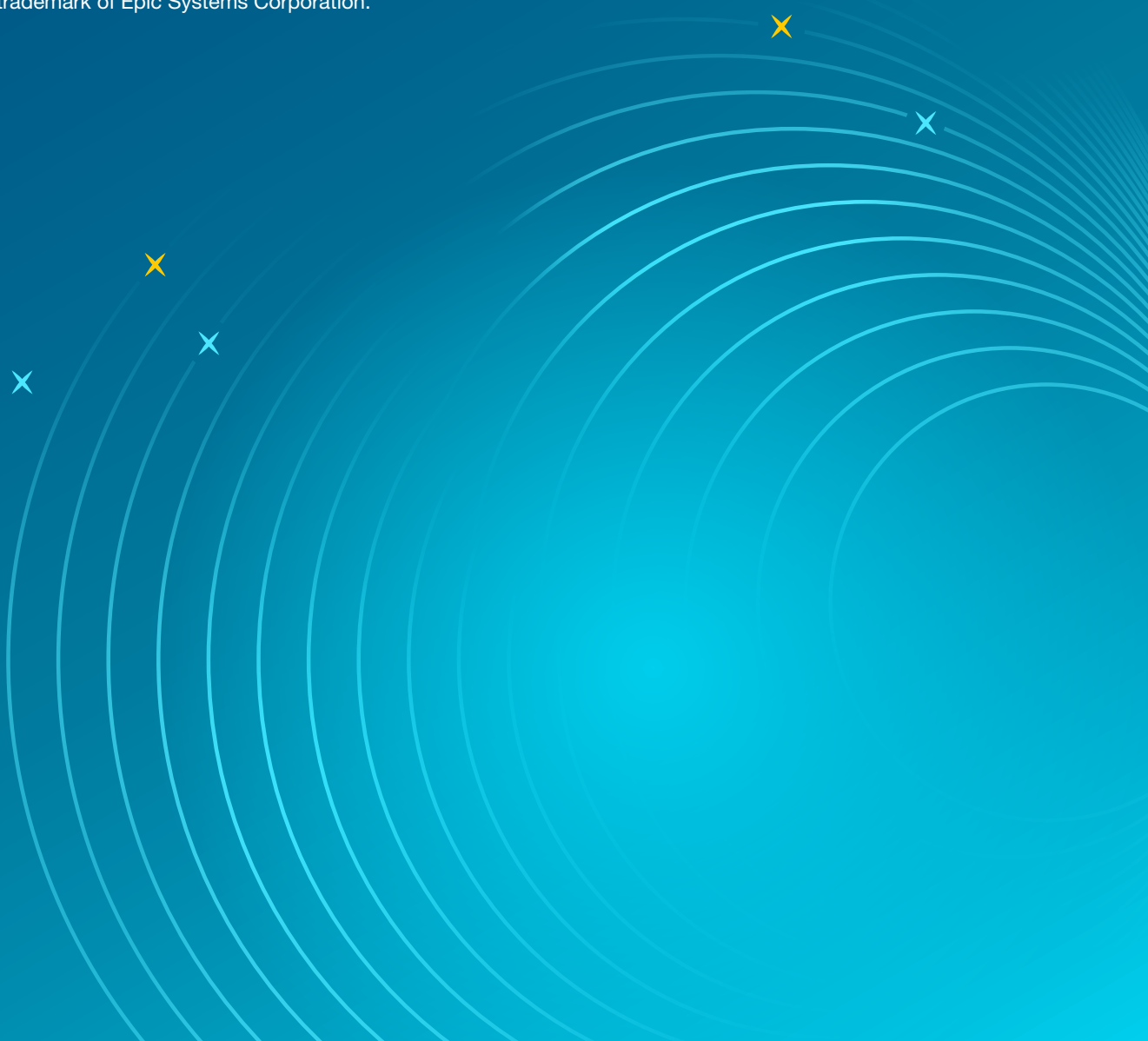
natera™ | Signatera™
Residual disease test (MRD)

Operationalizing Signatera™ testing using Epic®

A guide for oncology teams evaluating workflows for molecular residual disease (MRD) testing



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About this guide

Circulating tumor DNA (ctDNA) for molecular residual disease assay (MRD) is a powerful tool that can be measured to assess the absence or presence of MRD. Signatera™ is a highly sensitive and personalized MRD assay using ctDNA and is custom designed for each patient to help identify relapse earlier than standard-of-care tools.

