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Full Paper

PREDICT Plus: development and validation of a prognostic model for early breast cancer that includes HER2

GC Wishart[1], CD Bajdik[2], E Dicks[3], E Provenzano[3], MK Schmidt[4], M Sherman[5], DC Greenberg[6], AR Green[7], KA Gelmon[8], V-M Kosma[9,10], JE Olson[11], MW Beckmann[12], R Winqvist[13], SS Cross[14], G Severi[15], D Huntsman[16], K Pylkäs[17], I Ellis[18], TO Nielsen[16], G Giles[15], C Blomqvist[17], PA Fasching[12], FJ Couch[19], E Rakha[18], WD Foulkes[20], FM Blows[3], LR Bégin[21], LJ van't Veer[4], M Southey[15], H Nevanlinna[22], A Mannermaa[9,10], A Cox[23], M Cheang[16], L Baglietto[15], C Caldas[3], M Garcia-Closas[24] and PDP Pharoah*,[3]

[1]Cambridge Breast Unit, Addenbrookes Hospital, Cambridge, UK; [2]Cancer Control Research Program, British Columbia Cancer Agency, Vancouver, British Columbia, Canada; [3]Department of Oncology, Strangeways Research Laboratory, University of Cambridge, Worts Causeway, Cambridge CB1 8RN, UK; [4]Division of Molecular Pathology, and Division of Psychosocial Research and Epidemiology, Netherlands Cancer Institute, Amsterdam, The Netherlands; [5]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD, USA; [6]Eastern Cancer Registration and Information Centre, Cambridge, UK; [7]Department of Pathology, School of Molecular Medical Sciences, University of Nottingham, Nottingham, UK; [8]Department of Medical Oncology, British Columbia Cancer Agency, University of British Columbia, Vancouver, British Columbia, Canada; [9]School of Medicine, Institute of Clinical Medicine, Pathology and Forensic Medicine, University of Eastern Finland, Kuopio, Finland; [10]Department of Pathology, Kuopio University Hospital, Kuopio, Finland; [11]Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA; [12]University Breast Center Franconia, Department of Gynecology and Obstetrics, University Hospital Erlangen, Friedrich-Alexander-University, Erlangen, Germany; [13]Laboratory of Cancer Genetics, Department of Clinical Genetics and Biocenter Oulu, University of Oulu and Oulu University Hospital, Oulu, Finland; [14]Academic Unit of Pathology, Department of Neuroscience, University of Sheffield, Sheffield, UK; [15]Cancer Epidemiology Centre, The Cancer Council of Victoria, Melbourne, Victoria, Australia; [16]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, British Columbia, Canada; [17]Department of Oncology, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland; [18]Department of Histopathology, School of Molecular Medical Sciences, Nottingham University Hospitals NHS Trust and University of Nottingham, Nottingham, UK; [19]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA; [20]Program in Cancer Genetics, Departments of Oncology and Human Genetics, McGill University, Montréal, Quebec, Canada; [21]Department of Pathology, McGill University and Hôpital du Sacré, Montréal, Quebec, Canada; [22]Department of Obstetrics and Gynaecology, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland; [23]Department of Oncology University of Sheffield, Institute for Cancer Studies, Sheffield, UK; [24]Division of Genetics and Epidemiology and Breakthrough Breast Cancer Research Centre, Institute of Cancer Research, Sutton, UK

BACKGROUND: Predict (www.predict.nhs.uk) is an online, breast cancer prognostication and treatment benefit tool. The aim of this study was to incorporate the prognostic effect of HER2 status in a new version (Predict +), and to compare its performance with the original Predict and Adjuvant!.

METHODS: The prognostic effect of HER2 status was based on an analysis of data from 10 179 breast cancer patients from 14 studies in the Breast Cancer Association Consortium. The hazard ratio estimates were incorporated into Predict. The validation study was based on 1653 patients with early-stage invasive breast cancer identified from the British Columbia Breast Cancer Outcomes Unit. Predicted overall survival (OS) and breast cancer-specific survival (BCSS) for Predict +, Predict and Adjuvant! were compared with observed outcomes.

RESULTS: All three models performed well for both OS and BCSS. Both Predict models provided better BCSS estimates than Adjuvant!. In the subset of patients with HER2-positive tumours, Predict + performed substantially better than the other two models for both OS and BCSS.

