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Retrospective evaluation of whole exome and genome mutation calls in 746 cancer samples

Matthew H. Bailey ^{1,2,3}, William U. Meyerson^{4,5}, Lewis Jonathan Dursi ^{6,7}, Liang-Bo Wang ^{1,2}, Guanlan Dong ², Wen-Wei Liang^{1,2}, Amila Weerasinghe ^{1,2}, Shantao Li ⁵, Sean Kelso², MC3 Working Group*, PCAWG novel somatic mutation calling methods working group*, Gordon Saksena ⁸, Kyle Ellrott ⁹, Michael C. Wendt^{1,10,11}, David A. Wheeler ^{12,13}, Gad Getz ^{8,14,15,16}, Jared T. Simpson^{6,17}, Mark B. Gerstein ^{5,18,19}✉, Li Ding^{1,2,3,20}✉ & PCAWG Consortium*

The Cancer Genome Atlas (TCGA) and International Cancer Genome Consortium (ICGC) curated consensus somatic mutation calls using whole exome sequencing (WES) and whole genome sequencing (WGS), respectively. Here, as part of the ICGC/TCGA Pan-Cancer Analysis of Whole Genomes (PCAWG) Consortium, which aggregated whole genome sequencing data from 2,658 cancers across 38 tumour types, we compare WES and WGS side-by-side from 746 TCGA samples, finding that ~80% of mutations overlap in covered exonic regions. We estimate that low variant allele fraction (VAF < 15%) and clonal heterogeneity contribute up to 68% of private WGS mutations and 71% of private WES mutations. We observe that ~30% of private WGS mutations trace to mutations identified by a single variant caller in WES consensus efforts. WGS captures both ~50% more variation in exonic regions and un-observed mutations in loci with variable GC-content. Together, our analysis highlights technological divergences between two reproducible somatic variant detection efforts.

¹The McDonnell Genome Institute at Washington University, St. Louis, MO 63108, USA. ²Division of Oncology, Department of Medicine, Washington University School of Medicine, St. Louis, MO 63108, USA. ³Alvin J. Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO 63108, USA. ⁴Yale School of Medicine, Yale University, New Haven, CT 06520, USA. ⁵Program in Computational Biology and Bioinformatics, Yale University, New Haven, CT 06520, USA. ⁶Computational Biology Program, Ontario Institute for Cancer Research, Toronto, ON M5G 0A3, Canada. ⁷The Hospital for Sick Children, Toronto, ON M5G 1X8, Canada. ⁸Broad Institute of MIT and Harvard, Cambridge, MA 02142, USA. ⁹Biomedical Engineering, Oregon Health and Science University, Portland, OR 97239, USA. ¹⁰Department of Mathematics, Washington University in St. Louis, St. Louis, MO 63130, USA. ¹¹Department of Genetics, Washington University School of Medicine, St. Louis, MO 63110, USA. ¹²Human Genome Sequencing Center, Baylor College of Medicine, Houston, TX 77030, USA. ¹³Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX 77030, USA. ¹⁴Harvard Medical School, Boston, MA 02115, USA. ¹⁵Center for Cancer Research, Massachusetts General Hospital, Boston, MA 02114, USA. ¹⁶Department of Pathology, Massachusetts General Hospital, Boston, MA 02114, USA. ¹⁷Department of Computer Science, University of Toronto, Toronto, ON M5S, Canada. ¹⁸Department of Computer Science, Yale University, New Haven, CT 06520, USA. ¹⁹Department of Molecular Biophysics and Biochemistry, Yale University, New Haven, CT 06520, USA. ²⁰Department of Medicine and Department of Genetics, Washington University School of Medicine, St. Louis, MO 63110, USA. *Lists of authors and their affiliations appear at the end of the paper. ✉email: mark.gerstein@yale.edu; lding@wustl.edu

Complementary efforts of The Cancer Genome Atlas (TCGA) and the International Cancer Genome Consortium (ICGC) have recently produced two of the highest quality and most elaborate and reproducible somatic variant call sets from exome and whole genome-level data in cancer genomics, respectively. The motivation for these efforts stems from the notion that “scientific crowd sourcing” and combining mutation callers can provide very strong results.

These two efforts produced variant calls from 10 different callers, namely Radia¹, Varscan², MuSE³, MuTect⁴, Pindel^{5,6}, Indelocator⁷, SomaticSniper⁸ for WES and MuSE, Broad-Pipeline (anchored by MuTect), Sanger-pipeline, German Cancer Research Center pipeline (DKFZ), and SMuFin⁹, for WGS. Briefly, the PCAWG Consortium aggregated whole genome sequencing data from 2658 cancers across 38 tumor types generated by the ICGC and TCGA projects. These sequencing data were re-analyzed with standardized, high-accuracy pipelines to align to the human genome (reference build hs37d5) and identify germline variants and somatically acquired mutations¹⁰. Of the 885 TCGA samples in ICGC, 746 were included in the latest exome call set produced by both the Multi-Center Mutation Calling in Multiple Cancers (MC3) effort and the Pan-Cancer Analysis of Whole Genomes (PCAWG) Consortium set. These 746 samples represent a critical benchmark for high-level analysis of similarities and differences between exome and genome somatic variant detection methods.

Reproducibility of mutations identified by both whole exome capture sequencing and whole genome sequencing (WGS) techniques remains an important issue, not only for the scientific use of large, established data sets, but for data designs of future research projects. Previous work analyzing exome capture effects on sequence read quality has shown that GC-content bias is the major source of variation in coverage¹¹. A performance comparison across exome-captured platforms demonstrated that for most technologies, both high and low GC-content result in reduced coverage in read depth¹². Belkadi et al. compared mutation calls between WGS and WES, observing that ~3% of coding variants with high quality were only detected in WGS, and WGS also had a more uniform distribution of coverage depth, genotype quality, and minor read ratio¹³. Furthermore, due to the relatively high error rate per read in next-generation sequencing¹⁴, the detectability of mutations with low variant allele fractions (VAFs) is limited by background noise. Despite these studies’ nuanced preference towards WGS, others contend that WES will remain a better choice until costs of WGS fall¹⁵. The decision to sequence exomes or whole genomes is further confounded as more recent publications in oncology select either WGS^{16–20} or WES^{21–24}. Recognizing the unresolved nature of this issue, Schwarze et al. have called for more comprehensive studies comparing the WES and WGS studies, especially as this issue has important ramifications for the clinic²⁵.

Our analysis provides confidence that mutation calls within the captured exonic regions of these two data sets are largely consistent. We highlight common sample, cohort, and caller-specific challenges in cancer variant detection from the TCGA and ICGC efforts. We show that variants that are most confidently called in one database i.e., called by multiple callers, are very likely to be called in the other. We assess how reproducibility impacts higher-level mutation signature analysis and illustrate the need for caution in assessing performance that can only be identified by the overlap of these two data sets. Finally, we explore the capacity of WGS to detect recurrent non-coding mutations captured by whole exome sequencing.

Results

Data and workflow. We used publicly available data from the MC3 and PCAWG repositories, consisting of ~3.6 M and ~47 M variants, respectively (Fig. 1a). 746 samples were sequenced by both WES and WGS, comprising various aliquots and portions of the same tumor (Supplementary Data 1, Fig. 1b). Effects of these differences are discussed below for preliminary results, but we ultimately used the entire set of 746 samples in the variant overlap analysis, since the effects of tumor partitioning did not play a significant role (Supplementary Fig. 1). By restricting the public data sets to overlapping samples, we reduced the total corpus to ~220 K (6.1%) and ~23 M (49.6%) mutations for exome and whole genome, respectively. It is notable that there is an enrichment of variants in hypermutated samples from COAD, HNSC, LUAD, and STAD in the PCAWG set used in this study (Supplementary Fig. 2). To begin building a comparable set of mutations between these two studies, we further restricted the whole genome data set to exon regions provided by the MC3 analysis working group. This reduced the WGS data set to 1.6% of its original size, within range of total exome material estimations²⁶ (Fig. 1a). The next step involved removing poorly-covered variants potentially caused by technical anomalies by limiting mutations to those captured in coverage files (distributed as.wig files). A reciprocal coverage strategy was used, meaning PCAWG mutations were restricted to covered genomic regions in MC3 and vice versa, thereby maintaining a complementary set of callable genomic regions. Removal of mutations in uncovered regions reduced the remaining PCAWG data set by approximately one-half, from 387,166 to 183,424 mutations. We also identified 4241 MC3 and 2219 PCAWG mutations that were present in the respective MAF but were not marked as covered in the coverage files provided by a single group. This suggests that different tools consider different minimum coverage strategies. These mutations reflect 2.0% and 1.2%, respectively, of the total mutation discrepancy and were removed because some callers had limited capacity to identify mutations in poorly-covered regions (see “Methods” section). Finally, filter flags provided by MC3 were used to assess somatic mutation filtering strategies. At this stage, we performed filter optimization to comprehensively evaluate all possible combinations of MC3 filters (Supplementary Fig. 3a). Ultimately, we decided to only remove OxoG labeled artifacts and duplicated events produced by these filters (see “Methods” section, Supplementary Data 2). Since each stage of this filtering workflow resulted in many alternative decisions and outcomes, we built MAFit, a web-based graphical user interface that allows users to easily customize comparisons of merged mutations (<https://mbailey.shinyapps.io/MAFit/>). A MC3 filter assessment also shows that many variants with filter flags in MC3 are present in the PCAWG variant call set, suggesting a need for improved filtering strategies (Supplementary Fig. 3b).

TCGA samples comprise a sizable fraction of the PCAWG sample pool (~30%, Supplementary Data 1) Additional WGS sequencing from TCGA allowed for mutation validation²⁷ and insights into non-coding mutations, such as in *TET2*. However, this selection process could have potentially influenced our basic comparison of exome-sequenced samples and genome-sequenced samples in two fundamental ways. First, vagaries of tumor extraction and tissue storage protocols may have resulted in many different portions of a tumor being stored, introducing the possibility that different subclones of the same tumor could be present. These could have very different genetic makeups. This information was captured in different substrings of the TCGA identification barcode (see “Methods” section). From the 746 TCGA barcodes, we found that 64% (477) could be traced to the same well of a microtiter plate (Fig. 1b). After correcting for cancer type, we modeled both the impact of matching barcode

