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Corresponding author(s): Sohrab P Shah and Samuel Aparicio

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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	All commercial, open source and custom code software is detailed in the Supplementary Information. Custom software that is part of this study is available as specified in the Methods section: Software and source code implementing analytical and statistical methods available on github: [https://github.com/UBC-Stat-ML/fitclone]
Data analysis	All commercial, open source and custom code software is detailed in the Supplementary Information. Custom software that is part of this study is available as specified in the Methods section: Software and source code implementing analytical and statistical methods available on github: [https://github.com/UBC-Stat-ML/fitclone]

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.

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 list of figures that have associated raw data
- A description of any restrictions on data availability

Raw sequencing data for DLP+ and 10x scRNASeq will be available from the European Genome-Phenome archive prior to publication.

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	For each timeseries sample, we estimated power to detect clones to 2% for choosing the number of cells to sequence. For number of samples per timeseries, this was determined due to practical constraints, sampling tumours over a 2.5yr interval. As this was an exploratory study, no calculations were used to determine the number of samples/timeseries. We note that these series spanned 100s of days (or cell division generations) in the cell lines, and up to 10 serial passages in the PDX models.
Data exclusions	For all samples, low quality sequenced cells were excluded as per the predefined criteria reported in the Supplementary Information.
Replication	In cell line and PDX experiments, unperturbed timeseries were compared to perturbed timeseries. Replicates were performed in the cell lines and the TNBC-SA609 Line 1 untreated PDX, via one and two 'mixing' experiment respectively to reproduce the observation of fitness clones. Furthermore, multiple replicate observations were generated in the PDX models in two ways: parallel replicate timeseries with cisplatin treatment, and duplicate experiments of specific time points.
Randomization	Randomization was not applicable in this study as all experiments were controlled perturbation experiments, generating timeseries with or without isogenic TP53 mutation, or cisplatin dosing as described in the Supplementary Information.
Blinding	Blinding was not relevant due to the controlled perturbation nature of the experimental design.

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

n/a	Involved in the study
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☐	☒ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used	See Supplementary Table 4 in the Supplementary Information
Validation	See Section 2.1 Histopathology of PDX tumours in the Supplementary Information.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Section 1 of the Supplementary Information provides this in detail: "The human mammary epithelial cell line wild type 184-hTERT and isogenic 184-hTERT-P53 KO cell line, generated from 184hTERT WT-L9, were grown as previously described" References [1, 2].
Authentication	These cell lines were used previously and reported in previous papers from our laboratory: 1. Laks, E. et al. Clonal decomposition and dna replication states defined by scaled single-cell genome sequencing. Cell 179, 1207–1221 (2019). 2. Burleigh, A. et al. A co-culture genome-wide rnai screen with mammary epithelial cells reveals transmembrane signals required for growth and differentiation. Breast Cancer Research 17, 4 (2015).

Mycoplasma contamination	Mycoplasma testing was negative.
Commonly misidentified lines (See ICLAC register)	*Name any commonly misidentified cell lines used in the study and provide a rationale for their use.*

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals	The details on mouse strains for xenografting tumours is detailed in Section 2 of the Supplementary Information.
Wild animals	*Provide details on animals observed in or captured in the field; report species, sex and age where possible. Describe how animals were caught and transported and what happened to captive animals after the study (if killed, explain why and describe method; if released, say where and when) OR state that the study did not involve wild animals.*
Field-collected samples	*For laboratory work with field-collected samples, describe all relevant parameters such as housing, maintenance, temperature, photoperiod and end-of-experiment protocol OR state that the study did not involve samples collected from the field.*
Ethics oversight	The Ethics Committees at the University of British Columbia approved all the experiments using human resources. Patients in Vancouver, British Columbia were recruited, and samples were collected under the tumour tissue repository (TTRH06-00289) protocol and transplanted in mice under the Neoadjuvant PDX (University of British Columbia BC Cancer Research Ethics Board H20-00170) protocols. After informed consent, tumour fragments from patients undergoing excision or diagnostic core biopsy, were collected. Tumour materials were processed as described in [3] and transplanted in mice under the animal resource centre (ARC) bioethics protocol (A19-0298-A001) approved by the animal care committee.

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

Human research participants

Policy information about studies involving human research participants

Population characteristics	The Ethics Committees at the University of British Columbia approved all the experiments using human resources. Patients in Vancouver, British Columbia were recruited, and samples were collected under the tumour tissue repository (TTRH06-00289) protocol and transplanted in mice under the Neoadjuvant PDX (University of British Columbia BC Cancer Research Ethics Board H20-00170) protocols.
Recruitment	Bias and collection was not relevant here as this was not a population based study, nor a clinical trial. Breast cancer patients in Vancouver, British Columbia were recruited, and samples were collected under the tumour tissue repository (TTRH06-00289) protocol.
Ethics oversight	The Ethics Committees at the University of British Columbia

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