Integrating Signatera into Epic® tools and workflows may support ordering, result awareness, and follow-up. **This guide provides examples of considerations that may help oncology care teams evaluate the potential role of Signatera, as well as how Natera can support integration from Day 1.**

The information in this guide is provided for discussion purposes only and does not replace detailed instructions from internal or external EHR support resources. Capabilities vary by health system, system configuration, user permissions, and software version. Any examples shown are illustrative only and may not reflect every workflow or system limitation. Screen images, if included, represent hypothetical examples unless otherwise noted.

This guide does not constitute medical advice or treatment guidance. Health systems remain responsible for treatment decisions based on their independent medical judgment and the needs of each individual patient. Natera makes no claims or warranties regarding the applicability or appropriateness of this information for a particular organization or workflow. These materials have not been reviewed or endorsed by Epic.

Why this matters

While imaging is effective for detecting established tumors, very small amounts of residual cancer can fall below the threshold of detection and persist unnoticed. As a ctDNA test, Signatera can detect the presence of cancer in the blood before it becomes visible on imaging and may help alert care teams to a possible recurrence earlier to help enable timely evaluation.

Since Signatera supports longitudinal monitoring rather than a single data point, EHR integration and updating workflows to enable proper patient identification, initiate testing at the right time, track results over time, and prompt action when results warrant follow-up may be useful.

Integration for facilitation

Signatera readily integrates with Epic to streamline risk assessment, ordering, and results delivery. Bidirectional integration enables a seamless loop where orders are sent directly from the EHR and results are returned automatically to the patient's chart following direct HIPAA compliant data exchange.

- Automatic data transfer eliminates the need for manual entry, which can result in missing or misplaced information
- Integration with major platforms allows clinical teams to order tests and review results without switching between portals
- Inclusion in Longitudinal Monitoring populates oncology flowsheets, helping healthcare providers see MRD trends alongside CEA or other tumor markers
- Virtual Ordering Platform supports remote workflows, including mobile phlebotomy and in-home blood draws, while ensuring data still flows back into the centralized EHR system

Incorporating Signatera™ long-term

By integrating Signatera testing directly into the EHR oncology workflow, healthcare providers can place Signatera orders and receive structured, discrete result data directly in the chart rather than static PDFs.

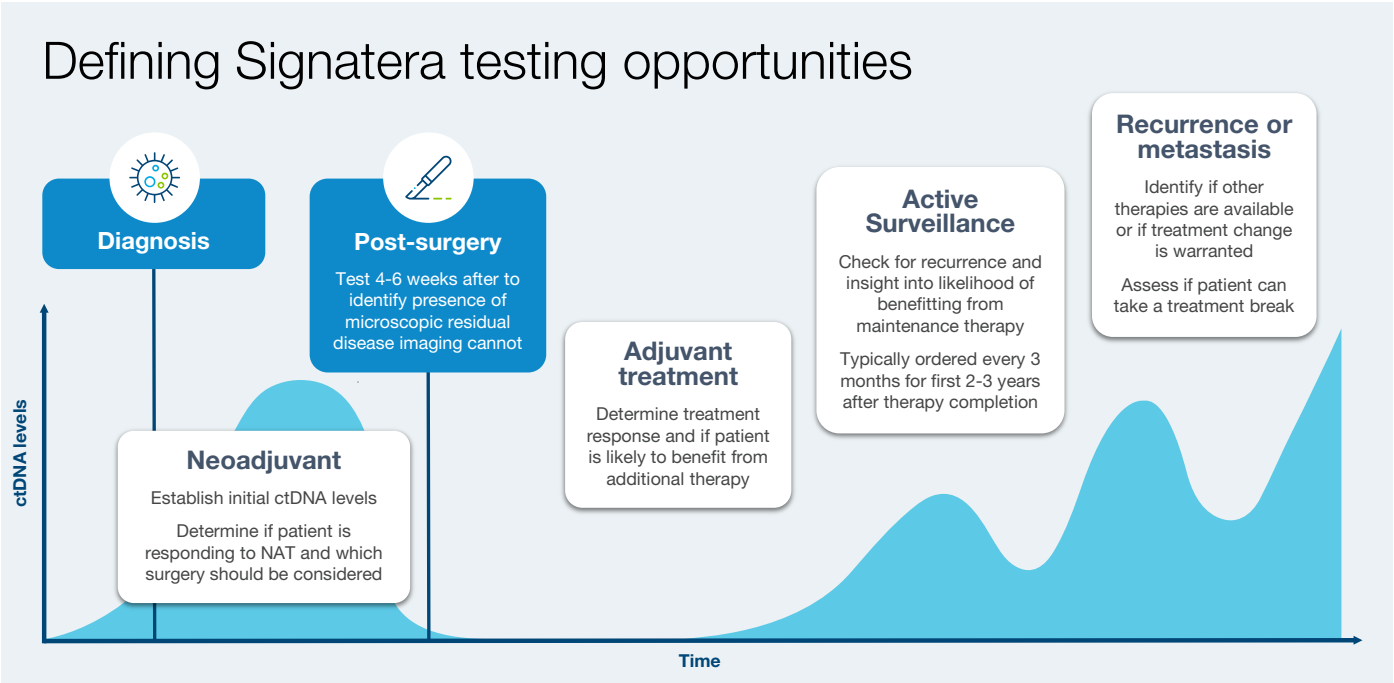
Adding Signatera testing to the workflow can be tailored to specific tumor types. Signatera is indicated for the following tumor types:

