Institution: Queen Mary University of London		
Unit of Assessment: 1		
Title of case study: Validating the Prolaris Prognostic Test for Prostate Cancer		
Period when the underpinning research was undertaken: 2010-2015		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
1) Jack Cuzick	1) Professor, Director of the Wolfson Institute	1) 12/2002 - present
2) Gabrielle Fisher	2) Senior Clinical Studies Manager	2) 03/1999 - 09/2015
3) Sue (Zihua) Yang	3) Statistician	3) 04/2010 - 12/2013
4) Bernard North	4) Senior Statistician	4) 04/2012 - 07/2016
Period when the claimed impact occurred: 2014-2018		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact (indicative maximum 100 words)

Queen Mary's research validated Prolaris, the market-leading prognostic prostate cancer genetic test, to predict 10-year prostate cancer-specific mortality. The test is used to accurately differentiate aggressive from indolent prostate cancer and thus to guide treatment. In October 2015, the Tufts Health Plan (a leading health plan in the north east US with more than 1,000,000 members) agreed to provide coverage of Prolaris to its members diagnosed with localised prostate cancer. In 2017, Prolaris was the first and only genetic test to receive Medicare approval for favourable intermediate prostate cancer patients, and by mid-2018 Prolaris had insurance coverage for 50% of US prostate cancer patients. In the US, over 60,000 patients have been tested. Since January 2018, BUPA members in the UK have been covered for Prolaris use. An independent study has shown that interventional treatment declined by over 37.2% when using Prolaris, with a 49.5% reduction in surgical interventions and a 29.6% reduction in radiation treatment. Thus, Prolaris has helped many thousands of men and their physicians make the difficult decision about whether to choose active surveillance or radical therapy (with its associated morbidity) to treat clinically localised prostate cancer.

2. Underpinning research (indicative maximum 500 words)

The natural history of prostate cancer is highly variable and difficult to predict accurately. Previously, management was based on clinical scores generated from Gleason scores (grading system for biopsies), baseline prostate specific antigen blood levels, clinical staging, and the extent of disease based on core biopsies. While these scores are useful, better markers were needed to guide management and avoid unnecessary or radical treatment associated with high morbidity. Large numbers of prostate cancer patients with clinically localised disease were left with an intermediate prognosis, and uncertainty about their need for radical treatment. Active surveillance has been the standard care for many men with clinically localised prostate cancer, but this option has been under-selected.

Addressing the need for a score to differentiate between indolent and aggressive prostate cancers, a unique collaboration of prostate cancer experts from the UK and US formed the Transatlantic Prostate Group, led by Prof. Cuzick and including other members from Queen Mary's Wolfson Institute. It was known that Ki-67 expression measured by immunohistochemistry in tumours is a marker for poor prognosis, but it could not be reproducibly assayed in different laboratories, and quality assurance standards could not be achieved. With commercial partner, Myriad Genetics, the research group sought to find a reliable assay of cell cycle progression (CCP). Two decisions were reached: to select an mRNA assay which would not require interpretation of a slide, and to use a panel of CCP genes that would all measure the same thing, but in different ways, to achieve robustness. Myriad Genetics performed the early laboratory work to develop an appropriate 31 gene expression profile, with analysis and evaluation throughout the process by the Transatlantic Prostate Group researchers. Cuzick and his team undertook preliminary work to retrospectively assess the prognostic value of the predefined CCP score in an active surveillance cohort, and worked with Dr. Gregory P. Swanson, from the University of Texas Health Science Center San Antonio, to analyse his radical treatment cohort, to produce the landmark paper demonstrating the clinical value of the CCP score [3.1]. The resulting paper provided strong evidence that the CCP

score was a robust prognostic marker, which could, with additional validation, play an essential role in determining appropriate treatment for prostate cancer patients.

