

• Review •

Evaluation methods for the efficacy of neoadjuvant chemotherapy for breast cancer

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[Abstract] With the widespread clinical application of neoadjuvant chemotherapy, it has become an essential part of combination therapy for patients with breast cancer. However, a rapid, accurate, and effective approach for assessing the therapeutic efficacy of neoadjuvant chemotherapy is unavailable. Routine physical examinations cannot provide effective clinical evaluation. Although imaging techniques play an important role in evaluating the therapeutic effect of neoadjuvant chemotherapy, this is limited because it only detects morphologic changes. Blood oxygen detection for breast diseases is an emerging diagnostic technique that has distinctive merit in assessing the efficacy of chemotherapy. Biologic markers are becoming more important in assessing the effect of neoadjuvant chemotherapy for patients with breast cancer. This review summarizes the principles and the current applied practice of these approaches to evaluate the effect of neoadjuvant chemotherapy for patients with breast cancer.

Key words: Breast neoplasm, neoadjuvant chemotherapy, therapeutic efficacy evaluation

Breast cancer is a common malignant tumor for women in China and its incidence and mortality rates have recently increased, which greatly threaten the health of the population of women. With the widespread application in clinical practice of neoadjuvant chemotherapy for patients with breast cancer, neoadjuvant chemotherapy has become an important component to comprehensive therapy for patients with breast cancer. Currently, assessing the therapeutic effect of neoadjuvant chemotherapy has become a focus for clinical research. This paper will summarize the evaluation methods for assessing the therapeutic effect of neoadjuvant chemotherapy.

Concepts and clinical significance of neoadjuvant chemotherapy

Neoadjuvant chemotherapy, also known as preoperative chemotherapy, refers to the systemic and systematic treatment with cytotoxic medicines before surgery for patients with local malignant tumors in late stages. With the broader application of breast preservation surgeries for patients with breast cancer, neoadjuvant chemotherapy has become the conventional method for reducing the staging and size of primary tumors¹. Also,

neoadjuvant chemotherapy has the following characteristics: it controls and kills systemic micrometastatic tumors and the spread of subclinical lesions and it tests the sensitivity of tumor cells to chemotherapy to guide postoperative treatment.

Current status of clinical applications of the evaluation methods for therapeutic efficacy of neoadjuvant chemotherapy for patients with breast cancer

At present, the clinical evaluation of therapeutic efficacy of neoadjuvant chemotherapy primarily relies on clinical and histopathologic assessments. Clinical assessment primarily includes clinical palpitation and radiologic measurement. Clinical palpitation compares the size of the tumor before and after neoadjuvant chemotherapy and thus it is more susceptible to subjectivity, such as the clinical experiences of the physician resulting in inconsistent evaluations of its effect. Also, it is more difficult to estimate the lesion in depth and negatively affects the ability to accurately evaluate the therapeutic effect. Pathologic examination has been the gold standard for evaluating response in tumor cells to chemotherapy. It is accurate for diagnosis, but it should be performed after surgery and neoadjuvant chemotherapy, and it provides information on the sensitivity of tumor cells to chemotherapy much later and does not allow time to adjust the chemotherapeutic regimen. It is much easier to miss the best opportunity for adjustment. In recent years, researchers have proposed the use of radiologic examination to evaluate the therapeutic effect because it has the advantage of being

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noninvasive, convenient, and repeatable, which can be more easily accepted by physicians and patients.

Currently, in clinical practice, radiologic examination for evaluating the therapeutic effect of chemotherapy includes target X-ray with molybdenum, high-frequency color ultrasound, positron emission tomography/computed tomography (PET/CT), and magnetic resonance imaging (MRI). These examinations, from different perspectives, describe, measure, and evaluate the changes in tumors before and after neoadjuvant chemotherapy, and each approach has its own advantages. In recent years, measuring the function of blood oxygen in breast tissue has gradually been developed and it is now applied in screening patients for breast cancer. Based on its effective evaluation of blood oxygen function in breast tumors and taking into account the principle of vascular dependence in breast cancer, it may well be a new, effective technique to evaluate the therapeutic effect of neoadjuvant chemotherapy in patients with breast cancer. Biologic tumor markers monitor changes in tumors at the molecular level and can serve as indices of biologic evaluation of the therapeutic effect of neoadjuvant chemotherapy as well.

