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Molecular Residual Disease (MRD) Testing: Advancing Clinical Decision-Making in Breast Cancer

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Abstract: Circulating tumor DNA (ctDNA) is emerging as a clinically meaningful biomarker across multiple solid tumors, including breast cancer. Advances in personalized, tumor-informed whole-genome sequencing have enabled highly sensitive detection of ctDNA, allowing for more precise assessment of tumor burden. Across treatment settings, ctDNA testing has demonstrated consistent prognostic value in patients with breast cancer.

In the neoadjuvant setting, ctDNA status is strongly prognostic at baseline and following completion of therapy. After definitive surgery, detection of molecular residual disease (MRD) by ctDNA testing is associated with a marked increased risk of recurrence, with positive predictive values approaching 100% and a lead time of approximately 13.5 months over conventional approaches. These data support the potential role of ctDNA testing as an adjunct to current surveillance strategies, with the aim of identifying recurrence before the onset of significant clinical symptoms.

Although ctDNA results are not yet used to guide treatment modification outside of established standards of care, the field is advancing rapidly. Multiple ongoing prospective, interventional trials are evaluating MRD-guided therapeutic strategies, and emerging evidence suggests that ctDNA may ultimately help individualize adjuvant therapy—either by identifying patients who may safely de-escalate treatment or by signaling when escalation could be beneficial. In the metastatic setting, ctDNA testing can complement radiographic assessment by providing an additional measure of treatment response, particularly in patients with nonmeasurable or difficult-to-visualize disease.

Across all settings, ctDNA testing is most informative when performed longitudinally, enabling assessment of dynamic changes over time. Although baseline ctDNA testing provides valuable prognostic information, its absence at this time point or at diagnosis does not limit the utility of ctDNA assessment at subsequent time points.

Addressing Late Detection of Systemic Relapse, the Clinical Blind Spot

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In the Clinic . . .

Whole-genome tumor-informed MRD testing, a significant advancement over exome-powered ctDNA assays, is associated with 100% sensitivity and specificity. It identifies recurrence before it is detectable via imaging and can be a valuable addition to current surveillance methods.

Although earlier detection and treatment advances have improved survival in breast cancer, distant recurrence remains a persistent risk and is the leading cause of breast cancer–related mortality.[1] In a cohort of 8007 patients with early breast cancer enrolled in clinical trials from 1997 to 2013, only 10% experienced recurrence within the first 5 years; however, nearly 70% of first recurrences involved distant disease, either alone (61.0%) or concurrently with local-regional recurrence (8.2%).[2] These findings highlight limitations in current surveillance strategies for detecting recurrence at an earlier, less symptomatic, more manageable stage.

Guideline-recommended surveillance for patients with early breast cancer who have completed adjuvant systemic therapy consists of annual mammography and routine history and physical examinations. Routine laboratory or imaging studies to screen for metastases are not recommended unless patients develop symptoms or clinical signs suggestive of recurrence.[3]

Even when imaging is clinically indicated, its sensitivity may be insufficient to detect early metastatic disease. Symptom-driven imaging and the limited sensitivity of conventional modalities can contribute to delayed detection of systemic recurrence. As a result, patients may present with significant symptoms by the time metastatic disease is identified. In some cases, symptoms such as musculoskeletal pain may be attributed to benign causes, leading patients to seek care from multiple providers—including primary care, orthopedics, physical therapy, sport medicine, rehabilitation, naturopathic therapy, and pain management—before cancer recurrence is recognized.

These gaps in surveillance have prompted evaluation of circulating tumor DNA (ctDNA) for detecting molecular residual disease (MRD) as a more sensitive method for identifying residual cancer. MRD positivity has been shown to precede overt metastatic recurrence, providing a substantial lead time over standard imaging.[4,5]

Use of ctDNA testing for surveillance requires high analytical sensitivity and specificity, which is technically challenging in early breast cancer owing to the low concentrations of ctDNA present.[6] Tumor-informed ctDNA assays, developed from sequencing the primary tumor, enable longitudinal monitoring for recurrence using multiplex polymerase chain reaction followed by

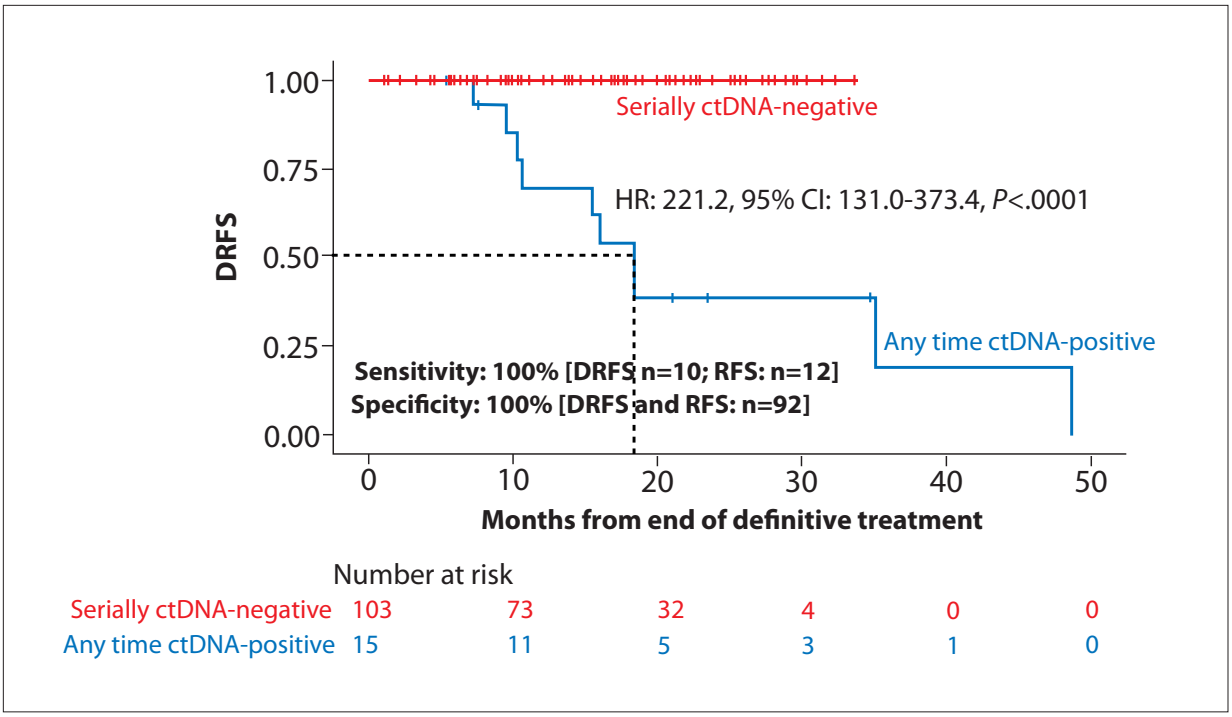

Figure 1. Longitudinal ctDNA status post-definitive treatment in a breast cancer subcohort (n=118).

ctDNA, circulating tumor DNA; DRFS, distant recurrence-free survival; RFS, recurrence-free survival.

