Supplementary Notes for "Analyses of non-coding somatic drivers in 2,658 cancer whole genomes" by Rheinbay, Nielsen, Abascal, Wala, Shapira et al.

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1. Overview of uncategorized non-coding hotspots in top 50

Six of the 35 non-coding hotspots, among the top 50, are not assigned to the mutational processes described in the main text (2 in the top 25 hotspots, **Fig. 1a**; 6 in the top 50 hotspots, **Extended Data Fig. 1b**). Below we describe these six hotspots in detail.

Four of the six remaining non-coding hotspots were found on the X chromosome (X:116579329, X:7791111, X:83966025, and X:83967552). The mutations in these hotspots were mainly contributed by males (61–94% of mutations per hotspot), suggesting the possibility of uncharacterized noise. Two of these hotspots (X:83966025, and X:83967552) are located in a self-chain region, where two stretches of approximately 400 bp (1000 bp apart) match each other except for 6 positions. All six of these positions have mutation calls in either or both of the regions. All but one of the 85 mutations in these positions match the reference base from the opposite region. Another one of these hotspots is located in palindromic DNA (X:7791111). The DNA sequence around this position is composed of two mononucleotide repeats of pairing bases (ATTTTTAAAAAAAAAT), which fits our definition of palindromic structures (**Methods**). The sequence context around this hotspot do not match the sequence recognized by APOBEC enzymes[1,2], and the hotspot had a low APOBEC signature probability (**Fig. 1a; Extended Data Fig. 1b**). It is therefore unlikely to be caused by the same mutational processes as the other palindromic hotspots in the top 50 hotspots, but rather likely represents noise associated with homopolymer runs (PCAWG variants paper). The last of these hotspots (X:116579329) has a median cancer allele fraction (CAF) of 0.21 (**Methods**), compared to a median CAF of 0.97 in the surrounding mutations in these patients. Generally, a CAF of one is expected on the X chromosome in males unless there are changes in ploidy in the region. The low CAF is thus consistent with a low frequency of mismatches caused by misaligned reads.

A hotspot (3:164903710) contained mutations in multiple cancer types, with most mutations contributed by Liver-HCC (6/17). It is located about 1 kb downstream of *SLITRK3*, two base pairs from an annotated CTCF transcription factor binding site. CTCF sites and the base pairs immediately downstream are known to be highly mutated in several cancer types including Liver-HCC. This position is lowly conserved, suggesting that it would not have a functional impact[3,4].

The last non-coding hotspot (1:103599442) had a high proportion of mutations attributed to the SBS5 signature. It overlaps a repetitive LINE region, suggesting potential mapping issues.

Moreover, the position is flanked by two other positions, two base pairs away in both directions, which also have mutations in the same samples and reads; however, these positions were called problematic in the Panel-of-Normals (PoN) filter, further suggesting mapping issues.

2. *P* value distributions under the null hypothesis for discrete statistics

When using continuous test statistics, the *P* value distribution under the null hypothesis is expected to follow a uniform distribution. However, when using discrete statistics (such as a function of the number of mutations in an element), with low counts, *P* values under the null can yield QQ plots with a point mass at *P* value = 1 (e.g., for elements with zero mutations), and the rest of the distribution below the diagonal, approaching it for small *P* values[5,6]. Thus, well-calibrated methods are expected to show QQ plots with values below the diagonal, in line with the results shown in **Extended Data Fig. 11**. In other words, discrete test statistics lead to sub-uniform distributions under the null ($Pr[P_i \leq t \mid H_0] \leq t$). For exactly this reason, the Benjamini–Hochberg method is still applicable to discrete data, although the resulting *Q* values will be conservative[55,6]. We note, however, that slightly conservative *Q* values are not undesirable in this study.

These considerations still apply to the integrated *P* values, at least under usual conditions. As described in **Methods S7**, Fisher's method uses the product of *P* values to calculate a statistic that follows a Chi-squared distribution ($X^2 \sim -2\Sigma\ln(p)$). Thus, when using conservative *P* values, the resulting X^2 statistic will be lower than that under non-conservative *P* values, resulting in a conservative integrated *P* value distribution. Brown's method is an extension of Fisher's method and thus will likely yield conservative *P* values, although the data-driven estimation of the covariance matrix between methods introduces some uncertainty. Nevertheless, the performance analyses shown in **Extended Data Fig. 3** reveal that the integrated approach performs well across datasets and tends to outperform individual methods, in terms of overall sensitivity and specificity.

3. Calibration of systematic element filters

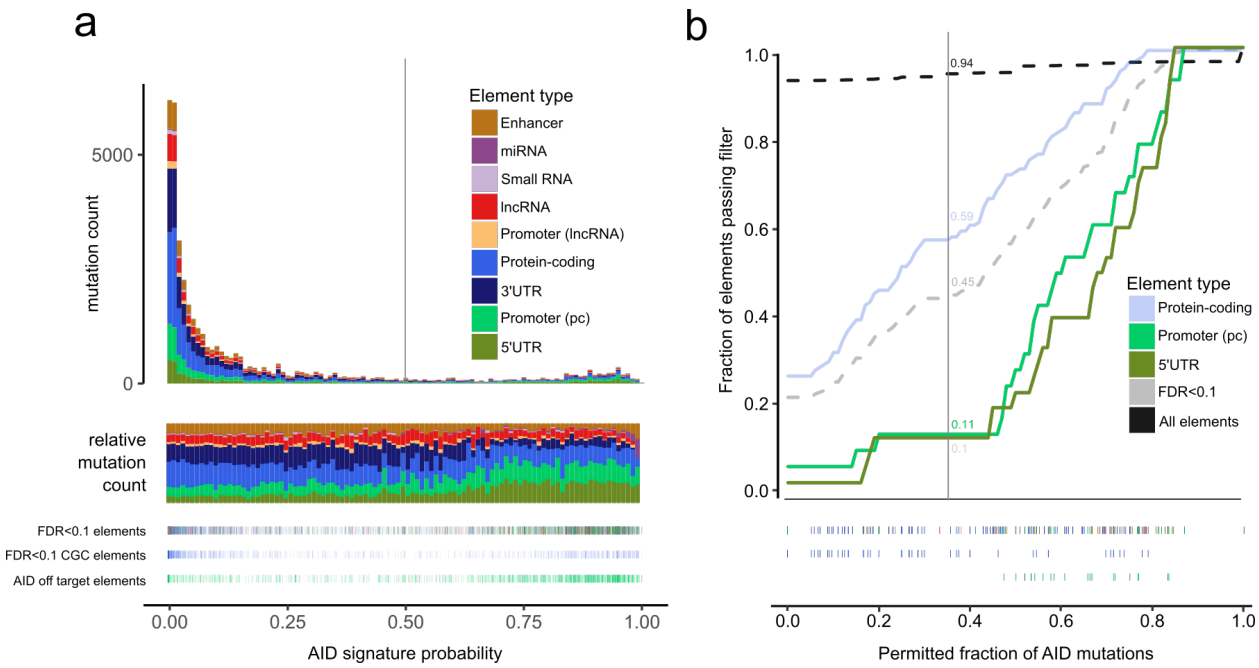
The performance of the driver discovery methods depends on how well their null models capture the mutational processes at play. Some mutational processes are hard to capture accurately. This includes localised mutational processes that affect some regions more than others. When localised mutational processes, not included in the null models, affect a given region and contribute significantly to the observed mutations, the region may be called as a false positive by the driver discovery methods. Though regions affected by localised mutational processes may be true drivers, it is challenging to distinguish them from neutral regions with passenger mutations, which *a priori* are expected to dominate.

To take a conservative approach, we identify and filter elements if a substantial amount of the mutations appear to be derived by localized mutational processes. This approach is applied to (i) activation-induced cytidine deaminase (AID)-derived mutations in lymphoma samples; (ii) UV-derived mutations in melanoma; and (iii) APOBEC-derived mutations in all cohorts.

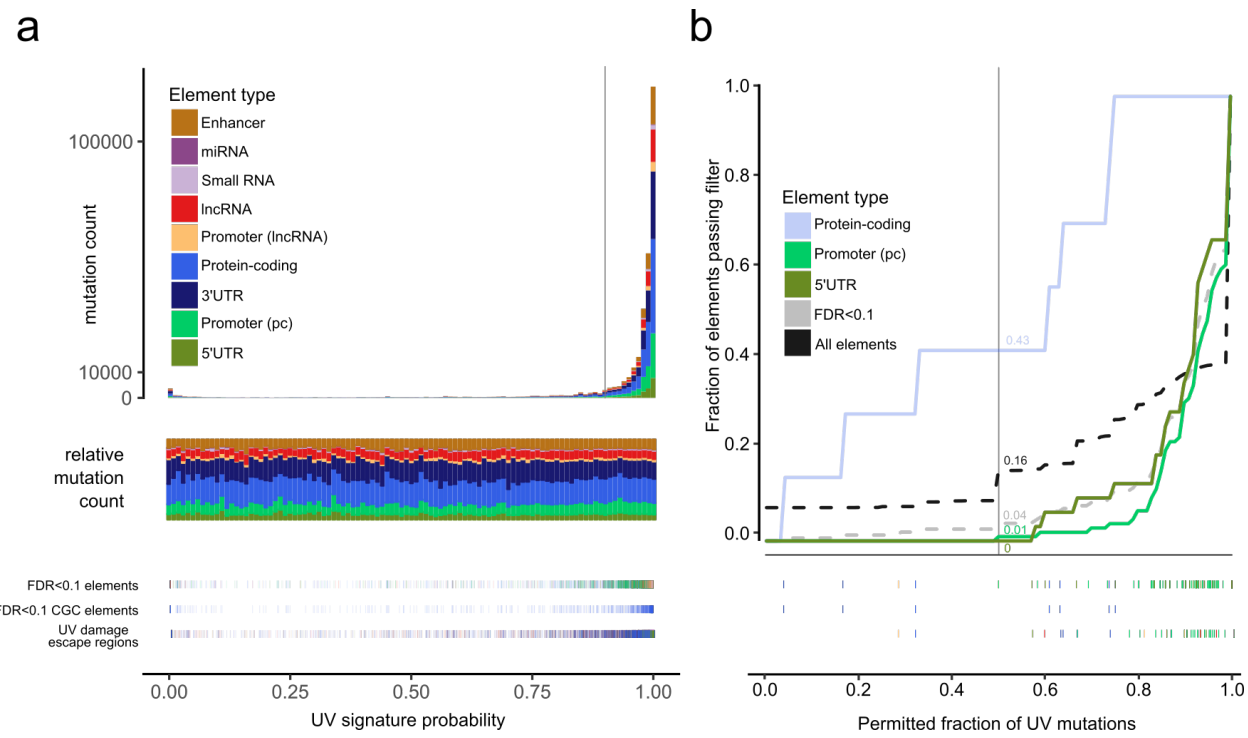
For the lymphoma cohorts, we first apply a threshold for calling mutations as AID based on the distribution of AID signature probabilities for all lymphoma mutations **(Supplementary Fig. 1a**). We next investigate what fraction of elements would be filtered at a given threshold for the fraction of permitted AID mutations (**Supplementary Fig. 1b**). The chosen threshold is trade-off between maximizing the number of filtered elements overlapping a set of known AID off-target regions[7] and minimizing the number of filtered coding elements in the Cancer Gene Census[8] (CGC).

A similar approach was used for melanoma mutations **(Supplementary Fig. 2)** to provide a filter for localized UV mutations known to be enriched in sites escaping nucleotide excision repair[9,10], and for mutations in all cohorts to provide a filter for mutations caused by APOBEC enzymes (**Supplementary Fig. 3**).

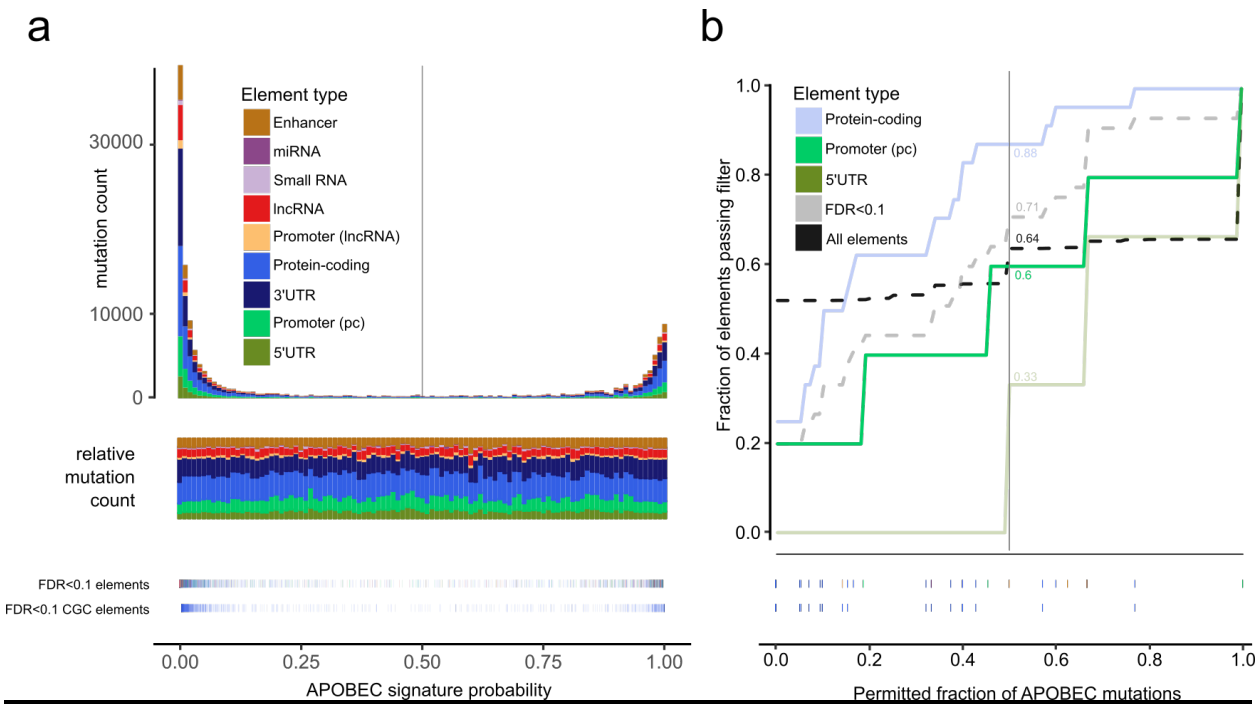
Given that APOBEC editing appears to target DNA-level palindromic sequences in several cases[1,11], we evaluated if SNVs in driver candidate RNA genes with palindromic sequences (*RMRP, RPPH1, RNU5A-1, RNU6-573P,* and *mir-142*) could be explained by APOBEC editing. Only 9.7% of SNVs had posterior APOBEC probability >0.5, suggesting that APOBEC editing contributed only a small fraction of their SNVs.