Target X-ray examination with molybdenum

Target X-ray with molybdenum is an important radiologic examination for screening patients for breast cancer. It is convenient to use and less expensive, and has higher diagnostic accuracy and practical value for the early discovery and diagnosis for patients with breast cancer. As for the characteristics of breast cancer on target X-ray with molybdenum, direct signs include tumor masses or nodules, local dense infiltration, spicular sign, and calcification; indirect signs include localized thickening of the skin or 'dimple sign', crater nipple, disordered mammary structure, and ductal expansion². Target X-ray with molybdenum has the following problems: (1) high breast density influences the accurate diagnosis on the range of lesions; (2) the existence of continuous micro-calcified lesions may be mistaken as malignancy; and (3) the characteristics of multiple compartments and multiple lesions of the tumor are difficult to recognize. As a result, the method is limited for evaluating the therapeutic effect of neoadjuvant chemotherapy³.

Clinically, most tumor masses or nodules in breast cancer present with unclear boundaries, irregular morphology, and spicular sign, which are the manifestations of infiltration by tumor cells into the surrounding tissue. The before-and-after contrast of target X-rays with molybdenum clearly illustrate changes in size of the tumor mass, the reduction of calcification, and changes in infiltration to the surrounding tissue (the clearer image of the tumor and changes in spicular sign). Spicular sign is caused by the proliferation of fibrous tissue around the tumor and the expansion of infiltration to the surrounding tissue. The reduction or disappearance of spicular sign usually signifies the death of tumor cells at the edge by effective chemotherapy⁴. By studying the direct and indirect signs on X-rays, we can effectively evaluate the effect of neoadjuvant chemotherapy. Liu *et al.*⁴ analyzed the changes in signs on target X-rays with Molybdenum before and after neoadjuvant chemotherapy in 47 patients with breast cancer and reported the incidence rates for changes in tumor mass at 89.3% (42/47), clearer boundary at 93% (15/16),

less spicular sign at 90.5% (19/21), and calcified lesions at 74.2% (23/31). There are fundamental changes in the range, number, and distribution of tumor lesions.

High-frequency color ultrasound

With the increase in incidence for patients with breast cancer in China and color ultrasound as the conventional technique used in hospitals, the use of ultrasonic examination for the diagnosis of breast cancer in early stages has become more sophisticated. For differential diagnoses of benign and malignant breast cancers, color ultrasound and target X-ray with molybdenum are the first choices, where the diagnostic rate can reach 92.6%⁵. In recent years, its use for evaluating the therapeutic effect of neoadjuvant chemotherapy has been broadly advocated.

Patients with breast cancer receive ultrasonic examination before and after each course of neoadjuvant chemotherapy, with the same imaging requirements: the same radiologist measures the size of the primary lesion (length × height × width), analyzes the blood flow in the primary lesion, measures the maximum velocity (Vmax) and the hemodynamic resistance index (RI), and scans lymphatic size and its internal blood flow. Comparing the before-and-after effect and basing the reactive standard for chemotherapy on World Health Organization (WHO) criteria, the therapeutic effect of neoadjuvant chemotherapy can be evaluated.

Hu *et al.*⁶ suggested that contrasting clinical evaluations and postoperative pathologic results, the overall efficacy for evaluating the remission of primary tumors by high-frequency color ultrasound was 79.31%, which matched the pathologic results (79.31%). In addition, the overall effectiveness assessed by clinical evaluation was 93.10%, which was 13.79% higher. High-frequency color ultrasound for evaluating the effect of neoadjuvant chemotherapy for patients with breast cancer is believed to be more convenient and accurate than clinical evaluation, and it is more beneficial for optimizing treatment in clinical practice.

PET/CT examinations

PET uses positrons as radioactive tracers to display the internal biochemical status of live tissues or organs. The combined use of PET and CT to create accurate and detailed images for the complex metabolism and anatomic structures of tumors can provide more correct imaging data for the diagnosis of tumors.

