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1 **Conservation of copy number profiles during engraftment and passaging of**
2 **patient-derived cancer xenografts**

3
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61

62

63 **ABSTRACT**

64 Patient-derived xenografts (PDXs) are resected human tumors engrafted into mice for preclinical
65 studies and therapeutic testing. It has been proposed that the mouse host affects tumor evolution
66 during PDX engraftment and propagation, impacting the accuracy of PDX modeling of human
67 cancer. Here we exhaustively analyze copy number alterations (CNAs) in 1451 PDX and matched
68 patient tumor (PT) samples from 509 PDX models. CNA inferences based on DNA sequencing

69 and microarray data displayed substantially higher resolution and dynamic range than gene
70 expression-based inferences, and they also showed strong CNA conservation from PTs through
71 late-passage PDXs. CNA recurrence analysis of 130 colorectal and breast PT/PDX-early/PDX-
72 late trios confirmed high-resolution CNA retention. We observed no significant enrichment of
73 cancer-related genes in PDX-specific CNAs across models. Moreover, CNA differences between
74 patient and PDX tumors were comparable to variations in multi-region samples within patients.
75 Our study demonstrates the lack of systematic copy number evolution driven by the PDX mouse
76 host.

77

78 **MAIN**

79 Human tumors engrafted into transplant-compliant recipient mice (patient-derived xenografts,
80 PDX) have advantages over prior model systems of human cancer (e.g genetically engineered
81 mouse models^{1,2} and cancer cell lines³) for preclinical drug efficacy studies because they allow
82 researchers to directly study human cells and tissues *in vivo*⁴⁻⁷. Comparisons of genome
83 characteristics and histopathology of primary tumors and xenografts of various cancer types⁸⁻¹⁴
84 have demonstrated that the biological properties of patient-derived tumors are largely preserved
85 in xenografts. A growing body of literature supports their use in cancer drug discovery and
86 development¹⁵⁻¹⁷.

87 A caveat to PDX models is that intratumoral evolution can occur during engraftment and
88 passaging¹⁸⁻²². Such evolution could potentially modify treatment response of PDXs with respect
89 to the patient tumors^{19,23,24}, particularly if the evolution were to systematically alter cancer-related
90 genes. Recently, Ben-David et al.²³ reported extensive PDX copy number divergence from the
91 patient tumor of origin and across passages, based mainly on large-scale assessment of copy
92 number alterations (CNA) profiles inferred from gene expression microarray data. They raised
93 concerns about genetic evolution in PDXs as a consequence of mouse-specific selective
94 pressures, which could impact the capacity of PDXs to faithfully model patient treatment
95 response. Such results contrast with reports that have observed genomic fidelity of PDX models
96 with respect to the originating patient tumors and from early to late passages by direct DNA
97 measurements in several dozen PDX models^{8,11,25}.

98 Here we resolve these contradicting observations by systematically evaluating CNA
99 changes and the genes they affect during engraftment and passaging in a large, internationally
100 collected set of PDX models, comparing both RNA and DNA-based approaches. The data
101 collected, as part of the U.S. National Cancer Institute (NCI) PDXNet (PDX Development and
102 Trial Centers Research Network) Consortium and EurOPDX consortium, comprises patient tumor

103 (PT) and PDX samples from >500 models. Our study demonstrates that prior reports of systematic
104 copy number divergence between PTs and PDXs are incorrect, and that there is high retention of
105 copy number during PDX engraftment and passaging. This work also finely enumerates the copy
106 number profiles in hundreds of publicly available models, which will enable researchers to assess
107 the suitability of each for individualized treatment studies.

108

109 **RESULTS**

110 **Catalog of copy number alterations in PDXs**

111 We have assembled copy number alteration (CNA) profiles of 1451 unique samples (324
112 PT, and 1127 PDX samples) corresponding to 509 PDX models contributed by participating
113 centers of the PDXNET, the EurOPDX consortium, and other published datasets^{11,26} (see
114 METHODS, Supplementary Methods, Supplementary Table 1, Supplementary Fig. 1). We
115 estimated copy number (CN) from five data types: single nucleotide polymorphism (SNP) array,
116 whole-exome sequencing (WES), low-pass whole-genome sequencing (WGS), RNA sequencing
117 (RNA-Seq) and gene expression array data, yielding 1548 tumor datasets including samples
118 assayed on multiple platforms (see METHODS, Supplementary Methods, Supplementary Data
119 1). Paired-normal DNA and in some cases, paired normal RNA, were also obtained to calibrate
120 WES and RNA-Seq tumor samples.

121 The combined PDX data represent 16 broad tumor types derived from American,
122 European and Asian cancer patients (see METHODS), with 64% (n=324) of the models having
123 their corresponding patient tumors assayed and another 64% (n=328) having multiple PDX
124 samples of either varying passages (P0 – P21) or varying lineages from propagation into distinct
125 mice (Fig. 1a, Supplementary Table 2). The distributions of PT and PDX samples across different
126 tumor types, passages and assay platforms (Fig. 1b, Supplementary Fig. 2-12) show the wide
127 spectrum of this combined dataset, which, to the best of our knowledge, is the most
128 comprehensive copy number profiling of PDXs compiled to date (Supplementary Note 1).
129 Additionally, our data include seven patients with multiple tumors collected either from different
130 relapse time points or different metastatic sites, resulting in multiple PDX models derived from a
131 single patient.

132

133 **Comparison of CNA profiles from SNP array, WES and gene expression data**

134 To compare the CNA profiles from different platforms in a controlled fashion, we assembled a
135 dataset with matched measurements across multiple platforms (Supplementary Table 3,
136 Supplementary Fig. 13-17). Copy number calling has been reported to be noisy for several data

137 types^{27,28}, and we observed that quantitative comparisons between CNA profiles are sensitive to:
138 (1) the thresholds and baselines used to define gains and losses, (2) the dynamic range of copy
139 number values from each platform, and (3) the differential impacts of normal cell contamination
140 for different measurements. To control for such systematic biases, we assessed the similarity
141 between two CNA profiles using the Pearson correlation of their $\log_2(\text{CN ratio})$ values across the
142 genome in 100kb windows. Regions with discrepant copy number were identified as those with
143 outlier values from the linear regression model (see METHODS).

144

145 **CNAs from WES are consistent with CNAs from SNP array data.** As earlier studies reported
146 that CNA estimates from WES data have more uncertainties than those from SNP arrays^{29,30}, we
147 implemented a WES-based CNA pipeline and validated it against SNP array-based estimates^{31,32}
148 for matched samples. Copy number gain/loss segments (see METHODS) from SNP arrays were
149 of a higher resolution (Fig. 2a; median/mean segment size: 1.49/4.05 Mb for SNP, 4.70/14.6 Mb
150 for WES, $p < 2.2e^{-16}$) and wider dynamic range (Fig. 2b; range of $\log_2(\text{CN ratio})$: $-8.62 - 2.84$ for
151 SNP, $-3.04 - 1.85$ for WES, $p < 2.2e^{-16}$). The difference in range is apparent in the linear
152 regressions between platforms (Supplementary Fig. 18). These observations take into account
153 the broad factors affecting CNA estimates across platforms, such as the positional distribution of
154 sequencing loci; the sequencing depth of WES; and the superior removal of normal cell
155 contamination by SNP array CNA analysis workflows using SNP allele frequencies³³.

