



Addressing the Challenges in the Identification of HER2-Low and Ultralow Breast Cancer in Asia: A Delphi Consensus

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ABSTRACT

Introduction: Human epidermal growth factor receptor type 2 (HER2) is overexpressed in 15–20% of primary invasive breast cancers, serving as a key predictive and prognostic factor. HER2-low is defined as immunohistochemistry (IHC) 1+ or 2+ with in situ hybridization

(ISH) negative and HER2-ultralow is defined as membrane staining that is incomplete, faint/barely perceptible, and in at most 10% of tumor cells (0+/with membrane staining). Trastuzumab deruxtecan has shown improved outcomes in multiple clinical trials between these groups. A Delphi study was conducted to address challenges in testing, sampling, and reporting, and to identify unmet needs in Asia.

Methods: The study comprised two online surveys and a participant meeting with 15 pathologists from nine countries in Asia and the Indo-Pacific region. Responses were recorded for 57

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close-ended and 33 open-ended statements using a 1–9-point Likert scale ranging from agreement to disagreement with a consensus threshold of 75%.

Results: All participants completed both surveys and the meeting (100% response). Consensus was reached on 33/57 closed-ended statements (survey 1, 27/47; survey 2, 6/21), while 24/57 did not reach consensus. Ninety-three percent of participants agreed that biopsies of recurrent lesions should be performed, especially if the primary tumor was HER2-zero. Initially, participants did not reach consensus (73% agreement) on reassessing HER2 results for metastatic lesions scored as HER2-zero but later reached consensus (80% agreement). All testing-related questions reached consensus in survey 1.

Conclusion: This Delphi study found strong consensus on key concepts for sampling, pathological testing, interpretation, and reporting of HER2-low and ultralow breast cancer. While the opinions expressed align with current guidelines, more evidence on the clinicopathological implications is needed.

PLAIN LANGUAGE SUMMARY

Human epidermal growth factor receptor type 2 (HER2) is a protein found in about 15–20% of invasive breast cancers and helps guide treatment decisions. HER2-low means the cancer shows low levels of HER2 (immunohistochemistry 1+ or 2+ with a negative in situ hybridization test), while HER2-ultralow refers to very minimal HER2 presence (immunohistochemistry 0 or slightly above). All participants completed both surveys and the meeting. This study found strong agreement on key concepts for sampling, pathological testing, interpretation, and reporting of HER2-low and ultralow breast cancer amongst experts. Agreement was reached on 33 of 57 statements, mostly in the first survey. A strong majority (93%) supported biopsying recurrent tumors, especially if the original was HER2-zero. Initially, there was no agreement on reassessing HER2 in metastatic HER2-zero cases (73% agreement), but this later improved to 80%. All testing-related questions reached agreement in the first round.

Keywords: HER-2-ultralow; HER-2-low; HER-2-low/ultralow breast cancer

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Key Summary Points

Why carry out this study?

HER2-low and ultralow breast cancers, previously classified as HER2-negative (IHC 0, 1+, or 2+ with ISH-negative), gained clinical importance after the DESTINY-Breast04 trial demonstrated that trastuzumab deruxtecan significantly improves progression-free and overall survival in this patient population. Despite these advancements, accurate identification of these subtypes remains challenging because of variability in testing and interpretation.

This Delphi consensus engaged experts from nine countries in Asia to address these challenges.

What was learned from the study?

Consensus was established on critical aspects of sampling, pathological testing, interpretation, and reporting of HER2-low and ultralow breast cancer.

The findings provide a framework for harmonized diagnostic practices and improved patient selection for HER2-targeted therapies across the Asia-Pacific region.

INTRODUCTION

Human epidermal growth factor receptor type 2 (HER2) is overexpressed in 15–20% of primary breast cancer, resulting from HER2 gene amplification. HER2 amplification and overexpression independently predict prognosis and disease progression, highlighting its significance as a prognostic factor in breast cancer [1, 2].

The American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) guidelines recommend HER2 testing for all patients newly diagnosed with breast cancer [3, 4]. A tumor is HER2-positive if it has an immunohistochemical (IHC) score of 3+ or 2+ with gene amplification confirmed by in situ

hybridization (ISH) [4, 5]. Tumors with IHC 0, 1+, or 2+ with negative ISH were historically classified as HER2-negative [6].

In the DESTINY-Breast04 (DB-04) trial involving patients with metastatic breast cancer, trastuzumab deruxtecan (T-DXd) resulted in significantly longer progression-free and overall survival than the physician's choice of chemotherapy in patients who were classified as HER2-low (defined as IHC HER2 1+ or 2+ and ISH negative). This questioned the binary HER2 pathological categorization system, which classified tumors as either HER2 positive or negative. DB-04 resulted in the approval of T-DXd for HER2-low metastatic breast cancer after ≥ 1 line of chemotherapy or disease recurrence during or within 6 months of completing adjuvant chemotherapy. However, DB-04 excluded patients with HER2 IHC score 0 status [5, 7–9].

DESTINY-Breast06 (DB-06) is a global, randomized, open-label, phase III trial which evaluates the efficacy and safety of T-DXd versus the investigator's choice of chemotherapy in patients with hormone receptor (HR)-positive, HER2-low or HER2-ultralow [defined as membrane staining that is incomplete, faint/barely perceptible, and at most 10% of tumor cells (0+/with membrane staining)] advanced or metastatic breast cancer. The primary findings revealed that T-DXd provided a statistically significant and clinically meaningful progression-free survival (PFS) advantage over chemotherapy (CT) in HER2-low metastatic breast cancer [T-DXd, 13.2 months (95% confidence interval [CI] 11.4–15.2); CT, 8.1 months (95% CI 7.0–9.0)]; HER2-ultralow results were consistent with HER2-low [10, 11].

Although the ASCO/CAP guidelines provide detailed information, HER2 testing for detection of HER2 expression at its lower range can be challenging in daily clinical practice. This has been highlighted in a study conducted in Denmark where the assessment of HER2-low breast cancer showed markedly higher interlaboratory variability. The availability of different antibody clones with varying specificity, and methodological and analytical variables that might influence the sensitivity and reproducibility of HER2 testing can lead to ambiguous results, particularly if the HER2 protein is ultralow level [12].

Furthermore, because of the alterations in the expression, regulation, or function, of the HER2 oncogene/oncoprotein, some cases may show significant intratumoral heterogeneity [5, 13, 14]. Combined with the distinct healthcare challenges in Asia such as limited access and availability of procedures, and higher out-of-pocket payment for availing testing, it is important to align these guidelines to the Asian perspective.

We invited a panel of Asian pathologists and conducted a Delphi consensus study to identify the challenges in testing, sampling, and reporting of HER2-low and ultralow breast cancer and to understand local unmet needs in Asia. The panel also deliberated on the potential solutions and recommendations to address these unmet needs.

METHODS

Study Design

This study employed the Delphi technique that included two rounds of cross-sectional surveys and a hybrid (attendance both in-person and online) meeting among 15 expert pathologists.