Adapted from McHayleh W et al. Presented at: San Antonio Breast Cancer Symposium 2025; December 9-12, 2025; San Antonio, Texas. PS2-07-26.[8]

next-generation sequencing (mPCR-NGS).

Early ctDNA assays relied on exome sequencing. Technological advances have enabled whole-genome tumor-informed approaches with substantially improved sensitivity.[4] Whole-genome assays have demonstrated limits of detection (LoD95: limit of detection with 95% confidence) in the range of 5 to 9 ppm, with detection capability down to 1 ppm, and have shown high analytical sensitivity and specificity.

In a retrospective analysis of patients with solid tumors, including those with breast cancer, serial ctDNA testing after definitive treatment demonstrated 100% clinical sensitivity and specificity for detecting distant recurrences (Figure 1).[7,8] Any ctDNA positivity was associated with a markedly increased risk of distant recurrence compared with persistent ctDNA negativity (hazard ratio, 221.2; 95% CI, 131.0-373.4; *P*<.0001). In the same analysis, ctDNA positivity provided a median 13.5-month lead time over radiographic detection.

At present, the high sensitivity and specificity of ctDNA testing for detecting recurrence underscore its value as an adjunct to current surveillance methods. In practice, ctDNA testing is being used to inform risk stratification and optimize management within the standard of care. The following articles discuss the clinical application of this technology.

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MRD Testing Across the Continuum of Care

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In the Clinic . . .

MRD assessment using ctDNA testing has demonstrated prognostic value across treatment settings and is a useful tool for estimating risk of recurrence and identifying patients who should receive staging imaging. Serial ctDNA results are helpful in gaining a complete picture of response and progression.

Growing evidence is demonstrating the utility of MRD testing using ctDNA across the continuum of care in breast cancer (Figure 2).

MRD Testing in the Neoadjuvant Setting

In early breast cancer, analyses from the I-SPY2 trial have demonstrated the prognostic value of ctDNA testing at baseline, while receiving neoadjuvant therapy, and after neoadjuvant therapy. Among 712 patients with high-risk early breast cancer, ctDNA was detected at baseline in 81.3% of patients. Those who were ctDNA-positive had a significantly higher risk of recurrence than those who were ctDNA-negative, with 3-year distant recurrence-free survival (DRFS) rates of 80.9% and 90.8%, respectively (hazard ratio, 5.5; 95% CI, 2.4-13; $P<.001$).[1] Baseline ctDNA concentration was also significantly associated with DRFS across receptor subtypes.

Pathologic complete response (pCR)—defined as no

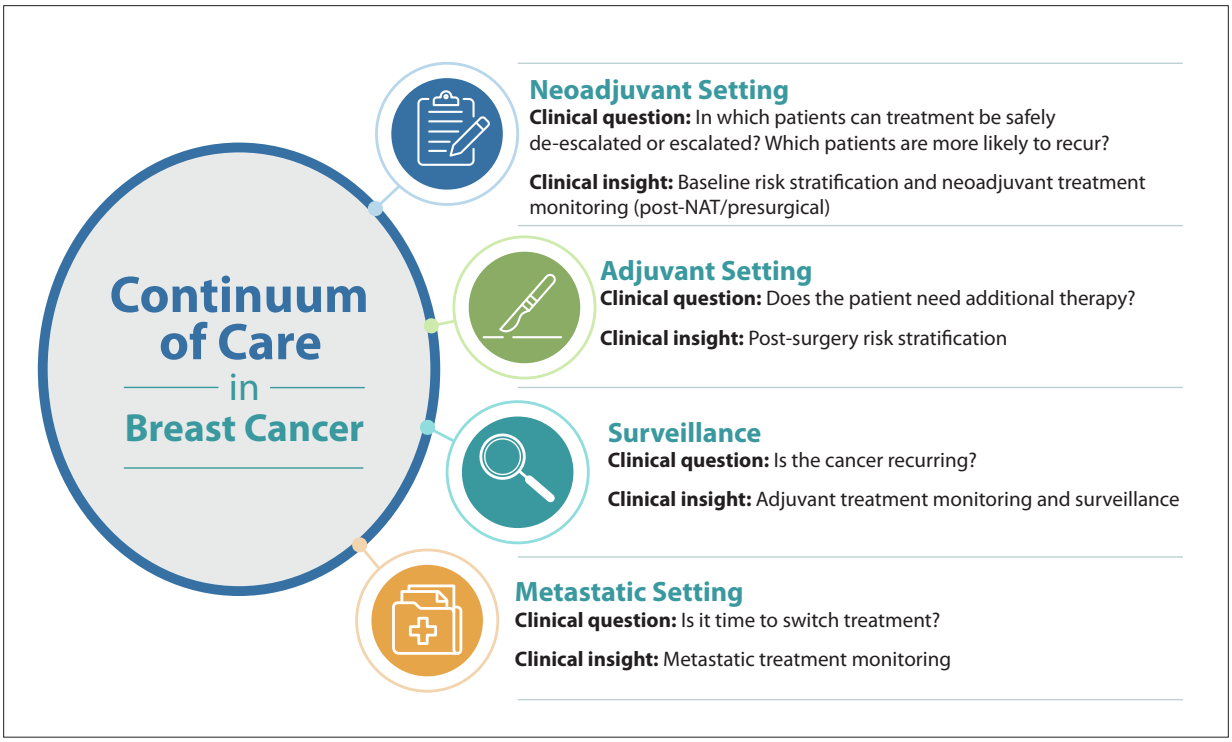

Figure 2. Role of MRD testing across the continuum of care in breast cancer.

MRD, molecular residual disease; NAT, neoadjuvant therapy.