- Gastrointestinal Cancers (Colorectal, anal, gastroesophageal, HCC, and pancreatic)
- Breast Cancer
- Lung Cancers (NCSLC)
- Genitourinary Cancers (Bladder, renal cell carcinoma, testicular cancer)
- Head and Neck Cancers
- Lymphoma (Large B-cell)
- Skin Cancers
- Sarcoma
- Gynecologic Cancers (Ovarian, uterine, cervical)
- Immunotherapy

To help maximize the utility of Signatera, health systems may consider a cadence from the point of diagnosis that extends through long-term surveillance.

- Baseline blood draw can ideally occur pre-op; in the case of post-surgical MRD assessment, it can occur exactly within the 2-to-4-week post-resection window to help capture residual disease before adjuvant therapy begins
- Serial testing (typically every 3-6 months) can be done alongside routine surveillance imaging and laboratory protocols

Defining Signatera testing opportunities



Epic® capabilities can support optimal Signatera™ use

By mapping incoming ctDNA results as discrete data points, Epic can automatically populate relevant oncological SmartLinks for easy inclusion in clinical documentation, trigger automated In Basket notifications for critical molecular progression, and surface results within treatment plans to help healthcare providers evaluate the path forward, whether it is active surveillance or treatment escalation.

Capability	Opportunity
Patient Reports	**Identify** potential patients, appropriate patients who have not yet been tested, or those due/overdue for the next test based on health-system defined criteria.
Treatment Protocols, SmartSets, and Order Sets	**Standardized ordering support** tools help place Signatera within relevant oncology workflows—including post-surgical surveillance and neoadjuvant protocols to facilitate ordering.
OPAs (Our Practice Advisory)	**Notifications** like OPAs may support ordering or help guide care teams towards results warranting provider review.
InBasket Notifications	**Alert** clinicians when Signatera results are received.
SmartText, SmartForms	**Documentation support** may assist with availability of results within workflow when captured as discrete data