156 We observed strong agreement between SNP arrays and WES, with significantly higher
157 Pearson correlation coefficients on matched samples than samples of different models (range:
158 $0.913 - 0.957$ for matched samples, $0.0366 - 0.354$ for unmatched samples, $p = 1.02e^{-06}$), with
159 the exception of two samples that lacked CNA aberrations and were removed (Fig. 2c,
160 Supplementary Fig. 13, 18, 19). The discordant copy number regions largely correspond to small
161 focal events (average size 1.53Mb) detectable by SNP arrays but missed by WES
162 (Supplementary Fig. 18, Extended Data Fig. 1a, see METHODS). Hence, CNA profiling by WES
163 is reliable in most regions in this small dataset, with 99% of the genome locations across the
164 samples consistent with the values from SNP arrays (Supplementary Note 2). These PT-based
165 observations are also applicable to PDXs given that mouse DNA is absent in SNP array signal
166 and removed from WES reads³⁴⁻³⁶.

167

168 **Low accuracy for gene expression-derived CNA profiles.** To compare the suitability of gene
169 expression for quantifying evolutionary changes in CNA, we adapted the e-karyotyping
170 method^{23,37,38} for RNA-Seq and gene expression array data (Supplementary Fig. 15, 17, see

171 METHODS). Copy number segments calibrated by non-tumor expression were of higher
172 resolution (Fig. 2a; median/mean segment size: 36.0/51.9 Mb for RNASEQ NORM, 48.2/65.3 Mb
173 for RNASEQ TUM, $p < 2.2e^{-16}$; 62.0/72.4 Mb for EXPARR NORM, 80.1/85.2 Mb for EXPARR
174 TUM, $p = 2.20e^{-07}$) and wider dynamic range (Fig. 2b; range of $\log_2(\text{CN ratio})$: $-2.07 - 2.17$ for
175 RNASEQ NORM, $-1.79 - 1.81$ for RNASEQ TUM, $p < 2.2e^{-16}$; $-1.40 - 1.89$ for EXPARR NORM,
176 $-1.13 - 1.59$ for EXPARR TUM, $p = 4.09e^{-07}$) compared to segments calculated by calibration
177 with tumor samples. These alternative expression calibrations yielded biased gain and loss
178 frequencies (Supplementary Note 3, Supplementary Fig. 20) and strong variability (Pearson
179 correlation range: $0.218 - 0.943$ for RNASEQ NORM vs TUM, $0.377 - 0.869$ for EXPARR NORM
180 vs TUM) in the CNA calls (Fig. 2c, Supplementary Fig. 21). This range of correlations was far
181 greater than was observed in comparisons between the DNA-based methods ($p = 9.37e^{-5}$ and p
182 $= 3.28e^{-07}$ relative to SNP vs WES). This indicates the problematic nature of RNA-based CNA
183 calling with calibration by tumor samples, which has been used when normal samples are not
184 available.

185 Furthermore, expression-based calling had segmental resolution an order of magnitude
186 worse than the DNA-based methods (Fig. 2a, Supplementary Fig. 14-17; median/mean segment
187 size: 3.45/14.0 Mb for WES, 36.0/51.9 Mb for RNASEQ NORM, $p < 2.2e^{-16}$; 1.73/ 5.18 Mb for
188 SNP, 62.0/72.4 Mb for EXPARR NORM, $p < 2.2e^{-16}$). The range of detectable copy number values
189 was also superior for DNA-based methods (Fig. 2b; range of $\log_2(\text{CN ratio})$: $-6.00 - 5.33$ for WES,
190 $-2.07 - 2.17$ for RNASEQ NORM, $p < 2.2e^{-16}$; $-9.19 - 4.65$ for SNP, $-1.40 - 1.89$ for EXPARR
191 NORM, $p < 2.2e^{-16}$). In addition, there was a lack of correlation between the expression-based
192 and DNA-based methods (range: $0.0541 - 0.942$ for WES vs RNASEQ (NORM); $0.00517 - 0.921$
193 for SNP vs EXPARR (NORM)) (Fig. 2c, Supplementary Fig. 22, 23). CNA estimates after tumor-
194 based expression normalization resulted in further discordance with DNA-based copy number
195 results (range: $-0.182 - 0.929$, $p = 0.0468$ for WES vs RNASEQ (TUM); $-0.0274 - 0.847$, $p =$
196 $2.20e^{-06}$ for SNP vs EXPARR (TUM)). Many focal copy number events detected by DNA-based
197 methods, as well as some larger segments, were missed by the expression-based methods
198 (Extended Data Fig. 1b-e). Representative examples illustrating the superior resolution and
199 accuracy from DNA-based estimates are given in Fig. 2d (correlations shown in Extended Data
200 Fig. 2).

201

202 **Concordance of PDXs with patient tumors and during passaging**

203 We next adopted a pan-cancer approach to elucidate potential tumor type-independent copy
204 number evolution in PDXs driven by the mouse host. We tracked the similarity of CNA profiles

205 during tumor engraftment and passaging by calculating the Pearson correlation of gene-level
206 copy-number for samples measured on the same platform (see METHODS, Extended Data Fig.
207 3, Supplementary Fig. 24-60, 62). All pairs of samples derived from the same PDX model were
208 compared – yielding 501 PT-PDX and 1257 PDX-PDX pairs (Supplementary Note 4).

209 For all DNA-based platforms we observed strong concordance between matched PT-PDX
210 and PDX-PDX pairs, significantly higher than between different models from the same tumor type
211 and the same center ($p < 2.2e^{-16}$) (Fig. 3a-c, correlation heatmaps in Supplementary Fig. 24-60).
212 We observed no significant difference in the correlation values between PT-PDX and PDX-PDX
213 pairs for SNP array data (median correlation PT-PDX = 0.950, PDX-PDX = 0.964; $p > 0.05$),
214 though there were small but statistically significant shifts for WES (PT-PDX = 0.874, PDX-PDX =
215 0.936; $p = 2.31e^{-16}$) and WGS data (PT-PDX = 0.914, PDX-PDX = 0.931; $p = 0.000299$). PT
216 samples have a smaller CNA range than their derived PDXs (median ratio PT/PDX / PDX/PDX:
217 0.832/0.982, $p = 0.000120$ for SNP; 0.626/0.996, $p < 2.2e^{-16}$ for WES; 0.667/1.00, $p < 2.2e^{-16}$ for
218 WGS; Supplementary Fig. 62b, Extended Data Fig. 4), which can be attributed to stromal DNA in
219 PT samples “diluting” the CNA signal. In PDXs, the human stromal DNA is reduced^{11,13}. The
220 minimal effect for SNP array data confirms this interpretation as human stromal DNA contributions
221 can be removed from SNP arrays based on allele frequencies of germline heterozygous sites,
222 while such contributions to WES and WGS have higher uncertainties. We also performed intra-
223 model comparisons using RNA-based approaches, which showed that the expression-based
224 comparison of CNA profiles between PT and PDXs can lead to the overestimation of copy number
225 changes during engraftment and passage (Supplementary Fig. 63, Supplementary Note 5).

226
227 **Late PDX passages maintain CNA profiles similar to early passages.** Systematic mouse
228 environment-driven evolution, if present, should reduce CN correlations at each subsequent
229 passage. However, we observed no apparent effect during passaging on the SNP, WES, or WGS
230 platforms (Fig. 3d-f, Extended Data Fig. 5). For example, the SNP data showed no significant
231 difference between passages (Fig. 3d, Extended Data Fig. 5a). For those models having very late
232 passages, there was a small but statistically significant correlation decrease compared to models
233 with earlier passages ($p < 8.98e^{-05}$, Extended Data Fig. 6b), indicating some copy number
234 changes can occur over long-term passaging (Supplementary Fig. 35). However even at these
235 late passages, the correlations to early passages remained high (median = 0.896). In any given
236 comparison, only a small proportion of the genes were affected by copy number changes (median:
237 2.72%, range: 1.03% – 11.9%). Genes that are deleted and subsequently gained in the later
238 passages (top left quadrant of regression plots, Extended Data Fig. 6a) suggest selection of

239 preexisting minor clones as the key mechanism in these regions. For WES and WGS data, more
240 variability in the correlations can be observed (Fig. 3e, f, Extended Data Fig. 5b, c), likely due to
241 a few samples having more stromal contamination or low aberration levels (Supplementary Fig.
242 62b, Extended Data Fig. 4). However, the lack of downward trend over passaging was also
243 apparent in these sets (Supplementary Note 6).