PET/CT, with its imaging of metabolic changes at the molecular level, can reflect the ability of malignant tumor cells to extract extrinsic glucose by probing the density of the local contrast agent (¹⁸F-fluorodipalmitin or ¹⁸F-FDP) in tumor tissue, to determine the malignancy and the biologic behaviors of a tumor. ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) is currently the most mature radioactive tracer. To monitor the effect of neoadjuvant chemotherapy and early discover recurrence, the most common measurement is the maximal standard uptake value (SUV_{max}). The predictive value of PET/CT in the early determination of the effect of neoadjuvant chemotherapy can be investigated by comparing the change in SUV_{max} before and after neoadjuvant chemotherapy in patients. It was reported that the accuracy of

PET/CT in the evaluation of effect was 89% to 95%⁷. Its predictive values for the positive and negative existence of lymph nodes were 90.9% and 73.9%, respectively, and thus, it had a higher diagnostic value. However, PET/CT examination is more expensive and the general population cannot afford its cost. Therefore, it is used less in clinical practice.

MRI

MRI not only includes conventional dynamic enhanced scans, but also includes functional MRI (fMRI). MRI has become a new method for evaluating the effect of neoadjuvant chemotherapy for patients with breast cancer. It has the following advantages⁸: (1) MRI has a maximum sensitivity in detecting primary infiltrative tumors at 98%; (2) MRI is highly sensitive in discovering and measuring the size of residual tumor masses after chemotherapy; (3) MRI can distinguish fibrous proliferation or necrosis in residual tissue after chemotherapy, to assist in the selection of appropriate patients for breast preservation after neoadjuvant chemotherapy; and (4) MRI is currently recognized as the most valuable technique to detect multiple lesions and multi-center lesions of breast cancer.

Primary indices of conventional MRI for evaluating the effect and response to chemotherapy in tumor cells include (1) size of the tumor (measures the maximum diameter and volume); and (2) changes in indices, such as suspicious regions under the enhanced mode or the level of intensity. The fMRI, by providing internal physiologic and biochemical metabolic information about the tumor, reflects biologic responses in the tumor to the target treatment, and not just the anatomic information. fMRI is good for the early evaluation of the effect of neoadjuvant chemotherapy before changes in tumor morphology and assists in designing effective therapy in clinical practice. More developed fMRI methods for clinical practice include: proton MR spectroscopy (¹H-MRS), diffusion weighted imaging (DWI), and perfusion weighted imaging (PWI).

DWI, by observing the diffusion of water molecules in tissue, analyzes tissue structure and the internal characteristics. It measures the maximum sectional surface area and the average signal intensity of the tumor before and after neoadjuvant chemotherapy to accurately identify its boundary. Also, it can measure the apparent diffusion coefficient (ADC) value to identify changes in the size of the tumor for the early evaluation of the effect of neoadjuvant chemotherapy in patients with breast cancer. Research showed a negative correlation between pretreatment ADC values and the retraction rate of tumor size.⁹ The smaller the pretreatment ADC, the more significant the retraction of tumor. This is related to differentiation of the tumor. Tumors with poor differentiation have higher metabolic rates and usually have more abundant blood supplies, allowing wider distribution of chemotherapeutic drugs. Therefore, they are usually more sensitive to chemotherapy and result in significant retraction of the tumor. While the tumor size shrinks during effective treatment, cellular density drops due to necrosis in the tumor cells, allowing more space for the diffusion of water molecules. As a result, ADC values increase. On the other hand, increased tumor size in patients where treatment is not effective accompanies the proliferation of tumor cells, where the density

increases and results in an unaltered ADC value or even a decrease. This suggests that the ADC value can be used as a diagnostic technique. However, the imaging quality and spatial differentiation of DWI is relatively lower and it is hard to display smaller lesions. Further improvement to the technique is still required for better imaging.

MRS is a noninvasive functional imaging technique for measuring internal metabolic and biochemical information by MRI and chemical relocation. Meisamy *et al.*¹⁰ reported the use of ¹H-MRS voxels as a localization technique for the prediction of the effect of neoadjuvant chemotherapy for patients with breast cancer, where the change in the quantity of internal choline in tumor tissue was measured to discover an overall decrease as a response by tumor cells to chemotherapy. There was a statistical significance in the difference to the nonresponsive group. It was believed that the measurement of the total choline by ¹H-MRS could be used as a predictive index for the effect of neoadjuvant chemotherapy. Katz-Brull *et al.*¹¹ reported that the sensitivity and specificity for the test were 81% and 85%, respectively.

