ORIGINAL ARTICLE

HER2 testing in the UK: consensus from a national consultation

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Objective: To gain an understanding of current attitudes among oncologists and pathologists to prospective HER2 testing in breast cancer and to gauge whether a national consensus exists regarding extent and quality of testing.
Design: Qualitative study, with semi-quantitative components, using emailed questionnaires and open-ended discussion documents.
Participants: 186 relevant specialists, including 76 breast oncologists and 99 pathologists, representing all but three of the UK cancer networks.
Results: A strong consensus was seen in favour of universal, non-selective testing for HER2 at the point of breast cancer diagnosis. Similarly, an overwhelming majority of participants agreed that, to optimise the quality of test results, all laboratories undertaking HER2 testing should be CPA-accredited, participate in the recognised national external quality assessment scheme (UK NEQAS), and carry out a formal annual audit of its testing service. A further recommendation that testing be restricted to laboratories undertaking a minimum 250 tests per annum for immunohistochemistry and 100 tests per annum for in situ hybridisation techniques met with majority support. However, this was not a clear consensus; a significant minority of participants favoured continued use of local services falling short of these criteria.
Conclusion: This study was successful in gauging national specialist opinion regarding the extent and quality assurance of HER2 testing in the UK.

The significance of HER2 overexpression in breast cancer, and its relevance to management decisions involving trastuzumab (Herceptin), has been well publicised following publication of data from landmark trials showing substantial benefit from adjuvant trastuzumab in women with HER2-positive disease.[1–3]

A directive issued in October 2005 by the UK Department of Health (DH) that the HER2 status of all women diagnosed with early breast cancer (and thus their suitability for trastuzumab) should be determined[4] was quickly followed by the licensing of trastuzumab for adjuvant treatment of early-stage breast cancer, and soon after that by draft guidance from the National Institute for Health and Clinical Excellence (NICE).[5]

The resulting heightened demand for trastuzumab in the adjuvant setting of early breast cancer will inevitably be matched by an increased need for effective and quality-assured determination of HER2 status, which is currently almost exclusively based on immunohistochemistry (IHC) or, where equivocal, by in situ hybridisation techniques (FISH). However, concern has been expressed that insufficient consideration has been given to the difficulty of obtaining accurate and reproducible assessment of HER2 status.[6]

The present study, a qualitative national consultation exercise carried out between August and November 2005, sought to assess the extent to which oncologists and pathologists subscribed to the concept of universal, prospective testing of HER2 in women diagnosed with breast cancer and to identify consensus regarding the most appropriate infrastructure and quality assessment protocols for HER2 testing, taking into account both funding and medicolegal considerations.

METHOD

The design and content of the UK National Consultation exercise was determined by a multidisciplinary steering group comprising four pathologists and two breast cancer clinicians. In order to explore all possible underlying issues, an open-ended, qualitative debate was deemed more valuable than a prompted, quantitative survey. Job type was recorded against all response data, which were otherwise anonymised.

Participation was invited via a third party database of 1760 breast cancer specialists and pathologists providing comprehensive coverage of all UK cancer networks. The database was procured through an independent commercial list hire company (Dendrite UK) to minimise selection bias. Respondents were required to provide an email address to allow the consultation to be conducted via email for the remainder of its duration. To maximise participation, a charity donation of £50 per participant was pledged.

Respondents to the invitation process received a semi-quantitative baseline questionnaire to provide an initial gauge of situation, opinions and issues.

Feedback from the questionnaire was used to inform the selection of topics for the key national discussion stage of the consultation. An open-ended discussion document was thus prepared providing a narrative of findings from the baseline survey and seeking national participants' views on the following issues.

