GUARDANT

**Guardant Health Test Requisition Form (TRF) Reference Information**
**ONC-US-00413 V4**

## Guardant Health Therapy Response Monitoring

By selecting "Therapy Response Monitoring" on the test requisition form (TRF), the patient will receive a series of Guardant Reveal tests for the purpose of therapy response monitoring. Therapy Response Monitoring is available via a Guardant Health standard outreach cadence (every 1 month), or at a provider-defined cadence.

**Important Note:** Guardant Reveal was developed as a Laboratory Developed Test (LDT), and its performance characteristics determined by the Guardant Health Clinical Laboratory in Redwood City, CA, USA, which is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing. This test has not been reviewed or approved by the US FDA.

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## Guardant Health Monitoring Regimens, Use Cases, and Cadences

- **Guardant Reveal Post-surgery:** The post-surgery program is a bundle of up to three Guardant Reveal tests. The first post-surgery draws must be initiated 3-13 weeks after surgery or completion of curative-intent therapy.
- **Guardant Reveal Surveillance:** Guardant Reveal surveillance is offered via the following cadences:
    - Guideline-based cadences (Default if no cadence is selected):
        - For CRC patients, blood draws occur every 3 months for 2 years after curative intent therapy completion and then every 6 months until canceled or a positive result is reported.
        - For Breast and Lung patients, blood draws occur every 6 months after curative intent therapy completion and then every 6 months until canceled or a positive result is reported.
        - **Note**: Not all clinical guidelines specifically recommend the use of MRD testing. These cadences are aligned with recommendations from national oncology guidelines[1] for other forms of monitoring in these tumor types.
    - Every 3 months (available via individual test menu only)
    - Every 6 months (available via individual test menu only)
    - One-time draw only (available via individual test menu only)
- **Guardant Reveal Therapy Response Monitoring:** Guardant Reveal therapy response monitoring is offered via the following cadences:
    - Guardant Health standard outreach cadence (Default if no cadence is selected): Every 1 month
    - Write-in cadence, based on provider preference (available via individual test menu only)

- **For MRD + Monitoring program (Guardant Reveal, Guardant360 Liquid):**
    - The post-surgery program is a bundle of up to three Guardant Reveal tests. The first post-surgery draws must be initiated 3-13 weeks after surgery or completion of curative-intent therapy.
    - Surveillance program orders follow the Guardant Reveal Surveillance guideline-based blood draw cadences outlined above.
- **For Complete Profiling + Monitoring** (Guardant360 Liquid CDx[2], Guardant360 Tissue + Tissue RNA, PD-L1, other optional IHCs, Guardant Reveal) **and Liquid Profiling + Monitoring** (Guardant360 Liquid, Guardant Reveal) **programs**: Guardant Health standard outreach cadence (every 1 month) for Guardant Reveal Therapy Response Monitoring is used.

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**Blood Draws for Monitoring Tests**

All Guardant Health monitoring tests offer the following options for blood draw management:

- First draw completed in-office; subsequent draws managed by Guardant Health phlebotomy services [Default for all Guardant Health monitoring programs, if no preference is selected, with the exception of Post-surgery]
- In-office draws only [Default for Post-surgery program, if no preference is selected]
- All draws managed by Guardant Health phlebotomy services

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**Molecular Recurrence / Progression Determination for Guardant Reveal**

- **Guardant Reveal for MRD Surveillance:**
    - If at any point, the patient is determined to be recurring or progressing, the ordering provider can order a Guardant Health treatment selection test to guide further treatment decisions
    - If a patient has evidence of molecular recurrence, a cascade to comprehensive molecular profiling with Guardant360 Liquid is available for qualifying patients. Initiation of follow up molecular profiling with Guardant360 Liquid requires that no Guardant Health liquid therapy selection test has been performed within the prior 45 days and that other program criteria are met: stage II–III surveillance (series or one-time order) with a positive Guardant Reveal MRD result, tumor fraction (TF) ≥0.05%.
    - Providers can opt out of this automatic cascade by checking the “opt out” box on the Guardant Health Test Requisition Form in the individual test selection menu. “Opt out” language is displayed as follows: “I opt out of ordering guideline-recommended therapy selection testing with Guardant360 Liquid for this progressing patient in the event of a positive Guardant Reveal result.”
    - Guardant Reveal Post-surgery and Guardant Reveal “one-time order” patients are not eligible for the cascade to Guardant360 Liquid outlined above

