Institution: University of Cambridge		
Unit of Assessment: 2 Public Health, Health Services and Primary Care		
Title of case study: Improving outcomes in breast cancer by enabling better targeting of chemotherapy		
Period when the underpinning research was undertaken: 2009 - 2017		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): Paul Pharoah	**Role(s) (e.g. job title):** Professor of Cancer Epidemiology	**Period(s) employed by submitting HEI:** Oct 1999 – present
Period when the claimed impact occurred: Aug 2013 – present		
Is this case study continued from a case study submitted in 2014? N		

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

Cambridge University-led collaborative research has addressed the challenge of improving health outcomes for women diagnosed with breast cancer. PREDICT– a powerful, user-friendly, web-based prediction tool – supports decision-making about potentially life-altering use of chemotherapy. Endorsed for use by NICE, the American Joint Committee on Cancer, and other major national and international bodies, PREDICT is used in more 200 countries and is accessed 350,000 times per year, supporting optimisation of decisions and counselling of women. In the UK alone, PREDICT has been used with at least 100,000 women, of whom at least 18,500 have been able to make better decisions about chemotherapy thanks to the more precise risk estimates offered by PREDICT, contributing towards improved prognosis, reduced distress, and decreased healthcare costs.

2. Underpinning research (indicative maximum 500 words)

Addressing a common dilemma – whether to use chemotherapy in early breast cancer

Women in the UK have a one in eight lifetime risk of being diagnosed with breast cancer, and more than 55,000 women are diagnosed with the disease each year. It remains one of the leading causes of death. Women with early breast cancer are often faced with the dilemma of whether to have supplementary ("adjuvant") chemotherapy – treatment given in addition to surgery, with the aim of stopping the cancer coming back.

Cross-sectoral, multidisciplinary research

Cambridge University-led research, carried out in close collaboration with women themselves, Public Health England, Cancer Research UK (CRUK), and other stakeholders, has led to the development of PREDICT, a highly practical online tool to support patients and healthcare professionals understand how different treatments for early invasive breast cancer might improve survival rates after surgery [1].

PREDICT was developed through a collaboration between the University of Cambridge, the Cambridge Breast Unit, and the UK's Eastern Cancer Registration and Information Centre (ECRIC, now part of the National Cancer Registration and Analysis Service). The website for PREDICT was built by the Winton Centre for Risk & Evidence Communication at the University of Cambridge.

Development of the prediction tool

The tool has evolved through two major versions as the evidence-base has advanced. Version 1 was based on Cambridge-led analysis of survival data on 5,700 women with early breast cancer treated between 1999 and 2003 [2] sourced from ECRIC after linkage to death certification data. This work allowed identification key predictors of survival and the production of a prognostic model, which was then validated in two independent datasets, one from the West Midlands and one from Canada [3].

An evaluation of PREDICT version 1 in a cohort of 3000 women aged 40 years at time of diagnosis showed accurate long-term (eight- and ten-year) prediction of outcomes for younger women. However, it was less accurate in its short-term predictions, and in particular was inclined to underestimate short-term (five-year) survival for younger women [4]. Among older patients, an evaluation found that PREDICT accurately predicted five-year overall survival, but slightly overestimated ten-year overall survival (de Glas et al. 2016).

Improvement of the tool

To build a new model that could address the limitations of the original, Cambridge researchers undertook a fresh analysis. Among other things, the updated model took into account age at diagnosis. It also more reliably characterised relationships between survival and initial tumour size and whether the cancer had already spread to lymph nodes in the armpit. This new version of PREDICT (version 2) offers improved accuracy of clinical predictions.

The improvements of the new model were demonstrated both in the accuracy of the newly developed model development and when evaluating the new model in separate "validation" datasets. In particular, the new version was more accurate in estimating the number of breast cancer deaths, and improved the estimation of cancer-specific mortality in younger women [5]. PREDICT version 2 has subsequently been robustly validated both by Cambridge researchers [6] and by several other research groups, using multiple independent datasets (Mokbel et al. 2017; van Maaren et al. 2017; Wu et al. 2017; Gray et al. 2018).

Facilitating wide access to the tool

A new web interface for PREDICT (version 2.1) was introduced in 2018, after co-production with users, including patients, doctors, and other key stakeholders to enhance its graphic design, comprehensiveness, and user-friendliness, and incorporate further refinements to the model. It is hosted by Public Health England at www.predict.nhs.uk.