The primary objectives of the study were to:

- (a) Examine the HER2 testing landscape
- (b) Identify unmet diagnostic needs for HER2-ultralow patients
- (c) Evaluate the potential role of digital and computational pathology in this domain

The study also focused on themes such as sampling, testing procedures, interpretation, reporting practices, and future directions.

The research team developed the survey questionnaire after a literature review, which was administered by an independent vendor using Decipher software (version Compact = 153). Responses were analyzed after each round of survey using Microsoft Excel. Participants' information was kept confidential and anonymous.

Participants

The study involved 15 expert pathologists from nine countries in Asia and Indo-Pacific regions: India ($n=2$), Indonesia ($n=2$), Malaysia ($n=1$), Singapore ($n=2$), South Korea ($n=1$), Taiwan ($n=1$), Thailand ($n=2$), Vietnam ($n=2$), and the Philippines ($n=2$). Participants were selected through non-random methods on the basis of their expertise, experience in the field of HER2 testing, and different regional, geographic, sociocultural, and health system conditions. Participants were invited to the study if they fulfilled the following criteria:

- Expertise in pathology or a related field
- Active involvement in HER2 testing, with working knowledge of identifying HER2-low and ultralow patients
- Experience with clinical decision-making in HER2 testing or interpretation
- Interested in understanding criteria for HER2-low and ultralow
- Willing to participate in the Delphi process, including two rounds of surveys and a participant meeting

The same group of experts were invited to participate in all stages of the Delphi process. Participation in survey 2 was independent of the participant meeting attendance.

Pathologists fulfilling inclusion and exclusion criteria were identified and invited for participation in the study. They were informed about the objectives of the study prior to study initiation and informed consent was taken at each round of survey. The consent form detailed the objectives of the study. The participation in the study was voluntary, and participants were free to withdraw consent or not participate in any parts of the study. All the data for the study were collected using unique links which did not collect any identifiable information. All collected data were anonymized further and stored securely on access-controlled servers after conclusion of study.

Study Stages

Development of the Survey Questionnaire

The survey questionnaire was developed on the basis of key statements drawn from a targeted literature review. A comprehensive search was conducted in the PubMed database. Only studies published in English and involving human populations were considered. A total of 90 statements were included across both surveys, consisting of 57 closed-ended Likert-style statements and 33 open-ended qualitative questions (survey 1, 69 statements (47 closed-ended, 22 open-ended); survey 2, 21 statements (10 closed-ended, 11 open-ended)). These statements were designed to explore various themes related to HER2 testing, including:

- Sampling (survey 1, $n=3$; survey 2, $n=12$)
- Definition of HER2-low and ultralow (survey 1, $n=2$; survey 2, $n=1$)
- Pathology testing procedures (survey 1, $n=20$; survey 2, $n=4$)
- HER2 interpretation (survey 1, $n=3$)
- Heterogeneity (survey 1, $n=4$; survey 2, $n=1$)
- Reporting practices (survey 1, $n=7$; survey 2, $n=1$)
- Computational pathology (survey 1, $n=3$)
- Unmet needs (survey 1, $n=3$; survey 2, $n=2$)
- Future directions (survey 1, $n=15$)
- Low priority questions (survey 1, $n=9$)

Survey 1 and Participant Meeting

The first round of survey (survey 1) was conducted online in August 2024. The results from survey 1 were analyzed, and a hybrid (participants attending both online and in-person) participant meeting was conducted in August 2024, where experts discussed the findings. This participant meeting was arranged and facilitated by the sponsor, but the sponsor did not participate in the surveys or the discussion during the meeting. The discussion focused on clarifying and refining statements that lacked consensus and incorporated new recommendations from the participants.

Survey 2 and Final Data Analysis

Statements which did not reach consensus in survey 1 and any additional statements deemed appropriate from the participant meeting were included in survey 2 which was conducted in October 2024. The second survey included 14 statements, with one open-ended question.

Data from both surveys were analyzed descriptively in Microsoft Excel. A 1–9-point Likert scale was used to phrase the statements and rate responses as per best practice. Participants rated their level of agreement with each statement anonymously, ranging from 1 (strongly disagree) to 9 (strongly agree). These scores were divided into three groups: agree (7–9 points), neither agree nor disagree (4–6 points), and disagree (1–3 points). Consensus was defined as over 75% of participants rating a statement within the same category (i.e., agree, neither agree nor disagree, or disagree).

Ethical Considerations

As this was a non-interventional, physician-based Delphi consensus, formal IRB approval was not required. The study did not involve vulnerable populations, identifiable personal or clinical data, or human tissue samples; therefore, the Declaration of Helsinki also does not apply. Prior to the consensus process, participants were fully informed of the study objectives. Participation was voluntary, responses reflected independent opinions and were anonymized, and no sensitive or patient-related information was collected. All data were handled confidentially, and informed consent was obtained from all participating pathologists before initiating the virtual surveys. Participants were aware that study results would be published. All data informing the consensus guideline were sourced from publicly available information.

RESULTS

All the invited participants completed the survey, making the response rate 100%. Consensus

Table 1 Survey responses on sampling, definition of HER2-low and ultralow, and pathology testing procedures

Statements	Survey 1	Survey 2	Overall
Overall responses for questions on “sampling”			
Considering the possibility of changes in HER2 expression during disease progression, do you agree that a biopsy of recurrent lesions should be performed if the primary tumor was previously scored as 0, whenever feasible from a clinical standpoint?	Consensus (93%)	NR	Consensus
Do you agree that when conducting a biopsy of metastatic lesions and obtaining a score of 0, it is necessary to take into account the initial HER2 testing result of the primary tumor and reassess it if it was initially diagnosed as HER2-zero?	No consensus (73%)	Consensus (80%)	Consensus
To what extent do you agree that the following are challenges associated with retesting an archival/historical sample?			
Cost	NR	No consensus (33%)	No consensus
Reimbursement	NR	No consensus (47%)	No consensus
Storage conditions of archival sample	NR	Consensus (87%)	Consensus
Age of archived sample	NR	Consensus (87%)	Consensus
Difficulty in accessing the initial biopsy sample	NR	Consensus (80%)	Consensus
Overall responses for questions on “definition”			
Do you agree that reporting IHC and ISH scores (as selected above) should be accompanied by specific categorization of HER2 expression for better clarity for oncologists, particularly for identifying patients with low HER2 expression levels who may benefit from ADC treatments?	Consensus (90%)	NR	Consensus
Overall responses for questions on “pathology testing”			
Do you agree that methodological and analytical variables influence the sensitivity and reproducibility of detecting low/ultralow HER2 expression levels in IHC* testing? [If the response is 7 or more, then answer the next 2 questions (a,b)]	(100%)	NR	Consensus
Do you agree that the following variables influence IHC* staining intensity in HER2-low/ultra-low scoring?			
Tissue fixation	Consensus (100%)	NR	Consensus
Antigen retrieval techniques	Consensus (100%)	NR	Consensus
Reaction time of enzyme-chromogen	Consensus (93%)	NR	Consensus
Embedding and dewaxing temperature	Consensus (80%)	NR	Consensus
Incubation temperature of antibody	Consensus (93%)	NR	Consensus
Inappropriate substrate/chromogen concentration (e.g., 3,3'-diaminobenzidine, DAB)	Consensus (93%)	NR	Consensus

