Reporting Summary

Nature Research 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 Research 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.

☐ n/a Confirmed
☐ 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
Patient DNA sequencing data was generated via plasma samples using the Illumina NovaSeq 6000. Data was stored and downloaded for analyses from the Tempus database.

Data analysis
Adapter trimmed FASTQ files are aligned to the 19th edition of the human reference genome build (hg19) using Burrows-Wheeler Aligner (BWA). Following alignment, reads are grouped by alignment position and UMI family, and collapsed into consensus sequences using bbtools tools. SNV and indel variants are detected using VarDict. Copy number variants (CNVs) are analyzed using CNVkit15 plus a Tempus CNV annotation and filtering algorithm. Rearrangements are detected using the SpeedSeq analysis pipeline. Gene rearrangements are detected by LUMPY. Circulating tumor fraction estimates (ctFES) were determined using a novel method, Off-Target Tumor Estimation Routine (OTTER), from both on- and off-target reads distributed across the human reference genome. For low pass whole genome sequencing, sequencing coverage metrics for these samples were calculated using Picard CollectWgsMetrics. The tumor fraction and ploidy values for each sample were estimated using ichorCNA. Additional information about statistical tests performed can be found in the methods section.

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 Research guidelines for submitting code & software for further information.
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.

| Sample size | We randomly selected a cohort of 1000 cancer patients who had clinical plasma specimens sequenced with the xF panel at CAP/CLIA-certified Tempus Labs, Inc. |
|-------------|----------------------------------------------------------------------------------------------------------------------------------|
| Data exclusions | Hematological malignancies were excluded. Samples with incomplete demographic data (e.g. gender, age, cancer type, etc.) were excluded. |
| Replication | n/a |
| Randomization | The xF 1000 cohort was allocated by cancer type diagnosis. xT/xF concordance samples were selected based on availability. Longitudinal xF samples were selected based on availability. Low-pass, whole-genome sequenced samples were allocated by cancer type and stage. |
| Blinding | Samples were de-identified during collection and analysis. |

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 | |