

Breast cancer biomarkers in clinical testing: analysis of a UK NEQAS ICC & ISH database containing results from 199,300 patients.***Supplementary Tables and Figures for the data from the Republic of Ireland***

FIGURE 1A. Chart shows the total number of records collected in each year as defined by 'Date of test' field. Data was collected until March 2016, and therefore that the figure shown for 2016 is for a partial year. Those shown as 'after 2016' are post-March 2016 and represent records entered with incorrect test dates.

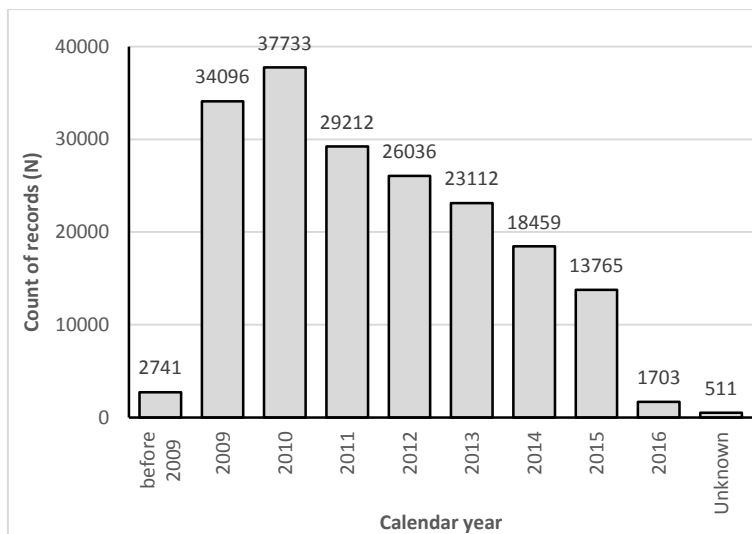
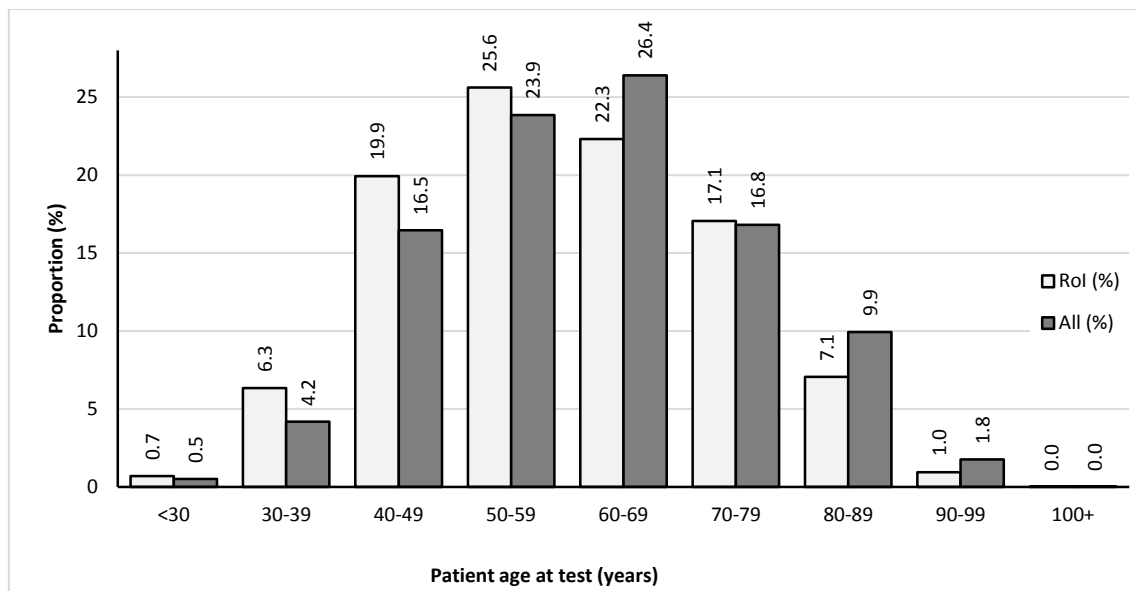


TABLE 1. Summary data for numbers of patient records and patient age at testing, together with data on other patient and tumour characteristics. Data are presented for RoI and for the whole set, the latter includes records where region was unknown. RoI = Republic of Ireland, N = number in group, % = proportion within group where characteristic was known, * = for 'Total records' the proportion is that of whole population, and thus indicates coverage, IDC = invasive carcinoma of ductal/no special type, ILC = invasive lobular carcinoma.

