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Medical Policy Manual Laboratory, Policy No. 46

Circulating Tumor DNA and Circulating Tumor Cells for Management (Liquid Biopsy) of Solid Tumor Cancers

Effective: December 1, 2018

Next Review: May 2019
Last Review: August 2018

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Liquid biopsy refers to the analysis of circulating tumor/cell-free DNA (ctDNA or cfDNA) or circulating tumor cells (CTCs) as methods of noninvasively characterizing tumors and tumor genome from the peripheral blood.

MEDICAL POLICY CRITERIA

Notes:

- This policy only addresses testing for solid tumor cancers.
- This policy does not address blood-based testing for epidermal growth factor receptor variants in non-small-cell lung cancer. See Genetic Testing, Policy No. 56 in the Cross References section below.

The use of circulating tumor/cell-free DNA (ctDNA or cfDNA) and/or circulating tumor cells is considered **investigational** for all indications.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Gene-Based Tests for Screening, Detection, and/or Management of Prostate Cancer, Genetic Testing, Policy No. 17
2. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
3. Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer, Genetic Testing, Policy No. 42
4. Molecular Analysis for Targeted Therapy of Non-Small Cell Lung Cancer (NSCLC), Genetic Testing, Policy 56
5. Analysis of Proteomic Patterns for Early Detection or Assessing Risk of Cancer, Laboratory, Policy No. 41

BACKGROUND

CIRCULATING TUMOR DNA

Normal and tumor cells release small fragments of DNA into the blood, which is referred to as cell-free DNA (cfDNA). Cell-free DNA from nonmalignant cells is released by apoptosis. Most cell-free tumor DNA is derived from apoptotic and/or necrotic tumor cells, either from the primary tumor, metastases, or CTCs.[1] Unlike apoptosis, necrosis is considered a pathologic process and generates larger DNA fragments due to incomplete and random digestion of genomic DNA. The length or integrity of the circulating DNA can potentially distinguish between apoptotic and necrotic origin. Circulating tumor DNA can be used for genomic characterization of the tumor.

CIRCULATING TUMOR CELLS

Intact CTCs are released from a primary tumor and/or a metastatic site into the bloodstream. The half-life of a CTC in the bloodstream is short (1-2 hours), and CTCs are cleared through extravasation into secondary organs.[1] Most assays detect CTCs through the use of surface epithelial markers such as EpCAM and cytokeratins. The primary reason for in detecting CTCs is prognostic, through quantification of circulating levels.

DETECTING CTDNA AND CTCS

Detection of ctDNA is challenging because ctDNA is diluted by nonmalignant circulating DNA and usually represents a small fraction (<1%) of total cfDNA. Therefore, more sensitive methods than the standard sequencing approaches (e.g., Sanger sequencing) are needed.

Highly sensitive and specific methods have been developed to detect ctDNA, for both single nucleotide variants (e.g. BEAMing [which combines emulsion polymerase chain reaction with magnetic beads and flow cytometry] and digital polymerase chain reaction) and copy-number variants. Digital genomic technologies allow for enumeration of rare variants in complex mixtures of DNA.

Approaches to detecting ctDNA can be considered targeted, which includes the analysis of known genetic mutations from the primary tumor in a small set of frequently occurring driver mutations, which can impact therapy decisions or untargeted without knowledge of specific variants present in the primary tumor, and include array comparative genomic hybridization, next-generation sequencing, and whole exome and genome sequencing.

CTC assays usually start with an enrichment step that increases the concentration of CTCs,

either by biologic properties (expression of protein markers) or physical properties (size, density, electric charge). CTCs can then be detected using immunologic, molecular, or functional assays.[1]

Examples of liquid biopsy tests related to indications covered in this review are shown in Table 1.

Table 1. Examples of Liquid Biopsy Tests

Manufacturer	Test	Type of Liquid Biopsy
Biocept	Liquid Biopsies for breast, colorectal, gastric, prostate, and melanoma	ctDNA
CellMax Life	CellMax-LBx Liquid Biopsy	CTC plus ctDNA
	CellMax-CRC Colorectal Cancer Early Detection Test	CTC
	CellMax-PanCa Monitoring Test	CTC
	CellMax-Prostate Cancer Test	CTC
Cynvenio	ClearID® Solid Tumor Panel	ctDNA
	ClearID® HER2 Expression LiquidBiopsy	CTC
Foundation Medicine	FoundationACT®	ctDNA
Guardant Health	Guardant360®	ctDNA
IVDIagnostics	Velox™	CTC
Pathway Genomics	CancerIntercept® Detect	
Personal Genome Diagnostics	PlasmaSELECT™	ctDNA
Sysmex Inostics	OncoBEAM™	ctDNA
Circulogene	Theranostics	ctDNA

CTC: circulating tumor cell; ctDNA: circulating tumor DNA.