244

245 ***PDX copy number profiles trace lineages.*** We next compared the similarity of engrafted PDXs
246 of the same model with the same passage number. Surprisingly, we discovered that these pairs
247 were not more similar than pairs of PDXs from different passage numbers (Fig. 3d-e, Extended
248 Data Fig. 5, Supplementary Note 7). Such similarity in correlations suggested that copy number
249 divergence might be associated with effects other than passaging. To further this analysis, we
250 defined, for JAX SNP array and PDMR WES datasets, samples within a lineage as those differing
251 only by consecutive serial passages, while we defined lineages as split when a tumor was divided
252 and propagated into multiple mice (Fig. 3g). For the EurOPDX CRC and BRCA WGS datasets,
253 such lineage splitting was due only to cases with initial engraftment of different fragments of the
254 PT, i.e., PDX samples of different passages were considered as different lineages if they originate
255 from different PT fragments. We observed lower correlation between PDX samples from different
256 lineages compared to within a lineage (Fig. 3h, $p = 0.0233$ for SNP, $p = 0.00119$ for WES, $p =$
257 0.000232 for WGS), despite a majority of these pairwise comparisons exhibiting high correlation
258 (>0.9) (Supplementary Note 8, 9). This suggests that lineage-splitting is often responsible for
259 deviations in CNAs between samples, and that copy number evolution during passaging mainly
260 arises from evolved spatial heterogeneity²⁴.

261 We further explored if the stability of copy number during engraftment and passaging is
262 affected by mutations in genes known to impact genome stability (see METHODS). Overall, we
263 observed that presence of mutations in such genes does not lead to increased copy number
264 changes during PDX engraftment and passaging (Supplementary Note 10, Supplementary Fig.
265 66).

266

267 **Genes with copy number alterations acquired during engraftment and passaging show no**
268 **preference for cancer or treatment-related functions.**

269 Next, we investigated which genes tend to undergo copy number changes. Genes with changes
270 during engraftment or during passaging were identified based on a residual threshold with respect
271 to the improved linear regression³⁹ (see METHODS, Extended Data Fig. 3). To test for functional
272 biases, we compared CNA-altered genes to gene sets with known cancer- and treatment-related

273 functions⁴⁰⁻⁴³ (see METHODS). We calculated the proportion of altered genes for sample pairs
274 from each model across all platforms and tumor types. In agreement with the high maintenance
275 of CNA profiles described above, we found the proportion of altered protein-coding genes to be
276 low (median/IQR: 1.90%/ 4.11% PT-PDX, 1.25%/ 3.60% PDX-PDX pairs, Fig. 4a). Only 8.78% of
277 PT-PDX pairs and 4.53% PDX-PDX pairs showed >10% of their protein-coding genes altered.
278 We observed no significant increase ($p > 0.1$) in alterations among any of the cancer gene sets
279 compared to the background of all protein-coding genes, for either the PT-PDX or PDX-PDX
280 comparisons. This provides evidence that there is no systematic selection for CNAs in oncogenic
281 or treatment-related pathways during engraftment or passaging. We next considered tumor-type-
282 specific effects, focusing on tumor types with larger numbers of models to ensure statistical
283 power. We observed no significant increase in alterations in tumor-type-specific driver gene sets
284 significantly altered in TCGA⁴⁴⁻⁴⁷ compared to the background ($p > 0.1$) for either PT-PDX or PDX-
285 PDX comparisons (Fig. 4b, Supplementary Note 11).

286

287 **Low recurrence of altered genes across models.** We observed a very low recurrent frequency
288 (Fig. 4c, see METHODS), with only 12 and 2 genes recurring at > 5% frequency for PT-PDX and
289 PDX-PDX comparisons, respectively (Supplementary Table 4). No gene had a recurrence
290 frequency higher than 8.96% (Supplementary Note 12). None of these recurrent genes
291 overlapped cancer- or treatment-related gene sets, nor did they intersect genes (n=3) reported
292 by Ben-David et al.²³ to have mouse-induced copy number changes associated with drug
293 response in the CCLE^{48,49} database (Supplementary Note 12).

294

295 **Absence of CNA shifts in 130 WGS patient tumor, early passage PDX and late passage**
296 **PDX trios**

297 We next investigated whether recurrent CNA changes occur in PDXs in a tumor-type specific
298 fashion. To this aim, we analysed further the WGS-based CNA profiles of large metastatic
299 colorectal (CRC) and breast cancer (BRCA) series, composed of matched trios of PT, PDX at
300 early passage (PDX-early) and PDX at later passage (PDX-late). Genomic Identification of
301 Significant Targets in Cancer (GISTIC)^{50,51} analysis was applied separately to identify recurrent
302 CNAs in each PT, PDX-early and PDX-late cohorts of CRC and BRCA (see METHODS,
303 Supplementary Table 6). As expected, CRCs and BRCA generated different patterns of
304 significant CNAs, but within each tumor type GISTIC profiles of the PT, PDX-early, and PDX-late
305 cohorts were virtually indistinguishable (Fig 5a, Extended Data Fig. 7, Supplementary Note 13),
306 demonstrating no gross genomic alteration systematically acquired or lost in PDXs.

307 We then carried out gene-level analysis, where each gene was attributed the GISTIC
308 score (G-score) of the respective segment (Supplementary Table 7). In both the CRC and BRCA
309 cohorts, gene-level G-scores of the PTs were highly correlated with the respective PDX-early and
310 PDX-late cohorts (Fig. 5b, c). Moreover, PT versus PDX correlations were comparable to PDX-
311 early versus PDX-late correlations. To search for progressive shifts, we compared the change in
312 G-score (ΔG): (i) from tumor to PDX-early and (ii) from PDX-early to PDX-late. Correlations in
313 these two ΔG values were absent or even slightly negative (bottom-right panels of Fig. 5b, c,
314 Supplementary Note 13). Overall, these results confirmed the absence of systematic CNA shifts
315 in PDXs even under high resolution, gene-level analysis. To evaluate the possibility of systematic
316 copy number evolution at the pathway level in these trios, we performed Gene Set Enrichment
317 Analysis (GSEA)^{52,53} using G-scores to rank genes in each cohort (See METHODS,
318 Supplementary Note 14). For both CRC and BRCA, the Normalized Enrichment Score (NES)
319 profiles for the ~8000 gene sets of PTs were highly correlated with the respective PDX-early and
320 PDX-late cohorts (Fig. 5d, e). Moreover, PT versus PDX correlations were comparable to PDX-
321 early versus PDX-late correlations. To search for progressive shifts, we calculated for each
322 significant gene set ΔNES values between PT and PDX-early, as well as between early and late
323 PDX. Similar to what was observed for the ΔG -scores, correlations were absent or at most slightly
324 negative (bottom-right panels of Fig. 5d, e), confirming the absence of systematic CNA-based
325 functional shifts in PDXs.