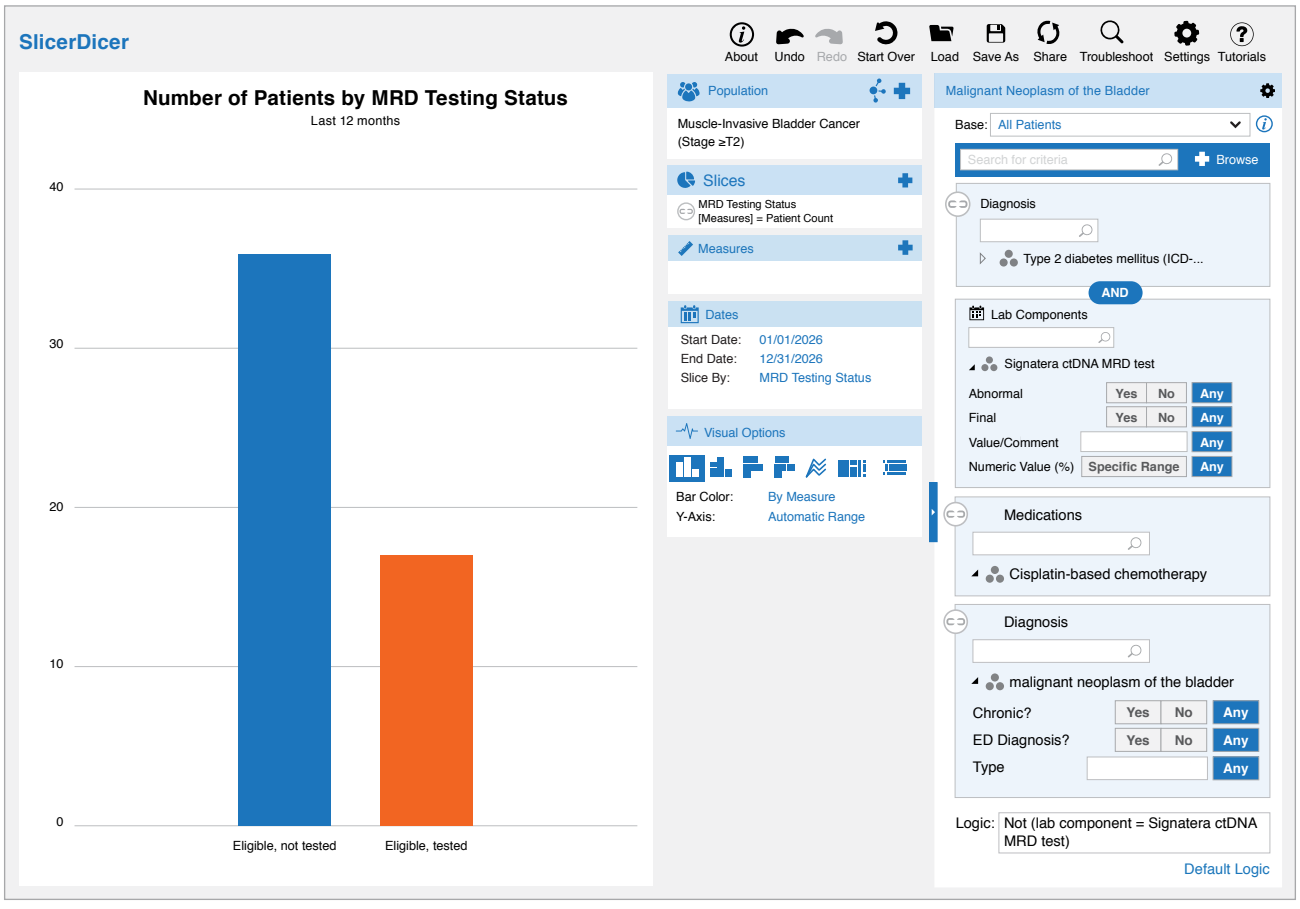
All of the highlighted Epic capabilities can be tailored as needed to be relevant to the tumor type.

Identifying appropriate patients for Signatera™ testing

Patient reports may help identify eligible patients who have not had MRD testing, those who may be due or overdue for the next test based on the health system's defined protocol, or patients whose treatment plan may need to be adjusted based on incoming results. Patient reports may be tailored to identify patients with any Signatera indicated tumor type. The example below highlights muscle-invasive bladder cancer for illustrative purposes.