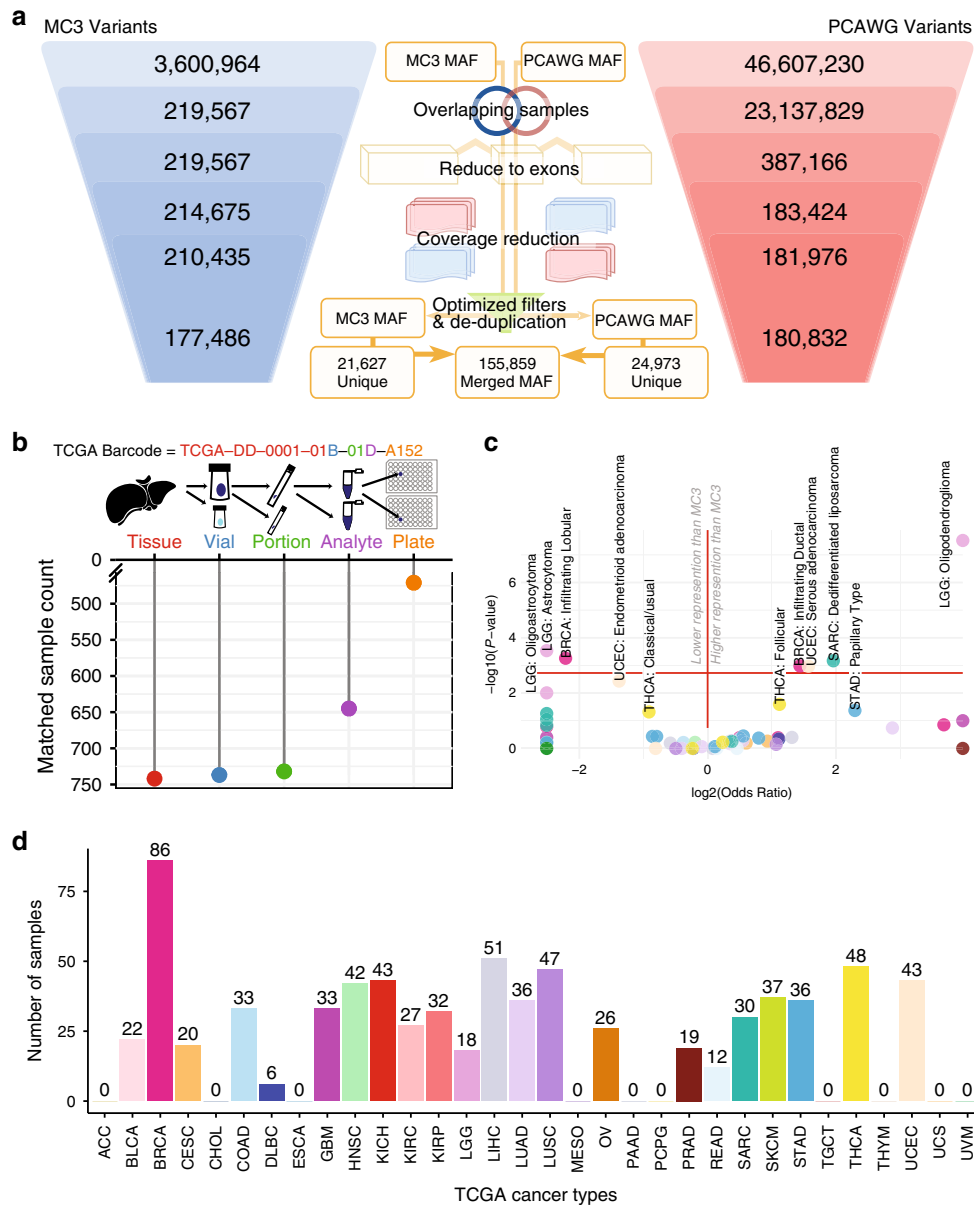


Fig. 1 Workflow and sample inclusion statistics. **a** A workflow diagram illustrates the number of mutations present during each step (gradient) of the filtering processes for MC3 (left, blue) and PCAWG (right, red). A brief description of each step of the intersection process is shown in between. **b** TCGA barcodes and aliquot IDs were used to match somatic sequencing. The exact match of these IDs is shown for various collection aliquots from tissue to plate. **c** A volcano plot highlights cancer subtype discrepancy between each PCAWG and MC3 with $-\log_{10}(p\text{-value})$ on the y-axis and $\log_2(\text{odds ratio})$ on the x-axis (Fisher’s exact test). The horizontal red bar indicates a significant threshold after multiple testing correction. Positive values indicate an over-representation of a cancer subtype in PCAWG, while negative values indicate an under-representation of a cancer subtype in PCAWG compared to MC3-separated by a vertical red bar. **d** Sample counts for each cancer type are shown in a bar chart. The colors coordinate with panel **c**.

identifiers between MC3 and PCAWG and variant concordance, finding that differing barcodes did not have an appreciable impact. This result was seen for all samples, even when excluding the hypermutator (Fig. 1). Second, each AWG was able to independently select samples for WGS, which, while not affecting mutation calling, does raise potential biases when comparing PCAWG results to TCGA exome cohort data. An enrichment analysis was performed to identify which tumor subtypes may have been preferentially selected for different cancer types. We found that four tumor subtypes were enriched in the PCAWG effort from TCGA samples: infiltrating ductal breast cancer, endometrial serous adenocarcinoma, differentiated liposarcoma, and low grade oligodendroglioma (FDR < 0.05, Fig. 1c,

Supplementary Data 3, and see “Methods” section). Final tumor sample counts for each cancer type are shown in Fig. 1d.

Landscape of mutational overlap between WGS and WES calls.

Limiting our analysis to coding regions with sufficient coverage yielded a total of 202,459 variants (155,859 matched, 21,627 unique MC3 variants, and 24,973 unique PCAWG mutations), with 76.7% in concordance between MC3 and PCAWG and 10.7% and 12.3% being unique in MC3 and PCAWG, respectively (Fig. 2a). Concordance can be further separated into SNPs and indels, with 79% and 57% overlapping, respectively (Supplementary Fig. 4). Variant overlap was further investigated to reveal

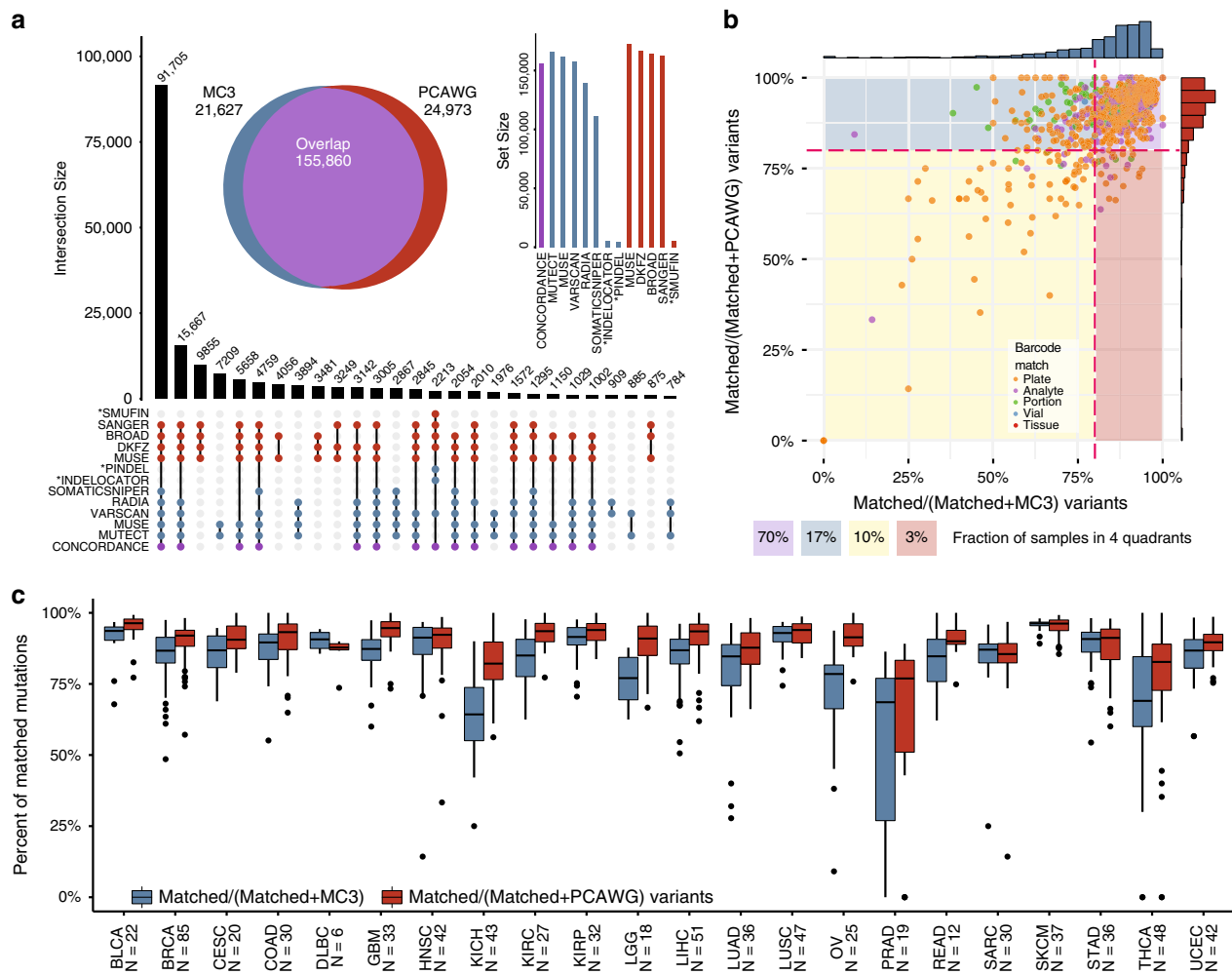


Fig. 2 Landscape of mutations overlap by caller, sample and cancer type. **a** UpSetR⁴¹ plot shows the variant calling set intersection by caller. The y-axis indicates set intersection size and the x-axis uses a connected dot plot to indicate which sets are considered. Only the largest 27 intersecting sets are shown. Two insets of the UpSetR plot highlight a classic Euler diagram (left), which indicates the total number of overlapping mutations. A set-size bar chart (right) illustrates the total number of mutations considered from each caller. The concordance set indicates the agreement between WES and WGS. Indel callers are indicated with an asterisk. **b** A scatter plot shows the amount of concordance by sample by calculating the fraction of matched variants divided by the total number of mutations made by MC3 exome sequencing and PCAWG whole genome sequencing (x and y-axis, respectively) below the total fraction of samples within each quadrant. Each point within the plot is related to tumor portion data collected from the TCGA barcode ID. **c** As shown above, this box plot separates panel b by cancer types (blue considers all MC3 variants, and red boxes indicate all PCAWG variants). Sample sizes are displayed for each cancer; points indicate samples that extend past 1.5 times the interquartile range; and horizontal bars within each box and whisker indicates median matched mutation fraction.

its association with mutation caller, sample, and cancer type (Fig. 2a–c). Consensus variant calling showed 91,705 (45.3%) concordant variants were captured in the intersection of Sanger, MuSE, DKFZ, and Broad callers from PCAWG, as well as VarScan, SomaticSniper, Radia, MuTect, and MuSE callers from MC3. Notably, an additional 7.7% were identified by all SNV mutation detection algorithms, except SomaticSniper. The reduced sensitivity of SomaticSniper is related to its algorithmic consideration of tumor contamination in the matched normal (e.g., skin) for liquid tumors⁸. After optimizing for filtering strategies, we performed a sample level comparison and found that 70% of samples had greater than 80% mutation concordance across the two cohorts. An additional 20% of samples had greater than 80% mutation recoverability in one or the other technique (Fig. 2b). Skin Cutaneous Melanoma performed the best among all cancer types and had the highest variant-matching rates for both MC3 and PCAWG (Fig. 2c). Generally, when considering all MC3 and all PCAWG mutations separately, we observed that

PCAWG variant matching rates were generally higher, especially for Kidney Chromophobe (KICH), Brain Lower Grade Glioma (LGG), Ovarian Serous Cystadenocarcinoma (OV), Rectum Adenocarcinoma (READ), and Thyroid Carcinoma (THCA). The differences in OV are likely driven by whole genome amplified library preparation. Generally, the median fractions for matching MC3 variants were lower than those of matching PCAWG variants. This result was unexpected because MC3 provided fewer unique variants overall, suggesting that a large fraction of PCAWG unique variants reside in a few samples. Furthermore, after accounting for hypermutators, we identified a correlation between non-silent mutations per megabase and mean consensus percentages at the cancer level in both PCAWG consensus percentages (Mann–Whitney p -value = 1.97×10^{-3}) and MC3 consensus percentages (Mann–Whitney p -value = 6.59×10^{-4} , see “Methods” section, Supplementary Fig. 1c, d). Despite strong rank statistics, neither set exhibited strong correlation values for MC3 variants or PCAWG variants, R^2 statistics = 0.31 and 0.17

respectively with the majority of cancer types exceeding 80% mean concordance. Thus, one may expect to observe slightly higher variant fidelity in samples with more mutations.

