Clinical practice guidelines for multigene assays in patients with early-stage breast cancer: Chinese Society of Breast Surgery (CSBrS) practice guidelines 2021

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The role of multigene assays in chemotherapy decision-making in patients with early invasive breast cancer has been widely recognized. In 2017, the American Society of Clinical Oncology (ASCO) clinical guidelines for multigene profiling assays focused on increasing the intensity of recommendations for the clinical use of MammaPrint®.[1] The 8th edition of the American Joint Committee on Cancer (AJCC) staging system, officially launched in 2018, established the concept of prognostic staging for the first time, adding the use of non-anatomical information to evaluate the prognosis. Initially, Oncotype Dx® was recommended for suitable patients based on Level I evidence. Subsequently, five testing techniques, Oncotype Dx®, MammaPrint®, EndoPredict®, PAM50®, and BCI, were formally incorporated into the system.[2] To assist breast disease specialists in China in their selection of appropriate multigene profiling assays and detection methods for patients, and also to instill caution on decision-making with reference to multigene assays, the Chinese Society of Breast Surgery (CSBrS) has, through literature investigation and expert discussion, provided information on the key clinical problems and guidelines for the use of multigene assays, evaluating the evidence with reference to the Grades of Recommendations Assessment Development and Evaluation (GRADE) system. Combined with the availability of these assays in China, the clinical practice guidelines for multigene assays were formulated and published. The purpose of this guideline is to provide a reference for clinicians specializing in breast diseases in China.

Level of evidence and recommendation strength

Level of evidence standard[3]

Recommendation strength standard[3]

Recommendation Strength Review Committee

There were 81 voting committee members for these guidelines: 70 from breast surgery departments (86.4%), 2 from medical oncology departments (2.5%), 4 from medical imaging departments (4.9%), 2 from a pathology department (2.5%), 2 from a radiotherapy department (2.5%), and 1 epidemiologist (1.2%).

Target Audience

Clinicians specializing in breast diseases in China.

Recommendations

Recommendation 1: Assay

	Assay	Level of evidence	Recommendation strength
1.1	70-gene (MammaPrint®) NGS	I[4]	A
1.2	21-gene (Oncotype Dx®) RT-PCR	I[5,6]	B

NGS: next generation sequencing; RT-PCR: reverse transcription-polymerase chain reaction.

Recommendation 2: Patients

2.1 70-gene (MammaPrint®)

Patients	Level of evidence	Recommendation strength
T1–T2, 0–3 positive nodes, HR+, HER2–	I[4]	A

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2.2 21-gene (Oncotype Dx®)

Patients	Level of evidence	Recommendation strength
T1–T2, pN0, HR+, HER2–	I[6]	B

Recommendation 3: Treatment implications

3.1 70-gene (MammaPrint®)

	Treatment implications		Level of evidence	Recommendation strength
3.1.1	Clinical low risk/ Genomic high risk	The additional benefit of adjuvant chemotherapy may be small. The assay cannot be used as a reference for the addition of chemotherapy in decision-making.	I[4]	A
3.1.2	Clinical high risk/ Genomic low risk	Consider omission of chemotherapy.	I[4,7]	A

3.2 21-gene (Oncotype Dx®)

	RS*	Treatment implications	Level of evidence	Recommendation strength
3.2.1	≤25	For patients with T1b/c-T2 and RS between 0–25, omission of chemotherapy should be considered. In women ≤50 years with RS 16–25, addition of chemotherapy should be considered.	I[6,8]	B
3.2.2	26–30	In patients with T1–T2, the omission of chemotherapy has not been studied prospectively. Clinicians should consider additional clinical and pathological factors with regard to chemotherapy in decision-making.	I[6]	B
3.2.3	≥31	For patients with T1b-T2, the addition of chemotherapy is recommended.	I[9]	B

* Oncotype Dx® Recurrence Score.

Discussion

In recent years, the US Food and Drug Administration (FDA) and numerous international bodies have approved and recommended the 70-gene (MammaPrint®) and 21-gene (Oncotype Dx®) assays for clinical practice with high-level evidence.[1,10] The expert panel agreed that multigene assays are of great value in adjuvant treatment decision-making, with 97% of experts voting for a strong recommendation for the 70-gene assay and 73% for a weaker recommendation for the 21-gene assay.