Criteria considerations for muscle-invasive bladder cancer may include:

- A diagnosis of malignant neoplasm of the bladder (ICD-10 C67.x)
- A procedure record for cystectomy (CPT 51595)
- Documentation of cisplatin-based chemotherapy

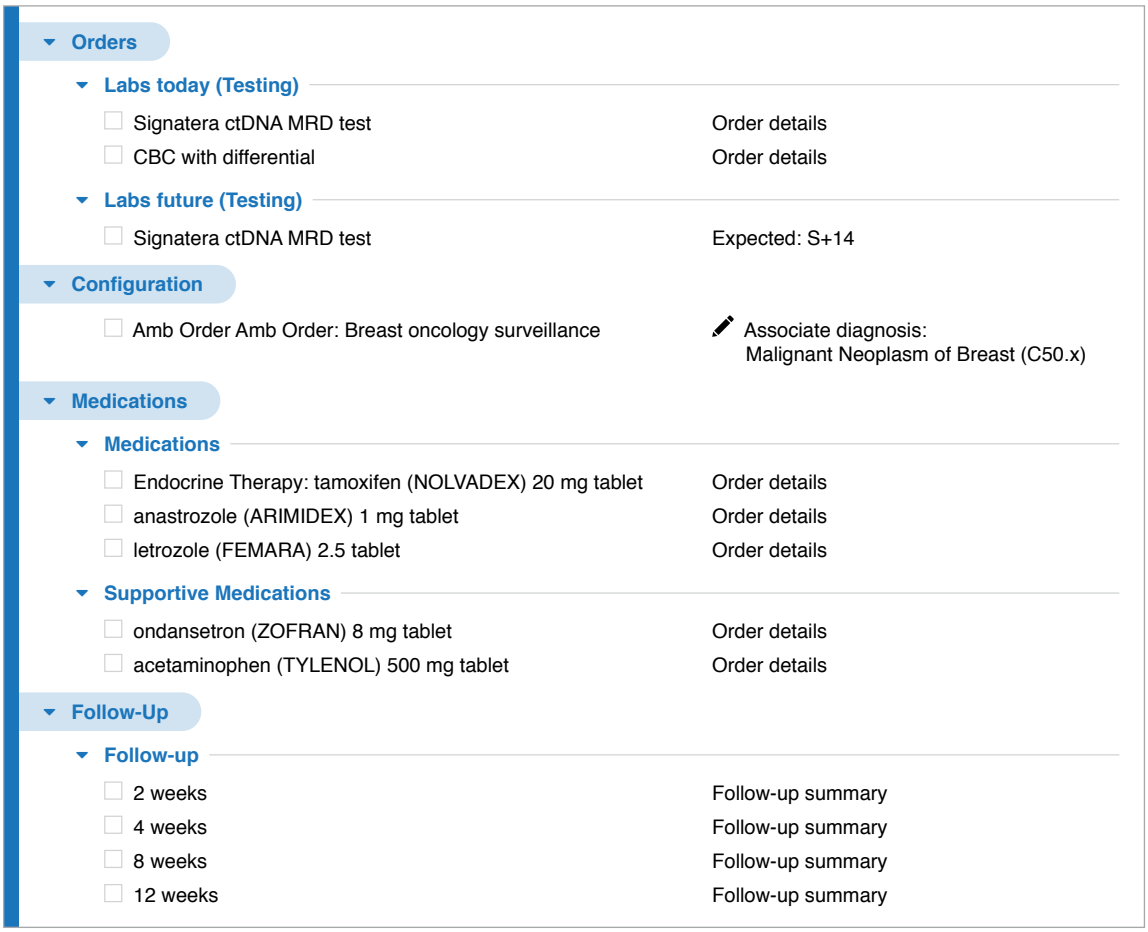


Example of a SlicerDicer report output

Supporting Signatera™ orders within existing workflows

Signatera may be ordered one test at a time as a standalone order or incorporated into existing Treatment Protocols, Order Sets, or SmartSets. Relevant workflow contexts may include post-surgical surveillance plans, neoadjuvant or adjuvant chemotherapy protocols, and other health system-defined oncology pathways.

Adding Signatera to existing ordering workflows may help reduce the need for separate manual steps and help clinicians find and place the order at the point of care. For health systems already using Treatment Protocols, Order Sets, or SmartSets to guide treatment and surveillance, this integration helps ensure Signatera appears alongside related orders rather than as a separate order. SmartSets may be tailored for any Signatera indicated tumor type. The example SmartSet highlights relevant orders for breast cancer for illustrative purposes.