CONCLUSION: Predict + is the first clinical breast cancer prognostication tool that includes tumour HER2 status. Use of the model might lead to more accurate absolute treatment benefit predictions for individual patients.
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Accurate prognostication is essential when selecting the most appropriate adjuvant therapy following surgery for early breast cancer. A number of predictive models are now available to help estimate the survival for individual patients, including the Nottingham Prognostic Index (NPI), Adjuvant and Predict, and to date, these have all been based on known pathological prognostic factors including tumour size, tumour grade and lymph node status. The NPI, first described in 1982 (Haybittle *et al*, 1982), has been prospectively validated (Todd *et al*, 1987; D'Eredita *et al*, 2001) and more recently updated (Blamey *et al*,

2007a) to provide accurate survival estimates following breast cancer surgery, including individual survival estimates (Blamey *et al*, 2007b). The introduction of Adjuvant!, a web-based (www.adjuvantonline.com) prognostication tool, in 2001 (Ravdin *et al*, 2001) went a step further by also providing absolute treatment benefits for hormone therapy and chemotherapy by applying risk reductions from the Early Breast Cancer Trialists Collaborative Group (1998a, b) to breast cancer-specific mortality estimates based on the Surveillance Epidemiology and End Results Program (www.seer.cancer.gov). This model has been validated in case cohorts from British Columbia (Olivotto *et al*, 2005), the Netherlands (Mook *et al*, 2009) and the United Kingdom (Campbell *et al*, 2009).

Prognostication is becoming more sophisticated, and additional prognostic and predictive factors need to be considered in any current prognostic and treatment benefit model. There is a growing body of evidence to show that screen detection confers an additional survival benefit beyond stage shift and also reduces the risk of systemic recurrence when compared with symptomatic cancers of a similar stage (Joensuu *et al*, 2004; Shen *et al*, 2005). Recent studies have shown that the majority of the survival advantage associated with breast screening can be explained by this shift to an earlier stage at diagnosis, and more favourable prognostic factors (Dawson *et al*, 2009), but approximately 25% of the survival advantage is still unexplained (Wishart *et al*, 2008). These findings were recently confirmed in a data set from the Netherlands in which screen detection was associated with a 26 and 38% reduction in all-cause and breast cancer-specific mortality, respectively (Mook *et al*, 2011). The authors from this paper concluded that method of detection should be taken into account when estimating individual prognosis.

Predict is an online prognostication and treatment benefit tool developed in the United Kingdom, which is based on 5694 women diagnosed in East Anglia from 1999 to 2003 (Wishart *et al*, 2010). The model includes mode of detection and provides 5- and 10-year survival estimates as well as treatment benefit predictions at both time points, and it has been validated in an independent case cohort from the United Kingdom and more recently in a British Columbia data set wherein it was also compared with Adjuvant! (Wishart *et al*, 2011). This comparison showed that Predict and Adjuvant! provide accurate overall and breast cancer-specific survival (BCSS) estimates that were comparable. However, the Predict estimates did not utilise the mode of detection component of the model as the mode of detection was not available for the British Columbia cohort. Moreover, Adjuvant! does not take account of the mode of detection. Predict was slightly better calibrated for breast cancer-specific mortality with predicted deaths being within 3.4% of observed deaths compared with 6.7% for Adjuvant!. Both models showed good discrimination with similar area under the receiver-operator characteristic curve (AUC; 0.723 *vs* 0.727 for Predict and Adjuvant, respectively). Predict is now available online at www.predict.nhs.uk.

The aim of this study was to incorporate the prognostic effect of HER2 status into Predict (hereafter referred to as Predict+), and to compare the 10-year survival estimates from Predict+ with Predict, Adjuvant! and the observed 10-year outcome from the British Columbia data set.

METHODS

Prognostic effect of tumour HER2 status

Estimates for the prognostic effect of HER2 status were based on an analysis of data from the Breast Cancer Association Consortium (BCAC). Pathology data from 12 of these studies has been previously published (Blows *et al*, 2010) and the analysis was updated to include data from another 3 studies excluded from

the previous publication because of missing data on basal markers that is not relevant for this analysis (Table 1). However, as the validation cohort for this study overlaps substantially with the British Columbia Cancer Agency (BCCA) case series published in Blows *et al* (2010), this case series was excluded from the BCAC data re-analysis. In addition, all patients diagnosed since 2004 were excluded, to exclude patients likely to have been treated with trastuzumab. In total, HER2 data were available for 10 179 cases (7278 ER-positive and 2931 ER-negative, Table 2) for whom data were also available for age at diagnosis, tumour size ($\leqslant 2$, 2–4.9 and 5+ cm), tumour grade and nodal status. We estimated the hazard ratio for HER2-positive disease compared with HER2-negative disease using a Cox proportional hazards model stratified by study and adjusted for size, grade and nodal status. Separate regression models were used for ER-positive and ER-negative cases. As we have shown previously (Blows *et al*, 2010), the hazard ratio for HER2-positive disease decreases over time in women with ER-positive breast cancer, so the log hazard ratio was modelled to vary linearly with time. The effect of HER2 in women with ER-negative breast cancer is not time-dependent.

