Estrogen receptor (ER) (Core and Non-core)

Use of hormone receptor scoring systems such as Allred, Quick score and H score are optional (see methodology details below).

Hormone receptor status is determined primarily to identify patients who may benefit from endocrine therapy. About 75 to 80% of invasive breast cancers are positive for estrogen receptor (ER) and progesterone receptor (PR), including almost all well-differentiated (grade 1) cancers and most moderately differentiated (grade 2) cancers, and studies have shown a substantial survival benefit from endocrine therapy among patients with ER positive tumours. Receptor status is only a weak prognostic factor. Currently ER status is used to select patients suitable for endocrine therapy. PR status has been shown to provide information on degree of response to endocrine therapy in patients for ER positive tumours.

Hormone receptor status

True ER negative, PR positive carcinomas are extremely rare, but patients with such tumours are also considered eligible for endocrine therapy.

The finding of an ER negative PR positive tumour can indicate a false negative ER assessment or a false positive PR assessment and audit or repeat staining is recommended.

Hormone receptor status is most often determined in formalin-fixed, paraffin-embedded tissue sections by immunohistochemistry (IHC). Only nuclear staining is considered positive. Single-gene expression assays are not recommended for routine use.

The American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP), The Royal College of Pathologists UK (RCPath), and The Royal College of Pathologists of Australasia (RCPA) have issued recommendations for reporting the results of IHC assays for ER and PR.[1-3] Studies using both IHC and the ligand binding assay suggest that patients with higher hormone receptor levels have a higher probability of response to endocrine therapy, but expression as low as 1% positive staining has been associated with a clinical response. As a result, the guidelines recommend classifying all cases with at least 1% positive cells as receptor positive. For patients with low ER expression (1 to 10% positive cells), the decision on endocrine therapy should be based on an analysis of its risks and potential benefits.[4]

Definition of a negative result

All current guidelines recommend that carcinomas with <1% positive cells be considered negative for ER and PR.[5-7] In the Allred system (see Table 4), the survival of patients whose carcinomas had a score of 2 (corresponding to <1% weakly positive cells) was similar to that of patients whose carcinomas were completely negative for ER.[8] Therefore, a score of 2 was considered to be a negative result. Using the Allred or Quickscore system[9] carcinomas with <1% positive cells and intensity scores of 2 or 3 would have a total score of 3 or 4 and historically were considered positive. These are rare carcinomas, and their response to endocrine therapy has not been specifically studied. Thus use of the Allred/Quickscore assessment methods can, in a small proportion of cases, conflict with the 1% cut point for positivity/negativity recommended above. It is recommended that all cases showing ≥1% of tumour cells positive should be classified as receptor positive regardless of their Allred/Quickscore. Reports should include the overall percentage of positive cells and the average intensity regardless of whether additional scoring systems, such as Allred or H score, are also reported. All cases showing <1% of tumour cells positive should be classified as receptor negative regardless of their Allred score.

It has become increasingly recognised that there are limited data on response to endocrine therapy in carcinomas with low level ER expression, defined as 1-10% positive cells, although the available information currently supports possible benefit. Furthermore, recent studies of ER gene expression have shown profiles more similar to ER negative cancers. It is recommended that these tumours remain classified as positive and considered eligible for endocrine treatment, but be designated Low ER Positive.[4] The following reporting comment is recommended in ER Low Positive cases, to aid in communicating the challenges and more limited data on cancers with this result: "The cancer in this sample has a low level (1-10%) of ER expression by immunohistochemistry (IHC). There are limited data on the overall benefit of endocrine therapies for patients with low level (1-10%) ER expression but they currently suggest possible benefit, so patients are considered eligible for endocrine treatment. There are data that suggest invasive cancers with these results are heterogeneous in both behaviour and biology and often have gene expression profiles more similar to ER negative cancers."

When a tumour is negative but no internal control cells are present, the pathologist must exercise judgment as to whether the assay can be interpreted as a true negative. If there is doubt then a recommendation to repeat on another block or specimen that contains internal controls should be made.