The MINDACT trial provided high-level evidence of the clinical use of the 70-gene (MammaPrint®) assay in assisting chemotherapy decisions (See details in the Supplementary file, http://links.lww.com/CM9/A820).

Several points need to be noted for this study. First, T3–T4 patients only accounted for 1.2% of the enrolled patients, the expert panel recommended that chemotherapy is appropriate for patients with T1–T2 disease. Second, majority of patients were node-negative (79%), while node-positive patients with 1–3 nodes accounted for 14.1%, 4.5%, and 2.3%, respectively, suggesting that this study is mainly applicable to 0–3 nodes-positive patients. Up to 88.4% of patients were HR-positive, and up to 90.3% were HER2-negative, suggesting that this study is mainly applicable to HR-positive and HER2-negative patients. Third, the clinical "risk" stratification of this study is based on the improved Adjuvant! Online tool, which includes tumor size, node stage, histological grade, HR and HER2 status, but does not include age and tumor thrombus. The so-called clinical "low-risk" or "high-risk" differs from the conventional St. Gallen expert consensus on the risk of recurrence after breast cancer surgery.[11]

The 21-gene assay (Oncotype Dx®) is currently the most widely used multigene panel and prognosis analysis method for HR-positive breast cancer patients in the USA.

The result of the TAILORx study provides high-level evidence for the clinical application of the 21-gene assay in practice (See details in the Supplementary file, http://links.lww.com/CM9/A820).

In recent years, three other breast cancer assay tools, EndoPredict,[12] PAM50,®[13,14] and BCI,[15] have also been widely recommended. These tools are not yet predictive of chemotherapy benefits and are not available in China, so they were not discussed by the expert panel.

The expert panel explicitly recommended that multigene assay indications include: T1-T2 and HR-positive, HER-2-negative, node-negative or limited metastasis (1–3), and high-risk patients. The expert panel emphasized that ER, PR, and HER-2 status should be determined before assay. The assays are not recommended for TNBC and HER-2-positive patients nor are they recommended for patients with >3 positive nodes. Decisions for chemotherapy are also not recommended for ER/PR-positive, HER-2-negative, node-negative, and clinically low-risk patients. Extended endocrine therapy based on gene test results is not recommended. Patients who are not suitable for chemotherapy due to complications, tumor stage, risk level, and other factors and who clearly need chemotherapy do not need routine genetic testing.

Multigene assays including the 70-gene and 21-gene assay have uniform and strict technology standards. The analysis and interpretation of biological data is tightly controlled, which provides an important guarantee for rigorous and credible results and lays the foundation for reasonable clinical application. The expert panel stressed that any 70-gene and 21-gene assay not labeled Mammaprint® or Oncotype Dx® is different from the genuine Mammaprint® and Oncotype Dx® assays. Clinicians should be cautious about evaluating the clinical value of these assays.

The expert panel suggested that the following should be clarified when recommending polygenic testing for patients.

First, accurate multigene assay information is helpful for clinicians to make treatment decisions based on clinical and pathological data. Gene information acquired from clinical pathology may be inconsistent, and clinicians should combine genetic and clinical-pathological results to formulate treatment plans. Multidisciplinary consultations (MDT) should be conducted when necessary.

Second, the sample used for polygenic testing should be the primary tumor of invasive cancer tissue in patients with indications. The accuracy of the test is closely related to the amount of tissue, and the representative and pathological fixation status. The specific slice requirements may vary according to different tools. It is recommended that doctors should have a detailed understanding of the methods used and the tissue section requirements of the cancer tissue sectioning before testing.

Third, the consistency of the results among the different tools is controversial.[16] That is, for the same patient, using different multigene assays, the results may not be the same.

Fourth, it must be objectively recognized that the current multigene research is mainly based on the results of the Western population, and the research on the Chinese population is still relatively small. The expert panel recommended that, with the support of national policies, multi-center research on multigene panels should be carried out to formulate national standards suitable for China's national conditions.

Fifth, the costs of gene assays are relatively expensive, and, as results between the different assays may be inconsistent, doctors need to make individualized selections according to the specific clinical conditions.

List of Compiling Committee Members (in alphabetical order by surname)

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Conflicts of interest

None.

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