Table 1 continued

Statements	Survey 1	Survey 2	Overall
Do you agree that the availability of different antibody clones with varying specificity poses a significant challenge in HER2-low/ultralow testing?	Consensus (93%)	NR	Consensus
Do you agree that the following pre-analytical conditions should be considered before carrying out the assay in a pathology lab?			
Minimization of cold ischemia time to < 1 h	Consensus (100%)	NR	Consensus
Fixation of tissue in neutral buffered formalin (10%) for at least 6 h but less than 72 h	Consensus (100%)	NR	Consensus
Ensure regular tissue processing and paraffin embedding/microtomy	Consensus (93%)	NR	Consensus
Use of an external control	Consensus (100%)	NR	Consensus
Do you agree that interobserver variability during post analytical phase has a significant influence on HER2 interpretation? [If the response is 7 or more, then ask the next question]	Consensus (87%)	NR	Consensus
Do you agree that the following factors lead to interobserver variability in the post-analytical phase			
Lack of an internal positive control for HER2 within non-neoplastic breast tissue (survey 1)	No consensus (62%)	No consensus (73%)	No consensus
Do you agree that having an internal control is important in HER2 testing? (survey 2)			
HER2 intratumoral heterogeneity	Consensus (100%)	NR	Consensus
Semiquantitative and subjective mode of HER2 assessment	Consensus (92%)	NR	Consensus
Do you agree with ASCO/CAP [#] recommendations to examine HER2 IHC* at high power (×40) when discriminating between 0 and 1+ staining?	Consensus (93%)	NR	Consensus
Do you agree that using controls with a range of protein expressions, including IHC* 1+ cases, could be an essential factor in interpreting and differentiating HER2-low and ultralow?	Consensus (87%)	NR	Consensus
Do you agree that reflex ISH [†] may be ordered for confirmation in cases where determining HER2 IHC* scores is difficult due to ambiguity between 1+ or 2+?	Consensus (87%)	NR	Consensus
Do you agree that, if there is a complete membrane staining of 3+ intensity in less than 10% of tumor cells, a reflex to ISH is needed to finalize the result?	NR	Consensus (100%)	Consensus
Do you agree that there exists a strong association between NES and false-positive HER2 IHC*?	NR	No consensus (60%)	No consensus

IHC immunohistochemistry, ISH in situ hybridization, HER2 human epidermal growth factor receptor 2, NR not reported, NES normal epithelium staining

*immunohistochemistry

[#]American Society of Clinical Oncology and the College of American Pathologists

[†]in situ hybridization

was reached for 33/57 closed-ended statements, while 24/57 did not reach consensus across both the rounds of survey. Of these, 27/47 statements reached consensus in survey 1 and 6/21 reached consensus in survey 2. The findings reflect varying levels of consensus across different aspects of HER2 diagnostics as presented below.

Overall Survey Response on “Sampling”

Of the seven closed-ended questions within this theme (survey 1, *n*=2; survey 2, *n*=5), consensus was achieved for four statements (survey 1, 1/2; survey 2, 3/5). Additionally, eight open-ended questions (survey 1, *n*=1; survey 2, *n*=7) elicited diverse perspectives on sampling techniques and challenges in HER2 detection. Notably, strong consensus emerged on HER2 testing practices, particularly for biopsies of recurrent lesions (Table 1). In survey 1, 93% of participants agreed that biopsies should be performed for recurrent lesions, especially when the primary tumor was HER2-zero, emphasizing the significance of tracking changes in HER2

expression. With 73% of respondents agreeing in survey 1, consensus was not reached on reassessing HER2 results in metastatic HER2-zero lesions; however, survey 2 revealed 80% agreement, indicating growing support for re-evaluation. Open-ended responses (Figs. S1–S5) underscored the importance of tissue biopsies, challenges in retesting, and methods to reliably identify HER2-low/ultralow subtypes.

A key theme from the analysis was the difficulty in selecting appropriate tumor samples for HER2 testing, especially historical samples. Experts highlighted the need for standardized testing protocols, consistent sample storage practices, and clear cutoff criteria for retesting older samples, with some suggesting a 5-year cutoff as a potential guideline.

Overall Survey Response on “Definition”

This theme included three questions (survey 1, *n*=2; survey 2, *n*=1), with consensus achieved for one closed-ended question (survey 1, 1/1). Two open-ended questions explored definitions and criteria for HER2-low and ultralow, highlighting the importance of reporting HER2

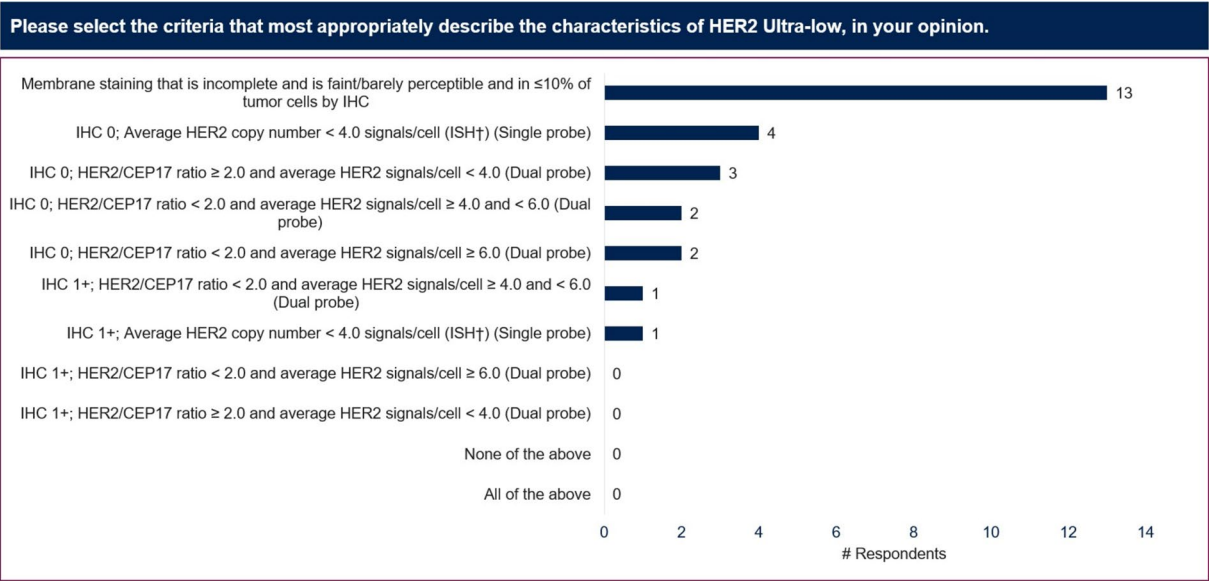


Fig. 1 Criteria that most appropriately describe the characteristics of HER2-ultralow (survey 2). *IHC* immunohistochemistry, *ISH* in situ hybridization, *HER2/CEP17* human epidermal growth factor receptor 2/centromere enumeration probe 17