PWI is a functional imaging technique for evaluating blood perfusion status in tumor lesions of patients with breast cancer. It has higher sensitivity and specificity. It measures the hemodynamic changes in breast cancer under neoadjuvant chemotherapy and provides information on the early determination of the effect. However, it is limited by a poorer scan range and spatial resolution, so it cannot be singly applied as an MRI diagnostic method for breast cancer. If the quantitative research studies the parameters of MRI perfusion images, it may be potentially effective for determining the therapeutic effect of chemotherapy, where accurate adjustments to treatment is beneficial in clinical practice¹².

Imaging by blood oxygen effect

Blood-oxygen functional imaging techniques of the breast have recently developed to become a new examination approach. The examination uses frequencies close to infrared for radiologic imaging. By using two infrared wavelengths to determine the quantities of oxygenated hemoglobin (O₂Hb) and deoxygenated hemoglobin (HHb) in breast tissue, it can provide a quantifiable value to directly reflect the metabolic status in the breasts. It can serve as an evaluative index for the metabolic growth in breast tumors. By infrared imaging, tumor size, boundary, morphology, and relation to blood vessels can be studied as well. The technique is painless, noninvasive, low cost, convenient, and has high diagnostic rates. Currently, the technique is primarily used for screening benign and malignant breast tumors.

Cerussi *et al.*¹³ reported the use of diffuse optical spectrometry (DOS) for evaluating the effect of neoadjuvant chemotherapy for patients with breast cancer. The principle of this technique is similar to measuring blood oxygen levels in breast tissue. The difference is that the index covers a wider range that includes not only O₂Hb and HHb, but also the concentration of water and lipids. The primary indices are O₂Hb and HHb, which reflect most of the metabolism and growth status in the breast tissue. By comparing changes in these indices, metabolism, atrophy, and necrosis can be studied. In China, there is still no report of using this method for measuring the

effect of neoadjuvant chemotherapy for patients with breast cancer. However, the authors are currently gathering patients with breast cancer to conduct a correlation study on the progression of tumors to changes in the local microcirculation of the tumor and blood oxygen in tissue to analyze the changes of blood oxygen function before and after neoadjuvant chemotherapy. This will be a bold attempt in evaluating the effect of neoadjuvant chemotherapy in China.

Molecular tumor markers

With the progress in immunology, biochemistry, molecular biology, cell engineering, and genetic study, as well as the interaction of these disciplines, technical breakthroughs are rapid. After the introduction of radiologic and pathologic diagnosis, tumor markers provide another new field and influence the diagnosis, monitoring, and treatment of tumors. Tumor markers refer to products manufactured by tumor cells or materials and biologic phenomenon closely related to tumor existence, which can be detected in body fluids or tissues to reflect the existence, differentiation status, prognostic estimation, and therapeutic effect for a tumor³. They can be classified into two categories: serum tumor markers and cellular tumor markers. Serum tumor markers are extracted from intravenous serum and can be dynamically observed. However, this has low sensitivity and specificity. On the contrary, cellular tumor markers have higher sensitivity and specificity. But, as diagnostic indices for therapeutic effect, they cannot be dynamically observed. Therefore, the combination of the two to monitor the therapeutic effect for tumors is more ideal.

Serum tumor markers Serum markers with the most clinical application include fetal antigen marker CEA and mucin antigen marker CA153.

CEA is an acidic protein with an antigen determinant in the human fetus and is a nonspecific tumor-associated antigen from colorectal adenocarcinoma and fetal intestinal tissue. However, it has poor specificity. In addition to colorectal cancer, it is also seen in breast cancer, pancreatic cancer, and pulmonary carcinoma. Normally, the level of serum CEA is less than 15 $\mu\text{g/L}$. The sensitivity and specificity of CEA for breast cancer are not strong. Zhang *et al.*¹⁴ analyzed 40 patients with breast cancer and reported that the level of serum CEA was $(21.55 \pm 6.96) \mu\text{g/L}$, where the positive rate was 32.5%. The level of serum CEA can reflect breast cancer progression. The positive rate of CEA in patients with breast cancer at stages I and II was 13% to 24%, respectively, while the rate for patients with stages III and IV was 40% to 73%, respectively³. After neoadjuvant chemotherapy, tumors receded to an earlier stage. No clinical data has yet to be reported on whether the level of CEA drops along with the recession and necrosis of tumors.

