# Circulating Tumor DNA Testing in Solid Tumors and Lymphoma: ASCO Guideline

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DOI https://doi.org/10.1200/OP-26-00311

## ABSTRACT

*ASCO Guidelines provide recommendations with comprehensive review and analyses of the relevant literature for each recommendation, following the guideline development process as outlined in the ASCO Guidelines Methodology Manual. ASCO Guidelines follow the ASCO Conflict of Interest Policy for Clinical Practice Guidelines.*

*Clinical Practice Guidelines and other guidance ("Guidance") provided by ASCO is not a comprehensive or definitive guide to treatment options. It is intended for voluntary use by clinicians and should be used in conjunction with independent professional judgment. Guidance may not be applicable to all patients, interventions, diseases, or stages of diseases. Guidance is based on review and analysis of relevant literature and is not intended as a statement of the standard of care. ASCO does not endorse third-party drugs, devices, services, or therapies and assumes no responsibility for any harm arising from or related to the use of this information. See complete disclaimer in Appendix 1 and 2 (online only) for more.*

**PURPOSE** To provide guidance on the use of circulating tumor DNA (ctDNA) testing in patients with solid tumors or lymphoma.

**METHODS** A systematic review by a multidisciplinary panel with patient representation was conducted. The PubMed database was searched from January 2017 to February 2025. Guideline recommendations were based on consideration of the identified evidence.

**RESULTS** Fifty-four meta-analyses and 22 study reports were identified, including reports of seven randomized trials.

**RECOMMENDATIONS** ctDNA testing for tumor genetic alterations may be used in situations where: tumor tissue testing is challenging, not feasible, or tumor biopsy represents unacceptable risks to the patient; tumor tissue testing results may not be available within a clinically actionable time frame to determine appropriate management options; or a drug's regulatory approved indication allows for or requires ctDNA testing. If ctDNA testing results are negative, inconclusive, or inconsistent with the clinical scenario, tissue-based confirmation should be sought. Other than testing for genetic alterations, ctDNA testing may be offered if a specific, evidence-based action can be taken with the results or there is conflict or ambiguity with standard-of-care assessment that may be resolved by ctDNA testing. Fractional, percentage, or concentration-based measures of ctDNA or total cell-free DNA concentration are not recommended as a surrogate measure of disease. The panel recognizes this is a rapidly evolving field and guidelines are anticipated to change, bringing in tumor-type specific recommendations and incorporating more data on molecular residual disease settings.

Additional information is available at www.asco.org/molecular-testing-and-biomarkers-guidelines.

ACCOMPANYING CONTENT

Appendix

Data Supplement

Accepted May 1, 2026
Published June 18, 2026

Evidence Based Medicine Committee approval: November 18, 2025

JCO Oncol Pract 00:1-22



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## TARGET POPULATION AND AUDIENCE

**Target Population**
All people with solid tumors or lymphoma.

**Target Audience**
Clinicians treating people with solid tumors or lymphoma and considering ctDNA testing.

## INTRODUCTION

Circulating tumor DNA (ctDNA) testing is an increasingly prevalent and important tool in the management and care of patients with cancer. In 2018, ASCO and the College of American Pathologists (CAP) undertook a joint systematic review[1] to address the value of ctDNA testing in terms of preanalytical variables, analytical validity, interpretation and reporting, and clinical validity and utility. At that time, a clinical practice guideline on the topic was not considered feasible and formal recommendations were not made. Since then, published data on ctDNA testing have increased tremendously, while controversy and uncertainty remain regarding when and how it should be used effectively. To provide guidance to clinicians, and to establish a set of baseline recommendations on ctDNA testing that could be used by future ASCO guideline expert panels, ASCO decided to develop a guideline on the topic.

The guideline recommendations focus on the analysis of ctDNA. However, it is critical to acknowledge that ctDNA represents a fraction of total cell-free DNA (cfDNA), which refers to all fragments of DNA released into the bloodstream from various cell processes, including normal turnover, apoptosis, and necrosis. ctDNA originates specifically from tumor cells and can provide valuable insights in cancer detection, monitoring, and treatment response. Understanding the distinction between cfDNA and ctDNA is crucial, as not all cfDNA is tumor-derived, and analyzing ctDNA requires sensitive techniques to distinguish it from background cfDNA, and potential interference from non–tumor-derived cfDNA must be considered in the interpretation of results. In this guideline, "ctDNA" is used nonspecifically in many cases where "cfDNA" may be preferred by some readers as the analytical techniques involved are not necessarily determining the source of the DNA. In addition, the following important topics were considered out of the scope of this guideline: screening of asymptomatic individuals for cancer; the value of other cell-free analytes (eg, viral DNA in viral associated cancers, microRNA [miRNA], exosomal nucleic acid); and ctDNA testing to identify germline pathogenic variants.

## GUIDELINE QUESTIONS

This clinical practice guideline addresses the following overarching clinical questions in its protocol:

When should ctDNA testing be used or not used (1) to support cancer diagnosis? (2) for choice of initial therapy and therapeutic monitoring? (eg, prediction of response to treatment)? (3) for surveillance, monitoring for recurrence, relapse, and/or progression (eg, molecular residual disease [MRD])? and (4) for prognosis?

These questions guided the systematic review and assisted in formulating recommendations. However, during the development of the guideline, the panel determined that different frameworks for organizing the evidence and recommendations were needed. Therefore, the subsequent sections do not address these questions directly on a one-to-one basis.

## METHODS

### Guideline Development Process

This systematic review-based guideline was developed by a multidisciplinary Expert Panel, which included a patient representative and an ASCO guidelines staff member with health research methodology expertise (Appendix Table A1, online only). It also included representatives from the CAP and the Association for Molecular Pathology (AMP).

The recommendations were developed based upon two sources:

- An earlier systematic review of evidence, Merker et al (2018),[1,2] developed jointly by ASCO and the CAP.
- A new systematic review of evidence based on an online search of PubMed in March 2023 and updated in February 2025 and searching for articles published on or after January 1, 2017, or later and not included in the review by Merker et al. In addition, in response to feedback from ASCO's Evidence Based Medicine Committee (EBMC), a focused systematic review was conducted on October 24, 2025 (including all articles back to February 1, 2025) for randomized trials where ctDNA testing was used per the protocol to select care (eg, only patients with certain ctDNA results were included, or one arm used ctDNA results to determine care while other arm did not).

Articles were selected for inclusion in the new systematic review based on the following criteria:

- Population: Patients with or being diagnosed for solid tumors or lymphoma
- Study type: Meta-analyses; randomized trials; prospective comparative studies of at least 50 patients per comparison group (this includes nonrandomized clinical trials); prospective single-group studies of at least 50 patients where each patient received both intervention and comparison testing (eg, to determine sensitivity and/or specificity)
- Interventions: ctDNA testing for important genetic markers or purpose
- Comparisons: Alternative testing for the same marker or purpose or reasonable means for that context (eg, imaging).

- Outcomes:
- Clinical validity: Sensitivity, specificity, positive or negative predictive value, diagnostic odds ratio, false-positive rates
- Clinical utility: Detection of MRD, detection of therapeutically actionable variants, response to therapy, establishing diagnosis of origin of unknown primary cancer, time to progression or recurrence, event (progression, recurrence, disease)-free survival, overall survival (OS)

For this guideline, evidence of clinical utility required studies that demonstrate acting upon information resulting from ctDNA testing (eg, initiation new therapy, initiating earlier therapy, or switching therapy) led to better patient outcomes.

Articles were excluded from the new systematic review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, or narrative reviews; and (3) published in a non-English language. Due to the large volume of studies that potentially met the previous criteria, a further set of exclusion criteria were applied after the search:

- Studies that were descriptive in intention, and not addressing clinical practice, were excluded.
- Studies did not report the desired outcomes in well-accepted and clearly clinically relevant manners were excluded. As an example, a study that reported on an experimental scoring scheme for ctDNA testing results would be excluded, even if it were prognostic in nature.
- Meta-analyses that did not use appropriate methods to account for the correlated nature of sensitivity and specificity were excluded.
- In the February 2025 update search, only studies of clinical utility and meta-analyses were included. The large volume of evidence of clinical validity but not utility, and the lack of value identified to that point in recommendations development for such studies, led the panel to decide to no longer include them in the updated search.

In developing these recommendations, the panel used a framework (Appendix Table A3) for the role of testing based on a similar framework from the GRADE handbook[3] to use more precise language in describing how ctDNA testing had been used in the available evidence and how it could or should be used in the recommendations and clinical interpretation.

Multiple full panel meetings were held, and members were asked to provide ongoing input on the guideline development protocol, quality and assessment of the evidence, generation of recommendations, draft content, as well as review and approve drafts during the entire development of the guideline. ASCO staff met routinely with the Expert Panel co-chairs and corresponded with the Panel via e-mail to coordinate the process to completion. Ratings for the strength of the recommendation and evidence quality are provided with each recommendation, as defined in Appendix Table A2. The quality of the evidence for each outcome was assessed using the Cochrane Risk of Bias tool and elements of the GRADE quality assessment and recommendations development process.[4,5] GRADE quality assessment labels (ie, high, moderate, low, very low) were assigned for each outcome by the project methodologist in collaboration with the Expert Panel co-chairs and reviewed by the full Expert Panel. All funding for the administration of the project was provided by ASCO.

The draft recommendations were released to the public for open comment from July 22 to August 4, 2025. Response categories of "Agree as written," "Agree with suggested modifications," and "Disagree, see comments" were captured for every proposed recommendation with many written comments received. Across the five recommendations, between 61% and 85% agreed with the recommendation as written, 3% to 20% disagreed, and the remainder agreed with modifications. Expert Panel members reviewed the feedback and comments from the open comment respondents. While no modifications to the recommendations themselves were made, the text in the clinical interpretation section was enhanced and clarified to address some comments. Good Practice Statement 1 had the lowest "agree as written" proportion (61%) and the highest "disagree" proportion (20%) and, on reviewing the feedback, the Expert Panel believes this was driven primarily by the nature in which the survey was implemented, with each recommendation appearing in turn and without the context of later recommendations and the full text of the manuscript.

The draft was submitted to multiple external reviewers with content expertise. Reviewers raised several points, which led to changes in the text, including sections that lack clarity and concerns regarding the validity of the included meta-analyses.

All changes were incorporated into the final manuscript before ASCO EBMC review and approval. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO EBMC before submission for editorial review and consideration for publication.

### Guideline Updating

The ASCO Expert Panel and guidelines staff will work with co-chairs to keep abreast of any substantive updates to the guideline. Based on formal review of the emerging literature, ASCO will determine the need to update. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the guideline update process. This is the most recent information as of the publication date.