Supplementary Figure 1: a, Top: distribution of AID signature probability for mutations in all tested elements divided into element types. The AID call threshold (0.5) used for mutations is indicated with a gray line. Middle: The relative distribution among element types. Bottom**:** AID signature probabilities for mutations in significant (Benjamini–Hochberg FDR $Q < 0.1$) elements (67% mutations above threshold), in significant known cancer elements from CGC (44% mutations above threshold), and in known AID off-target promoter elements (76% mutations above threshold). **b**, Top: Fraction of elements passing the AID filter at different thresholds of permitted AID called mutations. (fraction filtered: 57% significant elements; 27% significant known cancer elements; 100% AID off-target promoter elements). A gray line indicates the filter threshold (0.35). Bottom: Fraction of AID mutations in elements as defined in (a).



Supplementary Figure 2: a, Top: Distribution of UV signature probabilities for mutations in all tested elements divided into element types. The UV call threshold (0.9) used for mutations is indicated with a gray line. Middle: The relative distribution among element types. Bottom**:** UV signature probabilities for mutations in significant (Benjamin–Hochberg FDR<0.1) elements (86% mutations above threshold), in significant known cancer elements (71% mutations above threshold), and in regions escaping repair of UV induced damage[9] (87% mutations above threshold). **b**, Top: Fraction of elements passing the UV filter at different thresholds of permitted UV called mutations (fraction filtered: 96% significant elements; 57% significant known cancer elements; 97% UV damage escape overlapping elements). A gray line indicates the filter threshold (0.5). Bottom**:** Fraction of UV mutations in elements as defined in (a). UV damage escape elements are defined to contain one or more mutations in a UV damage escape region.



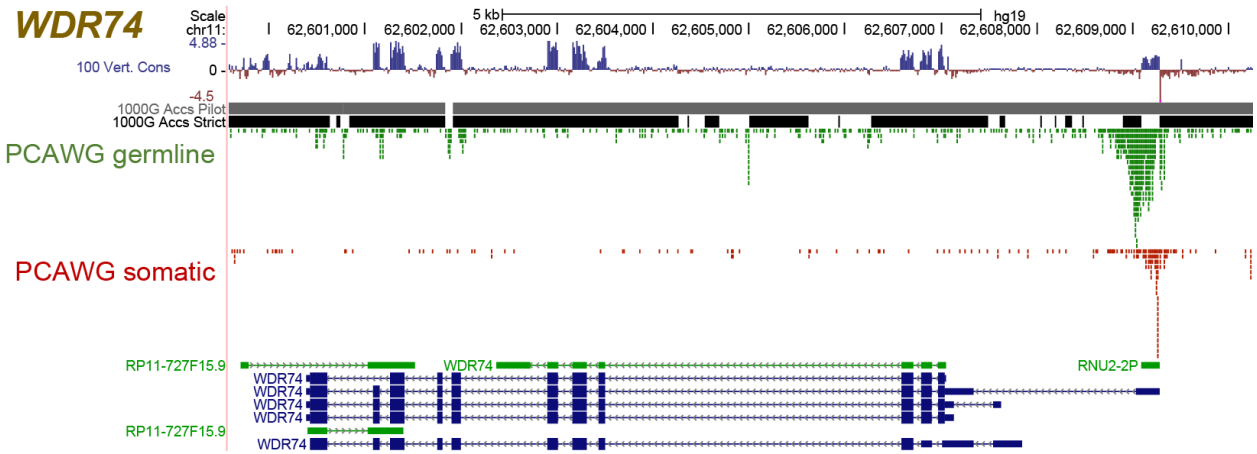
Supplementary Figure 3: a, Top: Distribution of APOBEC signature probabilities for mutations in cohorts with an average APOBEC signature probability above 0.3 (Bladder, Uterus, Head, Cervix, and Breast cancers) in all tested elements divided into element types. The APOBEC call threshold (0.5) used for mutations is indicated with a gray line. Middle: The relative distribution among element types. Bottom**:** APOBEC signature probabilities for mutations in significant (Benjamini–Hochberg FDR<0.1) elements (38% mutations above threshold) and in significant known cancer elements (32% mutations above threshold). **b**, Top: Fraction of elements passing the APOBEC filter at different thresholds of permitted APOBEC called mutations (fraction filtered: 29% significant elements; 10% significant known cancer elements). A gray line indicates the filter threshold (0.5). Bottom**:** Fraction of APOBEC mutations in elements as defined in (a).

4. Discussion of additional significant non-coding elements

Promoters:

WDR74

The *WDR74* promoter has already been suggested as a potential driver in several studies[11–14]. However, we found that mutations are concentrated inside a *U2* RNA where the density of putative polymorphisms is abnormally high (**Supplementary Fig. 4a** below). This outstanding level of diversity could in principle be due to higher mutability in the germline. However, given the repetitive nature of the *U2* element (there are hundreds of copies in the genome) and the extreme levels of putative diversity, it is more likely that this region is a source of mapping artifacts.



Supplementary Figure 4. PCAWG germline and somatic mutations overlapping a *U2* element in the promoter of *WDR74*.

HES1

HES1 promoter mutations were significant in Carcinoma and Pan-cancer, but showed no association with gene expression (**Extended Data Fig. 4a**). *HES1* is a NOTCH signalling target[15], and is focally amplified in gastric cancers (**Extended Data Fig. 4b**).

IFI44L, HIST1H2AM, GALNTL5, ZSWIM6, SDCCAG8/CEP170,* and *POLR3E

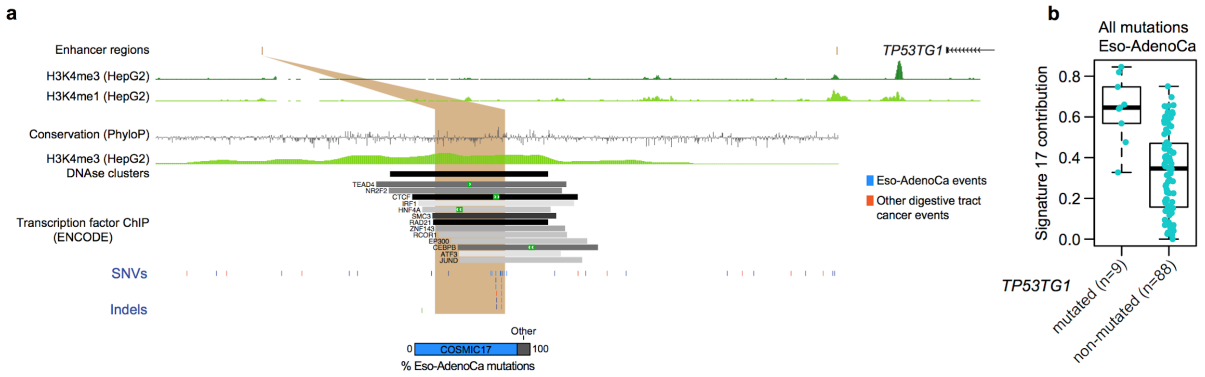
Tumors with mutations in the promoters of *IFI44L, GALNTL5, ZSWIM6, POLR3E* showed trends towards increased or decreased expression, although the small number of samples prevented us from drawing definitive conclusions (**Extended Data Fig. 4a**). *HIST1H2AM* lacks expression data as part of the histone family of genes, which are not polyadenylated and therefore not

represented in the RNA-seq libraries, and *SDCCAG8* is mutated in a cohort that lacks expression data. Both *GALNTL5* and *SDCCAG8* are located in an amplification peak in glioblastoma (http://portals.broadinstitute.org/tcga/gistic/browseGisticByGene). However, *SDCCAG8* is proximal to *AKT3*, which is likely the true driver of this focal amplification. The other recurrently mutated genes were not present in significantly amplified or deleted focal peaks (**Methods**). Validation of these hits with additional data in further studies will be needed to evaluate whether they are genuine drivers.

Enhancers:

TP53TG1

An enhancer near *TP53TG1* — an RNA gene suggested to be a p53-associated tumor suppressor epigenetically silenced in cancer[16] — reached significance in several cohorts. Mutations concentrated around a conserved region (**Supplementary Fig. 5**) and overlapped sites bound by NFIC and ZBTB7 transcription factors in HepG2 cells[17]. Ten of 16 mutations in this region were contributed by esophageal cancers: one di-nucleotide variant (DNV) and nine SNVs, of which five had a signature 17 contribution of >0.5 (the remaining four had contributions between 0.20 and 0.49), raising the possibility that these reflect a localized mutational process rather than a driver event[18].



Supplementary Figure 5: a, An enhancer associated with *TP53TG1* contains mutations mostly attributed to the COSMIC17 mutational signature associated with esophageal cancer. **b,** Boxplot showing the contribution of signature 17 in Eso-AdenoCa for TP53TG1 mutated and non-mutated samples. Boxes show the interquartile range and median.

Non-coding RNAs:

RMRP (additional information)

RMRP is presented in the main text, and we here provide some further details and results of the mutational analysis. The non-coding RNA *RMRP* is significantly mutated in multiple cancer types, in both its gene body and promoter (**Fig 1b; Extended Data Fig. 5c; Supplementary Table 5**). The gene body mutations (7 SNVs in pan-cancer) show a significant bias towards high structural impact (rank-sum test, $P = 0.011$). Three of these are individually significant (each with $P < 0.1$, sample level permutation tests; **Extended Data Fig. 5c**). Of the four gene-body indels, three are located in or near protein-binding sites ($P = 0.08$), including a deletion that is predicted to affect the secondary structure. Given *RMRP*'s role in replication of the mitochondrial genome[19–22], we tested whether mutations in this locus were associated with altered mitochondrial genome copy number. Indeed, mutated samples showed a trend towards higher mitochondrial copy number (two-sided rank-sum test, $P = 0.1$).

The high density of SNPs in the *RMRP* locus suggests that the *RMRP* locus may be either subject to an elevated germline mutation rate or to unidentified technical issues (**Supplementary Fig. 6a**). The consequence of somatic mutations should therefore be interpreted with caution.

Fifteen ncRNAs hits not described in detail in the main text passed the systematic post-filter (*RPPH1*, *G025135*, *CTD-2105E13.15*, and *G029190* lncRNAs; *MIR663A*, *RNU12*, *RP5-997D16.2*, and *RP11-440L14.1* lncRNA promoters; *RNU5A-1, RNY1, RNY5, and RNU6-573P* small RNAs; Ala.TGC [id.trna.192], Met.CAT [id.trna.419], and Gly.GCC [id.trna.336] tRNAs). The driver role of these were generally not supported by additional lines of evidence, lacked functional evidence, or appeared to be affected by technical artifacts. The candidates are described below, and individual *Q* values are in **Supplementary Table 5**.

RPPH1

RPPH1 forms the RNA component of the RNase P ribonucleoprotein, which matures precursor-tRNAs by cleaving their 5' end[23]. It is transcribed from a divergent promoter together with the protein-coding gene *PARP2*; however, no association with expression was observed for either gene. It was found significant in Adenocarcinoma, Carcinoma, Digestive tract tumors, and Pan-cancer. The region has a high level of germline polymorphisms, i.e., the SNP density is 5.1

times higher within the region compared to 5 kb flanking regions (inside/outside SNP density enrichment), which indicates mapping issues or a higher germline mutation rate (**Supplementary Fig. 6b**).

G025135

G025135 is a lncRNA element (from MiTranscriptome[24]) identified here as a significant driver candidate in Lymph-CLL. This ncRNA element was also found in Lymph-BNHL, Lymphomas and Hematopoietic system tumors, where it was filtered based on a high proportion of AID mutations. In Lymph-CLL, the number of AID mutations was just below our threshold. Furthermore, some individual patients have many mutations, further supporting that it may be a target of AID.