The hazard ratios estimated from the BCAC data set were then used to modify Predict, which is also based on a Cox proportional hazards models. However, Predict was developed using a case cohort of breast cancer cases of unknown HER2 status, and so the underlying baseline hazard is representative of cases of average HER2 status. The HER2 hazard ratio estimates based on the BCAC data are for HER2-positive cases compared with HER2-negative cases, and so these were rescaled to give an average hazard ratio of unity using an estimated prevalence of HER2 of 9% in ER-positive cases and 25% in ER-negative cases. The applied hazard ratios for ER-positive cases are shown in Table 3. A fixed hazard ratio of 0.93 for HER2–negative cases and 1.27 for HER2–positive cases compared with HER2 unknown cases was applied to the baseline hazard of the ER-negative model.

Validation study population

We used the same case cohort from British Columbia, Canada, which we used to validate the original version of Predict. The data set has previously been described (Olivotto *et al*, 2005), but, in brief, includes data from 1653 patients with information on HER2 status out of a total of 3140 patients with stage I or II invasive breast cancer diagnosed in British Columbia, Canada, from 1989 to 1993, who were identified from the Breast Cancer Outcomes Unit (BCOU) of the BCCA. The BCOU prospectively records demographical information, pathological information, staging, initial treatment and outcome information including first loco-regional and distant relapse, as well as date and cause of death. Outcome data were reported annually by the treating oncologist, family physician or by monthly death certificate flagging through the British Columbia Cancer Registry and Department of Vital Statistics for British Columbia.

Information obtained from the BCOU database included age at diagnosis, sex, menopausal status, year of diagnosis, histology (ductal, lobular, other), histological grade, tumour size, number of lymph nodes sampled and number of lymph nodes positive, lymphovascular invasion status, ER status, HER2 status, type of local therapy (wide local excision, mastectomy, radiotherapy) and type of adjuvant systemic therapy (none, chemotherapy, endocrine therapy, both). The HER2 status was evaluated using TMAs as previously described (Chia *et al*, 2008). Chemotherapy regimens were categorised as four cycles of doxorubicin plus cyclophosphamide; 6 months of cyclophosphamide, methotrexate and fluorouracil, or other chemotherapy during this time period. None of these patients received trastuzumab.

Study endpoints were overall survival (OS) and BCSS. Of 1653 cases used in this analysis, cause of death was unknown in 5, and so 1648 cases were used for the analysis of BCSS.

