Institution: University of Cambridge		
Unit of Assessment: UOA1		
Title of case study: PREDICT: New evidence-based, online tools for decision-making in the treatment of breast and prostate cancer.		
Period when the underpinning research was undertaken: October 2009 – October 2019		
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:**
Vincent J. Gnanapragasam	Reader in Urology & Consultant Urologist	October 2007- present
Carlos Caldas	Professor of Cancer Medicine	June 1996- present
David R. Thurtle	Academic Clinical Fellow	March 2017-March 2019
Period when the claimed impact occurred: August 2013 – July 2020		
Is this case study continued from a case study submitted in 2014? N		

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

Breast cancer is the most frequent cancer among women, affecting >2,000,000 women globally each year. Prostate cancer is the second most common cancer in men, with around 1,300,000 new cases globally each year. Cambridge University researchers led the development of the 'PREDICT' platforms. These are free-of-charge online tools which facilitate informed treatment decision making for clinicians and their patients with breast or prostate cancer. PREDICT Breast has had over 1,250,000 visits since 2014, including 330,000 in the UK and hundreds of thousands across North America, Europe, Australasia and South America. It is approved for clinical decision-making by the UK National Institute for Health and Clinical Excellence (NICE). It is estimated that PREDICT Breast led to 7,500 NHS patients being offered chemotherapy who would otherwise have not received it and, conversely, 11,000 women being appropriately spared unnecessary chemotherapy. Modelled on PREDICT Breast, PREDICT Prostate launched in 2019 has received 19,000 visits from the UK alone. 35% of men using this NICE endorsed decision-making tool opt against unnecessary radical treatment, producing potential savings to the NHS of GBP46,000,000.

2. Underpinning research (indicative maximum 500 words)

Cancer is a complex and heterogeneous disease. Following diagnosis, cancer patients and their physicians together make an informed decision about which treatment options will provide the greatest chance of extending or increasing the quality of life. This dialogue often occurs in a variety of clinical settings, from primary to tertiary care, and should consider the benefits and harm of treatment for the individual patient. Prior to 2010, there were very few tools freely or widely available to facilitate this decision-making process.

Development of evidence-based decision-making tools to inform cancer treatment

Breast cancer–the commonest cancer in woman–affects more than 2,000,000 women across the world each year (World Cancer Research Fund statistics). Those with early breast cancer are faced with the difficult decision of whether to have chemotherapy, in addition to surgery, to increase their chance of cure. In 2010, Cambridge University researchers developed PREDICT Breast 1.0 to help inform treatment decisions for patients with early breast cancer [1]. This model deployed survival-time data on 5,700 women with early breast cancer treated between 1999 and 2003 [1] and was validated using two independent data sets of over 8,000 women from the west Midlands and Canada [2]. The overall predictive accuracy of PREDICT Breast 1.0, particularly its ability to predict the value of chemotherapy in the context of other key variables, was confirmed in multiple independent case series. However, the model proved less accurate at predicting mortality risk in women aged <40 years [Wong et al, 2015]. Therefore, in 2017 PREDICT Breast 2.0 was developed to address this issue and is currently hosted by Public Health England as a free online tool (www.predict.nhs.uk). Extensive collaboration was undertaken with the Cambridge Winton Centre for Risk & Evidence Communication to ensure effective communication of the model data. PREDICT Breast 2.0 has subsequently been validated by several other research groups using multiple independent data sets (Mokbel et al 2017; van Maaren et al 2017; Wu et al 2017; Gray et

al 2018).

Prostate cancer accounts for 26% of all new cancer cases in males in the UK (Cancer Research UK statistics: 2017). This incidence is increasing as the mean age of the population increases and screening becomes more widespread. Cambridge University-led research has shown that >84% of UK men with prostate cancer have non-metastatic disease at diagnosis [3]. Immediate radical therapy for many of these patients carries a high risk of severe adverse effects, including incontinence, impotence and bowel dysfunction, while providing little therapeutic benefit [4]. Therefore, building on the success of PREDICT Breast 2.0, between 2016 and 2019 Cambridge University researchers developed PREDICT Prostate – using data from >12,000 prostate cancer patients in two international cohorts – as the first online resource for individualised treatment decision making in the management of non-metastatic prostate cancer [5]. This model estimated 10 and 15-year survival outcomes for men with newly diagnosed prostate cancer and was shown to outperform all other available international risk-stratification models ($p<0.001$) [5]. A validation study involving >69,000 men showed that PREDICT Prostate was more effective at predicting outcome and the need for treatment compared with all other risk-models [6]. PREDICT Prostate provides patients with estimated survival rates after treatment in the context of absolute mortality rate, i.e. the risk of death from prostate cancer alongside the absolute risk of dying, allowing the patient to make an informed decision as to the value of treatment and its potential side effects. Since March 2019 the model has been hosted by Public Health England as a free online tool (https://prostate.predict.nhs.uk) for men with non-metastatic disease, where both conservative management and radical treatment options are being considered.

