2021

Taiwan Breast Cancer Molecular Testing Consensus

主編·台灣乳房醫學會

TBCS

台灣乳房醫學會
TAIWAN BREAST CANCER SOCIETY

Preface

新穎治療日新月異，精準醫療已成為主流。多基因標記不僅能對預後風險做準確評估，伴隨式診斷生物標記還能夠指導用藥。但基因檢測結果複雜且陷阱眾多，需憑藉專業臨床醫師全面性正確闡釋才能落實於病人醫療，反之則可能會因檢測結果而影響了治療決策及方向。且目前因特管法規範對現階段 DTC 基因檢測生態的衝擊下，坊間生技產業廣泛宣傳，訊息繁雜，無法真實準確反映醫療現況水平。

學會為秉持加強乳癌疾病之醫療、教學及研究之宗旨精神，特參照國際準則及國內臨床實況，制定全國性的治療共識，給予乳癌領域相關醫師遵循參考，進而讓臨床醫師皆具備足夠的領域知識，全面精準分析臨床數據及基因資料，實踐病人個人化醫療。

此次乳癌分子檢測共識先於 2020 年 5 月成立共識會議工作小組，由趙祖怡及盧彥伸帶領林柏翰、洪志強、郭玟伶、陳芳銘、曾彥敦、黃其晟、劉峻宇、戴明燊、饒坤銘（依姓氏筆畫排列、職稱省略概以醫師稱謂）進行共識會議籌備，擬定乳癌分子檢測重要議題。本人衷心感謝工作小組的辛勞付出。 本會於 2020 年 12 月 06 日，假台北榮總致德樓正式舉辦「2020 Taiwan Breast Cancer Molecular Testing Conference」，與全國專家學者們共同討論，會後彙整專家建議，經台灣乳房醫學會第八屆理監事審議通過。鑑往知來，醫學與時俱進，共同促進醫學之進步發展為吾人終生努力職志，誠摯期待各界先進能不吝指教、提供新知，共同為台灣乳癌治療盡最大努力，讓精準醫療廣泛且準確運用於國人乳癌防治。

台灣乳房醫學會 理事長
曾令民 于 2021 年 5 月

特別感謝以下專家（依姓氏筆畫排列、職稱省略概以醫師稱謂）

于承平、王明暘、王惠暢、王甄、李國鼎、杜世興、沈士哲、沈陳石銘、林季宏、林柏翰、侯明鋒、俞志誠、洪志強、洪朝明、張金堅、張振祥、張源清、張獻崑、張耀仁、莊捷翰、許居誠、許桓銘、郭文宏、郭玟伶、陳守棟、陳芳銘、陳訓徹、陳達人、曾令民、曾彥敦、黃其晟、黃俊升、葉大成、葉顯堂、廖國秀、趙大中、趙祖怡、劉自嘉、劉良智、劉建良、劉峻宇、歐陽賦、蔡宜芳、蔡青樺、鄭翠芬、盧彥伸、戴明燊、鍾為邦、饒坤銘等諸位醫師。

Content

Levels of Evidence and Consensus for Recommendations

Definitions for NCCN Categories

The specific definitions of the NCCN categories for recommendations are included below.

- **Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
- **Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
- **Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
- **Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

For the 'uniform NCCN consensus' defined in Category 1 and Category 2A, a majority panel vote of at least 85% is required.

For the 'NCCN consensus' defined in Category 2B, a panel vote of at least 50% (but less than 85%) is required.

Lastly, for recommendations where there is strong panel disagreement regardless of the quality of the evidence, NCCN requires a panel vote of at least 25% to include and designate a recommendation as Category 3.

The large majority of the recommendations put forth in the guidelines are Category 2A. Where categories are not specified within the guidelines, the default designation for the recommendation is Category 2A.