	RoI		All	
	N	%	N	%
Patient records	15369	8.2	187368	100.0
	Median	IQR	Median	IQR
Patient age at testing (years)	58	49-70	61	51-71
	N	%	N	%
Age at test (years)				
<i>Age <56 years</i>	4851	43.3	49561	36.0
<i>Age ≥56 years</i>	6362	56.7	88281	64.0
<i>Total records*</i>	11213	73.0*	137842	73.6*
Referral pathway				
<i>Screen-detected</i>	1959	34.7	4620	35.4
<i>Symptomatic</i>	3693	65.3	8414	64.6
<i>Total records*</i>	5652	36.8*	13034	7.0*
Primary specimen sample type				
<i>Axilla/nodes</i>	295	2.5	6428	4.7
<i>Core biopsy</i>	7966	66.2	96269	71.0
<i>Excision</i>	3778	31.4	32931	24.3
<i>Total records*</i>	12039	78.3*	135628	72.4*
Metastatic presentation site				
<i>Bone</i>	130	23.3	445	11.4
<i>Cutaneous</i>	173	31.0	1483	37.9
<i>Visceral</i>	255	45.7	1984	50.7
<i>Total records*</i>	558	3.6*	3912	2.1*
Histological type				
<i>Carcinoma in-situ</i>	871	8.0	3753	4.5
<i>IDC</i>	8367	76.7	66432	79.4
<i>ILC</i>	1361	12.5	10416	12.4
<i>Mixed IDC/ILC</i>	146	1.3	1461	1.7
<i>Special type</i>	159	1.5	1652	2.0

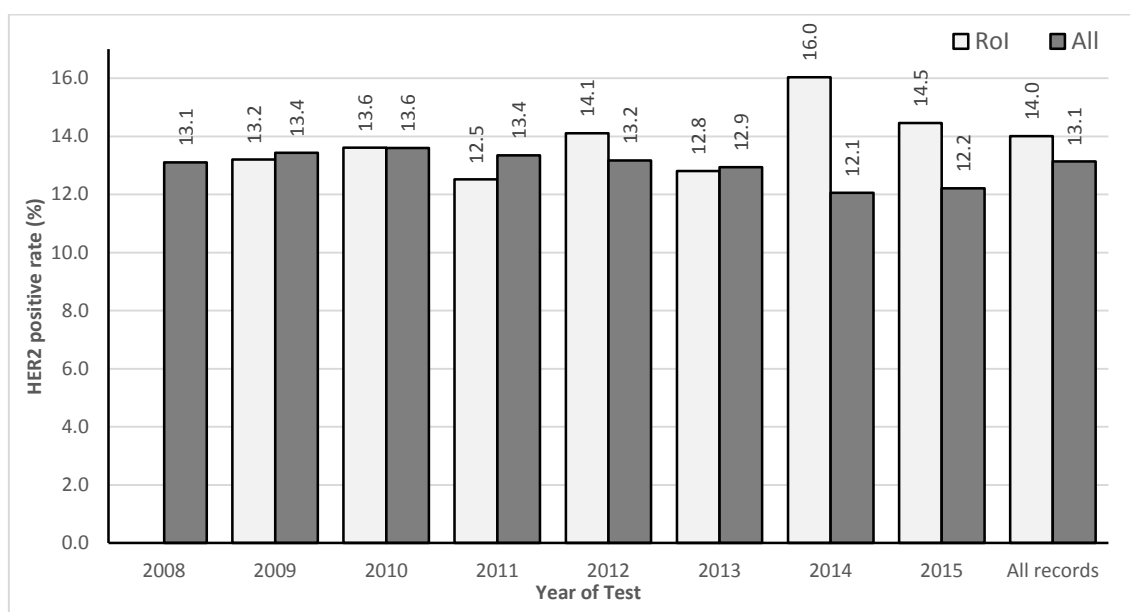
<i>Total records*</i>	10904	70.9*	83714	44.7*
Histological Grade				
<i>Grade 1</i>	1353	13.9	13032	16.1
<i>Grade 2</i>	5929	60.8	43519	53.7
<i>Grade 3</i>	2470	25.3	24424	30.2
<i>Total records*</i>	9752	63.5*	80975	43.2*
Histological tumour size				
<i>Diameter <20mm</i>	1459	44.2	10075	51.5
<i>Diameter 20-49mm</i>	1361	41.2	7596	38.9
<i>Diameter >=50mm</i>	482	14.6	1876	9.6
<i>Total records*</i>	3302	21.5*	19547	10.4*
Nodal status				
<i>N0</i>	1555	60.6	9138	62.4
<i>N1</i>	693	27.0	3613	24.7
<i>N2</i>	171	6.7	1054	7.2
<i>N3</i>	147	5.7	843	5.8
<i>Total records*</i>	2566	16.7*	14648	7.8*