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

Evidence of research quality: *Research published in peer-review journals. Research was supported by competitively won grants.

[1] *Wishart GC, Azzato EM, Greenberg DC, Rashbass J, Kearins O, Lawrence G, **Caldas C**, Pharoah PD. PREDICT: a new UK prognostic model that predicts survival following surgery for invasive breast cancer. **Breast Cancer Res**. 2010;12(1):R1. doi: 10.1186/bcr2464. Epub 2010 Jan 6.

[2] *Wishart GC, Bajdik CD, Azzato EM, Dicks E, Greenberg DC, Rashbass J, **Caldas C**, Pharoah PD. A population-based validation of the prognostic model PREDICT for early breast cancer. ***Eur J Surg Oncol.*** 2011 May;37(5):411-7. doi: 10.1016/j.ejso.2011.02.001.

[3] Greenberg DC, Wright KA, Lophathanon A, Muir KR, **Gnanapragasam VJ**. Changing presentation of prostate cancer in a UK population--10 year trends in prostate cancer risk profiles in the East of England. **Br J Cancer**. 2013 Oct 15;109(8):2115-20. doi: 10.1038/bjc.2013.589.

[4] ***Gnanapragasam VJ**, Bratt O, Muir K, Lee LS, Huang HH, Stattin P, Lophatananon A. The Cambridge Prognostic Groups for improved prediction of disease mortality at diagnosis in primary non-metastatic prostate cancer: a validation study. **BMC Med**. 2018 Feb 28;16(1):31. doi: 10.1186/s12916-018-1019-5.

[5] ***Thurtle DR**, Greenberg DC, Lee LS, Huang HH, Pharoah PD, **Gnanapragasam VJ**. Individual prognosis at diagnosis in nonmetastatic prostate cancer: Development and external validation of the PREDICT Prostate multivariable model. **PLoS Med**. 2019; 16(3):e1002758. doi: 10.1371/journal.pmed.1002758.

[6] *Thurtle D, Bratt O, Stattin P, Pharoah P, **Gnanapragasam V**. Comparative performance and external validation of the multivariable PREDICT Prostate tool for non-metastatic prostate cancer: a study in 69,206 men from Prostate Cancer data Base Sweden (PCBaSe). **BMC Med.** 2020 Jun 16;18(1):139. doi: 10.1186/s12916-020-01606-w. PMID: 32539712; PMCID: PMC7296776.

Funding:

- PREDICT Prostate: The Evelyn Trust GBP47,000 (2016)
- PREDICT Prostate: The Urology Foundation GBP50,000 (2018-2019)

Recognition for PREDICT Breast:

- 2018 Office for National Statistics Research Excellence People's Choice Award
- 2019 National Cancer Research Institute Research Excellence Impact Award.

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

Impact on clinical practice

Incorporation into UK guidelines:

- In 2018, PREDICT Breast became the only tool recommended by UK NICE for planning the use of adjuvant therapy for breast cancer and the management of early and locally advanced disease (Guideline NG101): *"Use the PREDICT tool to estimate prognosis and the absolute benefits of adjuvant therapy for women with invasive breast cancer*" [A].
- NICE also recommend the use of PREDICT Breast for all patients with early breast cancer prior to other advanced molecular profiling (Guideline NG34, 2018) [A].
- PREDICT Breast is also endorsed by the Breast Cancer Clinical Expert Group [A].
- In 2019, NICE endorsed PREDICT Prostate as a resource to support decision making in the management of prostate cancer (Guideline NG131) [B].
- The East of England Cancer Alliance (EOECA) also proposed PREDICT Prostate for clinical consideration in the Best Practice Prostate Pathway '*...to provide a standardised personalised tool to help men make decisions via the MDT and clinic*'.
- Both PREDICT Breast and PREDICT Prostate are suggested by Cancer Research UK (CRUK) as tools to help patients make treatment decisions [A, B].

Incorporation into international guidelines: In 2016, the American Joint Committee on Cancer (AJCC) established 13 criteria against which any new prognostic model should be evaluated before use in the clinical setting. PREDICT Breast was the only model to pass all criteria. It has since been officially endorsed in the 2018 edition of the AJCC: Cancer Staging manual*: "Thirty prognostication tools for breast cancer were identified and reviewed against a checklist derived from the PMC guidelines. Only two tools, Adjuvant! Online* [no longer available] *and PREDICTv1.2 (incorporation of HER2 into PREDICT, also known as PREDICT-Plus) were found to have met all predefined AJCC inclusion and none of the exclusion criteria"* [C].