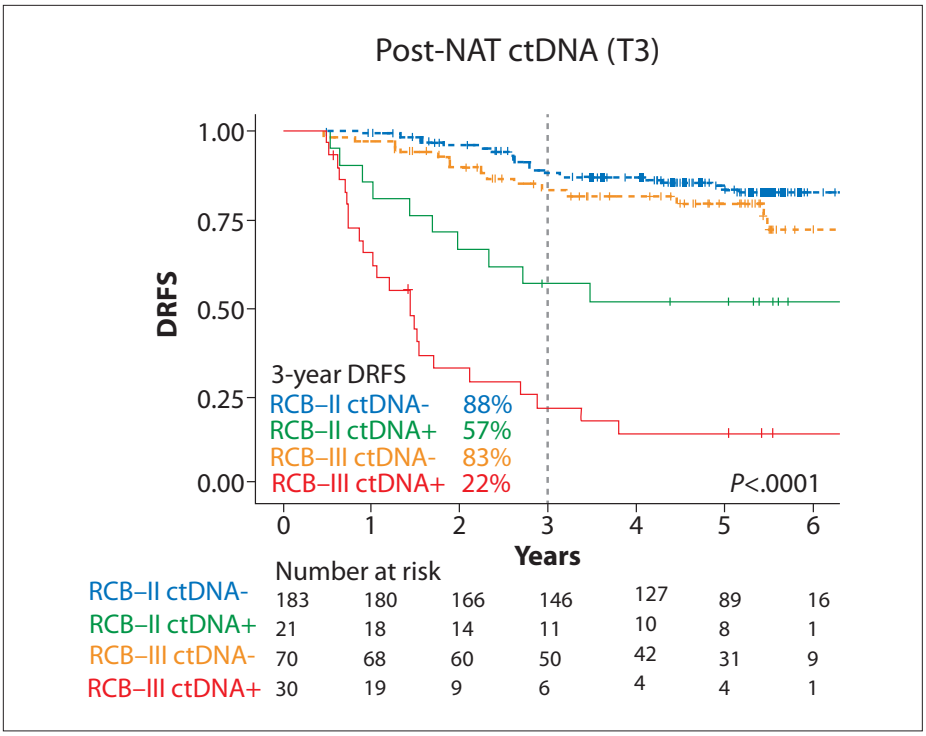

Figure 3. Post-NAT DRFS in Signatera™-negative vs Signatera™-positive patients with residual disease.

ctDNA, circulating tumor DNA; DRFS, distant recurrence-free survival; NAT, neoadjuvant therapy.

Adapted from Magbanua MJM et al. *Nat Commun.* 2025;16(1):9945.[3]

residual cancer in the breast or regional lymph nodes—remains strongly associated with lower recurrence risk, particularly in HER2-positive and triple-negative breast cancers.[2] However, ctDNA clearance has emerged as an equally, if not more, informative predictor of long-term outcomes. In an I-SPY2 analysis, lack of ctDNA clearance after neoadjuvant chemotherapy was strongly associated with poor response and metastatic recurrence, whereas ctDNA clearance correlated with improved DRFS, including among patients with residual disease. Among patients with moderate (RCB-II) or extensive (RCB-III) residual disease, 3-year DRFS was significantly higher in those who were ctDNA-negative than in those who remained ctDNA-positive (RCB-II: 88% vs 57%; RCB-III: 83% vs 22%; both *P*<.0001; Figure 3).[3]

Emerging evidence also suggests a potential role for ctDNA testing to tailor neoadjuvant therapy. In an analysis from the I-SPY2 trial, ctDNA clearance predicted favorable responses to neoadjuvant therapy as early as week 3 across receptor subtypes.[3]

Given the favorable outcomes previously associated with ctDNA clearance,[4] these findings raise the possibility that additional chemotherapy may not benefit this subgroup. Conversely, the 19% who remained MRD-positive may represent candidates for treatment escalation aimed at achieving MRD negativity before surgery.

Another application is the potential use of ctDNA to identify older patients who may safely de-escalate surgery. In an analysis of 43 older patients who elected primary endocrine therapy instead of surgery, pretreatment ctDNA levels were strongly associated with tumor progression (hazard ratio, 30; 95% CI, 4.4-209; *P*=.0011), and no ctDNA-negative patients experienced progression.[5]

In the Clinic . . .

Not all residual disease is associated with the same risk of recurrence despite neoadjuvant therapy.

ctDNA Testing in the Adjuvant Setting

A substantial body of evidence supports the role of MRD assessment using ctDNA in the adjuvant setting. Multiple tumor-informed assays have been developed, and across platforms, MRD positivity consistently predicts recurrence in early breast cancer, with positive predictive values approaching 100%.[6-10]

Current assays differ in analytical sensitivity, which contributes to variation in lead time relative to imaging, particularly in hormone receptor (HR)–positive disease. In more aggressive subtypes, such as triple-negative and HER2-positive breast cancers, the interval between MRD detection and clinical recurrence is typically shorter.

Across histologies, MRD positivity on ctDNA testing in early breast cancer generally prompts systemic staging imaging to evaluate for metastatic disease. When

metastases are identified, treatment for metastatic breast cancer is initiated.

In the Clinic . . .

While baseline ctDNA assessments are informative and prognostic, a lack of baseline ctDNA testing does not preclude future testing at any point in a patient's journey.

In HR-positive patients with detectable MRD but no radiographic recurrence, the evaluation should extend beyond imaging and symptom monitoring alone. It should prompt reassessment of endocrine therapy adherence, particularly given the adherence issues in up to 50% of patients. Re-engaging patients with guideline-directed endocrine therapy is important in such cases. In premenopausal women, confirming adequate ovarian suppression is also important to ensure endocrine therapy is effective. In addition, MRD positivity creates an opportunity to revisit standard-of-care options that may have previously been declined, such as CDK4/6 inhibitors or aromatase inhibitors. Overall, this setting provides a chance to optimize therapy within established care pathways.

Differences in ctDNA shedding have been observed across breast cancer subtypes and tumor sizes. Shedding levels may influence interpretation, as very low-level ctDNA (0.01%-0.05%) may occasionally be cleared by the immune system. In such cases, repeating ctDNA testing after approximately 1 month may help clarify MRD status.

The dynamics of ctDNA over time also provide important context. Rising ctDNA levels suggest molecular progression of disease and may warrant consideration of treatment modification within current standards of care, such as adjusting endocrine therapy or adding a CDK4/6 inhibitor in HR-positive disease. In triple-negative and HER2-positive breast cancers, metastatic disease is often radiographically detectable at the time ctDNA becomes detectable. These patterns underscore the value of initiation of ctDNA surveillance early and with serial or repeated testing.

Early MRD detection may also lead to detection of locoregional/oligometastatic disease, thus offering a chance for curative treatment.

Exploring the Possibility of MRD Conversion in the Adjuvant Setting

Currently, achievement of MRD negativity in the adjuvant setting is not a standard focus, although emerging data suggest that adjuvant therapy may facilitate MRD conversion in some cases.

In a pilot analysis from the monarchE trial involving patients with high-risk HR-positive, HER2-negative, node-positive early breast cancer, 41% of those who were MRD-positive prior to enrollment converted to MRD-negative.[11] The 4-year invasive disease-free survival (IDFS) rate in this group was 58.3%, whereas all patients who remained persistently MRD-positive experienced an IDFS event.

More recently, the phase 2 LEADER trial evaluated the addition of the CDK4/6 inhibitor ribociclib to endocrine therapy in 10 patients with estrogen receptor (ER)-positive, HER2-negative breast cancer testing ctDNA-positive after definitive surgery.[12] Among 9 evaluable patients, 6 patients (66%) had a ctDNA reduction of greater than 25% from baseline and 3 patients (33%) achieved complete ctDNA clearance. Median time to recurrence was 18.6 months in patients who achieved ctDNA clearance vs 7.2 months for those who did not.

In the DARE trial, patients who were persistently ctDNA-negative longitudinally had a negative predictive value (NPV) greater than 99% for recurrence over the follow-up period.[13] This can help reduce anxiety for ctDNA-negative patients, as it provides reassurance that recurrence is very unlikely.