- **Guardant Reveal for Therapy Response Monitoring:**
    - If at any point, the patient is determined to be progressing, the ordering provider can order a Guardant Health treatment selection test to guide further treatment decisions
    - If a patient has evidence of molecular progression (defined below), the provider will be offered a confirmatory TRF to confirm the provider's needs regarding continued testing. Offered testing includes the ability to:
        - Order Guardant360 Liquid + Therapy Response Monitoring (using Guardant Reveal) for this progressing patient
        - Continue monitoring this patient with a Guardant Reveal Therapy Response Monitoring series
        - Discontinue testing for this patient at this time
    - If a patient has evidence of molecular progression, initiation of follow up molecular profiling with Guardant360 Liquid requires a new order via Guardant Health Test Requestion Form (TRF) or confirmatory Guardant Health Test Requisition Form (TRF). Eligibility also requires that no Guardant Health liquid therapy selection test has been performed within the prior 45 days and that other program criteria are met: advanced disease on therapy with a positive Guardant Reveal result, tumor fraction (TF) increase >50% from the previous testing timepoint, and other predefined performance thresholds.

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**Individual Treatment Selection Tests**

If Guardant360 Liquid is ordered with Guardant360 Tissue, Guardant360 Liquid will be converted to Guardant360 Liquid CDx.

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**IHC Offerings**

Guardant Health offers a menu of IHC stains, which can be added on to orders for Guardant360 Tissue. These IHC stains can be added on to the Complete Profiling + Monitoring program or the Guardant360 Tissue offering on the individual test selection menu. All stains are individual "add-on" tests, with the exception of PD-L1. PD-L1 is included in the Complete Profiling + Monitoring program, but must be added to an individual Guardant360 Tissue order.

Relevant IHC stains by tumor at time of document development:

- **Breast:** ER/PR, HER2, Ki-67, PD-L1
- **Colorectal:** MMR, HER2
- **Gastric:** CLDN18, HER2, MMR, PD-L1
- **Lung:** c-MET, HER2, PD-L1
- **Ovarian:** FOLR1, HER2, MMR

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GUARDANT

**Guardant Health Testing Programs**

Guardant Health Testing Programs are designed to deliver relevant genomic testing throughout a patient's cancer journey, ensuring timely insights are available to support critical clinical decisions in the moments where these insights matter most. Guardant Health offers 3 testing programs accommodating patients at various points of their cancer journeys, and providing options that leverage Guardant Health's full portfolio of oncology diagnostic tests.

**Available Guardant Health Testing Program**

| | MRD + Monitoring | Complete Profiling + Monitoring | Liquid Profiling + Monitoring |
|---|---|---|---|
| **Eligible Patients** | Patients with stage II/III CRC, Breast, or Lung cancer, who have recently been treated with curative intent treatment | Patients with any advanced solid tumor malignancy | Patients with any advanced solid tumor malignancy |
| **Available Specimen** | Liquid | Liquid & Tissue | Liquid |
| **Guardant Tests that may be Included** | Guardant Reveal, Guardant360 Liquid | Guardant360 Liquid CDx[2], Guardant360 Tissue + Tissue RNA, PD-L1 & optional IHCs, Guardant Reveal | Guardant360 Liquid Guardant Reveal |

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**Liquid Profiling + Monitoring Program**
(Guardant360 Liquid, Guardant Reveal)
This program is intended for patients who would benefit from "liquid only" molecular profiling for treatment selection, followed by therapy response monitoring.

Patients with any advanced solid tumor malignancy are eligible for this program.

**Program Details**

- When ordering this program, patients are initially tested with a Guardant360 Liquid treatment selection assay.
- After report delivery, a confirmatory TRF is provided to gather relevant therapy information, in order to initiate the Therapy Response Monitoring series.
- Once the signed confirmatory TRF is received, Guardant Health runs a Guardant Reveal test to establish a baseline for Therapy Response Monitoring from the originally submitted specimen, if available. Guardant Health will then reach out for subsequent monitoring blood draws via standard outreach cadence of every 1 month.
- If, during Therapy Response Monitoring, a patient meets the criteria suggestive of molecular progression (defined above), the provider will be provided with a confirmatory TRF to assess the provider's desire to:

- Order Guardant360 Liquid + Therapy Response Monitoring (using Guardant Reveal) for this progressing patient
    - Molecular profiling with Guardant360 Liquid requires a completed and signed Guardant Health confirmatory TRF. Eligibility also requires that no Guardant Health liquid therapy selection test has been performed within the past 45 days and that program criteria are met, including advanced-stage disease, a positive Guardant Reveal result, a tumor fraction (TF) greater than 50% from the prior testing timepoint, and other predefined performance thresholds.
- Continue monitoring this patient with Guardant Reveal Therapy Response Monitoring series
- Discontinue testing for this patient at this time

- Upon delivery of the signed confirmatory TRF, testing is performed as requested by the provider.
- Guardant Health will continue to offer the provider the option to run relevant therapy response monitoring and treatment selection tests as the patient's cancer journey as it evolves.