Impact on patient health and wellbeing

Breast cancer affects >2,000,000 women globally each year, while around 1,300,000 new cases of prostate cancer are diagnosed globally each year. PREDICT Breast and PREDICT Prostate are both provided as free online tools by Public Health England (https://breast.predict.nhs.uk/ and https://prostate.predict.nhs.uk) to help cancer patients and physicians across the world make an informed decision about treatment options. Since 2014, PREDICT Breast received over 1,250,000 visits across the UK, North America, Europe, Australasia and South America [D]. Between its launch in March 2019 and November 2020, the PREDICT Prostate tool has been visited 28,000 times by 19,000 independent users from over 110 countries, and as of November 2020, it is averaging 250 visits a month with 51.5% as new users [D].

In the breast units of most UK hospitals, PREDICT Breast has, as recommended by NICE guidelines [A], been adopted as the clinical management decision tool of choice; as of 2018, according to NICE, '*most healthcare professionals […] use the PREDICT [Breast] tool*' [E]. The effectiveness and user-friendly nature of the PREDICT Breast online tool is evidenced by qualitative user feedback from oncologists, such as that provided by clinicians to the Cambridge Winton Centre for Risk and Evidence Communication [E], for example:

- "*I like the different ways of presenting the data to patients and the addition of the risk of death from causes other than breast cancer which provides a context for discussion*."
- "*We use PREDICT tool often in clinic and find it very helpful in order to help patients understand and make informed decisions about their adjuvant treatment. Thank you!*"

Patients have also provided feedback on PREDICT Breast [E]:

- 24th Feb 2020: "*Thank you, you have made my decision easier.*"
- 23rd January 2019: "*Hello. Thank you for this wonderful online tool for woman such as myself. By the way, I reside in Bangkok, Thailand*."

Similarly, PREDICT Prostate has received positive user feedback from UK based Consultant Urologists and Prostate Cancer International, a cancer support website [E]:

- "*Predict is simply brilliant, Using it on my iPad with patients on a daily basis. Well done for producing such a great patient aid* "– JA, Stevenage, May 2019.
- "*I use it and it's a fantastic tool to guide discussions and help reassure patients!*" -HY, Kent, July 2020.
- "*Men ask me all the time, What is my risk for ED / incontinence / bowel dysfunction. My answer now will be that, "That's impossible to project accurately on an individualized basis, but the PREDICT Prostate system can give you a decent estimate of that risk at 3 years post-diagnosis". I live in the very real world of "What do you think I should I do?" You've just made answering that question a lot easier for tens of thousands of men every year!*" – Prostate Cancer International website**,** April 2019.

Impact on treatment planning: A clinical review of 200 patients managed by the Cambridge Breast Unit Multidisciplinary Team found 7.5% of breast cancer patients who would have been classified as low risk and not offered chemotherapy, were classified as high risk by PREDICT Breast and offered chemotherapy. Conversely, 11% of patients who would have been classified as high risk and offered chemotherapy, were reclassified as low risk and spared chemotherapy [F]. A conservative estimate – based on PREDICT Breast being the only tool recommended for adjuvant therapy planning by NICE and the number of online recorded visits to the website – is PREDICT Breast was used for at least 25% (100,000) of 400,000 new UK breast cancer cases recorded between 2013 and 2020. Extrapolation suggests that in the UK since 2013, PREDICT Breast will have resulted in ~7,500 women being offered chemotherapy who would otherwise not have been, and ~11,000 women being spared unnecessary chemotherapy.

A significant impact of PREDICT Prostate on treatment planning was shown also in a study of ~200 doctors and specialist nurses. This revealed PREDICT Prostate led to a ~60% reduction in the likelihood of recommending radical treatment to patients, with 80% of clinicians stating PREDICT Prostate is a useful clinical tool [G].

The PREDICT Prostate patient impact study (2018-2020) further demonstrated benefit to patients. This study involved 156 patients across eight UK centres, randomised to either standard of care (SOC) information (n=75), or SOC and the PREDICT Prostate web-tool (n=81). Mean decisional conflict scores (a measure of perception of uncertainty in choosing options) were 21.5 and 15.9 in the SOC and PREDICT Prostate groups respectively, representing a 26% reduction (p=0.01). Anxiety was not increased in the PREDICT arm. In total, 58% of men reported PREDICT Prostate estimates for prostate cancer specific mortality were lower than expected and 35% were less likely to select radical treatment. Over 90% of patients in the PREDICT Prostate group found it useful and would recommend it to others [H].