## RESULTS

### Characteristics of Studies Identified in the Literature Search

A total of 555 articles met the formal inclusion criteria: 54 relevant meta-analyses,[6-30,31-45,46-59] 12 reports of 11

**TABLE 1.** Summary of All Recommendations

| Recommendation |
|---|
| *General Note.* The following recommendations (strong or conditional/weak) and terminology [see the Data Supplement] represent reasonable options for patients depending on clinical circumstances and in the context of individual patient preferences. Recommended care should be accessible to patients whenever possible |
| 1. Outside of a clinical trial, ctDNA testing should only be offered if the results of testing could be applied to clinical decision making. ctDNA testing to determine *eligibility* for participation in a clinical trial is reasonable and appropriate. (Good Practice Statement) |
| 2. ctDNA testing for tumor genetic alterations may be used as first assessment, replacement, or as additional testing to tissue-based testing in situations where<br>• Tissue testing is challenging, unfeasible, or tumor tissue biopsy represents unacceptable risks to the patient<br>• Tissue testing results may not be available within a clinically actionable time frame to determine appropriate management options<br>• A drug's regulatory approved indication allows for or requires ctDNA testing<br>If ctDNA testing results are negative, inconclusive, or inconsistent with the clinical scenario, tissue-based confirmation should be sought. See clinical interpretation for example situations of each bullet point. (Evidence quality: Moderate; Strength of recommendation: Conditional) |
| 3. Other than testing for tumor genetic alterations (Recommendation 2), ctDNA testing may be offered together with standard-of-care testing and procedures if<br>• A specific, evidence-based action can be taken with the results<br>• There is conflict or ambiguity with standard-of-care assessment that may be resolved by ctDNA testing. (Evidence quality: Low; Strength of recommendation: Conditional) |
| *Qualifying Statements for Recommendation 3*<br>• Evidence on the clinical utility of ctDNA testing is evolving rapidly and the relevance of this evidence is often tied closely to the specifics of the patient's cancer (eg, type of cancer, stage, etc). At the time of this guideline, there were few instances where the panel identified evidence of clinical utility, which are discussed in the text. The panel presents this recommendation to support the use of this testing when clear evidence of clinical utility is available and to discourage its use outside of clinical trials when this evidence is not available<br>• While there is a large volume of evidence showing a correlation between ctDNA findings and prognosis, there is very limited evidence around what, if any, action should be taken in response to those results<br>• Evidence-based recommendations around using ctDNA findings (outside of genetic alterations) for treatment selection cannot be made in a broad, non–disease-specific guideline. The panel's intention is to form a foundation that future ASCO guideline panels may use to make future recommendations |
| 4. ctDNA testing is not recommended as a replacement for any other form of testing, except as noted in Recommendations 2 and 3. (Evidence quality: Low; Strength of recommendation: Strong) |
| *Qualifying Statements for Recommendation 4*<br>• Per the Testing Role Framework (Appendix Table A3), "replacement" would mean using ctDNA instead of whatever the previous standard-of-care testing might be (eg, MRI, ultrasound, tumor biopsy, etc). At this time, there is no evidence of clinical utility in any situation where ctDNA testing can completely replace another form of testing<br>• As noted in Recommendation 3, evidence is evolving rapidly. Future disease-specific guidelines on diagnosis, treatment selection, response monitoring, and other topics will need to address ctDNA testing in detail as new evidence becomes available |
| 5. Fractional, percentage, or concentration-based measures of ctDNA or total cfDNA concentration are not recommended as a surrogate measure of disease burden to make treatment decisions outside the context of a clinical trial or clinical research. (Evidence quality: Low; Strength of recommendation: Strong) |

NOTE. The strength of the recommendation is defined as follows: Strong: In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects. In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects. All or almost all informed people would make the recommended choice for or against an intervention. Conditional: In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists. In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists. Most informed people would choose the recommended course of action, but a substantial number would not.
Abbreviations: ctDNA, circulating tumor DNA; cfDNA, cell-free DNA; MRI, magnetic resonance imaging.



randomized controlled trials,[60-71] and 489 other articles were identified that met the search criteria. Because of the large volume of articles that were identified, a full quality assessment of each study and full extraction of relevant data was not feasible. Therefore, the evidence base for this guideline consists of the 54 meta-analyses; the 11 randomized trials; five reports of comparative prospective studies of clinical utility[72-76]; and 10 additional reports of noncomparative studies[77-86] that provided information relevant to the guideline recommendations. The full citation list of all the other studies that met the formal inclusion criteria can be found in the Data Supplement (online only; Table 1).

## Evidence Quality Assessment

All the included meta-analyses used reasonable search methods and meta-analytic techniques and were considered well conducted and at low risk of bias based on their methods. However, the studies included in each meta-analysis varied widely in size and quality, and type of ctDNA or cfDNA analysis method. Given this heterogeneity, the Panel did not conduct a formal assessment of the quality of each included meta-analysis and its studies, and the evidence quality underlying each recommendation was rated informally with a default rating of low quality.

One issue of concern in interpretation of the evidence is the likelihood that when several meta-analyses have been published on the same topic, there is substantial overlap in the included studies. Therefore, the raw number of meta-analyses cannot be taken as a measure of the volume and certainty of underlying evidence. Because the meta-analyses rarely overlapped completely (due to differences in selection criteria, search window, etc), the Expert Panel has chosen to

present all the relevant meta-analyses instead of only on the most recent and/or the analysis with the most included studies or patients.

## RECOMMENDATIONS

All recommendations are available in Table 1.

### Summary of Literature

#### *Randomized Trials*

Twelve reports of 11 randomized trials[60,64-71] were identified. While some of the other identified studies were reports from randomized studies (eg, post hoc secondary analyses), these 11 trials all included ctDNA testing in some fashion for decision making, such as selecting therapy. The trial by Montagut et al (2018)[68] was conducted with Sym004, a novel mixture of antibodies directed against distinct epitopes on the extracellular domain of EGFR (epidermal growth factor receptor), which was not found to have any benefit and is not in clinical use and therefore is not discussed further.

#### *Lung Cancer*

The EORTC 1613 APPLE trial randomly assigned patients with advanced non–small cell lung cancer (NSCLC) to two relevant arms: gefitinib upfront with switch to osimertinib based on standard criteria for progression (51 patients), and gefitinib upfront with switch to osimertinib based on ctDNA monitoring for plasma *EGFR p.*T790M or standard criteria for progression (52 patients). In a comparison of the two arms, no difference in the primary end point, progression-free survival (PFS) at 18 months, was found.

The trial by Yang et al (2023)[60] randomly assigned 180 patients with suspected advanced NSCLC to either an arm where their clinician received results from ctDNA molecular profiling as soon as possible or an arm where the results were received with the results of tissue genotyping. Time to initiation of systemic treatment, the primary end point, was significantly shorter when ctDNA testing results were provided earlier (mean 20 days *v* 28 days, $P = .0079$). No significant difference in PFS was observed (11.1 months *v* 12.53 months, $P = .293$).

The LIBELULE trial[65] randomly assigned 319 patients with suspected advanced lung cancer to either a control arm where standard diagnostic procedures were performed or a liquid biopsy arm. Time to treatment initiation, the primary end point, did not differ significantly between the arms (mean 29.0 days on liquid biopsy *v* 34 days on control, $P = .264$). PFS did not differ significantly between the arms.

#### *Colorectal Cancer*

The DYNAMIC trial[64] randomly assigned patients with resected stage II colon cancer to either a ctDNA testing criteria to provide chemotherapy (302 patients) or standard clinicopathologic criteria for chemotherapy (153 patients). This trial found the primary end point, recurrence-free survival (RFS) at 2 years, to be noninferior with ctDNA-based decision making compared to standard decision making (2-year RFS, 93.5% *v* 92.4%; absolute difference, 1.1% [95% CI, −4.1% to 6.2%]). It also significantly reduced the proportion of patients receiving chemotherapy (15% *v* 28%; relative risk, 1.82 [95% CI, 1.25 to 2.65]). In the 5-year updated analysis,[63] there was no significant difference in OS (hazard ratio [HR], 1.05 [95% CI, 0.47 to 2.37]).

The DYNAMIC-III trial[62] randomly assigned 1,002 patients with resected stage III colorectal cancer to either ctDNA-guided therapy or standard management. On the ctDNA-guided arm, patients who were ctDNA-positive received escalated chemotherapy, while those who were ctDNA-negative received de-escalated therapy. Among ctDNA-negative patients, de-escalated therapy was not confirmed as noninferior to standard therapy (3-year RFS, 85.3% *v* 88.1%; absolute difference, −2.8%; 97.5% lower CI, −8.0%). Among ctDNA-positive patients, escalated therapy was not significantly different from standard management (RFS HR, 1.16 [95% CI, 0.87 to 1.53]).

The PARERE trial[69] included patients with metastatic colorectal cancer who had responded to or experienced stable disease on previous first-line anti-EGFR therapy and had one line of non–anti-EGFR therapy afterward. These 213 patients were also found to have *RAS* and *BRAF* wild-type disease with ctDNA testing. They were randomly assigned to either panitumumab followed by regorafenib or regorafenib followed by panitumumab. Neither OS (HR, 1.13 [95% CI, 0.90 to 1.41]), the primary outcome, nor PFS (HR, 1.26 [95% CI, 0.95 to 1.66]) significantly differed between the arms.

#### *Breast Cancer*

The PADA-1 trial[71] included 279 patients with advanced breast cancer who were receiving first-line aromatase inhibitor plus palbociclib therapy. The baseline *ESR1* ctDNA mutation level was measured for each patient. When these patients had newly detected or rising levels of *ESR1* mutation on ctDNA testing versus baseline, they were randomly assigned to either continue on the same therapy or switch to fulvestrant plus palbociclib. One hundred seventy-two patients were ultimately randomly assigned. Patients allocated to switch to fulvestrant had better PFS (HR, 0.61 [95% CI, 0.43 to 0.86]), with similar rates of toxicity after the switch.

The SERENA-6 trial[70] conducted ctDNA testing every 2-3 months for *ESR1* mutation on 3,256 patients with advanced breast cancer with estrogen receptor–positive, human epidermal growth factor receptor 2–negative tumors who received at least 6 months of aromatase inhibitor plus a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor. The 315 patients who tested positive were then randomly assigned to either camizestrant and placebo in place of aromatase

inhibitor, or continue with aromatase inhibitor with placebo in place of camizestrant. All patients continued to receive a CDK4/6 inhibitor. PFS, the primary outcome, was significantly longer with camizestrant versus aromatase inhibitor (HR, 0.44 [95% CI, 0.31 to 0.60]).