Example of a SmartSet

Using reminders and alerts to prompt action

Depending on the health system's Epic® configuration, **prompts related to Signatera™ may display as an OurPractice Advisory (OPA), In Basket message, or other notification type.**

Reminders and alerts in Epic can be configured as active or passive, depending on the urgency of the prompt and how disruptive an interruption to the workflow would be appropriate. Active alerts, like an OurPractice Advisory, surface during the clinical encounter and require the provider to acknowledge or act before moving forward. Passive alerts, like In Basket messages, appear in a healthcare provider's inbox and are reviewed when the provider navigates to them. When evaluating alert options, defining clear trigger criteria and selecting the notification type that best matches the urgency and context of the clinical prompt may help ensure reminders reach the right person at the right time.

OPA to remind the healthcare provider that the patient meets the criteria for Signatera

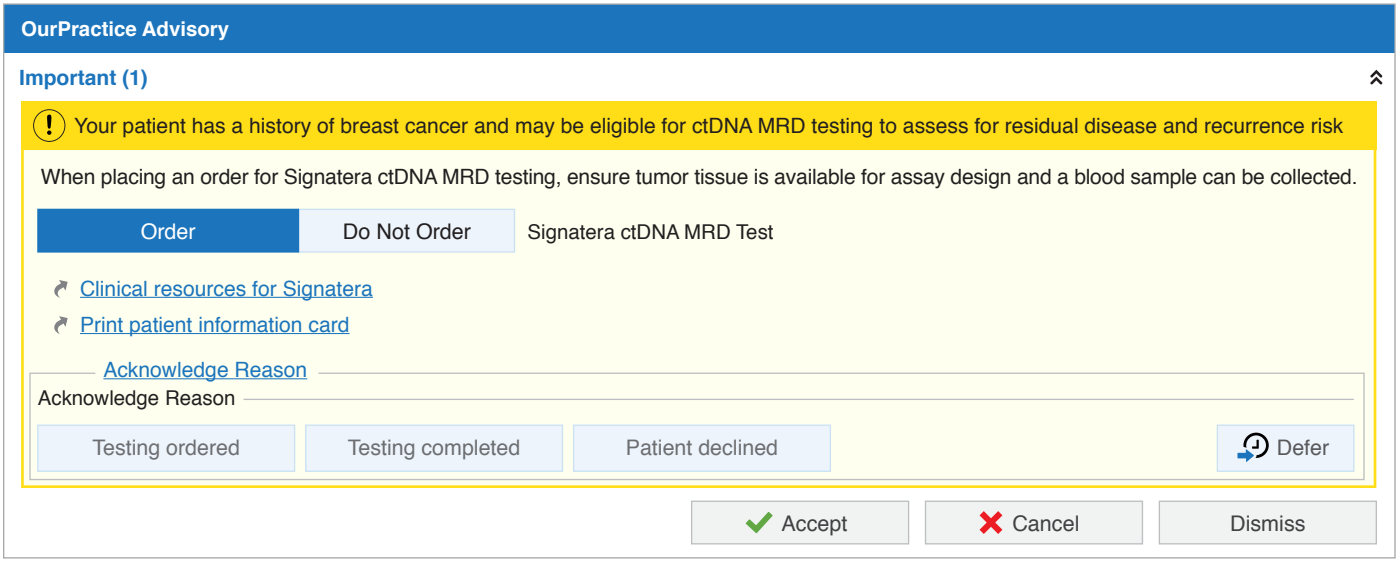
Reminders and alerts may support several use cases for implementing Signatera testing and may be tailored for any Signatera indicated tumor type.

- Eligibility criteria is met, but the care team has not placed an order
- Patient may be due or overdue for repeat testing based on the monitoring protocol
- Results have arrived and need a clinician review
- A positive result may warrant follow-up evaluation
- A patient has entered a surveillance window where the care team should consider testing

Example of when an OPA might trigger

Patients may meet criteria for Signatera testing based on diagnosis and treatment history. Signatera testing OPA criteria may include:

- Prior diagnosis of a solid tumor (eg, breast, muscle-invasive bladder, colorectal cancers)
- Availability of primary tumor tissue for testing
- Clinical intent of testing to monitor for MRD, disease recurrence or relapse, and evaluation of response to treatment



Example of an OPA

In Basket Message to alert provider of Signatera™ results

Result awareness is a critical component of the Signatera workflow.