FIGURE 1B. Distributions for patient age at date of HER2 testing. Median age in Irish patients was 58 years (IQR: 49 - 70 years). Total population had a median age of 61 years (IQR: 51 - 71 years). The trend for younger age at testing in Irish patients compared to the whole population was significant (P<0.001). RoI = Republic of Ireland.



Age at test (years)		<30	30-39	40-49	50-59	60-69	70-79	80-89	90-99	100+	Sum
RoI	N	78	712	2236	2872	2503	1913	791	107	1	11213
	%	0.7	6.3	19.9	25.6	22.3	17.1	7.1	1.0	0.0	100.0
All	N	707	5786	22697	32888	36405	23176	13691	2432	60	137842
	%	0.5	4.2	16.5	23.9	26.4	16.8	9.9	1.8	0.0	100.0

FIGURE 2A. HER2 positivity rates by year of test (2008 to 2015). These data are based on centre-assigned HER2 status data. For RoI patient data the median HER2 positive rate was 13.6% (IQR: 12.8 - 14.5%), for all patients it was 13.2% (IQR: 12.4 - 13.4%). The means were 13.8% (SD: 1.2%) and 13.0% (SD: 0.6%), respectively. RoI = Republic of Ireland, IQR = inter-quartile range, SD = standard deviation. RoI data for 2008, where less than 1,000 patient tests were available for analysis have been excluded.



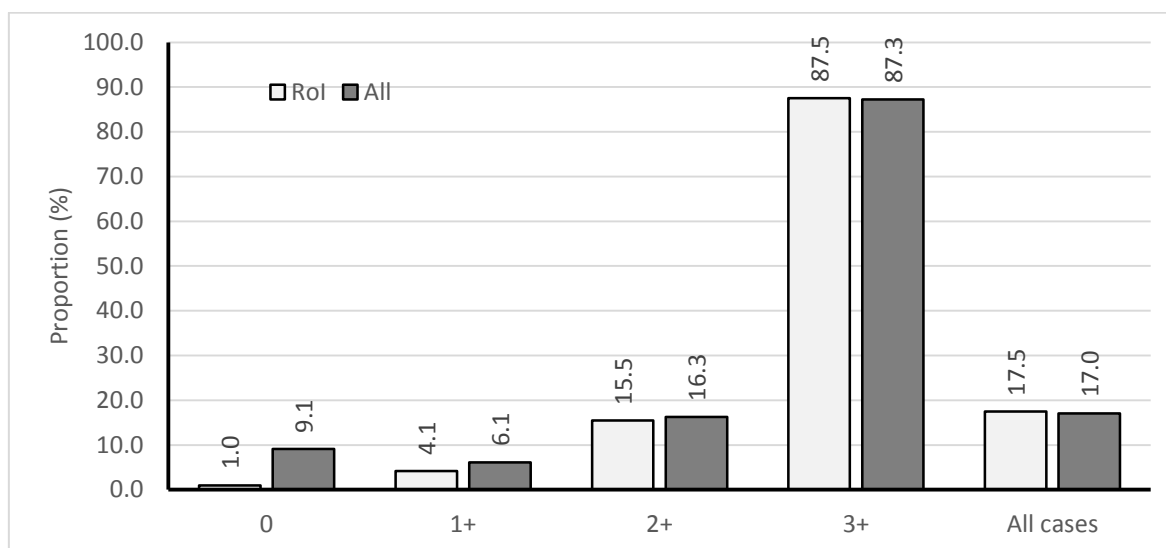
Year of test	RoI				All			
	HER2 negative		HER2 positive		HER2 negative		HER2 positive	
	N	%	N	%	N	%	N	%
2008					1916	86.9	289	13.1
2009	1196	86.8	182	13.2	29515	86.6	4581	13.4
2010	1815	86.4	286	13.6	32603	86.4	5130	13.6
2011	1817	87.5	260	12.5	25312	86.6	3900	13.4
2012	2545	85.9	418	14.1	22606	86.8	3430	13.2
2013	2077	87.2	305	12.8	20122	87.1	2990	12.9
2014	1974	84.0	377	16.0	16234	87.9	2225	12.1
2015	1307	85.5	221	14.5	12084	87.8	1681	12.2
Totals	13217	86.0	2152	14.0	162754	86.9	24614	13.1