Table I Description of participating studies

Study	Country	Case ascertainment	Case definition	Age range (years)	References
Amsterdam Breast Cancer Study	The Netherlands	Hospital-based	All cases of operable, invasive cancer diagnosed from 1974–1994 in four Dutch hospitals. Familial non-BRCA1/2 cases <50 from the Clinical Genetic Centre at the Netherlands Cancer Institute	23–50	Schmidt et al (2007)
Bavarian Breast Cancer Case–Control Study	Germany	Hospital-based cases	Consecutive, unselected cases with invasive breast cancer recruited at the University Breast Centre, Franconia in Northern Bavaria during 2002–2006	27–86	Fasching et al (2008)
Helsinki Breast Cancer Study	Finland	Hospital-based	(1) Consecutive cases (883) from the Department of Oncology, Helsinki University Central Hospital 1997–1998 and 2000, (2) consecutive cases (986) from the Department of Surgery, Helsinki University Central Hospital 2001–2004, (3) familial breast cancer patients (536) from the Departments of Oncology and Clinical Genetics, Helsinki University Central Hospital(1995)	22–96	Syrjakoski et al (2000); Kilpivaara et al (2005); Fagerholm et al (2008)
Jewish General Hospital	Canada	Hospital-based	Ashkenazi Jewish women diagnosed with non-metastatic, invasive breast cancer at Jewish General Hospital, Montreal, between 1980 and 1995	26–66	Tischkowitz et al (2007)
Kuopio Breast Cancer Study	Finland		Women seen at Kuopio University Hospital between 1990 and 1995 because of breast lump, mammographic abnormality, or other breast symptom, who were found to have breast cancer	23–92	Hartikainen et al (2005)
Mayo Clinic Breast Cancer Study	USA	Hospital-based	Incident cases residing in six states (MN, WI, IA, IL, ND, SD) seen at the Mayo Clinic in Rochester, MN, from 2002–2005	22–89	Olson et al (2007)
Melbourne Collaborative Cohort Study	Australia	Cohort	Incident cases diagnosed within the Melbourne Collaborative Cohort Study during the follow-up from baseline (1990–1994) to 2004 of the 2 4469 participating women	30–82	Giles and English (2002)
Nottingham Breast Cancer Case Series	UK	Hospital-based	Primary operable breast carcinoma patients presenting from 1986 to 1998, and entered into the Nottingham Tenovus Primary Breast Carcinoma Series	26–93	Rakha et al (2007)
Oulu Breast Cancer Study	Finland	Hospital-based	Consecutive incident cases diagnosed at the Oulu University Hospital, 2000–2004	28–92	Erkko et al (2007)
NCI Polish Breast Cancer Study	Poland	Population-based	Incident cases from 2000–2003 identified through a rapid identification system in participating hospitals covering ~90% of all eligible cases; periodic check against the cancer registries in Warsaw and Łódź to assure complete identification of cases	27–75	Garcia-Closas et al (2006)
Sheffield Breast Cancer Study	UK	Hospital-based	Women with pathologically confirmed breast cancer, recruited from surgical outpatient clinics at the Royal Hallamshire Hospital, Sheffield, 1998–2002; cases are a mixture of prevalent and incident disease	29–93	Rafii et al (2002); MacPherson et al (2004)
Study of Epidemiology and Risk factors in Cancer Heredity	UK	Population-based	Two groups of cases identified through East Anglian Cancer Registry: (1) prevalent cases diagnosed age <55 years from 1991–1996 and alive when study started in 1996; (2) incident cases diagnosed age <70 years diagnosed after 1996	23–69	Callagy et al (2006)
University of British Columbia Breast Cancer Trials	Canada	Hospital-based	Women with stage I to III breast cancer, who participated in four different British Columbia Cancer Agency clinical trials between 1970 and 1990, and all received chemotherapy	22–90	Ragaz et al (1997); Ragaz et al (2005)
Vancouver General Hospital	Canada	Hospital-based	Women with primary breast cancer, who underwent surgery at Vancouver General Hospital 1975–1995	28–91	Tischkowitz et al (2007)

Table 2 Number of cases by study, ER status and HER2 status

Study	ER-positive					ER-negative				
	HER2−	(%)	HER2+	(%)	Total	HER2−	(%)	HER2+	(%)	Total
ABCS	512	(87)	74	(13)	586	231	(77)	69	(23)	300
BBCC	585	(88)	77	(12)	662	164	(73)	62	(27)	226
HEBCS	173	(88)	23	(12)	196	37	(77)	11	(23)	48
JGH	166	(94)	11	(6)	177	77	(79)	21	(21)	98
KBCS	281	(93)	20	(7)	301	59	(67)	29	(33)	88
MCBCS	386	(84)	71	(16)	457	67	(77)	20	(23)	87
MCCS	307	(93)	24	(7)	331	99	(76)	31	(24)	130
NOBCS	1006	(96)	40	(4)	1046	346	(82)	76	(18)	422
OBCS	390	(91)	39	(9)	429	72	(68)	34	(32)	106
PBCS	656	(95)	34	(5)	690	289	(80)	71	(20)	360
SBCS	201	(93)	15	(7)	216	70	(84)	13	(16)	83
SEARCH	1447	(91)	135	(9)	1582	334	(75)	113	(25)	447
UBC	299	(76)	93	(24)	392	296	(66)	152	(34)	448
VGH	201	(94)	12	(6)	213	42	(72)	16	(28)	58
Total	6610	(91)	668	(9)	7278	2183	(75)	718	(25)	2901

Abbreviations: ABCS = Amsterdam Breast Cancer Study; BBCC = Bavarian Breast Cancer Case–Control Study; ER = oestrogen receptor; HEBCS = Helsinki Breast Cancer Study; HER2 = human epidermal growth factor receptor-2; JGH = Jewish General Hospital; KBCS = Kuopio Breast Cancer Study; MCBCS = Mayo Clinic Breast Cancer Study; MCCS = Melbourne Collaborative Cohort Study; NOBCS = Nottingham Breast Cancer Case Series; OBCS = Oulu Breast Cancer Study; PBCS = NCI Polish Breast Cancer Study; SBCS = Sheffield Breast Cancer Study; SEARCH = Study of Epidemiology and Risk factors in Cancer Heredity; UBCBCT = University of British Columbia Breast Cancer Trials; VGH = Vancouver General Hospital.