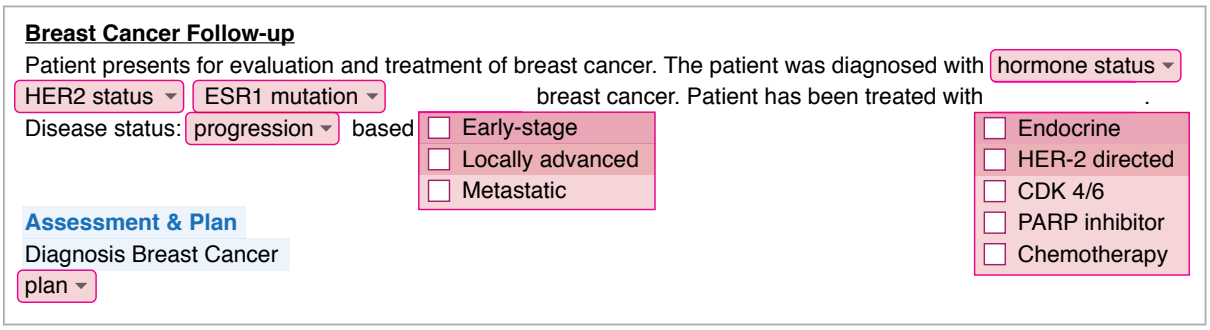
In Basket notifications alert the appropriate clinician when Signatera results are received. Health systems can also configure additional notifications when positive results warrant follow-up review or evaluation.

This process connects Signatera test ordering, result review, and follow-up planning within the oncology workflow.

Capturing key clinical details

SmartText and SmartForms may help oncology care teams document key Signatera™ related information in a consistent, structured way. Relevant fields may include cancer type, stage, date of diagnosis, surgery date, recurrence history, Signatera order date, result, and result date.

Structured documentation supports the other capabilities in this guide. When care teams capture data in discrete fields, reports, reminders, and follow-up workflows can use that data to drive action. The documentation required may vary based on tumor type. The example highlights clinical data for breast cancer for illustrative purposes.



Example of SmartText

Operationalizing the Signatera test in Epic®

Your Natera representative may help you identify which Epic capabilities may support your patient population. A conversation with Natera can help your team:

- Review current workflows for appropriate tumor types to identify where Signatera is consistently present and where it is not
- Evaluate which Epic capabilities address the most significant gaps in your current workflow
- Prioritize updates based on your clinical protocols, EHR configuration, available data, and implementation resources
- Align Signatera ordering and monitoring in existing oncology surveillance and treatment pathways

Specialized implementation support from dedicated teams

Natera recognizes the effort required to integrate Signatera™ into the EHR. To assist with the process—as well as provide support following integration, Natera offers dedicated project teams to manage the lifecycle. To date, more than 3000 accounts have been integrated.

Dedicated team typically includes:

- **EHR Integration Managers:** Primary point of contact; provides coordination between your organization's IT department and Natera's internal engineering teams
- **Clinical Informaticists:** Design consultation and assistance with mapping clinical catalogs to ensure tests are correctly represented in order sets and that results display intuitively
- **Interface Analysts:** Technical specialists who handle the HL7 messaging or API connectivity, ensuring that discrete data points (such as "MRD status") flow correctly into specific fields in the patient chart

Technical expertise: Natera provides specialized EHR analysts to support the setup from kickoff through go-live

As a founding member of the Epic® Aura™ network, Natera can implement interfaces in approximately 6–10 weeks. This hub-based connection avoids the complexities of traditional point-to-point HL7 integrations.

Additional support comes through:

- **Pre-built Order Sets:** Natera uses Turbochargers: pre-configured assets for Signatera to accelerate the "go-live" process
- **Patient Engagement:** NateraSync provides genetic screening education before appointments, while NEVA (Natera's Educational Virtual Assistant) is an AI-enabled tool that helps guide patients through health history questions and hereditary cancer risk assessments (summary is automatically delivered to the EHR record for review during appointments)

Resources to reduce the technical burden: Technical frameworks, testing, and continuous optimization

To help both clinical and IT teams, Natera offers a structured implementation model designed to ensure integration is both clinically accurate and technically sound.