326

327 **CNA evolution across PDXs is no greater than variation in patient multi-region samples**

328 As a reference for the treatment relevance of PDX-specific evolution, we compared to levels of
329 copy number variation in multi-region samples of patient tumors. For this we used copy number
330 data from multi-region sampling of non-small-cell lung cancer from the TRACERx Consortium⁵⁴,
331 performing analogous CNA correlation and gene analyses between multi-region pairs
332 (Supplementary Fig. 69). We observed no significant differences in correlation ($p > 0.05$) between
333 patient multi-region and lung cancer PT-PDX pairs, while PDX-PDX pairs in fact showed
334 significantly better correlation than the multi-region pairs ($p < 0.05$, Fig. 6a), consistent across all
335 lung cancer subtypes. Cancer gene set analyses confirmed these results, with multi-region
336 samples showing greater differences than either PT-PDX or PDX-PDX comparisons, across all
337 the cancer gene sets considered ($p < 0.05$, Fig. 6b, Extended Data Fig. 8). These results show
338 that PDX-associated CNA evolution is no greater than what patients experience naturally within
339 their tumors. Our PDX collection also contains a few cases in which the patient tumor was
340 assayed at multiple time points (relapse/metastasis) or multiple metastatic sites, allowing for

341 controlled comparison of intra-patient variation versus PDX evolution (Supplementary Fig. 3, 4,
342 7). Despite a lower median in correlations among intra-patient samples, the difference compared
343 to CNA evolution during engraftment (PT-PDX) is not statistically significant ($p > 0.05$, Fig. 6c).
344 CNA profiles for these samples are shown visually in Fig. 6d.

345

346 **DISCUSSION**

347 Here we have investigated the evolutionary stability of patient-derived xenografts, an important
348 model system for which there have been prior reports of mouse-induced copy number evolution.
349 To better address this, we assembled the largest collection of CNA profiles of PDX models
350 reported to date, comprising PDX models with multiple passages and their originating patient
351 tumors. Our analysis demonstrated the reliability of copy number estimation by DNA-based
352 measurements over RNA-based inferences, which are substantially inferior in terms of resolution
353 and accuracy (Supplementary Note 15). The importance of DNA measurements is supported by
354 the inconsistent conclusions by two independent studies, Ben-David et al.^{23,55} and Mer et al.⁵⁶, on
355 the same PDX expression array dataset by Gao et al.¹⁵ Ben-David et al. concluded that drastic
356 copy number changes, driven by mouse-specific selection, often occur within a few passages. On
357 the other hand, Mer et al. reported high similarity between passages of the same PDX model
358 based on direct correlations of gene expression, consistent with our findings in large, independent
359 DNA-based datasets.

360 The CN shifts inferred by Ben-David et al. are inherently impacted by major technical
361 issues. First, the microarray signal for PT samples is diluted by introgressed human stromal cells,
362 while in PDXs mouse stromal transcripts hybridize only to a fraction of the human probes⁵⁷.
363 Consequently, PT samples with substantial stromal content would display a reduced signal
364 compared to the corresponding PDX, which can lead to an erroneous inference of systematic
365 increase in aberrations during PDX engraftment when gain/loss regions are directly compared.
366 Second, the mouse host microenvironment can affect the transcriptional profile of the PDX
367 tumor⁵⁸ and the quantity of mouse stroma can vary across passages. This can result in variability
368 in the expression signal which can be wrongly inferred as CN changes, both from the tumor itself
369 and through cross hybridization of mouse RNA to the human microarray. Although improved
370 concordance in expression between PT and PDX can be achieved with RNA sequencing with the
371 removal of mouse reads^{59,60}, we observed that expression-based copy number inferences still
372 have low resolution and robustness. Hence, many cancer-driving genes, which are found mainly
373 in focal events with a size of 3Mb or lower⁶¹⁻⁶⁴, cannot be evaluated for PDX-specific alterations.
374 These issues are further worsened by the lack of tissue-matched normal gene expression profiles

375 for calibration³⁷, which have been only intermittently available but can substantially impact copy
376 number inferences. Because of these considerations, the question of how much PDXs evolve as
377 a consequence of mouse-specific selective pressures cannot be adequately addressed by
378 expression data.

379 The studies we have presented here take into account the above issues by use of DNA
380 data, as well as by assessing copy number changes by pairwise correlation/residual analysis to
381 control for systematic biases, and they overall confirm the high retention of CNA profiles from
382 PDX engraftment to passaging. We do observe larger deviations between PT-PDX than in PDX-
383 PDX comparisons, though this is likely due to dilution of PT signal by human stromal cells.
384 Interestingly, we found that a major contributor to the differences between PDX samples is
385 lineage-specific drift associated with splitting of tumors into fragments during PDX propagation.
386 This spatial evolution within tumors appears to affect sample comparisons more than time or the
387 number of passages. This suggests that PDX expansion and passaging is the bottleneck of copy
388 number evolution in PDXs, reflecting stochasticity in sampling within spatially heterogeneous
389 tumors (Supplementary Note 16).

390 A challenge for evaluating any model system is that there is no clear threshold for genomic
391 change that determines whether the model will still reflect patient response. Genetic variation
392 among multi-region samples within a patient can shed light on this point^{54,65-68} since the goal of a
393 successful treatment would be to eradicate all of the multiple regions of the tumor. We found that
394 the copy number differences between PT and PDX are no greater than the variations among
395 multi-region tumor samples or intra-patient samples. Thus, concerns about the genetic stability of
396 the PDX system are likely to be less important than the spatial heterogeneity of solid tumors
397 themselves. This result is consistent with our results on lineage effects during passaging, which
398 indicate that intratumoral spatial evolution is the major reason for genetic drift.

399 We observed no evidence for systematic mouse environment-induced selection for cancer
400 or treatment-related genes via copy number changes, though individual cases vary (see example
401 in Extended Data Fig. 6c). Moreover, only a small fraction of sample pairs (2.44%, 43 out of 1758)
402 shows large CNA discordance (see METHODS), suggesting that clonal selection out of a complex
403 population is rare. These results indicate that the variations observed in PDXs are mainly due to
404 spontaneous intratumoral evolution rather than murine pressures (Supplementary Note 17).

405 In summary, our in-depth tracking of CNAs throughout PDX engraftment and passaging
406 confirms that tumors engrafted and passaged in PDX models maintain a high degree of molecular
407 fidelity to the original patient tumors and their suitability for pre-clinical drug testing. At the same
408 time, our study does not rule out that PDXs will evolve in individual trajectories over time, and for

409 therapeutic dosing studies, the best practice is to confirm the existence of expected molecular
410 targets and obtain sequence characterizations in the cohorts used for testing as close to the time
411 of the treatment study as is practicable.

412

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475

476 **AUTHOR CONTRIBUTIONS**

477 X.Y.W., C.J.B., J.J., A.T.B., L.T., J.A.M., C.I., E.Medico and J.H.C. conceived and jointly
478 supervised the study. X.Y.W. organized the study, collected and structured the data, and
479 designed and carried out the analyses. J.G. collected and organized the EurOPDX data and
480 carried out the analyses. X.Y.W., E.Medico and J.H.C. wrote the manuscript. J.G, C.I., Z.-M.Z.,
481 A.S., and M.W.L. contributed to the refinement of the manuscript. A.S. and M.W.L. developed the
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495

496 **ETHICS COMPLIANCE**

497 All xenograft studies were completed in accordance with animal research ethics regulations. For
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499

500 **COMPETING INTERESTS**

501 A.L.W and B.E.W receive a portion of royalties if University of Utah licenses certain PDX models
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503 founder of, and limited partner in, StemMed Ltd., and a Manager in StemMed Holdings LLC. He
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518

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- 673
- 674

675 **FIGURE LEGENDS**

676 **Fig. 1: Patient derived xenograft datasets used for copy number profiling across 16 tumor**
677 **types.** (a) Numbers of PDX models for each tumor type, with models also having multiple PDX
678 samples or having matched patient tumor samples specified. (b) Distributions of datasets by
679 passage number and assay platform for patient tumors and PDX samples, separated by tumor
680 type. “Late” passages include P18, P19 and P21 samples.