REGULATORY STATUS

The CellSearch® System (Janssen Diagnostics, formerly Veridex) is the only FDA-approved device for monitoring patients with metastatic disease and CTCs. In 2004, the CellSearch® System was cleared by FDA for marketing through the 510(k) process for monitoring metastatic breast cancer, in 2007 for monitoring metastatic colorectal cancer, and in 2008 for monitoring metastatic prostate cancer. The system uses automated instruments manufactured by Immunicon for sample preparation (CellTracks® AutoPrep) and analysis (CellSpotter Analyzer®), together with supplies, reagents, and epithelial cell control kits manufactured by Veridex. FDA product code: NQI.

EVIDENCE SUMMARY

Validation of the clinical use of any diagnostic test focuses on three main principles:

1. Analytic validity of the test;
2. Clinical validity of the test (i.e., sensitivity, specificity, and positive and negative predictive values in relevant populations of patients and compared to the gold standard); and
3. Clinical utility of the test (i.e., how the results of the diagnostic test will be used to improve the management of the patient).

The context of this literature search focuses on treatment selection, monitoring treatment response, risk prediction, and screening in asymptomatic individuals. Validation studies are

limited, therefore, this review is predominately focused on studies that correlate survival and risk of disease progression.

SELECTING TREATMENT IN ADVANCED CANCER

Treatment selection is informed by tumor type, grade, stage, patient performance status and preference, prior treatments, and the molecular characteristics of the tumor such as the presence of driver mutations. One purpose of liquid biopsy testing of patients who have advanced cancer is to inform a decision regarding treatment selection (e.g., whether to select a targeted treatment or standard treatment).

Liquid biopsies are easier to obtain and less invasive than tissue biopsies. True-positive liquid biopsy test results lead to the initiation of appropriate treatment (e.g., targeted therapy) without tissue biopsy. False-positive liquid biopsy test results lead to the initiation of inappropriate therapy, which could shorten progression-free survival.

In patients able to undergo tissue biopsy, negative liquid biopsies reflex to tissue testing. In patients unable to undergo tissue biopsy, a negative liquid biopsy result would not change empirical treatment. Therefore, health outcomes related to negative test results do not differ between liquid biopsy and tissue biopsy.

CIRCULATING TUMOR DNA

The American Society of Clinical Oncology and College of American Pathologists jointly convened an expert panel to review the current evidence on the use of ctDNA assays.[2] The literature review included a search for publications on the use of ctDNA assays for solid tumors in March 2017 and covers several different indications for the use of liquid biopsy. The search identified 1338 references to which an additional 31 references were supplied by the expert panel. Seventy-seven articles were selected for inclusion. The summary findings are discussed in the following sections, by indication.

Merker (2018) concluded that while a wide range of ctDNA assays have been developed to detect driver mutations, there is limited evidence of the clinical validity of ctDNA analysis in tumor types outside of lung cancer and colorectal cancer (CRC). Preliminary clinical studies of ctDNA assays for detection of potentially targetable variants in other cancers such as *BRAF* variants in melanoma[3] and *PIK3CA* and *ESR1* variants in breast cancer were identified.[4,5]

The clinical validity of the OncoBEAM RAS CRC assay has been evaluated in 115 patients with metastatic CRC.[6] Given the breadth of molecular diagnostic methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently. Multiple high-quality studies are needed to establish the clinical validity of a test.

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

Merker (2018) concluded that no such trials have been reported for ctDNA tests.[2]

CIRCULATING TUMOR CELLS

In breast cancer, observations that estrogen receptor–positive tumors can harbor estrogen receptor–negative CTCs,[7,8] that overt distant metastases and CTCs can have discrepant human epidermal growth factor receptor 2 status compared with the primary tumor,[9-11] and that the programmed death-ligand 1 is frequently expressed on CTCs in patients with hormone receptor–positive, *HER2*-negative breast cancer[12] have suggested that trials investigating whether CTCs can be used to select targeted treatment are needed.

The clinical validity of each commercially available CTC test must be established independently. Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

The evidence is insufficient to demonstrate test performance for currently available CTC tests; therefore, no inferences can be made about clinical utility.

MONITORING TREATMENT RESPONSE IN CANCER

Monitoring of treatment response in cancer may be performed using tissue biopsy or imaging methods. Another proposed purpose of liquid biopsy testing in patients who have advanced cancer is to monitor treatment response, which could allow for changing therapy before clinical progression and potentially improve outcomes. Standard monitoring methods for assessing treatment response are tissue biopsy or imaging methods.