MIR663A

The promoter of *MIR663A* was recurrently mutated in Carcinoma. It is the primary transcript of *MiR-663*, which has tumorigenic functions in gastric cancer and nasopharyngeal carcinoma[25]. The mutations were not correlated with expression. Unexpectedly high SNP density in this element suggests the presence of mapping artefacts.

RNY1

RNY1 encodes Y1 that is a Y RNA. Y RNAs constitutes the RNA part of ribonucleoproteins and they are required for chromosomal DNA replication[26]. It was found significant in Digestive tract tumors. The expression of Y1 has previously been found elevated in several types of cancer, including colorectal cancer[27]. The inside/outside SNP density enrichment is 5.6, suggesting mapping issues or a high germline mutation rate.

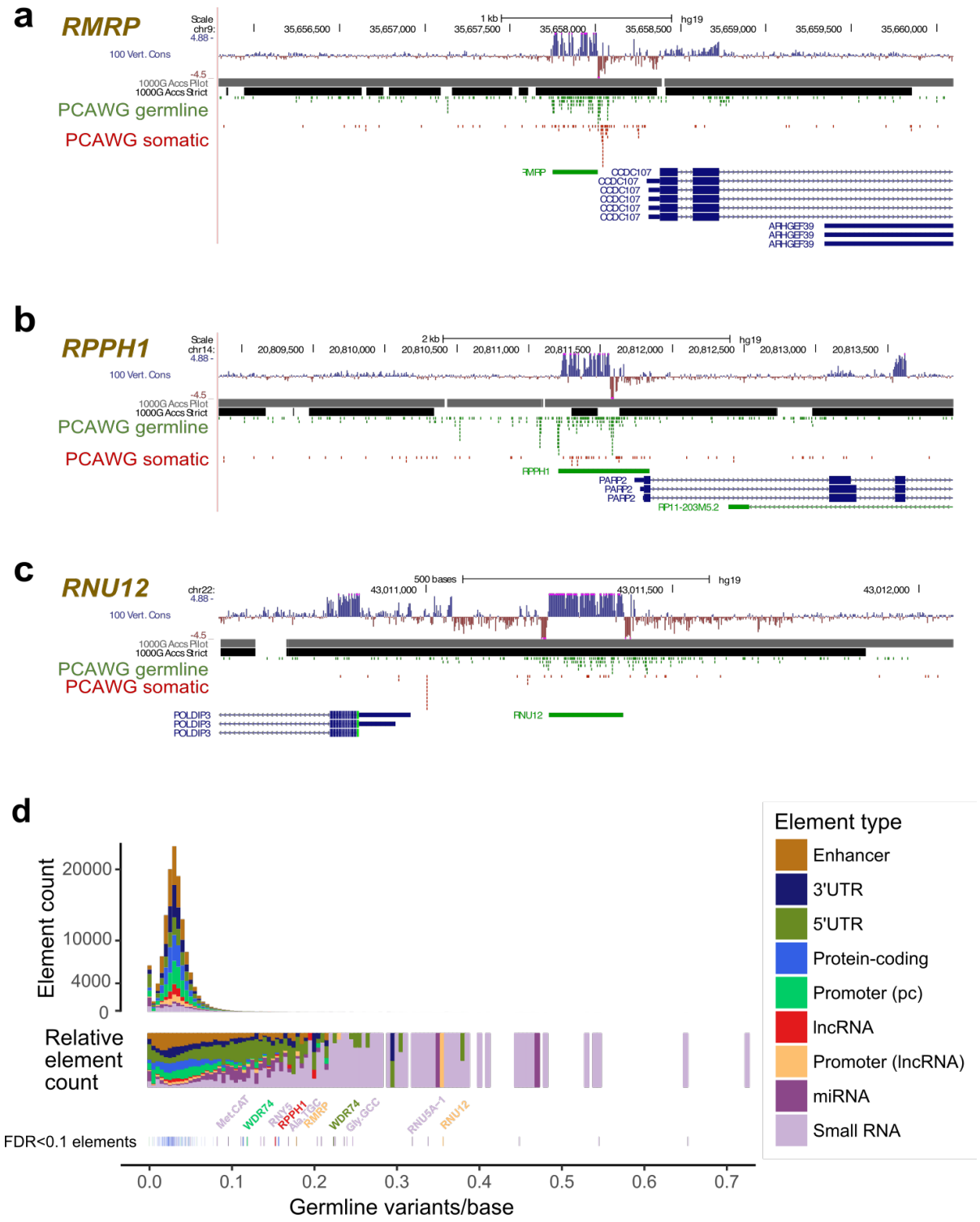
Other ncRNAs

Five functionally uncharacterised ncRNAs were found significant in one, two, or three cohorts, but we could not find any further supporting driver evidence: (1) The lncRNA *CTD-2105E13.15*, which partially overlaps three exons of *TMEM190*, was found significant in Carcinoma and Pan-cancer. (2) The *G029190* lncRNA (from MiTranscriptome) had significance in Adenocarcinoma and Pan-cancer. (3) The promoter of *RP5-997D16.2* was found significant in Prost-AdenoCa, and it has a hotspot with two mutations in this cohort. (4) The promoter of *RP11-440L14.1* was significant in Ovary-AdenoCa, Carcinoma, and Pan-cancer. It has a hotspot position with four mutations overlapping two different deletions. Finally, (5) the small RNA *RNU6-573P* was

detected in Panc-Endocrine with three mutations. However, it appears to be a nonfunctional pseudogene recently inserted in the human lineage. Not only the locus, but the wider region is subject to increased mutational burden, further supporting that mutational mechanisms or technical issues rather than selection underlies the mutational recurrence.

In addition, six ncRNA hits overlap regions with high densities of germline mutations, which suggests mapping issues or high germline mutation rates. These include (1) the promoter of the lncRNA *RNU12* (Lymph-BNHL, Lymphomas and Hematopoietic system tumors; inside/outside SNP density enrichment: 8.7; **Supplementary Fig. 6c**); (2) the small RNAs *RNY5* (Adenocarcinoma and Digestive tract tumors; inside/outside SNP density enrichment: 4.5) and (3) *RNU5A-1* (Adenocarcinoma; inside/outside SNP density enrichment: 5.4); the tRNAs (4) Ala.TGC (Adenocarcinoma and Carcinoma; inside/outside SNP density enrichment: 3.7), (5) Met.CAT (Digestive tract tumors; inside/outside SNP density enrichment: 2.9), and (6) Gly.GCC (Female reproductive system tumors; inside/outside SNP density enrichment: 7.7).

Finally, the promoter of the lncRNA *RNU12* overlap the promoter of *POLDIP3* without significant expression-correlation in any of the cohorts.



Supplementary Figure 6: The non-coding RNA candidates (**a**) *RMRP,* (**b**) *RPPH1,* and (**c**) *RNU12* all had high SNP densities. **d**, SNP density among element types. (Top) Stacked distribution of SNP densities for different element types. (Middle) Relative distribution among element types for given SNP density. (Bottom) Distribution of significant (Benjamini–Hochberg

FDR<0.1) elements. Non-coding RNA candidates generally have high densities of SNPs, including the candidates shown in **a-c**, amongst the highest in genome, which raises concerns about the relevance or authenticity of the somatic mutations hitting these loci.

5. Driver discovery in 2 kb genomic bins and mutational processes

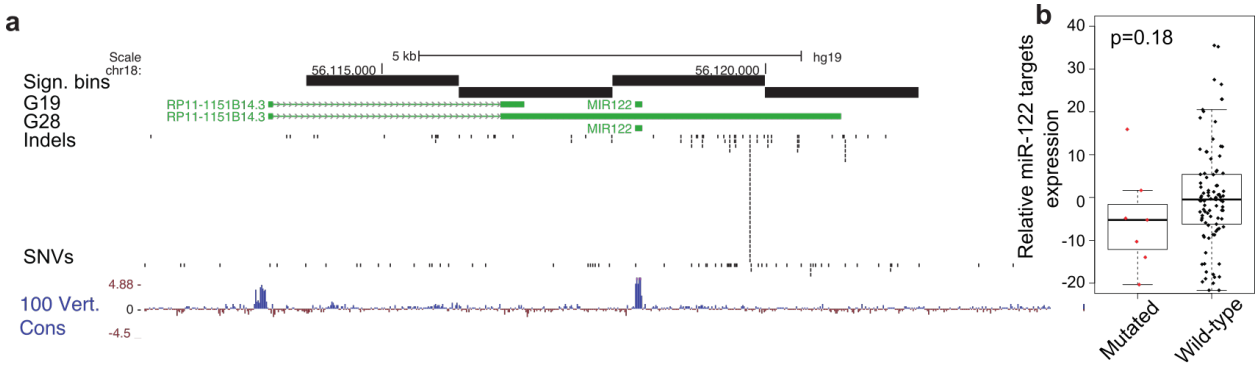
The paucity of non-coding driver mutations identified in our analyses could in principle be due to the list of functional elements used, which cover only a small fraction of the genome. We partially addressed this limitation in the unbiased analysis of hotspots, finding no convincing non-coding driver candidates other than the *TERT* promoter. Here we interrogate the rest of the genome in a similarly unbiased way. We divided the genome in 2-kb bins and looked for bins with an excess of mutations, while accounting for sequence composition and trinucleotide substitution rates (NBR method). To avoid the risk of mapping artifacts, we first excluded bins with potential mappability problems, considering a total of 1.2M bins covering 66% of the genome (**Methods**). This analysis was performed on all cohorts and meta-cohorts of more than 100 samples, using a global FDR adjustment across all of them. Many bins were recurrently mutated in lymphoid tumors, likely due to AID-derived localized somatic hypermutations. Lymphoid tumors were therefore excluded from the analysis. The NBR method without covariates identified 67 significantly mutated bins across meta-cohorts and tumor types (178 significant hits in total; **Extended Data Fig. 5a; Supplementary Table 9**). 22 bins (74 hits) overlap 17 known cancer drivers, including *TP53* (28 hits)*, KRAS* (6)*, APC* (5) or *ARID1A* (5)*.* Of the remaining significant bins, 29 (87 hits) overlap genes and regions affected by localized mutational processes. Mutations in one of these bins (4 hits) lie within a CTCF binding site; the rest of the bins overlap highly transcribed loci and are rich in indels, particularly of length 2–5 bp (**Fig. 2e; Supplementary Table 9**), hence likely being associated to the transcriptional mutational process described for *ALB*, *MALAT1*, *NEAT1,* and other genes.

Interestingly, *MIR122*, a known tumor suppressor, overlapped significantly mutated bins in liver. However, the scattered distribution of mutations along several consecutive bins and the enrichment of indels (especially of length 2–5 bp) suggests that this locus is also affected by the transcriptional mutational process described in the manuscript (**Supplementary Fig. 7a; Fig. 2e**) — indeed, *MIR122* is one of the most highly transcribed genes in liver[28,29]. To explore the potential functional implications of these mutations, we investigated if *MIR122* mutations are associated with altered expression. Since only two mutated samples had miRNA expression profiling, we did this by associating mutations with different expression of *MIR122* target genes by integrating expression across genes with *MIR122* target sites in their 3'UTRs[4]. Mutations were associated with a weak non-significant decrease in target gene expression. This provided no convincing evidence that mutations may be associated with decreased *MIR122* expression (**Supplementary Fig. 7b**). No single mutation hit the miR-122, and the indel hotspot occurs in a

region with four direct AAG repeats (**Supplementary Fig. 7a**). Overall, it is thus plausible that most mutations in *MIR122* are passenger mutations resulting from the mechanism of transcription-associated mutagenesis described for *MALAT1*, *NEAT1,* and *ALB*, among others.

Within the remaining 16 bins (17 hits) that were not associated to known drivers or mutational processes, some appear to be caused by mapping artefacts. For instance, the bin chrX:83966001-83968000 contains a duplication-inversion (chrX:83966018-83966396 and chrX:83967485-83967863) with somatic mutations hitting divergent sites between the two duplicated regions. Other unreliable cases include a bin overlapping an olfactory receptor in a region with very high germline SNP density, and four bins with mutations in LINE elements and poor mappability according to 1,000 Genomes masks (**Supplementary Table 9**). For the rest of the significant bins (10), we found no obvious potential association to cancer, as most were far from genes in regions with no apparent regulatory functions, while others were borderline significant.

One limitation of this binned approach is that the signal of mutational recurrence may become diluted in the relatively long bins. We conducted a complementary analysis focusing on non-coding ultraconserved regions, of which only 36% overlapped our defined functional elements. Here, regions are less numerous (n = 4,351) and much smaller (mean length 325 bp), avoiding the dilution of the signal and increasing the statistical power, though the fraction of the genome covered is largely restricted (1.4 Mb; 0.05%). None of the ultraconserved regions tested were significant (**Extended Data Fig. 5e**). Overall, these results suggest that drivers are rare in the fraction of the genome not represented in our definition of functional elements.



Supplementary Figure 7: **a,** Scattered distribution of mutations in the *MIR122* locus in Liver-HCC across four different 2-kb bins. **b,** Lack of enriched expression of genes containing miR-

122 target motifs in their 3'UTRs between tumors mutated (n = 7) in *MIR122* and the corresponding wild type (n = 93). For each sample, we evaluated if target genes show higher expression than non-target genes given the overall gene expression in the cohort. Lower expression of target genes leads to a negative value indicative of a correspondingly higher activity of *MIR122*[30]. Box plots indicate inter quartile range with median lines. *P* values evaluated with two-sided Wilcoxon rank sum test.