The c-TRAK TN trial[61] randomly assigned patients with early-stage high-risk triple-negative breast cancer who were ctDNA-positive to pembrolizumab or observation. Due to a combination of factors, including the COVID-19 pandemic, only 40 patients were randomly assigned and only five patients commenced therapy with pembrolizumab.

### *Bladder Cancer*

The IMvigor011 trial[67] included 761 patients with muscle-invasive bladder cancer who were considered disease-free after surgery on radiographic assessment. Patients received MRD ctDNA testing every 6 weeks for 1 year. The 379 patients with positive tests were then randomly assigned to either atezolizumab or placebo. Both disease-free survival (DFS; HR, 0.64 [95% CI, 0.47 to 0.87]), the primary outcome, and OS (HR, 0.59 [95% CI, 0.39 to 0.90]) were significantly improved with atezolizumab therapy.

### *Detection of Actionable and/or Specific Tumor Genetic Alterations*

In the Merker 2018 review, while evidence of clinical validity of ctDNA testing for tumor genotyping was identified, very limited evidence of clinical utility was found. The reviewers concluded that, at least in the case of *EGFR* testing, a positive ctDNA test was conclusive, but a negative test would need tissue confirmation. Otherwise, they concluded that the available evidence showed a "discordance in results between ctDNA assays and tumor tissue genotyping and supports value of tumor tissue genotyping to confirm undetected ctDNA findings." The review found no evidence of clinical utility for the use of ctDNA in monitoring therapy effectiveness.

The new review identified 16 meta-analyses[9,11,23,28,29,32,33,35,36,40,42,45,47,48,55,57] of ctDNA testing for the identification of specific pathogenic variants, described in Table 2. Four of the meta-analyses were in colorectal cancer, 13 in lung cancer, and one in neuroblastoma. The colorectal meta-analyses all reported on the identification of *KRAS* pathogenic variants. One meta-analysis by Ye et al (2021)[48] found that digital droplet polymerase chain reaction (PCR) and beads, emulsions, amplification, and magnetics (BEAM) were associated with generally better sensitivity (>80%) than next-generation sequencing (NGS; 65%) with similar specificity for *KRAS* pathogenic variant identification. However, the sensitivity of ctDNA testing primarily by PCR testing to identify *KRAS* pathogenic variants was estimated to be <70% in the other two analyses. The NSCLC meta-analyses primarily addressed identification of *EGFR* pathogenic variants. Sensitivity was estimated at 60% to 70% in most of the analyses, with specificity generally >90%. Three of the NSCLC meta-analyses also reported on other pathogenic variants.[9,11,35]

In addition to the meta-analyses of pathogenic variant detection, 118 articles were identified that reported on studies of ctDNA used in the detection of specific pathogenic variants; their references can be found in the Data Supplement. The reported studies primarily used ctDNA for the detection of *EGFR*, *KRAS*, and *BRAF* pathogenic variants, but other variants were also addressed. These articles are mentioned in the clinical interpretation section when relevant.

### *Diagnosis of Cancer*

Twelve meta-analyses[8,11,12,24,25,38,46,51–53,58,59] of ctDNA testing for cancer diagnosis were identified in the new review and are described in Table 3. The sensitivity and specificity of ctDNA testing for diagnosis ranged from 54% to 89% and 70% to 90%, respectively. Substantial statistical heterogeneity was reported, as well as heterogeneity in testing method and source of sample (plasma or serum).

Twenty-six additional articles reported on studies of ctDNA testing as part of diagnosis were identified; the Data Supplement lists the articles' references. These articles are mentioned in the clinical interpretation section where relevant.

## Selection of Treatment

### *New Evidence on Treatment Selection*

Three meta-analyses[26,41,43] addressed the use of ctDNA testing to help select treatment. These meta-analyses are described in Table 4.

Forty articles were identified that reported on studies relevant to the use of ctDNA for treatment selection but not addressing specific pathogenic variant detection; the references are available in the Data Supplement.

Several of the nonrandomized studies warrant further details. ACCELERATE[73] was a nonrandomized controlled trial that compared the time to treatment initiation in a cohort of 90 patients with suspected advanced lung cancer receiving ctDNA molecular profiling versus a control cohort of 89 similar patients receiving only tissue-based molecular profiling. The median time to treatment was significantly shorted in the ctDNA testing versus control cohorts (39 days *v* 62 days, $P < .001$).

The study by Rathor et al (2024)[76] conducted ctDNA testing for *EGFR* alterations in 236 patients with advanced NSCLC. In patients with positive results, treatment was initiated without tissue-based confirmation. In patients with negative results, tissue-based testing was sought, and then

**TABLE 2.** Meta-Analyses of Studies of Circulating Tumor DNA Testing to Detect Specific Pathogenic Variants

| Analysis | Patient Population and Context | Purpose of Testing | Testing Methods | No. of Studies<br>No. of Patients[a] | Outcomes |
|---|---|---|---|---|---|
| Hao et al, 2017[23] | Colorectal cancer | Detection of *KRAS* pathogenic variants | Primarily PCR using multiple methods | 21 studies<br>Patients NR | Sens 67% (95% CI, 55% to 78%)<br>Spec 96% (95% CI, 93% to 98%)<br>$I^2$ = 96.27%, chi$^2$ $P$ < .001 |
| Tang et al, 2017[40] | Colorectal cancer | Detection of *KRAS* pathogenic variants | Primarily PCR using multiple methods | 23 studies<br>1,715 patients | Sens 75% (95% CI, 66% to 82%, $I^2$ = 83.26%)<br>Spec 98% (95% CI, 95% to 99%, $I^2$ = 81.03%) |
| Xie et al, 2019[47] | Colorectal cancer | Detection of *KRAS* pathogenic variants | Primarily PCR using multiple methods | 31 studies<br>2,565 patients | Sens 67% (95% CI, 56% to 76%, $I^2$ = 88.48%)<br>Spec 96% (95% CI, 94% to 98%, $I^2$ = 77.51%) |
| Ye et al, 2021[48] | Colorectal cancer | Detection of *KRAS* variants | Digital droplet PCR, BEAM, NGS, ARMS | 33 studies<br>Patients NR | Digital PCR<br>Sens 81% (95% CI, 78% to 85%)<br>Spec 85% (95% CI, 83% to 88%)<br>NGS<br>Sens 65% (95% CI, 59% to 71%)<br>Spec 88% (95% CI, 85% to 91%)<br>BEAM<br>Sens 87% (95% CI, 83% to 90%)<br>Spec 90% (95% CI, 85% to 93%)<br>$I^2$ NR |
| Chen et al, 2020[11] | NSCLC | Detection of *KRAS* pathogenic variants | Multiple methods | 6 studies<br>Patients NR | Sens 62.8% (95% CI, 24.4% to 91.9%)<br>Spec 95.9% (95% CI, 93.2% to 99.8%)<br>$I^2$ NR |
| Li et al, 2020[28] | NSCLC | Detection of *EGFR* variants, overall | Digital droplet PCR or ARMS-PCR | 25 studies<br>4,881 patients (overall) | Digital droplet PCR<br>Sens 72.1% (95% CI, 68.2% to 75.7%, $I^2$ = 58%)<br>Spec 95.6% (95% CI, 93.5% to 97.1%, $I^2$ = 53.5%)<br>ARMS-PCR<br>Sens 65.3% (95% CI, 62.9% to 67.6%, $I^2$ = 63.5%)<br>Spec 98.2% (95% CI, 97.6% to 98.7%, $I^2$ = 65.9%) |
| | | Detection of *EGFR* exon 19 deletion | | | Digital droplet PCR<br>Sens 72.9% (95% CI, 67.2% to 78.2%, $I^2$ = 46.0%)<br>Spec 99.1% (95% CI, 98.2% to 99.7%, $I^2$ = 18.0%)<br>ARMS-PCR<br>Sens 66.3% (95% CI, 60.9% to 71.3%, $I^2$ = 44.3%)<br>Spec 99.3% (95% CI, 98.6% to 99.7%, $I^2$ = 68.9%) |
| | | Detection of *EGFR* L858R pathogenic variant | | | Digital droplet PCR<br>Sens 69.7% (95% CI, 63.3% to 75.5%, $I^2$ = 45.6%)<br>Spec 98.2% (95% CI, 97.0% to 99.0%, $I^2$ = 31.3%)<br>ARMS-PCR<br>Sens 61.6% (95% CI, 54.9% to 68.0%, $I^2$ = 51.1%)<br>Spec 99.3% (95% CI, 98.7% to 99.7%, $I^2$ = 33.8%) |
| Wang et al, 2021[45] | NSCLC | Detection of *EGFR* pathogenic variants | Multiple methods | 40 studies<br>5,995 patients | Sens 68% (95% CI, 60% to 75%, $I^2$ = 85.56%)<br>Spec 96% (95% CI, 95% to 99%, $I^2$ = 90.58%) |
| Chen et al, 2020[11] | NSCLC | Detection of *EGFR* pathogenic variants | Multiple methods | 37 studies<br>Patients NR | Sens 78.0% (95% CI, 71.1% to 85.3%)<br>Spec 96.2% (95% CI, 94.2% to 98.4%)<br>$I^2$ NR |

(continued on following page)