Impact on the economy

Cost savings due to reduction in overtreatment of cancer: Overtreatment of cancer incurs unnecessary costs for the NHS, principally through avoidable treatment expenses and the management of any side effects. As detailed above, it is estimated that PREDICT Breast has resulted in ~7,500 more women with breast cancer in the UK being offered chemotherapy, and ~11,000 women being spared unnecessary treatment, with associated cost savings to the NHS relating to the cost of adjuvant chemotherapy for 4,500 women.

Overtreatment of prostate cancer can result in significant costs for unnecessary therapy (e.g. prostatectomy costs ~GBP7,000 [2020/21 NHS National Tariff Payment System]) and side effect management (e.g. incontinence, erectile failure, bowel dysfunction) without any clear benefit to patient survival. Data from the National Prostate Cancer Audit shows that 4-8% of men with low-risk disease and 30-40% of men with intermediate risk disease for whom use of PREDICT Prostate would be suitable, are receiving potentially unnecessary radical therapy every year [G]. Based on 19,000 UK visitors to PREDICT Prostate since 2019 [A, H], and on the figures from the PREDICT Prostate Study [G] in which 35% (approximately 6,600) decided not to proceed with radical treatment, such as prostatectomy, this would equate to NHS savings of approximately GBP46,000,000 per year.

Licensing of PREDICT algorithm: the PREDICT Breast algorithm has been licensed to Portable Medical Technologies and is incorporated into their OncoAssist app. The PREDICT algorithm has been licensed by Cambridge Enterprise to Portable Medical Technologies (whose clients include Microsoft, AMGEN, Dorset Healthcare NHS Foundation Trust and The Clatterbridge NHS Cancer Centre) and it is incorporated into their OncoAssist app. **[text removed for publication]** [I]. In March 2020 PREDICT Breast and PREDICT Prostate were approved as medical devices under EU Directive 93/42/EEC allowing for rollout and use in clinical settings across Europe [J].

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

[A] Impact of PREDICT Breast on UK guidelines and clinical practice:
(i) NICE Guideline 101: Early and locally advanced breast cancer: diagnosis and management (p13, section 1.6.8). (ii) NICE Diagnostic Guideline 34: Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer (p4, section1). (iii) Breast Cancer Clinical Expert Group clinical advice to cancer alliances for the provision of breast cancer services, 2017. (p13, s 5.2.34 and p14, 5.2.41). (iv) CRUK support for PREDICT Breast (p 3).

[B] Impact of PREDICT Prostate on UK guidelines and clinical practice:
(i) NICE listing of PREDICT Prostate as an 'Endorsed Resource'. (ii) CRUK support for the PREDICT Prostate (p5). (iii) The East of England Cancer Alliance recommendation that PREDICT Prostate is adopted as a tool in Multidisciplinary meetings across the region in their East of England Cancer Alliance Best Practice Prostate Pathway (p3, p11).

[C] Impact of PREDICT tools on international clinical recommendations: The American Joint Committee on Cancer. AJCC Cancer Staging Manual. 8 ed: 2016 (Table 48.6, p 623)

[D] Evidence of global usage of the PREDICT tools: (Source: Google Analytics).

[E] Evidence of support from clinicians for use of the PREDICT tools:
(i) Qualitative user feedback statements collected by the Winton Centre for Risk and Evidence Communication, University of Cambridge, UK. (ii) Qualitative user feedback statements collected by Vincent Gnanapragasm (iii) NICE guidance referencing wide use of PREDICT Breast

[F] Evidence PREDICT Breast spares unnecessary treatment: Loh SW *et al*. A comparison of chemotherapy recommendations using Predict and Adjuvant models. *European Journal of Surgical Oncology* 2011; 37(5):S21-S22.

[G] Evidence PREDICT Prostate spares unnecessary treatment:
(i) Thurtle DR, *et al*. Understanding of prognosis in non-metastatic prostate cancer: a randomised comparative study of clinician estimates measured against the PREDICT Prostate prognostic model. Br J Cancer. 2019 Oct;121(8):715-718. doi: 10.1038/s41416-019-0569-4. (ii) Parry MG, *et al.* Risk stratification for prostate cancer management: value of the Cambridge Prognostic Group classification for assessing treatment allocation. *BMC Med* 18, 114 (2020). https://doi.org/10.1186/s12916-020-01588-9 (iii) National Prostate Cancer Audit: Patient Summary of Annual Report 2019.

[H] Impact on patient wellbeing: Thurtle DR, *et al*. Clinical impact of the Predict Prostate risk communication tool in men newly diagnosed with non-metastatic prostate cancer: a multi-centre randomised controlled trial. Submitted January 2021.

[I] Impact on economy: Confidential - Report from Cambridge Enterprise.

[J] Evidence of EU approval of PREDICT Breast and PREDICT Prostate as medical devices: EU Declaration of Conformity.