However, whether higher rates of ctDNA clearance translate into improved long-term outcomes remains unknown.

In the Clinic . . .

Standardized frequency of ctDNA testing has not been established, and it will vary depending on the aggressiveness of the cancer.

- For patients with early-stage HR-positive breast cancer, conducting ctDNA testing every 6 months is probably sufficient, given the lead time of 12 to 18 months across tests.
- For patients with aggressive histologies, ctDNA testing every 2 or 3 months is considered more appropriate for at least the first few years, when the risk of recurrence is highest.
- In the metastatic setting, a frequency of every 2 to 3 months may be considered.

MRD Testing in the Metastatic Setting

MRD testing may also have utility in metastatic breast cancer, particularly in settings where disease is difficult to visualize radiographically, such as bone-only metastases or invasive lobular carcinoma (ILC), which is nonmeasurable by RECIST. In these situations, ctDNA dynamics can pro-

vide information about treatment response and if a switch is warranted.

A real-world retrospective analysis demonstrated the feasibility of longitudinal ctDNA monitoring in patients with metastatic ILC using a personalized, tumor-informed mPCR-NGS assay.[14] Among 66 patients, on-treatment ctDNA trends correlated closely with radiographic response. ctDNA positivity was associated with higher mortality, whereas ctDNA negativity corresponded to favorable short-term outcomes, with overall survival rates of 97% at 6 months and approximately 90% at 12 months.

These findings suggest that ctDNA analysis may serve as a useful adjunct for monitoring treatment response in patients with ILC.

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Interpreting MRD Results and Integrating Assays Into Practice

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The implementation of ctDNA testing in clinical practice, and the implications of ctDNA test results for clinical care, are topics of evolving and ongoing interest.

Prognostic Significance of MRD Informs Appropriate ctDNA Testing Intervals

Results from a biomarker substudy of the PALLAS trial confirm the prognostic significance of MRD in predicting recurrence risk in the adjuvant setting.[1] This preplanned analysis included 420 patients with HR-positive, HER2-negative stage II-III breast cancer randomized to adjuvant endocrine therapy with or without palbociclib. MRD, assessed using a validated personalized, tumor-informed ctDNA assay, was highly prognostic across all time points. At the postsurgical baseline assessment, 8% of patients tested MRD-positive and had poor outcomes, with a 5-year distant recurrence-free interval (DRFI) of 28%. Among the 92% who were MRD-negative at baseline, the 5-year DRFI was 93%. At the end of 2 years of adjuvant

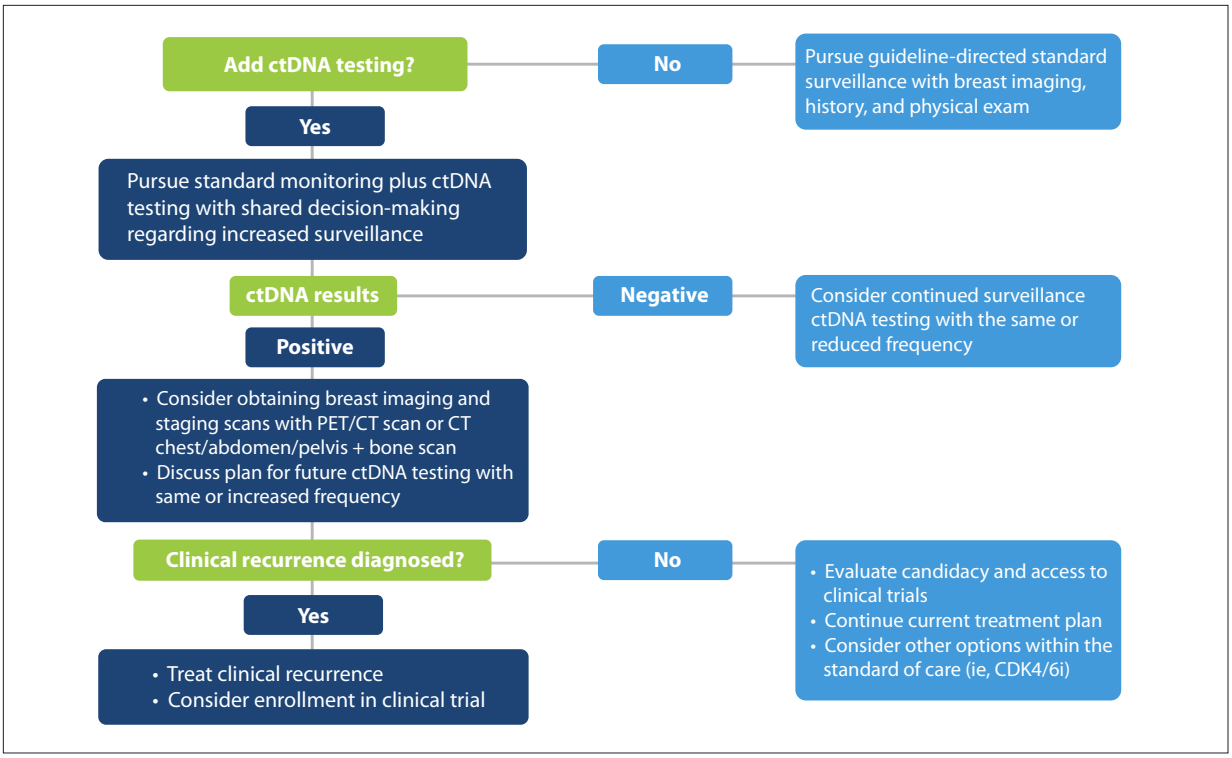

Figure 4. Real-world framework for how oncologists can use ctDNA testing for adjuvant surveillance in patients with early breast cancer.

CDK4/6i, CDK4/6 inhibitors; CT, computed tomography, ctDNA, circulating tumor DNA; PET, positron emission tomography.

Adapted from Lipsyc-Sharf M et al. Presented at: 2024 Annual Meeting of the American Society of Clinical Oncology; May 31-June 4, 2024; Chicago, Illinois. Abstract 549.[3]

treatment, the 5-year DRFI was 95% in MRD-negative patients vs 32% in those who were MRD-positive.

Real-world analyses also provide insight into the significance of MRD outside clinical trials. A multi-institutional initiative retrospectively evaluated MRD status in patients with early breast cancer. Among those testing MRD-negative at a single time point, the risk of recurrence in the subsequent 3 to 6 months was less than 3% across subtypes, [2] underscoring the high NPV of MRD negativity in early breast cancer.