TABLE 2A. HER2 positive rates for RoI and for all cases. HER2 status was defined using the centre's categorical assignment. Refer to Table 1 for data on the total numbers of cases in each category. RoI = Republic of Ireland, (1) = the 'All' category includes patients where country was unknown; IDC: invasive carcinoma of ductal/no special type; ILC: invasive lobular carcinoma, na: not applicable, ns: not significant at $P < 0.05$ Hormone receptor status definitions: ER negative = Centre assignment as negative, Allred 0 or 2, % positive $< 1\%$, H-score < 1 ; ER positive = Centre assignment as positive, Allred > 2 , % positive $\geq 1\%$, H-score ≥ 1 ; PR negative = Centre assignment as negative, Allred 0, 2 or 3, % positive $< 10\%$, H-score < 10 ; PR positive = Centre assignment as positive, Allred > 3 , % positive $\geq 10\%$, H-score ≥ 10 . (a) Axilla/nodes vs Primary tumour - core biopsy, (b) Axilla/nodes vs Primary tumour - excision, (c) Primary tumour - core biopsy vs Primary tumour - excision, (d) Metastatic site - Bone vs Cutaneous, (e) Metastatic site - Bone vs Visceral, (f) Metastatic site - Cutaneous vs Visceral, (g) Rate for invasive carcinoma of ductal/no special type was significantly different from all other groups ($P < 0.001$), which were not significantly different from each other, (h) test for trend.

	RoI			All(1)		
	N	%	P	N	%	P
All cases	2152	14.0	na	24614	13.1	na
Age at test (years)						
<56 years	782	16.1	<0.05	8002	16.1	<0.0001
-≥56 years	845	13.3		10091	11.4	
Referral pathway						
Screen detected	213	10.9	<0.0001	418	9.0	<0.0001
Symptomatic	599	16.2		1119	13.3	
Tissue type (sample type)						
Axilla/nodes	65	22.0	<0.05 (a)	1006	15.7	<0.0001 (a)
Primary tumour - core biopsy	1244	15.6	<0.0001 (b)	12516	13.0	<0.0001 (b)
Primary tumour – excision	395	10.5	<0.0001 (c)	4330	13.1	ns (c)
Metastatic disease by site						
Bone	13	10.0	<0.05 (d)	41	9.2	<0.05 (d)
Cutaneous	39	22.5	<0.05 (e)	222	15.0	<0.05 (e)
Visceral	53	20.8	ns (f)	304	15.3	ns (f)
Histological type						
Carcinoma in-situ	59	6.8	See legend notes (g)	302	8.0	See legend notes (g)
IDC	1410	16.9		10134	15.3	

<i>ILC</i>	73	5.4		573	5.5	
<i>Mixed IDC/ILC</i>	6	4.1		115	7.9	
<i>Special type</i>	11	6.9		87	5.3	
Tumour Grade						
<i>Grade 1</i>	44	3.3	<0.0001 (h)	332	2.5	<0.0001 (h)
<i>Grade 2</i>	779	13.1		4716	10.8	
<i>Grade 3</i>	585	23.7		5821	23.8	
Tumour size category (diameter)						
<i><20mm</i>	164	11.2	ns (h)	1188	11.8	<0.0001 (h)
<i>20mm to <50mm</i>	123	9.0		1053	13.9	
<i>≥50mm</i>	43	8.9		274	14.6	
Nodal status						
<i>N0</i>	159	10.2	ns (h)	1006	11.0	<0.0001 (h)
<i>N1</i>	67	9.7		482	13.3	
<i>N2</i>	26	15.2		172	16.3	
<i>N3</i>	17	11.6		184	21.8	
ER status						
<i>Negative</i>	627	32.1	<0.0001	4183	25.5	<0.0001
<i>Positive</i>	1204	12.4		8317	10.6	
PR status						
<i>Negative</i>	900	27.6	<0.0001	5566	23.4	<0.0001
<i>Positive</i>	512	10.8		3836	8.7	
Combined ER and PR status						
<i>ER negative / PR negative</i>	570	31.8	ns	3388	26.1	ns
<i>ER negative / PR positive</i>	16	38.1		197	25.9	
<i>ER positive / PR negative</i>	317	22.3	<0.0001	2155	20.1	<0.0001
<i>ER positive / PR positive</i>	495	10.6		3633	8.4	