**TABLE 2.** Meta-Analyses of Studies of Circulating Tumor DNA Testing to Detect Specific Pathogenic Variants (continued)

| Analysis | Patient Population and Context | Purpose of Testing | Testing Methods | No. of Studies<br>No. of Patients[a] | Outcomes |
|---|---|---|---|---|---|
| Zhou et al, 2020[57] | NSCLC | Detection of *EGFR* pathogenic variants | Primarily PCR using multiple methods | 32 studies<br>4,527 patients | Sens 70% (95% CI, 63% to 75%, $I^2$ = 81.76%)<br>Spec 98% (95% CI, 96% to 99%, $I^2$ = 88.33%) |
| Passiglia et al, 2018[36] | Advanced NSCLC with disease progression on EGFR-TKI | Detection of *EGFR-T790M* pathogenic variant | Multiple methods | 19 studies<br>1,639 patients | Overall<br>Sens 67% (95% CI, 64% to 70%, $I^2$ = 61.9%)<br>Spec 80% (95% CI, 77% to 83%, $I^2$ = 83.2%)<br>RT-PCR<br>Sens 61% (95% CI, 57% to 65%, $I^2$ = 31.5%)<br>Spec 82% (95% CI, 77% to 87%, $I^2$ = 83.5%)<br>dPCR<br>Sens 72% (95% CI, 68% to 76%, $I^2$ = 28.8%)<br>Spec 73% (95% CI, 67% to 79%, $I^2$ = 84.1%)<br>NGS<br>Sens 87% (95% CI, 76% to 95%, $I^2$ = 59.3%)<br>Spec 89% (95% CI, 82% to 94%, $I^2$ = 64.5%) |
| Zhang et al, 2018[55] | Primarily NSCLC, but some adenocarcinoma | Detection of *EGFR-T790M* pathogenic variant | Digital droplet PCR | 11 studies<br>872 patients | Sens 70% (95% CI, 63% to 77%, $I^2$ = 35.8%)<br>Spec 87% (95% CI, 81% to 92%, $I^2$ = 48.9%) |
| Liao et al, 2020[29] | Primarily NSCLC (some adenocarcinoma) | Detection of *EGFR T790M* pathogenic variants | Digital droplet PCR | 15 studies (3 in adenocarcinoma)<br>1,139 patients | Sens 68% (95% CI, 61% to 75%, $I^2$ = 35.51%)<br>Spec 85% (95% CI, 75% to 91%, $I^2$ = 58.47%) |
| Lyu et al, 2019[32] | Lung cancer | Detection of multiple pathogenic variants | Multiple methods | 42 studies overall<br>Patients NR | *EGFR* overall<br>Sens 67.1% (95% CI, 64.7% to 69.5%)<br>Spec 96.1% (95% CI, 95.4% to 96.8%)<br>$I^2$ NR<br>*EGFR* exon 19 deletion<br>Sens 79.0% (95% CI, 76.7% to 81.2%, $I^2$ = 91.5%)<br>Spec 95.8% (95% CI, 94.8% to 96.7%, $I^2$ = 93.1%)<br>*EGFR L858R*<br>Sens 76.7% (95% CI, 73.1% to 80.0%, $I^2$ = 70.2%)<br>Spec 97.2% (95% CI, 96.4% to 97.9%, $I^2$ = 70.9%)<br>*EGFR T790M*<br>Sens 61.2% (95% CI, 57.0% to 65.4%, $I^2$ = 41.3%)<br>Spec 92.7% (95% CI, 90.9% to 94.3%, $I^2$ = 86.7%)<br>*KRAS*<br>Sens 65.1% (95% CI, 55.8% to 73.6%)<br>Spec 95.5% (95% CI, 93.2% to 97.2%)<br>$I^2$ NR<br>*BRAF*<br>Sens 31.3% (95% CI, 14.1% to 53.2%)<br>Spec 99.5% (95% CI, 97.8% to 100%)<br>$I^2$ NR |
| Chen et al, 2024[9] | NSCLC | Detection of pathogenic variants | Multiple methods | *EGFR*: 14 studies; 2,047 samples<br>*KRAS*: 11 studies; 1,067 samples<br>*BRAF*: 8 studies; 920 samples<br>*ALK*: 6 studies; 889 samples<br>*ROS1*: 4 studies; 631 samples<br>*MET*: 5 studies; 927 samples<br>*RET*: 3 studies; 478 samples | *EGFR*: Sens 68%; spec 98%<br>*KRAS*: Sens 77%; spec 96%<br>*BRAF*: Sens 60%; spec 99%<br>*ALK*: Sens 59%; spec 99%<br>*ROS1*: Sens 29%; spec 99%<br>*MET*: Sens 47%; spec 98%<br>*RET*: Sens 38%; spec 99% |

(continued on following page)

**TABLE 2.** Meta-Analyses of Studies of Circulating Tumor DNA Testing to Detect Specific Pathogenic Variants (continued)

| Analysis | Patient Population and Context | Purpose of Testing | Testing Methods | No. of Studies<br>No. of Patients[a] | Outcomes |
|---|---|---|---|---|---|
| Palmieri et al, 2022[35] | NSCLC | Detection of *KRAS* pathogenic variants | Multiple methods<br>Urine was tested in 1 study | 40 studies<br>2,805 patients | Sens 71% (95% CI, 68% to 74%, $I^2$ = 65.7%, chi$^2$ $P$ < .0001)<br>Spec 93% (95% CI, 92% to 94%, $I^2$ = 92.3%, chi$^2$ $P$ < .0001) |
| Mao et al, 2017[33] | NSCLC | Detection of *EGFR* pathogenic variants | Primarily PCR using multiple methods | 15 studies<br>2,094 patients | Sens 69% (95% CI, 59% to 78%, $I^2$ = 86.53%)<br>Spec 97% (95% CI, 94% to 99%, $I^2$ = 83.61%) |
| Trigg et al, 2020[42] | Neuroblastoma | Determination of *MYCN* amplification status | PCR, specifics not reported | 7 studies<br>529 patients | Sens 90.8% (95% CI, 81.8% to 95.6%)<br>Spec 97.6% (95% CI, 94.0% to 99.1%)<br>$I^2$ NR |

Abbreviations: ARMS, amplification-refractory mutation system; BEAM, beads, emulsions, amplification, and magnetics; NGS, next-generation sequencing; NR, not reported; NSCLC, non–small cell lung cancer; PCR, polymerase chain reaction; RT, reverse transcription; Sens, sensitivity; Spec, specificity; TKI, tyrosine kinase inhibitor.
[a]This is the total studies and total patients included in the paper. Individual analyses may include fewer studies and patients.

**TABLE 3.** Meta-Analyses of Studies of Circulating Tumor DNA Testing During Cancer Diagnosis

| Analysis | Patient Population and Context | Testing Methods | No. of Studies<br>No. of Patients[a] | Outcomes |
|---|---|---|---|---|
| Singh et al, 2022[38] | Biliary tract cancer | Testing methods not reported | 8 studies<br>Patients NR | Sens 89% (95% CI, 87% to 92%)<br>Spec 94% (95% CI, 91% to 96%)<br>$I^2$ NR |
| Cao et al, 2019[8] | Bladder cancer | Primarily PCR, details not reported | 11 studies<br>1,454 patients | For blood test<br>Sens 69% (95% CI, 65% to 72%, $I^2$ = 96.5%)<br>Spec 77% (95% CI, 73% to 81%, $I^2$ = 94.8%)<br>For urine test<br>Sens 69% (95% CI, 66% to 71%, $I^2$ = 84.6%)<br>Spec 70% (95% CI, 68% to 72%, $I^2$ = 93.9%) |
| Wang et al, 2018[46] | Colorectal cancer | Primarily PCR | 14 studies<br>1,258 patients | Sens 74% (95% CI, 71% to 76%, $I^2$ = 88.6%)<br>Spec 92% (95% CI, 90% to 93%, $I^2$ = 82.8%) |
| Zhu et al, 2020[58] | Colorectal cancer | Not reported in detail, but including cell-free DNA level, DNA integrity, and DNA methylation | 51 studies<br>Patients NR | Overall sens 76% (95% CI, 75% to 77%)<br>Overall spec 88% (95% CI, 87% to 89%)<br>$I^2$ NR |
| Chidambaram et al, 2022[12] | Esophageal cancer | Primarily NGS | 4 studies<br>453 patients | Sens 71% (95% CI, 56% to 83%)<br>Spec 99% (95% CI, 34% to 100%)<br>$I^2$ NR |
| Kang et al, 2020[25] | Glioma | Primarily methylation-specific PCR for *MGMT* pathogenic variants, although also *IDH* and *TERT*<br>Includes CSF testing | 11 studies<br>552 patients | Sens 69% (95% CI, 66% to 73%, $I^2$ = 73.1%)<br>Spec 98% (95% CI, 96% to 99%, $I^2$ = 0.0%) |
| Yinzhong et al, 2023[51] | Hepatocellular carcinoma | Multiple methods | PCR: 7 studies, 1,571 patients<br>NGS: 4 studies, 256 patients | PCR - $I^2$ NR<br>Sens 85% (95% CI, 77% to 91%)<br>Spec 87% (95% CI, 77% to 94%)<br>NGS - $I^2$ NR<br>Sens 77% (95% CI, 62% to 89%)<br>Spec 92% (95% CI, 87% to 96%) |
| Zhang et al, 2021[53] | Hepatocellular carcinoma | Multiple methods | 38 articles[b]<br>2,527 patients | Sens 54% (95% CI, 47% to 61%, $I^2$ = 95.31%)<br>Spec 90% (95% CI, 86% to 92%, $I^2$ = 95.68%) |
| Zhang et al, 2022[52] | Melanoma | Primarily PCR for *BRAF* pathogenic variants, details not reported | 10 studies<br>1,430 patients | Sens 73% (95% CI, 70% to 75%, $I^2$ = 89.1%)<br>Spec 94% (95% CI, 91% to 96%, $I^2$ = 33.7%) |
| Chen et al, 2020[11] | NSCLC | Multiple methods | 13 studies<br>Patients NR | Sens 80% (95% CI, 72% to 87%)<br>Spec 81% (95% CI, 68% to 91%)<br>$I^2$ NR |
| Zhu et al, 2020[59] | Pancreatic cancer | PCR, details not reported | 7 studies<br>507 patients | Sens 64% (95% CI, 58% to 70%, $I^2$ = 91.7%)<br>Spec 92% (95% CI, 88% to 95%, $I^2$ = 0.0%) |
| Hou et al, 2023[24] | Thyroid cancer | Primarily PCR using multiple methods | 14 studies<br>622 patients | Sens 76% (95% CI, 62% to 85%, $I^2$ = 90.69%)<br>Spec 87% (95% CI, 78% to 93%, $I^2$ = 91.75%) |

Abbreviations: HR, hazard ratio; NGS, next-generation sequencing; NR, not reported; NSCLC, non–small cell lung cancer; PCR, polymerase chain reaction; Sens, sensitivity; Spec, specificity.
[a]This is the total studies and total patients included in the paper. Individual analyses may include fewer studies and patients.
[b]This analysis seems to have treated each variation in assay and threshold as a separate "study" within a particular article for the purpose of meta-analysis, and therefore reports 72 studies.