We eagerly await the results of prospective clinical trials designed to evaluate the optimal use, actionability, and testing intervals. However, while awaiting such results, the real-world data may help inform the interpretation of ctDNA results and guide ctDNA testing intervals. Given the high NPV of MRD negativity over a 3- to 6-month period, obtaining ctDNA testing at this 3- to 6-month interval may be reasonable. Regarding current interpretation of results, common real-world practice patterns are described in the depicted proposed framework (Figure 4).[3] For patients with a negative ctDNA result, management typically remains unchanged. For patients with a positive result, clinicians often repeat the test, obtain systemic staging imaging, and explore relevant clinical trials. Some clinicians and patients may also consider treatment adjustments within current standards of care.

In the Clinic . . .

In patients with early breast cancer undergoing post-treatment surveillance with ctDNA testing, real-world data suggest that a positive ctDNA test prompts most clinicians to pursue additional investigations, including a repeat ctDNA test to confirm positivity and systemic staging imaging to further assess disease status.

Interpreting MRD Results

Routine systemic staging imaging is not recommended for surveillance in early breast cancer and is typically performed only when patients develop symptoms or clinical signs suggestive of recurrence.

In clinical practice, MRD status informs prognosis, but there are currently no guidelines regarding

MRD-based treatment decisions. A negative ctDNA result does not equate to omission of indicated therapy, and a positive result does not automatically warrant treatment modification. Nonetheless, MRD positivity clearly indicates an elevated risk of recurrence, and real-world data suggest that many clinicians respond by repeating the test and obtaining systemic staging imaging to evaluate for radiographic disease.

Emerging real-world data illustrate how ctDNA surveillance is being incorporated into care. A multi-institutional study conducted between November 2020 and January 2024 found that when ctDNA-triggered imaging revealed a recurrence, patients generally proceeded to treatment for metastatic breast cancer.[3] Whether initiating therapy at this asymptomatic stage improves long-term outcomes remains unknown, and prospective trials are expected to clarify the impact of early intervention.

Not all positive ctDNA tests lead to radiographic findings. In some cases, imaging remains negative, suggesting molecular relapse without clinically or radiographically detectable disease. These situations often prompt multidisciplinary review. Some clinicians, in collaboration with patients, may elect to adjust systemic therapy within existing standards of care—for example, changing endocrine therapy from tamoxifen to an aromatase inhibitor or initiating a CDK4/6 inhibitor in an eligible patient who had previously declined this treatment. For patients with triple-negative breast cancer, limited adjuvant options make decision-making more challenging, underscoring the importance of proactive discussions. Clinical trial enrollment is generally viewed as the preferred pathway in these cases.

In the Clinic . . .

The amount of ctDNA detected is a consideration when interpreting ctDNA test results, as the immune system may be able to eliminate low levels of shedding. For patients with low ctDNA concentrations (0.01%-0.05%), rechecking ctDNA in a short interval (ie, a month) may be considered, as clearance may be observed with these low levels. Additional research on ctDNA biology and testing will inform how ctDNA concentration may be used in future trials and practice.

Several studies are now evaluating MRD-guided treatment strategies. Among them is the newly launched SIGNAL-ER 101 trial (NCT07214532), which is enrolling patients with intermediate-risk HR-positive, HER2-negative early breast cancer. The study uses ctDNA results to stratify patients. Those that remain ctDNA-negative on serial testing will receive endocrine therapy alone. CDK4/6 inhibitor will be initiated only upon a ctDNA-positive result.

Quality of Life and ctDNA Testing

Patient quality of life (QoL) is an important consideration when evaluating the role of ctDNA testing in clinical practice. Although it is often assumed that patients may avoid ctDNA testing because of concerns about increased anxiety, emerging evidence suggests otherwise.

In the Clinic . . .

Decisions regarding obtaining ctDNA testing surveillance should be made through shared decision-making. Both patients and clinicians should understand the potential risks, benefits, and limitations of current testing. Prior to pursuing testing, clinicians should explain the implications of different MRD results and how patients' care would or would not be affected by these results. This way, patients can have appropriate expectations about how the information may be used.

In the prospective real-world I-SURV study of 58 patients with early breast cancer, most participants valued ctDNA surveillance and wished to continue testing.[4] Patients reported that a negative ctDNA result reduced anxiety and fear of recurrence. Although this cohort may be subject to self-selection bias, similar findings have been observed elsewhere. In the single-institution pilot CIPHER study of 30 patients with early breast cancer, most participants reported that ctDNA testing provided meaningful information, and approximately one-third experienced reduced anxiety about recurrence.[5]

Prior to shared decision-making about pursuing ctDNA testing, patients should be counseled on the potential risks and benefits of testing, and one potential risk includes the possibility of increased anxiety from a positive ctDNA test result. Further data are needed to understand how a positive ctDNA result affects anxiety and fear of recurrence. Effective strategies to address such concerns are also needed. The scenario of a positive ctDNA result with negative imaging may introduce uncertainty, as patients become aware of a potential recurrence that may not manifest radiographically for many months. In these cases, clear communication and patient education are essential to help patients understand the implications of the result. It is often helpful to discuss prior to obtaining the ctDNA testing what could be done or not done based on a positive or negative result. This

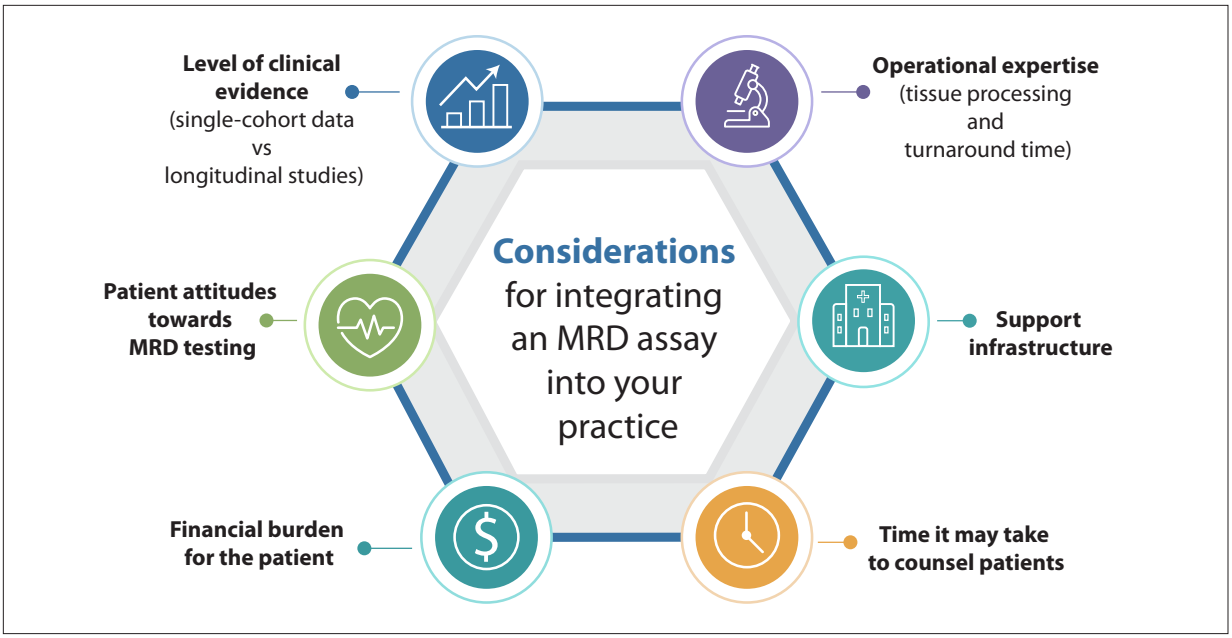

Figure 5. Considerations for integrating MRD testing in clinical practice.