6. Quantifying the performance of the pan-cancer breakpoint significance model

Background and Motivation

For tumors with very low burdens of somatic alterations, the probability that a single gene would be recurrently altered simply by chance is low. Barring confounding by technical artifacts, in very simple cancer genomes, it is relatively straightforward to conclude that recurrent alterations reflect evidence of positive selection by the tumor. However, most tumors acquire a vast number of alterations throughout their evolution, and distinguishing "driver" alterations (those that are positively selected for in cancer evolution) from "passenger" alterations (those that are under neutral or negative selection) is more challenging. This is likely more challenging for SVs than point mutations, for reasons given below.

Building a background model: positive selection, negative selection, and mechanism

The ideal background model would account for every biological process (mechanism) that generates alterations, thereby perfectly recreating the expected distribution under neutral selection and allowing for accurate identification of the effects of positive selection. Currently, such strong *a priori* predictions of the background distribution are not sufficient to develop background models owing to our still limited understanding of each possible mechanism by which cells sustain somatic alterations as well as the vast heterogeneity in tumor tissue of origin, germline background, and environmental exposures.

To overcome our limited ability to predict alteration distributions from first principles, background models are typically estimated from the observed alteration distribution. The most naive background model would simply assume as the background distribution the observed distribution. In this scenario, no sites of positive selection would be identified because the difference between the observed and expected at each gene would be zero by definition. Instead, since the distribution of alterations is a combination of the mechanisms by which alterations form and selective pressures, a more useful background model would capture the genome-wide *patterns* found in the observed data, but without overfitting and washing out signal from true positive selection. To do this, background models are parameterized by known mechanisms of alteration formation (e.g., a tendency for errors to accrue in regions of late replication timing), while the effect sizes of each alteration are estimated from the observed data. This method carries the

assumption that the vast majority of alterations are passenger alterations (i.e., determined solely by mechanistic explanations rather than selection), rather than drivers. This appears to largely be the case, as the average number of driver alterations per tumor is estimated to be fewer than ten[31] while the number of total alterations per tumor can be in the tens of thousands[32]. However, such assumptions break down for very low mutation tumors like leukemias and pediatric malignancies, in which case the background model can be assumed from other tumor types. It should be noted that the assumption that passenger alterations are truly under neutral selection is being questioned[33].

Somatic alterations that disrupt essential cellular functions, expose a cancer cell to immune surveillance, or in any other way decrease the fitness of a cell, are said to be under negative selection. Negative selection is particularly challenging to estimate, as it is marked by the absence of alterations. In principle, with enough biological knowledge about cellular function, one could predict *a priori* whether an alteration affecting a given gene will decrease cellular fitness. In practice, as with modeling the effects of mechanism, understanding the effects of negative selection requires an interplay between known biological processes (e.g., essential genes) and tracking backward from the observed data. Distinguishing the effects of mechanism from negative selection is difficult, as there is no known bound on the number of genes / loci that could be under negative selection. Recent studies evaluating SNVs indicate minimal negative selection in regions with two or more copies[34]. However, SVs were not evaluated in these studies. Without explicit accounting for negative selection, the effect sizes in the background model obtained from modeling the observed data will be a combination of mechanism and negative selection.

Detection of somatic alterations relies on a technical pipeline that includes sample collection; library preparation and sequence or microarray generation; read mapping to the reference genome; and finally variant calling and filtering. As such, the observed distribution of alterations is not only shaped by mechanism and selection, but by the technical biases inherent to any detection pipeline. In practice, such technical biases tend to surface quickly, as regions that have a high number of false positive variant calls will tend to deviate significantly from the background model and come to early attention. However, more subtle technical variations (e.g., from batch effects[35]) are still possible and must be accounted for whenever identified.

Considering the above effects, when compared with the density predicted by the background distribution, the density of an alteration could be observed to be at a higher rate than predicted

for four reasons: (i) there are unaccounted for mechanistic reasons for a higher alteration density at a certain locus; (ii) there is a relative lack of negative selection at a site compared with similar loci elsewhere in the genome; (iii) there is a systematic technical artifact; or (iv) the alteration confers a growth or survival advantage to a cell and it is under positive selection. One approach to testing the robustness of significant "hits" is to determine how high the true background rate would have to be for the locus to become insignificant. For example, most RSJs detected in our analysis would remain significant even if the background rate were twice as high as we have estimated (**Extended Data Fig. 9a**)

Driver alterations have been systematically distinguished from passenger alteration using pan-cancer data for both somatic SNVs/indels[32,36–38] and for SCNAs[39,40]. However, to our knowledge, this has never been done for rearrangements. We decided to use a similar overall approach, but with new methods that account for the specific challenges of rearrangements. In our approach, we first build a model to account for as much of the variation in the breakpoint distribution as possible, similar to approaches that have used replication timing and gene expression to account for variance in the somatic SNV distribution[32]. Our approach uses an expanded set of covariates that have more relevance for breakpoints (e.g., fragility, repetitive elements). We further build a model that accounts for the two-dimensional connections that are unique to rearrangement data, and utilize this to discover recurrent fusions.

Accounting for stochastic variation

In any finite dataset, the fraction of samples exhibiting a rearrangement ("rearrangement rate") at any single locus will differ from the actual prevalence of rearrangements at that locus, due to random chance. We estimate the level of stochastic variation in our dataset by comparing rearrangement rates determined from half the samples (chosen at random) to rearrangement rates determined from the other half, to generate a correlation coefficient (R); R^2 roughly corresponds to the fraction of the variation in rearrangement rates that can be attributed to random chance, and therefore cannot be predicted. We then calculate the fraction of the "predictable" variation that can be attributed to known mechanistic and selective sources of variation, and to unknown sources.

Given the size of the genome, and the relatively small number of rearrangements in our dataset, it is uncommon for a single base to be involved in a rearrangement twice. Therefore, when

comparing rearrangement rates between datasets at a given “locus”, we aggregated all rearrangements in a “bin” encompassing that locus. Specifically, we divided the genome into a set of bins, and compared rates of rearrangements within each bin between datasets. We also determined the expected rates of rearrangement at the bin level from our mechanistic models, and considered loci under selection to involve the entirety of the bin encompassing them.

This bin size can determine the amount of variation one attributes to stochastic, mechanistic, and selective forces. Larger bins will aggregate larger numbers of rearrangements, and therefore appear to exhibit less stochastic variation. In contrast, larger bins will also average over more widely varying sources of mechanistic and selective variation, reducing the apparent variation attributed to each of these sources. Therefore, the specific R^2 values we report need to be considered in light of the bin size, or resolution of the analysis.

We performed three analyses to determine the quality and robustness of the pan-cancer breakpoint significance model. First, we used the Akaike Information Criteria (AIC) to evaluate the quality of the model and to avoid over-fitting. Second, using an R^2 coefficient, (the squared Pearson correlation coefficient) between the predicted breakpoint counts per bin and the observed breakpoint counts as a metric for the goodness-of-fit, we estimated the relative effects of breakpoint formation mechanism, positive selection, stochasticity, and statistical power to explain the distribution of breakpoints in our cohort. Third, we compared the breakpoint model with a somatic SNV model. In addition, we accounted for additional sources of non-stochastic variation that were not accounted for in our model by using a Gamma-Poisson function to estimate the distribution of rearrangement breakpoints per bin. This fits the observed data better than a simple Poisson distribution (**Supplementary Fig. 8a**).

Evaluating model performance with AIC

To determine the covariates to use in the optimal pan-cancer model, we used forward selection to create a set of nested models reflecting different combinations of 28 genomic covariates. We generated a one-covariate model by searching all 28 covariates for the one covariate that minimized AIC. We then searched for a second covariate out of the remaining 27, which minimized the AIC to add to the one covariate model. We repeated this process until we had all 28 covariates in the model. We standardize the AIC by subtracting the minimized AIC at each model size by the minimum AIC over all model sizes. Each model is then ranked by this value

(AIC - minimum AIC), which we define as delta_i, where i denotes the model size. **Supplementary Fig. 8b** shows the AIC for the best model at all possible model sizes. According to and Burnham & Anderson[41], a delta_i of less than seven indicates a covariate that may be adding significant information. We therefore used this cutoff, resulting in the selection of seven covariates: Hyper-Fragility, Fragility, Gene Density, SINE, Mappability, Expression, and Weak Repressed Polycomb. Finally, we provide a quantile–quantile (QQ) plot comparing the observed *P* value distribution to the expected distribution (**Supplementary Fig. 8c-d**). The strengths of these covariates differed slightly, but reproducibly, between cancer types, as can be observed by clustering together two independent breast cancer datasets (**Supplementary Fig. 8e**).

Estimating the effect size of positive selection, mechanism, and stochasticity in the pan-cancer breakpoint model

As described above, the distribution of breakpoints in the cancer genome is influenced by the physical mechanisms by which they are formed; by the effects of positive and negative selection; and by inherent stochasticity. We calculated a goodness-of-fit metric (Pearson R^2) and estimated how much of it could be attributed to positive selection and inherent breakpoint stochasticity in addition to fragile sites and novel breakpoints.

We next evaluated the source of the missing explanatory power between a perfect model and our pan-cancer model. A model that perfectly predicts the distribution of breakpoints would have an R^2 of 1.0. However, we expect that inherent randomness in the physical process of breakpoint production (e.g., random thermodynamic fluctuation in DNA conformation) implies an inherent upper limit to the predictive power of a model in a finite dataset. Further, because the statistical power to distinguish stochasticity from true effects is dependent on the size of the dataset, the size of the dataset itself contributes to an upper bound on the goodness-of-fit for even a perfectly specified model. The breakpoint distribution itself is a reflection of the combined effects of selection, mechanism and stochasticity.

To estimate the effect of stochasticity versus mechanism and selection, we randomly divided the sample set into two halves and calculated the fraction of breakpoints in each genomic bin separately for each half. We then calculated the R^2 between these measurements, hereafter termed “self-correlation”. Self-correlation provides an estimate for the stochasticity in the data

because the effects of selection and mechanism should be the same across two random halves of the data and contribute to a higher R^2. Conversely, stochasticity should generate variations between random halves of the data, leading to lower R^2. Using this procedure and a bin size of 50 Kbp, we obtained an R^2 of 0.510 (+/- 0.02, S.D. of random samplings).

This is similar to the expected level of stochasticity in a dataset of our size. We used our mechanistic model that predicts breakpoint density from genomic features to simulate breakpoints perfectly consistent with the model. In a simulated dataset with 584,506 breakpoints, as in our actual dataset, we obtained an R^2 of 0.56 when comparing the simulated breakpoint counts to the known model.

To obtain an estimate of the effect of positive selection, we took the bins with significantly recurrent breakpoints (FDR < 0.1) as predicted by the pan-cancer GP model and re-ran the model using them as a covariate. Because the significant bins could either be from positive selection or unaccounted-for mechanisms, we used only the significant bins that were within 500 Kbp of a known cancer gene as defined by the Cancer Gene Census[8]. This provided 31 bins (**Supplementary Table 17**). Adding these as covariates to the pan-cancer model, we obtained an R^2 of 0.30 (increased from 0.22). Thus, we find that a substantial fraction of the remaining explanatory power of our model is due to positive selection. We also obtained estimates of the effect of fragile sites and novel RSBs using a similar method. We found that adding RSBs (known and novel) increased the R^2 to 0.36.