Variant allele fraction affects call-rates. After achieving a comparable data set and merging MC3 and PCAWG variants, we found that low VAF is the prevailing attribute of unique mutations. VAF is a fundamental factor in somatic variant detection, as well as sub-clonal structure prediction, and is used to predict subclonal tumor growth rates and metastatic potential. To explore the contribution of VAF, we sought to distinguish the contribution of subclonal structure and statistical chance when exploring private mutations in a single call set. We articulate our findings in six broad categories: modeling sequence noise, departure from idealized behavior, sub-clonal modeling, annotation differences, variant-caller effects, and analysis correlations.

Association of variant allele fraction with recoverability. We have observed that variants with low VAF are less likely to be reported in both call-sets. This finding relates to the lower sensitivity of somatic variant callers for variants with low VAF. To illustrate this principle, we estimated the expected overlap rate between MC3 and PCAWG at different VAFs. The sensitivity of MuSE across a range of VAFs and read depths in synthetic data was reported in Fan et al., 2016³. We used these reported benchmarking characteristics of MuSE to estimate the expected overlap rate between the MuSE call-sets of MC3 and PCAWG across a range of VAFs (see “Methods” section). These expectations, which involve lower overlap rates at lower VAFs, generally tracked observed data but tended to overestimate observed overlap rates, especially for predicting the recovery fraction of MC3 variants in PCAWG. (Fig. 3a) The discrepancies between expectations and observations may relate to simplifying assumptions that made this modeling possible (see “Methods” section).

More generally, we observed that VAF had a greater association with variant recovery rates than predicted by the binomial model (Fig. 3b). A random forest regression model trained on five statistics characteristics of VAF distribution per PCAWG sample and another five for that of the corresponding MC3 call-set predicted the fraction of variants per sample unique to PCAWG with 0.85 (0.86—when restricting to variants called by MuSE) Spearman correlation of test-set observations and a 0.68 (0.78) coefficient of determination (R^2).

The strong association of VAF with recovery rates by call-set, despite modest explanatory power of the binomial, indicates important departures from idealized behavior. These departures could include explanations such as: PCR amplification violates the assumption of independence of reads, imputed read depths are systematically inflated, or some low-VAF variants represent sequencing artifacts. We conclude that non-ideal effects of VAF predict the majority of sample-level variance in fraction of co-called variants.

Exploring subclonality. One possible explanation for some variants being private to one call-set is that the sequencing aliquots for the two sequencing projects came from subclonally-distinct microregions of the same tumor. To investigate this possibility, we tested whether the MC3 and PCAWG call-sets differed from each other systematically at the subclonal level (Fig. 3c, d). We hypothesized that tumors with a more complex subclonal structure (i.e., greater number of subclones) would have larger systematic differences in the VAF of shared variants between the MC3 and PCAWG call-sets. We found a small but highly significant effect: each additional subclone increased the average

absolute difference in VAF of the shared variants between MC3 and PCAWG by 0.003, with a p -value of 1.3×10^{-11} (linear regression); this effect reversed after controlling for tumor purity, indicating that the observed trend does not provide evidence of this interesting concept in re-sequencing (see “Methods” section for details). We do not have evidence that systematic VAF differences between call-sets of the same underlying sample associate with tumor heterogeneity. Real time effects of VAF differences between these two data sets can be observed using the online MAFit tool (Fig. 4).

Annotation differs by call-set. Genome annotation is critical for biological interpretation and downstream analysis of sequencing data. In order to avoid issues that arise from annotation differences, we only considered genomic locations in our intersection strategy. In doing so, we observed 2153 annotation differences where MC3 and PCAWG had different genes annotated for the same mutation. After restricting the mutation type to missense mutations and indels, 789 annotations differences remained. Most of these had the same mutation types annotated by both call-sets (690 SNPs, 15 insertions, 50 deletions), but some discrepancies remained. Notably, 413 out of 789 mismatch variants are labeled coding in MC3 but non-coding in PCAWG (Supplementary Data 4). We also observed four mutations that were annotated as cancer gene mutations by MC3, but as non-cancer gene mutations by PCAWG, and another four mutations that were annotated as cancer gene mutations by PCAWG, but as non-cancer gene mutations by MC3. One such example subsumed two mutations on chromosomal location 3p21.1 (genomic locations chr3:52442525 and chr3:52442604) that were annotated as missense mutations of *BAP1* by MC3, but as 5'Flank SNPs of *PHF7* by PCAWG. While identical pipelines resolve such differences, we stress the potential for misinterpretations when combining these publicly-available datasets.

Effects of software. Another important issue we assess is the degree to which differences in bioinformatics pipelines impact concordance. We extracted calls from MuSE and MuTect, both of which were executed on each dataset, and examined 6 subsets of results: MuSE-only-calls and all calls save MuSE-calls (the complement), MuTect-only-calls and their complement, and MuSE + MuTect calls and their complement. MuSE and MuTect each generate around 95% of the total calls, of which each respective subset shows close to 80% concordance between WES and WGS (Supplementary Fig. 5). These call sets themselves overlap almost completely, with their combination (MuSE + MuTect) giving a marginally higher concordance. Conversely, the data-specific caller combinations (referred to above as the complements) each furnish small call sets which vary considerably between WES and WGS (concordance as low as 15%). Because of the vast difference in the sizes of the MuSE/MuTect and the complementary call sets, there is little difference in the original analysis versus analyses restricted to variant callers common to both platforms. Differences in software pipelines do not appear to be significant confounding factors in concordance here.

Effects on higher-level analysis. We also sought to assess how higher-level analyses might be impacted using mutation signature analysis as a representative. We ran SignatureAnalyzer28 to ascertain signatures between matched WGS and WES samples for each case. A total of 563 of 739 cases (76%) showed the same dominant signature between WES and WGS and the multi-element signature vectors for each case are very highly correlated with one another, the average Pearson coefficient being almost 90%, with a cohort significance of $<2 \times 10^{-6}$ (Fisher's Test,

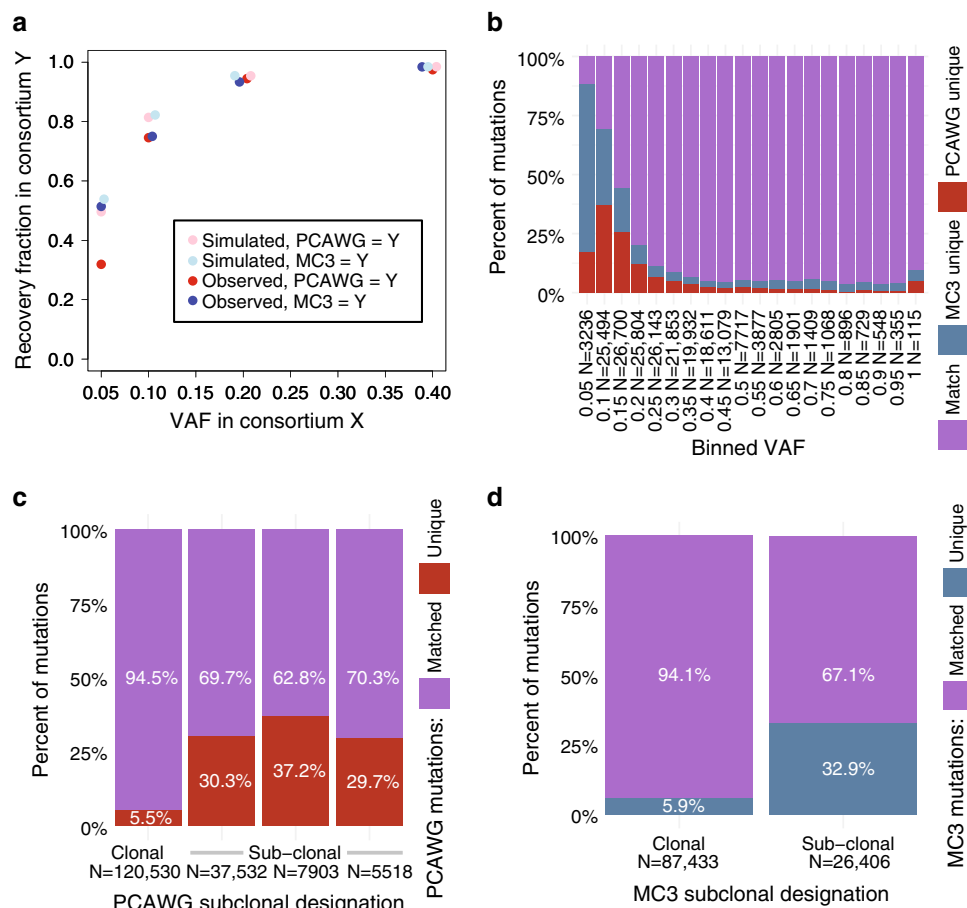


Fig. 3 Recoverability simulation and effects of subclones on mutation concordance. **a** Observed recovery rate of PCAWG variants in MC3 (red) and of MC3 variants in PCAWG (blue), alongside sequencing noise simulations calculated from random draws of a binomial model that incorporates the VAF and estimated read depth at each site (light red simulates PCAWG recoverability of MC3 variants, and light blue simulated MC3 recoverability of PCAWG variants). Y-axis is described with legend. X-axis displays VAF of the comparative data set in regard to Y. **b** A stacked bar chart displays the proportion of matched and unique variants (y-axis) for different VAF bins (x-axis). 180 variants did not provide read count information and were removed from this figure. **c** Stacked proportional histogram shows the fractions of PCAWG matched mutations (purple) and PCAWG-unique mutations (red). Mutations were restricted to SNVs, and subclonality predictions are indicated as either 'Clonal' or 'Sub-clonal'. Columns 2–4 reflect sub-clonal assignment provided by PCAWG (Note: only a few samples reported five predicted subclones and were not included in this analysis). The number of variants represented for each clonal assignment is shown on the x-axis. **d** Similar to panel **c**, a stacked proportional histogram illustrates the proportion of matched and unique variants for MC3 which provide estimates of total number of matched or unique variants called by MC3.

"Methods" section, Supplementary Fig. 6). These observations suggest that signature analysis is relatively insensitive to data type when concordance is high, as it is here.

Landscape of private WES and WGS mutations. After identifying many possible sources of variation among private variants, we sought to characterize the fraction of variation explained by previously identified factors (Supplementary Fig. 7, see "Methods" section). As displayed, subclonal and low VAF variants make up the largest fractions of explained variants for private MC3 and PCAWG variants. Notably, for private MC3 calls, indels (not called by MuSE or MuTect) are the next highest source of variation explained. GC-content and poor performing cancers such as THCA, KICH, and PRAD make up a smaller portion of the total number of private mutations.