CIRCULATING TUMOR DNA

Merker (2018) identified several proof-of-principle studies demonstrating correlations between changes in ctDNA levels and tumor response or outcomes as well as studies demonstrating that ctDNA can identify the emergence of resistance variants.[2] However, authors reported a lack of rigorous, prospective validation studies of ctDNA-based monitoring and concluded that clinical validity had not been established. Additionally, the authors concluded that there is no evidence that changing treatment before clinical progression, at the time of ctDNA progression, improves patient outcomes. Therefore, no inferences can be made about clinical utility.

CIRCULATING TUMOR CELLS

Smerage (2014) reported on the results of a randomized controlled trial of patients with metastatic breast cancer and persistently increased CTC levels to test whether changing chemotherapy after one cycle of first-line therapy could improve overall survival (OS; the primary study outcome).[13] Patients who did not have increased CTC levels at baseline remained on initial therapy until progression (arm A), patients with initially increased CTC levels that decreased after 21 days of therapy remained on initial therapy (arm B), and patients with persistently increased CTC levels after 21 days of therapy were randomized to continue initial therapy (arm C1) or change to an alternative chemotherapy (arm C2). There were 595 eligible and evaluable patients, 276 (46%) of whom did not have increased CTC levels (arm A). Of patients with initially increased CTC levels, 31 (10%) were not retested, 165 were assigned to arm B, and 123 were randomized to arms C1 or C2. There was no difference in median OS between arms C1 (10.7 months) and C2 12.5 months; p=0.98). CTC levels were strongly prognostic, with a median OS for arms A, B, and C (C1 and C2 combined) of 35 months, 23 months, and 13 months, respectively (p<0.001). This trial showed the prognostic significance of CTCs in patients with metastatic breast cancer receiving first-line chemotherapy, but also that there was no effect on OS if patients with persistently increased

CTC levels after 21 days of first-line chemotherapy were switched to alternative cytotoxic therapy.

Trials demonstrating that use of CTCs to monitor treatment for the purpose of making treatment changes are needed to demonstrate clinical utility. Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. The evidence is insufficient to demonstrate test performance for currently available CTC tests; therefore, no inferences can be made about clinical utility through a chain of evidence.

PREDICTING RISK OF RELAPSE

Monitoring for relapse after curative therapy in patients with cancer may be performed using imaging methods and clinical examination. Another proposed purpose of liquid biopsy testing in patients who have cancer is to detect and monitor for residual tumor, which could lead to early treatment that would eradicate residual disease and potentially improve outcomes. Standard monitoring methods for detecting relapse are imaging methods and clinical examination.

CIRCULATING TUMOR DNA AND CIRCULATING TUMOR CELLS

Merker (2018) identified several proof-of-principle studies demonstrating an association between persistent detection of ctDNA after local therapy and high risk of relapse.[2] However, current studies are retrospective and have not systematically confirmed that ctDNA is being detected before the metastatic disease has developed. They concluded that the performance characteristics had not been established for any assays.

Rack (2014) published results of a large multicenter study in which CTCs were analyzed in 2026 patients with early breast cancer before adjuvant chemotherapy and in 1492 patients after chemotherapy using the CellSearch System.[14] After chemotherapy, 22% of patients were CTC-positive, and CTC positivity was negatively associated with prognosis.

Smaller studies demonstrating associations between persistent CTCs and relapse have been published in prostate cancer,[15] CRC,[16] bladder cancer,[17,18] liver cancer,[19] and esophageal cancer.[20]

Merker (2018) concluded that there is no evidence that early treatment before relapse, based on changes in ctDNA, improves patient outcomes.[2] Similarly, no trials were identified demonstrating that treatment before relapse based on changes in CTCs improves patient outcomes. The evidence is insufficient to demonstrate test performance for currently available ctDNA and CTC tests for predicting relapse; therefore, no inferences can be made about clinical utility.

SCREENING FOR CANCER IN ASYMPTOMATIC INDIVIDUALS

It has also been proposed that liquid biopsies could be used to screen asymptomatic patients for early detection of cancer, which could allow for initiating treatment at an early stage, potentially improving outcomes. The outcome of primary interest is progression-free survival. Diagnosis of cancer that is not present or would not have become clinically important (false-positives and overdiagnosis) would lead to unnecessary treatment and treatment-related morbidity.

