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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	No software was used.
Data analysis	Microsoft Excel version 16 Adobe Illustrator version 24 GraphPad Prism version 8 Getz Lab CGA WES Characterization pipeline (https://github.com/broadinstitute/CGA_Production_Analysis_Pipeline) developed at the Broad Institute employs the following tools: MuTect, ContEst, Strelka, Orientation Bias Filter, DeTiN, AllelicCapSeg, MAFPoNFilter, RealignmentFilter, ABSOLUTE, GATK, PicardTools, Variant Effect Predictor, Oncotator. GATK4 copy number pipeline (https://github.com/broadinstitute/gatk/) GTEx pipeline (https://github.com/broadinstitute/gtex-pipeline/) STAR-Fusion (https://github.com/STAR-Fusion/STAR-Fusion/) MutSig2CV version 3.11 MATLAB runtime environment R2013a RStudio version 1.2.5033 R version 3.6.2 (2019-12-12) R packages: AnnotationDbi 1.48.0, ape 5.3, askpass 1.1, assertthat 0.2.1, backports 1.1.6, bibtex 0.4.2.2, Biobase 2.46.0, BiocGenerics 0.32.0, BiocManager 1.30.10, BiocParallel 1.20.1, bit 1.1-15.2, bit64 0.9-7, bitops 1.0-6, blob 1.2.1, broom 0.5.5, callr 3.4.3, caTools 1.18.0, cellranger 1.1.0, cli 2.0.2, cluster 2.1.0, clusterProfiler 3.14.3, codetools 0.2-16, colorspace 1.4-1, cowplot 1.0.0, crayon 1.3.4, crosstalk 1.1.0.1, data.table 1.12.8, DBI 1.1.0, dbplyr 1.4.2, desc 1.2.0, devtools 2.3.0, digest 0.6.25, DO.db 2.9, DOSE 3.12.0, dplyr 0.8.5, DT 0.13, ellipsis 0.3.0, enrichplot 1.6.1, europepmc 0.3, evaluate 0.14, extrafont 0.17, extrafontdb 1, fansi 0.4.1, farver 2.0.3, fastmatch 1.1-0, fgsea 1.12.0, fitdistrplus 1.0-14, forcats 0.5.0, fs 1.4.1, future 1.16.0, future.apply 1.4.0, gbRd 0.4-11, gdata 2.18.0, generics 0.0.2, ggforce 0.3.1, ggplot2 3.3.0, ggplotify 0.0.5, ggpubr 0.2.5, ggraph 2.0.2, ggrepel 0.8.2, ggridges 0.5.2, ggsignif 0.6.0, ggthemes 4.2.0, globals 0.12.5, glue 1.4.0, GO.db 3.10.0, GOSemSim 2.12.1, gplots 3.0.3, graphlayouts 0.6.0, gridExtra 2.3, gridGraphics 0.5-0, gtable 0.3.0, gtools 3.8.2, haven 2.2.0, hms 0.5.3, htmltools 0.4.0,