expression using IHC and ISH scores (Table 1). In survey 1, 90% supported specific categorizations to enhance clarity for oncologists and identify patients for antibody–drug conjugate (ADC) therapies, aligning with the shift toward precision medicine in HER2 diagnostics. In survey 2, the most common criterion for HER2-ultralow was faint membrane staining in $\leq 10\%$ of tumor cells by IHC ($n=13$). Less frequent criteria included IHC 0 with HER2 copy numbers of 4.0 signals/cell (single probe, $n=4$) or HER2/chromosome 17 (CEP17) ratios ≤ 2.0 (dual probe, $n=3-4$). These findings underscore the need for dynamic testing and detailed reporting to optimize HER2-targeted treatment strategies (Figs. 1, S6).

A major theme identified was the lack of consensus on diagnosing HER2-low and HER2-ultralow categories. The advisory board discussions revealed heterogeneity in expert opinions, with some experts diverging opinions on the criteria and clinical relevance of these definitions. These opinions included concerns over the practicality of reporting HER2-low and ultralow classifications due to reliance on fluorescence in situ hybridization (FISH) testing and shifting thresholds, reluctance to use the term “ultralow” until more confidence is gained, and adherence to standard reporting guidelines while awaiting further studies to define HER2-low and ultralow subtypes more clearly.

Overall Survey Response on “Pathology Testing”

Pathology testing was a major focus, with 22 closed-ended questions (survey 1, $n=19$; survey 2, $n=3$). Consensus was achieved for 19 statements (survey 1, 18/19; survey 2, 1/3), while three did not reach consensus. Two open-ended questions explored advancements and limitations in procedural practices. The survey examined perspectives on HER2-low/ultralow expression levels, highlighting challenges in methodology, pre-analytical and post-analytical variables, and standard practices (Table 1). In survey 1, respondents unanimously agreed

(100%) that analytical variables impact HER2-low/ultralow detection sensitivity, with factors such as tissue fixation, antigen retrieval, enzyme-chromogen reaction time, and antibody incubation all receiving 80–100% agreement. Challenges regarding antibody clones were also noted, with 93% agreement. Pre-analytical conditions, such as minimizing cold ischemia time and proper tissue fixation, were seen as critical, with 93–100% agreement.

Post-analytical variability, driven by intratumoral heterogeneity (100%) and subjective assessment (92%), was a concern. The lack of internal control in non-neoplastic tissue remained unresolved, with 62% in survey 1 and 73% in survey 2 agreeing. Respondents supported ASCO/CAP recommendations, with 93% agreeing on high-power microscopy for distinguishing 0 and 1+ staining and 87% supporting protein expression controls. Survey 2 showed 100% agreement on reflex ISH testing when the IHC result was equivocal/borderline, but no consensus was reached on the association between normal epithelium staining and false positives. These findings emphasize the need for rigorous methods and standardized practices in HER2 diagnostics. Figures S7 and S8 provide insights into assay preferences and concerns over false positives.

A central theme identified in the advisory board meeting was the uncertainty regarding whether HER2-low or ultralow patients exhibit distinct clinicopathological characteristics. The advisory board discussions reflected mixed opinions, with some experts noting no significant differences, while others suggested that patients with low HER2 expression may have a better prognosis compared to those classified as HER2 null. Additionally, the analysis highlighted considerable subjectivity in the classification of HER2 status, especially when evaluating older biopsy samples. Subjectivity refers to differing views among pathologists on retesting historical samples. The main challenges include storage conditions (87% consensus), age of samples (87% consensus), and difficulty accessing initial biopsy samples (80% consensus).

Table 2 Survey responses on HER2 interpretation and heterogeneity, reporting practices, computational pathology, unmet needs, and future directions

Statements	Survey 1	Survey 2	Overall
Overall responses for questions on “HER 2 interpretation”			
Do you agree that HR β expression is more common in HER2-ultralow tumors than HER2-low?	No consensus (33%)	NR	No consensus
Overall responses for questions on “heterogeneity”			
Do you agree with the ASCO/CAP# definition of intratumor heterogeneity of HER2 amplification, “HER2/CEP17 signal ratios > 2.2 in 5–50% of the neoplastic cells”?	No consensus (53%)	NR	No consensus
Do you agree that the heterogeneity of HER2 expression further complicates the pathological interpretation between HER2 score 0 and score 1+?	Consensus (87%)	NR	Consensus
Do you agree that intratumoral HER2 IHC* heterogeneity (i.e., uneven distribution of HER2 expression or different intensities of HER2 staining in tumor cells) is more frequent in the HER2-low/ultralow samples?	No consensus (60%)	NR	No consensus
Do you agree that heterogeneity of HER2 expression is an independent risk factor for decreased disease-free survival and poses difficulties in selecting appropriate treatments for HER2-low/ultralow patients?	No consensus (60%)	NR	No consensus
Do you agree that HER2 negative groups are heterogenous in terms of presence of both HER2 staining and HER2-negative cells within a tumor?	NR	Consensus (100%)	Consensus
Overall responses for questions on “reporting”			
Do you agree with ASCO/CAP# recommendation that pathology laboratories should include a footnote in their HER2 IHC* and ISH [†] testing reports with the following comment			
No consensus (53%)			
(a) Patients with breast cancers that are HER2 IHC* 3+ or IHC* 2+/ISH [†] amplified may be eligible for several therapies that disrupt HER2 signalling pathways	No consensus (67%)	NR	No consensus
(b) Invasive breast cancers that test “HER2–” (IHC* 0, 1+ or 2+/ISH [†] not-amplified) are more specifically considered “HER2– for protein overexpression/gene amplification”, as non-overexpressed levels of the HER2 protein may be present in these cases	No consensus (67%)	NR	No consensus