A 2012 study from the same group, and with Cuzick again as lead author [3.2], acknowledged that to make a significant impact, research needed to demonstrate clinical utility of the score when generated from diagnostic needle biopsies. Assessing the prognostic value of the CCP signature in a conservatively managed needle biopsy cohort, the study concluded that it was the strongest independent predictor of cancer death outcome yet described.

The definitive research was a needle biopsy-based validation study of both the CCP score alone and as part of a pre-specified linear combination with standard clinical variables (combined clinical cell cycle risk (CCR)) for predicting prostate cancer death in a cohort of men with clinically localised disease who were initially managed conservatively. Patients with clinically localised prostate cancer diagnosed mostly by needle biopsy between 2000 and 2003 were identified from three British cancer registries. Histological specimens from the original diagnosis were processed at Myriad Genetics (US). A CCP score was obtained from a cohort of 989 men, and clinical variables were available for 585 men, who were followed up for a median of 9.52 years. The results showed that for conservatively managed patients, the CCP score was highly prognostic for death from prostate cancer [3.3].

Thus, Queen Mary's research showed that the Prolaris CCP score differentiates aggressive from indolent prostate cancer, providing significant pre-treatment prognostic information that cannot be obtained from clinical variables. The test is useful for determining which patients can be safely managed conservatively, thereby avoiding unnecessary or radical treatment, which is associated with significant morbidity. The score can also help to determine the need for adjuvant endocrine or chemotherapy.

3. References to the research (indicative maximum of six references)

[3.1] Cuzick, J., Swanson, G. P., Fisher, G., Brothman, A. R., Berney, D. M., Reid, J. E., Mesher, D., Speights, V. O., Stankiewicz, E., Foster, C. S., Møller, H., Scardino, P., Warren, J. D., Park, J., Younus, A., Flake, D. D., Wagner, S., Gutin, A., Lanchbury, J. S., Stone, S. & The Transatlantic Prostate Group. (2011). Prognostic value of an RNA expression signature derived from cell cycle proliferation genes in patients with prostate cancer: a retrospective study. *The Lancet Oncology, 12* (3), 245-255. https://doi.org/10.1016/S1470-2045(10)70295-3

[3.2] Cuzick, J., Berney, D. M., Fisher, G., Mesher, D., Møller, H., Reid, J. E., Perry, M., Park, J., Younus, A., Gutin, A., Foster, C. S., Scardino, P., Lanchbury, J. S., Stone, S. & The Transatlantic Prostate Group. (2012). Prognostic value of a cell cycle progression signature for prostate cancer death in a conservatively managed needle biopsy cohort. *British Journal of Cancer, 106* (6), 1095-1099. https://doi.org/10.1038/bjc.2012.39

[3.3] Cuzick, J., Stone, S., Fisher, G., Yang, Z. H., North, B. V., Berney, D. M., Beltran, L., Greenberg, D., Møller, H., Reid, J. E., Gutin, A., Lanchbury, J. S., Brawer, M., Scardino, P. & The Transatlantic Prostate Group. (2015). Validation of an RNA cell cycle progression score for predicting death from prostate cancer in a conservatively managed needle biopsy cohort. *British Journal of Cancer, 113* (3), 382-389. https://doi.org/10.1038/bjc.2015.223

Evidence of the quality of the research

[EQR. 1] Cuzick, J. (1 April 2009 - 31 March 2014). Prevention of Hormone Related Cancers [C569/A10404]. *Cancer Research UK*. Programme Grant. GBP5,309,643.

4. Details of the impact (indicative maximum 750 words)

Queen Mary's research validated Prolaris, the market-leading prognostic prostate cancer genetic test, to predict 10-year prostate cancer-specific mortality. The test is used to accurately differentiate aggressive from indolent prostate cancer and thus to guide treatment.