(1) Whether any argument still remained for the exclusion of some patients with breast cancer from HER2 testing
(2) Whether there remained a place for retrospective, rather than prospective, HER2 testing
(3) Whether centralisation of IHC and FISH HER2 testing services would help to overcome cost and quality barriers
(4) How shortfalls in HER2 testing expertise and experience can be addressed
(5) How quality can best be assured
(6) How medicolegal risk can be minimised

Abbreviations: DH, Department of Health; FISH, in situ hybridisation; IHC, immunohistochemistry; NEQAS, national external quality assessment scheme; NICE, National Institute for Health and Clinical Excellence

Table 1 Breakdown of participants (oncologist/pathologist breakdown shown in parentheses)*

Total signing up to participate	238 (103/123)	
Respondents to questionnaire	156 (62/84)	60%
Respondents to discussion stage	93 (34/53)	39%
Respondents to consensus stage	148 (58/82)	62%
Respondents to any stage	186 (76/99)	78%
Respondents to all stages	74 (25/44)	31%

*12 registered participants had unknown specialty.

In addition, participants deeming themselves to have relevant experience or knowledge were given the option to comment on a range of technical issues, including:

(1) The ideal frequency of the national external quality assessment scheme (NEQAS) and the ideal number of samples per circulation
(2) The value of using human tissue versus cell lines
(3) The value of tissue micro-array in HER2 quality assessment

In an attempt to determine support for a previously published recommendation[7] that minimum numbers of test per year for IHC and FISH (250 and 100 respectively) served as an appropriate indicator of robustness and accuracy, participants were asked to note how many tests (IHC and FISH) the laboratory they currently use performed per year, and whether they envisaged continuing to use these services.

Responses to the consultation phase were studied and analysed using a categorisation (semi-quantification) technique, thus facilitating the drafting of three statements which were offered to the national consultation for consensus. For each statement, participants were given three consensus options: unqualified agreement; qualified agreement; or disagreement.

RESULTS

Participants

A total of 238 responded to the initial mailing, indicating their willingness to participate. Of these, 186 (78%) responded to at least one stage of the process (table 1), representing all but three of the UK cancer networks.

Baseline survey findings

Responses to the baseline survey (table 2) were received from 156 participants, a 60% response. Before the DH directive in October 2005, 23% of these respondents said that their centre already operated a policy of blanket prospective testing. Of these, 20% believed that the infrastructure was not adequate to service this policy.

Another 37% reported that their centres tested prospectively, but only selectively, while 36% employed selective retrospective HER2 testing only. A blanket retrospective approach was operated by 4% of respondents.

In response to the directive, 90% of respondents stated that their centre planned to initiate blanket prospective HER2 testing of women diagnosed with breast cancer. Of these, one third said the infrastructure was already in place, while two thirds planned to begin blanket testing as soon as the infrastructure was established. In the majority of cases (77%), the anticipated time frame within which such an infrastructure could be put in place was at worst within 12 months, with 39% stating that this would happen within 6 months. It was believed by 9% that it would take 12–24 months to establish an adequate infrastructure.

Of those respondents continuing to undertake prospective HER2 testing selectively, whether in the short term (pending the initiation of blanket testing) or longer term, over a quarter stated that selection was made on the basis of carcinoma type, and a similar proportion selected on the basis of suitability or fitness for chemotherapy. Other criteria given, by a small minority of respondents, included: disease grade, node positivity, oestrogen receptor negativity and age.

A significant majority of these respondents, however, stated that factors including new NICE/SMC guidance, increased funding, new trial data for trastuzumab, patient pressure and experience from other centres may influence change.

HER2 testing resources and standards

The most important barriers to initiating universal prospective HER2 testing were inadequate funds (scoring an average of 4.54 on an importance scale of 1–5) and insufficient capacity to cope with the extra demand (3.46). A shortfall of pathologists (2.29) and local laboratory services (2.44) were cited as significant but less important barriers.

Medicolegal considerations

Virtually all responders (98%) acknowledged that the DH directive to implement blanket prospective HER2 testing carried an increased risk of litigation (arising, for example, from patients being denied access to testing through infrastructural deficiencies, and risk of misdiagnosis or mis-scoring), with 41% believing that the risk increases ''greatly''.

Response from open-ended discussion stage

Blanket HER2 testing

Feedback from the discussion document was received from 93 (39%) of all participants. Analysis of respondents to the discussion stage showed a strong consensus in favour of universal testing for HER2 at the point of diagnosis (table 3). Of the minority of responders who did not favour this blanket testing approach, most advocated selectivity on the grounds that some women are very unlikely to be given trastuzumab. This fact was acknowledged by many of those in favour of blanket testing, but there was a strong consensus that the benefits of blanket testing outweigh any arguments against.