Table 2 continued

Statements	Survey 1	Survey 2	Overall
(c) Patients with breast cancers that are HER2 IHC* 1+ or IHC* 2+/ISH [†] not-amplified may be eligible for a treatment that targets non-amplified/non-overexpressed levels of HER2 expression for cytotoxic drug delivery (IHC* 0 results do not result in eligibility currently)	Consensus (80%)	NR	Consensus
Overall responses for questions on “computational pathology”			
Do you agree that AI-assisted interpretation could significantly improve the accuracy and consistency of interpretation of HER2 0 and HER2 1+ tumors, such as breast cancers with heterogeneity?	No consensus (73%)	NR	No consensus
Do you agree that computational pathology can serve as a complementary tool for HER2 scoring in future?	Consensus (80%)	NR	Consensus
Overall responses for questions on “future directions”			
Do you agree that CISH and SISH have an advantage in HER2 heterogeneity? [If response is more than 7, then ask the next question]	No consensus (47%)	NR	No consensus
Do you agree that CISH and SISH offer advantages over FISH in terms of the following aspects			
Allows histologic evaluation of tumors	Consensus (100%)	NR	Consensus
Utilizes ordinary microscope	Consensus (100%)	NR	Consensus
Leaves permanent signals for archival storage	Consensus (100%)	NR	Consensus
Fully automated	No consensus (71%)	NR	No consensus
High reproducibility	No consensus (71%)	NR	No consensus
Overall responses for questions on “unmet needs”			
Do you agree that seeking certification from international partners will enhance individual laboratory practices for HER2 pathology testing?	NR	Consensus (80%)	Consensus

IHC immunohistochemistry, *ISH* in situ hybridization, *HER2* human epidermal growth factor receptor 2, *NR* not reported, *FISH* fluorescence in situ hybridization, *CISH* chromogenic in situ hybridization, *SISH* silver in situ hybridization

*immunohistochemistry

American Society of Clinical Oncology and the College of American Pathologists

[†]in situ hybridization

Overall Survey Response on “HER2 Interpretation”

This theme included three questions in survey 1, one closed-ended question, which did not achieve consensus (0/1), and two open-ended questions on interpretative variability and potential solutions. The survey explored HER2 interpretation and heterogeneity, revealing no consensus on whether hormone receptor beta (HR β) expression is more common in HER2-ultralow compared to HER2-low. Survey 1 showed only 33% agreement. Figure S9 illustrates the differences in clinicopathological features between HER2-ultralow and patients with low HER2 expression. Advisory board discussions emphasized variability in HER2 interpretation and the need for standardized criteria and clearer clinical guidance to improve reliability and reduce ambiguity (Table 2).

Overall Survey Response on “Heterogeneity”

Heterogeneity included five closed-ended questions (survey 1, $n=4$; survey 2, $n=1$), with consensus achieved for two statements (survey 1, 1/4; survey 2, 1/1). Responses highlighted challenges posed by tumor heterogeneity in HER2 testing. Agreement on the ASCO/CAP definition of intratumor heterogeneity was limited to 53% in survey 1, resulting in no consensus. However, 87% of survey 1 respondents agreed that HER2 expression heterogeneity complicates the interpretation between HER2 scores 0 and 1+, yielding a positive consensus. Regarding intratumoral HER2 IHC heterogeneity, 60% of survey 1 respondents acknowledged its frequency in HER2-low/ultralow samples, but no consensus emerged. There was also no agreement on whether HER2 expression heterogeneity is an independent risk factor for decreased disease-free survival or treatment selection challenges, with 60% agreement. This lack of consensus could be due to unfamiliarity with the topic or variations in clinical experience and exposure to emerging evidence on HER2 heterogeneity and its implications. In survey 2, 100% of respondents agreed that HER2-negative groups exhibit

heterogeneity, including both HER2-staining and HER2-negative cells within tumors.

The variability in HER2 expression, both spatially within a tumor and temporally over time, emerged as a critical challenge. This heterogeneity complicates the reliability of test results and impacts the interpretation of HER2 status, particularly when comparing old versus recent tumor samples (Table 2).

Overall Survey Response on “Reporting”

This theme included eight questions (survey 1, $n=7$; survey 2, $n=1$), with consensus achieved for one closed-ended question (survey 1, 1/3). Five open-ended questions focused on standardization and discrepancies in reporting practices. Survey results showed varied opinions. Regarding the ASCO/CAP recommendation on including footnotes in HER2 IHC and ISH testing reports, there was no consensus. Specifically, 33% of survey 1 respondents disagreed with including a footnote suggesting HER2 IHC 3+ or 2+/ISH amplified tumors may be eligible for HER2-targeted therapies. However, 67% agreed that HER2-negative tumors should be categorized as “HER2-negative for protein overexpression/gene amplification.” Additionally, 80% of respondents agreed that patients with HER2 IHC 1+ or 2+/ISH non-amplified tumors may be eligible for treatments targeting non-overexpressed HER2. Figures S10–S12 illustrate preferences for reporting “HER2-ultralow,” the importance of reporting HER2 protein expression, and the varied approaches to reporting HER2 test results in breast cancer.

The advisory board highlighted inconsistencies in reporting HER2 status, particularly around the term “HER2-ultralow.” Many experts expressed reluctance to adopt this terminology because of limited clinical evidence and unclear guidelines. Preferences leaned toward using specific IHC scores for clarity, emphasizing the need for standardized reporting practices to ensure consistent interpretation and application in clinical settings (Table 2).

Overall Survey Response on “Computational Pathology”

Survey 1 addressed this theme with three questions, including two closed-ended (1/2 achieved consensus) and one open-ended exploring the integration of AI and computational tools in pathology workflows. Regarding “computational pathology,” there was no consensus on whether AI-assisted interpretation could improve the accuracy of HER2 0 and HER2 1+ tumors, with 73% of respondents expressing uncertainty. However, 80% agreed that computational pathology could complement HER2 scoring in the future, suggesting optimism for AI in enhancing HER2 testing. Figure S13 illustrates various computational pathology devices and methods for HER2 interpretation. A key theme was the need for standardized HER2 testing procedures, including clear scoring criteria and better pathology training. Experts also emphasized the importance of establishing national cancer registries to address gaps in breast cancer data in Asia, such as incidence and mortality rates. Variability in HER2 testing results across laboratories highlighted the need for improved quality control (Table 2).

Overall Survey Response on “Future Direction”

Survey 1 included 15 questions under this theme, with six closed-ended (consensus achieved for 3/6) and nine open-ended. Responses highlighted potential advancements and improvements in HER2 testing. Regarding “future directions” and “unmet needs,” there was no consensus (47%) on the advantages of chromogenic ISH (CISH) and silver-enhanced ISH (SISH) for HER2 heterogeneity, indicating uncertainty about their benefits. However, 100% agreed that CISH and SISH provide significant advantages over FISH, including histological evaluation, use of ordinary light microscopes, and permanent archival signals, making them highly practical in clinical settings. In contrast, there was no consensus (71%) on high reproducibility and full automation, suggesting doubts

about technical consistency and automation. Figures S14–S18 highlight potential solutions to unmet needs in detecting and sampling HER2-low/ultralow breast cancers, as well as comparisons between traditional and new methods for improved detection accuracy. Experts emphasized the need for biopsy recurrent lesions to reassess HER2 status, aiding better treatment decisions (Table 2).