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

1. Loh SW, Rodriguez-Miguelez M, **Pharoah P**, Wishart G. A comparison of chemotherapy recommendations using Predict and Adjuvant models. *European Journal of Surgical Oncology* 2011; 37(5):S21-S22.
2. 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 Research* 2010; 12(1):R1. doi:10.1186/bcr246 *
3. Wishart GC, Rakha E, Green A, Ellis I, Ali HR, Provenzano E, Blows FM, Caldas C, **Pharoah PD.** Inclusion of KI67 significantly improves performance of the PREDICT prognostication and prediction model for early breast cancer. *BMC Cancer* 2014;14:908. doi:10.1186/1471-2407-14-908*
4. Maishman T, Copson E, Stanton L, Gerty S, Dicks E, Durcan L, Wishart GC, **Pharoah PD**, Group PS, Eccles D. An evaluation of the prognostic model PREDICT using the POSH cohort of women aged 40 years at breast cancer diagnosis. *British Journal of Cancer* 2015; 112(6):983-991. doi:10.1038/bjc.2015.57*
5. Candido Dos Reis FJ, Wishart GC, Dicks EM, Greenberg D, Rashbass J, Schmidt MK, van den Broek AJ, Ellis IO, Green A, Rakha E, Maishman T, Eccles DM, **Pharoah PD**. An updated PREDICT breast cancer prognostication and treatment benefit prediction model with independent validation. *Breast Cancer Research* 2017;19:58. doi:10.1186/s13058-017-0852-3*
6. Engelhardt EG, van den Broek AJ, Linn SC, Wishart GC, Rutgers EJT, van de Velde AO, Smit V, Voogd AC, Siesling S, Brinkhuis M, Seynaeve C, Westenend PJ, Stiggelbout AM, Tollenaar R, van Leeuwen FE, van 't Veer LJ, Ravdin PM, **Pharoah PD**, Schmidt MK. Accuracy of the online prognostication tools PREDICT and Adjuvant! for early-stage breast cancer patients younger than 50 years. *European Journal of Cancer* 2017; 78:37-44. doi:10.1016/j.ejca.2017.03.015 *

*These publications have been peer reviewed, providing evidence of research quality.

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

Improving health outcomes for women diagnosed with breast cancer

The most common cancer among women**,** breast cancer affects more than two million women each year worldwide (World Cancer Research Fund statistics). Women with early breast cancer are often faced with making decisions about whether to have adjuvant chemotherapy – treatment given in addition to surgery to reduce the chances of the cancer coming back.

One risk is over-treatment: women may have an invasive and unpleasant therapy that perhaps

they do not need, since it will not increase their chances of survival. Another risk is under-treatment, where the therapy is not provided even though it might improve outcome. Information provided by the PREDICT tool helps patients make decisions about whether or not adjuvant chemotherapy is right for them.

The value of the PREDICT tool has been recognised by policy-makers and professional organisations worldwide. By improving the effective and efficient targeting of treatment, PREDICT has globally contributed towards better clinical outcomes, reduced patient distress, and avoided unnecessary healthcare procedures and costs.

International endorsement of PREDICT

In March 2020 PREDICT was approved as a medical device under EU Directive 93/42/EEC [A]. Guideline statements nationally and internationally recommend use of the PREDICT tool to help better target chemotherapy among women with early breast cancer. In 2016, the American Joint Committee on Cancer (AJCC), a world-leading organisation in the promotion of evidence-based standards for cancer management, officially endorsed the use of PREDICT. It affirmed this endorsement in the most recent edition of the AJCC Cancer Staging manual. PREDICT is the only available model that has passed all 13 criteria established by AJCC for the evaluation of a prognostic model before introduction in clinical settings [B].

> *"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]

PREDICT is also the only tool recommended by the UK's National Institute for Health and Care Excellence (NICE) for adjuvant therapy planning for breast cancer, per its guideline on diagnosis and management of early and locally advanced disease (2018): *"Use the PREDICT tool to estimate prognosis and the absolute benefits of adjuvant therapy for women with invasive breast cancer"* [D].

Use of PREDICT is also directed by NICE prior to use of costly gene-expression profiling tests to guide adjuvant chemotherapy decisions in early breast cancer, in its *Diagnostic Guideline 34: Tumour profiling tests* (2018) [E].

Recognition of PREDICT

PREDICT has won several national awards, including the 2018 Office for National Statistics Research Excellence People's Choice Award and the 2019 National Cancer Research Institute Research Excellence Impact Award. 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] [F].