Service infrastructure

Most respondents supported centralising testing services; however, a significant minority (approximately a quarter) were not in favour of centralisation, many believing that local services were adequate. There was a general suggestion among many of those who did not favour centralisation that investment in local services (in terms of training and funding) was a realistic solution.

In some cases, HER2 testing was already centralised, but there was a trend towards considering localising (de-centralising) IHC testing as experience grew.

Quality assurance

There was a clear consensus recommending rigorous external quality assessment in order to ensure high standards and to minimise medicolegal risk. Many respondents favoured making NEQAS mandatory, but with added robustness and supplemented with an audit process.

There was no clear consensus on the ideal frequency of NEQAS evaluation, nor the ideal number of samples per circulation. Recommendations ranged generally between 2 and 6 per annum, averaging around 4.

Human tissue was preferred by the vast majority over cell lines; many respondents offered the rationale that this approach reflects life more realistically. Those who favoured cell lines felt this was a more stable approach.

Table 2 Data from pre-consultation baseline survey

	Number	%	Mean	Median	SD
(1) Before the announcement by the DH that all women presenting with early breast cancer should be tested for HER2 (i.e. ''blanket'' HER2 testing*), which of the following most accurately reflects the practice at your centre?					
	n = 154				
Blanket prospective	38	25	–	–	–
Selective prospective	58	38	–	–	–
Blanket retrospective	4	3	–	–	–
Selective retrospective (only)	54	35	–	–	–
(2) After the announcement by the DH, which of the following now applies most accurately to your centre?					
	n = 154				
(a) Plans and infrastructure in place for blanket testing	52	34	–	–	–
(b) Blanket HER2 testing when infrastructure in place	88	57	–	–	–
(c) No plans to introduce blanket testing	14	9	–	–	–
(3) Which of the following currently represent the greatest barriers to initiating blanket prospective HER2 testing in your centre? (Respondents checking 2b only)					
	n = 89				
Shortfall of pathologists	84	–	2.39	2	1.20
Inadequate funds	89	–	4.54	5	0.98
Inadequate capacity to cope with extra demand	83	–	3.46	4	1.34
Shortfall of adequate expertise/experience in HER2 testing	83	–	2.29	2	1.53
Absence of local laboratory services with HER2 testing capability	81	–	2.44	1	1.72
Absence of central laboratory services with HER2 testing capability	81	–	1.74	1	1.22
Ability to meet NEQAS standards for QA/QC	78	–	1.97	1	1.33
(4) On what basis will women diagnosed with breast cancer be selected for HER2 testing? (Respondents checking 2c only)					
	n = 55				
On the basis of type of carcinoma	22	27	–	–	–
On the basis of fitness for chemotherapy	24	30	–	–	–
Other selection criteria (stated)	22	27	–	–	–
(5) In your opinion does an adequate infrastructure already in your area exist to service blanket HER2 testing?					
	n = 116				
Yes	47	41	–	–	–
No	69	59	–	–	–
(If No to above) within what timeframe do you expect an effective infrastructure to be in place?					
	n = 63				
Less than 6 months	20	32	–	–	–
6–12 months	24	38	–	–	–
12–24 months	14	22	–	–	–
More than 24 months	5	8	–	–	–
(6) Thinking generally about the development of an effective infrastructure required for blanket testing of HER2, how important, in your opinion, do you think the following issues are (on a scale of 1–5, with 5 being the most important)?					
	n = 156				
Availability of local laboratory services with HER2 testing capability	147	–	3.29	3	1.54
Availability of central laboratory services with HER2 testing capability	151	–	3.81	4	1.33
Increased capacity within current testing structure	150	–	4.15	5	1.12
Availability/number of pathologists	153	–	3.84	4	1.13
Adequate training of pathologists	151	–	3.99	4	1.13
Ability to meet NEQAS standards for QA/QC	149	–	4.39	5	1.01
Adequate funding	155	–	4.80	5	0.78
Availability of adequate expertise/experience in HER2 testing	155	–	4.43	5	0.94
Ability to link up with other networks/centres with FISH capacity	154	–	4.23	5	1.14
(7) To what extent do you think there will be an increased litigation risk to trusts as a result of the Hewitt decision—for example, in those cases where patients were denied access to HER2 testing because infrastructure was not able to cope with demand, or else the testing was not carried to the required standard resulting in missed positives?					
	n = 153				
Greatly	66	43	–	–	–
Somewhat	83	54	–	–	–
Not at all	4	3	–	–	–

DH, Department of Health; FISH, in situ hybridisation; NEQAS, national external quality assessment scheme; QA, quality assessment; QC, quality control.