**TABLE 4.** Meta-Analyses of Studies of ctDNA Testing for Treatment Selection

| Analysis | Patient Population and Context | Purpose of Testing | Testing Methods | No. of Studies<br>No. of Patients[a] | Outcomes |
|---|---|---|---|---|---|
| Vlachou et al, 2021[43] | Metastatic colorectal cancer with *RAS* wild-type before anti-EGFR therapy | Decide whether anti-EGFR rechallenge is appropriate | Multiple methods not stated<br>All patients received ctDNA testing before anti-EGFR rechallenge | 4 studies<br>117 patients | RAS *wild-type v* RAS *mutation after initial anti-EGFR therapy*<br>PFS HR, 0.40 (95% CI, 0.22 to 0.70, $I^2$ = 0%)<br>OS HR, 0.37 (95% CI, 0.16 to 0.85, $I^2$ = 74%)<br>HR <1 indicates more benefit after anti-EGFR rechallenge |
| Kok et al, 2021[26] | Advanced lung cancer | Select between EGFR-TKI–based therapy or chemotherapy | Multiple methods | 6 studies (all RCT)<br>628 patients randomly assigned to EGFR-TKI–based therapy; 430 assigned to chemotherapy | *PFS*<br>In ctDNA+ patients: HR, 0.28 (95% CI, 0.22 to 0.36)<br>In ctDNA– patients: HR, 0.37 (95% CI, 0.28 to 0.49)<br>$I^2$ = 53.7%<br>*OS*<br>In ctDNA+ patients: HR, 0.84 (95% CI, 0.69 to 1.02)<br>In ctDNA– patients: HR, 0.77 (95% CI, 0.59 to 1.00)<br>$I^2$ = 0%<br>HR <1 indicates benefit of EGFR-TKI therapy *v* control |
| Tolmeijer et al, 2020[41] | Castration-resistant prostate cancer | Select between ARSI-based therapy or taxane-based therapy | Detection of *AR* copy gain primarily by digital droplet PCR | 23 patient cohorts[b]<br>1,249 patients treated with ARSIs<br>424 patients treated with taxane chemotherapy | *Receiving ARSI*<br>PFS HR, 2.33 (95% CI, 2.00 to 2.72, $I^2$ = 0%)<br>OS HR, 3.82 (95% CI, 3.11 to 4.70, $I^2$ = 0%)<br>*Receiving taxane*<br>PFS HR, 1.41 (95% CI, 0.88 to 2.27, $I^2$ = 72%)<br>OS HR, 1.76 (95% CI, 1.13 to 2.72, $I^2$ = 54%)<br>HR >1 indicates less benefit in patients with *AR* copy-number gain |

Abbreviations: ARSI, androgen receptor signaling inhibitors; ctDNA, circulating tumor DNA; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; TKI, tyrosine kinase inhibitor.

[a]This is the total studies and total patients included in the paper. Individual analyses may include fewer studies and patients.

[b]The included studies often had overlapping patient populations; the meta-analysis authors attempted to distinguish these cohorts to minimize the potential of a patient appearing more than once in the analysis.

appropriate treatment was initiated. The turnaround from the time the patient was first seen in the clinic to the time *EGFR*-positive status was known was significantly shorter in those whose tumors were ctDNA-positive (3 days *v* 12 days, $P < .05$). PFS was similar between patients who were treated solely based on ctDNA results versus those who were treated after tissue results (11.5 months *v* 11.9 months).

The study by Dong et al (2024)[72] was a nonrandomized controlled trial in 60 patients with advanced NSCLC who were considered to have complete remission after receiving local consolidative treatment and tyrosine kinase inhibitor (TKI) therapy. TKI therapy was discontinued, and then ctDNA testing and other surveillance was conducted every 3 months. Treatment was restarted if ctDNA or carcinoembryonic antigen (CEA) results were positive, or if progressive disease was identified. Patients were analyzed in three groups: those with no evidence of progressive disease (Group A), those in whom ctDNA or CEA results preceded identifiable progressive disease (Group B), and those who had progressive disease (Group C). Median PFS differed markedly between the groups: A, not reached; B, 20.2 months; and C, 5.5 months.

### *Measurement of Treatment Response*

Two meta-analyses[6,7] were identified that looked at using ctDNA to measure treatment response, one in patients with advanced solid tumors receiving immune checkpoint inhibitor (ICI) therapy and one in metastatic colorectal cancer; they are described in Appendix Table A4. The presence of ctDNA was associated with worse outcomes in both analyses.

104 studies were identified that investigated the use of ctDNA to measure treatment response. These references are included in the Data Supplement. These studies generally reported OS and/or event (eg, progression, recurrence, disease)-free survival in patients with ctDNA presence at some time point before, during, or after therapy with those with less or no ctDNA presence.

### *Detection of Relapse, Recurrence, or Progression*

Three meta-analyses[12,19,34] were identified and are detailed in Table 5. All reported on the association between ctDNA and recurrence. Gögenur et al (2022)[19] and Mi et al (2022)[34] reported a greater relative risk of recurrence in patients with detected ctDNA versus those without in patients receiving neoadjuvant therapy and those with operable colon cancer, respectively. Chidambaram et al (2022)[12] found low sensitivity (49%) and high specificity (96%) for the use of ctDNA to detect recurrence in patients with esophageal cancer.

An additional nine identified articles were classified as relevant to ctDNA in monitoring relapse or recurrence; their references are provided in the Data Supplement. They included patients with breast cancer, colorectal cancer, bladder cancer, and uveal melanoma. These articles generally found a correlation between ctDNA testing and the risk of, presence of, and/or severity of relapse or recurrence.

### *Detection of Residual Disease*

Two meta-analyses[16,22] were identified. Faulkner et al (2023)[16] reported substantially worse PFS and OS in patients with colorectal cancer and ctDNA detection. Guo et al (2022)[22] reported low sensitivity (58%) and high specificity (93%) for ctDNA testing to detect residual disease in patients with localized NSCLC.

**TABLE 5.** Meta-Analyses of Studies of ctDNA Testing for Surveillance and/or Monitoring for Recurrence, Relapse, and/or Progression

| Analysis | Patient Population and Context | Purpose of Testing | Testing Methods | No. of Studies No. of Patients[a] | Outcomes |
|---|---|---|---|---|---|
| Gögenur et al, 2022[19] | Patients who have received neoadjuvant therapy (primarily rectal cancer, but including breast, gastric, and bladder cancers) | Surveillance for recurrence | Digital droplet PCR or NGS | 10 studies 727 patients | ctDNA at baseline: RR, 2.86 (95% CI, 1.33 to 6.14, $I^2$ = 33%)<br>ctDNA during treatment: RR, 3.81 (95% CI, 2.09 to 6.92, $I^2$ = 0%)<br>ctDNA after treatment: RR, 4.29 (95% CI, 2.79 to 6.60, $I^2$ = 50%)<br>ctDNA after surgery: RR, 8.03 (95% CI, 3.16 to 20.43, $I^2$ = 65%) |
| Mi et al, 2022[34] | Operable colorectal cancer | Recurrence | ddPCR or NGS | 14 studies 2,393 patients | RR of recurrence, ctDNA+ *v* ctDNA−: 4.43 (95% CI, 3.58 to 5.48, $I^2$ = 24.9%) |
| Chidambaram et al, 2022[12] | Esophageal cancer | Recurrence detection | Primarily NGS | 4 studies 381 patients | Sens 49% (95% CI, 29% to 69%)<br>Spec 96% (95% CI, 91% to 98%)<br>$I^2$ NR |

Abbreviations: ctDNA, circulating tumor DNA; NGS, next-generation sequencing; NR, not reported; RR, relative risk; Sens, sensitivity; Spec, specificity.
[a]This is the total studies and total patients included in the paper. Individual analyses may include fewer studies and patients.

An additional 23 identified articles were classified as relevant to ctDNA for detection of residual disease: the references are included in the Data Supplement. Of these, one study warrants a detailed description. The GALAXY study[74,75] was a subset of the CIRCULATE-Japan study. In this study, 2,109 patients receiving adjuvant chemotherapy for stage II-IV colorectal cancer received personalized ctDNA testing within 2 to 10 weeks after surgery and before adjuvant therapy. The personalized assays were designed using whole-exome sequencing on formalin-fixed, paraffin-embedded tumor tissue samples with up to 16 patient-specific clonal, somatic single-nucleotide variants selected per study participant. Patients with positive ctDNA testing had substantial worse DFS than those with negative ctDNA testing (HR, 11.99 [95% CI, 10.02 to 14.35]). The remaining studies generally demonstrated a correlation between residual disease detected by ctDNA and outcome, including residual disease detected in urine, but the definitions of what counted as residual disease and the testing methods and time points used varied widely.

Studies of ctDNA to detect residual disease were not easily classified according to the panel's original research questions. An example of this is the DYNAMIC trial[74] discussed in the randomized trial section. The panel considered all studies potentially relevant to this topic, regardless of the classification made during the systematic review.

### *Prognosis*

Nineteen meta-analyses[10,11,13,15,17,18,20,21,27,30,31,34,37,39,44,49,50,54,56] were identified that addressed ctDNA testing to determine prognosis and are detailed in Table 6. All but one[54] found an association between ctDNA positivity and event-free survival (EFS) and/or OS, although the strength of the association varied based on cancer type, time point of ctDNA testing, and other factors.

An additional 174 articles were identified that evaluated ctDNA testing as a prognostic tool; the references are included in the Data Supplement. All the reported studies conducted initial or serial ctDNA testing, measured long-term outcomes (eg, OS and PFS), and evaluated the correlation between the ctDNA results and these outcomes. Given the large number of these articles identified across multiple cancers, their detailed results are not described. There was a consistent pattern that early ctDNA detection is a negative prognostic factor across many tumor types.

## CLINICAL INTERPRETATION

### Overall Interpretation

The Expert Panel believes that it is difficult to draw general recommendations across multiple cancer types from evidence that was collected in specific cancer types For example, the results of the DYNAMIC trial[64] could provide the basis for a specific recommendation for care for patients with stage II colon cancer, as could the results of the IMvigor011 trial[67] for muscle-invasive bladder cancer. However, such recommendations are far better made in the context of a disease-focused guideline, where the overall balance of benefit and harms for that specific population of patients can be assessed. The panel has tried to make recommendations that are broadly applicable across cancer types and avoided cancer-type specific recommendations, which are more appropriate in cancer type–specific guidelines. Potential use cases for ctDNA testing are described in this section but should not be considered formal recommendations.

### Good Practice Statement 1

The clinical validity of ctDNA testing has been demonstrated across many contexts and applications, but despite the large volume of evidence identified in this updated systematic review, prospective studies of the clinical utility of ctDNA testing is sparse. Good Practice Statement 1 makes clear that the Expert Panel believes that evidence of the clinical utility of ctDNA testing compared with some previous standard of care is important and necessary.