Patient access to Prolaris

In the US

In 2014, following the second Transatlantic Prostate Group publication [3.2], the Prolaris test was included in the US National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines on Oncology for all men with localised prostate cancer, regardless of risk category. The NCCN

estimated that "Prolaris has changed treatment recommendations in 32-65% of cases" [5.1]. A study published in 2014 evaluated the impact of the Prolaris report on physician treatment recommendations for prostate cancer and showed that interventional treatment declined by 37.2% when Prolaris was utilised. The study reported a 49.5% reduction in surgical interventions, and a 29.6% reduction in radiation treatment [5.2].

Following Prof. Cuzick's 2015 validation publication [3.3], in October 2015, the Tufts Health Plan (a leading health plan in the north east US with more than 1,000,000 members) agreed to provide coverage of Prolaris to its members diagnosed with localised prostate cancer [5.3]. Shortly after this announcement, Medicare also approved coverage for men with low and very low risk prostate cancer [5.4]. In May 2017, Prolaris became the first and only genetic test to receive Medicare coverage for favourable intermediate prostate cancer patients [5.5]. Among newly diagnosed prostate cancer patients, approximately 20% will have favourable intermediate risk prostate cancer. When combined with the previous Medicare coverage decision, Prolaris is now accessible to 70% of Medicare prostate cancer patients. In May 2018, an additional seven commercial insurers announced coverage decisions in favour of Prolaris, with an aggregate of 6,000,000 additional new lives covered for the test. As of May 2018, Prolaris had insurance coverage for 50% of prostate cancer patients in the US, and over 60,000 prostate cancer patients had received the test [5.6].

In Europe
Prolaris has now received European CE marking for the specimen collection set, and the entire test (all processes, consumables, equipment and software) [5.7]. Under commission from NHS England, in 2016 NICE issued a Medtech Innovation Briefing on Prolaris as part of the NHS 5 year Forward View [5.7]. Since January 2018, BUPA members in the UK have been covered for the use of Prolaris [5.8].

Improving patient and medical practitioner treatment choices
In the US there are an estimated 191,930 new cases of prostate cancer (10.6% of all new cancer cases) and 33,330 deaths from this disease annually, with over 3,000,000 men living with prostate cancer every year [5.9]. While active surveillance is recommended for very low or low risk prostate cancer, men continue to under-select this option, largely because of uncertainty about the risk of disease progression. Prolaris predicts 10-year prostate cancer-specific mortality, providing patients and medical practitioners with independent information beyond clinicopathologic variables, and accurately differentiates aggressive prostate cancer from indolent cancer, thereby guiding medical practice and management [5.10]. Patients and their clinicians are able to work together to prioritise their preferences for treatment or watchful waiting. Urologists report that "the Prolaris test has helped many thousands of men and their physicians make the difficult decision whether to choose active surveillance or radical therapy for treatment of their clinically localised prostate cancer" [5.11].

Improving health economics
An economic model of a cohort of prostate cancer patients with localised disease followed for 10 years compared total cost of care for current clinical practice with costs where management was altered based on Prolaris test results. The study found that the test reduced costs by USD2,850 per patient over 10 years. For a health plan with 10,000,000 members, this translates to over USD16,000,000 in savings, with two-thirds of the savings achieved in the first year after testing. Savings were due to increased use of active surveillance in low- and intermediate-risk patients with less aggressive disease, but also from reduced progression rates in high-risk patients with more aggressive disease who transition to multi-modality therapy [5.12].

Commercial success of Prolaris
As a result of the Medicare coverage expansion to intermediate-risk patients, revenue from the Prolaris test nearly doubled in the quarter ending 31 March 2018, from USD3,400,000 to USD6,500,000, compared with the same quarter in the previous year [5.13]. Prolaris testing revenue in the 2018 fiscal year reached USD20,900,000 [5.13].

5. Sources to corroborate the impact (indicative maximum of 10 references)

[5.1] Genome Web. (2014, 27 October). *NCCN Mentions Prolaris, Oncotype DX in Updated Prostate Cancer Guidelines*. https://www.genomeweb.com/clinical-genomics/nccn-mentions-prolaris-oncotype-dx-updated-prostate-cancer-guidelines#.YEI4ZI77Q2w. Accessed 5 March 2021.