* NCCN:2021 National Comprehensive Cancer Network

Introduction of Precision Medicine in Breast Cancer

Consensus statement	Recommendation level	Expert Consistency	Reference
1. Precision medicine for breast cancer is an evolving approach that uses information from genes, gene expression and proteins to diagnose, treat, and prevent cancer. Its goal is to match patients to safe, effective, and individualized treatments that have a high probability of success and to avoid treatments that will not work or carry a high risk of toxicities.		>85%	[1,2]
2. DNA sequencing of region of interest (ROI) offers the potential to deliver personalized medicine by matching appropriate targeted therapies with unique molecular aberrations within an individual's cancer.		>85%	[3]
3. Whole genome sequencing, especially DNA sequencing, is now the most common used technique. Origin of specimens depend on the ROI.	I		
4. Massively parallel sequencing, such as whole genome sequencing can be used to identify biomarkers associated with response to experimental targeted therapies.		>85%	[4]
5. mBC patients can be included in molecular screening programs and include them in trials testing targeted therapies matched to genomic expression.		>85%	[5]
6. Multigene panels have not yet proven beneficial in clinical trials for advanced breast cancer; their impact on outcome remains undefined and should not be used in clinical practice routinely.		>85%	[6]
7. Physicians and patients should understand the indication, application and limitation before they apply NGS for precision medicine.		>85%	

References

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2. Laura A. Levit, Edward S. Kim, Barbara L. McAneny et al.(2019) Implementing Precision Medicine in Community-Based Oncology Programs: Three Models. J Oncol Pract 15:325-329
3. Lucy R. Yates and Christine Desmedt. (2017) Translational Genomics: Practical Applications of the Genomic Revolution in Breast Cancer. Clin Cancer Res; 23(11); 2630–9
4. Avila M, Meric-Bernstam F. (2019) Next-Generation Sequencing for the General Cancer Patient. Clin Adv Hematol Oncol. Aug; 17(8): 447–454
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6. F. Mosele, J. Remon, J. Mateo, C.B. Westphalen, F. Barlesi, M.P. Lolkema, N. Normanno, A. Scarpa et al. (2020) Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group. Annals of Oncology, Vol. 31, Issue 11, p1491–1505

Genomic Landscape and Molecular Subtyping of Breast Cancer

Consensus statement	Recommendation level	Expert Consistency	Reference
1. Genomic research support molecular subtyping in addition to traditional histologic classification.	I		[1,2]
2. It is not suggested to evaluate all the molecular taxonomy by NGS before initiation of MBC treatment in routine clinical practice at present.		>85%	[3,4,5]
3. Multigene panels help understanding breast cancer biology and contributing to an accelerated phase of targeted drug development and providing insights into resistance mechanisms.		>85%	[5,7]
4. It is not required to evaluate all the molecular taxonomy by NGS in the EBC setting. (beyond the Oncotype Dx, MammaPrint.et al)		>85%	[7]
5. Specific tests (as distinguished from broad mutation profiles, ex. PIK3CA, MSI-high, NTRK fusion) are useful as the treatments they are linked.	I		[5,7]

References

1. Perou CM, Sorlie T, Eisen MB et al. (2000) Molecular portraits of human breast tumours. Nature 406:747–752
2. Perou CM, Jeffrey SS, van de Rijn M et al. (1999) Distinctive gene expression patterns in human mammary epithelial cells and breast cancers. Proc Natl Acad Sci USA 96:9212–9217
3. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020, 31(12): 1623-1649
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5. Lucy R, Yates, Christine Desmedt. Translational Genomics: Practical Applications of the Genomic Revolution in Breast Cancer. Clin Cancer Res; 23(11); 2630-9
6. Cancer Genome Atlas Network (2012) Comprehensive molecular portraits of human breast tumours. Nature 490:61-70
7. Angus, L., Smid, M., Wilting, S.M., et al. The genomic landscape of metastatic breast cancer highlights changes in mutation and signature frequencies. Nature Genetics 2019;51(10):1450-1458

Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer

Consensus statement	Recommendation level	Expert Consistency	Reference
1. For Germline mutations, genetic testing of cancer susceptibility genes is now widely applied in clinical practice to predict risk of developing cancer. We suggest a system of five classes of variants based on the degree of likelihood of pathogenicity (as "pathogenic", "likely pathogenic", "uncertain significance", "likely benign" or "benign"). Each class is associated with specific recommendations for clinical management of at-risk relatives that will depend on the hereditary syndrome. The guidelines also state that a variant of uncertain significance (VUS) should NOT be used in clinical decision making.		>85%	[1,2,3]
2. Somatic variants include SNVs, indels, fusion genes resulting from genomic rearrangements, and CNVs. Unlike interpretation of germline sequence variations, which focuses on pathogenicity of a variant for a specific disease or disease causality, interpretation of somatic variants should be focused on their impact on clinical care.		>85%	[1,2,3]
3. According to the Joint Consensus Recommendation of the AMP/ASCO/CAP, a four-tiered system to categorize somatic sequence variations based on their clinical significances is proposed: tier I, variants with strong clinical significance; tier II, variants with potential clinical significance; tier III, variants of unknown clinical significance; and tier IV, variants deemed benign or likely benign.		>85%	[1,4]
4. Cancer genomics is a rapidly evolving field; therefore, the clinical significance of any variant in therapy, diagnosis, or prognosis should be reevaluated on an ongoing basis. Reporting of genomic variants should follow standard nomenclature, with testing method and limitations clearly described. Clinical recommendations should be concise and correlate with histological and clinical findings.		>85%	[1,4]

References

1. Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. Li MM, Datto M, Duncavage EJ, Kulkarni S, Lindeman NI, Roy S, Tsimberidou AM, Vnencak-Jones CL, Wolff DJ, Younes A, Nikiforova MN. J Mol Diagn. 2017 Jan;19(1):4-23
2. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology.Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; ACMG Laboratory Quality Assurance Committee. Genet Med. 2015 May;17(5):405-24
3. ACGS best practice guidelines for variant classification in rare disease 2020: Association for Clinical Genomic Science (ACGS), 2020. Available: https://www.acgs.uk.com/quality/bestpractice-guidelines/#VariantGuideline
4. Cancer Variant Interpretation Group UK (CanVIG-UK): an exemplar national subspecialty multidisciplinary network. J Med Genet. 2020 Mar. 13

Consensus on Genetic Testing for Hereditary Breast Cancer

- Gene test: Indication and Genes -

Consensus statement	Recommendation level	Expert Consistency	Reference
1. We suggest genetic testing for breast cancer patients with family cancer history. The family cancer histories are - breast cancer (if one relative had breast cancer, at least one of the patient and this relative had breast cancer less than 50 year-old; or more than two relatives had breast cancer). - ovarian cancer, pancreatic cancer or prostate cancer.	IIA		[1,2,3]
2. Patients with bilateral breast cancer may be considered to receive genetic testing.		>85%	[1,2,3]
3. We suggest genetic testing for male breast cancer patients.	IIA		[1,2,3]
4. Patients with breast cancer patients < 60 year-old with triple-negative breast cancer may be considered to receive gene test.	IIA		[1,2,3]
5. Genetic testing for early-onset breast cancer, despite family history, may be considered. Early-onset for Taiwan breast cancer patients is ≦ 40 year-old.	IIA		[1,2,3]
6. The genetic testing includes BRCA1 and BRCA2. Other genes such as ATM, BARD1, BRIP1, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, PMS2, PTEN, STK11, TP53, NBN, NF1, PALB2, RAD51C, RAD51D may be considered.	IIA		[1,2,3]
7. When patients were diagnosed as mutation carriers, we suggest genetic counseling for patients and relatives. Germline testing of the pathogenic variants is recommended for the relatives.	IIA		[1,2,3]