### Recommendation 2

The new systematic review identified a wide body of literature across multiple cancers that ctDNA testing has high specificity and moderate sensitivity for detecting specific genetic alterations and is generally in concordance with tissue-based testing. While any single study or meta-analysis is likely flawed and difficult to interpret, the panel concluded that the consistency of this evidence across many contexts and tumor types shows that this non-randomized evidence could be considered moderate certainty for the value of ctDNA testing for first assessment, replacement, or as additional testing for tissue-based testing. The specific contexts in which ctDNA testing is appropriate are:

- Tumor tissue testing is challenging, unfeasible, or tumor biopsy represents unacceptable risks to the patient. Clinical judgment is crucial in determining when tumor biopsy is too challenging to perform immediately, or is unfeasible, or presents a risk that is unacceptable to the clinician or the patient. A few examples can illustrate this point. In patients with lung cancer, sometimes the location of the tumor or the requirement for oxygen makes tissue biopsy dangerous. In pancreatic cancer, a biopsy may be associated with unacceptable risks due to the anatomical location and concerns about procedural complications. Biopsies of primary or metastatic brain tumors may be impossible. When a tumor is located near a major blood vessel, it might be too challenging or impossible to biopsy without a high risk for complications. A patient with a recent deep vein thrombosis and/or pulmonary embolism on anticoagulation therapy may not be able to undergo a tumor biopsy. Finally, sometimes it may not be feasible to assess specific genetic alterations with tumor biopsy. For

**TABLE 6.** Meta-Analyses of Studies of Circulating Tumor DNA Testing for Prognosis

| Analysis | Patient Population and Context | Testing Methods | No. of Studies<br>No. of Patients[a] | Outcomes NOTE: HR >1 Shows Worse Outcome With ctDNA Detection and/or Presence |
|---|---|---|---|---|
| Cullinane et al, 2020[13] | Breast cancer | PCR or NGS | 8 studies<br>739 patients | DFS HR, 4.44 (95% CI, 2.29 to 8.61, $I^2$ = 79%, Chi$^2$ $P$ = .001)<br>Only with pretreatment sampling: EFS HR, 3.30 (95% CI, 1.98 to 5.52, $I^2$ = 28%, Chi$^2$ $P$ = .24)<br>Only early-stage: EFS HR, 8.32 (95% CI, 3.01 to 22.99, $I^2$ = 28%, Chi$^2$ $P$ = .24)<br>Only late-stage: EFS HR, 1.91 (95% CI, 1.35 to 2.71, $I^2$ = 28%, Chi$^2$ $P$ = .25) |
| Tan et al, 2018[39] | Breast cancer | Primarily PCR | 10 studies<br>1,127 patients | OS HR, 2.41 (95% CI, 1.83 to 3.16, $I^2$ = 13.7%)<br>DFS or RFS HR, 2.73 (95% CI, 2.04 to 3.67, $I^2$ = 0%) |
| Guo et al, 2024[21] | Breast cancer | Not reported | At baseline: 6 studies; 401 patients<br>During neoadjuvant therapy: 3 studies; 159 patients<br>Before surgery: 5 studies, 209 patients<br>After surgery: 8 studies, 548 patients | Time point of ctDNA testing<br>At baseline: RFS HR, 1.95 (95% CI, 0.84 to 4.55, $I^2$ = 66%)<br>During neoadjuvant therapy: RFS HR, 2.72 (95% CI, 1.27 to 5.81, $I^2$ = 0%)<br>Before surgery: RFS HR, 6.55 (95% CI, 2.94 to 14.61, $I^2$ = 38%)<br>After surgery: RFS HR, 6.74 (95% CI, 3.73 to 12.17, $I^2$ = 57%) |
| Chen et al, 2022[10] | Primarily nonmetastatic colorectal cancer | Not reported | 8 studies<br>879 patients | RFS HR, 5.41 (95% CI, 2.37 to 8.45, $I^2$ = 0%) |
| Mi et al, 2022[34] | Operable colorectal cancer | Digital droplet PCR or NGS | 14 studies<br>2,393 patients | RFS HR, 7.26 (95% CI, 5.48 to 9.62, $I^2$ = 29.9%) |
| Yekedüz et al, 2021[49] | Operable colon cancer | NGS | 4 studies<br>489 patients | *Postoperative ctDNA+* vs *ctDNA*-RFS HR, 5.88 (95% CI, 3.62 to 9.56, $I^2$ = 10%)<br>*After adjuvant chemotherapy ctDNA+ vs ctDNA*-RFS HR, 9.88 (95% CI, 5.52 to 17.68, $I^2$ = 0%) |
| Gao et al, 2019[18] | Gastric cancer | Multiple methods | 6 studies<br>624 patients | DFS or PFS HR, 2.38 (95% CI, 1.31 to 4.32, $I^2$ = 87.2%)<br>OS HR, 1.78 (95% CI, 1.36 to 2.34, $I^2$ = 46.7%) |
| Liu et al, 2022[30] | Hepatocellular carcinoma<br>Note: only studies in Japan and China were identified | Multiple methods<br>Primarily ctDNA but in some studies specific gene (*TERT*, *SOCS3*) | 8 studies<br>577 patients | OS HR, 2.44 (95% CI, 1.42 to 4.20, $I^2$ = 77.6%)<br>DFS HR, 2.63 (95% CI, 1.96 to 3.53, $I^2$ = 40.3%) |
| Zheng et al, 2021[56] | Melanoma | Primarily PCR<br>Baseline ctDNA only | 4 studies<br>Patient NR | OS HR, 1.97 (95% CI, 1.64 to 2.36, $I^2$ = 0%) |
| Gandini et al, 2021[17] | Melanoma | Primarily digital droplet PCR<br>Primarily *BRAF* pathogenic variant | 22 studies<br>1,960 patients | *ctDNA at surgery*<br>PFS HR, 2.47 (95% CI, 1.85 to 3.29, $I^2$ = 30%)<br>OS HR, 2.98 (95% CI, 2.26 to 3.92, $I^2$ = 0%)<br>*ctDNA during therapy*<br>PFS HR, 4.27 (95% CI, 2.75 to 6.63, $I^2$ = 0%)<br>OS HR, 3.91 (95% CI, 1.97 to 7.78, $I^2$ = 25%) |
| Fang et al, 2020[15] | Pancreatic cancer | PCR or NGS<br>Primarily *KRAS* pathogenic variant | 25 studies<br>2,326 patients | OS HR, 2.54 (95% CI, 2.05 to 3.14, $I^2$ = 87.7%, Chi$^2$ $P$ < .001)<br>PFS HR, 2.18 (95% CI, 1.41 to 3.37, $I^2$ = 65.9%, Chi$^2$ $P$ = .005) |
| Chen et al, 2020[11] | NSCLC | Multiple methods | OS: 11 studies, 1,778 patients<br>PFS: 7 studies, 1,050 patients | OS HR, 1.70 (95% CI, 1.37 to 2.11, $I^2$ = 70.9%)<br>PFS HR, 1.46 (95% CI, 1.14 to 1.86, $I^2$ = 76.3%) |
| Phan et al, 2022[37] | NSCLC receiving EGFR-TKI therapy | Testing for *EGFR* mutation<br>Primarily PCR | Pretreatment<br>21 studies<br>2,483 patients<br>Post-treatment<br>22 studies<br>1,623 patients | *Pretreatment*<br>PFS HR, 2.00 (95% CI 1.73 to 2.31, $I^2$ = 32%)<br>OS HR, 2.31 (95% CI, 1.89 to 2.83, $I^2$ = 33%)<br>*Post-treatment*<br>PFS HR, 3.84 (95% CI, 2.96 to 4.99, $I^2$ = 68%)<br>OS HR, 3.22 (95% CI, 2.35 to 4.42, $I^2$ = 39%) |

(continued on following page)

**TABLE 6.** Meta-Analyses of Studies of Circulating Tumor DNA Testing for Prognosis (continued)

| Analysis | Patient Population and Context | Testing Methods | No. of Studies<br>No. of Patients[a] | Outcomes NOTE: HR >1 Shows Worse Outcome With ctDNA Detection and/or Presence |
|---|---|---|---|---|
| Zhang et al, 2022[54] | NSCLC receiving ICI therapy | Tumor mutational burden established by ctDNA testing of blood | 7 studies<br>2,610 patients | OS HR, 1.09 (95% CI, 0.62 to 1.91, $I^2$ = 58.6%)<br>PFS HR, 0.73 (95% CI, 0.20 to 2.65, $I^2$ = 83.7%) |
| Wang et al, 2021[44] | Advanced NSCLC receiving ICI | Primarily NGS | 10 studies<br>1,017 patients | For baseline ctDNA<br>OS HR, 1.18 (95% CI, 0.93 to 1.51, $I^2$<0.1%, $P$ = .181)<br>PFS HR, 0.98 (95% CI, 0.80 to 1.21, $I^2$ = 38.1%, $P$ = .865)<br>For early reduction in ctDNA<br>OS HR, 0.19 (95% CI, 0.10 to 0.35, $I^2$<0.1%, $P$ < .001)<br>PFS HR, 0.25 (95% CI, 0.16 to 0.40; $I^2$ = 44.8%, $P$ < .001) |
| Yi et al, 2017[50] | NSCLC | Primarily PCR | 9 studies<br>1,170 patients | OS HR, 1.57 (95% CI, 1.18 to 2.10, $I^2$ = 71.1%) |
| Guo et al, 2023[20] | Early NSCLC | Not reported | 11 studies<br>1,134 patients | RFS HR, 4.39 (95% CI, 2.98 to 6.47, $I^2$ = 28%) |
| Lu et al, 2021[31] | Ovarian cancer | Primarily PCR | 8 studies<br>627 patients | OS HR, 2.36 (95% CI, 1.76 to 3.17, $I^2$ = 48.3%)<br>PFS HR, 2.33 (95% CI, 1.30 to 4.19, $I^2$ = 85.6%) |
| Lee et al, 2022[27] | Pancreatic ductal adenocarcinoma | Primarily PCR<br>Primarily *KRAS* mutation | 5 studies<br>375 patients | OS HR, 2.80 (95% CI, 1.81 to 4.32, $I^2$ = 6.0%)<br>DFS HR, 1.99 (95% CI, 1.10 to 3.60, $I^2$ = 20.2%) |

Abbreviations: ctDNA, circulating tumor DNA; DFS, disease-free survival; EFS, event-free survival; HR, hazard ratio; ICI, immune checkpoint inhibitor; NGS, next-generation sequencing; NR, not reported; NSCLC, non–small cell lung cancer; OS, overall survival; PCR, polymerase chain reaction; PFS, progression-free survival; RFS, recurrence-free survival; TKI, tyrosine kinase inhibitor.
[a]This is the total studies and total patients included in the paper. Individual analyses may include fewer studies and patients.

example, when patients have bone-only metastases, which present difficulties with NGS due to decalcification.