CIRCULATING TUMOR DNA AND CIRCULATING TUMOR CELLS

Merker (2018) reported that there is no evidence of clinical validity for the use of ctDNA in asymptomatic individuals.[2]

Systematic reviews with meta-analyses have evaluated the diagnostic accuracy of CTCs in patients with gastric and bladder/urothelial cancer.[21,22] Reported sensitivity was low in both cancers (42% and 35%) overall. Sensitivity was lower in patients with early-stage cancer, suggesting that the test would not be useful as an initial screen.

The evidence is insufficient to demonstrate test performance for currently available ctDNA and CTC tests as a screening test for cancer; therefore, no inferences can be made about clinical utility through a chain of evidence.

PRACTICE GUIDELINE SUMMARY

AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Based on a review of the recent evidence, the American Society of Clinical Oncology (2016) recommends clinicians not use circulating tumor cells to guide decisions on adjuvant systemic therapy in the clinical practice guideline on appropriate use of breast tumor biomarker assay to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer.[23]

NATIONAL COMPREHENSIVE CARE NETWORK

The National Comprehensive Care Network (NCCN) Clinical Practice Guidelines for colon (v.3.2018) and prostate cancer (v.4.2018) do not address circulating tumor cells or circulating tumor DNA.[24,25] The guidelines for breast cancer (v.1.2018) state that the use of circulating tumor cells in metastatic breast cancer is not yet included in algorithms for disease assessment and monitoring.[26]

NATIONAL ACADEMY OF CLINICAL BIOCHEMISTRY

In 2008, the National Academy of Clinical Biochemistry (NACB) issued a guideline on the use of tumor markers in testicular, prostate, colorectal, breast, and ovarian cancer.[27] Circulating tumor cells were discussed in the future developments section related to prostate cancer. The panel concluded that the measurement of circulating prostate cancer cells was not sufficiently validated to recommend testing for CTCs in routine clinical practice.

SUMMARY

There is not enough research to know if measurement for circulating tumor/cell-free DNA (ctDNA or cfDNA) or circulating tumor cells (CTCs) improves overall health outcomes for people with solid tumor cancer. Levels may be associated with the presence of metastatic disease and prognosis, however, the prospective use of this information to impact care (i.e., clinical utility) has not been demonstrated. In addition, no clinical practice guidelines based on research recommended the use of CTCs in patient management. Therefore, detection and quantification of circulating tumor cells and/or circulating tumor DNA is considered investigational in the management of patients with cancer.

REFERENCES

1. Alix-Panabieres, C, Pantel, K. Clinical Applications of Circulating Tumor Cells and Circulating Tumor DNA as Liquid Biopsy. *Cancer discovery*. 2016 May;6(5):479-91. PMID: 26969689
2. Merker, JD, Oxnard, GR, Compton, C, et al. Circulating tumor DNA analysis in patients with cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review. *J Clin Oncol*. 2018 Mar 5:Jco2017768671. PMID: 29504847
3. Ascierto, PA, Minor, D, Ribas, A, et al. Phase II trial (BREAK-2) of the BRAF inhibitor dabrafenib (GSK2118436) in patients with metastatic melanoma. *J Clin Oncol*. 2013 Sep 10;31(26):3205-11. PMID: 23918947
4. Baselga, J, Im, SA, Iwata, H, et al. Buparlisib plus fulvestrant versus placebo plus fulvestrant in postmenopausal, hormone receptor-positive, HER2-negative, advanced breast cancer (BELLE-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Oncology*. 2017 Jul;18(7):904-16. PMID: 28576675
5. Schiavon, G, Hrebien, S, Garcia-Murillas, I, et al. Analysis of ESR1 mutation in circulating tumor DNA demonstrates evolution during therapy for metastatic breast cancer. *Science translational medicine*. 2015 Nov 11;7(313):313ra182. PMID: 26560360
6. Vidal, J, Muinelo, L, Dalmases, A, et al. Plasma ctDNA RAS mutation analysis for the diagnosis and treatment monitoring of metastatic colorectal cancer patients. *Ann Oncol*. 2017 Jun 1;28(6):1325-32. PMID: 28419195
7. Babayan, A, Hannemann, J, Spotter, J, Muller, V, Pantel, K, Joosse, SA. Heterogeneity of estrogen receptor expression in circulating tumor cells from metastatic breast cancer patients. *PLoS One*. 2013 Sep;8(9):e75038. PMID: 24058649
8. Liu, Y, Liu, Q, Wang, T, et al. Circulating tumor cells in HER2-positive metastatic breast cancer patients: a valuable prognostic and predictive biomarker. *BMC Cancer*. 2013 Apr 23;13:202. PMID: 23617715
9. Fehm, T, Muller, V, Aktas, B, et al. HER2 status of circulating tumor cells in patients with metastatic breast cancer: a prospective, multicenter trial. *Breast cancer research and treatment*. 2010 Nov;124(2):403-12. PMID: 20859679
10. Riethdorf, S, Muller, V, Zhang, L, et al. Detection and HER2 expression of circulating tumor cells: prospective monitoring in breast cancer patients treated in the neoadjuvant GeparQuattro trial. *Clin Cancer Res*. 2010 May 1;16(9):2634-45. PMID: 20406831
11. Ignatiadis, M, Rothe, F, Chaboteaux, C, et al. HER2-positive circulating tumor cells in breast cancer. *PLoS One*. 2011 Jan 10;6(1):e15624. PMID: 21264346
12. Mazel, M, Jacot, W, Pantel, K, et al. Frequent expression of PD-L1 on circulating breast cancer cells. *Molecular oncology*. 2015 Nov;9(9):1773-82. PMID: 26093818
13. Smerage, JB, Barlow, WE, Hortobagyi, GN, et al. Circulating tumor cells and response to chemotherapy in metastatic breast cancer: SWOG S0500. *J Clin Oncol*. 2014 Nov 1;32(31):3483-9. PMID: 24888818
14. Rack, B, Schindlbeck, C, Juckstock, J, et al. Circulating tumor cells predict survival in early average-to-high risk breast cancer patients. *Journal of the National Cancer Institute*. 2014 May;106(5). PMID: 24832787
15. Thalgott, M, Rack, B, Horn, T, et al. Detection of circulating tumor cells in locally advanced high-risk prostate cancer during neoadjuvant chemotherapy and radical prostatectomy. *Anticancer research*. 2015 Oct;35(10):5679-85. PMID: 26408743