681

682 **Fig. 2: Comparisons of resolution and accuracy for copy number alterations estimated by**
683 **DNA-based and expression-based methods.** (a) Pairwise comparisons of distributions of
684 segment size (Mb) of CNAs estimated by different measurement platforms in the validation
685 dataset. CNAs are regions with $(|\log_2(\text{CN ratio})| \geq 0.1)$. P-values indicate significance of difference
686 between distributions by two-sided Wilcoxon rank sum test. (b) Pairwise comparisons of
687 distributions of $\log_2(\text{CN ratio})$ of CNA segments. P-values were computed by two-sided
688 Kolmogorov-Smirnov test. (c) Distributions of Pearson correlation coefficient of median-centered
689 $\log_2(\text{CN ratio})$ in 100-kb windows from CNA segments between pairs of samples estimated by
690 different platforms. Samples with non-aberrant profiles in SNP array and WES data are omitted
691 (5-95% inter-percentile range of $\log_2(\text{CN ratio}) < 0.3$). P-values were computed by two-sided
692 Wilcoxon rank sum test. In the boxplots, the center line is the median, box limits are the upper
693 and lower quantiles, whiskers extend $1.5 \times$ the interquartile range, dots represent the outliers. (d)
694 Examples of CNA profiles in comparisons of different platforms. Pearson correlation coefficients
695 of CNA segments between pairs of samples are shown on the right. In all the plots, SNP: SNP

696 array, WES: whole-exome sequencing, RNASEQ: RNA sequencing, EXPARR: gene expression
697 array, NORM: normalization by median expression of normal samples, TUM: normalization by
698 median expression of tumor samples, see Supplementary Table 3 for number of samples per
699 group.

700

701 **Fig. 3: Comparisons of copy number alterations from patient tumor to early and late PDX**
702 **passages. (a-c)** Distributions of Pearson correlation coefficient of gene-based copy number,
703 estimated by (a) SNP array, (b) WES, and (c) WGS, between: PT-PDX samples from the same
704 model; PDX-PDX samples of the same model; samples of different models from a common tumor
705 type and contributing center. P-values were computed by one-sided Wilcoxon rank sum test (ns:
706 not significant, $p > 0.05$). Number of data points are indicated in the legend. (d-f) Distributions of
707 Pearson correlation coefficients of gene-based copy number, estimated by (d) SNP array, (e)
708 WES, and (f) WGS, among patient tumor and PDX passages of the same model. Comparisons
709 relative to PT and P0 are shown (higher passages are shown in Extended Data Fig. 5). In the
710 boxplots, the center line is the median, box limits are the upper and lower quantiles, whiskers
711 extend $1.5 \times$ the interquartile range, dots represent the all data points. (g) Schematic of lineage
712 splitting during passaging and expansion of tumors into multiple mice. This is a simplified
713 illustration for passaging procedures in which different fragments of a tumor are implanted into
714 different mice. (h) Pearson correlation distributions for PDX sample pairs of different lineages and
715 sample pairs within the same lineage: for JAX SNP array, PDMR WES, and EuroPDX WGS
716 datasets. P-values were computed by one-sided Wilcoxon rank sum test. For all boxplots and
717 violin plots, number of pairwise correlations are indicated in the horizontal axis labels.
718

719 **Fig. 4: Cancer gene sets analysis for copy number altered genes during engraftment and**
720 **passaging. (a)** Distribution of proportion of altered genes between pairwise PT-PDX or PDX-PDX
721 comparisons of the same model in various gene sets. Protein-coding: protein-coding genes
722 annotated by Ensembl; Oncogenic pathways: genes in oncogenic signaling pathways identified
723 by TCGA; JAX CKB Amp/Del: genes with copy number gain or over-expression / copy number
724 loss or under-expression associated with therapeutic sensitivity or resistance or changes in drug
725 response; Census Amp Del: genes from Cancer Gene Census frequently altered by amplifications
726 or deletions. CNA genes were identified by $|\text{residual}| > 0.5$ from linear regression model. (b)
727 Distribution of proportion of altered genes between pairwise PT-PDX or PDX-PDX comparisons
728 of the same model in various gene sets within breast cancer, colorectal cancer, lung
729 adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) models. TCGA Gistic

730 Amp/Del: significantly amplified/deleted genes from TCGA GISTIC analysis for the corresponding
731 tumor type. For all violin plots, P-values were computed by one-sided Wilcoxon rank sum test (ns:
732 not significant, $p > 0.1$); number of pairwise comparisons are indicated in the plot title, number of
733 genes per gene set is indicated in the horizontal axis labels. (c) Recurrence frequency of protein
734 coding genes with copy number alterations, $|\text{residual}| > 1$, across all models in PT-PDX and PDX-
735 PDX comparisons. Number of models is indicated in the horizontal axis labels.

736

737 **Fig. 5: Absence of mouse-driven recurrent CNAs during engraftment and propagation of**
738 **colorectal (CRC) and breast cancer (BRCA) PDXs.** (a) Bar charts representing genome-wide
739 GISTIC G-score for amplifications and deletions in each of the three cohorts of CRC (87 trios)
740 and BRCA (43 trios): PT, PDX-early (P0-P1 for CRC, P0-P2 for BRCA), PDX-late (P2-P7 for CRC,
741 P3-P9 for BRCA). (b-c) Scatter plots comparing gene-level GISTIC G-score between each of the
742 three cohorts, for (b) CRC and (c) BRCA. Bottom-right panels of (b) and (c): scatter plots
743 comparing Δ G-scores from PT to PDX-early and from PDX early to PDX-late. (d-e) Scatter plots
744 comparing GSEA Normalized Enrichment Score (NES) for gene sets between each of the three
745 cohorts, for (d) CRC (e) and BRCA. Bottom-right panels of (d) and (e): scatter plots comparing
746 Δ NES from PT to PDX-early and from PDX-early to PDX-late.

747

748 **Fig. 6: Comparison of CNA variation during PDX engraftment and passaging to CNA**
749 **variation among patient multi-region, tumor relapse, and metastasis samples.** (a)
750 Distributions of Pearson correlation coefficients of gene-based copy number for lung
751 adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), and other lung cancer
752 subtypes, comparing different datasets. TracerX multiregion: multi-region tumor samples of the
753 same patient from TRACERx (92 patient tumors, 295 multi-region samples); PT-PDX samples of
754 the same model; PDX-PDX samples of the same model. P-values were computed by two-sided
755 Wilcoxon rank sum test (ns: not significant, $p > 0.05$). (b) Distributions of proportion of altered
756 genes between multi-region tumor pairs from TRACERx, and PT-PDX and PDX-PDX pairs for
757 various gene sets for LUAD and LUSC. Gene sets and CNA thresholds are the same as Fig. 4.
758 TCGA Gistic Amp/Del and JAX CKB Amp Del gene sets are shown (other gene sets are shown
759 in Extended Data Fig. 8). P-values were computed by one-sided Wilcoxon rank sum test. Number
760 of genes per gene set are indicated in the plot title. (c) Distributions of Pearson correlation
761 coefficients of gene-based copy number between intra-patient PT (primary/relapse/metastasis)
762 pairs from the same patient and corresponding PT-PDX (derived from the same model; a different
763 PT sample from the same patient generates a different model) pairs for the same set of patients.

764 P-values were computed by two-sided Wilcoxon rank sum test (ns: not significant, $p > 0.05$).
765 Number of patients and models are indicated in the plot title. For all box plots and violin plots,
766 number of pairwise comparisons are indicated in the horizontal axis labels. In all boxplots, the
767 center line is the median, box limits are the upper and lower quantiles, whiskers extend $1.5 \times$ the
768 interquartile range, dots represent the all data points. (d) CNA profiles of PT and PDX samples
769 from patients with PDX models derived from multiple PT collection (primary/relapse/metastasis).

770

771

772 **METHODS**

773

774 **Experimental details for sample collection, PDX engraftment and passaging, and array or** 775 **sequencing**

776 See Supplementary Methods.

777

778 **Consolidating tumor types from different datasets**

779 As the terminology of tumor types/subtypes by the different contributing centers were not
780 consistent, we used the Disease Ontology database⁶⁹ (<http://disease-ontology.org/>), cancer types
781 listed in NCI website (<https://www.cancer.gov/types>) and in TCGA publications^{70,71} to unify and
782 group the tumor types/subtypes under broader terms as shown in Fig.1 and Supplementary Table
783 2.

