Institution:
University of Cambridge

Unit of Assessment:
UoA2

Title of case study:
Development of risk prediction algorithms for familial breast and ovarian cancer and their use for genetic counselling and screening purposes.

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

Basic and applied research at the University of Cambridge has culminated in a widely-used risk prediction algorithm ("BOADICEA") for familial breast and ovarian cancer. This user-friendly web-based tool predicts the likelihood of carrying mutations in breast and ovarian cancer high-risk genes (*BRCA1* and *BRCA2*), and the risks of developing breast or ovarian cancer. BOADICEA has been adopted by several national bodies including NICE in the UK (2006 until present), the American Cancer Society and the Ontario Breast Screening Program (both since 2011) for identifying women who would benefit from *BRCA1/2* mutation screening, intensified breast cancer screening and chemoprevention.

2. Underpinning research (indicative maximum 500 words)

Researchers: Department of Public Health and Primary Care: Prof Easton (University Lecturer, 1995-1999; Reader, 1993-2003; Professor, since 2003) and Dr Antoniou (post-doctoral fellow 2001-2009; CR-UK Senior Research Fellow 2009-13; Reader since 2013).

Research setting: BOADICEA was developed using primary research findings from the Centre for Genetic Epidemiology at the University of Cambridge since 1995. The Centre is the host for a number of large-scale epidemiological studies and has played a leading role in the identification and characterisation of breast (and other) cancer susceptibility variants.

Underpinning data and methods: The models were developed using data from local and national studies collected from 1996, combined with data from large international collaborative studies coordinated at the Centre for Cancer Genetic Epidemiology [Research ref 2]. Using the largest world-wide series of breast cancer patients screened for *BRCA1* and *BRCA2* mutations, Dr Antoniou and Prof Easton used advanced statistical methods in 2002-2003 to estimate the breast and ovarian cancer risks for *BRCA1* and *BRCA2* mutation carriers [Research ref 1]. In parallel between 2001-2008, Dr Antoniou and Prof Easton developed novel statistical techniques to model susceptibility to disease within families [Research ref 2]. These data and methods formed the basis of developing the BOADICEA algorithm [Research ref 2]. This was the first algorithm to model comprehensively genetic susceptibility to breast cancer, based on the largest available data resources worldwide. Between 2006 and 2008, Dr Antoniou led the analysis to evaluate risk prediction algorithms for familial breast cancer which involved the large majority of clinical genetics centres in the UK [Research ref 3]. This was the largest study of its kind, including 1934 families. It demonstrated that BOADICEA was well-calibrated and that it provided the best discrimination among available risk models. Thus, BOADICEA was shown to be a valid tool that could be used for genetic counselling of familial breast cancer.

Additional research to broaden applicability of BOADICEA: Since 2007 Prof Easton has been leading world-wide efforts to identify common breast cancer susceptibility alleles through genome-wide association studies. Sixty of the 67 known breast cancer alleles have been identified through studies at the University of Cambridge [Research ref 4]. Prof Easton and Dr Antoniou have been coordinating the analytical efforts for the Breast Cancer Association Consortium (BCAC) and Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA). These consortia have played a key role in the characterisation of novel genetic variants and of risks for *BRCA1* and *BRCA2* mutation carriers [Research refs 4,5]. Recent risk modelling work, by Dr Antoniou and Prof Easton, has also demonstrated that the research has direct clinical applicability for women who carry the BRCA1 and BRCA2 mutations who are among the first patients for whom the common breast cancer susceptibility variants can be used for risk prediction [Research ref 5]. Similarly, they have shown that common breast cancer susceptibility alleles identified from BCAC may have a role in targeted prevention of breast

cancer [Research ref 6].