htmlwidgets 1.5.1, httr 1.4.1, ica 1.0-2, igraph 1.2.5, IRanges 2.20.2, irlba 2.3.3, jsonlite 1.6.1, KernSmooth 2.23-16, knitr 1.28, lattice 0.20-41, lazyeval 0.2.2, leiden 0.3.3, lifecycle 0.2.0, limma 3.42.2, listenv 0.8.0, lmtest 0.9-37, lsei 1.2-0, lubridate 1.7.8, magrittr 1.5, MASS 7.3-51.5, Matrix 1.2-18, matrixStats 0.56.0, memoise 1.1.0, metap 1.3, mnormt 1.5-6, modelr 0.1.6, multcomp 1.4-13, multtest 2.42.0, munsell 0.5.0, mutoss 0.1-12, mvtnorm 1.1-0, nlme 3.1-145, npsurv 0.4-0, numDeriv 2016.8-1.1, openssl 1.4.1, patchwork 1.0.0, pbapply 1.4-2, pheatmap 1.0.12, pillar 1.4.3, pkgbuild 1.0.6, pkgconfig 2.0.3, pkgload 1.0.2, plotly 4.9.2.1, plotrix 3.7-7, plyr 1.8.6, png 0.1-7, polyclip 1.10-0, prettyunits 1.1.1, processx 3.4.2, progress 1.2.2, ps 1.3.2, purrr 0.3.3, qvalue 2.18.0, R6 2.4.1, RANN 2.6.1, RColorBrewer 1.1-2, Rcpp 1.0.4.6, RcppAnnoy 0.0.16, Rdpack 0.11-1, readr 1.3.1, readxl 1.3.1, remotes 2.1.1, reprex 0.3.0, reshape2 1.4.4, reticulate 1.15, rlang 0.4.5, rmarkdown 2.1, ROCR 1.0-7, rprojroot 1.3-2, RSpectra 0.16-0, RSQLite 2.2.0, rstudioapi 0.11, rsvd 1.0.3, Rtsne 0.15, Rttf2pt1 1.3.8, rvcheck 0.1.8, rvest 0.3.5, S4Vectors 0.24.4, sandwich 2.5-1, scales 1.1.0, sctransform 0.2.1, sessioninfo 1.1.1, Seurat 3.1.4, sn 1.6-1, stringi 1.4.6, stringr 1.4.0, survival 3.1-12, testthat 2.3.2, TFisher 0.2.0, TH.data 1.0-10, tibble 3.0.0, tidygraph 1.1.2, tidyr 1.0.2, tidyselect 1.0.0, tidyverse 1.3.0, triebeard 0.3.0, tsne 0.1-3, tweenr 1.0.1, umap 0.2.5.0, urltools 1.7.3, usethis 1.6.0, uwot 0.1.8, vctrs 0.2.4, viridis 0.5.1, viridisLite 0.3.0, withr 2.1.2, xfun 0.13, xml2 1.3.1, yaml 2.2.1, zoo 1.8-7

Code availability
Code to complete the analyses presented in this manuscript and generate corresponding figure panels and tables is publicly available on GitHub at https://github.com/ndharia-broad/peddep.

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

Data availability
CRISPR-Cas9 screening results for DepMap version 20Q1 (including raw data) and the genomic characterization of cancer cell lines (whole-exome sequencing and RNA sequencing) used in this study are publicly available at https://depmap.org and also on figshare (https://figshare.com/articles/dataset/DepMap_20Q1_Public/11791698). Subsets of the raw sequencing data from whole exome sequencing and RNA sequencing used in this study are available at Sequence Read Archive (SRA, https://www.ncbi.nlm.nih.gov/sra) and European Genome-phenome Archive (EGA, https://www.ebi.ac.uk/ega/) accession numbers: SRA PRJNA523380 (CCLE), SRA PRJNA261990 (Ewing sarcoma), and EGAS00001000978 (Sanger) (Supplementary Data Table 1). The remainder of the raw sequencing data is in the process of being deposited in SRA via dbGaP (https://dbgap.ncbi.nlm.nih.gov/), delayed in part as these are legacy cell lines. In the interim, we will work with specific requests to expedite the process (contact depmap@broadinstitute.org). Additionally, the pediatric-specific subsets of the processed DepMap version 20Q1 data presented in this study (dependency, mutations, copy number, expression, fusions) are available at our companion website at https://depmap.org/peddep.