FIGURE 2D. *HER2* gene amplification rates by *HER2* IHC category. The data are shown for those sub-groups where sufficient numbers of cases were available to allow reliable assessment ($N \geq 100$). Overall for the whole population, >90% of data were present within the *HER2* 2+ category; for RoI data in contrast, 78.7% was presented for 2+ cases, 13.0% for 1+ and 5.4% for 3+, indicative of differing ISH testing policies in that country. See also Supplementary Table 5A-C. RoI = Republic of Ireland.



HER2 IHC category	RoI				All			
	Non-amplified		Amplified		Non-amplified		Amplified	
	N	%	N	%	N	%	N	%
0	102	99.0	1	1.0	179	90.9	18	9.1
1+	439	95.9	19	4.1	645	93.9	42	6.1
2+	2347	84.5	429	15.5	26342	83.7	5129	16.3
3+	24	12.5	168	87.5	59	12.7	404	87.3
All cases	2912	82.5	617	17.5	28932	83.1	5886	16.9

FIGURE 3A. Distribution of ER positivity rate by patient age at test. The final categorical status has been used to define ER positivity. Data are shown for RoI and for all patients. A polynomial trend-line (orange dotted-line) and overall mean (82.5%) (black dotted-line) are displayed for all patient data. RoI = Republic of Ireland.

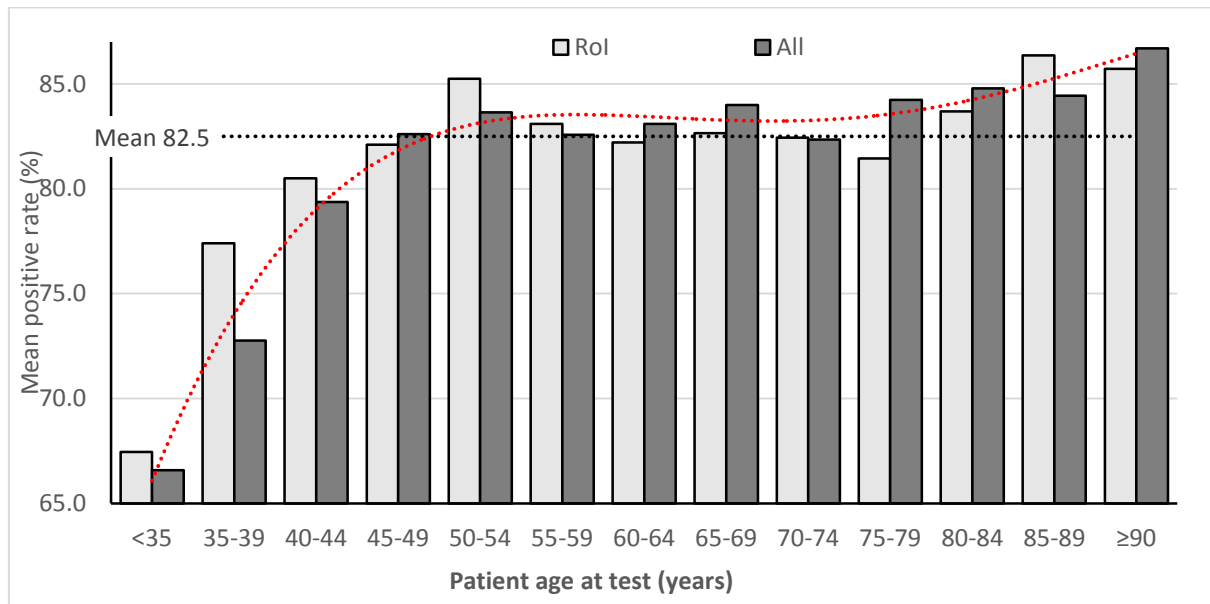


FIGURE 3C. PR positive rates by patient age. Distribution of PR positivity rate according to patient age at test. The final categorical status has been used to define PR positivity. Data are shown individually for ROI and for all patients. A polynomial trend-line (orange dotted-line) and overall mean (64.9%) (black dotted-line) are displayed for all patient data. ROI = Republic of Ireland.