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

1. Antoniou A, Pharoah PD, Narod S, ….. Easton DF (2003). Average Risks of Breast and Ovarian Cancer Associated with BRCA1 or BRCA2 Mutations Detected in Case Series Unselected for Family History: A Combined Analysis of 22 Studies. Am J Human Genet 72: 1117-30 (>1000 citations)

2. Antoniou AC, Cunningham AP……. Easton DF (2008) The BOADICEA model of genetic susceptibility to breast and ovarian cancers: updates and extensions. Br J Cancer 98:1457-66

3. Antoniou AC, …, Easton DF, Pharoah PD (2008) Predicting the likelihood of carrying a BRCA1 or BRCA2 mutation: validation of BOADICEA, BRCAPRO, IBIS, Myriad and the Manchester scoring system using data from UK genetics clinics. J Med Genet 45:425-31

4. Easton DF, Pooley KA et al (2007) Genome-wide association study identifies novel breast cancer susceptibility loci. Nature 447: 1087-93 (>1000 citations)

5. Antoniou AC, Beesley J, McGuffog L,…., Easton DF (2010) Common breast cancer susceptibility alleles and the risk of breast cancer for BRCA1 and BRCA2 mutation carriers: implications for risk prediction. Cancer Res 70:9742-54

6. Pharoah PDP, Antoniou AC, Easton DF, Ponder BAJ (2008) Polygenes, Risk Prediction, and Targeted Prevention of Breast Cancer. New England Journal of Medicine 358: 2796-803

Grants:

- Four programme Grants from Cancer Research Campaign and CR-UK: “Genetic Epidemiology of Cancer”, 1993-2013 (PI for all: D. Easton, funding from 1998 to 2013 £4.5m).
- CR-UK Senior Cancer Research Fellowship (PI: A. Antoniou) “Development of risk prediction algorithms for breast, ovarian and other cancers” 2009-12. £582,038
- CR-UK Project Grant (PI: D. Easton) "Follow-up of Genome Wide Association Studies in Breast Cancer". 2009-11. £161,390
- EC Seventh Framework Programme (FP7) HEALTH-F2-2009-223175 (PI: P Hall, co-PI: D Easton) "Collaborative Oncological Gene-environment Study (COGS)" 2009-14 £3,064,186
- Genome Canada/CIHR (PI: J. Simard, Co-I D. Easton, Co-I A. Antoniou) "Personalised Risk Stratification for Prevention and Early Detection of Breast Cancer" 2013-17 Total Budget: $11 559 128 ($483,782 to D. Easton; $330,450 to A. Antoniou)

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

Outcome of research: A web-based user-friendly interface was developed for BOADICEA (Impact reference 5.1) which allows users to obtain rapid estimates of *BRCA1* and *BRCA2* carrier probabilities and risks of developing breast or ovarian cancer. This web-tool was made available for general use in January 2008.

Scope and reach of BOADICEA: The web-interface of BOADICEA currently has more than 2500 registered users from the UK and 45 other countries (Europe, North America and Australia and other). Periodic monitoring of the web servers during 2012 revealed an average of 50 concurrent users at any given time during a working week. The chief beneficiaries of BOADICEA have so far been healthcare providers, notably organisers of genetic testing (clinical geneticists and genetic counsellors), breast cancer screening and chemoprevention programmes, oncologists and general practitioners, family members of women with breast cancer or otherwise at high risk of the disease, women with *BRCA1* or *BRCA2* mutations and their families who could be counselled for their breast or ovarian cancer risks, the general public and bodies involved in the planning of screening or intervention trials.

Indicators of extent of impact: BOADICEA is one of the risk prediction algorithms currently recommended by the UK National Institutes of Health and Clinical Excellence (NICE, Impact reference 5.2, since 2006). It was also recommended by equivalent bodies in other countries (e.g. American Cancer Society and Ontario Breast Screening program incorporated in guidelines since

2011 for determining eligibility for screening of high risk patients (Impact references 5.3-5.6).