16. Deneve, E, Riethdorf, S, Ramos, J, et al. Capture of viable circulating tumor cells in the liver of colorectal cancer patients. *Clinical chemistry*. 2013 Sep;59(9):1384-92. PMID: 23695297
17. Rink, M, Chun, FK, Dahlem, R, et al. Prognostic role and HER2 expression of circulating tumor cells in peripheral blood of patients prior to radical cystectomy: a prospective study. *European urology*. 2012 Apr;61(4):810-7. PMID: 22277196
18. Gazzaniga, P, de Berardinis, E, Raimondi, C, et al. Circulating tumor cells detection has independent prognostic impact in high-risk non-muscle invasive bladder cancer. *International journal of cancer Journal international du cancer*. 2014 Oct 15;135(8):1978-82. PMID: 24599551
19. Schulze, K, Gasch, C, Staufer, K, et al. Presence of EpCAM-positive circulating tumor cells as biomarker for systemic disease strongly correlates to survival in patients with hepatocellular carcinoma. *International journal of cancer Journal international du cancer*. 2013 Nov;133(9):2165-71. PMID: 23616258
20. Vashist, YK, Effenberger, KE, Vettorazzi, E, et al. Disseminated tumor cells in bone marrow and the natural course of resected esophageal cancer. *Annals of surgery*. 2012 Jun;255(6):1105-12. PMID: 22580852
21. Msaouel, P, Koutsilieris, M. Diagnostic value of circulating tumor cell detection in bladder and urothelial cancer: systematic review and meta-analysis. *BMC Cancer*. 2011 Aug 4;11:336. PMID: 21816094
22. Tang, L, Zhao, S, Liu, W, et al. Diagnostic accuracy of circulating tumor cells detection in gastric cancer: systematic review and meta-analysis. *BMC Cancer*. 2013;13:314. PMID: 23806209
23. Harris, LN, Ismaila, N, McShane, LM, et al. Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2016 Apr 1;34(10):1134-50. PMID: 26858339
24. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Colon cancer. v.2.2017. [cited 06/20/2017]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf
25. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology™: Prostate Cancer v.2.2017. [cited 06/20/2017]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf
26. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Breast Cancer. V.2.2017. [cited 06/20/2017]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
27. Sturgeon, CM, Duffy, MJ, Stenman, UH, et al. National Academy of Clinical Biochemistry laboratory medicine practice guidelines for use of tumor markers in testicular, prostate, colorectal, breast, and ovarian cancers. *Clin Chem*. 2008;54:e11-79. PMID: 19042984
28. BlueCross BlueShield Association Medical Policy Reference Manual "Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)." Policy No. 2.04.141

CODES

Codes	Number	Description
CPT	86152	Cell enumeration using immunologic selection and identification in fluid specimen (eg, circulating tumor cells in blood);

Codes	Number	Description
	86153	Cell enumeration using immunologic selection and identification in fluid specimen (eg, circulating tumor cells in blood); physician interpretation and report, when required
HCPCS	None	

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