784

785 **Copy number alteration (CNA) estimation methods**

786 **SNP array.** The estimation of CNA profiles from SNP array were detailed previously³⁴. In short,
787 for Affymetrix Human SNP 6.0 arrays, PennCNV-Affy and Affymetrix Power Tools⁷² were used to
788 extract the B-allele frequency (BAF) and Log R Ratio (LRR) from the CEL files. Due to the
789 absence of paired-normal samples, the allele-specific signal intensity for each PDX tumor were
790 normalized relative to 300 randomly selected sex-matched Affymetrix Human SNP 6.0 array CEL
791 files obtained from the International HapMap project⁷³. For Illumina Infinium Omni2.5Exome-8
792 SNP arrays (v1.3 and v1.4 kit), the Illumina GenomeStudio software was used to extract the B-
793 allele frequency (BAF) and Log R Ratio (LRR) from the signal intensity of each probe. The single
794 sample mode of the Illumina GenomeStudio was used, which normalizes the signal intensities of
795 the probes with an Illumina in-house dataset. The single tumor version of ASCAT³³ (v2.4.3 for
796 JAX SNP data, v2.5.1 for SIBS SNP data) was used for GC correction, predictions of the
797 heterozygous germline SNPs based on the SNP array platform, and estimation of ploidy, tumor

798 content and allele-specific copy number segments. The resultant copy number segments were
799 annotated with \log_2 ratio of total copy number relative to predicted ploidy from ASCAT.

800 **Whole-exome sequencing (WES) data.** Aligned bam (See Supplementary Methods) were
801 subset to target region by GATK 4.0.5.1, and SAMTools⁷⁴ v0.1.18 was used to generate the pileup
802 for each sample. Pileup data were used for CNA estimation as calculated with Sequenza²⁹ v2.1.2.
803 Both tumor and normal data, that utilized the same capture array, were used as input. pileup2seqz
804 and GC-windows (-w 50) modules from sequenza-utils.py utility were used to create the native
805 seqz format file for Sequenza and compute the average GC content in sliding windows from hg38
806 genome, respectively. Finally, we ran the three Sequenza modules with these modified
807 parameters (sequenza.extract: assembly = "hg38", sequenza.fit: chromosome.list = 1:23, and
808 sequenza.results: chromosome.list = 1:23) to estimate the segments of copy number
809 gains/losses. Finally, segments lacking read counts, in which $\geq 50\%$ of the segment with zero read
810 coverage, were removed. A reference implementation of this workflow (Supplementary Fig. 71)
811 is developed and deployed in the Cancer Genomics Cloud by Seven Bridges
812 ([https://cgc.sbgenomics.com/public/apps#pdxnet/pdx-wf-commit2/wes-cnv-tumor-normal-](https://cgc.sbgenomics.com/public/apps#pdxnet/pdx-wf-commit2/wes-cnv-tumor-normal-workflow/)
813 [workflow/](https://cgc.sbgenomics.com/public/apps#pdxnet/pdx-wf-commit2/pdx-wes-cnv-xenome-tumor-normal-workflow/), [https://cgc.sbgenomics.com/public/apps#pdxnet/pdx-wf-commit2/pdx-wes-cnv-](https://cgc.sbgenomics.com/public/apps#pdxnet/pdx-wf-commit2/pdx-wes-cnv-xenome-tumor-normal-workflow/)
814 [xenome-tumor-normal-workflow/](https://cgc.sbgenomics.com/public/apps#pdxnet/pdx-wf-commit2/pdx-wes-cnv-xenome-tumor-normal-workflow/)).

815 **Low-pass whole-genome sequencing (WGS) data.** For EuroPDX CRC liver metastasis data,
816 raw copy number profiles for each sample were estimated by QDNAseq⁷⁵ R package v1.20 by
817 dividing the human reference genome in non-overlapping 50 kb windows and counting the
818 number of reads (See Supplementary Methods) in each bin. Bins in problematic regions were
819 removed⁷⁶. Read counts were corrected for GC content and mappability by a LOESS regression,
820 median-normalized and \log_2 -transformed. Values below -1000 in each chromosome were floored
821 to the first value greater than -1000 in the same chromosome. Raw \log_2 ratio values were then
822 segmented using the ASCAT³³ algorithm implemented in the ASCAT R package v2.0.7. For
823 EuroPDX BRCA tumors, raw copy number profiles were estimated for each sample by dividing
824 the human reference genome in non-overlapping 20 kb windows and counting the number of
825 reads (See Supplementary Methods) in each bin. Only reads with at least mapping quality 37
826 were considered. Bins within problematic regions (i.e. multimapper regions) were excluded.
827 Downstream analysis to estimate copy number was conducted as described above.

828 **RNA-sequencing (RNA-Seq) and gene expression microarray (EXPARR) data.** For
829 expression-based copy number inference, we referred to the previous protocols for e-karyotyping
830 and CGH-Explorer^{37,38,77,78}. For each cancer type, expression values (see Supplementary
831 Methods) of tumor and corresponding normal samples were merged in a single table, and gene

832 identifiers were annotated with chromosomal nucleotide positions. Genes located on sex
833 chromosomes were excluded. Genes which values below 1 TPM (RNAseq) or probeset log₂-
834 values below 6 (microarray) in more than 20% of the analyzed dataset were removed. Remaining
835 gene expression values below the thresholds were respectively raised to 1 TPM or log₂-value of
836 6. In the case of multiple transcripts (RNA-seq) or probesets (microarray) per gene, the one with
837 the highest median value across the entire dataset was selected. According to the e-karyotyping
838 protocol, the sum of squares of the expression values relative to their median expression across
839 all samples was calculated for each gene, and 10% most highly variable genes were removed.
840 For each gene, the median log₂ expression value in normal samples was subtracted from the log₂
841 expression value in each tumor sample and subsequently input in CGH-explorer. For tumor-only
842 datasets, the median log₂ expression value in the same set of tumor samples was instead
843 subtracted. The preprocessed expression profiles of each sample were individually analyzed
844 using CGH-Explorer (<http://heim.ifi.uio.no/bioinf/Projects/CGHExplorer/>). CGH-PCF analysis was
845 carried out to call copy number according to parameters previously reported²³: least allowed
846 deviation = 0.25; least allowed aberration size = 30; winsorize at quantile = 0.001; penalty = 12;
847 threshold = 0.01.

848

849 **Statistical Methods**

850 All statistical analysis for data comparison were performed using either one-tailed or two-tailed
851 Wilcoxon rank sum test, two-tailed Kolmogorov–Smirnov test, or one-tailed Wilcoxon signed rank
852 test.

853

854 **Filtering and gene annotation of copy number segments**

855 Copy number (CN) segments with log₂ copy number ratio estimated from the various platforms
856 were processed in the following steps (Extended Data Fig. 3). Segments <1kb were filtered based
857 on the definition of CNA⁷⁹. In addition, SNP array segments had to be covered by >10 probes,
858 with an average probe density of 1 probe per 5kb. The copy number segments were then binned
859 into 10kb windows to derive the median log₂(CN ratio), which was subsequently used to re-center
860 the copy number segments. Median-centered copy number segments were visualized using IGV⁸⁰
861 v2.4.13 and GenVisR⁸¹ v1.16.1. Median-centered copy number of genes were calculated by
862 intersecting the genome coordinates of copy number segments with the genome coordinates of
863 genes (Ensembl Genes 93 for human genome assembly GRCh38, Ensembl Genes 96 for human
864 genome assembly GRCh37). In the case where a gene overlaps multiple segments, the most

865 conservative (lowest) estimate of copy number was used to represent the copy number of the
866 entire intact gene.