Variants present in only one public call-set. We sought to classify cancer driver mutations uniquely identified by MC3. After removing two outlier samples having excesses of unique mutations (TCGA-CA-6717-01A-11D-1835-10, TCGA-BR-6452-

01A-12D-1800-08), we observed 424 mutations in cancer genes²⁸ (median read depth = 97, median alternative allele count = 9). The four most frequently mutated genes were: *KMT2C* (22-mutations), *PIK3CA* (12), *SPTA1* (9), and *NCOR1* (9). Interestingly, the majority of unique *PIK3CA* mutations not identified by PCAWG were at 2 locations: E542K/G (5), and E545K (4). Whether this phenomenon reflects technical bias of WGS or is a product of subclonality warrants further investigation.

The MC3 effort produced two mutation files: one controlled access somatic mutation file that represents nearly all mutations found by all callers, and a second was modified by the scientific community for public use. There are two critical differences in these files involving the reporting of mutations in exonic regions and mutations reported by a single variant caller. Since we limited our analysis strictly to exonic regions, we observed that 92% of the 9138 PCAWG private mutations found in the MC3 controlled access file were only identified by a single variant caller (Supplementary Fig. 8). As expected, the highest unique variant caller overlap was observed in MuTect and MuSE, two tools that were used by both MC3 and PCAWG. This observation accounts for 30% of PCAWG private variants.

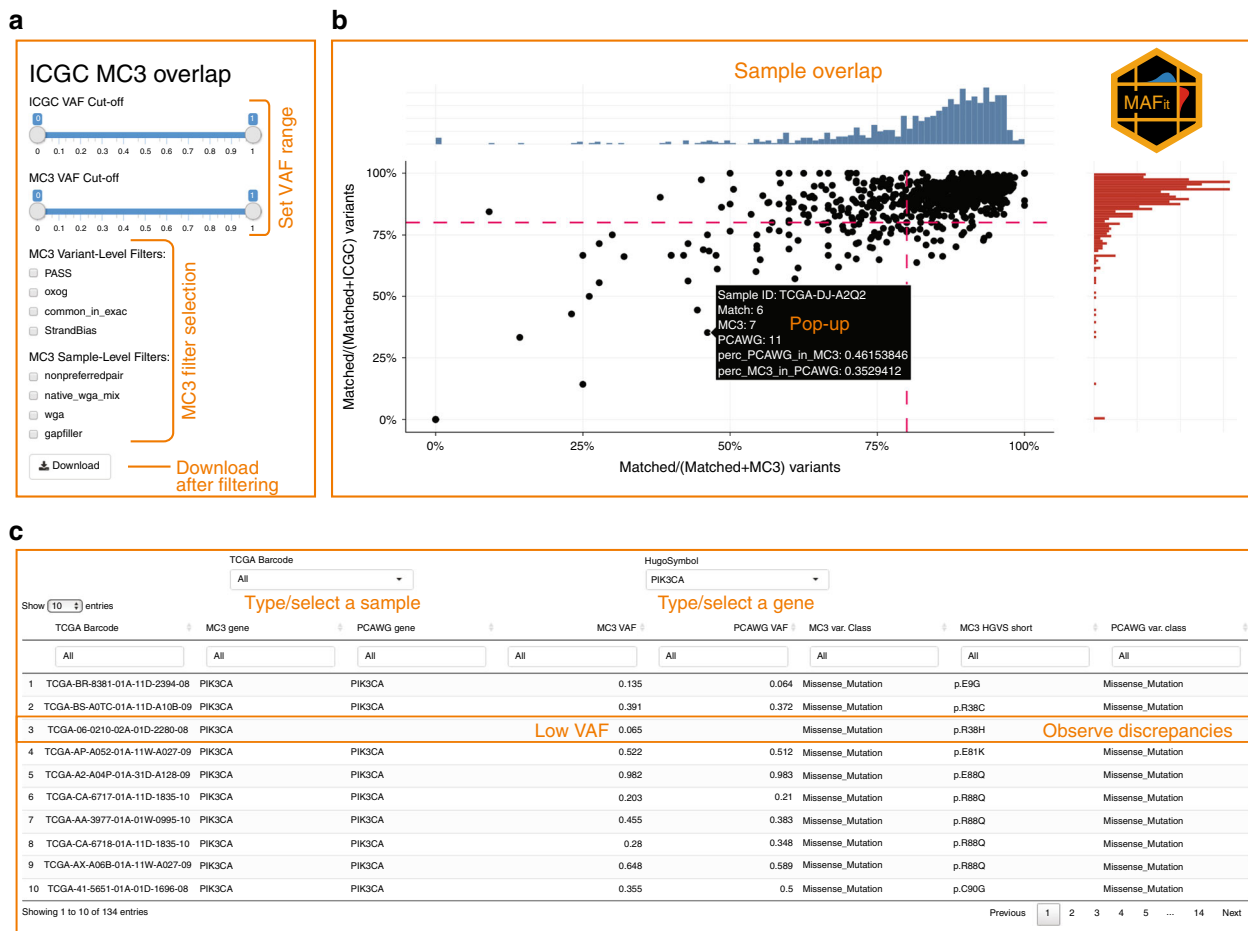


Fig. 4 Screenshots of online tool MAFit. Here we display screenshots from the MAFit on-line interface. Currently there are three main components to the interface: **a** A side panel shows sliders and radio buttons to filter data set to remain inclusive. In addition, a download button is available that will download the underlying data table. **b** MAFit rebuilds Fig. 2b in the first tab of the on-line interface. Each alteration to the radio buttons or VAF sliders will result in an updated figure. In addition, if one’s hovers over a point on the scatter plot, a pop-up window will automatically display, providing the user with basic statistics used to calculate that point, i.e., total number of mutations, number of unique and matched mutations. **c** A table is also presented based on the selection criteria in panel **a**.

We investigated how many variants unique to the MC3 somatic public access call-set could be found in the PCAWG germline call-set for the same patients. We identified a total of six such variants (each in a different sample), five of which were flagged in the MC3 public call-set with one filter or another. Overall, this indicates that variants that have been incorrectly designated as germline or somatic are an extremely uncommon source of variation between the two projects.

Variants in GC-extreme intervals. Since it is well-known that the efficiency of exome capture is adversely affected by very high or very low GC-content^{29,30}, we sought to test whether GC-content was associated with call rates in MC3 and PCAWG. We used a plug-in for VEP³¹ to annotate all matched and private SNVs with CADD³² in order to annotate each variant with the percentage of the neighboring 100 bases that are a G or C. First, we assessed how the distribution of read depth across GC-content changes between MC3 and PCAWG (Fig. 5b). PCAWG was found to have a fairly uniform read depth across GC-content bins, while MC3 read depth was concentrated in regions of moderate GC-content (Fig. 5c). The low read depth in MC3 at regions of extreme GC-content was in turn associated with lower variant recovery rates in these regions but did not grossly affect the number of variants

recovered by MC3 because regions of extreme GC-content are relatively rare in the genome overall and in exome-capture regions in particular.

An in-depth analysis of these regions revealed that 76 mutations in known driver genes, identified in the combined TCGA data by Bailey et al. 2018, were missed in GC poor (GC fraction < 0.3) or GC rich (GC > 0.7) regions²⁸. Three such instances revealed *VHL* mutations in *KIRC* that were overlooked in GC rich regions of this gene (two of these three recur). In addition, these 3 samples are not reported to carry a *VHL* mutation in the MC3 public data set. Other such instances include 7 *SOX17* mutations, *LATS2* (6), and *CACNA1A* (6). These findings emphasize the advantages of uniform coverage using WGS.

The bases flanking a mutation (tri-nucleotide context) affect mutation rate, which should be approximately equal between MC3 and PCAWG, and also the rate of introduction of sequencing artifacts. Large differences in the call-rates of MC3 and PCAWG and particular nucleotide sequences could indicate a sequencing artifact unique to one or the other call-set, which might arise from different procedures for computationally filtering or biochemically preventing sequencing oxidation products. Therefore, we sought to test whether the trinucleotide context of variants correlated with relative call-rates in MC3 and