Comparison between the GP breakpoint model and GP SNV model

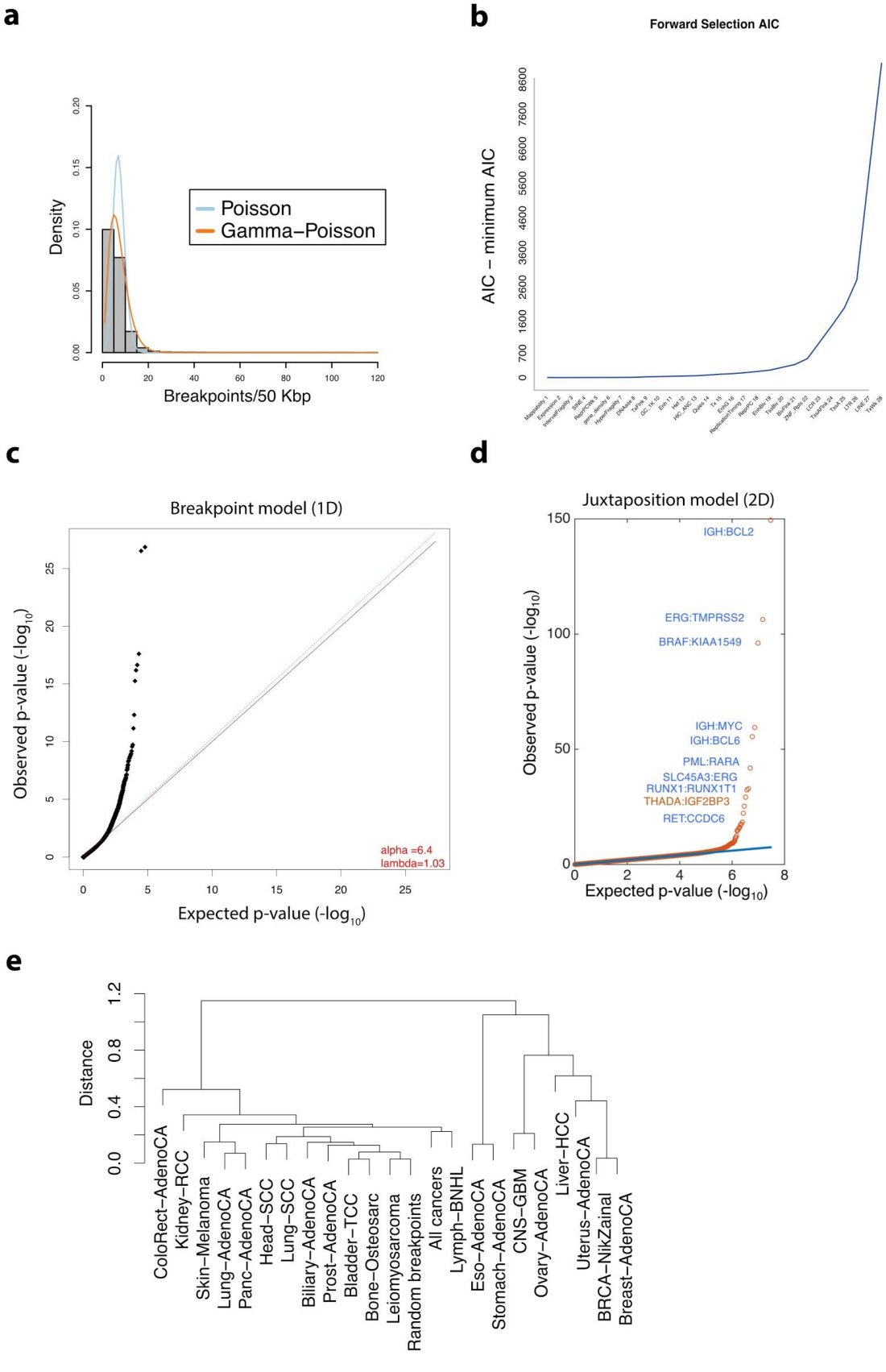
We next sought to compare the performance of the breakpoint model with a similar model for SNVs. To build a GP model for SNVs, we used replication timing, gene expression, GC%, heterochromatin, and mappability as covariates, which have been shown to account for a majority of the non-selection variance in somatic SNV distribution[32]. (Note that this model, designed to mirror the SV background model, is different from the models used in this manuscript for SNV driver discovery.) We used 44.6 million somatic SNVs called by the PCAWG consortium on the same genomes used for the breakpoint analysis. This produced an R^2 of 0.669. To estimate the limit of what could be explained given a perfect model operating on this dataset, we calculated the self-correlation to be 0.964. When operating on a downsampled dataset of 580,00 SNVs (to match the number of breakpoints), the R^2 for the full model becomes 0.460, with a self-correlation

of 0.509. We conclude that we are better able to account for the distribution of SNVs than SVs. Note that for both SNVs and SVs, our analyses are restricted to the mappable genome. It is possible that SVs are more biased towards unmappable regions because they are composed of repetitive sequences that are likely to recombine.

Variability among tumor-types of genomic features predicting breakpoint density

Although we could predict much of the variability in breakpoint density using these genomic features, breakpoint densities in sarcomas, cervical cancer, and prostate cancer were substantially less predictable than in other tumors, particularly adenocarcinomas. This suggests their breakpoints are generated by mechanisms that are governed either by stochasticity or genomic features that we have not yet considered. These tumor types tend to undergo singular catastrophic rearrangements: prostate tumors through chains of deletions in chromoplexy[42], and sarcomas through high rates of chromothripsis[43,44].

To quantify the extent to which different tumor types have shared mechanisms of breakpoint formation, we clustered the tumor types by their correlations with genomic features (using the *hclust* R package; **Supplementary Fig. 8c**). Tumors from similar tissues and cell types tended to cluster together (e.g., esophageal and stomach adenocarcinomas). Breast tumors from PCAWG closely clustered with an independent cohort of breast tumors from Nik-Zainal et al[11], supporting the robustness of our approach across different patients and rearrangement analysis pipelines. Interestingly, ovarian and glioblastoma tumors were closely clustered, as were lung and pancreatic adenocarcinomas, suggesting similar rearrangement mechanisms despite different cell types and tumor microenvironments.


a
Density
Poisson
Gamma−Poisson
Breakpoints/50 Kbp
b
Forward Selection AIC
AIC − minimum AIC
c
Breakpoint model (1D)
Observed p-value (-log10)
Expected p-value (-log10)
alpha =6.4
lambda=1.03
d
Juxtaposition model (2D)
IGH:BCL2
ERG:TMPRSS2
BRAF:KIAA1549
IGH:MYC
IGH:BCL6
PML:RARA
SLC45A3:ERG
RUNX1:RUNX1T1
THADA:IGF2BP3
RET:CCDC6
e
Distance
ColoRect−AdenoCA
Kidney−RCC
Skin−Melanoma
Lung−AdenoCA
Panc−AdenoCA
Head−SCC
Lung−SCC
Biliary−AdenoCA
Prost−AdenoCA
Bladder−TCC
Bone−Osteosarc
Leiomyosarcoma
Random breakpoints
All cancers
Lymph−BNHL
Eso−AdenoCA
Stomach−AdenoCA
CNS−GBM
Ovary−AdenoCA
Liver−HCC
Uterus−AdenoCA
BRCA−NikZainal
Breast−AdenoCA

Supplementary Figure 8: a, Histogram of breakpoint counts per 50 Kbp bin (with only one sample-breakpoint per donor per bin). The distribution more closely follows a Gamma-Poisson (orange) than a Poisson (blue). **b,** Standardized Akaike Information Criteria (AIC) of the best model for each number of covariates. The best model was chosen to have seven covariates based on cutoffs cited in Burnham & Anderson[41]. **c,** Quantile–quantile (QQ) plot for the 61,920 bins in the 1D model. The overdispersion (alpha) parameter is 6.4 for the Gamma-Poisson regression. The slope of the QQ plot (lambda) is slightly above 1. Most bins are not undergoing positive selection, while the remaining bins that are positively selected lie to the left of the y = x line. These fit parameters indicate a good model fit. **d,** QQ plot for the $3x10^7$ tiles in the 2D model. **e,** Clustering of tumor-types by the genomic feature effect sizes from the 1D Gamma-Poisson model.

7. Distinguishing fragile sites from positive selection in regions of recurrent breakpoints

Among SCNAs, a major difficulty has been distinguishing recurrent alterations that are primarily driven by genome fragility from those resulting from positive selection, which has particularly hampered the detection of deleted tumor suppressor genes[45]. Further, common fragile sites are defined by aphidicolin break experiments, and are non-specific and poorly predictive of somatic rearrangements. For instance, 17% of the non-centromeric genome is covered by a fragile site, including known cancer genes like *BCL2* (FRA18B). Late-replicating regions have been proposed as fragile sites, and SCNA breakpoints have been found to be enriched in late-replicating regions[46]. However, SCNA breakpoints are imprecise, and rearrangements encompass a potentially larger set of breakpoints than SCNAs. Whether replication timing alone can robustly distinguish fragile sites in regions of recurrent rearrangements is unknown.

We enquired whether the precise breakpoint locations of the rearrangements that generate frequently rearranged regions might make the distinction between fragility and positive selection clearer. Among the 53 RSBs, 8 overlapped common fragile sites from aphidicolin break experiments. Among these, two were clearly driven by selection rather than fragility (*BCL2* and *MIR21*), and one was part of a large and non-specific fragile site (20 Mbp). The remaining five RSBs had markedly late-replication timing (mean: -0.76). We further noted that 13 of the 15 most frequently rearranged genes in the genome had a replication timing later than -0.5; notably, although many of these were adjacent to known common fragile sites, only 3 overlapped with one. Twelve RSBs also had replication times later than -0.5, including nine that have not been identified by aphidicolin break-induction experiments[47]. Although eight of these 12 RSBs had previously been described as recurrently deleted, none involve known oncogenes or tumor suppressor genes. Conversely, 26 of the other 41 RSBs involve known oncogenes or tumor suppressor genes. We therefore considered all of these late-replicating RSBs to reflect DNA fragility rather than positive selection.

8. Comparison of known SCNAs and fusions with recurrent breakpoints and rearrangements

We compared the recurrent breakpoints (RSBs) and recurrent juxtapositions (RSJ) detected in our 1D and 2D models with databases of known SCNAs and fusions. We defined known SCNAs as those that overlap with peak regions of recurrent focal amplifications or deletions in GISTIC pan-cancer analyses of 10,844 TCGA samples, as indicated in the TCGA copy number portal (www.broadinstitute.org/tcga). In total, 19 of 53 RSBs are novel, including 1 deletion, 3 amplifications, 4 fragile sites, and 11 neutral rearrangements. These results are available in **Supplementary Table 14**.

For recurrent juxtapositions, we used the COSMIC[48] fusions list (v87; cancer.sanger.ac.uk) to annotate known fusions. We only considered fusions that appear in more than one sample in COSMIC. To supplement the COSMIC list, we also searched for papers describing the RSJs in PubMed. For each RSJ, we queried both affected genes along with the terms “cancer” and “fusion”. Among the 90 RSJs, we found 77 to be novel. These results are available in **Supplementary Table 15**.

To further evaluate the applicability of our statistical methods and power calculations to the detection of RSJs, we evaluated how well our model performed at detecting known fusions from the curated COSMIC fusion list. From 167 COSMIC fusions represented in > 1 non-review article and > 1 sample, we identified 23 COSMIC fusions with at least one rearrangement bridging the two genes to within 100 Kbp of each gene (note that the majority of COSMIC fusions are reported in rare tumors not included in PCAWG). Of these 23 fusions, 10 were detected as an RSJ, and 7 were present in a single sample and thus could not be detected as recurrent. Of the remaining fusions, 5 had spans < 100 Kbp and fell below our power to detect. On further inspection, of the 39 samples that harbored these 5 fusions, only two (*FGFR3–TACC3* rearrangements in bladder cancer, neither supported by fusion transcripts) were consistent with the previously reported tumor type. Rather, the observed counts are consistent with the expected number of background rearrangements between neighboring genes separated by < 50 Kbp. The only bonafide oncogenic fusion our statistical methods missed was an in-frame *ERC1–RET* fusion in two thyroid adenocarcinoma samples (4% prevalence in thyroid adenocarcinoma, 0.1% overall prevalence). However, our models accurately detected four other bonafide rearrangements with tumor-type specific prevalences < 5% in our cohort (*QKI–NTRK2*, *TMPRSS2–ETV1*, *RNF130–BRAF*,

MYH11–CBFB), indicating that our overall false-negative rate is consistent with our power calculations for very low prevalence rearrangements. Thus, we find that accounting for statistical power to detect recurrent rearrangements avoids the pitfall of attributing selection to low-frequency rearrangements that could be more parsimoniously explained by background noise.

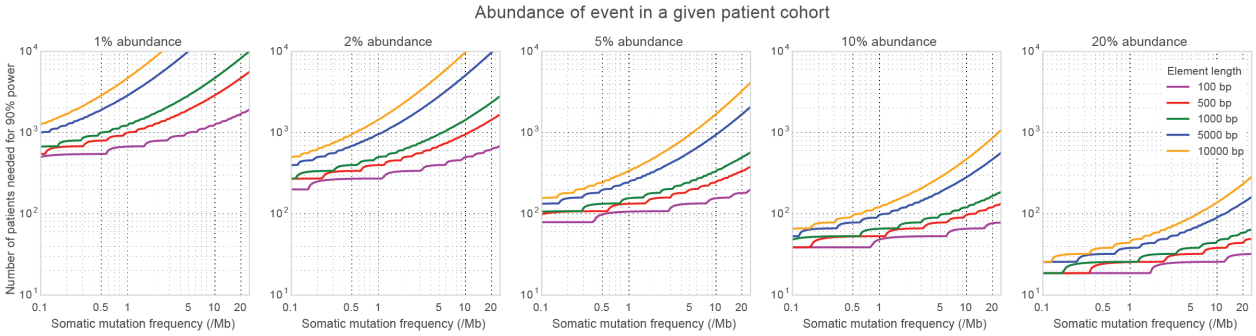
In the comparisons between the ten most significant SRJs and the ten most significant SNVs and SCNAs, we used SNV and SCNA lists from www.tumorportal.org and www.broadinstitute.org/tcga, respectively.

9. Amplification structure of the *BRD4/NOTCH3* locus in the context of recurrent *BRD4* deletion

The broad amplifications involving the *BRD4* and *NOTCH3* locus, in cases with a focal *BRD4* deletion, were typically tens of Mbps in length, sometimes involving the entire chromosome (**Extended Data Fig. 8f**). The *BRD4*/*NOTCH3* locus is in a significant amplification peak (GISTIC analysis) in breast and ovarian cancers. The only other recurrent amplification on chromosome 19 in breast and ovarian cancers is *CCNE1* (chr19: 30.3 Mbp). Indeed, many of these amplifications involved both loci, and more samples would be required to determine the exact amplification target. Regardless, the finding that these focal deletions tend to occur concomitantly with amplifications implies that amplification of the *NOTCH3*/*BRD4* region changes the selective landscape to favor *BRD4* intron 1 deletions.

