GUARDANT

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

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 cadence (monitoring every 3 months), 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 cleared or approved by the US FDA.

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**: Clinical guidelines do not specifically recommend the use of MRD testing. The guideline-based cadences are based on recommendations for other forms of monitoring in these tumor types, per National Oncology Guidelines
    - 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 cadence (Default if no cadence is selected): Every 3 months
    - Write-in cadence, based on provider preference (available via individual test menu only)
- **For MRD + Monitoring program:**

  - 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 and Liquid Profiling + Monitoring programs**: Guardant Health standard cadence for Guardant Reveal Therapy Response Monitoring is used.

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

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 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.
- Providers can opt out of this cascade offering 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: "In the event of Guardant Reveal reporting increasing tumor fraction that meets the threshold for molecular progression, I opt out of ordering guideline recommended therapy selection testing with Guardant360 Liquid for this progressing patient."

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

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 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

Liquid Profiling + Monitoring Program

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 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. The patient can then follow a standard monitoring blood draw cadence of every 3 months.
- 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

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 CDx.
- Upon delivery of the Guardant360 CDx result, a confirmatory TRF is provided, and the ordering provider must sign the confirmatory TRF to indicate that tissue testing is medically necessary
- 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. The patient can then follow a standard monitoring blood draw cadence of every 3 months.
- 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.

MRD + Monitoring Program

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 I, II, or III. Stage IV is only acceptable if oligometastatic.

Program Details

- When ordering this program, patients are tested with Guardant Reveal, which tests measures tumor fraction based on epigenomics of the patient's sample
- 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 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**: Clinical guidelines do not specifically recommend the use of MRD testing. The guideline-based cadences are based on recommendations for other forms of monitoring in these tumor types, per National Oncology Guidelines
- 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:
    - 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 (either monotherapy or combination therapy)
- Guardant360 CDx
    - A patient who has previously had a Guardant360 CDx test and has not progressed since the previous test was performed
- Guardant360 Liquid
    - A patient for whom the relevant clinical history questions are marked in the following manner:
        - An ABN is required for NSCLC patients if (1) question 2 is marked “Yes” or (2) if question 5 is marked “Yes” or (3) if tissue-based CGP from a recent biopsy was feasible but not performed (indicated by a combination of question 3 marked “Yes” and question 4 marked “No”)
            - Question 2: Has the patient received a Guardant360 Liquid or Guardant360 CDx report since their non-response to therapy?
            - Question 3: Is tissue-based comprehensive genomic profiling (CGP) from a recent biopsy feasible?
            - Question 4: Has tissue-based CGP from a recent biopsy been performed with a non-QNS result?
            - Question 5: Has tissue-based CGP from a recent biopsy already returned an actionable result?
        - An ABN is required for non-CNS solid tumor patients other than NSCLC if any relevant clinical history question is marked “Yes” (see relevant questions above)
    - All patients with CNS solid tumors
- Guardant360 Tissue
    - If a CGP test has previously been successfully run on the tissue from the same date of service (i.e. if either question 4 or 5 is marked “Yes” for a Treatment Selection and Therapy Response Monitoring test) or if a Guardant360 Tissue has previously been performed and the patient has subsequently not progressed since the new tissue specimen was obtained
        - Question 4: Has tissue-based CGP from a recent biopsy been performed with a non-QNS result?
        - Question 5: Has tissue-based CGP from a recent biopsy already returned an actionable result?