Widespread use of PREDICT in the NHS

In the breast units of most UK hospitals, PREDICT has, as recommended by NICE guidelines, been adopted as the clinical management decision tool of choice; as of 2018, according to NICE, "most healthcare professionals […] use the PREDICT tool" [G]. Recommended as a risk prediction tool by the Breast Cancer Clinical Expert Group report [H], it is also the only tool mentioned by Cancer Research UK, the world's largest independent cancer research charity, in its information for patients on treatment options for breast cancer:

> *"The computer tells how much each treatment reduces the chance of the cancer coming back. The computer programmes also give information about the risk of side effects from each treatment. One commonly used programme is called Predict."* [I]

The usefulness and user-friendly nature of the PREDICT online tool is evidenced by qualitative user feedback. For example, testimony provided to the Winton Centre for Risk and Evidence Communication by clinicians includes statements such as:

- *"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!" [G]*

Many women with breast cancer use the tool themselves to better understand their own risk, enabling them to be more informed in their discussions with oncologists about treatment options. The close involvement of patients in their treatment options is evidenced through the Breast Cancer Now patient forum (forum.breastcancernow.org) where patients regularly discuss the PREDICT tool and share personal experiences. An online survey conducted by the Winton Centre found that women generally favoured taking part in the decision-making process and understanding the risks involved. Comments included the following:

- *"If I were being offered alternatives I would want to take ownership of that."*
- *"I would want to know information to have a better conversation the next time I see my doctor."*
- *"I don't want to go through a lot of extra suffering if it's not really going to make me live much longer." [J]*

Global uptake of PREDICT

Since its initial launch in 2011, worldwide usage of PREDICT has grown substantially. It is now used in over 200 countries. Use of the tool has increased dramatically since 2014, with a cumulative total of over 1.25 million sessions (Figure 1 Panel A). This includes around 330,000 sessions in the UK, plus hundreds of thousands across North America, Europe, Australasia and South America (Figure 1 Panel B). By early 2020, the tool was being accessed at a rate of around 30,000 times per month [K].

Because PREDICT is a freely available open access tool, its uptake in low- and middle-income countries has been high. A 2019 online survey of 100 breast cancer oncologists in India found