Nature of impacts: *BRCA1* and *BRCA2* mutation screening is expensive and is associated with adverse psychosocial effects. Similarly, breast cancer screening is expensive and has adverse consequences including over-diagnosis. Chemoprevention is effective for breast cancer prevention but has adverse side effects. Thus, it is crucial that these interventions are targeted at the individuals most likely to benefit. Use of BOADICEA has had several inter-related impacts in this regard:

(1) To identify women eligible for screening by magnetic resonance imaging (MRI) so that available resources are targeted to those most likely to benefit most from early cancer diagnosis, while minimising the associated health service costs [Impact references 5.2, 5.5].
Under NICE current guidelines, women at raised risk of developing breast cancer are offered mammographic screening from age 40, and a subset of high risk women, including BRCA1 and BRCA2 mutation carriers, are offered screening by MRI. MRI screening is more sensitive than mammography but is approximately ten-fold more expensive. BOADICEA was first adopted by NICE in 2006 as a risk prediction algorithm for classifying women at risk of familial cancer into three risk categories: women at or near population risk, raised risk, or high risk. BOADICEA remains one of only two recommended breast cancer/carrier risk assessment tools by the revised NICE guidelines (June 2013, Impact reference 5.2). Women predicted to be at raised or high risk are offered annual mammographic surveillance from age 40, compared to age 50 under the standard NHS screening programme. Women at high risk are offered MRI screening.

(*2) Clinical genetics services are now using BOADICEA to refer women for BRCA1 and BRCA2 mutation screening.*
Predictions obtained by BOADICEA are being used to provide a consistent way for referring individuals for *BRCA1* and *BRCA2* mutation screening (NICE guidelines currently recommend a combined mutation carrier prediction of over 10% although the threshold varies across countries, Impact reference 5.2). This allows targeting mutation screening to those individuals most likely to carry *BRCA1* and *BRCA2* mutations, thus minimising the psychosocial effects related to mutation screening and the associated costs of mutation screening. Women found to carry *BRCA1* and *BRCA2* mutations could then be offered more intensive screening, prophylactic surgery or other risk reduction options.

(3) To guide chemoprevention and prophylactic surgery options for women at high risk.
The predicted risks provided by BOADICEA are helping clinicians and high-risk women take informed decisions when faced with the options of risk reducing surgery, regular screening or chemoprevention. According to the revised NICE guidelines (Impact reference 5.2) women classified to be at high-risk of developing breast cancer may be offered chemoprevention with Tamoxifen or Raloxifene.

(4) To counsel women carrying BRCA1 and BRCA2 mutations
BRCA1 and *BRCA2* cancer risk estimates based on BOADICEA are being used to counsel women carrying such mutations. These estimates have also been widely used by various support groups such as the patient support group FORCE (impact reference 5.7)

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

5.1 BOADICEA web application: http://ccge.medschl.cam.ac.uk/boadicea/

5.2 National Institutes of Health and Clinical Excellence, UK: CG41 Familial breast cancer: full guideline. 2013: http://www.nice.org.uk/nicemedia/live/14188/64202/64202.pdf (paper 2 cited on pages 8,13, 30).
5.3 American Cancer Society: Smith RA, et al. Cancer Screening in the United States, 2012. A Review of Current American Cancer Society Guidelines and Current Issues in Cancer Screening CA Cancer J Clin. 2012, 62:129-142 (paper 2 cited)
5.4 The U.S. National Society of Genetic Counselors. Riley BD, et al (2012) Essential Elements of Genetic Cancer Risk Assessment, Counseling, and Testing: Updated Recommendations of the

National Society of Genetic Counselors. J Genet Counsel (2012) 21:151–161 (paper 2 cited)
5.5 Ontario Breast Screening Program (Canada): https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=99492 [Paper 2 cited, pages 1, 3, 4]
5.6 Cancer Australia (Australian Government): Familial Risk Assessment – Breast and Ovarian Cancer: http://canceraustralia.gov.au/clinical-best-practice/gynaecological-cancers/familial-risk-assessment-fra-boc. (papers 1, 2 cited: http://canceraustralia.gov.au/clinical-best-practice/gynaecological-cancers/familial-risk-assessment-fra-boc/references.
5.7 FORCE (Facing Our Risk of Cancer Empowered) www.facingourrisk.org/ cites research references 1 and 4 in: http://www.facingourrisk.org/info_research/risk-factors/breast-cancer-risks/advanced.php, specific page at www.facingourrisk.org/search/index.php?query=easton&type=and&results=10&search=1