Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

- The exact sample size (n) for each experimental group/condition, given as a discrete number and unit of measurement
- A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
- The statistical test(s) used AND whether they are one- or two-sided
  Only common tests should be described solely by name; describe more complex techniques in the Methods section.
- A description of all covariates tested
- A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
- A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
- For null hypothesis testing, the test statistic (e.g. F, t, r) with confidence intervals, effect sizes, degrees of freedom and P value noted
  Give P values as exact values whenever suitable.
- For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
- For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
- Estimates of effect sizes (e.g. Cohen’s d, Pearson’s r), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about: availability of computer code

Data collection: Guardant360 database utilized

Data analysis: GraphPad Prism version 9.1.0 for macOS, GraphPad Software, San Diego, California, USA, www.graphpad.com.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about: availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Data from a Guardant360® database was utilized for this study and is available on reasonable request. Given that these data contain patient information, they are not publicly available.
Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

- Life sciences
- Behavioural & social sciences
- Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

| Category          | Details                                                                 |
|-------------------|-------------------------------------------------------------------------|
| Sample size       | 6718 patients with advanced breast cancer with at least 1 alteration in cfDNA; 42 with MSI-H (with 43 samples) |
| Data exclusions   | None                                                                    |
| Replication       | Guardant testing already has clinical validation                        |
| Randomization     | N/A - not a clinical trial                                              |
| Blinding          | N/A - not a clinical trial                                              |

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

| Materials & experimental systems | Methods                                      |
|----------------------------------|----------------------------------------------|
| n/a                              | n/a                                          |
| ☑ Antibodies                     | ☑ Involved in the study                      |
| ☑ Eukaryotic cell lines          | ☑ ChIP-seq                                   |
| ☑ Palaeontology and archaeology  | ☑ Flow cytometry                             |
| ☑ Animals and other organisms    | ☑ MRI-based neuroimaging                     |
| ☑ Human research participants    |                                              |
| ☑ Clinical data                  |                                              |
| ☑ Dual use research of concern   |                                              |

Human research participants

Policy information about: studies involving human research participants

| Policy information | Details                                                                 |
|--------------------|-------------------------------------------------------------------------|
| Population         | Patients with advanced breast cancer undergoing cfDNA testing          |
| Recruitment        | N/A- retrospective study                                                |
| Ethics oversight   | Approved by Quorum Institutional Review Board                           |

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about: clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

| Clinical trial registration | Study protocol                                    | Data collection | Outcomes |
|----------------------------|---------------------------------------------------|-----------------|----------|
| N/A- not a clinical trial  | N/A- approved by Quorum Institutional Review Board| Guardant 360 database | N/A      |