- Tumor tissue testing results may not be available within a clinically actionable time frame to determine appropriate management options. The new systematic review identified several recent studies[60,65,73,76] that jointly provide low-quality evidence in patients with advanced lung cancer that ctDNA testing can decrease time to treatment initiation by days to several weeks without a significant effect on PFS. However, an evaluation of the likelihood of a positive benefit across all cancers and all lines of treatment (eg, first-line, second-line, etc) is outside the scope of this guideline. The time needed for both ctDNA testing and tissue-based testing will vary substantially depending on the site of care; large academic centers may be able to provide rapid turnaround for both types of testing, while smaller and more rural centers may have substantially longer times. Given the high specificity of ctDNA testing, it is unlikely that patients would be started on completely inappropriate therapy. However, clonal hematopoiesis of indeterminate potential is a mechanism by which false positives for therapy indicating genetic alterations may arise. Caution is needed in interpreting variants that may be mutated in clonal hematopoiesis. For example, mutations in *PIK3CA* are nearly always of tumor origin, whereas somatic variants in *BRCA1*/*BRCA2* may originate from clonal hematopoiesis.[87] Germline variants may be identified in ctDNA assays, and pathogenic variants that may be germline should trigger germline testing for that variant.
- A drug's regulatory approved indication allows for or requires ctDNA testing. Recent drug approvals from the US Food and Drug Administration and European Medicines Agency have allowed for or required ctDNA testing to determine eligibility for the regimen. In such cases, it is appropriate to use ctDNA testing and may be the preferred testing modality in some cases. For example, *ESR1* mutations in breast cancer are tested preferably in ctDNA; see ASCO's guideline on the topic.[88]

Sensitivity of a ctDNA analysis is dependent on the analytical performance of the individual assay used. Levels of ctDNA are frequently low in plasma, and only assays specifically optimized for ctDNA analysis should be used. Sensitivity may vary between different assays, and this may impact the performance of the assay in the clinic.

## Recommendations 3 and 4

Despite the large volume of identified studies, there are no clear contexts in which the clinical utility of ctDNA testing as a *replacement* for some accepted form of testing has been proven except in the case of using ctDNA testing to identify specific genetic alterations (eg, *EGFR*, *KRAS*) as an addition to or alternative to tumor tissue testing. Until such evidence becomes available, ctDNA testing should not replace any other standard-of-care testing protocol or procedure. A potential example of replacement is presented in the study by Dong et al (2024),[72] described in the treatment selection section of the systematic review. This study proposes the idea that ctDNA testing could be used as an alternative to frequent imaging in patients with advanced lung cancer who are in complete remission. Theoretically, the frequency of imaging could be reduced substantially if the results of that small study were confirmed in larger studies. However, in the absence of clear and compelling evidence that ctDNA testing provides some benefit (eg, less burden on patients, decreased radiation exposure) without causing any harm (eg, decreased survival), there are no scenarios where ctDNA testing can completely replace current standard-of-care procedures. Therefore, Recommendation 4 recommends against ctDNA as a replacement.

However, the Expert Panel recognizes that there is substantial evidence in many contexts of the clinical validity of ctDNA testing, although the evidence of clinical utility remains sparse. In Recommendation 3, the Expert Panel allows for cases where the clinician believes a specific, evidence-based action can be taken based on ctDNA testing results, or where such results would resolve a conflict or ambiguity from a standard-of-care assessment. Also, the Expert Panel believes it is very likely that evidence of clinical utility for ctDNA testing will become available over the next few years that will more clearly outline important use cases. Recommendation 3 provides a framework for clinicians to take this newer evidence into account in their decision making. In the following sections, the Expert Panel outlines some use cases where the "specific, evidence-based action" test may currently apply.

### *Initial Diagnosis and Staging*

There have been no controlled clinical trials (randomized or otherwise) that have prospectively reported results of ctDNA testing during initial diagnosis and workup where the added value of ctDNA testing can be assessed. All studies identified in our systematic review were descriptive in nature.

Despite this lack of evidence, the Expert Panel believes ctDNA testing may be of some value to supplement initial workup and staging:

- If the malignant potential of the tumor remains unclear through initial workup. As an example, several studies were identified in the systematic review[77,79,85] that provide some evidence that ctDNA testing may be sensitive in discriminating between benign and malignant thyroid nodules and breast lesions.
- To determine the specific subtype of disease. As an example, several studies[78,83,84] have shown potential value for ctDNA testing in discriminating between neuroendocrine and non-neuroendocrine tumors, primarily in patients with lung tumors.
- When solid tumor biopsy is incomplete or insufficient and repeat biopsies pose additional risks, or where metastatic disease is suspected but has not been clearly identified through standard means. As examples, Hata et al[80] found

ctDNA testing correlated with the presence of radiographically occult metastases of pancreatic cancer identified by abdominal exploration. Lak et al[81] and Li et al[82] found cDNA testing potentially useful in patients with pediatric rhabdomyosarcoma and pediatric medulloblastoma, respectively, given the potentially increased barriers to biopsy in the pediatric population. Xie et al[86] reports that alterations in *FGFR* may be associated with the presence of brain metastases in patients with breast cancer. Where imaging is equivocal for cancer recurrence and metastatic recurrence is suspected, a ctDNA test optimized for the detection of cancer may provide confirmatory evidence of recurrence. Assay selection is highly important in these circumstances. An assay that does not detect clonal hematopoiesis should be used, or if an assay is used that may detect clonal hematopoiesis then appropriate consideration must be given to the possibility of detecting variants that originate from clonal hematopoiesis instead of metastatic disease.

Even when a relevant purpose is identified, it is crucial that an assay reporting relevant information is used.

### *Local Disease: Initial Therapy Selection*

Recommendation 2 clarifies that ctDNA testing has a role in treatment selection to identify important genetic alterations (eg, *KRAS*, *EGFR*). Recommendation 3 considers the role of ctDNA testing outside of specific genetic alterations to select nontargeted therapy. The DYNAMIC randomized trial,[64] for example, reported that patients with stage II colorectal cancer who received ctDNA-guided chemotherapy had noninferior RFS and received fewer cycles of chemotherapy than those who therapy was guided by standard-of-care testing and evaluation. Multiple studies have found that the presence of ctDNA at baseline is correlated with EFS on therapy. However, there are few studies beyond the DYNAMIC trial that indicate clinical utility for the replacement of or modification of standard-of-care treatment selection with ctDNA testing. It is difficult to assess the relative weight that ctDNA testing should be given in therapy selection in cases where the underlying randomized trials that are the basis of selecting therapy did not do that testing.

### *Local Disease: Measurement of Residual Disease*

The identified evidence indicates there may be clinical validity for MRD testing via ctDNA. However, this is complicated by several factors.

- Correct assays: It is unclear whether all identified studies used analytically and clinically valid MRD assays. For some diseases, MRD assays may not be available.
- Appropriate measurement and clear definitions of MRD: Studies used various measures of MRD, including aggregate ctDNA frequency (%), analyte-specific variant allele frequency (%), aggregate tumor DNA concentration (haploid genome equivalents/mL plasma), etc. This underlines the deeper issue that, in most of these diseases, there is no standard or clear definition of MRD, unlike in some hematologic malignancies.
- Duration and frequency of testing: There was substantial variation in the duration and frequency of MRD in the studies.

The panel identified no studies provided evidence of clinical utility of MRD testing; that is, that acting upon the results of ctDNA-based MRD testing led to benefits in patient outcome, with one potential exception. Imvigor011[67] demonstrated that patients with nonmetastatic muscle-invasive bladder cancer who were considered inappropriate for adjuvant chemotherapy and were MRD-positive benefited from atezolizumab compared with placebo. Current AUA/ASCO/SUO guidelines[89] do not recommend atezolizumab; a future update to that guideline will hopefully address the role of atezolizumab and MRD testing in response to the IMvigor011 findings. This systematic review identified only one study, c-TRAK TN,[61] that was designed to provide that evidence. Even the large GALAXY study[74,75] of over 2,000 patients does not provide this evidence; it shows that MRD measured after surgery and before adjuvant therapy is strongly correlated with substantially worse DFS in patients with colorectal cancer. In the absence of this evidence, as well as the standardization of definitions and measurement that would naturally arise, the role of MRD testing in solid tumors is unclear.

The panel recognizes that the underlying papers vary in the use of "minimal," "measurable," or "molecular" residual disease, and does not believe this variation makes a substantial difference to the clinical interpretation of the available evidence.

### *Local Disease: Monitoring for Recurrence*

The identified evidence shows that ctDNA testing may have clinical validity in predicting the risk of a patient experiencing relapse, recurrence, or progression, and in detecting the presence of those events. However, no prospective studies were found that establish the clinical utility of ctDNA testing replacing or augmenting standard-of-care strategies for monitoring or surveillance. Without such evidence, the true benefit of ctDNA is highly uncertain, and there is the potential for harm in unfounded patient anxiety in response to false-positive results or inappropriate reassurance and potentially changes in surveillance in response to false-negative results. ctDNA testing cannot be recommended generally or, at this time, in any specific context for recurrence monitoring.

### *Metastatic Disease: Treatment Selection*

As with local disease, Recommendation 2 addresses the role of ctDNA testing in identifying specific genetic alterations that might help select therapy. This would apply equally to the metastatic setting. The systematic review did not identify

any potential use cases for ctDNA testing to select non-targeted therapy.

*Metastatic Disease: Serial Testing for Progression*

There is substantial evidence that changes in ctDNA during therapy are correlated with patient outcomes such as PFS. Negative ctDNA, or decreasing ctDNA levels in serial monitoring, generally heralds better outcomes and positive or increasing ctDNA levels worse. However, there is no evidence of clinical utility for making therapeutic choices based on these results. The potential frequency and seriousness of harms from discontinuing a therapy too early or continuing a therapy for too long based on ctDNA testing compared with standard-of-care practice are unknown and vary substantially depending on context (eg, type of cancer and stage, specific therapies involved, overall prognosis of the patient, etc). Prospective studies are needed to confirm the clinical utility of ctDNA-guided strategies of response monitoring and choice to change or discontinue therapy.

*Prognosis*

There is a substantial volume of evidence across many cancer types and in many contexts that the presence of ctDNA is correlated with a worse prognosis. However, the strength of that correlation varies widely and there have been no prospective studies of the value of acting upon that information. For example, a strategy of stratifying patients based on their ctDNA results and providing more intense interventions (eg, more frequent surveillance, different therapy combinations) to those with worse prognosis could be valuable. However, there have been very few comparative studies, and no studies support specific recommendations. While prognostic information is valuable to clinicians and patients, ctDNA testing simply for prognostication, or identifying risk of relapse, without an evidence-based intervention is not considered to have clinical utility. At this time, the panel cannot provide general guidance across cancers and does not broadly recommend testing solely for prognosis.

