Impact case study template (REF3b)

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

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

Basic, clinical 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 web-based, user-friendly tool predicts the likelihood of carrying mutations in breast and ovarian cancer high risk genes (BRCA1 and BRCA2), and the risk of developing breast or ovarian cancer. In 2006, BOADICEA was been recommended by the UK National Institutes of Health and Clinical Excellence (NICE: CG41, 2006) and the American Cancer Society (since 2011). In June 2013, NICE recommended BOADICEA in subsequent guidance (CG164). Furthermore, several national bodies have designated BOADICEA as the standard tool to assess eligibility for high risk breast cancer screening.

2. Underpinning research (indicative maximum 500 words)

The defined impact: BOADICEA was developed by researchers (Antonis and Easton) based in the Department of Public Health and Primary Care at Cambridge in 2004 , which was underpinned by primary research carried out over many years by Ponder. The large meta-analysis of BRCA 1 and 2 families ascertained through population based methods (1 - 3) and performed by researchers at Cambridge formed the basis of development for this clinical tool.

Sir Bruce Ponder (Professor of Human Cancer Genetics; 1993; Professor of Oncology 1996 – present; Director, CRUK Cambridge Research Institute 2005-2013; Director, Cambridge Cancer Centre 2005- present) led efforts to collect blood samples and clinical data on large numbers of high risk families with breast cancer, and from 10,000 prevalent and incident cases within the Anglian region. He did this because he realised that these would be required to support the on-going scientific efforts to identify the BRCA1 and 2 genes; and subsequently to define the clinico pathological correlates of these mutations and also for GWAS to find other novel predisposition alleles, which were more common, but less penetrant. Consequently Ponder established the UK Consortium for Breast Cancer Linkage (a national/worldwide network of oncology specialists/ researchers) and was the first chair of the International Consortium for Breast and Ovarian cancer linkage (1989-1993). In order to carry out the collection and genetic research on these large data sets he also co-founded and was Director of the Strangeways Laboratories for Genetic Epidemiology where much of the internationally leading work on the genetics of breast, ovarian and prostate cancer has been done (1996 – 2008).

Work by Ponder and collaborators others refined the mapping of the BRCA1 gene within chromosome 17 q12-21 in 1994/5 (4). In 1995, Ponder's laboratory contributed to the linkage mapping that identified a second susceptibility gene (BRCA2) within a 6-centimorgan interval on chromosome 13q12-13 (5, 6). Ponder's highly significant and ongoing research contributions have led to over 150 high impact papers on breast cancer genetics; 70 of them on BRCA1 and BRCA2, with over 20 of them cited >100 times. Following the cloning of BRCA1 and 2 by MYRIAD Genetics in Utah, Ponder and others led the work to define the penetrance and clinic-pathological correlates of BRCA1 and BRCA2 mutations in familial cancers of the breast, ovary and prostate in 1995 onwards, and also showed the phenotype

such cancers in familial cases (2) and the incidence of such mutations in apparently sporadic cases (3). His more recent work sought to uncover the mechanisms whereby the single nucleotide polymorphisms in the genome (7, 8) that underpin the common genetic risk factors for breast cancer, affect breast cell biology. He recently contributed critical functional analysis to elucidation of the mechanism by which the SNP rs554219 affects risk through altered regulation of cyclin D1, providing new, generalizable, insights into the mechanisms by which risk SNPs have their effects (9).

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

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2. Gayther SA, Warren W, Mazoyer S, Russell PA, Harrington PA, Chiano M, Seal S, Hamoudi R, van Rensburg EJ, Dunning AM, Love R, Evans G, Easton D, Clayton D, Stratton MR, **Ponder BA**. Germline mutations of the BRCA1 gene in breast and ovarian cancer families provide evidence for a genotype-phenotype correlation. Nat Genet. 1995 Dec;11(4):428-33. (cited > 350)
3. **Ponder BAJ**, Day NE, Easton DF, Pharoah PDP, Lipscombe JM, Redman K, Antoniou A, Basham V, Gregory J, Gayther S & Dunning A (2000). Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Br J Cancer 83, 1301-1308. Peer-reviewed article, citations as of July 2013: 62
4. Cornelis RS, Neuhausen SL, Johansson O, Arason A, Kelsell D, **Ponder BA**, Tonin P, Hamann U, Lindblom A, Lalle P, et al. High allele loss rates at 17q12-q21 in breast and ovarian tumors from BRCA1-linked families. The Breast Cancer Linkage Consortium. Genes Chromosomes Cancer. 1995 Jul;13(3):203-10.
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6. Wooster R, Neuhausen SL, Mangion J, …. **Ponder BAJ**, Skolnick MH, Easton DF, Goldgar DE, Stratton MR. Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12-13. Science. 1994;265(5181):2088-90. (cited > 1,000)
7. Easton DF, Pooley KA, …. **Ponder BAJ** (2007) Genome-wide association study identifies novel breast cancer susceptibility loci. Nature 447: 1087-93, DOI: 10.1038/nature05887. (cited > 1,000)
8. Ghoussaini M, Fletcher O, Michailidou K, et al, **Ponder BA**, Chenevix-Trench G, Pharoah PD, Lathrop M, Dunning AM, Rahman N, Peto J, Easton DF. Genome-wide association analysis identifies three new breast cancer susceptibility loci. Nat Genet. 2012 Mar;44(3):312-8
9. French JD, Ghoussaini M, Edwards SL, Meyer KB, …. et al, Ponder BA, Nevanlinna H, Brown MA, Chenevix-Trench G, Easton DF, Dunning AM. Functional variants at the 11q13 risk locus for breast cancer regulate cyclin D1 expression through long-range enhancers. Am J Hum Genet. 2013 Apr 4;92(4):489-503.