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**Complete Profiling + Monitoring Program**

(Guardant360 Liquid CDx[2], Guardant360 Tissue + Tissue RNA, PD-L1 & Optional IHCs, Guardant Reveal)

This program is intended for patients who would benefit from a liquid & tissue-based molecular profiling for treatment selection, followed by therapy response monitoring.

Patients with any advanced solid tumor malignancy are eligible for this program.

**Program Details**

- When ordering this program, patients are initially tested with Guardant360 Liquid CDx.
- Upon delivery of the Guardant360 Liquid CDx result, a confirmatory TRF is provided, and the ordering provider must sign the confirmatory TRF to indicate that tissue testing is medically necessary[2]
- Upon receipt of the signed confirmatory TRF, the patient's tissue sample is tested with Guardant360 Tissue (testing both DNA and RNA). PD-L1 IHC is also performed. Additional IHC stains can be ordered, if desired.
- After report delivery, a confirmatory TRF is provided to gather relevant therapy information, in order to initiate the Therapy Response Monitoring series.
- Once the signed confirmatory TRF is received, Guardant Health runs a Guardant Reveal test to establish a baseline for Therapy Response Monitoring from the originally submitted specimen, if available. Guardant Health will then reach out for subsequent monitoring blood draws via standard outreach cadence of every 1 month.
- If, during Therapy Response Monitoring, a patient meets the criteria suggestive of molecular progression (defined above), the provider will be provided with a confirmatory TRF to assess the provider's desire to:
    - Order Guardant360 Liquid + Therapy Response Monitoring (using Guardant Reveal) for this progressing patient
        - Molecular profiling with Guardant360 Liquid requires a completed and signed Guardant Health confirmatory TRF. Eligibility also requires that no Guardant Health liquid therapy selection test has been performed within the past 45 days and that program criteria are met, including advanced-stage disease, a positive Guardant Reveal result, a tumor

fraction (TF) greater than 50% from the prior testing timepoint, and other predefined performance thresholds.
    - Continue monitoring this patient with Guardant Reveal Therapy Response Monitoring series
    - Discontinue testing for this patient at this time
- Upon delivery of the signed confirmatory TRF, testing is performed as requested by the provider.
- Guardant Health will continue to offer the provider the option to run relevant therapy response monitoring and treatment selection tests as the patient's cancer journey as it evolves.

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**MRD + Monitoring Program**

(Guardant Reveal, Guardant360 Liquid)

This program is intended for patients who have recently completed curative intent treatment who would benefit from MRD monitoring in a Post-Surgery and/or Surveillance series. If patient has evidence of recurrence (defined above), molecular profiling will be performed for treatment selection, followed by therapy response monitoring.

Eligible patients must have CRC, Lung or Breast cancer with a current cancer stage of stage II or III. (While not eligible for the MRD + Monitoring program, patients with stage I or IV-oligometastatic disease may order Guardant Reveal for MRD monitoring from the individual test selection menu.)

**Program Details**

- When ordering this program, patients are tested with Guardant Reveal, which measures the proportion of tumor molecules present in the cfDNA using epigenomic signals.
- Patients should be assigned to one of two different Guardant Reveal programs: Post-Surgery Program or Surveillance Program

**Post-Surgery Program:**

- The Post-Surgery Program is for patients who have recently completed curative intent therapy (within the last 13 weeks at time of order) who are being considered for adjuvant therapy.
- Patients who complete the Post-Surgery Program may be offered the opportunity to continue monitoring by enrolling in a Surveillance Program (if eligible) or discontinue testing at that time. Patients who discontinue at that time will discontinue the MRD + Monitoring Program as well.

**Surveillance Program:**

- The Surveillance Program is for patients who have been treated with curative intent therapy and are being monitored for minimal residual disease.
- The patient's blood will then be drawn at a recommended guideline-based cadence:
    - For CRC patients – For the first 2 years post-curative intent therapy, the blood draw cadence is every 3 months. Afterwards, the patient's blood will be drawn every 6 months
    - For Breast and Lung patients – The patient's blood is drawn every 6 months
    - **Note**: Not all clinical guidelines specifically recommend the use of MRD testing. These cadences are aligned with recommendations from national oncology guidelines[1] for other forms of monitoring in these tumor types.
- The patient follows the recommended blood draw cadence until the Reveal result reports ctDNA Detected. Patients who meet the following criteria will proceed to the Liquid Profiling + Monitoring program (see the Liquid Profiling + Monitoring program for further details.) To qualify, patients must meet the following criteria:

- Reveal results reported ctDNA Detected with tumor fraction at or above 0.05%
- May not have had a Guardant Health liquid therapy selection test within the last 45 days
- Must have been stage II or III at program enrollment
- All other patients will not proceed to Liquid Profiling + Monitoring program and will discontinue testing at this time

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**Medicare Advance Beneficiary Notice (ABN) Requirements and Other Details for Medicare Beneficiaries -** A Medicare Advance Beneficiary Notice (ABN) must be provided to Medicare patients noted to meet one or more of the following criteria:

- MRD Monitoring with Guardant Reveal
  - All lung cancer patients
  - A patient with breast cancer, lung cancer, or colorectal cancer with no history of curative-intent treatment (such as surgical resection) for this cancer diagnosis
  - A patient with breast cancer or colorectal cancer who has submitted a blood sample >14 days before the recommended blood draw cadence
- Therapy Response Monitoring with Guardant Reveal
  - The patient is being treated with a treatment regimen that does not include immunotherapy or chemotherapy (either monotherapy or combination therapy)
- Guardant360 Liquid CDx
  - An ABN is required for all non-CNS solid tumor patients if the first relevant clinical history question is unanswered
    - Question 1: The patient is seeking further treatment, has not received the ordered Guardant product since their most recent diagnosis / non-response to therapy, and is: “Newly diagnosed (Stage III/IV)” or “Not responding to therapy”
  - All patients with CNS solid tumors
- Guardant360 Tissue
  - An ABN is required if the patient has not been confirmed to be either newly diagnosed or not responding to therapy (i.e., relevant clinical history question 1 is left blank)
    - Question 1: The patient is seeking further treatment, has not received the ordered Guardant product since their most recent diagnosis / non-response to therapy, and is: “Newly diagnosed (Stage III/IV)” or “Not responding to therapy”
  - An ABN is required if the patient is not advanced stage with a covered ICD 10 code
- Guardant360 Liquid
  - An ABN is required for all non-CNS solid tumor patients if question 1 is unanswered or question 2 is marked “Yes”
    - Question 1: The patient is seeking further treatment, has not received the ordered Guardant product since their most recent diagnosis / non-response to therapy, and is: “Newly diagnosed (Stage III/IV)” or “Not responding to therapy”
    - Question 2: Is tissue-based comprehensive genomic profiling (CGP) from a recent biopsy feasible?
  - All patients with CNS solid tumors

**Important note:** Guardant360® Liquid, Guardant360® Tissue and Guardant Reveal were developed as Laboratory Developed Tests (LDT), and their performance characteristics determined, by the Guardant Health Clinical Laboratory in Redwood City, CA, USA, which is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing. These tests have not been reviewed or approved by the US FDA.

[1] National oncology guidelines include:


- Meyerhardt JA, Mangu PB, Flynn PJ, Korde L, Loprinzi CL, Minsky BD, Petrelli NJ, Ryan K, Schrag DH, Wong SL, Benson AB. Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer: American society of clinical oncology clinical practice guideline endorsement. *Journal of Clinical Oncology*, 2013; 31(35), 4465-4470. https://doi.org/10.1200/JCO.2013.50.7442
- Khatcheressian JL, Hurley P, Bantug E, Esserman LJ, Grunfeld E, Halberg F, Hantel A, Henry NL, Muss HB, Smith TJ, Vogel VG, Wolff AC, Somerfield MR, Davidson NE, American Society of Clinical Oncology. Breast cancer follow-up and management after primary treatment: American Society of Clinical Oncology clinical practice guideline update. *Journal of Clinical Oncology,* 2013; 31(7): 961-965. https://pubmed.ncbi.nlm.nih.gov/23129741
- Schneider BJ, Ismaila N, Aerts J, Chiles C, Daly ME, Detterbeck FC, Hearn JWD, Katz SI, Leighl NB, Levy B, Meyers B, Murgu S, Nekhlyudov L, Santos ES, Singh N, Tashbar J, Yankelevitz D, Altorki N. Lung Cancer Surveillance After Definitive Curative-Intent Therapy: ASCO Guideline. *Journal of Clinical Oncology*, 2020; 38(7), 753-766. https://ascopubs.org/doi/10.1200/JCO.19.02748


[2] Patients who have a negative Guardant360® Liquid CDx test result for an indicated companion diagnostic biomarker should be reflexed to tissue biopsy testing using an FDA-approved tumor tissue test, if feasible. Liquid and tissue testing may be initiated at the same time, but sample processing does not occur concurrently.