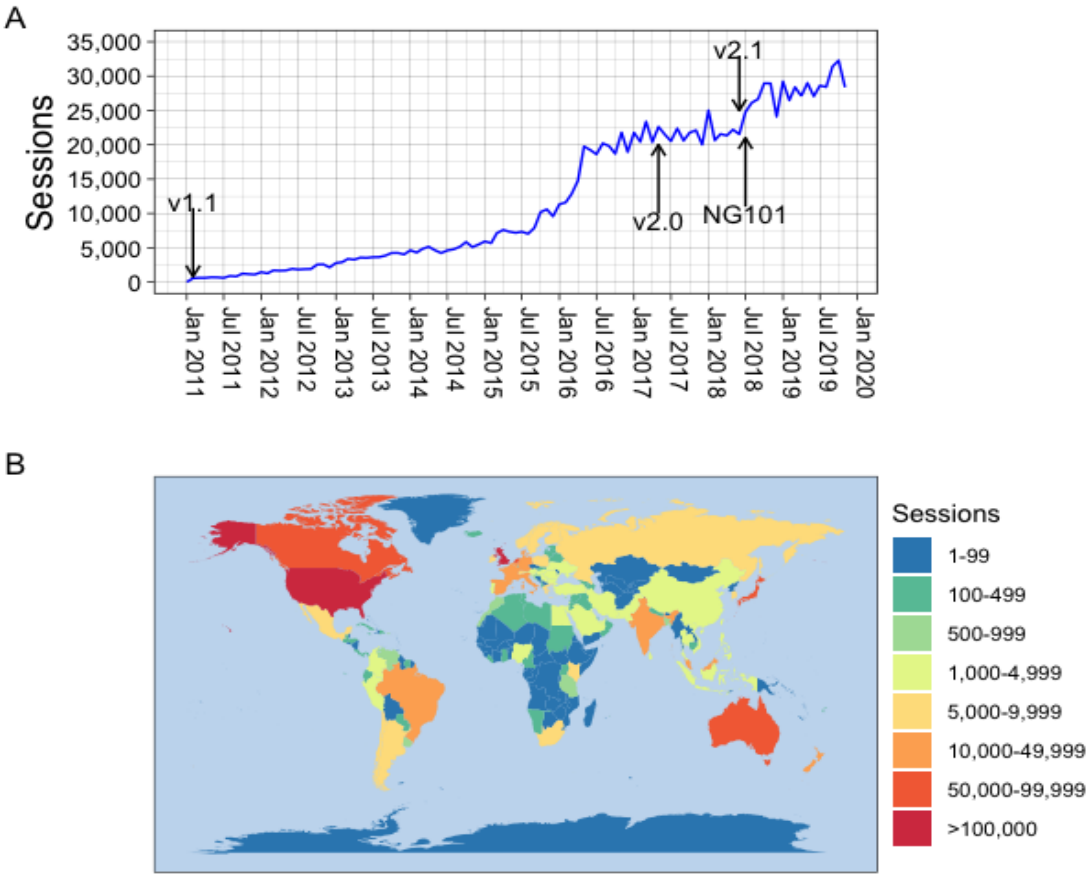

Figure 1. Panel A: Web sessions each month since launch in 2011. NG101 is when the NICE Guideline 101 [D] was released. Panel B: Web sessions by country since August 2013 [Source: K].

that 58% reported using PREDICT online for adjuvant decision making, and 94% felt that PREDICT online could be used as an alternative to genomic tools in resource-constrained

settings [L]. Versions of PREDICT have been released in French and Spanish [J].

Impact on clinical practice and health outcomes

A clinical review of 200 patients managed by the Cambridge Breast Unit multidisciplinary team found that 7.5% of patients who would otherwise have been classified as low risk and therefore would not have been offered chemotherapy were classified as high risk by PREDICT and appropriately offered chemotherapy. Conversely, 11% of patients who would have been classified as high risk – and therefore offered chemotherapy – were reclassified as low risk and spared chemotherapy [1]. If these women had instead received unnecessary treatment requiring resource-intensive care in hospital or clinic, most would have suffered side-effects and other morbidities related to the therapy.

A conservative assumption – given the number of recorded sessions, and given that it is the only tool recommended for adjuvant therapy planning by NICE – is that PREDICT was used for at least 25% of the approximately 400,000 new breast cancer cases recorded in the UK between 2013 and 2020. Extrapolation would then suggest that, because of PREDICT, around 7,500 women with breast cancer will have been offered appropriate chemotherapy who would otherwise have not received it. Conversely, around 11,000 women will have been appropriately spared chemotherapy that they did not need. According to NICE [D], adjuvant chemotherapy costs tens of thousands of pounds per women treated, implying that, by sparing thousands of women from unnecessary chemotherapy, PREDICT has helped the NHS save many millions of pounds in addition to its direct health benefits.

These estimates of impact are likely to be conservative because the assumption of use of PREDICT for 25% of patients diagnosed during 2013-2020 is modest. PREDICT is the only tool recommended for adjuvant therapy planning by NICE, and over 300,000 PREDICT sessions were recorded in the UK during this period.

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

A. EU declaration of conformity of PREDICT as a medical device.
B. Kattan MW, Hess KR, *et al.* American Joint Committee on Cancer acceptance criteria for inclusion of risk models for individualized prognosis in the practice of precision medicine. CA Cancer J Clin 2016, 66(5):370-374.
C. American Joint Committee on Cancer: AJCC Cancer Staging Manual, 8th edn: Springer International Publishing; 2016 p. 1.
D. National Institute for Health and Care Excellence: Early and locally advanced breast cancer: diagnosis and management. 2018 (NG101) pp. 13–14, section 1.6.8
E. National Institute for Health and Care Excellence: Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer. 2018 (vol. DG34).
F. **Confidential** report from Cambridge Enterprise.
G. **(i)** https://www.nice.org.uk/guidance/ng101/chapter/Rationale-and-impact; **(ii) Confidential** statements from clinicians and patients who have benefited from PREDICT Breast from survey conducted by the University of Cambridge Winton Centre for Risk and Evidence Communication.
H. Breast Cancer Clinical Expert Group: Clinical Advice to Cancer Alliances for the Provision of Breast Cancer Services 2017 p. 14.
I. Cancer Research UK website Treatment options p. 2.
J. Effective patient communication: **(i)** Facilitating clear communication of breast cancer treatment options: User-centred design (in press). University of Cambridge Winton Centre for Risk and Evidence Communication; **(ii)** Making prognostic algorithms useful in shared decision-making: Patients and clinicians' requirements for the Predict: Breast Cancer interface G.D. Farmer, G.M. Pearson, W.J. Skylark, A.L.J. Freeman, D.J. Spiegelhalter doi: 10.1101/2020.11.16.20232348
K. Google Analytics data showing the global number of users accessing PREDICT Breast.
L. Batra A, Patel A, Gupta VG, et al. Oncotype DX: Where Does It Stand in India?. *J Glob Oncol*. 2019;5:1-2. doi:10.1200/JGO.19.00151