Overall Survey Response on “Unmet Needs”

Unmet needs in HER2-low/ultralow breast cancer detection were explored through five questions (survey 1, $n=3$; survey 2, $n=2$). Consensus was achieved for one closed-ended question (survey 2, 1/1), and four were open-ended. Key unmet needs identified in survey 1 included challenges with early detection, lack of clear healthcare policies, absence of national cancer registries and clinical databases, and the need for standardized data on incidence, prevalence, and mortality rates (Fig. 2a). Sampling challenges included the lack of re-biopsy strategies at recurrence limited access to CT-guided biopsies, and inadequate financing for re-biopsies (Fig. 2b). Respondents emphasized the need for standardization and quality control in pathology testing across centers, as well as improved reporting systems (Fig. 2c). To enhance AI-assisted HER2 interpretation, recommendations included further research validation and ongoing expert diagnosis integration (Fig. 2d). In survey 2, 80% agreed that international certification could improve HER2 testing practices. The advisory board highlighted the importance of clear clinical guidelines, better infrastructure, and pathologist training (Table 2).

DISCUSSION

This Delphi study gathered expert opinions on HER2 testing in Asia, focusing on protocols, procedures, and challenges faced in testing. Consensus was reached on key aspects such as defining HER2-low/ultralow status, testing methodology, and interpretation. Disagreements emerged on sample selection, heterogeneity, and reporting.

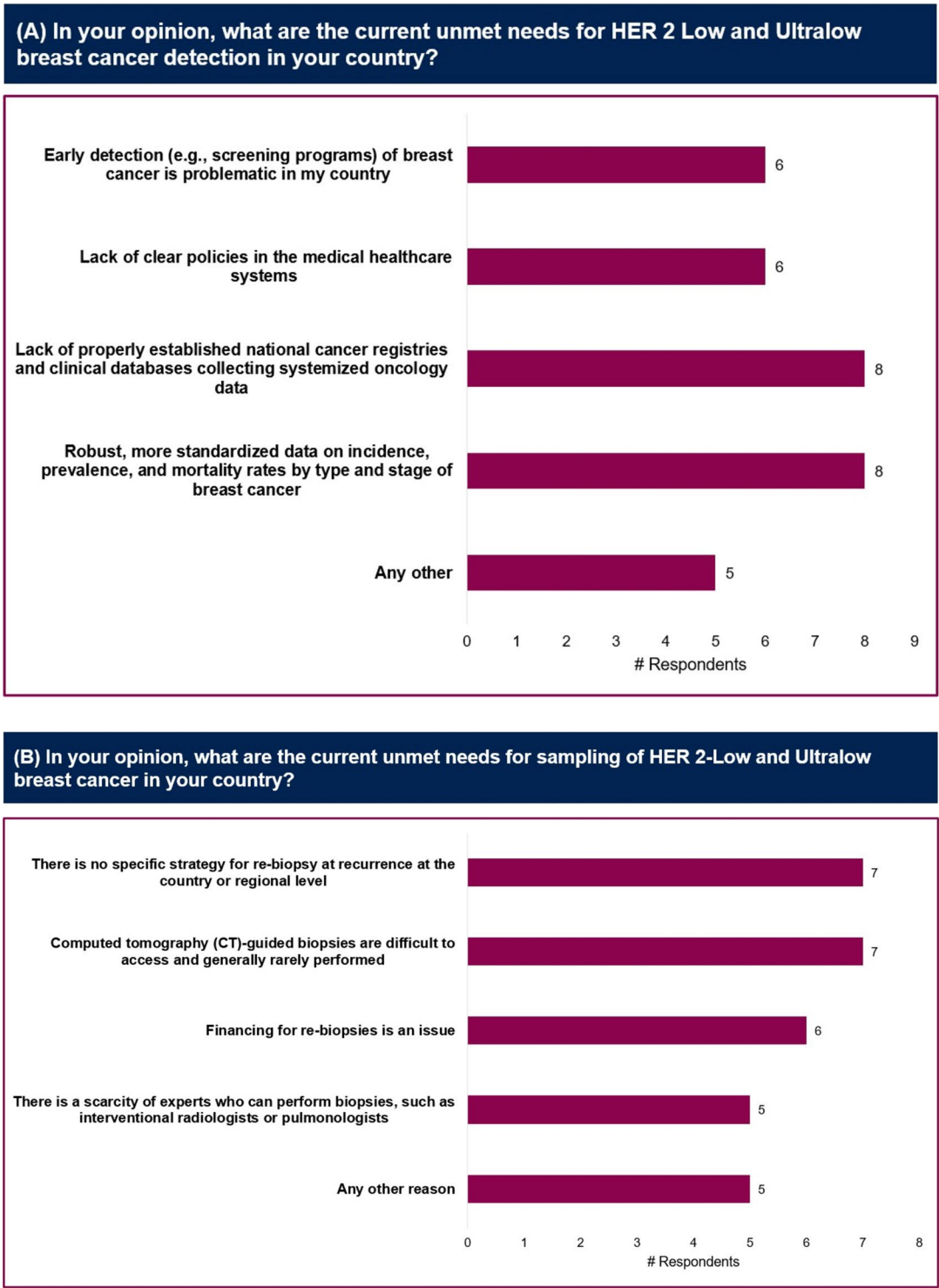
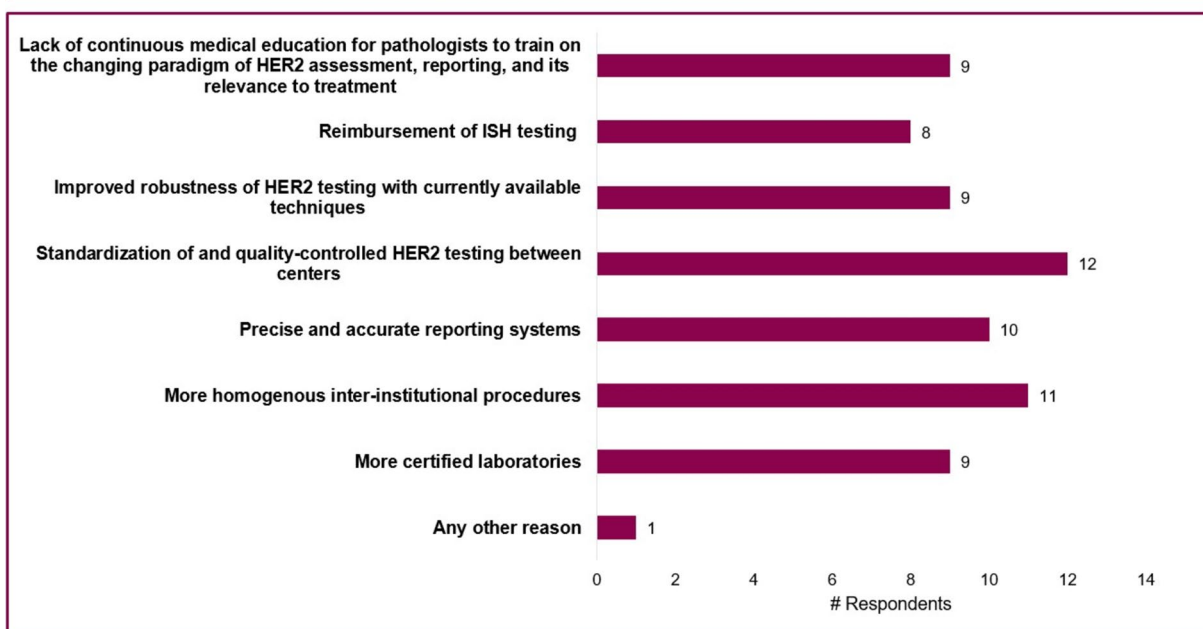