CA153 is an mucin membranous protein and belongs to a breast cancer-related antigen. It includes a membranous zone, an intracellular zone, and an extracellular zone with glycol. When carcinogenesis occurs, the activities of proteinase and sialidase increase and the cytoskeleton is destroyed. The glycol antigen of CA increases and is isolated from the membrane of the tumor cell¹⁴. It is released into the blood and can be detected. It has specificity to human milk fat globular antigens and segments of breast cancer cell membranes, suggesting specificities to organs

and tumor tissue. It is the index with the highest specificity for evaluating the therapeutic effect and diagnosis of patients with breast cancer and it is considered as the best tumor marker for breast cancer¹⁵. It had lower positive rates for breast cancer in early stages, where it was 0%–25% for stage I and 8%–41.7% for stage II. It had higher positive rates for breast cancer in late stages, where it was 19%–80% for stage III and 38%–100% for stage IV, while the specificity was 89%–100%¹⁶. Because of inconsistencies in the approaches to measuring and manufacturing the test agent, the threshold value for positive detection is also different at around 25–30 u/mL. Research suggests that the overall level in patients with positive CA153 dropped from $(45.8 \pm 6.3) \text{ u/mL}$ to $(32.5 \pm 6.8) \text{ u/mL}$ after neoadjuvant chemotherapy ($t = 3.358$, $P < 0.05$) and this drop had statistical significance¹⁵. The increase in the level of serum CA153 is positively correlated to the increase in tumor load. With effective treatment, the tumor load would decrease¹⁷ and the level of CA153 would decrease, too. The change of CA153 is basically parallel to the therapeutic effect.

In addition to CEA and CA153, there are other serum tumor markers for the early diagnosis and measurement of breast cancer, including CA125, CA242, and so on. The specificity and sensitivity of these markers are lower. To improve the accuracy of the detection of breast cancer will require the combination of various indices.

Cellular tumor markers Common clinical cellular tumor markers are divided into four categories: (1) cellular proliferative markers, such as Ki-67; (2) hormone receptors, such as estrogen receptor (ER) and progesterone receptor (PR); (3) effective factors for microcirculation for tumor cells, such as glutathione S-transferase (GST) and matrix metalloproteinase (MMP); and (4) oncogenes and their expression proteins, such as C-erbB-2, P53, BRCA1, and BRCA2.

Ki-67 is a nonhistone nuclear protein with short half-life. It exists in cells in every other cell cycle phase except G0 and it is related to synthetic metabolism. Ki-67 has certain significance in predicting prognosis, studying biologic behaviors of tumors, and evaluating the proliferative status of cells. Liu *et al.*¹⁸ reported that a decrease in the expression of Ki-67 after neoadjuvant chemotherapy was related to reduced tumor size and a decrease in the number of tumor cells in the cycle. The decreasing status of the expression in the residual tumor cells can provide a better prognostic index for the survival rate without disease. Liu *et al.*¹⁹ found in 37 patients with breast cancer after two courses of neoadjuvant chemotherapy, the positive rate of Ki-67 was reduced to 14% from 32.4%.

ER and PR are the most important biomarkers for breast cancer. They have important significance for determining the prognosis of breast cancer, selecting endocrine/chemical treatment, and predicting therapeutic effect. The overall efficacy for patients with negative ER, negative PR, or both, undergoing neoadjuvant chemotherapy is higher than the efficacy for patients with positive ER, positive PR, or both. The current controversy involves whether the expression of a hormone receptor can predict the therapeutic effect of neoadjuvant chemotherapy. Yang *et al.*²⁰ reported that neoadjuvant chemotherapy could reverse the

positive expression of ER, PR, or both, to a negative expression. Wang *et al.*²¹ reported that the effect of neoadjuvant chemotherapy on the genetic expression of hormone receptors was by downregulation. Taucher *et al.*²² reported that there was no influence on the expressions of either ER or PR by neoadjuvant chemotherapy. Jain *et al.*²³ reported a change by 33% in the expressions of ER and PR after neoadjuvant chemotherapy.