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

BOADICEA: Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (1) is a risk model for familial breast and ovarian cancer, which computes BRCA1

and BRCA2 mutation carrier probabilities and age specific risks for breast and ovarian cancer. This model was developed by Antonis and Easton, (Department of Public Health and Primary Care at Cambridge) as a direct result of Ponder's work on the relationship between BRCA1/2 and breast cancer susceptibility, and made use of the large data sets of epidemiological data developed by Ponder. BOADICEA models the simultaneous effects of BRCA1 and BRCA2 mutations. BOADICEA was adopted by NICE in 2006 (CG41; 2) and incorporated into subsequent guidance in June 2013 (3).

Beneficiaries: The beneficiaries of BOADICEA are: 1) healthcare providers, notably organisers of breast cancer screening programmes (e.g., the NHS in the UK); 2) clinicians and genetic counsellors; 3) family members of women with breast cancer or otherwise at high risk of the disease; 4) the general public; 5) research scientists for planning screening or intervention trials and for designing research studies.

Indicators of extent of impact: The web-interface of BOADICEA has been available since November 2007 and currently has more than 1,500 registered users. These include not only clinical geneticists and genetic counsellors but researchers and users from the insurance sector (anonymised ethical data). Users are located in the UK, elsewhere in Europe, North America, Australia, and several other countries. Recent monitoring of the web servers revealed an average of 50 concurrent users at any given time. Clinics in North America and Australia recommend BOADICEA as part of their guidelines and oncology programmes (4, 5).

Nature of impacts: BRCA1 and BRCA2 mutation screening is expensive and is also associated with adverse psychosocial effects. Hence, it is crucial that genetic testing for BRCA1 and BRCA2 is targeted at individuals most likely to be carriers, particularly in the context of the National Health Service (NHS) and other publicly funded health care systems. Use of BOADICEA has had several inter-related impacts in this regard:

(1) To identify women eligible for screening by magnetic resonance imaging (MRI)

Under the guidelines adopted by the UK National Institutes of Health and Clinical Excellence (NICE), women at moderate or high 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 should be offered screening by MRI. MRI screening is more sensitive than mammography but is approximately ten-fold more expensive. BOADICEA was adopted by NICE (2, 3) from 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 and remains the tool of choice to date. Since 2006, women predicted to be at raised or high risk by BOADICEA have been 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. As an ancillary impact in the same vein, BOADICEA has also been used to determine eligibility for entry into the MARIBS screening trial evaluating the efficacy of x-ray mammography and MRI (6). Other guidelines also include BOADICEA data (7)

(2) To refer women for BRCA1 and BRCA2 mutation screening

Predictions obtained by BOADICEA are used by geneticists to refer individuals for BRCA1 and BRCA2 mutation screening (usually a combined mutation carrier prediction of over 20%).

(3) To guide prophylactic surgery and chemoprevention options for women at high risk
The cancer risk predictions of BOADICEA are being used to guide prophylactic surgery and chemoprevention options for women at high risk. As noted above, BOADICEA is one of the risk prediction algorithms recommended in the UK and other countries (e.g. American Cancer

Society and Ontario Breast Screening program incorporated in guidelines since 2011) for determining eligibility for high risk screening (8, 9, 10).

(4) To counsel women carrying BRCA1 and BRCA2 mutations

BRCA1 and BRCA2 cancer risk estimates obtained from the studies in the list of references provided above and 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 FORCE for providing information to individuals at risk of hereditary breast and ovarian cancer (http://www.facingourrisk.org/).

Process of dissemination:

BOADICEA is well established internationally as indicated above. A recent high impact review noted: *"BOADICEA also provided the best discrimination between mutation carriers and non-carriers*" (11)

A web-based user-friendly interface was developed for BOADICEA (http://www.srl.cam.ac.uk/genepi/boadicea/boadicea_home.html) allows users to obtain rapid estimates of BRCA1 and BRCA2 carrier probabilities and risks of developing breast or ovarian cancer.

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

1. Antoniou AC, Pharoah PDP, Smith P, Easton DF (2004). The BOADICEA model of genetic susceptibility to breast and ovarian cancer. Br J Cancer 91:1580-90
2. National Institutes of Health and Clinical Excellence, UK: CG41 Familial breast cancer: full guideline (the new recommendations and the evidence they are based on), October 2006: http://guidance.nice.org.uk/cg41/guidance/pdf/English
3. National Institutes of Health and Clinical Excellence, UK: CG164. Familial breast cancer. June 2013. http://www.nice.org.uk/nicemedia/live/14188/64202/64202.pdf
4. https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=99500
5. http://canceraustralia.gov.au/clinical-best-practice/gynaecological-cancers/familial-risk-assessment-fra-boc/references
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9. Ontario Breast Screening Program: https://www.cancercare.on.ca/pcs/screening/breastscreening/OBSP/
10. 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
11. Amir E, Freedman OC, Seruga B, et al. (2010) Assessing Women at High Risk of Breast Cancer: A Review of Risk Assessment Models. J Natl Cancer Inst: 102: 680-691