- "Hub" technologies and pre-built assets reduce time spent on custom coding
- Quality Assurance (QA) resources are available to assist with connectivity validation, parallel testing, allowing your team to verify result accuracy in a non-production environment before go-live
- Post-launch, dedicated channels for technical support and test catalogue updates allow your compendium to update as new tests are released without disrupting the existing interface

Non-technical assistance: Establishing desired functionality for your organization through strategic design

Beyond the technical aspects of integration, decisions made during design consultation shape the integration so that it meets the clinical standards of your organization.

Here are some key facets to consider before the build:

- Deciding which roles are authorized to trigger these tests (eg, attendings only; should orders be available system-wide)
- Determining how order appearance affects “click count” and clinical accuracy (eg, standalone orders vs part of larger protocol, if OPAs should fire, what clinical questions are hard stops to prevent errors)
- Creating a Criteria Worksheet to ensure testing is consistently applied
- Deciding how the EHR should manage next steps, such as patient journey reminders
- Establishing testing cadence for ongoing monitoring

Moving forward with implementation

A key step is to establish coordination between the clinical champion and IT leadership. Steps to consider:

1. **Initiate the request** by contacting the Director of Clinical Informatics or the Laboratory Information System (LIS) Manager who oversee lab compendia and are responsible for the project intake process.
2. **Reach out to Natera** to assign a dedicated EHR Implementation Manager.
3. **Establish the clinical need** for IT which may involve identifying patient populations, volume metrics, and safety & compliance.
4. **Help IT understand the technical burden** which is lessened by Epic® Aura™.
5. **Create a timeline to establish the commitment**, keeping in mind the resources Natera can offer to provide assistance along the way from design consultation to post-launch assistance.

Setting post-integration expectations

Here are some things to expect once integration is completed.

- **As a closed-loop system, Natera tests will be native to the existing workflow**
  - Natera tests will appear directly in the **Lookup** or **Preference List** searches alongside internal hospital labs
  - Orders are bundled into relevant specialty workflows using the Epic® Foundation assets
  - All required "Ask at Order Entry" questions (eg, clinical indications) are embedded in the order composer (Smart Forms AOEs)
- **Critical order-related documentation (eg, progress notes, pathology reports, pedigree charts) can be seamlessly transmitted to Natera at the point of order without the need for manual uploads**
  - Additionally, comprehensive risk context (eg, personal and family cancer history) is automatically included to reduce administrative back-and-forth
- **Delivery options are customizable to the organization based on the clinical needs of the health system**
  - Key values (like "High/Low Risk") are delivered as discrete data points and can automatically be pulled into flowsheets and SmartPhrases
  - A high-resolution, full-color PDF of the official Natera report is automatically attached to the Lab Results activity so healthcare providers have access to the full diagnostic context and visual charts provided
  - Results are automatically routed to the InBasket of the ordering healthcare provider and any cc'd clinicians based on the organization's standard "Results Routing" logic
- **Natera tests mirror other hospital-performed labs; typing "Signatera™" in the Orders activity allows the Natera test to appear immediately in search results alongside internal labs**
  - Since Natera uses Epic Turbochargers, orders come pre-loaded with all required AOEs (Ask at Order Entry)
  - Natera orders can be embedded into existing clinical protocols as part of clinical bundling (SmartSets)
- **Natera integration supports their price transparency program, which sends an automated text/email estimate to the patient after the integrated order is placed but before the lab is processed**
  - For healthcare providers, integration helps ensure that insurance information already in the EHR is accurately transmitted to Natera to reduce the potential for back-and-forth

Next steps

Connect with your Natera representative to discuss how Epic capabilities may support the implementation of the Signatera test in your oncology workflows and determine which next steps align with the needs of your health system.

References: 1. Baskin AS, Keshwani A, Bains M, Fleischer C, Dossett LA. Characterizing Surveillance Recommendations From National Comprehensive Cancer Network Guidelines. *JAMA Netw Open.* 2025;8(10):e2540727. doi:10.1001/jamanetworkopen.2025.40727. **2.** Bekaii-Saab TS, Schoen RE. The promise of molecular residual disease (MRD) testing for patients with colorectal cancer. *Clin Adv Hematol Oncol.* 2025 Jun;23 Suppl 7(4):1-11. PMID: 40590865.

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