- Prevention: (Prophylactic) Surgery and Image Screening -

Consensus statement	Recommendation level	Expert Consistency	Reference
8. Physicians caring for patients with breast cancer with germline BRCA1/2 mutations should discuss treatment options related to the index cancer and the increased risk of contralateral breast cancer (CBC) and new ipsilateral breast cancer.	IIA		[1,2,3]
9. Germline BRCA status should not preclude a patient with newly diagnosed breast cancer otherwise eligible for breast conserving therapy (BCT) from receiving BCT.	IIA		[1,2,3]
10. Surgical management of the index malignancy (BCT ipsilateral therapeutic and contralateral risk-reducing mastectomy [CRRM]) in BRCA1/2 mutation carriers should be discussed, considering the increased risk of CBC and possible increased risk of an ipsilateral new primary breast cancer compared with noncarriers.	IIA		[1,2,3]
11. The factors should be considered for assessing risk of CBC and role of risk-reducing mastectomy in BRCA1/2 mutation carriers: - age at diagnosis (the strongest predictor of future CBC) - family history of breast cancer, overall prognosis from this or other cancers (eg, ovarian) - ability of patient to undergo appropriate breast surveillance, comorbidities, and life expectancy	IIA		[1,2,3]
12. BRCA1/2 mutation carriers who do not have bilateral mastectomy are suggested to undergo high-risk breast screening of remaining breast tissue, such as annual mammogram, breast ultrasound and/or MRI.	IIA		[1,2,3]

Consensus on Genetic Testing for Hereditary Breast Cancer

- Moderate-penetrance Gene -

Consensus statement	Recommendation level	Expert Consistency	Reference
13. For women with newly diagnosed breast cancer who have a mutation in a moderate-penetrance breast cancer susceptibility gene, mutation status alone should not determine local therapy decisions for the index tumor or CRRM.	IIA		[1,2,3]
14. In patients with breast cancer with a mutation in a moderate-penetrance breast cancer susceptibility gene, BCT can be offered to those for whom BCT is an appropriate treatment option. There is a lack of data regarding ipsilateral breast cancer events after BCT among patients with moderate-risk mutations.	IIA		[1,2,3]
15. Patients with mutations in moderate-penetrance genes who do not have bilateral mastectomy are suggested to undergo high-risk breast screening of remaining breast tissue with image study, such as annual mammogram, breast ultrasound and/or MRI.	IIA		[1,2,3]

- CRRM and NSM -

Consensus statement	Recommendation level	Expert Consistency	Reference
16. For women with newly diagnosed breast cancer undergoing mastectomy who have a deleterious mutation in BRCA1/2 or a moderate penetrance gene, nipple sparing mastectomy is a reasonable oncologic approach to consider in appropriately selected patients.	IIA		[1,2,3]
17. For women with breast cancer who have a BRCA1/2 mutation and who have been treated or are being treated with unilateral mastectomy, CRRM should be discussed. CRRM is associated with a decreased risk of CBC; there is insufficient evidence for improved survival. The following factors should be considered for assessing risk of CBC and role of risk-reducing mastectomy: - age at diagnosis (the strongest predictor of future CBC) - family history of breast cancer, overall prognosis from this or other cancers (eg, ovarian) - ability of patient to undergo appropriate breast surveillance (MRI), comorbidities, and life expectancy.	IIA		[1,2,3]
18. For women with breast cancer who have a mutation in a moderate-penetrance breast cancer predisposition gene and who have been treated or are being treated with unilateral mastectomy, the decision regarding CRRM should not be based predominantly on mutation status. Additional factors that predict CBC such as age at diagnosis and family history should be considered, as they are in all cases. The impact of CRRM on decreasing risk of CBC is dependent on the risk of CBC for each individual gene. Data regarding the risk of CBC resulting from moderate-penetrance genes are limited.	IIA		[1,2,3]
19. For patients with breast cancer with a deleterious germline BRCA1/2 mutation interested in CRRM, physicians should discuss the option of nipple-sparing mastectomy as a reasonable oncologic option.	IIA		[1,2,3]
20. For patients with breast cancer with a mutation in a moderate-penetrance gene who are interested in CRRM, physicians should discuss the option of nipple-sparing mastectomy as a reasonable oncologic option.	IIA		[1,2,3]