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 CRISPR-Cas9 screening of cancer cell lines, no sample size was predetermined as the goal is to screen all possible human cancer cell lines. At this time, data for 739 human cancer cell lines were available and the subset of 655 cancer cell lines relevant to this study were used. The sample size for cell line expression, copy number, and mutation analyses were limited to the available data in the DepMap as of 20Q1 as well as TreeHouse, and there were determined to be adequate sample sizes as they are the largest, most comprehensive collection of such data to date.
Data exclusions	Data for cell lines of tumor types defined by characteristic genetic aberrations that did not contain the genetic aberration were excluded (in this study data for cell line CHLA57).
Replication	For CRISPR-Cas9 screening of cancer cell lines, replicate information is available at depmap.org. All biologic validation experiments including MCL1 knockout, inhibitor viability studies and rescue experiments were performed at least in duplicate, with all replicates with similar successful results. One representative example is shown.
Randomization	Not applicable to this study as this study involved the analyses of large in vitro datasets without animal or patient data.
Blinding	Not applicable to this study as this study involved the analyses of large in vitro datasets without animal or patient data.

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

Immunoblotting was carried out with the following antibodies, all at a dilution of 1:1000.
MCL1 (Cell Signaling Technology Cat. No. 94296S)
PARP (Cell Signaling Technology Cat. No. 9542S)
Caspase 3 (Cell Signaling Cat. No. 9662S)
Cleaved Caspase 3 (Cell Signaling Technology Cat. No. 9664S)
Tubulin (Sigma Cat. No. T6199)

Secondary antibodies (dilution 1:4000):
Horseradish peroxidase, mouse (Fisher Cat. No. 45000680)
Horseradish peroxidase, rabbit (Fisher Cat. No. 45000682)

Validation

All above antibodies were confirmed as specified by the manufacturer. Please see validation statements from the manufacturers for further validation information specific to each antibody: Cell Signaling Technology (https://www.cellsignal.com/about-us/our-approach-process/antibody-validation-western-blotting); Sigma (https://www.sigmaaldrich.com/technical-documents/articles/biology/antibody-standard-validation.html).

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)

The cell line sources for the >1,000 cell lines employed in this study are available at depmap.org or on figshare in the following file: https://figshare.com/articles/dataset/DepMap_20Q1_Public/11791698?file=21781221.

Authentication

All cell lines used were STR tested for identity at either the Dana-Farber Cancer Institute molecular diagnostics core facility or The Broad Institute of MIT and Harvard.

Mycoplasma contamination

All cells were routinely tested for mycoplasma and confirmed negative.

Commonly misidentified lines
(See ICLAC register)

The following lines were included in the CRISPR-Cas9 screen or genomic characterization and are on the commonly misidentified lines list version 9 ICLAC: ACCS, AZ521, CGTHW1, COLO818, ETK1, GOS3, GRM, GT3TKB, JHU028, K2, KCIMOH1, KP1N, KPL1, LN319, LN443, MELHO, MKN28, NCIH1304, NCIH630, ONCODG1, OVMIU, SKNMC, SF767, SKMG1, SNB19, SW527, TE12, YMB1, YMB1E.

Pediatric Cell Lines:
SKNMC: Included in ICLAC as misidentified tumor type, actual cell type Ewing's sarcoma. Used in this study since DepMap and our study classifies this correctly as the actual cell type Ewing's sarcoma.

Adult Cell Lines:
The commonly misidentified adult cell lines (ACCS, AZ521, CGTHW1, COLO818, ETK1, GOS3, GRM, GT3TKB, JHU028, K2, KCIMOH1, KP1N, KPL1, LN319, LN443, MELHO, MKN28, NCIH1304, NCIH630, ONCODG1, OVMIU, SF767, SKMG1, SNB19, SW527, TE12, YMB1, YMB1E) were used in this study as the focus for adult cancer cell lines were large bulk trends without focusing on individual adult cell lines. Despite misclassification, these cell lines are adult cancer cell lines and therefore inform our pediatric vs adult cancer analyses. Additionally, as DepMap continues to correctly identifies cell lines, the majority of these adult cell lines have the correct tumor type assigned in our study as indicated at depmap.org or on figshare in the following file: https://figshare.com/articles/dataset/DepMap_20Q1_Public/11791698?file=21781221.