There was no clear-cut consensus on whether there should be approved antibodies for HER2 testing. However, the general opinion tended towards favouring a limited number of approved antibodies. Only very few respondents recommended a single approved test or antibody.

Medicolegal risk

The two main levers cited to minimise medicolegal risk were: clear national or local guidelines or protocols; and blanket HER2 testing with retrospective retesting where relevant.

Table 3 Categorisation of discussion feedback

Discussion question	Response category	No	%
There is a widely held view that the dependence on diagnostic accuracy and robust evidence base required for selective testing, coupled with the increase in medicolegal risk and the potential cost-effectiveness of blanket testing, makes a compelling case for carrying out HER2 tests on all women diagnosed with breast cancer. What are your views on this? (n=83)	Unqualified agreement	51	61
	Qualified agreement	23	28
	Qualified disagreement	8	10
	Unqualified disagreement	1	1
In your centre, would a greater use of centralised laboratory services help surmount barriers to initiating effective blanket HER2 testing? (n=79)	No	6	8
	Local services adequate	16	20
	Already centralised	30	38
	Yes	23	29
	Other	4	5
Given adequate funding, how do you feel existing shortfalls in HER2 testing expertise would be best addressed? (n=83)	Through centralisation	29	35
	Through training	34	41
	Other	20	24
How do you think the need to ensure high standards of quality control and quality assessment should be met? (n=76)	Only through centralisation	11	14
	External QA/audit	59	78
	Other	20	26
What steps do you feel should be taken by trusts to minimise the medicolegal risk involved in implementing a HER2 testing policy? (n=77)	Guidelines/policy	23	30
	Blanket testing	32	42
	Other	30	39
Tests per year (IHC) (n=64)	<150	7	11
	151–250	14	22
	>250	43	67
Tests per year (FISH) (n=58)	<50	14	24
	51–100	12	21
	>100	32	55
Continue with same laboratory	IHC (n=69)	60	87
	FISH (n=66)	50	76

FISH, in situ hybridisation; IHC, immunohistochemistry; QA, quality assessment.

Consensus stage

After full analysis of the consultation stage feedback, we drafted, for national voting, the three consensus statements (table 4), which reflected the weight and breadth of opinion: voting on these statements (table 5) showed a clear consensus to statements 1 and 3. Consensus on statement 2 was less clear; a significant number of respondents felt that the minimum test numbers put forward were arbitrary and had no evidence basis. There was also a significant minority of responders who did not subscribe to the mandate for centralisation of laboratory services.

DISCUSSION

This study has served to highlight the challenges that arise from the emergence of new, expensive treatments that have been proven to have significant survival benefit in a distinct and identifiable sub-group of patients. The demand created by positive, robust trial data may be irresistible, while limited funds mandate the identification of suitable patients.

Over 40 000 women have been diagnosed with breast cancer annually in the UK in recent years.[8] Amplification of the HER2/neu oncogene occurs in about 20% of human primary breast cancers,[9 10] although frequencies will be lower if all breast cancers are tested.

The derivation of a false-negative diagnosis will deny potentially life-extending therapy to a truly HER2-positive patient. A false-positive will result in exposure to a drug that has significant side effects in a minority of patients and in unnecessary drug cost of around £24 000 for the recommended 1 year of treatment.

Table 4 Draft consensus statements

Consensus statement 1
All women diagnosed with breast cancers of all types should be tested for HER2 status directly post-surgery alongside hormone receptor testing. This approach will ensure that no-one falls through the net, will avoid the burden and risk of subjective selectivity and will help inform the treatment pathway.
It is acknowledged that this approach will entail the testing of some women very unlikely to be prescribed Herceptin; however, the arguments in favour of blanket testing, both clinical and medicolegal, far outweigh any arguments for selectivity.
This approach should be audited over a two year period and adapted if necessary in line with the audit findings.