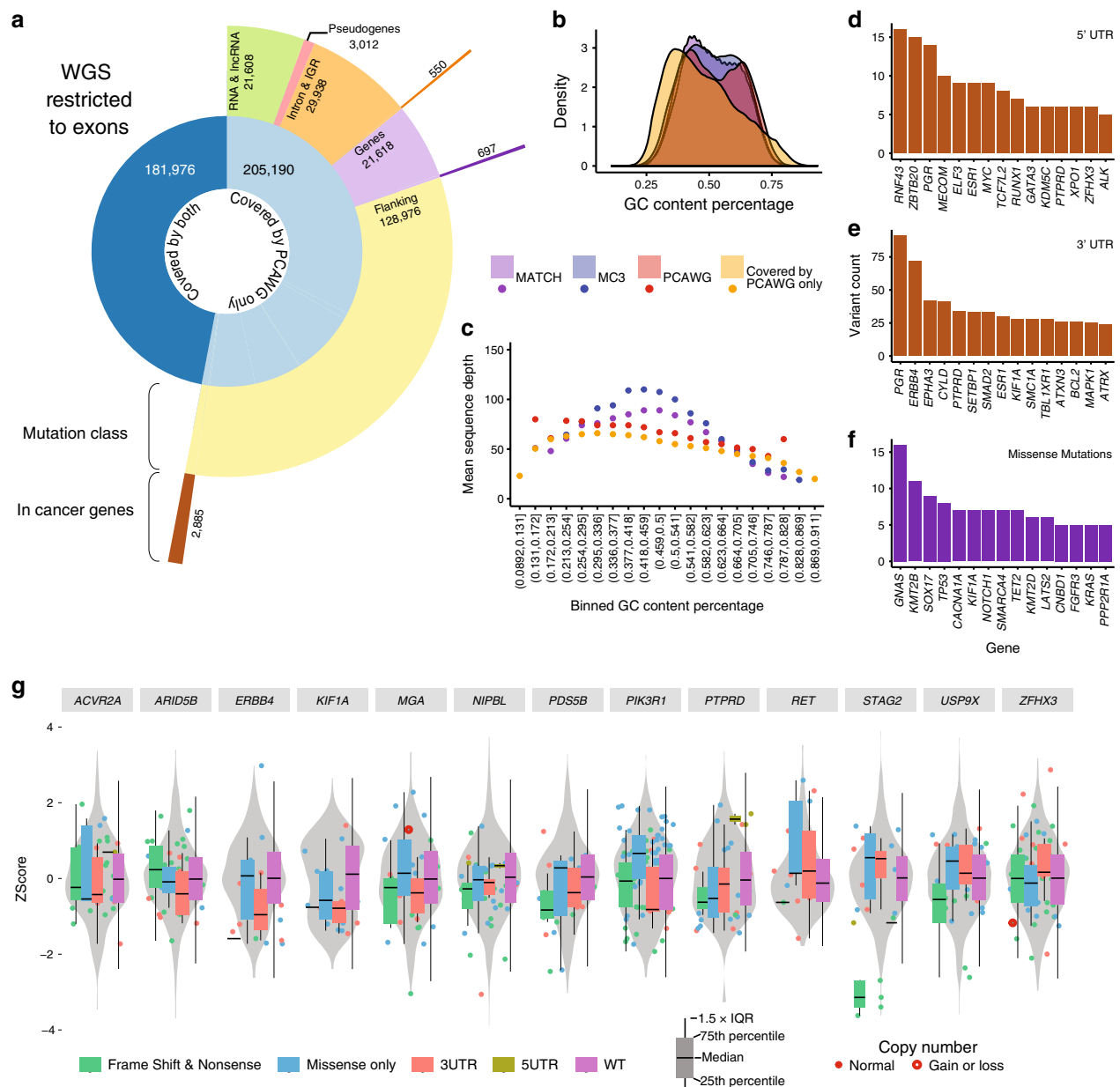


Fig. 5 WGS mutations in exonic regions not captured by WES. **a** A sunburst diagram provides a breakdown of variants that are removed during the coverage step of the tool. The innermost circle represents the total number of variants identified upon filtering for exome beds used by MC3. Then, we restrict PCAWG variants to well-covered MC3 regions for each sample. The majority of gencode.v19 annotated and the BROAD target bed file of exonic regions are sufficiently covered by PCAWG in flanking regions: 3'UTRs, 5'UTR, and 5'Flanking. The outermost ring illustrates the number mutations identified by PCAWG that were poorly covered by MC3. **b** A density plot illustrates the density of percent GC-content from a 100 bp window surrounding a variant. Four variant-sets are displayed: matched, private to MC3, private to PCAWG, and we extend our dataset to include exonic variants not covered by WES but sufficiently covered in WGS (Covered by PCAWG only). **c** A scatter plot displays mean sequence depth (y-axis) by increasing GC-content bins (x-axis). Points are colored according to variant set (same as panel **b**). **d-f** Total annotated mutations counts from 3 different annotated regions are shown for 5UTR, 3UTR, and missense mutations, respectively. **g** Expression Z-Scores for 3'UTR using all TCGA-UCEC samples. Cis-RNAseq expression violin plots are displayed for 13 genes. On top of the gene-level distribution violin plot, box and whisker plots display sample expression based on mutation classification (box include 25th quantile to 75th quantiles, and whiskers extend to 1.5 times the interquartile range).

PCAWG. Before applying the MC3 OxoG filters, we found a huge predominance of CA variants unique to MC3, with the trinucleotide contexts most specific to one database or another being 7-9 times more specific than the least specific trinucleotide contexts. After applying the MC3 OxoG filters, nucleotide contexts differed by less than four-fold in their specificities. The residual differential specificity by trinucleotide context after filtering can either indicate differences in sequencing artifact

abundance and filtration by project, or could merely be a consequence of the fact that nucleotide context is also correlated with VAF and the distance from transcription start sites, which may independently affect MC3 and PCAWG relative call-rates.

We extended the nucleotide context and performed mutation spectrum analysis, comparing all MC3 and all PCAWG mutations found after restricting the two data sets to exonic regions as described above (Step 3 of Fig. 1a). We then calculated

transition and transversion frequencies in each cancer type. After removing hypermutated samples and OxoG artifacts, we used a chi-squared test to determine the similarities and differences between cancer types in the full exome space compared versus the captured exome space. Strikingly, we did not identify significant differences in mutation spectrum in the majority of cancers. We did observe significant differences (FDR < 0.05) in the mutation spectrum for COAD, KICH, LUAD, and OV (Supplementary Data 5). These observations included strong discrepancies for AG and CG transition differences in KICH and OV, respectively. AT and CA transversions contributed mostly to COAD and LUAD differences (Supplementary Fig. 9). While these differences may reflect sequencing artifacts, such as whole genome amplified DNA in OV or low sample size, we believe the data can still provide more information pertaining to additional cancer genes and oncogenic mechanisms.

Non-Coding/Flanking intersections with low coverage. With the growing use of WGS in many labs, we sought to identify which mutations are gained by extending to this form of data. One major observation from our pipeline highlighted that some variants in exome regions were not well covered by WES (Fig. 1a Step 3). Using this mutation set we investigated the most recurrent members as derived by WGS but not by MC3 in exonic regions as defined by gencode.v19 (Fig. 5a). We observed 697 mutations in cancer genes²⁸ uniquely called by WGS (Supplementary Data 6). We defined flanking mutations as all non-translated mutations near exons, i.e., 5'UTR, 3'UTR, 5'Flanking, and 3'Flanking regions, as they make up the majority of mutations not present in the MC3 public MAF. Recurrent mutation analysis identified the most frequently mutated genes in 5'UTR (Fig. 5d), 3'UTR (Fig. 5e), and missense mutations (Fig. 5f). We found the most frequently mutated 3'UTR in cancer genes was *PGR* (91 mutations allowing for multiple mutations per sample), followed by *ERBB4* (72), *EPHA3* (42), *CYLD* (41), and *PTPRD* (34). To extend this analysis, we used RNAseq data collected by TCGA to determine mutation type specific *cis*-expression patterns, which clearly shows correlation of UTR mutations on RNA abundance (Fig. 5g).

Finally, similar to previous studies^{33,34}, we investigated the potential effect of non-coding mutations when determining significantly mutated genes (SMG). Using MuSiC³⁵ with the no-skip-non-coding option, we rescued non-coding mutations annotated by PCAWG and included them in the significantly mutated gene (SMG) analysis. We only performed SMG analysis on cancer types having greater than 35 samples (BRCA-Breast-AdenoCa, HNSC-Head-SCC, KICH-Kidney-ChRCC, LIHC-Liver-HCC, LUAD-Lung-AdenoCa, LUSC-Lung-SCC, SKCM-Skin-Melanoma, STAD-Stomach-AdenoCa, THCA-Thy-AdenoCa, and UCEC-Uterus-AdenoCa). We initially identified potential driver-gene candidates (*FUT9*, *MMP16*, *SNHG14*, and *SFTPB*, Fig. 6) not previously reported in Pan-Cancer whole genome analysis, but further investigation did not support these candidates with the exception of *SFTPB*.

SFTPB (FDR 1.56e-07) in LUAD was recently reported to be significantly mutated using a larger set of these same data³⁴. As reported, this gene is involved in a lineage-defining surfactant protein. While six mutations contributed to its SMG status, only 1 3'UTR mutation was reported for LUAD in the MC3 controlled data set. Furthermore, this single indel was only found by one variant caller (Varscan). We confirmed the impact of *SFTPB* UTR mutations by performing a genome-wide association analysis of expression differences and found that samples with *SFTPB* mutations showed lower RNA abundance in *PCDHA7*, a gene

known to be involved in cells' self-recognition and non-self-discrimination (chi-squared *p*-value 3.6×10^{-8}). While other promising candidates exist, such as *FUT9*, a fucosyltransferase involved in organ bud progression during embryogenesis and has been implicated in cancer initiation³⁶, we found no additional evidence for supporting its driver status.

Discussion

The research community is increasingly leveraging technology advances to integrate data at larger scales. We performed a comparative evaluation of ~750 samples with joint exome and whole genome sequencing mutation calls provided by two consensus mutation calling efforts, MC3 and PCAWG. This joint data set is encouraging, suggesting that ~80% of the predicted somatic mutations were captured by both efforts. Furthermore, a combined 90% of samples have greater than 80% variant concordance when considering covered exonic mutations from individual cohorts separately. Analysis of this data set also revealed three major contributors to variant discrepancies: (1) low variant allele fraction, (2) variant filtering decisions, and (3) technological limitations. Software differences were not an appreciable confounder.

Distinct advantages and disadvantages accompany somatic mutation calling when utilizing captured WES or WGS. We found that ~70% of the discrepancies between whole genome and whole exome sequencing are influenced by low variant allele fraction. This information holds many implications in identifying subclonal heterogeneity in the tumor of interest. Other discrepant calls originate from the decisions made on how to filter and distribute publicly available mutation calls. Higher-order mutation signature analysis does not appear to be inordinately affected by these differences. We show that reported germline variants were negligible, but nearly 30% of the private PCAWG mutations were not reported by MC3 because only a single variant detection algorithm identified them. We want to emphasize that, while somatic variant detection in cancer is commonplace, there are still many issues to reconcile.

Finally, we found additional mutations only observable in exonic regions using either WES or WGS. For example, WES uniquely identified 424 mutations in cancer genes with median VAF of ~10%. We also highlight ~700 WGS mutations from cancer genes, of which ~10% are attributable to regions of high and low CG-content; thus, highlighting the advantages of more uniform coverage from WGS.

Only about 2% of the genome is protein coding. For the last dozen years, cancer genomics has provided a comprehensive molecular characterization of many different tumor types, thanks in large part to The Cancer Genome Atlas and other publicly funded efforts. The community is just starting to explore how exomics, transcriptomics, proteomics, and methylomics can be woven together across this 2% of the genome. We anticipate a general transition from WES to WGS, but this analysis is meanwhile reassuring that few clerical mutations were overlooked in WES and that WGS is capable of recapitulating previous genomic findings.

Methods

Human research participants. The Cancer Genome Atlas (TCGA) collected both tumor and non-tumor biospecimens from human samples with informed consent under authorization of local institutional review boards (<https://cancergenome.nih.gov/abouttcga/policies/informedconsent>).

Sample overlap. TCGA barcodes carry metadata that reflect tumor portions and different aliquots. As noted in Fig. 1b, TCGA barcode differ slightly in the comparison between MC3 and WGS aliquots. A brief description of the breakdown of the TCGA barcode is outlined below.