Fig. 2 **a** Current unmet needs for HER 2-low and ultralow breast cancer detection (survey 1). **b** Current unmet needs for sampling of HER 2-low and ultralow breast cancer (survey 1). **c** Current unmet needs for pathology testing of HER 2-low and ultralow breast cancer (sur-

vey 1). **d** Recommended steps for overcoming the problems and improving AI-assisted HER2 interpretation (survey 2). *HER2* human epidermal growth factor receptor 2, *ISH* in situ hybridization, *AI* artificial intelligence

(C) In your opinion, what are the current unmet needs for pathology testing of HER 2-Low and Ultralow breast cancer in your country?



(D) What steps would you recommend overcoming the problems and improve AI-assisted HER2 interpretation in your country?

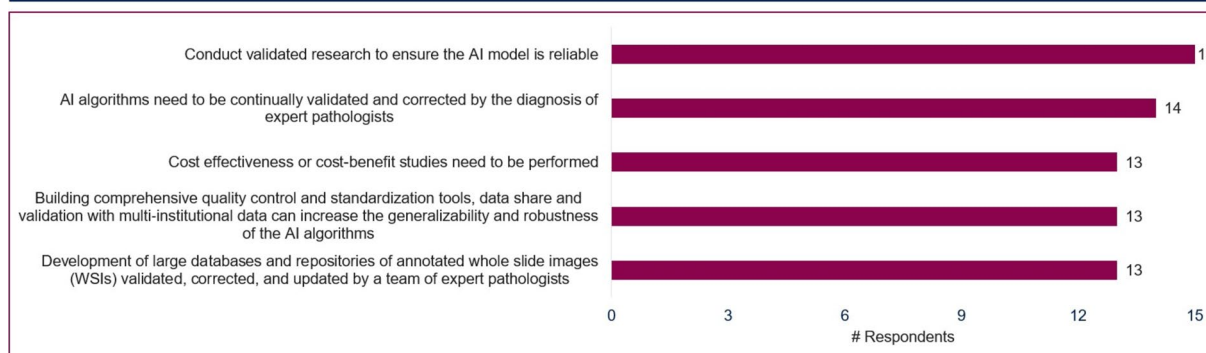


Fig. 2 continued

The advisory board discussions emphasized the importance of standardized definitions and reporting for HER2 status to ensure consistent clinical outcomes. Clear, uniform definitions are crucial for aligning HER2 terminology with actionable clinical evidence, as ambiguity can hinder treatment decisions. Identifying future directions and unmet needs highlighted areas for improvement in testing and clinical practice.

In the DB-04 trial, patients were eligible for enrolment if they had HER2-low status on any tumor sample: archived sample, new biopsy or sample from metastasis [9]. However, in the DB-06 trial, the most recent pre-randomization tumor sample was utilized to assess the HER2 status in patients [10]. This difference in eligibility criteria between these two trials may have resulted in the heterogeneous opinions obtained

in the present study. During both surveys, 67% of the participants agreed that both the historical and most recent samples can be used to define the tumor as HER2-low/ultralow. Ivanova et al. recommended conducting a biopsy of the recurrent lesions when the primary tumor was previously classified as HER2-zero, provided it is clinically feasible. They also recommended considering the results of HER2 testing of the primary tumor in case the biopsy from the metastatic tumors yielded a result of HER2-zero [5]. The panel reached a consensus on both these statements, although there was initial disagreement in survey 1. The participants highlighted that the availability and storage condition of the historical sample may be suboptimal, rendering the reassessment of the historical sample difficult. Additionally, the age of the sample and cost of reassessment were also highlighted as concerns for reassessment. Testing methodology and sample selection emerged as a critical theme, with experts emphasizing the importance of standardized protocols for HER2 testing, particularly for retesting older tumor samples. While a 5-year cutoff is suggested by experts, further research on antigen stability is needed for reliable interpretation [15]. The panel recommended establishing clear guidelines for HER2 IHC testing, including time frames for historical sample storage. However, they emphasized that rigid time limitations should be carefully evaluated, especially when there is even a small possibility of the patient benefiting from HER2-targeted therapy. Additionally, they suggested integrating advanced diagnostic techniques to enhance the accuracy of HER2 status assessment. This would help address the inherent heterogeneity in HER2 expression and ensure consistent identification of actionable targets.

A cutoff of 5 years for the initial sample to be eligible for a retest was recommended by four participants. Standardization with regard to the storage conditions is desirable from the future testing perspective.

Experts in this study highlighted inadequate financing for re-biopsies and the lack of standardized quality control across diagnostic centers as barriers to the effective implementation of HER2-low testing. These challenges mirror findings from recent studies, which demonstrate

that financial constraints can limit access to re-biopsy procedures and that variability in HER2-low assessment across institutions may compromise diagnostic accuracy and equitable treatment decisions. Together, these issues present significant obstacles to accessing innovative therapies and underscore a broader public health concern that requires attention from healthcare systems [16, 17].

Although a majority of the panelists voted for the “Some staining/membrane staining that is incomplete and is faint/barely perceptible and in $\leq 10\%$ of tumor cells by IHC” definition of HER2-ultralow, it was not considered to be entirely accurate, with only eight participants accepting this definition in survey 1. According to the 2018 ASCO/CAP guidelines, IHC 0 is defined as some staining but not in more than 10%, and there is also a category of no staining at all [3], which is now referred to as HER2 null. Interestingly, in survey 1, 5/15 participants disagreed with all the prevalent definitions of HER2-ultralow, demonstrating a need for an improved definition of the term. The need to refine the criteria on the basis of the evolving evidence is also highlighted in a study conducted by Farshid et al. in which they revisited old biopsy samples which were previously categorized as HER2-zero or 1+. Upon re-evaluation based on revised criteria, approximately 72% of all re-evaluated samples were categorized to be HER2-low cancers. Of the HER2-zero cases, 41% were found to be HER2-low, while approximately 22% of the previously scored 1+ were reclassified as ultralow or null. These findings highlight subjectivity, imprecision, and also the need for more neutral and objective scoring criteria [18].

No consensus was reached on normal epithelium staining and false positives. In normal tissues, HER2 expression is typically low or absent. However, in some cases, normal tissue may show distinct expression necessitating further testing to rule out false positive results. In contrast, Gown et al.’s study demonstrated that replacing the standard IHC scoring system with a normalized approach, which subtracts the score from normal epithelium, significantly reduced false positives from 30.6% to 5.3% [19]. A further study reviewing HER2 IHC in normal breast tissue in patients with HER2-ultralow/low treated

by T-DXd (good response VS poor response) may be of interest.