10. Effect of element length on power calculations

The number of patients that need to be sequenced to achieve a certain power to discover a recurrently mutated driver with specific mutation abundance in the cohort also depends on the length of the analyzed elements. Prior power calculations have focused on fixed mean element lengths for either coding[49] or promoter regions[49,50]. We here add power calculations for different driver abundances and different element lengths of the range representative of coding and non-coding functional regions (**Supplementary Fig. 9).**



Supplementary Figure 9: Changes in discovery power depending on element length for different abundances.

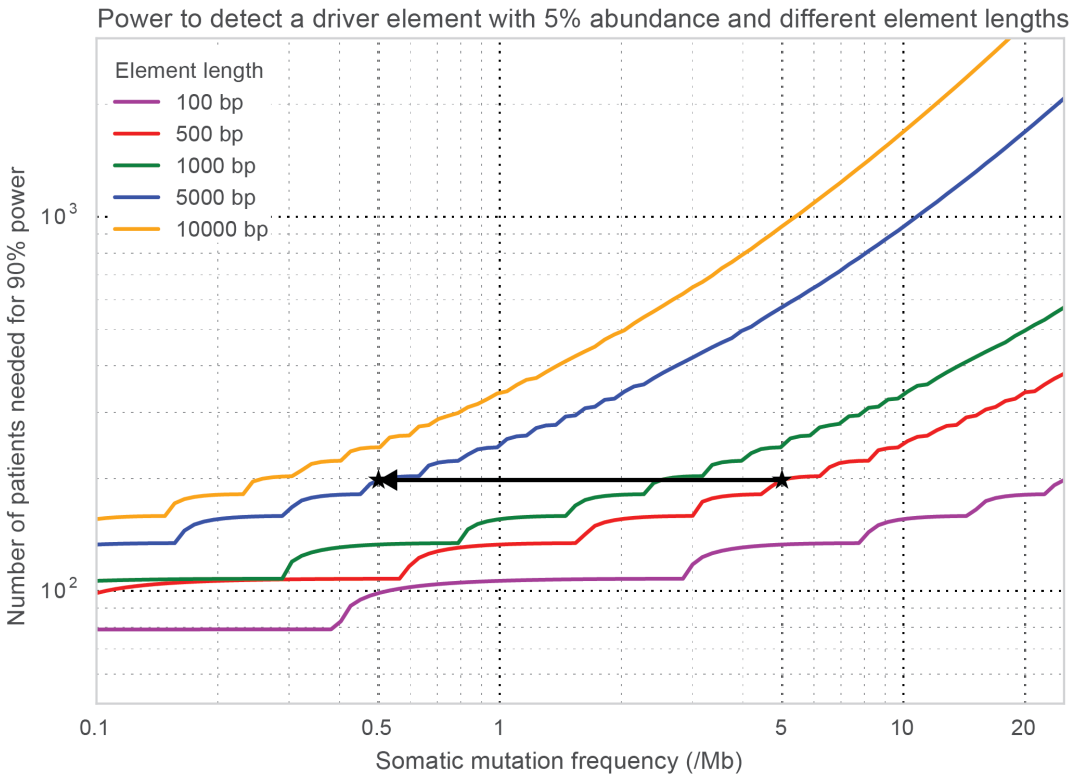
We further note that element length L and background mutation frequency f are mathematically related in the power calculation, such that the number of patients required for a new length L_2 can be obtained from a power plot using element length L_1 (for example, from Lawrence et al, 2014). This can be obtained through the following relationship between the two background mutation frequencies f_1 and f_2 as follows:

$$f_2 = 1 - (1 - f_1)^{L_1/L_2}$$

The number of patients required for length L_2 given a fixed driver abundance in the population can then be read off the plot at the x-axis position f_2, representing an adjustment of the background mutation rate to achieve the same power as with element length L_1 and background mutation frequency f_1.

For example for $L_1 = 500\ bp$, $f_1 = 5 * 10^{-6}$ mut/bp and new element length $L_2 = 5000\ bp$, $f_2 = 1 - (1 - f_1)^{L_1/L_2} = 1 - (1 - 5 * 10^{-6})^{(500/5000)} = 5 * 10^{-7} = 0.5 * 10^{-6}$mut/bp.

In **Supplementary Fig. 10**, we can see that the number of patients required for 90% power to detect an element with 5% frequency in a patient cohort is equivalent for elements of length 500 bp (red line) and background mutation frequency $5 * 10^{-6}$mut/bp and elements of length 5000 bp (blue line) and background mutation frequency $0.5 * 10^{-6}$mut/bp, as calculated above.



Supplementary Figure 10: Background mutation frequency and element length are mathematically related in the power equation. For a power calculation with fixed driver abundance in the population, one can calculate the position on the power graph for length L_1 for a new length L_2.

11. Impact of covariates on the estimation of driver mutations in functional regions of cancer genes

As described in **Methods**, we estimated the abundance of driver mutations in coding and regulatory regions (promoter and UTRs) of 603 known cancer genes using the NBR background model fitted on putative passenger genes.

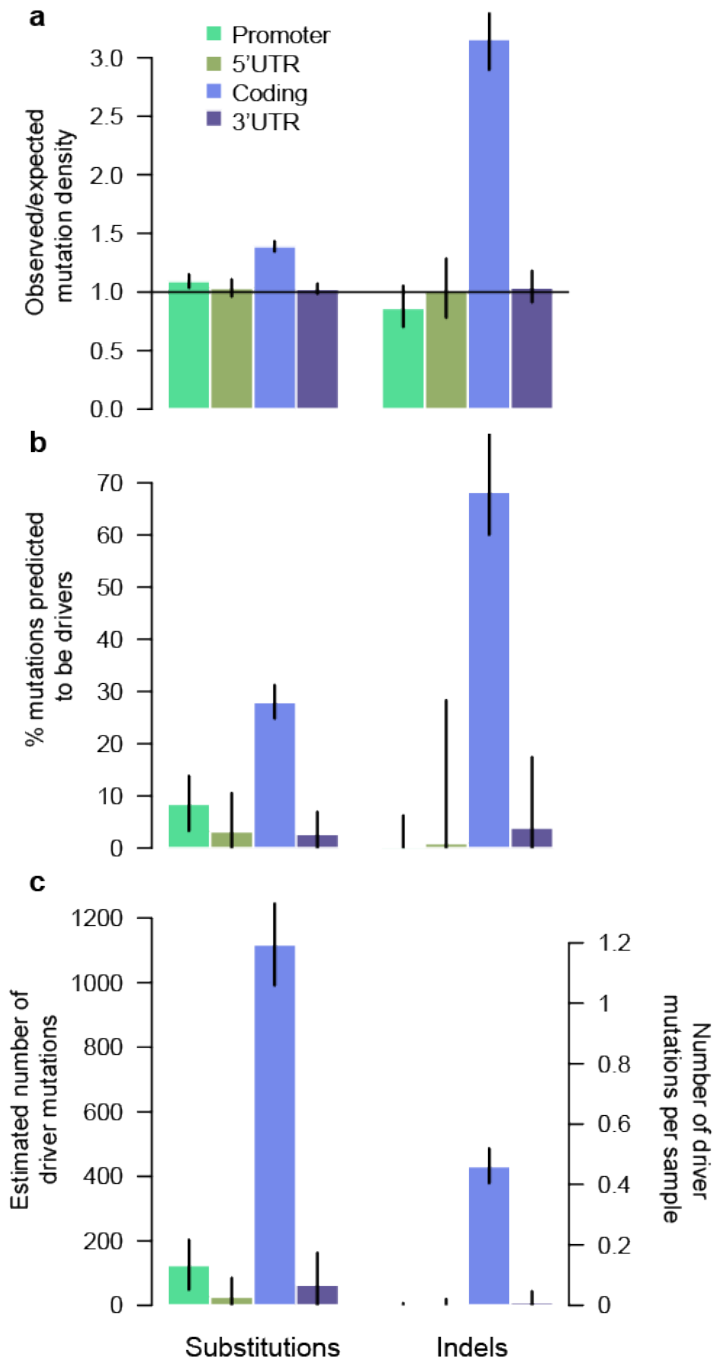
Promoters and 5'UTR regions are particularly sensitive to GC-sequencing biases, resulting in overall lower detection sensitivities. To alleviate these biases, we selected a set of samples with good d.s. by requiring each sample to have sensitivity > 90% in the two main *TERT* promoter hotspots. After this selection, despite some outliers, average sensitivity was much higher. We compared detection sensitivity in putative passenger genes and the 603 cancer genes to search for potential systematic biases that may compromise the analysis. Although there are some differences between passengers and drivers, these are small, and overall detection sensitivity values are high (**Extended Data Fig. 10e**).

Different covariates were included to improve the fit of the model. The local mutation rate, calculated on neutral regions within +/-100 kb around each element, was included to account for regional variation of mutation rates. A second type of covariate was included in the model to account for associations between gene expression levels and mutation rates. Starting with a matrix of mean FPKM expression values for each gene and tumor type, we log-transformed and scaled the expression matrix using pseudocounts and applied Principal Component Analysis to reduce the dimensionality. We selected the first 8 components as covariates, which together explained 95.5% of the variance. In addition, we added two additional covariates to account for non-linearity between expression and mutation rate in the tails of the expression spectrum. To accomplish this, we created two binary variables, one marking the 500 genes with highest maximum expression values across tumor types, the other marking 1,229 genes whose expression did not exceed FPKM values of 0.1 in any tumor type. Finally, since tumors are rich in amplifications and deletions and these events may result in seemingly increased or decreased mutation rates, we included a copy-number covariate, calculated as the average copy number of each gene across all PCAWG samples.

Supplementary Table 8 shows the impact of using different covariates on the 603 genes selected for this analysis. Reassuringly, this shows that the estimates are broadly consistent across models with different covariates, with variations typically within the confidence intervals

of alternative models. This confirms that the overall conclusions are largely unaffected by the use of different models. **Supplementary Fig. 11** shows the results of this analysis, including the observed-to-expected ratios, the percentage of mutations predicted to be drivers, and the estimated numbers of driver mutations.

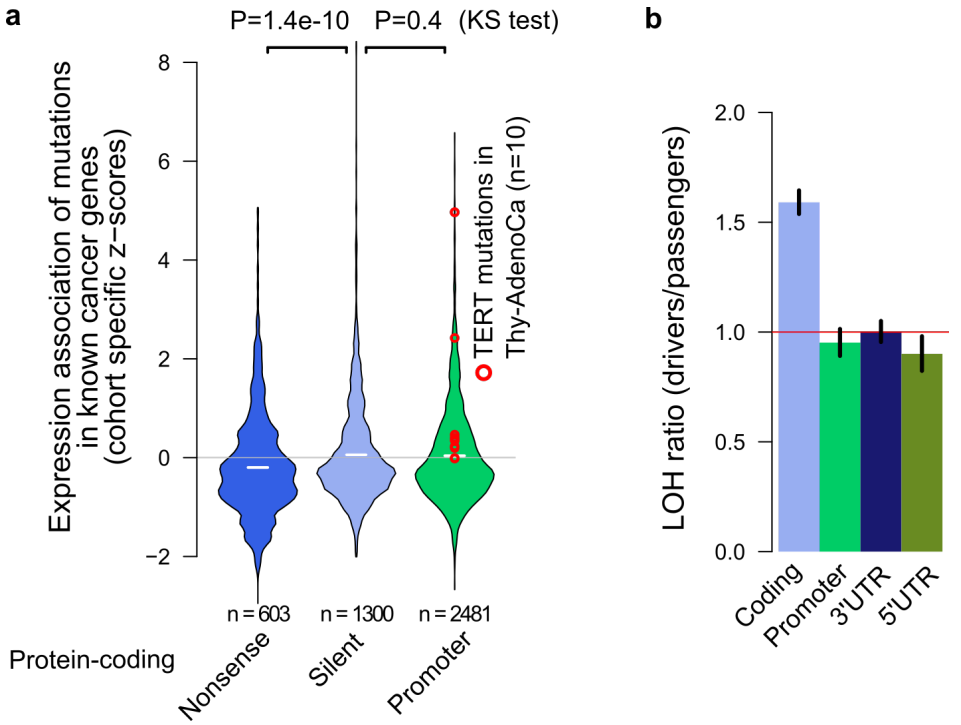
To evaluate the performance of the NBR model, we compared the number of driver substitutions predicted by NBR in the CDS regions of the 603 cancer genes to the number predicted by dN/dS (calculated by dNdScv). dN/dS offers an independent estimate of the number of driver substitutions in a group of genes using the local density of synonymous mutations to estimate the neutral expectation[51], instead of predicting the background mutation rate by extrapolation from putative passenger genes using a regression model. Reassuringly, in these 603 genes, NBR predicts 1,118 ($CI_{95\%}$: 991–1,248) driver substitutions, and dN/dS predicts 1,176 ($CI_{95\%}$: 914–1,460).



Supplementary Figure 11: Estimation of the excess substitutions (left) and indels (right) in regulatory and protein-coding regions of 603 known cancer genes. **a**, Ratios of observed vs. expected number of mutations; **b**, the percentage of mutations predicted to be drivers; **c**, and the total number of predicted drivers in all cancers and in each patient. **a-c,** Black bars are Binomial 95% confidence intervals; only samples with high detection sensitivity from the Pancancer cohort excluding Skin-Melanoma and lymphoid malignancies included (n = 936).