Consensus statement 2
In order to ensure adequate and appropriate resourcing of prospective HER2 testing, only those laboratories undertaking a minimum of 250 tests should provide IHC HER2 testing services, preferably acting as a network testing centre. Ideally, there would ultimately be one—and at most two—testing centres per Network. There should be one named HER2 testing lead per centre.
All 2+ IHC results should be FISH tested. Only those centres undertaking a minimum of 100 FISH tests per year—and preferably at least 150—should be accredited to offer this service. It will probably not be necessary for any new FISH testing centres to be established, since existing centres already provide sufficient capacity to meet the demand.

Consensus statement 3
Other than in exceptional circumstances, all laboratories providing IHC and FISH testing services according to the minimum criteria outlined in statement 2 should be CPA-accredited and should carry out rigorous internal quality control and participate in UK NEQAS.
In addition, each laboratory should carry out a formal annual audit of its services, which should include, but not be limited to, an assessment of the positivity rate of IHC and FISH HER2 tests carried out.

FISH, in situ hybridisation; IHC, immunohistochemistry; NEQAS, national external quality assessment scheme.

Table 5 Levels of consensus

	Consensus response S1	Consensus response S2	Consensus response S3
Total respondents	148	145	147
Unqualified agreement	129 (87%)	99 (68%)	133 (90%)
Qualified agreement	17 (11%)	30 (21%)	10 (7%)
Disagreement	2 (1%)	16 (11%)	4 (3%)

Estimations of the cost of HER2 testing have rightly been included in health economic analyses of trastuzumab treatment on which NICE has based its draft guidance on its adjuvant use.[5] These were presumably based on the situation pertaining at the time of the analysis. Efficiency of testing is thus a crucial factor in the cost–benefit equation. Our study suggests that there is considerable opportunity to reduce the total economic cost of trastuzumab treatment for HER2-positive breast cancer through blanket, prospective testing supported by an improved laboratory infrastructure with rigorous quality assessment.

Of those respondents who were currently using or providing services undertaking fewer than the recommended minimum number of tests per annum (ie, minimum 250 IHC, minimum 100 FISH), around half had no plans to change; thus the issue of centralisation of laboratory services remains an area of only partial consensus. These centres may consider the data from two large evaluations of concordance between local and central laboratory HER2 testing, which underlined the superior robustness of central services.[11 12]

CONCLUSION

As an action research exercise, this national consultation was qualitative in nature and did not produce hard data; further studies would be required to robustly quantify national opinion. However, a wealth of valuable qualitative information was harvested, providing what we believe to be a relatively accurate national snapshot of practices and attitudes with regard to HER2 testing. It could be argued that evidence-based discussions are preferable to variably informed opinions; however, the process of obtaining this consensus had the advantage of gathering views from a wide population of people closely associated with testing practice.

The possibility of self-selection of respondents cannot be ignored. It may be considered that those more motivated to establish blanket HER2 testing may have been more likely to participate in the consultation. Equally, it may be considered that those opposing the recommended practice would seize the opportunity to express their misgivings. The authors believe that these drivers most likely offset one another. Similarly, it is thought that the provision of a charity donation incentive, while helping to optimise response, also served to buffer the possibility of self-selection.

Take-home messages

Oncologists and pathologists strongly agree that:

- HER2 testing should be undertaken in all women with breast cancer at the point of diagnosis, irrespective of age or cancer type.
- Laboratories providing IHC and FISH testing services should be CPA-accredited and should carry out rigorous internal quality control and participate in UK NEQAS.
- All laboratories should carry out a formal annual audit of HER2 testing service.

A significant majority (89%) agree that:

- To ensure optimum resourcing of HER2 testing, only those laboratories undertaking a minimum of 250 tests should provide IHC HER2 testing services, preferably acting as a network testing centre.
- Only those centres undertaking a minimum of 100 FISH tests per year—and preferably at least 150—should be accredited to offer this service.

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