Table 3 Hazard ratio by HER2 status by time since diagnosis in ER-positive breast cancer

Year after diagnosis	HER2 status		
	Unknown	Positive	Negative
1	1	1.84	0.95
2	1	1.70	0.95
3	1	1.58	0.96
4	1	1.47	0.97
5	1	1.36	0.97
6	1	1.26	0.98
7	1	1.17	0.99
8	1	1.08	0.99
9	1	1.01	1.00
10	1	0.93	1.01

Abbreviations: ER = oestrogen receptor; HER2 = human epidermal growth factor receptor-2. Weighted average hazard ratio for HER2 + and HER2 − = 1.

Ten-year-predicted OS and BCSS were calculated for each patient using Predict +, Predict and Adjuvant! (standard version 8) by investigators blinded to the actual outcome data for each patient after entry of patient age, tumour size, number of positive nodes, tumour grade, ER status, HER2 status (Predict + only) and adjuvant systemic therapy. The default comorbidity setting of 'minor symptoms' and the chemotherapy option chosen was 'anthracycline-containing; $\geqslant 4$ cycles' were used in Adjuvant!. The 'second-generation' chemotherapy option (anthracycline-containing regimens) was used in Predict + and Predict. The mode of detection input was not used in Predict or Predict +, as this information was not available in the British Columbia data set. Ten-year-predicted OS and BCSS from Predict +, Predict and Adjuvant were compared with observed 10-year OS and BCSS.

Model calibration is a comparison of the predicted mortality estimates from each model with the observed mortality. In addition to comparing calibration in the complete data set, we evaluated calibration within strata of other prognostic variables. We also evaluated calibration within quartiles of predicted mortality. A goodness-of-fit test was carried out by using a χ^2-test based on the observed and predicted number of events (4 d.f.). Model discrimination was evaluated by calculating the AUC calculated for 10-year breast cancer-specific and overall mortality. This is a measure of how well the models identify those patients with worse survival. The AUC is the probability that the predicted mortality from a randomly selected patient who died will be higher than the predicted mortality from a randomly selected survivor.

RESULTS

The calibration of Predict for both all-cause mortality and for breast cancer-specific mortality was improved by the incorporation of HER2 status. Adjuvant! performed slightly better than Predict and Predict + for all-cause mortality, but both Predict and Predict + outperformed Adjuvant! for breast cancer-specific mortality. All three models slightly underestimated the observed number of deaths. The total number of deaths predicted by Adjuvant was within 6.1% of that observed (492 *vs* 524, $P = 0.16$) compared with 8.8% for Predict (478 *vs* 524, $P = 0.04$) and 8.4% for Predict + (480 *vs* 524, $P = 0.05$). The total number of breast cancer-specific deaths predicted by Adjuvant was within 14% of that observed (311 *vs* 360, $P = 0.01$) compared with 3.6% for Predict (347 *vs* 360, $P = 0.49$) and 2.5% for Predict + (351 *vs* 360, $P = 0.60$). Table 4 shows the observed and predicted all-cause 10-year OS by various clinico-pathological sub-groups. All models performed well in most subgroups. Notable exceptions were the performance in women aged 20–35 years, in which all three models underpredicted the actual number of deaths by 32%, and in HER2-

Table 4 Observed and predicted 10-year all-cause mortality by demographic, pathological and treatment characteristics

	Number	Deaths			
		Observed	Adjuvant	Predict	Predict +
Age group (years)					
20–35	55	22	15	15	15
36–50	492	120	112	119	119
51–65	523	152	133	132	133
66–75	433	153	153	141	142
76 +	150	76	79	71	71
Menopausal status					
Pre-	520	135	121	128	128
Post	1089	380	360	339	341
Peri-/unknown	44	8	10	11	11
Morphology					
Ductal	1489	479	440	428	432
Lobular	132	38	43	40	40
Other	32	5	8	8	8
Grade					
1	104	22	19	15	15
2	778	208	203	176	177
3	694	269	247	265	268
Unknown	77	24	23	20	20
LV invasion					
Negative	868	233	230	218	218
Positive	715	262	239	238	241
Unknown	70	26	22	20	20
Node status					
Negative	976	235	230	215	216
Positive	677	288	262	262	265
Tumour size					
1–10	210	40	39	40	40
11–20	745	196	189	186	187
21–50	698	287	264	251	253
ER status					
ER −	350	123	124	129	130
ER +	1303	400	367	348	350
Local Rx					
BCS + RT	814	200	205	200	200
Mast + RT	169	77	74	77	78
Mast	670	246	213	201	202
Systemic Rx					
None	660	175	170	161	162
Hormone	526	201	188	175	176
Chemo	317	96	93	97	98
Both	150	51	41	43	44
HER2					
Negative	1450	434	420	405	398
Positive	203	90	72	73	82
Total	1653	524	492	478	480