867

868 **Comparison of CN gains and losses**

869 For the comparison of resolution, range of CN values and frequency of gains and losses between
870 different platforms and analysis methods, we defined copy number gain or loss segments as –
871 Gain: $\log_2(\text{CNratio}) > 0.1$; Loss: $\log_2(\text{CN ratio}) < -0.1$.

872

873 **Correlation of CNA profiles**

874 The overall workflow to compare CNA profiles is shown in Extended Data Fig. 3. PDX samples
875 without passage information were omitted in the following downstream analysis. The copy number
876 segments were binned into 100kb-windows or smaller using Bedtools⁸² v2.26.0, and the variance
877 of $\log_2(\text{CN ratio})$ and 5-95% inter-percentile range of $\log_2(\text{CN ratio})$ values across all the bins were
878 calculated as a measure of degree of aberration for each CNA profile. A non-aberrant profile
879 results in a low variance or range. While variance can be biased for CNA profiles with small
880 segments of extreme gains or losses, we preferred the use of 5-95% inter-percentile range of
881 $\log_2(\text{CN ratio})$ to identify samples with low degree of aberration, such that a narrow range indicates
882 $\geq 90\%$ of the genome has very low-level gains and losses. The similarity of two CNA profiles is
883 quantified by the Pearson correlation coefficient of $\log_2(\text{CN ratio})$ of 100kb-windows binned from
884 segments or genes between 2 samples. Gene-based and segment-based (100kb windows)
885 correlations were highly similar (data not shown). Using correlation avoided the issue of making
886 copy number gain and loss calls based on thresholds. Sample-based variations in baseline due
887 to median-normalization and range in copy number values could introduce further inconsistencies
888 gain and loss calls between samples. Such variations are further impacted by sample-specific
889 variation in human stromal contamination or sensitivity of copy number detection by different
890 platforms. As median-centering of each CNA profile approximates normalization by the sample
891 ploidy, we confirmed that in general ploidy (estimated from ASCAT analysis of SNP array
892 samples) had no association with the copy number correlation values (Pearson's product-moment
893 correlation, $p > 0.05$, $\text{cor} = 0.0248$). One caveat of our approach, however, is that it cannot
894 distinguish genome-wide multiplication of ploidy between samples, as the correlation statistic is
895 invariant to such genome-wide transformations. As such we cannot assess whether ploidy
896 changes occur between samples of a given model.

897 **Comparison of CNA profiles between different platforms.** The copy number segments of each
898 pair of data were intersected and binned into 100kb-windows or smaller using Bedtools. The

899 Pearson correlation coefficient and linear regression model was calculated for the $\log_2(\text{CN ratio})$
900 of the windows. Windows with discrepant copy number were identified by outliers of the linear
901 regression model defined by $|\text{studentized residual}| > 3$. These outlier windows were mapped to
902 their corresponding segments to identify the size of CNA events that were discordant between
903 the different copy number estimation methods. The proportion of the genome discordant CNA
904 was calculated from the summation of the outlier windows.

905 **Identification of genes with CNA between different samples of the same model.** To compare
906 the CNA profiles between different samples (PT or PDX) of the same model, the Pearson
907 correlation coefficient and linear regression model was calculated for the $\log_2(\text{CN ratio})$ of the
908 genes for each pair of data. Prior to that, deleted genes with $\log_2(\text{CN ratio}) < -3$ were rescaled to
909 -3 to avoid large shifts in the correlation coefficient and linear regression model due to extremely
910 negative values on the log scale. Extreme outliers of the linear regression model defined by
911 $|\text{studentized residual}| > 3$ were removed to derive an improved linear regression model³⁹ not
912 biased by few extreme values. Genes with copy number changes between the samples were
913 identified by the difference in $\log_2(\text{CN ratio})$ relative to the improved linear regression model of
914 $|\text{standard residual}| < 0.5$. We also removed some samples with low correlation due to sample
915 mislabeling as they displayed high correlation with samples from other models. We also omitted
916 samples with low correlation values (< 0.6) which resulted from non-aberrant CNA profiles in
917 genomically stable tumors (5-95% inter-percentile range of $\log_2(\text{CN ratio}) < 0.3$, Supplementary
918 Fig. 62).

919 **Identification of aberrant sample pairs with highly discordant CNA profiles.** Aberrant CNA
920 profiles were identified based on the 5-95% inter-percentile range of $\log_2(\text{CN ratio}) > 0.5$, for both
921 samples. Sample pairs with Pearson correlation < 0.6 were selected as highly discordant CNA
922 profiles between them.

923 **Association of mutations with copy number correlations.** Mutational calls for each WES
924 sample used in this study were obtained using a tumor-normal variant calling workflow developed
925 for patient tumor and PDXs³⁵. Subsequently, genes with either germline and somatic variants that
926 pass through the quality filters (FILTER = PASS or germline) and IMPACT = MODERATE or
927 HIGH by SnpEff (v4.3) annotation are labeled as mutated, and wildtype if otherwise. For SNP
928 array and WGS data, we collected the mutational status (wildtype or mutated) of TP53, BRCA1
929 and BRCA2 per model where available, which may or may not be obtained from the exact same
930 tumor samples used in this study. For the JAX SNP array dataset, variant calls (tumor-only) were
931 made from various targeted sequencing approaches (TruSeq Amplicon Cancel Panel, JAX
932 Cancer Treatment Profile panel and whole exome). The workflow and filtering criteria to call

933 mutations is described elsewhere³⁴. For the HCI SNP array data, mutations were obtained from
934 whole exome sequencing (unpublished data) and were filtered for frameshift, inframe, missense,
935 and nonsense and splice-site mutations. For BCM SNP array data, mutational status were
936 obtained from clinical samples by immunohistochemistry or Sequenom⁸³ (unpublished data). For
937 WGS data, mutations were obtained from whole exome or targeted panel sequencing⁸⁴
938 (unpublished data) and high-quality and likely functional mutations were retained. For each
939 sample pair with copy number correlations, mutational status of *TP53* or *BRCA* was obtained for
940 each individual sample for WES data, while the mutational status was available on a per model
941 basis for SNP and WGS data. *BRCA* is labelled as mutated when either *BRCA1* or *BRCA2* is
942 mutated. For mutations in DNA repair genes⁸⁵ from the WES data, each pair of samples was
943 classified as mutated if any DNA repair gene was reported to be mutated in either sample.

944

945 **Annotation with gene sets with known cancer or treatment-related functions**

946 A low copy number change threshold ($|\log_2(\text{CN ratio}) \text{ change}| > 0.5$) was selected to include
947 genes with subclonal alterations. Copy number altered genes ($|\text{residual}| > 0.5$) were annotated
948 by various gene sets with cancer or treatment-related functions gathered from various databases
949 and publications (Extended Data Fig. 3):

- 950 1. Genes in 10 oncogenic signaling pathways curated by TCGA and were found to be frequently
951 altered in different cancer types⁴⁰.
- 952 2. Genes with gain in copy number or expression, or loss in copy number or expression that
953 conferred therapeutic sensitivity, resistance or increase/decrease in drug response from the JAX
954 Clinical Knowledgebase^{41,42} (JAX-CKB) based on literature curation (<https://ckbhome.jax.org/>, as
955 of 06-18-2019).
- 956 3. Genes with evidence of promoting oncogenic transformation by amplification or deletion from
957 the Cancer Gene Census⁴³ (COSMIC v89).
- 958 4. Significantly amplified or deleted genes in TCGA cohorts of breast cancer⁴⁴, colorectal cancer⁴⁵,
959 lung adenocarcinoma⁴⁶ and lung squamous cell carcinoma⁴⁷ by GISTIC analysis, which identified
960 significantly altered genomic driver regions which can be used to differentiate tumor types and
961 subtypes.