12. Relative paucity of regulatory non-coding drivers at cancer genes

Collectively, mutations occurring in the promoter region of the 757 cancer genes (603 CGC genes combined with 157 genes recurrently mutated in exome studies; **Methods**) did not have a significantly different association with expression than synonymous mutations (**Supplementary Fig. 12a**). Similarly, promoter and UTR mutations in cancer genes are not significantly enriched in LOH with respect to mutations in putative passenger genes (**Methods**; **Supplementary Fig. 12b**). This is consistent with the prediction that only a very small fraction of the mutations observed in the promoters and UTRs of known cancer genes are genuine driver events.



Supplementary Figure 12: a, Expression associated with mutations in coding and promoter regions of cancer genes. Z-score expressions associated with nonsense mutations deviate significantly from silent mutations, likely through nonsense mediated decay, whereas expressions associated with promoter mutations do not differ from that of silent mutations. Only mutations in diploid positions were used. White bars indicate means. Two-sided Kolmogorov–Smirnov (KS) test was used to evaluate *P* values. **b,** Excess of LOH associated to mutation in regulatory and coding regions of cancer genes. The y-axis shows the ratio of fold changes in cancer vs. passenger genes, with fold changes representing the excess or depletion of LOH associated with mutation. The analysis is performed across the full set of PCAWG samples (n = 2,583) and the set of 757 cancer genes (**Supplementary Table 7**), using 19,107 genes as

putative passengers or controls (**Methods**). Confidence intervals were estimated using parametric bootstrapping (100,000 pseudoreplicates) for both cancer and passenger genes (**Methods**). Details available in **Supplementary Table 19**.

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Germline cancer genome

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Ayellet V Segre[3,3,355], Tal Shmaya[59], Suyash S Shringarpure[61], Nikos Sidiropoulos[112], Reiner Siebert[261,262], Jared T Simpson[9,158], Lei Song[333], Oliver Stegle[7,8,265], Hana Susak[134,145], Tomas J Tanskanen[356], Grace Tiao[3], Marta Tojo[288], Jose MC Tubio[286,287,288], Daniel J Turner[352], Lara Urban[7,8], Sebastian M Waszak[8], David C Wedge[1,357,358], Joachim Weischenfeldt[8,112,113], David A Wheeler[162,163], Mark H Wright[61], Dai-Ying Wu[59], Tian Xia[359], Sergei Yakneen[8], Kai Ye[159,164], Venkata D Yellapantula[165,166], Jorge Zamora[1,286,287,288] and Bin Zhu[333]

Tumour subtypes and clinical translation

Fatima Al-Shahrour[360], Gurnit Atwal[9,10,361], Peter J Bailey[235], **Andrew V Biankin#**[362,363,364,365], Paul C Boutros[9,131,140,141], Peter J Campbell[1,2], David K Chang[363,365], Susanna L Cooke[365], Vikram Deshpande[104], Bishoy M Faltas[108], William C Faquin[104], **Levi Garraway#**[49], Gad Getz[3,4,5,6], **Sean M Grimmond#**[366], Syed Haider[9], **Katherine A Hoadley#**[247,248], Wei Jiao[9], Vera B Kaiser[367], Rosa Karlić[368], Mamoru Kato[369], Kirsten Kübler[3,6,104], Alexander J Lazar[370], Constance H Li[9,131], David N Louis[104], Adam Margolin[371], Sancha Martin[1,372], Hardeep K Nahal-Bose[45], G Petur Nielsen[104], Serena Nik-Zainal[1,324,325,326], Larsson Omberg[99], Christine P'ng[9], Marc D Perry[45,102], Paz Polak[3,4,6], Esther Rheinbay[3,6,104], Mark A Rubin[129,193,211,212,213], Colin A Semple[367], Dennis C Sgroi[104], Tatsuhiro Shibata[33,34], Reiner Siebert[261,262], Jaclyn Smith[371], **Lincoln D Stein#**[9,10], Miranda D Stobbe[133,134], Ren X Sun[9], Kevin Thai[45], Derek W Wright[373,374], Chin-Lee Wu[104], Ke Yuan[294,372,375] and Junjun Zhang[45]

Evolution and heterogeneity

David J Adams[1], Pavana Anur[376], Rameen Beroukhim[3,6,172], Paul C Boutros[9,131,140,141], David D L Bowtell[188,290], Peter J Campbell[1,2], Shaolong Cao[146], Elizabeth L Christie[188], Marek Cmero[377,378,379], Yupeng Cun[380], Kevin J Dawson[1], Jonas Demeulemeester[63,64], Stefan C Dentro[1,64,357], Amit G Deshwar[381], Nilgun Donmez[149,157], Ruben M Drews[294], Roland Eils[52,54,66,67], Yu Fan[146], Matthew W Fittall[64], Dale W Garsed[188,189], Moritz Gerstung[7,8], Gad Getz[3,4,5,6], Santiago Gonzalez[7,8], Gavin Ha[3], Kerstin Haase[64], Marcin Imielinski[299,300], Lara Jerman[8,382], Yuan Ji[383,384], Clemency Jolly[64], Kortine Kleinheinz[52,54], Juhee Lee[385], Henry Lee-Six[1], Ignaty Leshchiner[3], Dimitri Livitz[3], Geoff Macintyre[294], Salem Malikic[149,157], Florian Markowetz[294,295], Iñigo Martincorena[1], Thomas J Mitchell[1,295,386], Quaid D Morris[361,387], Ville Mustonen[320,321,322], Layla Oesper[388], Martin Peifer[380], Myron Peto[389], Benjamin J Raphael[210], Daniel Rosebrock[3], Yulia Rubanova[158,361], S Cenk Sahinalp[149,156,157], Adriana Salcedo[9], Matthias Schlesner[52,109], Steven E Schumacher[3,217], Subhajit Sengupta[390], Ruian Shi[387], Seung Jun Shin[264], **Paul T Spellman#**[391], Oliver Spiro[3], Lincoln D Stein[9,10], Maxime Tarabichi[1,64], **Peter Van Loo#**[63,64], Shankar Vembu[387,392], Ignacio Vázquez-García[1,165,328,329], Wenyi Wang[146], **David C Wedge#**[1,357,358], David A Wheeler[162,163], Jeffrey A Wintersinger[191,361,393], Tsun-Po Yang[380], Xiaotong Yao[299,316], Kaixian Yu[394], Ke Yuan[294,372,375] and Hongtu Zhu[395,396]

Exploratory: portals, visualization and software infrastructure

Fatima Al-Shahrour[360], Elisabet Barrera[7], Wojciech Bazant[7], Alvis Brazma[7], Isidro Cortés-Ciriano[236,237,238], Brian Craft[239], David Craft[3,240], Vincent Ferretti[45,68], Nuno A Fonseca[7,69], Anja Füllgrabe[7], Mary J Goldman[239], **David Haussler#**[239,397], Wolfgang Huber[8], Maria Keays[7], Alfonso Muñoz[7], Brian D O'Connor[45,50], Irene Papatheodorou[7], Robert Petryszak[7], Elena Piñeiro-Yáñez[360], Alfonso Valencia[46,110], **Miguel Vazquez#**[46,111], John N Weinstein[398,399], Qian Xiang[115], Junjun Zhang[45] and **Jingchun Zhu#**[239]

Exploratory: mitochondrial variants and HLA/immunogenicity

Peter J Campbell[1,2], Yiwen Chen[146], Chad J Creighton[241], Li Ding[136,137,144], Akihiro Fujimoto[48], Masashi Fujita[48], Gad Getz[3,4,5,6], Leng Han[230], Takanori Hasegawa[86], Shuto Hayashi[86], Seiya Imoto[85,86], Young Seok Ju[1,182], Hyung-Lae Kim[27], Youngwook Kim[95,96], Youngil Koh[307,308], Mitsuhiro Komura[86], Jun Li[146], **Han Liang#**[400], Iñigo Martincorena[1], Satoru Miyano[86], Shinichi Mizuno[401], **Hidewaki Nakagawa#**[48], Keunchil Park[206,207], Eigo Shimizu[86], Yumeng Wang[146,402], John N Weinstein[398,399], Yanxun Xu[403], Rui Yamaguchi[86], Fan Yang[387], Yang Yang[230], Christopher J Yoon[182], Sung-Soo Yoon[308], Yuan Yuan[146], Fan Zhang[246] and Zemin Zhang[246,271]

Exploratory: pathogens

Malik Alawi[404,405], Ivan Borozan[9], Daniel S Brewer[406,407], Colin S Cooper[407,408,409], Nikita Desai[45], **Roland Eils#**[52,54,66,67], Vincent Ferretti[45,68], Adam Grundhoff[404,410], Murat Iskar[411], Kortine Kleinheinz[52,54], **Peter Lichter#**[79,411], Hidewaki Nakagawa[48], Akinyemi I Ojesina[255,256,257], Chandra Sekhar Pedamallu[3,6,172], Matthias Schlesner[52,109], Xiaoping Su[142] and Marc Zapatka[411]

Tumor Specific Providers – Australia (Ovarian cancer)

Kathryn Alsop[412,413], Australian Ovarian Cancer Study Group[188,311,414], **David D L Bowtell#**[188,290], Timothy JC Bruxner[186], Angelika N Christ[186], Elizabeth L Christie[188], Stephen M Cordner[415], Prue A Cowin[188], Ronny Drapkin[416], Dariush Etemadmoghadam[188,189], Sian Fereday[417], Dale W Garsed[188,189], Joshy George[168], Sean M Grimmond[366], Anne Hamilton[188], Oliver Holmes[311,312], Jillian A Hung[418,419], Karin S Kassahn[186,420], Stephen H Kazakoff[311,312], Catherine J Kennedy[421,422], Conrad R Leonard[311,312], Linda Mileshkin[188], David K Miller[186,363,423], Gisela Mir Arnau[188], Chris Mitchell[188], Felicity Newell[311,312], Katia Nones[311,312], Ann-Marie Patch[311,312], John V Pearson[311,312], Michael C Quinn[311,312], Mark Shackleton[189,218], Darrin F Taylor[186], Heather Thorne[188], Nadia Traficante[188], Ravikiran Vedururu[188], Nick M Waddell[312], Nicola Waddell[311,312], Paul M Waring[253], Scott Wood[311,312], Qinying Xu[311,312] and Anna deFazio[424,425,426]

Tumor Specific Providers – Australia (Pancreatic cancer)

Matthew J Anderson[186], Davide Antonello[427], Andrew P Barbour[428,429], Claudio Bassi[427], Samantha Bersani[430], **Andrew V Biankin#**[362,363,364,365], Timothy JC Bruxner[186], Ivana Cataldo[430,431], David K Chang[363,365], Lorraine A Chantrill[363,432], Yoke-Eng Chiew[424], Angela Chou[363,433], Angelika N Christ[186], Sara Cingarlini[37], Nicole Cloonan[434], Vincenzo Corbo[431,435,436], M V Davi[436],Fraser R Duthie[437,438], J Lynn Fink[46,186], Anthony J Gill[363,439], Janet S Graham[365,440], **Sean M Grimmond#**[366], Ivon Harliwong[186], Oliver Holmes[311,312], Nigel B Jamieson[364,365,441], Amber L Johns[363,423], Karin S Kassahn[186,420], Stephen H Kazakoff[311,312], James G Kench[363,439,442], Luca Landoni[427], Rita T Lawlor[431], Conrad R Leonard[311,312], Andrea Mafficini[431], Neil D Merrett[427,443], David K Miller[186,363,423], Marco Miotto[427], Elizabeth A Musgrove[365], Adnan M Nagrial[363], Felicity Newell[311,312], Katia Nones[311,312], Karin A Oien[253,444], Marina Pajic[363], Ann-Marie Patch[311,312], John V Pearson[311,312], Mark Pinese[445], Michael C Quinn[311,312], Alan J Robertson[186], Ilse Rooman[363], Borislav C Rusev[431], Jaswinder S Samra[427,439], Maria Scardoni[430], Christopher J Scarlett[363,446], Aldo Scarpa[431], Elisabetta Sereni[427], Katarzyna O Sikora[431], Michele Simbolo[435], Morgan L Taschuk[45], Christopher W Toon[363], Giampaolo Tortora[37,38], Caterina Vicentini[431], Nick M Waddell[312], Nicola Waddell[311,312], Scott Wood[311,312], Jianmin Wu[363], Qinying Xu[311,312] and Nikolajs Zeps[447]

Tumor Specific Providers – Australia (Skin cancer)

Lauri A Aaltonen[448], Andreas Behren[449], Hazel Burke[450], Jonathan Cebon[449], Rebecca A Dagg[451], Ricardo De Paoli-Iseppi[452], Ken Dutton-Regester[311], Matthew A Field[453], Anna Fitzgerald[454], Sean M Grimmond[366], **Nicholas K Hayward#**[311,450], Peter Hersey[450], Oliver Holmes[311,312], Valerie Jakrot[450], Peter A Johansson[311], Hojabr Kakavand[452], Stephen H Kazakoff[311,312], Richard F Kefford[455], Loretta MS Lau[456], Conrad R Leonard[311,312], Georgina V Long[457], **Graham J Mann#**[458,459], Felicity Newell[311,312], Katia Nones[311,312], Ann-Marie Patch[311,312], John V Pearson[311,312], Hilda A Pickett[456], Antonia L Pritchard[311], Gulietta M Pupo[460], Robyn PM Saw[457], Sarah-Jane Schramm[461], **Richard A Scolyer#**[425,457,462,463], Mark Shackleton[189,218], Catherine A Shang[464], Ping Shang[457], Andrew J Spillane[457], Jonathan R Stretch[457], Varsha Tembe[461], John F Thompson[457], Ricardo E Vilain[462], Nick M Waddell[312], Nicola Waddell[311,312], James S Wilmott[457], Scott Wood[311,312], Qinying Xu[311,312] and Jean Y Yang[465]