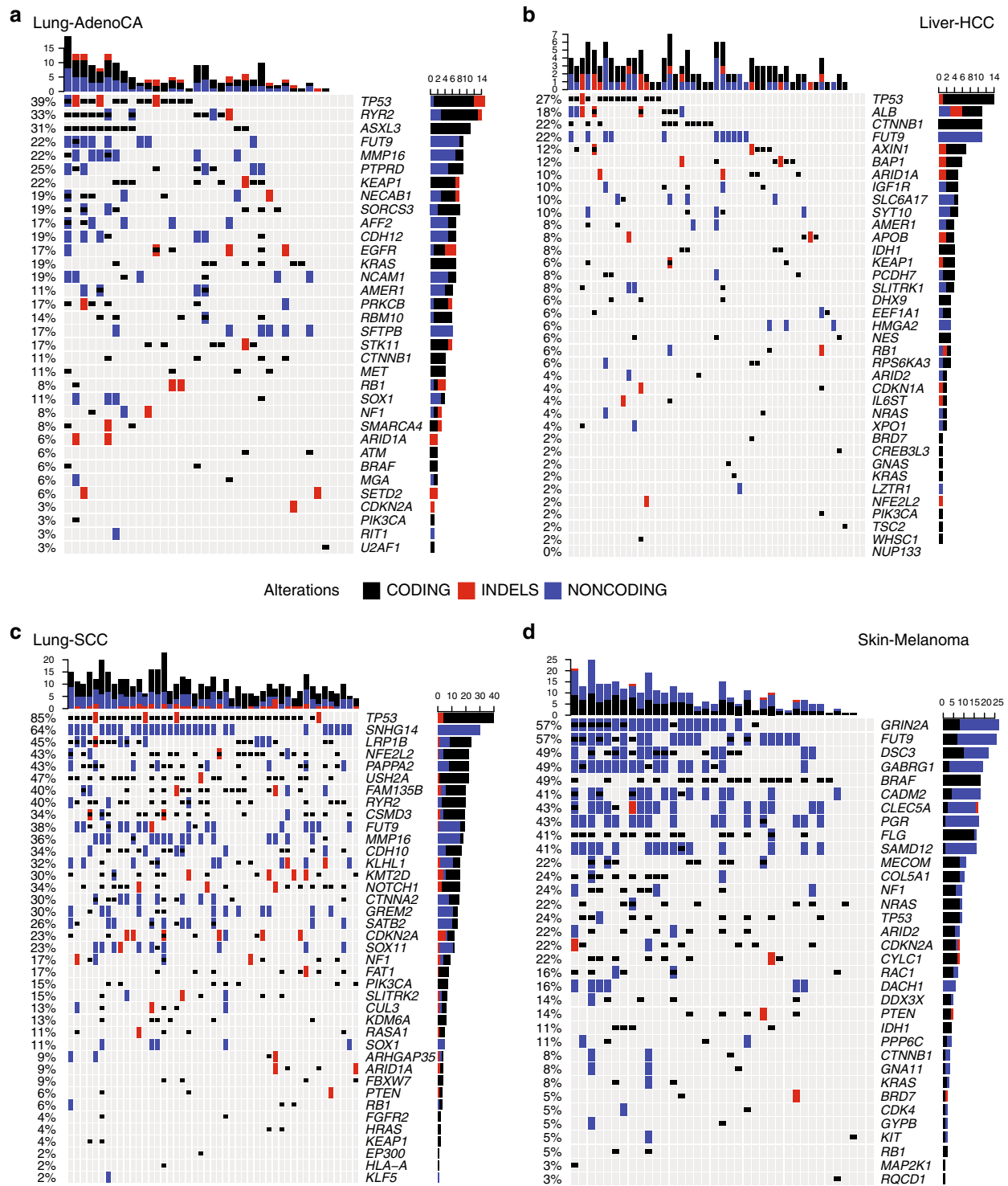


Fig. 6 Significantly mutated gene analysis with the inclusion of UTR mutations. OncoPrint plots were generated using the R package ComplexHeatmap⁴² for four cancer types: LUAD (a), LIHC (b), LUSC (c), and SKCM (d). We report all SMGs identified by Bailey et al. 2018²⁸, as well as top significantly mutated gene hits from MuSiC that include non-coding mutations. While many non-coding mutations look promising, further investigation yielded little support for driver identification status.

Example: TCGA-DD-0001-01B-01D-A152

- TCGA-Project
- DD-Tissue source site: the tissue location of tumor that matches clinical metadata.
- 0001-Participant code
- 01-Sample type: i.e., solid tumor (01), primary blood derived tumor (03), solid

- tissue normal (11), blood derived normal (10)
- B-Vial: the order in a sequence of samples, i.e., A = first in sequence, B = second in sequence
- 01-Portion: sequential order of the 100–120 mg of samples
- D-Analyte: molecular analyte type for analysis, i.e., D for DNA and W for WGA.
- A152-Plate: sequential location of a 96-well plate

A lookup table outlining these fields is located at the GDC: <https://gdc.cancer.gov/resources-tcga-users/tcga-code-tables>. In order to determine the role of aliquot differences in assessing mutation concordance, we re-analyzed the clonality and overall mutation overlap after stratifying for exact barcode differences. We observed that the effect of matching barcodes on match variant frequency has little effect.

Assessing cancer subtype selection preference. Analysis working groups for TCGA projects were primarily subdivided according to cancer types. Scientific experts gathered in consortia from around the country to participate in characterizing many tumors using high throughput data generated on many substrates, e.g., WES, RNAseq, etc. At the conclusion of these projects, groups were asked to hand-select a subset of samples to perform validation sequencing (WGS, the samples used in this analysis). The selection criteria differed from group-to-group and sometimes resulted in an overabundance of one subtype over another. To determine cancer subtype selection bias, we performed an enrichment analysis. Using clinical data we calculated (for each cancer type) the subtype fraction in the WES cancer cohort and measured whether the fraction was similar to WGS set of samples using a Fisher's exact test.

Defining exonic regions. We used the same definition as Ellrott et al. to reduce whole genome and exome calls to define genomic coordinates²⁷.

Coverage calculations. Fixed-step (step = 1) Wiggle coverage files (.wig) for both MC3 and PCAWG were provided by the Broad Institute. The wig format is a binary readout of sufficient sequencing coverage for genomic data. Here, sufficient coverage is defined as bases with 8 or more reads at a given location. These wig files were processed and reduced to exonic regions using the wig2bed function from BEDOPTS³⁷.

After the preliminary screen of coverage-reduced MAF files, we observed that matching mutations (identified by PCAWG and MC3) were removed from one technology and not the other after the coverage reduction step. To account for this issue, we performed a self-coverage reduction step to that identified 6460 mutations. We describe some properties of those mutations here. The median tumor depth reported by MC3 from these variants is 12 reads (+/- 3 median absolute difference). The median tumor depth reported by PCAWG in this region is 39 reads (+/- 35.6 median absolute difference), suggesting wide variance of tumor read depths that were removed. However, the mode tumor depth of the PCAWG variants was 13, justifying this removal of variants with low read support. Finally, we determined how many of these poorly-covered variants originated from cancer driver genes. We observed 126 mutations from the MC3 file, and 156 cancer mutations were eliminated at this stage in the comparison.

Overlapping mutations. After reducing the variants to be within exome sequencing target region, within same exon definitions, and having enough sequencing depth, the remaining variants from ICGC and PCAWG were stored in a SQLite database to enable fast lookup. We then executed a full join between the two sources of variants by matching the donor ID, sample ID, and the genomic range of each variant. The full join output was further cleaned up to remove duplicated filters due to naming variations and duplicated variants due to DNPs.

- Matching IDs
- Matching chromosomes
- End position greater than or equal to start position
- Start position is less than or equal to end position.

Deduplication of variants. After merging the PCAWG and MC3 data, we observed different strategies were taken by MC3 and PCAWG to capture neighboring variants, i.e., complex indels, di-nucleotide (DNP) and tri-nucleotide (TNP) polymorphisms. To address complex indel events (SNVs in indel regions), the MC3 working group absorbed the variants made by SNV callers into the assignment made by Pindel. Conversely, PCAWG merged DNP and TNP events into a single event. These strategies resulted in many duplication events from MC3 and PCAWG: 1731 and 62, respectively. These events encompassed 3457 and 119 events, respectively. To address these differences, we merged PCAWG variants into MC3s complex indel events, and MC3 variants into single DNP or TNP events.

Filtering optimization. After reducing the starting pool of possible mutations from 746 samples to covered exons, we sought to identify the optimal set of MC3 filters that provide the largest number of samples with greater than 80% concordance from the two technologies with the simplest schema. This was performed comprehensively using all possible combinations of filters, often with more than one filter per variant, with the MC3 cohort (131,071 filter combinations). Filter flags include: "common_in_exac", "gapfiller", "native_wga_mix", "nonpreferredpair", "oxog", "StrandBias", and "wga". We pre-defined the exclusion of variants in MC3 flagged as OxoG along with the inclusion of all PASS variants. The comprehensive filter analysis resulted in two major clusters of variant recoverability (Supplementary Fig. 3). Here, we observed the computational trade-off of identifying more

matched variants at the cost of more unique MC3 calls. Below, we highlight five strategies considered for analysis (Supplementary Data 2).

1. Only consider variants labeled PASS by the MC3 filter column.
2. Only remove variants labeled OxoG by MC3.
3. Prioritize G1 (samples in the most recoverable quadrant, MC3 and PCAWG samples with greater than or equal to 80% from both efforts.)
4. Prioritize total number of matched variants.
5. Maximize total number of samples in the most recoverable quadrant (Fig. 2b) while maximizing the difference between unique MC3 variants and matched variants thus generating fewer unique calls.

After considering complexity, we chose to move forward with strategy 2 for the entirety of this study due to its simplicity and relative similarity to other filtering schemes. We recognize that by selecting a single filtering strategy, we are limiting the data slightly and likely introducing some false positive variant calls. However, this strategy allowed us to maintain larger sample sizes and to capture ~15,000 more matched variants than the PASS only strategy at the cost of ~3500 unique mutations calls for MC3.

Assessing mutations per megabase and cancer type concordance. Mutations per megabase data were collected from the broader TCGA dataset and reduced following the same methods outlined previously²⁸. Briefly, this systematically removed hypermutators from the dataset. This resulted in a set of 625 samples from the MC3/PCAWG dataset studied here and 8852 TCGA samples. Both Pearson and Mann-Whitney correlations statistics were performed to assess the association of non-silent mutations per megabase and concordance statistics.

Simulation of sequencing noise and recoverability. Fan et al. benchmarked the sensitivity of MuSE at recovering somatic variants across 24 combinations of VAF and read depth³. When simulating the recovery of PCAWG variants in MC3 we assumed that the VAF observed in PCAWG was the true VAF. We matched the observed VAF of each variant to the closest VAF reported in Fan et al.

For our analysis, the best value to use as the read depth when predicting the MC3 recovery rate of PCAWG variants would be the MC3 read depth at the same site and sample as the PCAWG variant. However, it was not practical to obtain MC3 read depths at sites without MC3 variants, so instead we simulated an MC3 read depth for each PCAWG variant by randomly sampling from the read depths of observed MC3 variants from the same sample as the PCAWG sample. We then matched these simulated read depths for each variant to the closest read depths reported in Fan et al.

For the binned VAFs and read depths for each PCAWG variant obtained as above, we pulled the corresponding sensitivities of MuSE from the Fan et al. paper and simulated MC3 variants with probability equal to these sensitivities.

Integrating clonality. Both consortia considered clonality in their comprehensive characterization of the somatic mutations. Locations of these files are provided in the data availability section. Here, we provide a brief summary of the strategies used to compile these resources. First, the PanCancer Atlas working-groups used MC3 mutations to predict subclonal structures using ABSOLUTE³⁸. This tool uses copy number, recurrent karyotype, and mutation data to calculate copy number purity and cluster identification. Furthermore, the PanCancer Atlas working group only made the distinction of clonal and subclonal mutations and did not attempt to further assign sub-clonal mutations to other likely heterogeneous clusters. PCAWG, on the other hand, used a consensus calling approach incorporating 11 different clustering tools. Here, we evaluated cluster-ID which represents those mutations that are clonal (ID = 1), with other clusters representing mutations that are subclonal (ID = 2 through 4). For this analysis, we restricted our data to SNVs to be consistent with calls made by the PanCancer Atlas calls of MC3 mutations.

Fraction of private variation explained. In Supplementary Fig. 7 we provide a breakdown of different sources of variant described in our analysis using publicly available data. For MC3 all private variants were classified as into 3 variant types (Indel, MissensePlus, and Other). Specifically, indels are comprised of: "Frame_Shift_Del", "In_Frame_Ins", "Frame_Shift_Ins", and "In_Frame_Del". MissensePlus variants are comprised of: "Missense_Mutation", "Nonsense_Mutation", "Nonstop_Mutation", "Splice_Site". And Other variants are comprised of: "RNA", "3'UTR", "5'UTR", "5'Flank", "Silent", "3'Flank", "Intron", "Translation_Start_Site".

On the other hand, PCAWG variants were also categorized into Indels, MissensePlus, and Other. Specifically, indels are comprised of: "Frame_Shift_Del", "Frame_Shift_Ins", "De_novo_Start_InFrame", "Start_Codon_Ins", "Stop_Codon_Ins", "In_Frame_Del", "In_Frame_Ins", "Stop_Codon_Del", and "Start_Codon_Del". MissensePlus variants are comprised of: "Missense_Mutation", "Nonsense_Mutation", "Nonstop_Mutation", "Splice_Site". And other variants are comprised of: "5'UTR", "RNA", "5'Flank", "Silent", "3'UTR", "Intron", "IGR", "lincRNA", "De_novo_Start_OutOfFrame", and "Start_Codon_SNP".