MRD, molecular residual disease.

In the Clinic . . .

Serial ctDNA testing increases sensitivity compared with testing at a single time point.

- In less aggressive subtypes, like ER-positive/HER2-negative breast cancer where recurrence may emerge years after an initial test, serial testing provides a more accurate view of MRD status over time.
- In aggressive subtypes like triple-negative and HER2-positive breast cancer, serial testing may increase the chance of catching molecular recurrence before patients develop clinical or radiographic recurrence.

way, patients are more likely to feel comfortable with the plan for follow-up and management.

ctDNA Assay Considerations

At this time, the use of ctDNA testing in patients with early-stage breast cancer remains a clinical decision made in partnership with the patient. Once the decision is made to proceed, selecting the appropriate assay becomes an important next step (Figure 5).

Multiple ctDNA assays are commercially available for use in breast cancer, and different tests may be considered depending on the disease setting. In metastatic breast cancer, tissue-agnostic ctDNA assays are particularly important, as these can identify emergent resistance mutations, such as *ESR1* mutations, that were not present in the primary tumor. In contrast, in early-stage breast cancer, tumor-informed assays are particularly useful because they are designed to detect recurrence of previously characterized tumors.

Most of the longitudinal data on ctDNA testing in breast cancer come from studies using the Signatera™ assay (Natera, Inc.), although several additional assays are commercially available and in development and may expand available options in the future. Operational considerations also influence assay selection. Insurance coverage and patient support programs vary across platforms. In metastatic disease, robust patient support programs are generally available. In early-stage breast cancer, coverage is more variable; Medicare covers certain ctDNA assays, whereas commercial insurance policies differ widely.

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Practical Approach to MRD Testing in Breast Cancer: Q&A

Jason A. Mouabbi, MD; Marla D. Lipsyc-Sharf, MD; and Fengting Yan, MD, PhD

Addressing Late Detection of Systemic Relapse, the Clinical Blind Spot

H&O What are the limitations of relying solely on symptom-focused imaging? How do you reconcile current surveillance guidelines with recurrence biology?

JAM Relying on imaging means detecting recurrence only after metastasis has already developed, when cure is no longer possible. ctDNA allows detection at the earliest stages—when only a few cells are shedding—creating a window to intervene early and intercept that rising ctDNA before overt disease appears. Our guidelines are built around imaging, but recurrence biology happens much earlier. These assays shift surveillance from waiting for visible disease to identifying recurrence as it emerges, enabling earlier, more effective action.

FY Symptom-driven imaging often leads to delayed detection, with patients presenting after multiple evaluations and sometimes with advanced symptoms such as severe pain, pathologic fracture, pleural effusion, or organ dysfunction. Imaging alone may lack sensitivity, underscoring the value of complementary molecular tools.

H&O Do you see molecular monitoring as complementing existing surveillance tools?

JAM Right now, MRD testing works alongside imaging because clinicians are accustomed to scans. Over time, molecular testing will likely become the primary surveillance tool, but for now, both approaches are used together.

FY MRD is a complementary tool that enhances long-term surveillance, particularly in HR-positive/HER2-negative disease with prolonged recurrence risk. Molecular monitoring supports more informed decision-making and improves patient quality of life without replacing clinical judgment or imaging.

MRD Testing Across the Continuum of Care

H&O What is the value in obtaining a true pre-treatment baseline ctDNA level before neoadjuvant therapy?

JAM A baseline ctDNA result is helpful. When a patient is negative at baseline, they generally have excellent outcomes regardless of the treatment approach, so the baseline mainly helps with risk understanding rather than treatment selection.

MLS Baseline ctDNA provides prognostic insight by showing patients' baseline risk, and also allows for determining how quickly a patient clears ctDNA after starting therapy. Early clearance strongly correlates with better long-term outcomes, as shown in I-SPY data. It also helps interpret ambiguous clinical response, ambiguous imaging, or uninformative tumor markers and can guide decisions when assessing response or progression in complex metastatic presentations.

FY A true pretreatment ctDNA baseline enables more individualized induction therapy, particularly in HER2-positive disease where uniform cycle counts are suboptimal. Recent published TRAIN-3 data support MRI-based personalization of neoadjuvant chemotherapy duration in HER2-positive early breast cancer but small residual cancer could be missed by MRI. Baseline levels help assess depth of response, support earlier transition to maintenance therapy, and provide clarity when tumor markers are uninformative or imaging is ambiguous, especially in bone-only metastatic disease.

H&O How do ctDNA results shape your counseling and management discussions with patients who do not achieve pCR?

JAM ctDNA negativity is a stronger predictor of outcome than pCR. Patients who clear ctDNA, even if they still

have residual disease, tend to do just as well as those who achieve pCR. This allows me to reassure patients that their prognosis remains favorable. I also emphasize the value of tracking ctDNA dynamics over time because trends, not single values, provide the most meaningful guidance.

MLS Although it doesn't yet dictate therapy—as current clinical trials in triple-negative and HER2-positive breast cancers are based on the presence or absence of residual disease—ctDNA may help further stratify risk and overall prognosis. When lack of pCR aligns with positive ctDNA, I view the patient as extremely high risk and even more strongly encourage optimal adjuvant therapy. If such patients still decline optimal adjuvant therapy, I engage in shared decision-making with these patients to determine if more frequent follow-up visits and/or testing are warranted. For these patients I will have a particularly high suspicion for recurrent disease if they develop concerning symptoms. If ctDNA is negative despite residual disease, I do see these patients as lower risk than those with positive ctDNA although I still recommend guideline-concordant adjuvant treatment for patients with residual disease.

FY For patients without pCR, ctDNA helps refine conversations about adjuvant therapy. A negative result reassures me when residual disease is minimal and we're debating whether aggressive treatment truly adds benefit. A positive result, especially after pCR, prompts closer imaging and ctDNA monitoring, because we lack guidelines for treating molecular recurrence. It adds nuance, not automatic treatment changes.

In the Clinic . . .

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–Jason A. Mouabbi, MD

H&O How do you use MRD status to guide escalation or de-escalation of therapy in the adjuvant setting?

JAM I use MRD testing primarily to guide escalation when ctDNA is positive. Many eligible patients never receive CDK4/6 inhibitors, and starting these agents often drives ctDNA back to undetectable levels. I also adjust endocrine therapy, such as switching from tamoxifen to an aromatase inhibitor or changing between aromatase inhibitor classes with similar benefit. I should note that a negative MRD testing result should not justify de-escalation, because data from ctDNA trials currently support the fact that its level reflects only the current moment and cannot predict future recurrence. Adjuvant therapy remains essential even when ctDNA is negative.