Consensus on Genetic Testing for Hereditary Breast Cancer

- Radiation Therapy and Chemotherapy -

Consensus statement	Recommendation level	Expert Consistency	Reference
21. For women with breast cancer who are treated with BCT or with mastectomy for whom postmastectomy radiation therapy (RT) is considered, RT should not be withheld because of mutation status, except for mutations in TP53. There is no evidence of a significant increase in toxicity or CBC related to radiation exposure among patients with a mutation in a BRCA1/2 or a moderate-penetrance gene.	IIA		[1,2,3]
22. For women with breast cancer who are carriers of an ATM mutation, RT should be offered when clinically indicated. Data regarding rates of toxicity between ATM mutation carriers and noncarriers are limited and inconsistent. Potential absolute risks seem to be small; however, more research is needed. Discussion with ATM carriers interested in BCT is encouraged.	IIA		[1,2,3]
23. For women with breast cancer who are carriers of a germline TP53 mutation, irradiation of the intact breast is contraindicated. Mastectomy is the recommended therapeutic option. Postmastectomy RT should only be considered in patients with significant risk of locoregional recurrence.	IIA		[1,2,3]
24. When offering chemotherapy for germline BRCA mutation carriers with metastatic breast cancer, platinum chemotherapy is preferred to taxane therapy for patients who have not previously received platinum. There are no data to address platinum efficacy in other germline mutation carriers.	IIA		[1,2,3]
25. For germline BRCA mutation carriers with breast cancer treated with (neo)adjuvant therapy, data do not support the routine addition of platinum to anthracycline- and taxane-based chemotherapy. While single-agent platinum has demonstrated activity in the neoadjuvant setting, there are no data yet comparing it with standard chemotherapy. There are no data to address platinum efficacy in other germline mutation carriers.	IIA		[1,2,3]

- PARP Inhibitor -

Consensus statement	Recommendation level	Expert Consistency	Reference
26. For BRCA1/2 mutation carriers with metastatic human epidermal growth factor receptor 2 (HER2) –negative breast cancer, olaparib or talazoparib could be offered as an alternative to chemotherapy in the first- to third-line settings. For BRCA1/2 mutation carriers with metastatic HER2-negative breast cancer, there are no data directly comparing efficacy of poly (ADPribose) polymerase (PARP) inhibitors with platinum chemotherapy.*	IIA		[1][2][3]
27. For patients with breast cancer with mutations in moderate-penetrance genes, there are currently no robust data to support the use of PARP inhibitors.**	IIA		[1][2][3]

* For patients with somatic BRCA1/2 mutated metastatic breast cancer, TBCRC048 study showed PARP inhibitor could be a treatment option.

** For patients with germline PALB2 mutated metastatic breast cancer, TBCRC048 study showed PARP inhibitor could be a treatment option.

References

1. 2020 ASCO guideline: For germline BRCA mutation carriers, there are insufficient data at this time to recommend a PARP inhibitor for patients with nonmetastatic breast cancer

2. TBCRC 048: A phase II study of olaparib monotherapy in metastatic breast cancer patients with germline or somatic mutations in DNA damage response (DDR) pathway genes (Olaparib Expanded). 2020.38.15_suppl.1002 Journal of Clinical Oncology 38, no. 15_suppl (May 20, 2020) 1002-1002

3. Talazoparib beyond BRCA: A phase II trial of talazoparib monotherapy in BRCA1 and BRCA2 wild-type patients with advanced HER2-negative breast cancer or other solid tumors with a mutation in homologous recombination (HR) pathway genes. 2019.37.15_suppl.3006 Journal of Clinical Oncology 37, no. 15_suppl (May 20, 2019) 3006-3006

Multigene Expression Signature for Prognostic Information and Therapeutic Guidance for Early Breast Cancer

Consensus statement	Recommendation level	Expert Consistency	Reference
1. Multigene expression signature is clinically applicable only for HR+ and HER2- early breast cancer, to gain optional genomic prognostic information in addition to clinical risk assessment.	I		[1]
2. Clinical assessment of recurrence risk based on clinicopathological factors is required for all stage I/II HR+ HER2- breast cancer. The use of validated risk scoring tools (eg., CTS5, modified Adjuvant Online, IHC4, PREDICT v1.3 , Nottingham prognostic index....etc.) is encouraged.	I-IIA		[4][6][7] [10][15]
3. Multigene prognostic testing can be performed for cases with tumor size T1 (preferably >0.5cm, but also for <0.5cm with unfavorable histological features) and T2, and with nodal status pN0 (including N0i+/Nmi) and pN1 (1-3 positive nodes).	I		[1] [4] [5]
4. The selection of the multigene expression signature to be tested should be based on their validated indications, laboratory platforms, analyzing algorithms and clinical implications. Testing more than one expression panel is not recommended as their concordance beyond node-negative luminal A is low.	I-IIA		[2] [16] [18][19]
5. 21-gene (OncotypeDx), 70-gene (MammaPrint), 50-gene (PAM50), and 12-gene (EndoPredcit) are all validated prognostic panels for pN0 and pN1 (1-3 positive nodes). The predictivity of adjuvant chemotherapy benefit for pN0 is currently of stronger evidence with 21-gene signature than with 70-gene signature.	I		[1] [5] [6] [18] [19]
6. OncotypeDx is the only multigene panel currently included in AJCC 8th to classify pathologic prognostic stage. When RS score is less than 11,	I		[1] [5] [21]