In addition to the three variant type categories, six additional sources of variation were added to private variants: Subclonal, VAF5, VAF10, MMcomplement, THCA KICH or PRAD, and GCcontents. As mentioned, subclonal variants are tagged if labeled as identified by the TCGA or ICGC

consortia. VAF5 tags all variants with less than 5% VAF. VAF10 tags all variants with VAF greater than or equal to 5% and less than 10%. MMComplement tags all variants not detected by MuSE or MuTect. And finally, GCcontent was calculated as the fraction of G or C nucleotides in a 100 bp window surrounding a variant. This was calculated using a CADD plug-in to VEP. The GCcontent flag was assigned to a variant if GC fraction was less than 0.3 or greater than 0.7.

MAFit: online comparison and visualization tool. MAFit (maf Interaction Tool) is a shinyapp³⁹ tool to visualize and extract mutations from the intersection of PCAWG and MC3 call sets. It is an interactive and graphical web-based interface built using R Shiny. The interface consists of three panels: a main scatter plot display, a side box of control widgets, and a mutation table in the bottom pane. Any alteration of a control widget will update the scatter plot and the mutation table, enabling very rapid browsing. There is also a button to download the current data set displayed in the scatter plot.

The main panel displays a scatter plot with marginal histograms of mutations grouped by sample. The axes are percentage of matched mutations versus matched plus call-set-unique mutations. Mouse-hovering on a data point initiates a pop-up window showing specific information for this sample, such as TCGA barcode, number of matched mutations, and numbers of mutations unique to each call-set.

The side panel contains two sets of control widgets which can be used to select data based on different criteria. The top control set consists of two sliders to set the VAF cut-offs for each call-set. Both ends of the slider can be adjusted so that users can obtain a desired interval of the VAF. The bottom control set consists of checkboxes of both variant-level and sample-level MC3 filters. If only variant-level filters are checked, all PCAWG-only mutations will be retained; if at least one sample-level filter is checked, mutations from samples that do not have any checked filters flagged (variant-level or sample-level) will be filtered out. Both variant-level and sample-level filters result in the union of mutations with any checked filter will be shown.

The bottom panel displays a table of mutations based on the selection criteria from the side panel. Columns include information on each mutation, such as TCGA barcode, gene name, VAF, variant class, Human Genome Variant Society (HGVS) nomenclature, etc. Users can sort the table by each column. There are two drop-down selection boxes where users can view mutations from a specific TCGA barcode or Hugo symbol. There is also a search bar, which results in mutations that contain the input in any columns.

Controlled access files. Having worked with both the TCGA and ICGC consortia, we were privy to the controlled access data (all MC3 somatic variant calls and PCAWG germline calls). These data sets allowed for the further interrogation of unique variants called by both groups.

We performed a mutation variant intersection of MC3 controlled access mutations with unique PCAWG variants in the captured exonic regions. These data can be downloaded using necessary credentials from <https://gdc.cancer.gov/about-data/publications/mc3-2017>.

We intersected the MC3 public MAF with the PCAWG germline call-set, donor-by-donor. Six MC3 somatic variants were identified as germline variants in PCAWG for the same donor. Of these, five were flagged in MC3 as OxoG or non-preferred-pair artifacts, and only one was marked PASS in MC3. This PASS variant had a depth in the matched MC3 normal of well over 100 with no alternate reads. The minimal intersection between the MC3 somatic call-set and the donor-matched PCAWG germline call-set is evidence that germline contamination in MC3 calls is low.

Assessment of impact on mutation signature analysis. We ran SignatureAnalyzer⁴⁰ on the corpus of WES and WGS samples from our TCGA cases. This tool reports a vector of $J = 7$ normalized weights corresponding to mutational signatures. Once weights were computed, we used COSMIC signatures as a reference in order to synchronize labels of the fractional weights between WES and WGS data for each case to enable proper comparison. We excluded 5 cases in which signatures were not computed for WGS data. Using the synchronized results, we then assessed both the number of cases for which the tool identified the same dominant signature between WES and WGS data and also evaluated the correlation between WES and WGS vectors for each case using least-squares regression. Statistical significance of each correlation was calculated using a 2-tailed t -test. Statistical power of each correlation was limited by the paucity of signature weights because the underlying t -statistic is proportional to the square root of $J - 2$. However, because these cases, and therefore their hypothesis tests, are independent, the cohort constitutes multiple tests of the same hypothesis regarding signatures derived from WES and WGS data. Therefore, we combined individual P -values into an overall cohort P -value using Fisher's log-transform. Namely, the transform of negative 2 times the natural log of the product of the $K = 739$ individual P -values is, itself, chi-square distributed with $2K$ degrees of freedom. Using this transform, we found an overall cohort P -value of $< 2 \times 10^{-6}$.

Reporting summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

Somatic and germline variant calls, mutational signatures, subclonal reconstructions, transcript abundance, splice calls and other core data generated by the ICGC/TCGA Pan-cancer Analysis of Whole Genomes Consortium are described in another publication¹⁰ and available for download at <https://dcc.icgc.org/releases/PCAWG>. Additional information on accessing the data, including raw read files, can be found at <https://docs.icgc.org/pcawg/data/>. In accordance with the data access policies of the ICGC and TCGA projects, most molecular, clinical and specimen data are in an open tier which does not require access approval. To access potentially identification information, such as germline alleles and underlying sequencing data, researchers will need to apply to the TCGA Data Access Committee (DAC) via dbGaP (<https://dbgap.ncbi.nlm.nih.gov/aa/wga.cgi?page=login>) for access to the TCGA portion of the dataset, and to the ICGC Data Access Compliance Office (DACO; <http://icgc.org/daco>) for the ICGC portion. In addition, to access somatic single nucleotide variants derived from TCGA donors, researchers will also need to obtain dbGaP authorization. Additional links to data resources used for this project can be found using the following urls: MC3 public MAF file (<https://api.gdc.cancer.gov/data/1c8cfe5f-e52d-41ba-94da-f15ea1337efc>), PCAWG Public MAF file (<https://www.synapse.org/#!Synapse:syn7364923>), bed files used for exome restrictions (MC3) (<https://api.gdc.cancer.gov/data/7f0d3ab9-8bef-4e3b-928a-6090caae885b>), bed files used for exome restrictions (THE BROAD) (<https://api.gdc.cancer.gov/data/b1e303a5-a542-4389-8ddb-1d151218be75>), wiggle files MC3 (<https://www.synapse.org/#!Synapse:syn21785741>), wiggle files PCAWG (<https://www.synapse.org/#!Synapse:syn8492850>), clonality files MC3 (<https://www.synapse.org/#!Synapse:syn7870168>), clonality files PCAWG (<https://www.synapse.org/#!Synapse:syn8532460>), cancer subtypes and histological data (<https://www.synapse.org/#!Synapse:syn4983466>), MAFit online comparison tool (<https://m Bailey.shinyapps.io/MAFit/>), GitHub Repo (https://github.com/ding-lab/mc3_icgc_variant_pipeline), side-by-side MC3-PCAWG comparison (MAF-like) (<https://www.synapse.org/#!Synapse:syn21041380>). The remaining data is available within the Article, Supplementary Information or available from the authors upon reasonable request.

Code availability

A public GitHub repository (under an MIT opensource license) at https://github.com/ding-lab/mc3_icgc_variant_pipeline furnishes work-flows, scripts, figures, and computational tools used to assess mutation concordance between maf files. For this project we refrained from accessing alignment files, i.e., BAM files or fastq files. Furthermore, due to the memory footprint of mutation and coverage files we have not included them in the repository. Thus, by removing core data files from the repository the software provided supplies the user with processes and decisions, not a fully automated tool for deployment on additional datasets. In addition to our analysis, the core computational pipelines used by the PCAWG Consortium for alignment, quality control and variant calling are available to the public at <https://dockstore.org/search?search=pcawg> under the GNU General Public License v3.0, which allows for reuse and distribution.

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Author contributions

L.D. and M.H.B. conceived the project. L.D. and M.B.G. supervised the project. M.H.B., W.M., and G.D. drafted the manuscript. M.H.B., L.-B.W., W.M., S.L., G.S., M.C.W., G.D., M.B.G., L.D., D.A.W., J.T.S., G.G., and L.J.D. provided scientific input. G.S. and K.E. provided sample mapping and quality control files. T.C.G.A.R.N. and P.C. organized, generated, and distributed raw data. P.C. and N.S.M.C.M. produced original whole-genome variant calls. M.H.B., W.M., G.D., and L.-B.W. produced figures. Analysis was performed by M.H.B., W.M., L.-B.W., G.D., Y.L., W.-W.L., M.C.W., and A.W. All authors approve the submission of this manuscript. We thank S.K. for providing text edits.

Competing interests

The authors declare the following competing interests: G.G. receives research funds from IBM and Pharmacyclics. G.G. is an inventor on patent applications related to MuTect, ABSOLUTE, and other tools. The remaining authors declare no competing interests.

Additional information


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Correspondence and requests for materials should be addressed to M.B.G. or L.D.

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MC3 Working Group

Rehan Akbani²¹, Pavana Anur²², Matthew H. Bailey^{1,2,3}, Alex Buchanan⁹, Kami Chiotti⁹, Kyle Covington^{12,23}, Allison Creason⁹, Li Ding^{1,2,3,20}, Kyle Ellrott⁹, Yu Fan²¹, Steven Foltz^{1,2}, Gad Getz^{8,14,15,16}, Walker Hale¹², David Haussler^{24,25}, Julian M. Hess^{8,26}, Carolyn M. Hutter²⁷, Cyriac Kandoth²⁸, Katayoon Kasaian^{29,30}, Melpomeni Kasapi²⁷, Dave Larson¹, Ignaty Leshchiner⁸, John Letaw³¹, Singer Ma³², Michael D. McLellan^{1,3,20}, Yifei Men³², Gordon B. Mills^{33,34}, Beifang Niu³⁵, Myron Peto²², Amie Radenbaugh²⁴, Sheila M. Reynolds³⁶, Gordon Saksena⁸, Heidi Sofia²⁷, Chip Stewart⁸, Adam J. Struck³¹, Joshua M. Stuart^{24,37}, Wenyi Wang²¹, John N. Weinstein³⁸, David A. Wheeler^{12,13}, Christopher K. Wong^{24,39}, Liu Xi¹² & Kai Ye^{40,41}

²¹Department of Bioinformatics and Computational Biology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA. ²²Molecular and Medical Genetics, OHSU Knight Cancer Institute, Oregon Health and Science University, Portland, OR 97239, USA. ²³Castle Biosciences Inc, Friendswood, TX 77546, USA. ²⁴UC Santa Cruz Genomics Institute, University of California Santa Cruz, Santa Cruz, CA 95064, USA. ²⁵Howard Hughes Medical Institute, University of California Santa Cruz, Santa Cruz, CA 95064, USA. ²⁶Massachusetts General Hospital Center for Cancer Research, Charlestown, MA 02114, USA. ²⁷National Human Genome Research Institute, National Institutes of Health, Bethesda, MD 20894, USA. ²⁸Marie-Josée and Henry R. Kravis Center for Molecular Oncology, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA. ²⁹Ontario Institute for Cancer Research, Toronto, ON M5G 0A3, Canada. ³⁰Canada's Michael Smith Genome Sciences Centre, BC Cancer, Vancouver, BC V5Z 4S6, Canada. ³¹Computational Biology Program, School of Medicine, Oregon Health and Science University, Portland, OR 97239, USA. ³²DNAexus Inc, Mountain View, CA 94040, USA. ³³Department of Systems Biology, UT MD Anderson Cancer Center, Houston, TX 77030, USA. ³⁴Precision Oncology, OHSU Knight Cancer Institute, Oregon Health and Science University, Portland, OR 97239, USA. ³⁵Computer Network Information Center, Chinese Academy of Sciences, Beijing, China. ³⁶Institute for Systems Biology, Seattle, WA 98109, USA. ³⁷Department of Biomolecular Engineering, University of California Santa Cruz, Santa Cruz, CA 95064, USA. ³⁸Department of Bioinformatics and Computational Biology and Department of Systems Biology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA. ³⁹Biomolecular Engineering Department, University of California Santa Cruz, Santa Cruz, CA 95064, USA. ⁴⁰School of Electronic and Information Engineering, Xi'an Jiaotong University, Xi'an, China. ⁴¹The First Affiliated Hospital, Xi'an Jiaotong University, Xi'an, China.