Tumor Specific Providers – Canada (Pancreatic cancer)

John Bartlett[466,467], Prashant Bavi[468], Ivan Borozan[9], Dianne E Chadwick[469], Michelle Chan-Seng-Yue[468], Sean Cleary[468,470], Ashton A Connor[471,472], Karolina Czajka[473], Robert E Denroche[468], Neesha C Dhani[474], Jenna Eagles[78], Vincent Ferretti[45,68], Steven Gallinger[468,471,472], Robert C Grant[468,475], David Hedley[474], Michael A Hollingsworth[476], **Thomas J Hudson#**[77,78], Gun Ho Jang[468], Jeremy Johns[78], Sangeetha Kalimuthu[468], Sheng-Ben Liang[477], Ilinca Lungu[468,478], Xuemei

Luo[9], Faridah Mbabaali[78], **John D McPherson#**[78,468,479], Treasa A McPherson[475], Jessica K Miller[78], Malcolm J Moore[474], Faiyaz Notta[468,480], Danielle Pasternack[78], Gloria M Petersen[481], Michael H A Roehrl[131,468,482,483,484], Michelle Sam[78], Iris Selander[475], Stefano Serra[253], Sagedeh Shahabi[477], **Lincoln D Stein#**[9,10], Morgan L Taschuk[45], Sarah P Thayer[485], Lee E Timms[78], Gavin W Wilson[9,468], Julie M Wilson[468] and Bradly G Wouters[486]

Tumor Specific Providers – Canada (Prostate cancer)

Timothy A Beck[45,487], Vinayak Bhandari[9], **Paul C Boutros#**[9,131,140,141], **Robert G Bristow#**[131,488,489,490,491], Colin C Collins[149], Shadrielle MG Espiritu[9], Neil E Fleshner[492], Natalie S Fox[9], Michael Fraser[9], Syed Haider[9], Lawrence E Heisler[493], Vincent Huang[9], Emilie Lalonde[9], Julie Livingstone[9], John D McPherson[78,468,479], Alice Meng[494], Veronica Y Sabelnykova[9], Adriana Salcedo[9], Yu-Jia Shiah[9], Theodorus Van der Kwast[495] and Takafumi N Yamaguchi[9]

Tumor Specific Providers – China (Gastric cancer)

Shuai Ding[496], Daiming Fan[497], Yong Hou[39,249], Yi Huang[151,152], Lin Li[39], Siliang Li[39,249], Dongbing Liu[39,249], Xingmin Liu[39,249], **Youyong Lu#**[28,29,30], Yongzhan Nie[497,498], Hong Su[39,249], Jian Wang[39], Kui Wu[39,249], Xiao Xiao[152], Rui Xing[29,499], **Huanming Yang#**[39], Shanlin Yang[496], Yingyan Yu[500], Xiuqing Zhang[39], Yong Zhou[39] and Shida Zhu[39,249]

Tumor Specific Providers – EU: France (Renal cancer)

Rosamonde E Banks[501], Guillaume Bourque[502,503], Alvis Brazma[7], Paul Brennan[504], **Mark Lathrop#**[503], Louis Letourneau[505], Yasser Riazalhosseini[503], Ghislaine Scelo[504], **Jörg Tost#**[506], Naveen Vasudev[507] and Juris Viksna[508]

Tumor Specific Providers – EU: United Kingdom (Breast cancer)

Sung-Min Ahn[509], Ludmil B Alexandrov[1,317], Samuel Aparicio[510], Laurent Arnould[511], MR Aure[512], Shriram G Bhosle[1], E Birney[7], Ake Borg[513], S Boyault[514], AB Brinkman[515], JE Brock[516], A Broeks[517], Adam P Butler[1], AL Børresen-Dale[512], C Caldas[518,519], Peter J Campbell[1,2], Suet-Feung Chin[518,519], Helen Davies[1,324,325], C Desmedt[520], L Dirix[521], S Dronov[1], Anna Ehinger[522], JE Eyfjord[523], GG Van den Eynden[524], A Fatima[217], Jorge Reis-Filho[525], JA Foekens[526], PA Futreal[527], Øystein Garred[528,529], Moritz Gerstung[7,8], Dilip D Giri[525], D Glodzik[1], Dorthe Grabau[530], Holmfridur Hilmarsdottir[523], GK Hooijer[531], Jocelyne Jacquemier[532], SJ Jang[533], Jon G Jonasson[523], Jos Jonkers[534], HY Kim[532], Tari A King[535,536], Stian Knappskog[1,537], G Kong[532], S Krishnamurthy[538], S Van Laere[521], SR Lakhani[539], Denis Larsimont[540], HJ Lee[533], JY Lee[541], Ming Ta Michael Lee[527], Yilong Li[1], Ole Christian Lingjærde[542], Gaetan MacGrogan[543], Sancha Martin[1,372], Iñigo Martincorena[1], Andrew Menzies[1], Sandro Morganella[1], Ville Mustonen[320,321,322], Serena Nik-

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Tumor Specific Providers – Germany (Malignant lymphoma)

Ole Ammerpohl[564,565], Sietse Aukema[566,567], Anke K Bergmann[568], Stephan H Bernhart[276,277,280], Hans Binder[276,277], Arndt Borkhardt[569], Christoph Borst[570], Benedikt Brors[81,118,278], Birgit Burkhardt[571], Alexander Claviez[572], Roland Eils[52,54,66,67], Maria Elisabeth Goebler[573], Andrea Haake[564], Siegfried Haas[570], Martin Hansmann[574], Jessica I Hoell[569], Steve Hoffmann[276,277,279,280], Michael Hummel[575], Daniel Hübschmann[54,66,82,83,84], Dennis Karsch[576], Wolfram Klapper[567], Kortine Kleinheinz[52,54], Michael Kneba[576], Jan O Korbel[7,8], Helene Kretzmer[277,280], Markus Kreuz[577], Dieter Kube[578], Ralf Küppers[579], Chris Lawerenz[67], Dido Lenze[575], Peter Lichter[79,411], Markus Loeffler[577], Cristina López[262,564], Luisa Mantovani-Löffler[580], Peter Möller[581], German Ott[582], Bernhard Radlwimmer[411], Julia Richter[564,567], Marius Rohde[583], Philip C Rosenstiel[584], Andreas Rosenwald[585], Markus B Schilhabel[584], Matthias Schlesner[52,109], Stefan Schreiber[586], **Reiner Siebert#**[261,262], Peter F Stadler[276,277,280], Peter Staib[587], Stephan Stilgenbauer[588], Stephanie Sungalee[8], Monika Szczepanowski[567], Umut H Toprak[54,589], Lorenz HP Trümper[578], Rabea Wagener[262,564] and Thorsten Zenz[81]

Tumor Specific Providers – Germany (Pediatric Brain cancer)

Ivo Buchhalter[52,53,54], Juergen Eils[66,67], Roland Eils[52,54,66,67], Volker Hovestadt[411], Barbara Hutter[79,80,81], David TW Jones[301,302], Natalie Jäger[52], Christof von Kalle[83], Marcel Kool[97,301], Jan O Korbel[7,8], Andrey Korshunov[97], Pablo Landgraf[590, 770], Chris Lawerenz[67], Hans Lehrach[591], **Peter Lichter#**[79,411], Paul A Northcott[592], Stefan M Pfister[97,301,593], Bernhard Radlwimmer[411], Guido Reifenberger[590], Matthias Schlesner[52,109], Hans-Jörg Warnatz[591], Joachim Weischenfeldt[8,112,113], Stephan Wolf[594], Marie-Laure Yaspo[591] and Marc Zapatka[411]

Tumor Specific Providers – Germany (Prostate cancer)

Yassen Assenov[595], Benedikt Brors[81,118,278], Juergen Eils[66,67], Roland Eils[52,54,66,67], Lars Feuerbach[118], Clarissa Gerhauser[284], Jan O Korbel[7,8], Chris Lawerenz[67], Hans Lehrach[591], Sarah Minner[596], Christoph Plass[284], **Guido Sauter#**[597], Thorsten Schlomm[113,598], Nikos Sidiropoulos[112],

Ronald Simon[597], **Holger Sültmann#**[81,599], Hans-Jörg Warnatz[591], Dieter Weichenhan[284], Joachim Weischenfeldt[8,112,113] and Marie-Laure Yaspo[591]

Tumor Specific Providers – India (Oral cancer)

Nidhan K Biswas[600], Luca Landoni[427], Arindam Maitra[600], **Partha P Majumder#**[600] and **Rajiv Sarin#**[601]

Tumor Specific Providers – Italy (Pancreatic cancer)

Davide Antonello[427], Stefano Barbi[435], Claudio Bassi[427], Samantha Bersani[430], Giada Bonizzato[431], Cinzia Cantù[431], Ivana Cataldo[430,431], Sara Cingarlini[37], Vincenzo Corbo[431,435, 436], M V Davi[436],Angelo P Dei Tos[602], Matteo Fassan[603], Sonia Grimaldi[431], Luca Landoni[427], Rita T Lawlor[431], Claudio Luchini[430], Andrea Mafficini[431], Giuseppe Malleo[427], Giovanni Marchegiani[427], Michele Milella[37], Marco Miotto[427], Salvatore Paiella[427], Antonio Pea[427], Paolo Pederzoli[427], Borislav C Rusev[431], Andrea Ruzzenente[427], Roberto Salvia[427], Maria Scardoni[430], **Aldo Scarpa#**[431], Elisabetta Sereni[427], Michele Simbolo[435], Nicola Sperandio[431], Giampaolo Tortora[37,38] and Caterina Vicentini[431]

Tumor Specific Providers – Japan (Biliary tract cancer)

Yasuhito Arai[33], Natsuko Hama[33], Nobuyoshi Hiraoka[604], Fumie Hosoda[33,605], Mamoru Kato[369], Hiromi Nakamura[33], Hidenori Ojima[606], Takuji Okusaka[607], **Tatsuhiro Shibata#**[33,34], Yasushi Totoki[33] and Tomoko Urushidate[34]

Tumor Specific Providers – Japan (Gastric cancer)

Hiroyuki Aburatani#[272], Yasuhito Arai[33], Masashi Fukayama[608], Natsuko Hama[33], Fumie Hosoda[33,605], Shumpei Ishikawa[609], Hitoshi Katai[610], Mamoru Kato[369], Hiroto Katoh[611], Daisuke Komura[609], Genta Nagae[272,283], Hiromi Nakamura[33], Hirofumi Rokutan[612], Mihoko Saito-Adachi[33], **Tatsuhiro Shibata#**[33,34], Akihiro Suzuki[272,613], Hirokazu Taniguchi[614], Kenji Tatsuno[272], Yasushi Totoki[33], Tetsuo Ushiku[608], Shinichi Yachida[33,615] and Shogo Yamamoto[272]

Tumor Specific Providers – Japan (Liver cancer)

Hiroyuki Aburatani[272], Hiroshi Aikata[616], Koji Arihiro[616], Shun-ichi Ariizumi[617], Keith A Boroevich[47,48], Kazuaki Chayama[616], Akihiro Fujimoto[48], Masashi Fujita[48], Mayuko Furuta[48], Kunihito Gotoh[618], Natsuko Hama[33], Takanori Hasegawa[86], Shinya Hayami[619], Shuto Hayashi[86], Satoshi Hirano[620], Seiya Imoto[85,86], Mamoru Kato[369], Yoshiiku Kawakami[616], Kazuhiro Maejima[48],

Satoru Miyano[86], Genta Nagae[272,283], **Hidewaki Nakagawa#**[48], Hiromi Nakamura[33], Toru Nakamura[620], Kaoru Nakano[48], Hideki Ohdan[616], Aya Sasaki-Oku[48], **Tatsuhiro Shibata#**[33,34], Yuichi Shiraishi[86], Hiroko Tanaka[86], Yasushi Totoki[33], Tatsuhiko Tsunoda[47,220,221,222], Masaki Ueno[619], Rui Yamaguchi[86], Masakazu Yamamoto[617] and Hiroki Yamaue[619]

Tumor Specific Providers – Singapore (Biliary tract cancer)

Su Pin Choo[621], Ioana Cutcutache[267,319], Narong Khuntikeo[427,622], John R McPherson[267,319], Choon Kiat Ong[623], Chawalit Pairojkul[253], Irinel Popescu[624], **Steven G Rozen#**[267,268,319], **Patrick Tan#**[254,266,267,268] and **Bin Tean Teh#**[266,267,268,269,270]

Tumor Specific Providers – South Korea (Blood cancer)

Keun Soo Ahn[625], Hyung-Lae Kim[27], Youngil Koh[307,308] and **Sung-Soo Yoon#**[308]

Tumor Specific Providers – Spain (Chronic Lymphocytic Leukemia)

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