk prostate cancer	Direct medical costs (for example drugs, staff time, and equipment)	At a hypothetical cost of €2,000 for the test, the lower limit of lifetime costs (discounted) is €1709 with an incremental gain of 0.23 QALYs.	An assumption of £1,502 for the test resulted in a discounted lifetime cost of £1,284
Abbreviations: ER, exchange rate; PPP, purchasing power parity; QALY, quality-adjusted life year.						

Search strategy and evidence selection

Search strategy

For the clinical evidence

Ovid MEDLINE(R) 1946 to January Week 1 2016, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations January 18, 2016.

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- 6. myriad genetics.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, ui]
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- 1 or 2 or 3 or 4 or 5 or 6

- 7 and 8
- "cost benefit analysis"/ or "cost minimization analysis"/ or cost.mp. or "cost"/ or "cost effectiveness analysis"/
- economic.mp
- 10 or 11
- 9 and 12
- limit 13 to (english language and yr="2010-current")

Cochrane Database of Systematic Reviews: Issue 1 of 12, January 2016

Cochrane Central Register of Controlled Trials: Issue 12 of 12, December 2015

Database of Abstracts of Reviews of Effect: Issue 2 of 4, April 2015

Health Technology Assessment Database: Issue 4 of 4, October 2015

NHS Economic Evaluation Database: Issue 2 of 4, April 2015

Cochrane Methodology Register: Issue 3 of 4, July 2012

Evidence selection

For the clinical evidence

- Total number of publications reviewed: 71
- Total number of publications considered relevant: 19
- Total number of publications selected for inclusion in this briefing: 9

Shore et al. 2016 has been included instead of Shore et al. 2014 as this provides better quality evidence for the effect of Prolaris on change in treatment. Shore et al. 2014 is a relatively small study in terms of number of clinicians and is based on intention. Shore et al. 2016 evaluates actual treatment decisions so has more weight.

For the economic evidence

- Total abstracts: 14
- Duplicates: 4
- Abstracts reviewed: 10
- Full papers reviewed: 4
- Studies for review: 2

Exclusion criteria: case studies, editorials, letters, reviews, animal studies, non-English language studies.

About this briefing

Medtech innovation briefings summarise the published evidence and information available for individual medical technologies. The briefings provide information to aid local decision-making by clinicians, managers and procurement professionals.

Medtech innovation briefings aim to present information and critically review the strengths and weaknesses of the relevant evidence, but contain no recommendations and **are not formal NICE guidance**.

Development of this briefing

This briefing was developed for NICE by King's Technology Evaluation Centre. 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.

Project team

- King's Technology Evaluation Centre (KiTEC)
- Medical Technologies Evaluation Programme, NICE

Peer reviewers and contributors

- Anastasia Chalkidou, Senior Health Technology Assessor, KiTEC
- Kate Goddard, Health Technology Assessor, KiTEC
- Naomi Herz, Health Technology Assessor and Health Economist, KiTEC
- Lamprini Kaftantzi, Health Technology Assessor, KiTEC
- Murali Radhakrishnan Kartha, Senior Health Economist, KiTEC
- Stephen Keevil, Director, KiTEC
- Cornelius Lewis, Director, KiTEC
- Viktoria McMillan, Centre Manager, KiTEC

Specialist commentators

The following specialist commentators provided comments on a draft of this briefing:

- Ashish Chandra, Lead Consultant for cytopathology and urological histopathology, Guy's and St. Thomas' NHS Trust
- Isabel Syndikus, Consultant Clinical Oncologist, The Clatterbridge Cancer Centre NHS Foundation Trust
- Jeremy Crew, Consultant Urological Surgeon, Oxford University Hospitals NHS Foundation Trust
- Shahzad Shah, Consultant Urologist, West Hertfordshire Hospitals NHS Foundation Trust.

Declarations of interest

No relevant interests declared.

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