## RECOMMENDATION 5

No evidence of clinical utility was identified for using fractional, percentage, or concentration-based measures of ctDNA or total cfDNA concentration as surrogates of disease burden. Until such evidence becomes available, these measures cannot be recommended outside of clinical trials.

## PATIENT AND CLINICIAN COMMUNICATION

Given the topic of this guideline, it is difficult to provide anything other than broad advice to clinicians on communication with their patients with respect to ctDNA testing. The guideline itself is general, covering all cancer types and all testing contexts, but patient-clinician conversations will always be specific to the patient. Also, conversations about ctDNA testing will often be incorporated into a discussion about specific care decisions, such as testing to determine eligibility for certain therapies or overall plan for surveillance after therapy. It is likely that patients will care more about the "bottom line" in such discussions and ctDNA testing itself may not be the most important aspect to discuss.

We reinforce some basic principles of such conversations that become especially important in the context of any developing technology, as outlined in the recommendations of ASCO's patient provider communications guideline,[90] such as:

- Providing diagnostic and prognostic information that is tailored to the patient's needs and that provides hope and reassurance without misleading the patient.
- Providing information in simple and direct terms.
- Clarifying the goals of care so that the patient understands likely outcomes.
- Providing information about the potential benefits and burdens of any care and checking the patient's understanding.

### DISCUSSION POINTS BETWEEN PATIENTS AND CLINICIANS REGARDING THE USE OF CTDNA TESTING

- When Thinking About Ordering ctDNA Testing
  - If clinician thinks ctDNA testing is valuable:
    - Explain what ctDNA is and why you are testing for it.
    - Explain the purpose of the ctDNA testing and what will change based on the test results.
    - Explain potential benefits, harms, and uncertainties with the test.
    - Ensure the patient knows that ctDNA testing for eligibility for clinical trials is reasonable; it allows more options but does not require a decision.
  - If patient is requesting it, but it is not recommended:
    - Clarify what the patient hopes to resolve with a ctDNA test and discuss why this would not be resolved through ctDNA testing or redirect to the relevant concern.
  - NOTE: Discuss how the testing would be paid for.
- After Test Results Are Available
  - Explain what the test results mean and what will change in the patient's care.
  - If test results are uncertain or inconclusive, make this clear for the patient as well.

For recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: ASCO Consensus Guideline.[90]

## COST IMPLICATIONS

A full consideration of the potential cost implications of ctDNA testing is not possible in this guideline, which addresses a wide range of potential cases and makes only general recommendations. The panel can only suggest that differences in cost, and who pays for those differences, must be taken into consideration when determining the full implications of a ctDNA testing based strategy versus alternatives.

## GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline includes a community oncologist member on the panel. The additional role of this community oncologist member on the guideline panel is to assess the suitability of the recommendations for implementation in the community setting, but also to identify any other barrier to implementation a reader should be aware of. Barriers to implementation include the need to increase awareness of the guideline recommendations among frontline practitioners and survivors of cancer and caregivers, and also to provide adequate services in the face of limited resources. The guideline recommendations table and accompanying tools (available at www.asco.org/molecular-testing-and-biomarkers-guidelines) were designed to facilitate implementation of recommendations. This guideline will be distributed widely. ASCO guidelines are posted on the ASCO website and most often published in the *Journal of Clinical Oncology*.

**ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.**

## ADDITIONAL RESOURCES

For current information, including selected updates, supplements, and clinical tools and resources, visit www.asco.org/molecular-testing-and-biomarkers-guidelines. The Data Supplement for this guideline includes a full list of non–meta-analysis studies that met inclusion criteria, the systematic review search strategy, and PRISMA diagram. Guideline recommendations and algorithms are also available in the free ASCO Guidelines app (available for download in the Apple App Store and Google Play Store). Listen to key recommendations and insights from panel members on the ASCO Guidelines podcast. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.org.

ASCO welcomes your comments on this guideline, including implementation challenges, new evidence, and how this guideline impacts you. To provide feedback, contact us at guidelines@asco.org. Comments may be incorporated into a future guideline update. To submit new evidence or suggest a topic for guideline development, complete the form available at www.asco.org/guidelines.

### RELATED ASCO GUIDELINES

- Patient-Clinician Communication[90] (https://ascopubs.org/doi/10.1200/JCO.2017.75.2311)
- Germline and Somatic Genomic Testing for Metastatic Prostate Cancer[91] (https://ascopubs.org/doi/10.1200/JCO-24-02608)
- Selection of Germline Genetic Testing Panels in Patients With Cancer[92] (https://ascopubs.org/doi/10.1200/JCO.24.00662)
- Germline Testing in Patients With Breast Cancer[93] (https://ascopubs.org/doi/10.1200/JCO.23.02225)
- Somatic Genomic Testing in Patients With Metastatic or Advanced Cancer[94] (https://ascopubs.org/doi/10.1200/JCO.21.02767)
- Germline and Somatic Tumor Testing in Epithelial Ovarian Cancer[95] (https://ascopubs.org/doi/10.1200/JCO.19.02960)
- Testing for *ESR1* Mutations to Guide Therapy for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer[88] (https://ascopubs.org/doi/10.1200/JCO.23.00638)

## INCLUSIVE LANGUAGE

ASCO is committed to promoting the health and well-being of all patients. ASCO guidelines are intended to apply to, and be discussed clearly and compassionately with, all patients. For this reason, guideline authors use appropriately inclusive language. In instances in which the guideline draws upon data based on research in a specified population (eg, studies regarding women with ovarian cancer), the guideline authors describe the characteristics and results of the research as reported.


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## EDITOR'S NOTE

This ASCO Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, clinical tools and resources, and links to patient information at www.cancer.org, is available at www.asco.org/molecular-testing-and-biomarkers-guidelines.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/OP-26-00311.

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**Conception and design:** All authors
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## ACKNOWLEDGMENT

The Expert Panel wishes to thank Drs Valsamo Anagnostou, Christian Rolfo, Natasha B. Leighl, and members of the Gastrointestinal Guideline Advisory Group, Supportive Care Guideline Advisory Group, and Breast Cancer Posttreatment Surveillance Guideline Update Panel for external review. The panel also thanks Drs Lisa Hicks, Sunnie Kim, and the Evidence Based Medicine Committee for their thoughtful reviews and insightful comments on this guideline.



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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**Circulating Tumor DNA Testing in Solid Tumors and Lymphoma: ASCO Guideline**

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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No other potential conflicts of interest were reported.

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## APPENDIX 2. GUIDELINE AND CONFLICTS OF INTEREST

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/guideline-methodology). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

**TABLE A1.** Circulating Tumor DNA Testing in Solid Tumors and Lymphoma Guideline Expert Panel Membership

| Name | Affiliation | Role or Area of Expertise |
|---|---|---|
| Christina M. Lockwood, PhD | University of Washington School of Medicine Seattle, WA | Pathology, Medical Genomics (Co-Chair) |
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| Nicholas C. Turner, MD | The Royal Marsden NHS Foundation Trust, London, United Kingdom | Medical Oncology (Breast) |
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| Hans J. Messersmith, MPH | American Society of Clinical Oncology (ASCO), Alexandria, VA | ASCO Practice Guideline Staff (Health Research Methods) |

**TABLE A2.** Evidence Quality and Recommendation Rating Definitions

| Term | Definitions |
|---|---|
| Evidence quality | |
| High | We are very confident that the true effect lies close to that of the estimate of the effect |
| Moderate | We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different |
| Low | Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect |
| Very low | We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect |
| Strength of recommendation | |
| Strong | In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects<br>In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects<br>All or almost all informed people would make the recommended choice for or against an intervention |
| Conditional/weak | In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists<br>In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists<br>Most informed people would choose the recommended course of action, but a substantial number would not |

NOTE. Adapted from the GRADE Handbook.[3]

**TABLE A3.** Testing Role Framework

| Term | Definition |
|---|---|
| Replacement | A new test might substitute an old one, because it is more accurate, less invasive, less risky or uncomfortable for patients, organizationally or technically less challenging, quicker to yield results or more easily interpreted, or less costly |
| First assessment | A new test is added before the existing pathway and only patients with a particular result on the first assessment test continue the testing pathway; first assessment tests are not necessarily more accurate but usually simpler and less costly |
| Additional information | A new test<br>• Is added after the existing pathway and may be used to limit the number of either false-positive or false-negative results after the existing diagnostic pathway; additional tests are usually more accurate<br>and/or<br>• Provides actionable information that was not previously available from the existing pathway and will meaningfully improve care |

**TABLE A4.** Meta-Analyses of Studies of ctDNA Testing to Measure Treatment Response

| Analysis | Patient Population and Context | Purpose of Testing | Testing Methods | No. of Studies No. of Patients[a] | Outcomes |
|---|---|---|---|---|---|
| Al-Showbaki et al, 2023[6] | Advanced solid tumors receiving ICI therapy | Measure treatment response | NGS or droplet PCR | 18 studies 552 patients | *In patients with ctDNA clearance v no ctDNA clearance*<br>OS HR, 0.18 (95% CI, 0.12 to 0.26, $I^2$ = 27%)<br>PFS HR, 0.23 (95% CI, 0.17 to 0.31, $I^2$ = 40%)<br>HR <1 indicates patients had better survival with clearance |
| Callesen et al, 2022[7] | Metastatic colorectal cancer | Measure treatment response | Multiple methods | See outcome Patients NR | *Unfavorable v favorable baseline ctDNA*<br>PFS HR, 2.2 (95% CI, 1.8 to 2.8, $I^2$ = 0.0%) (11 studies)<br>OS HR, 2.4 (95% CI, 1.9 to 3.1, $I^2$ = 45.8%) (13 studies)<br>*Unfavorable v favorable early ctDNA dynamics*<br>PFS HR, 3.0 (95% CI, 2.2 to 4.2, $I^2$ = 35.2%) (11 studies)<br>OS HR, 2.8 (95% CI, 2.1 to 3.9, $I^2$ = 27.3%) (7 studies)<br>HR >1 indicates patients had worse survival with unfavorable results |

Abbreviations: ctDNA, circulating tumor DNA; HR, hazard ratio; ICI, immune checkpoint inhibitor; NGS, next-generation sequencing; NR, not reported; OS, overall survival; PCR, polymerase chain reaction; PFS, progression-free survival.
[a]This is the total studies and total patients included in the paper. Individual analyses may include fewer studies and patients.