The p53 gene is localized in region 17p13.1 of the chromosome and exists in two forms-wild type and mutant type. Wild-type p53 is an important tumor suppressor gene and participates in the proliferation and regulation of cells. It plays an important role in the process of extrinsic stimulation of apoptosis in tumor cells and is usually recognized as a valuable determinant for therapeutic effect. Mutant p53 is a tumor promoter gene. It can form an oligopolymer with subunits of the wild type, to prevent the effect of the subunit of the wild type. It can prevent the inhibitory function on tumor formation by wild-type p53, where it results in the transformation and carcinogenesis of cells²⁴. Because of the short half-life of p53 (approximately 6–21 min), it cannot be easily detected. The only detectable form is mutant p53. Because of mutant p53, it cannot effectively induce apoptosis in tumor cells and leads to poor sensitivity to chemotherapy. Liu *et al.*²⁵ studied 168 patients with breast cancer undergoing neoadjuvant chemotherapy, and the rate of chemotherapeutic effectiveness in the group with positive expression of p53 was 58.6%, while the rate of chemotherapeutic effectiveness in the group with negative expression of p53 was 83.5%, with a significant difference ($P < 0.05$). The effect of chemotherapy was reported as greater in patients with negative expressions of p53 than in patients with positive expressions of p53.

C-erbB-2, also known as neu or HER2, is considered an oncogene and is localized in region 17p21 of the chromosome. It has same homogeneity as the epidermal growth factor, primarily participates in regulating cell growth and differentiation, and has the activities of tyrosine protein kinase. According to published reports, the positive rate of C-erbB-2 is approximately 20% to 30%. However, whether neoadjuvant chemotherapy could change the expression of C-erbB-2 is also controversial. Taucher *et al.*²⁶ reported that there was no influence on the expression of C-erbB-2 by neoadjuvant chemotherapy. Gregory *et al.*²⁷ reported that neoadjuvant chemotherapy had a reducing effect on the positive expression of C-erbB-2, even though the variation showed no statistical significance, but it was closely related to clinical remission in tumors.

Cellular tumor markers are closely related to tumor genes and are highly specific. However, for assessing the therapeutic effect of neoadjuvant chemotherapy, they lack sensitivity to changes, such as they cannot change the expressions of ER, PR, and C-erbB-2 after neoadjuvant chemotherapy. Thus, they cannot help to understand the influence on tumor cells by effective neoadjuvant chemotherapy. As a result, the therapeutic effect cannot be evaluated by these markers. Oncogenes such as Ki-67 and P53 were closely related to differentiation, proliferation, and prognosis of breast cancer. Research demonstrated an existing

statistical significance to changes in their expressions before and after neoadjuvant chemotherapy. Therapeutic effect can then be evaluated by changes in oncogenetic expression.

Summary and a glance into the future

Overall, each approach has its own advantages and inadequacies. Target X-ray with molybdenum can observe tumor size and calcification, even though there is a high false-positive rate and there is a risk of radioactive injury. It is used less for observing the therapeutic effect of neoadjuvant chemotherapy. Color ultrasound provides a clearer description of the tumor mass, the morphologic features of the axillary lymph nodes, and blood flow, but it is usually subject to the experience of the physician. PET/CT and MRI have higher accuracy for evaluating the therapeutic effect, but they are expensive and cannot be afforded by the general public. Blood oxygen functional examination in breast tissue, although it has no associated study, still shows some potential for further development. The blood oxygen examination, as a noninvasive approach, can serve as a complement to radiologic examination. It can be a creative breakthrough to the conventional methods. And there are many biomarkers for tumors. Although they have low sensitivity and specificity, they can still supplement physical examinations.

With the emergence and application of new concepts and approaches for the treatment of patients with breast cancer, a trustworthy, plausible, and repeatable monitoring technique for the evaluation of the therapeutic effect of chemotherapeutic drugs and treatment is needed, where it hopefully can assess tumor size and angiogenesis, as well as functionally evaluate the growth and metabolism of the tumor. We can expect that the progression of future evaluation methods for the therapeutic effect of neoadjuvant chemotherapy from several perspectives: interactions with radiologic examinations to increase the accuracy of determining the therapeutic effect; interactive cooperation between radiologic examinations and functional tests to understand completely the response of the tumor to chemotherapy; and the application of molecular biomarkers in the evaluation of the therapeutic effect.

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