FY In HR-positive/HER2-negative high-risk patients, I use ctDNA negativity to support safe de-escalation, especially when patients are anxious about stopping therapy. If ctDNA is positive, I prefer clinical trial enrollment and closer monitoring rather than immediate treatment, because evidence is still evolving. I do not alter management for triple-negative or HER2-positive disease owing to faster relapse kinetics and limited data.

MLS Without prospective clinical trial data, MRD-guided escalation or de-escalation must be individualized. At this time, I do not recommend omitting adjuvant therapy solely because ctDNA is negative, although the prognostic reassurance can certainly help patients independent of their choices for adjuvant therapy. For ctDNA-positive/scan-negative cases, some clinicians adjust endocrine therapy or add CDK4/6 inhibitors, but options are limited in triple-negative and HER2-positive breast cancers. My first recommendation remains clinical trial enrollment.

H&O In the absence of formal guidelines for molecular relapse in breast cancer, what decision framework do you rely on or would you propose?

JAM Guidelines inevitably lag behind emerging evidence, so waiting for formal recommendations would delay meaningful adoption of MRD testing, which is already supported by clinical data and widely reimbursed by Medicare, Medicaid, and many commercial insurers, reflecting the recognition of its value. I believe that evidence, and not the timing of guidelines, should drive practice, and growing data on effective interventions, including CDK4/6 inhibitors, support using MRD testing now while guidelines continue to evolve.

MLS We lack formal guidelines, but real-world practice patterns offer a useful starting point. In our ASCO 2024 analysis, most clinicians made no changes to clinical care when ctDNA was negative. When ctDNA was positive, the most common approach was to repeat the test, obtain systemic staging imaging, explore clinical trial options, and consider changing therapies within standard-of-care options. This emerging pattern can serve as a practical framework while we wait for prospective trials to clarify how best to act on molecular recurrence.

FY In cases of molecular recurrence without clinical or radiographic evidence, I never take a positive ctDNA result lightly. Because lead times can range from 3 to 24 months, I always obtain appropriate imaging and monitor closely,

knowing the positive predictive value is high. Imaging modality matters: in HR-positive/HER2-negative disease, I've detected small recurrences with ^{18}F-fluoroestradiol PET/CT even when CT and bone scans were negative.

Without formal guidelines, my preferred framework is to confirm there is no radiographic recurrence using the most sensitive modality available, consider clinical trial enrollment when possible, monitor ctDNA kinetics closely if imaging is negative, and avoid initiating systemic therapy solely for molecular recurrence until we have stronger evidence, because we may expose patients to toxicity without proven survival benefit. This approach balances vigilance with caution while we await prospective data such as the DARE study.

In the Clinic . . .

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–Jason A. Mouabbi, MD

H&O How would you educate/address clinicians who may be hesitant to adopting MRD testing earlier in the disease continuum?

JAM ctDNA is here to stay, and clinicians should become comfortable with it early rather than fall behind as the field evolves. Although adopting new tools can feel uncomfortable at first, this adjustment is both necessary and inevitable. Learning to use MRD testing now, while the landscape is still manageable, will better prepare clinicians for its expanding role in the future.

MLS I think it's reasonable for clinicians to be cautious about using MRD testing early, because we still don't fully know how to act on results. In my own practice, I prioritize testing for patients who meet eligibility for ongoing clinical trials, where the evidence is strongest. When I use MRD in routine care, this is largely driven by patient-provider shared decision-making. I make sure to have clear conversations about what positive and negative results mean and how they would or would not influence management. We discuss risks, benefits, and limitations of testing. Some patients, after our discussions, are more motivated to pursue testing, whereas others decline to pursue testing. Because clinic time is limited, I utilize existing educational materials from industry partners for patients who are interested in learning more information. This way, patients come into their next visit better informed and our discussions can focus on decision-making rather than basic test explanations.

FY Hesitation usually comes from not knowing the test well yet. I start by asking colleagues to think about challenging cases—situations where decision-making felt uncertain or where a patient was anxious and the visit ran long. Those are the scenarios where an additional tool like ctDNA could add real value. I share examples from my own practice to show how MRD has helped in similar situations. My approach is to begin with cases where the information would genuinely help rather than trying to apply MRD universally.

Interpreting MRD Results and Integrating Assays Into Practice

H&O How do you address concerns that MRD testing may increase patient anxiety?

JAM Many concerns about "test anxiety" originate from physicians rather than patients. Clinicians may feel uneasy when they receive MRD results they are unsure how to act on, and they project that anxiety onto patients. In contrast, patient surveys consistently show that individuals value the information MRD testing provides, including those with positive results. Patients tend to feel more empowered and engaged in their care, and the testing often prompts more proactive management. For this reason, the notion of test-induced anxiety reflects physician discomfort more than patient experience, and patient perspectives should guide how these tools are used.

MLS Because ctDNA testing in my practice is currently based on interest in clinical trials and patient-provider shared decision-making, patients typically only elect to pursue testing if they think they will be comfortable receiving the results. So, currently, patients generally do not become more anxious because of MRD testing. Historical studies have actually showed that patients have preferred more testing/surveillance to less testing/surveillance. Anxiety is highly individual: some patients want minimal information and decline genomic tests altogether, whereas others are motivated and feel reassured by MRD monitoring. For clinicians who worry the test will cause distress, the simplest approach is to discuss this with patients directly—many will say they want the information, and those who don't will choose not to pursue the testing.

FY A small subset of patients may feel more anxious with additional testing, but this is true across many aspects of

cancer care. Some individuals prefer limited information and are overwhelmed by any genomic testing; those patients should not be pushed toward MRD testing. Others may feel anxious when ctDNA is positive but imaging is negative, given the uncertainty that can last months. Still, most patients in my practice request MRD testing, feel more informed, and even appreciate early detection of recurrence. Anxiety is rare and manageable, underscoring the need for individualized discussions rather than universal testing.

H&O When you receive a positive MRD result with negative imaging, what is your next step?

JAM Positive MRD results reveal recurrence before it becomes visible on imaging, making immediate imaging essential. A positive ctDNA but negative scan allows early action in HR-positive disease, where most evidence exists. In this setting, clinicians may add a CDK4/6 inhibitor, adjust endocrine therapy, or intensify surveillance, especially if ctDNA levels continue to rise.

FY If imaging is negative, I increase ctDNA monitoring frequency and repeat imaging if ctDNA levels rise or remain persistently elevated.

MLS I follow the same approach and also bring the case to a molecular tumor board while exploring clinical trial options.

H&O How do you incorporate kinetics and dynamics into decision-making?

JAM I focus on how ctDNA changes over time. Rising, falling, or clearing levels tell me whether treatment is working. The speed of change reflects aggressiveness, but the overall trend is what guides most decisions today.