[5.2] Crawford, E. D., Scholz, M. C., Kar, A. J., Fegan, J. E., Haregewoin, A., Kaldate, R. R. & Brawer, M. K. (2014). Cell cycle progression score and treatment decisions in prostate cancer: results from an ongoing registry. *Current Medical Research and Opinion, 30* (6), 1025-1031. https://doi.org/10.1185/03007995.2014.899208

[5.3] Myriad. (2015, 7 October). *Myriad Genetics and Tufts Health Plan Sign Agreement to Cover Prolaris® for Members With Localized Prostate Cancer*. https://investor.myriad.com/news-releases/news-release-details/myriad-genetics-and-tufts-health-plan-sign-agreement-cover

[5.4] Centers for Medicare and Medicaid Services. (2017). *Local Coverage Determination MolDX:Prolaris™ Prostate Cancer Genomic Assay for men with low and very low risk disease. LCD ID L36350.*

[5.5] Centers for Medicare and Medicaid Services. (2017). *Local Coverage Determination. MolDX: Prolaris™ Prostate Cancer Genomic Assay for Men with Favorable Intermediate Risk Disease. LCD ID L37082*. https://www.cms.gov/medicare-coverage-database/search/search-results.aspx?CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=prolaris&KeyWordLookUp=Title&KeyWordSearchType=And&articleId=52974&ver=3&ContrId=370&ContrVer=1&bc=gAAAAAAAAAAA%3D%3D&=&

[5.6] Myriad. (2018, 23 May). *Myriad Announces Seven New Payer Coverage Decisions for Prolaris®*. https://globenewswire.com/news-release/2018/05/23/1511144/0/en/Myriad-Announces-Seven-New-Payer-Coverage-Decisions-for-Prolaris.html

[5.7] NICE. (2016). *Prolaris gene expression assay for assessing long-term risk of prostate cancer progression*. https://www.nice.org.uk/advice/mib65

[5.8] L. C. Calleja. Senior Hospital Contracts Executive, Healthcare Management. *Bupa* (testimonial letter, 28 August 2020).

[5.9] National Cancer Institute: Surveillance, Epidemiology and End Results Program. (2020). *Cancer Stat Facts: Prostate Cancer*. https://seer.cancer.gov/statfacts/html/prost.html. Accessed 20 November 2020.

[5.10] Davis, J. W. (2015, 1 June). Use of genomic markers to risk stratify men with prostate cancer. *Trends in Urology and Men's Health*. https://doi.org/10.1002/tre.461

[5.11] P. T Scardino. Head, Prostate Cancer Program. *Memorial Sloan Kettering Cancer Center* (testimonial letter, 2 December 2019). [Corroborator 1]

[5.12] Crawford, E. D., Cole, D., Lewine, N. & Gustavsen, G. (2015). Evaluation of the economic impact of the CCP assay in localized prostate cancer. *Journal of Clinical Oncology, 33* (15). http://ascopubs.org/doi/abs/10.1200/jco.2015.33.15_suppl.e16037

[5.13] Media stories on Myriad's Prolaris sales. Genome Web. (2018, 8 May). *Myriad's Fiscal Q3 Revenues Fall 2 Percent but Beat Wall Street Expectations*. https://www.genomeweb.com/business-news/myriads-fiscal-q3-revenues-fall-2-percent-beat-wall-street-expectations#.YEEPI477SUk. Accessed 28 May 2020. Myriad. (2018, 21 August). *Myriad Genetics Reports Fiscal Fourth-Quarter and Full-Year 2018 Financial Results*. https://investor.myriad.com/news-releases/news-release-details/myriad-genetics-reports-fiscal-fourth-quarter-and-full-year-2018. Accessed 28 May 2020.