Abbreviations: BCS = breast conserving surgery; ER = oestrogen receptor; HER2 = human epidermal growth factor receptor-2; LV = lymphovascular; RT = radiotherapy. The sum of the predicted events within categories may differ from the sum of the observed events because of rounding errors in the predicted events.

positive cases, in which Adjuvant and Predict underestimated the number of deaths by close to 20% compared with just 9% for Predict +. None of these differences were statistically significant ($P > 0.05$). We also compared the predicted mortality with that observed for women in each quartile of predicted risk. Calibration

was good for Adjuvant! across all risk categories (goodness-of-fit, $P = 0.51$), and reasonable for Predict + (goodness-of-fit, $P = 0.042$) and Predict (goodness-of-fit, $P = 0.032$) (Figures 1A–C). Table 5 shows the observed 10-year breast cancer-specific mortality compared with that predicted by Predict +, Predict and Adjuvant. Again, each model performed well across most subgroups, except in women aged 20–35 years wherein they all underpredicted the actual number of deaths by 32% ($P > 0.05$). In HER2-positive patients, the total number of breast cancer-specific deaths predicted by Predict + was within 5% of observed (71 *vs* 75, $P = 0.64$) compared with 20% for Predict ($n = 60$ *vs* 75, $P = 0.08$) and 29% for Adjuvant (53 *vs* 75, $P = 0.01$). Calibration across the

quartiles of predicted breast cancer risk was good for Predict + (goodness-of-fit, $P = 0.11$) and Predict (goodness-of-fit, $P = 0.068$), and reasonable for Adjuvant! (goodness-of-fit, $P = 0.001$) (Figures 1D–F). Model discrimination was similar for all three models with AUCs for breast cancer-specific mortality of 0.665, 0.661 and 0.649 for Predict +, Predict and Adjuvant!, respectively.