FY I rely on longitudinal monitoring because trends are far more informative than single values. Whether ctDNA is positive or negative, serial testing improves sensitivity and specificity. For high-risk patients, I typically monitor every 3 months early on, then extend to every 6 months once they have had several stable negatives. In select situations, I have monitored even more closely, every 4 to 6 weeks, when clinical concern warranted it.

H&O When MRD becomes detectable, how do you approach subtype-specific management (HR-positive, *BRCA*-mutated, triple-negative)?

FY I monitor triple-negative and HER2-positive disease more aggressively because of rapid recurrence patterns, with more frequent imaging and ctDNA checks. HR-positive/HER2-negative disease may allow slightly less intensive monitoring owing to more indolent behavior.

H&O How do you approach lobular breast cancer, which is typically missed on imaging?

JAM Because most lobular cancers are hormone-positive, I manage them the same way I manage other hormone-positive tumors, using MRD testing in the same manner.

FY This is exactly the population where closer monitoring is essential. I've had several lobular cancer patients who "graduated" from oncology but returned with symptoms, and we detected recurrence—sometimes only through ctDNA when imaging was negative. Because lobular disease is harder to detect and often unpredictable, I take a more proactive approach, making sure patients understand the risk of subtle recurrence and advocating for additional monitoring tools when available.

In the Clinic . . .

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–Fengting Yan, MD

H&O How do you feel about the use of ctDNA in older women with ER-positive breast cancer to facilitate surgical de-escalation?

JAM ctDNA can meaningfully refine decisions around surgical de-escalation in elderly patients who may not tolerate surgery well. Historically, clinicians relied on imaging to judge whether primary endocrine therapy was sufficient, continuing treatment if the tumor remained stable and proceeding to surgery only if it progressed. ctDNA now removes much of that uncertainty.

In older women with ER-positive tumors, those who are non-shedders at baseline tend to do exceptionally well with endocrine therapy alone and may not require surgery at all. In contrast, patients who shed ctDNA at baseline are more likely to progress despite endocrine therapy and will ultimately need surgery, making early surgical intervention more appropriate.

FY Surgical de-escalation has been an active area of discussion, especially for older women with ER-positive disease who may prefer to avoid surgery. In my practice, I already individualize care for women in their 80s or 90s by offering endocrine therapy when surgery is risky or

undesirable, although I've often felt uncertain about missing occult metastatic disease. Having ctDNA as an additional tool could help guide these gray-zone decisions, offering reassurance to both patients and clinicians. Although not yet the standard of care, ctDNA may provide valuable supplemental information when comorbidities or patient preference make surgery less appropriate.

H&O A criticism of MRD testing is that it lacks proven overall survival benefit. In your own practice, have you seen cases where ctDNA detection prompted action that you believe changed the course of disease or potentially extended a patient's life?

JAM Overall survival, although critical, isn't the only meaningful endpoint here. The whole point of MRD monitoring is to act *before* metastatic disease is overtly established, when the patient is still asymptomatic, the tumor burden is low, and our therapeutic options carry the most leverage. Waiting for an overall survival readout to validate that timing is asking the wrong question. In my own practice, ctDNA has changed the trajectory of disease in 2 distinct settings.

In the early setting, I regularly see patients who come to me for a second opinion with a rising ctDNA on standard adjuvant endocrine therapy. In many of those cases, a simple modification (switching the endocrine backbone, or adding a CDK4/6 inhibitor) has been enough to intercept the signal. The ctDNA converts to negative, and to date, those patients have no evidence of metastatic disease. Without MRD testing, we would have waited for a symptom or a scan, and by then we'd be treating overt metastatic disease (often symptomatic) rather than preventing it.

In the metastatic setting, ctDNA testing has been especially valuable in lobular breast cancer, which doesn't visualize well on conventional imaging. I've had patients whose scans looked stable but whose ctDNA was rising significantly. Acting on that signal and changing therapy produced a marked decline in ctDNA, favorable dynamics, and a prolonged response with progression prevented. The imaging would have told us the same story months later after the disease had already advanced and when often we are not in charge of the situation.

FY Overall survival data typically take time to mature. However, in the adjuvant setting, I did have cases where routine imaging, such as CT and bone scans, was negative, yet the presence of positive MRD allowed for the early detection of asymptomatic local axillary recurrence or oligometastatic recurrence, rather than symptomatic widespread metastatic disease. Detecting recurrence at this earlier stage, as local or oligometastatic disease, opens up treatment options with curative intent, which strongly suggests that MRD detection can increase the likelihood of identifying recurrence when curative treatment is still viable, thereby preserving quality of life awaiting definitive overall survival data. This approach aligns with the common practice of adopting treatments with demonstrated PFS benefit while awaiting overall survival data.

H&O What are your main considerations when integrating an MRD assay into your practice?

JAM The primary challenge is not logistics or access, but intra-institutional variability. In a large group of oncologists, only some clinicians feel ready to adopt MRD testing, creating inconsistency for patients who compare care across providers. This leads to friction among colleagues and confusion for patients. Operationally, there are no barriers: ordering is streamlined, tissue retrieval is efficient, and mobile phlebotomy ensures universal access. I primarily use Signatera because of its extensive data, including long-term evidence in lobular breast cancer. The only meaningful limitation is rare cases with insufficient tissue, typically after neoadjuvant therapy with MRD. Otherwise, logistics, turnaround time, and support infrastructure are highly optimized.

FY My patients are highly educated and often arrive already informed about MRD testing, so staying updated and prepared to answer detailed questions is essential. Logistically, I've had very few financial issues—tests are typically covered by Medicare, commercial insurance, or the company—though explanation of benefits statements can still cause temporary anxiety. Ordering is straightforward through our integrated system or online portals, and patients often see their results before I do. Overall, I've encountered minimal logistical barriers, and nearly all patients are grateful to have access to this technology.

Disclosures

Dr Mouabbi is a consultant for: BostonGene, GE HealthCare, AstraZeneca, PreludeDx, Community Health Media, Agendia, Stemline, Natera, Celcuity; has received grant/research support from: Bristol Myers Squibb, Summit Therapeutics, Eli Lilly; has received honoraria from: Novartis, Puma Biotechnology, Gilead, Pfizer, Omni Health, Dava Oncology, MJH Life Sciences; serves on the Steering Committee of: AstraZeneca, Novartis; and serves on the DSMB of: Greenwich LifeSciences.

Dr Lipsyc-Sharf has served on advisory boards/panels for: Natera, Novartis, Guardant Health, TerSera Therapeutics, Eli Lilly, and Stemline Therapeutics; has participated in speakers bureaus and received honoraria from: Exact Sciences, Natera, Eli Lilly, and Stemline Therapeutics; and has received research funding from the Conquer Cancer Foundation and the Terri Brodeur Breast Cancer Foundation.

Dr Yan has served on advisory boards of and received honoraria from: Genentech, Gilead, Intellisphere, LLC, and Natera.