There was a heterogeneous response concerning the clinicopathological differences between HER2-low and ultralow patients. Experts in this study stated that because there is a lack of data on HER2-ultralow patients, who have historically been reported as zero, it is challenging to conclude whether the patients differ in terms of clinicopathological features. The discussion also highlighted the need for more robust studies to better understand the clinicopathological features and prognostic implications of HER2-low and ultralow categories. The advisory board stressed the importance of standardizing classification methods to minimize subjectivity, especially when dealing with older biopsy samples, where variability can be significant.

This opinion resonates with the study conducted by Chen et al. which suggests that while HR-positive tumors were more common than HR-negative ones in HER2-ultralow patients, HER2 status alone had no prognostic value [20]. These findings were also substantiated by a large-scale retrospective cohort analysis conducted by Peiffer et al. The authors concluded that HER2-low cannot be considered a biologically distinct subset of breast cancer [21]. Despite the lack of differences in clinicopathological features, certain researchers have concluded that patients with low HER2 expression have better prognosis as compared to those with HER2-zero [22].

Participating experts in the study mentioned that they use external controls, positive and negative, to address interobserver variability. European Society for Medical Oncology (ESMO) expert consensus recommends the utilization of external controls calibrated with low-intensity staining and using controls with a range of protein expression including 1+ cases to optimize decision-making regarding the HER2 status of the specimen [23]. According to the ASCO/CAP guidelines, a sample can be rejected in case the controls are inappropriate or internal controls demonstrate abnormal staining, highlighting the importance of selection of controls [3]. The panelists in the present study also mentioned that selecting a sample for HER2-low as an external control is challenging as the section assessed may come from a zone from HER2-low/ultralow

sample but may not have any staining, leading to a false negative control.

Despite the importance of HER2-low/ultralow status, approximately half of the respondents disagreed with using the term “HER2-ultralow” in the report. Lack of recommendations mentioning HER2-ultralow, lack of clarity in interpretation, and lack of adequate clinical evidence were some of the reasons provided for not using this terminology. This opinion aligns with the ESMO expert consensus which recommends using specific IHC scores for reporting, rather than stating the clinical interpretation (positive, negative, low, or ultralow) [23]. This recommended practice was reportedly followed unanimously by the expert panel.

The experts in this study did not agree with the ASCO/CAP definition of intratumor heterogeneity of HER2 amplification, “HER2/CEP17 signal ratios > 2.2 in 5–50% of the neoplastic cells” [3]. Heterogeneity in HER2 expression is a clinically significant issue considering its impact on selecting the appropriate treatment for patients. HER2 expression is not limited only to differences in expression in the sample (spatial/geographical heterogeneity) but also may evolve over time with HER2-targeted therapies (temporal heterogeneity). Although the experts in this study did not reach consensus, evidence suggests that heterogeneity is regarded as an independent risk factor for reduced disease-free survival. This presents challenges in selecting optimal treatments, though the bystander effect of trastuzumab-deruxtecan may still offer therapeutic benefits in tumors with heterogeneous HER2 expression. Further research is needed to clarify its efficacy in this context [5]. This indicates a necessity for further exploration of heterogeneity and its clinical consequences in HER2-low/ultralow patients. Our study has several strengths. In addition to including experts from nine different Asian countries for a structured discussion on existing evidence, we also attempted to generate insights regarding the unmet needs, next steps, and future trends for HER2 testing. Lack of properly established national cancer registries providing systemized data such as incidence, prevalence, and mortality rates and lack of clearly defined criteria and training and skill development were some of the

unmet needs identified. Standardization of testing and lack of homogeneity between testing centers were further unmet needs. In terms of infrastructure, the board recommended implementing standardized HER2 testing protocols and improving training for pathologists to reduce inconsistencies. Additionally, there was a consensus on the need for comprehensive cancer registries and stronger quality control mechanisms to enhance interlaboratory consistency. The Delphi method is an established process known for reaching consensus through expert opinions in situations of uncertainty or dichotomous evidence or where formal clinical trials are particularly challenging or impractical [24, 25]. Furthermore, the 100% response rate for both the surveys and also for participant meeting attendance demonstrate high engagement, interest, and relevance of the topic to practice.

Our study is not without limitations. Firstly, the participants of the study are highly engaged at the expert pathologists interested in research; however, their opinions may not be representative of other pathologists not involved in research. It is unknown whether a different group of experts or experts from different countries would reach similar conclusions, thereby limiting the generalizability of these results. The results of this study have temporal validity and may change with evolving knowledge, evidence, and practices in HER2 testing.

CONCLUSION

This Delphi study demonstrated a high level of consensus regarding key concepts for sampling, pathological testing, interpretation, and reporting of HER2-low and ultralow breast cancer. There was a clear preference for using both historical and most recent samples for identification HER2 status. The panel was also aligned with the current guidelines for pathological testing; however, differences in opinion existed for reporting the findings. Finally, a lack of evidence was noted and the need for standardization and skill enhancement for optimal identification of HER2 status was highlighted.

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Editing. Puay Hoon Tan: Roles: Conceptualization, Data Curation, Formal Analysis, Validation, Visualization, Writing – Original Draft, Writing – Review & Editing. Tikamporn Jitpasutham: Roles: Conceptualization, Data Curation, Formal Analysis, Validation, Visualization, Writing – Original Draft, Writing – Review & Editing.

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Data Availability. All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Declarations

Conflict of Interest. Milap Shah, Bethy S Hernowo, Trung Nguyen Cong, Gong Gyungyub, Irianiwati, Lu Bach Kim, Manuelito A. Madrid, Pathmanathan Rajadurai, Sunil Pasricha, Benjamin Yongcheng Tan and Tikamporn Jitpasutham declare no conflicts in this work. Rowen T. Yolo, Pichet Sampatanukul have received honorarium and travel support from AstraZeneca. Shir-Hwa Ueng has received honorarium and travel support from AstraZeneca and Discovery Life Science and serves as Council member of the Taiwan Society of Pathology, Breast Cancer Committee. Puay Hoon Tan has received honoraria and travel support from AstraZeneca and Singapore Pathology and also holds shares in Tamarind Health.

Ethical Approval. As this was a non-interventional, physician-based Delphi consensus, formal IRB approval was not required. The study did not involve vulnerable populations, identifiable personal or clinical data, or human tissue samples; therefore, the Declaration of Helsinki also does not apply. Prior to the consensus process, participants were fully informed of the study objectives. Participation was voluntary, responses reflected independent opinions and were anonymized, and no sensitive or

patient-related information was collected. All data were handled confidentially, and informed consent was obtained from all participating pathologists before initiating the virtual surveys. Participants were aware that study results would be published. All data informing the consensus guideline were sourced from publicly available information.

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