TNM	Grade	HER2	ER	PR	Stage
T1N0M0 T2N0M0	Any	Negative	Positive	Any	IA

Consensus statement	Recommendation level	Expert Consistency	Reference
7. RS score by OncotypeDx (21-gene signature) is both prognostic and predictive to inform adjuvant chemotherapy benefit for pN0 breast cancer regarding 5-year recurrence risk. Endocrine therapy can be modified for premenopausal women with the consideration of both clinical and genomic risks.	I		[13] [5]
• For patients age > 50 years, RS score			
26-30 | No chemotherapy benefit | Standard endocrine therapy	I		[13] [5]
> 31 | Addition of chemotherapy with additional consideration of clinicopathological factors | Standard endocrine therapy			
26-30 | Addition of chemotherapy is recommended | Standard endocrine therapy			
• For patients age ≤50 years, with consideration of clinical risk, RS score			
< 15 | No chemotherapy benefit | Standard endocrine therapy	I-IIA		[6] [9]
16-25 | Consideration of chemotherapy | Consider endocrine therapy plus ovarian function suppression			
> 26 | Addition of chemotherapy is recommended | Consider endocrine therapy plus ovarian function suppression			

Multigene Expression Signature for Prognostic Information and Therapeutic Guidance for Early Breast Cancer

Consensus statement	Recommendation level	Expert Consistency	Reference
8. RS score by Oncotype Dx (21-gene signature) is prognostic for pN1 (1-3 positive nodes) breast cancer, and predictive of chemotherapy benefit depending on menopausal status according to the early results of RxPONDER trial.	IIA		[22]
9. MammaPrint (70-gene signature) is prognostic for both pN0 and pN1 (1 to 3 nodes positive), with clinical high risk (based on modified Adjuvant online criteria).	I		[4] [12]
• 70-gene signature can identify a group of postmenopausal patients with indolent disease after surgery alone.	IIA		[20]

Postmenopausal	RS 0-25	No benefit from adjuvant chemotherapy
	RS >25	Adjuvant chemotherapy
Premenopausal	RS 0-25#, and >25	Adjuvant chemotherapy#

#For premenopausal patients with RS 0-25, the 5-year overall survival absolute improvement by adjuvant chemotherapy is 1.3%, with 53% decrease in death, and 46% decrease in invasive disease-free survival.

Low	No chemotherapy benefit	At 8 years of follow up, the DMFS with and without chemotherapy was 92.0% vs 89.4%. The OS with CT was 95.7% vs 94.3%.
High	Chemotherapy benefit	Addition of chemotherapy

Ultralow Risk	20-year disease-specific survival rate is 97% vs 94% in cases treated with and without tamoxifen alone (indolent disease)	No need for chemotherapy nor endocrine therapy

Consensus statement	Recommendation level	Expert Consistency	Reference
10. ROR (risk of recurrence) score by PAM 50 (50-gene signature) is prognostic for pN0 and pN1 for 10-year distant recurrence in postmenopausal women. The ongoing OPTIMA trial will address its role as a predictive factor. The calculation of ROR needs to refer to tumor size ≤ or > 2cm), and nodal status (pN0 or pN1).	IIA		[8] [14]

pN0	ROR score 0-40	Low
	ROR score 41-60	Intermediate
	ROR score 61-100	High
pN1	ROR score 0-15	Low
	ROR score 16 -40	Intermediate
	ROR score 41-100	High