DISCUSSION

Predict was developed using a flexible, Cox proportional hazards model that enables the easy incorporation of additional prognostic
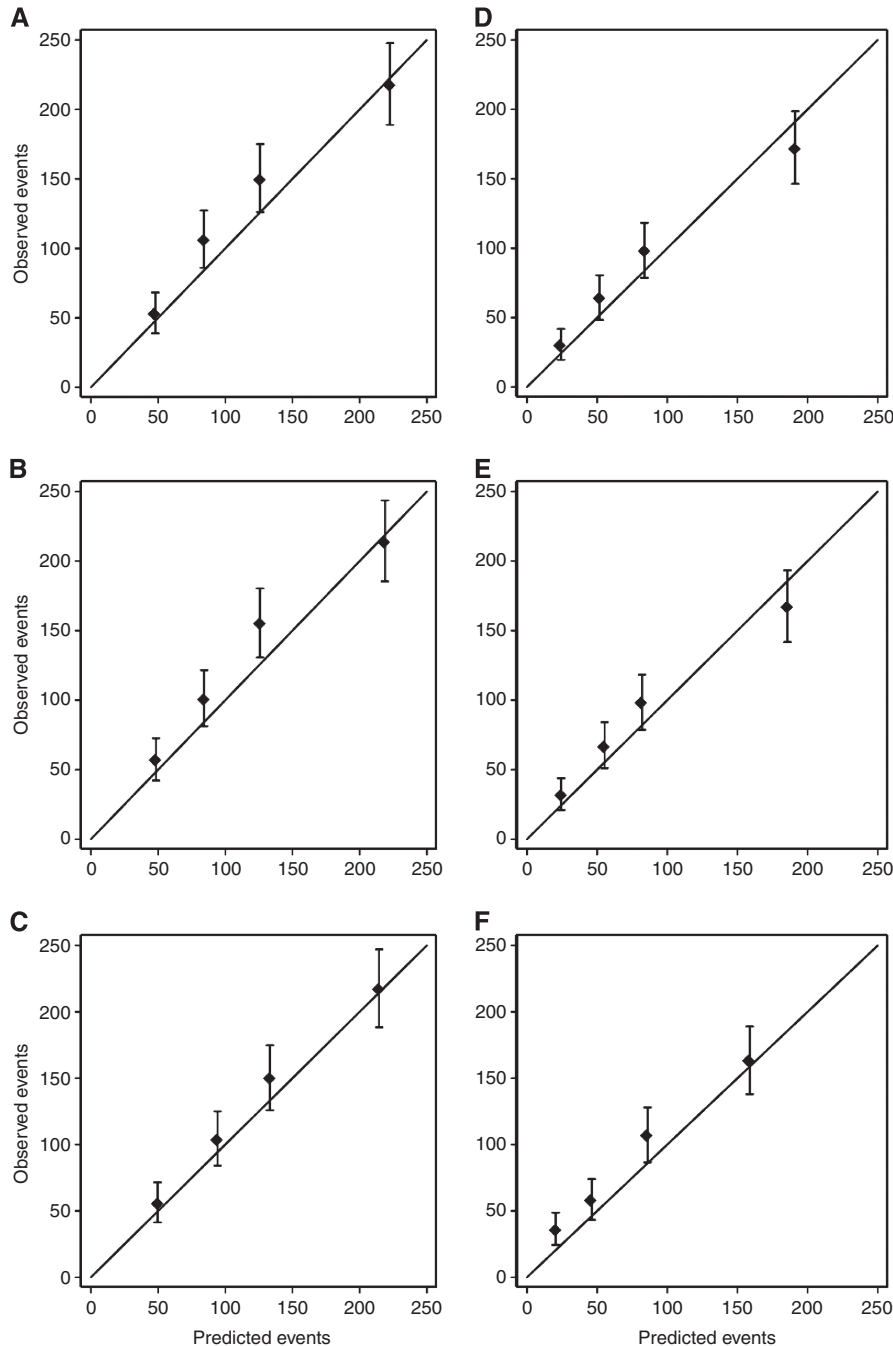
Figure 1 Calibration plots of observed outcomes with 95% confidence intervals against predicted outcomes by quartiles of the predicted value. Overall survival predicted by (**A**) Predict + (**B**) Predict and (**C**) Adjuvant!, and breast cancer-specific survival predicted by (**D**) Predict + (**E**) Predict and (**F**) Adjuvant!.

Table 5 Observed and predicted 10-year breast cancer-specific mortality by demographical, pathological and treatment characteristics

		Deaths from breast cancer			
	Number	Observed	Adjuvant	Predict	Predict +
Age group					
20–35	55	22	15	15	15
36–50	492	118	102	110	110
51–65	522	102	96	106	108
66–75	430	88	76	86	87
76 +	149	30	23	31	31
Menopausal status					
Pre –	520	133	110	118	119
Peri-/Unknown	1085	221	192	220	222
Post –	43	6	9	9	9
Morphology					
Ductal	1485	340	281	314	318
Lobular	131	18	24	26	26
Other	32	2	7	7	7
Grade					
1	104	4	5	5	5
2	775	133	108	104	104
3	693	206	183	225	228
Unknown	76	17	15	14	14
LV invasion					
Negative	864	144	129	142	142
Positive	714	196	168	190	193
Unknown	70	18	13	14	14
Node status					
Negative	972	132	117	128	129
Positive	676	228	194	219	221
Tumour size					
1–10	210	22	14	21	21
11–20	741	118	101	121	122
21–50	697	220	196	205	208
ER status					
ER –	350	104	102	113	114
ER +	1298	256	209	234	236
Local Rx					
BCS + RT	810	140	128	142	142
Mast + RT	169	59	59	69	70
Mast	669	161	124	137	139
Systemic Rx					
None	658	100	88	99	99
Hormone	523	121	102	117	118
Chemo	317	94	86	92	93
Both	150	45	36	40	40
HER2					
Negative	1445	285	258	287	280
Positive	203	75	53	60	71
Total	1648	360	311	347	351

Abbreviations: BCS = breast conserving surgery; ER = oestrogen receptor; HER2 = human epidermal growth factor receptor-2; LV = lymphovascular; RT = radiotherapy. The sum of the predicted events within categories may differ from the sum of the observed events because of rounding errors in the predicted events.