'Cannot be determined' is used when any issue prevents reliable interpretation of the result. This can include suboptimal specimen handling, presence of artefacts (crush or edge artefacts) making interpretation difficult, or if the analytical testing procedure failed.

Quantification of ER and PR

There is a wide range of receptor levels in cancers as shown by the biochemical ligand binding assay and as observed with IHC. Patients whose carcinomas have higher levels have improved survival when treated with endocrine therapy. Quantification systems may use only the proportion of positive cells or may include the intensity of immunoreactivity:

- Number of positive cells: The number of positive cells can be reported as a percentage or within discrete categories (Figure 4).
- Intensity: Refers to the degree of nuclear positivity (i.e., pale to dark). The intensity can be affected by the amount of protein present, as well as the antibody used, the antigen retrieval system and the detection system. In most cancers, there is heterogeneous immunoreactivity with pale to darkly positive cells present.

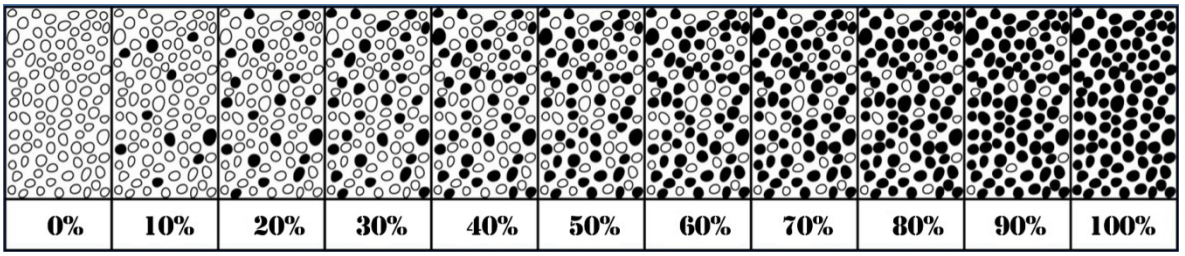

Figure 4: Quantification of immunohistochemical findings.

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Two methods of quantifying ER by using both intensity and percentage of positive cells are the Allred score (Table 4) and the H score (Table 5). The two systems classify carcinomas into similar, but not identical, groups. If high-affinity antibodies are used with sensitive detection systems, most carcinomas will fall into clearly positive (score 7 or 8) or clearly negative (score 0) categories by Allred score. A small group of carcinomas (<1% of total) show intermediate levels of immunoreactivity.

Table 4: Allred score* for estrogen and progesterone receptor evaluation.

Proportion Score	Positive Cells, %	Intensity	Intensity Score
0	0	None	0
1	<1	Weak	1
2	1 to 10	Intermediate	2
3	11 to 33	Strong	3
4	34 to 66		
5	≥67		

* The Allred score combines the percentage of positive cells and the intensity of the reaction product in most of the carcinoma.[8] The two scores are added together for a final score with eight positive values. Scores of 0 and 2 are considered negative. Scores of 3 to 8 are considered positive.

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Table 5: H score* for estrogen and progesterone receptor evaluation.

Calculation of H Score		
Cell Signal	**Percentage of Cells**	**Value Multiplied**
Cells with no signal		% x 0 = 0
Cells with weak signal		% x 1 =
Cells with moderate signal		% x 2 =
Cells with strong signal		% x 3 =
Total score =		

* The H score is determined by multiplying the percentage of cells demonstrating each intensity (scored from 0 to 3) and adding the results.[11] There are 300 possible values. In this system, <1% positive cells is considered to be a negative result.

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Quality assurance

There are many preanalytic, analytic and postanalytic variables that can affect test results, and the assays must be validated to ensure their accuracy. External quality assurance proficiency testing surveys for ER and PR are invaluable tools to help ensure that assays perform as expected, and they are available from established immunocytochemistry external quality assurance (EQA) scheme providers (CAP, United Kingdom NEQAS, NordiQC, CPQA, CBQA etc).

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