962

963 **Identification of genes with recurrent copy number changes**

964 A stringent CNA threshold ($|\log_2(\text{CN ratio}) \text{ change}| > 1.0$ with respect to linear regression model)
965 was selected to distinguish genes with possible functional impact. Genes with $|\text{residual}| > 1.0$ with
966 respect to the improved regression linear model (without discriminating gain or loss) were

967 selected for each pairwise comparison between different samples of the same model. Pairwise
968 cases in which genes are deleted in both samples ($\log_2(\text{CN ratio}) \leq -3$) are omitted. Recurrent
969 frequency for each gene across all models was calculated on a model basis such that genes with
970 copy number between multiple pairs of the same model was counted as once. This avoided the
971 bias towards models with many samples of similar copy number changes between the different
972 pairs.

973

974 **Drug response analysis using CCLE data**

975 We developed a pipeline to evaluate gene copy number effects on drug sensitivity^{86,87} by using
976 the Cancer Cell Line Encyclopedia^{48,88} (CCLE) cell line genomic and drug response data (CTRP
977 v2). We downloaded the CCLE drug response data from Cancer Therapeutics Response Portal
978 (www.broadinstitute.org/ctrp), and CCLE gene-level CNA and gene expression data from depMap
979 data portal ('public_19Q1_gene_cn.csv' and 'CCLE_depMap_19Q1_TPM.csv',
980 <https://depmap.org/portal/download/>). For CCLE drug response data, we used the area-under-
981 concentration-response curve (AUC) sensitivity scores for each cancer cell line and each drug. In
982 total, we collected gene-level \log_2 copy number ratio data derived from the Affymetrix SNP 6.0
983 platform from 668 pan-cancer CCLE cell lines, with a total of 545 cancer drugs tested. With the
984 CCLE gene-level CNA and AUC drug sensitivity scores, we performed gene-drug response
985 association analyses for genes with recurrent copy number changes. Pearson correlation p-
986 values between each gene's \log_2 (CN ratio) and each drug's AUC score across all cell lines were
987 calculated, and q-values were calculated by multiple testing Bonferroni correction. Significant
988 gene-CNA and drug associations were kept (q-value < 0.1) to further evaluate gene-expression
989 and drug response associations. If a gene's expression was also significantly correlated with AUC
990 drug sensitivity scores, particularly in the same direction (either positively or negatively correlated)
991 as the gene-CNA and drug association, that gene would be considered as significantly correlated
992 with drug response based on both its CNA and gene expression.

993

994 **Genomic Identification of Significant Targets in Cancer (GISTIC) analysis of WGS data**

995 We carried out GISTIC analysis to identify recurrent CNAs by evaluating the frequency and
996 amplitude of observed events. To obtain perfectly matching and comparable PT-PDX cohorts,
997 for GISTIC analysis, CRC trios in which at least one sample displaying non-aberrant CNA profiles
998 were excluded from the analysis resulting in a total of 87 triplets. The GISTIC⁵¹ algorithm (GISTIC
999 2.0 v6.15.28) was applied on the segmented profiles using the GISTIC GenePattern module
1000 (<https://cloud.genepattern.org/>), with default parameters and genome reference files

1001 Human_Hg19.mat for EuroPDX CRC data and hg38.UCSC.add_miR.160920.refgene.mat for
1002 EuroPDX BRCA data. For each dataset, GISTIC provides separate results (including segments,
1003 G-scores and FDR q-values) separately for recurrent amplifications and recurrent deletions.
1004 Deletion G-scores were assigned negative values for visualization. We observed that the G-Score
1005 range was systematically lower in PT cohorts, which is likely the result of the dilution of CNA by
1006 normal stromal DNA. In contrast, human stromal DNA in PDX samples were lower or negligible.
1007 To account for this difference in gene-level G-scores, PDXs at early and late passages were
1008 scaled with respect to PT gene-level G-score values using global linear regression, separately for
1009 amplification and deletion outputs.

1010

1011 **Gene set enrichment analysis (GSEA) of WGS data**

1012 To assess the biological functions associated with the recurrent alterations detected by the
1013 GISTIC analysis, we performed GSEAPreranked analysis^{52,53} (GSEA v3.0) on gene-level GISTIC
1014 G-score profiles, for both amplifications and deletions. In particular, we applied the algorithm with
1015 1000 permutations on various gene set collections from the Molecular Signatures Database^{89,90}
1016 (MSigDB v6.2): H (Hallmark), C2 (Curated : CGP chemical and genetic perturbations, CP
1017 canonical pathways), C5 (Gene Ontology: BP biological process, MF molecular function, CC
1018 cellular component) and C6 (Oncogenic Signatures) composed of gene sets respectively. We
1019 also included gene sets with known cancer or treatment-related functions described in an earlier
1020 section. We noted that multiple genes with contiguous chromosomal locations, typically in
1021 recurrent amplicons, generated spurious enrichment for gene sets which consists of multiple
1022 genes of adjacent positions, while very few or none of them had a significant GISTIC G-score. To
1023 avoid this confounding issue, we only considered the “leading edge genes”, i.e. those genes with
1024 increasing Normalized Enrichment Score (NES) up to its maximum value, that contribute to the
1025 GSEA significance for a given gene set. The leading-edge subset can be interpreted as the core
1026 that accounts for the gene set’s enrichment signal (<http://software.broadinstitute.org/gsea>). We
1027 included a requirement that the leading edge genes passing the GISTIC G-score significant
1028 thresholds based on GISTIC q-value 0.25 (Supplementary Table 8 and Extended Fig. 7) make up
1029 at least 20% of the gene set. This 20% threshold was chosen as the minimal threshold at which
1030 gene sets assembled from TCGA-generated lists of genes with recurrent CNA in CRC or BRCA
1031 were identified as significant in GSEA (see Supplementary Table 9). Finally, gene sets with a NES
1032 greater than 1.5 and a FDR q-value of less than 0.05, which passed the leading edge criteria,
1033 were considered significantly enriched in genes affected by recurrent CNAs.

1034

1035

1036 **DATA AVAILABILITY**

1037 Copy number calls from all datasets are available in Supplementary Data 1, and these are used
1038 for all figures. Raw sequence data for these calls are a combination of previously
1039 described sources (notably the publicly available NCI Patient Derived Models Repository,
1040 pdmr.cancer.gov) and newly sequenced data. New sequence data from the PDXNet are being
1041 shared as part of the NCI Cancer Moonshot initiative through the Cancer Data Service. For further
1042 details, contact the authors. The SNP array data generated by The Jackson Laboratory can be
1043 requested via the Mouse Models of Human Cancer Database (tumor.informatics.jax.org). The
1044 whole genome sequencing data generated by EurOPDX can be made available by directly
1045 contacting the EurOPDX consortium (dataportal.europdx.eu). Other publicly available data used
1046 in the analyses include GSE90653, GSE3526, GSE33006 and E-MTAB-1503-3, CCLE cell line
1047 genomic and drug response data (CTRP v2), MSigDB v6.2 and TRACERx NSCLC data (DOI:
1048 10.1056/NEJMoa1616288).

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1050 **CODE AVAILABILITY**

1051 We have used well-established computational sequence analysis and statistical analysis
1052 techniques, so no code is provided. Full descriptions of all analysis techniques are provided in
1053 the Methods. The implementation of the copy number estimation workflow from whole-exome
1054 sequencing data is deployed in the cancer genomics cloud at SevenBridges
1055 (<https://cgc.sbgenomics.com/public/apps#pdxnet/pdx-wf-commit2/wes-cnv-tumor-normal-workflow/>,
1056 <https://cgc.sbgenomics.com/public/apps#pdxnet/pdx-wf-commit2/pdx-wes-cnv-xenome-tumor-normal-workflow/>).

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