factors using external estimates of the prognostic effect of such a factor. We have used this flexibility to incorporate the prognostic effect of HER2 derived from a large multi-centre study. A key feature of Predict, and one that differentiates it from Adjuvant!,

is that it uses different underlying models for ER-positive and ER-negative disease. This is particularly important as the effect of other prognostic variables is often different according to ER status. This difference is particularly marked for HER2 status, where the effect of HER2 is strongly time-dependent in ER-positive cases but not for ER-negative cases. Our results confirm that the inclusion of HER2 status in the clinical prognostication tool Predict improves both model discrimination and calibration. The improvement in model fit was most pronounced in the HER2-positive subset of patients and was particularly marked for breast cancer-specific mortality. Given that it is breast cancer-specific mortality that is reduced by adjuvant therapy (Early Breast Cancer Trialists Collaborative Group, 1998a, b), it is likely that improved model performance will lead to more accurate predictions of the absolute benefit of treatment. Adjuvant! performed better than either Predict or Predict + for overall mortality. This might be expected as the background mortality data on which Adjuvant! is based are from North America, whereas Predict is based on background mortality data from the United Kingdom.

The weaknesses of our study also need to be considered in interpreting our results. There were some missing data for the BCAC cohorts used to derive the HER2-specific hazard ratios and for the BCOU cohort. Data were missing for multiple reasons, but the major reason was because of unavailability of archival pathology material. Although it is possible that there is some selection bias in the missing data – for example, pathology material is more likely to be unavailable for small tumours – any bias is unlikely to be large. This notion is supported by the results of the validation in the independent data from the BCOU cohort. As we have described previously, none of the models performed very well in the youngest age group. The reasons for this are unclear, but probably reflect the fact that the data on which the models were based included relatively small numbers of patients in this age group.

The online version of Predict includes survival estimates and treatment benefit at 5 and 10 years post diagnosis. Four clinical trials have now reported on the benefit of trastuzumab therapy – FinHER (Joensuu *et al*, 2009), HERA (Smith *et al*, 2007), B31/N9831 (Romond *et al*, 2005; Perez *et al*, 2010) and BCIRG006 (Slamon *et al*, 2011). The relative reduction in the all-cause mortality has ranged from 0.33 to 0.45. Two studies reported results stratified by tumour hormone-receptor status neither of which found evidence for heterogeneity (Romond *et al*, 2005; Smith *et al*, 2007; Perez *et al*, 2010). The new version of Predict +, including trastuzumab benefit at 5 years is available at www.predict.nhs.uk.

One of the key advantages of the Predict models is that they include mode of detection as one of the input parameters. As previously discussed, screen detection appears to confer an additional survival advantage over and above known prognostic factors. Unfortunately, as screening data was not available in the British Columbia data set, it was not possible to use this feature when running the Predict models, so the default setting was 'unknown' for all patients. Thus, we cannot estimate the performance of the Predict models if the mode of detection were known. However, it is very likely that model performance would improve with the addition of mode-of-detection data. In addition, a recent publication has called for the mode of detection to be taken into account when deciding optimal adjuvant therapy for an individual patient (Mook *et al*, 2011). Predict + can now provide such a model with the added benefit of the inclusion of HER2 status as well as the absolute treatment benefit of trastuzumab at 5 years. Further validations of Predict + in data sets where the mode of detection, HER2 status and trastuzumab treatment are recorded are planned in the near future.

This study reports the first successful inclusion of HER2 status in a prognostic model (Predict +) based on known clinical and pathological factors. The study has demonstrated a marked

improvement in 10-year BCSS estimates using Predict+ compared with the original Predict model for HER2-positive patients. Both Predict models provide better BCSS estimates than Adjuvant! in HER2-positive patients in this data set. This improvement in BCSS prognostication for HER2-positive patients was not achieved at the expense of the HER2-negative cohort, wherein both Predict and Predict+ performed better than Adjuvant. Predict+ also provided better breast cancer-specific mortality estimates that Predict and Adjuvant. This is extremely important for optimal model function, as it is the breast cancer-specific mortality that is reduced by the relative risk reductions of adjuvant therapy, and this improvement in model performance by Predict+ should lead to more accurate absolute treatment benefit predictions for individual patients.

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Conflict of Interest

The authors declare no conflicts of interest.

Author contributions

The Predict project was initiated by GCW, CC and PDPP. Study design: GCW, CDB and PDPP. Data analysis: ED, CDB and PDPP. Patient enrolment and data collection: DCG, MKS, LJvtV, AB, PAF, MWB, MC, TON, KG, DH, HN, TH, LRB, WDF, RW, KP, AM, GG, GS, IE, AG, MG-C, MS, AC, SSC, FMB, EP, CC and PDPP. Drafting of the manuscript: GCW and PDPP. All authors contributed to the editing of the final manuscript.

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