Consensus statement	Recommendation level	Expert Consistency	Reference
11. EPclin score combines EP genomic score and clinical factor by EndoPredict (12-gene signature) with reference to is prognostic for pN0 and pN1 postmenopausal women for distant recurrence at 10 years.	IIA		[3]

pN0	Low risk, < 3.33	4% distant recurrence risk at 10 years
	High risk, ≥ 3.33	
pN1	Low risk, < 3.33	5.6% distant recurrence risk at 10 years
	High risk, ≥ 3.33	

• The laboratory test of EndoPredict does not have to be centralized.			[11]

Multigene Expression Signature for Prognostic Information and Therapeutic Guidance for Early Breast Cancer

Consensus statement	Recommendation level	Expert Consistency	Reference
12. Other prognostic expression signatures are actively evolving, and some have their own unique features or clinical implications. For example, RecurIndex is developed from Chinese/Taiwanese breast cancer population and is prognostic for both local and distant recurrence within 5 years. The use and interpretation should also follow their respective validated scenario.	IIA		

References

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Current Knowledge and Implication of Liquid Biopsy in Breast Cancer

Consensus statement	Recommendation level	Expert Consistency	Reference
1. Liquid biopsy is a complement to tissue biopsy. However, negative liquid biopsy result should trigger a reflex tumor tissue biopsy if feasible.		>85%	[1]
2. Clinical use of Circulating Tumor Cells (CTC) and ctDNA in metastatic breast cancer is not recommended for disease screening, detecting and monitoring. Further investigation is suggested.		>85%	[2,3]

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3. NCCN guidelines Version 6.2020 Breast Cancer

Genomic Alterations in Breast Cancer: Level of Evidence for Actionability

Consensus statement	Recommendation level	Expert Consistency	Reference
1. Level of evidence for actionability of genomic variants (clinical actionability for molecular targets) defines clinical evidence-based criteria to prioritise genomic alterations (either Germline or Somatic) as markers to select patients for therapies. This classification system aims to offer a common language for all the relevant stakeholders in cancer medicine and drug development.		>85%	[1,2]
2. For prioritizing multiple actionable molecular targets in a single cancer patient, we recommend establishing a molecular tumor board (MTB) to discuss patient cases with genetic alterations and to guide treatment decisions. There are also several online-tools of precision oncology knowledge databases that aid clinical interpretation of variants in cancer.		>85%	[3.4.5]
3. For ranking the level of evidence for actionability of genomic variants in breast cancer, we recommend using ESCAT or the Joint Consensus Recommendation published by the AMP/ASCO/CAP.		>85%	[1,2,3,6]
4. The level of evidence for actionability in general is comprised of 4 levels, including Level 1: FDA-approved matching drugs or standards of care. Level 2: potential clinical significance (including retrospective, expert consensus). Level 3: investigational, cancer repurposing. Level 4: preclinical. There maybe overlapping, controversial definitions for Level 2, Level 3 among different guidelines.		>85%	[1,2,3,4]

Footnote: ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; AMP, Association for Molecular Pathology; ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists

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How to Enrich the Detection Rate for Uncommon but Significant Genomic Alterations? - For Clinical Available Drugs

Consensus statement	Recommendation level	Expert Consistency	Reference
1. For secretory breast cancer, NTRK fusion prevalence rate is around 90%. Suggestion of NTRK gene fusion screened by IHC, then confirmed by NGS for secretory breast cancer patients.		>85%	[1,2]
2. Recommend TRK inhibitors for patients with NTRK gene fusion without other satisfactory treatment options.	IIA		[3]
3. The standard method for detection of PIK3CA mutation is PCR testing from tumor tissue(metastasis or primary), whereas NGS or circulating tumour DNA (ctDNA) can be an alternative sample source if tumor tissue unavailable. PIK3CA mutation is a prerequisite for indicated use of Alpelisib, an approved PI3K inhibitor.		>85%	[4,5,6]

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Taiwan Breast Cancer Molecular Testing Consensus