PCAWG novel somatic mutation calling methods working group

Matthew H. Bailey^{1,2,3}, Beifang Niu³⁵, Matthias Bieg^{42,43}, Paul C. Boutros^{6,44,45,46}, Ivo Buchhalter^{43,47,48}, Adam P. Butler⁴⁹, Ken Chen⁵⁰, Zechen Chong⁵¹, Li Ding^{1,2,3,20}, Oliver Drechsel^{52,53}, Lewis Jonathan Dursi^{6,7}, Roland Eils^{47,48,54,55}, Kyle Ellrott⁹, Shadrielle M. G. Espiritu⁶, Yu Fan²¹, Robert S. Fulton^{1,3,20}, Shengjie Gao⁵⁶, Josep L. I. Gelpi^{57,58}, Mark B. Gerstein^{5,18,19}, Gad Getz^{8,14,15,16}, Santiago Gonzalez^{59,60}, Ivo G. Gut^{52,61}, Faraz Hach^{62,63}, Michael C. Heinold^{47,48}, Julian M. Hess^{8,26}, Jonathan Hinton⁴⁹, Taobo Hu⁶⁴, Vincent Huang⁶, Yi Huang^{65,66}, Barbara Hutter^{43,67,68}, David R. Jones⁴⁹, Jongsun Jung⁶⁹, Natalie Jäger⁴⁷, Hyung-Lae Kim⁷⁰, Kortine Kleinheinz^{47,48}, Sushant Kumar^{5,19}, Yogesh Kumar⁶⁴, Christopher M. Lalansingh⁶, Ignaty Leshchiner⁸, Ivica Letunic⁷¹, Dimitri Livitz⁸, Eric Z. Ma⁶⁴, Yosef E. Maruvka^{8,26,72}, R. Jay Mashl^{1,2}, Michael D. McLellan^{1,3,20}, Andrew Menzies⁴⁹, Ana Milovanovic⁵⁷, Morten Muhlig Nielsen⁷³, Stephan Ossowski^{52,53,74}, Nagarajan Paramasivam^{43,47}, Jakob Skou Pedersen^{73,75}, Marc D. Perry^{76,77}, Montserrat Puiggròs⁵⁷, Keiran M. Raine⁴⁹, Esther Rheinbay^{8,14,72}, Romina Royo⁵⁷, S. Cenik Sahinalp^{62,78,79}, Gordon Saksena⁸, Iman Sarrafi^{62,78}, Matthias Schlesner^{47,80}, Jared T. Simpson^{6,17}, Lucy Stebbings⁴⁹, Chip Stewart⁸, Miranda D. Stobbe^{52,61}, Jon W. Teague⁴⁹, Grace Tiao⁸, David Torrents^{57,81}, Jeremiah A. Wala^{8,14,82}, Jiayin Wang^{1,40,66}, Wenyi Wang²¹, Sebastian M. Waszak⁶⁰, Joachim Weischenfeldt^{60,83,84}, Michael C. Wendt^{1,10,11}, Johannes Werner^{47,85}, Zhenggang Wu⁶⁴, Hong Xue⁶⁴, Sergei Yakneen⁶⁰, Takafumi N. Yamaguchi⁶, Kai Ye^{40,41}, Venkata D. Yellapantula^{20,86}, Christina K. Yung⁷⁶ & Junjun Zhang⁷⁶

⁴²Center for Digital Health, Berlin Institute of Health and Charité-Universitätsmedizin Berlin, 10178 Berlin, Germany. ⁴³Heidelberg Center for Personalized Oncology (DKFZ-HIPO), German Cancer Research Center (DKFZ), 69120 Heidelberg, Germany. ⁴⁴Department of Medical Biophysics, University of Toronto, Toronto, ON M5S, Canada. ⁴⁵Department of Human Genetics, University of California Los Angeles, Los Angeles, CA 90095, USA. ⁴⁶Department of Pharmacology, University of Toronto, Toronto, ON M5S, Canada. ⁴⁷Division of Theoretical Bioinformatics, German Cancer Research Center (DKFZ), 69120 Heidelberg, Germany. ⁴⁸Institute of Pharmacy and Molecular Biotechnology and BioQuant, Heidelberg University, 69117 Heidelberg, Germany. ⁴⁹Wellcome Sanger Institute, Wellcome Genome Campus, Hinxton CB10 1SA, UK. ⁵⁰University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA. ⁵¹Department of Genetics, Informatics Institute, University of Alabama at Birmingham, Birmingham, AL 77030, USA. ⁵²Universitat Pompeu Fabra (UPF), 08002 Barcelona, Spain. ⁵³Centre for Genomic Regulation (CRG), The Barcelona Institute of Science and Technology, Barcelona, Spain. ⁵⁴Heidelberg University, 69117 Heidelberg, Germany. ⁵⁵New BIH Digital Health Center, Berlin Institute of Health (BIH) and Charité-Universitätsmedizin Berlin, 08036 Berlin, Germany. ⁵⁶BGI-Shenzhen, Shenzhen, China.

⁵⁷Barcelona Supercomputing Center (BSC), 08034 Barcelona, Spain. ⁵⁸Department Biochemistry and Molecular Biomedicine, University of Barcelona, 08007 Barcelona, Spain. ⁵⁹European Molecular Biology Laboratory, European Bioinformatics Institute (EMBL-EBI), Cambridge CB10 1SD, UK. ⁶⁰Genome Biology Unit, European Molecular Biology Laboratory (EMBL), 22607 Heidelberg, Germany. ⁶¹CNAG-CRG, Centre for Genomic Regulation (CRG), Barcelona Institute of Science and Technology (BIST), 08036 Barcelona, Spain. ⁶²Vancouver Prostate Centre, Vancouver, BC V6H 3Z6, Canada. ⁶³Department of Urologic Sciences, University of British Columbia, Vancouver, BC V6T 1Z4, Canada. ⁶⁴Division of Life Science and Applied Genomics Center, Hong Kong University of Science and Technology, Clear Water Bay, Hong Kong, China. ⁶⁵Geneplus-Shenzhen, Shenzhen, China. ⁶⁶School of Computer Science and Technology, Xi'an Jiaotong University, Xi'an, China. ⁶⁷National Center for Tumor Diseases (NCT) Heidelberg, 69120 Heidelberg, Germany. ⁶⁸German Cancer Consortium (DKTK), 69120 Heidelberg, Germany. ⁶⁹Genome Integration Data Center, Syntekabio, Inc, Daejeon, South Korea. ⁷⁰Department of Biochemistry, College of Medicine, Ewha Womans University, Seoul, South Korea. ⁷¹Biobyte solutions GmbH, 69126 Heidelberg, Germany. ⁷²Massachusetts General Hospital, Boston, MA 02114, USA. ⁷³Department of Molecular Medicine (MOMA), Aarhus University Hospital, 8200 Aarhus N, Denmark. ⁷⁴Institute of Medical Genetics and Applied Genomics, University of Tübingen, 72074 Tübingen, Germany. ⁷⁵Bioinformatics Research Centre (BiRC), Aarhus University, 8000 Aarhus, Denmark. ⁷⁶Genome Informatics Program, Ontario Institute for Cancer Research, Toronto, ON M5G 0A3, Canada. ⁷⁷Department of Radiation Oncology, University of California San Francisco, San Francisco, CA 94110, USA. ⁷⁸Simon Fraser University, Burnaby, BC V5A 1S6, Canada. ⁷⁹Indiana University, Bloomington, IN 47405, USA. ⁸⁰Bioinformatics and Omics Data Analytics, German Cancer Research Center (DKFZ), 69120 Heidelberg, Germany. ⁸¹Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Spain. ⁸²Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA 02215, USA. ⁸³Finsen Laboratory and Biotech Research and Innovation Centre (BRIC), University of Copenhagen, 1165 Copenhagen, Denmark. ⁸⁴Department of Urology, Charité Universitätsmedizin Berlin, 10117 Berlin, Germany. ⁸⁵Department of Biological Oceanography, Leibniz Institute of Baltic Sea Research, 18119 Rostock, Germany. ⁸⁶Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA.

PCAWG Consortium

Lauri A. Aaltonen⁸⁷, Federico Abascal⁴⁹, Adam Abeshouse⁸⁸, Hiroyuki Aburatani⁸⁹, David J. Adams⁴⁹, Nishant Agrawal⁹⁰, Keun Soo Ahn⁹¹, Sung-Min Ahn⁹², Hiroshi Aikata⁹³, Rehan Akbani²¹, Kadir C. Akdemir⁵⁰, Hikmat Al-Ahmadie⁸⁸, Sultan T. Al-Sedairy⁹⁴, Fatima Al-Shahrour⁹⁵, Malik Alawi^{96,97}, Monique Albert⁹⁸, Kenneth Aldape^{99,100}, Ludmil B. Alexandrov^{49,101,102}, Adrian Ally³⁰, Kathryn Alsop¹⁰³, Eva G. Alvarez^{104,105,106}, Fernanda Amary¹⁰⁷, Samirkumar B. Amin^{108,109,110}, Brice Aminou⁷⁶, Ole Ammerpohl^{111,112}, Matthew J. Anderson¹¹³, Yeng Ang¹¹⁴, Davide Antonello¹¹⁵, Pavana Anur²², Samuel Aparicio¹¹⁶, Elizabeth L. Appelbaum^{1,117}, Yasuhito Arai¹¹⁸, Axel Aretz¹¹⁹, Koji Arihiro⁹³, Shun-ichi Ariizumi¹²⁰, Joshua Armenia¹²¹, Laurent Arnould¹²², Sylvia Asa^{123,124}, Yassen Assenov¹²⁵, Gurnit Atwal^{6,126,127}, Sietse Aukema^{112,128}, J. Todd Auman¹²⁹, Miriam R. Aure¹³⁰, Philip Awadalla^{6,126}, Marta Aymerich¹³¹, Gary D. Bader¹²⁶, Adrian Baez-Ortega¹³², Matthew H. Bailey^{1,2,3}, Peter J. Bailey¹³³, Miruna Balasundaram³⁰, Saianand Balu¹³⁴, Pratiti Bandopadhyay^{8,135,136}, Rosamonde E. Banks¹³⁷, Stefano Barbi¹³⁸, Andrew P. Barbour^{139,140}, Jonathan Barenboim⁶, Jill Barnholtz-Sloan^{141,142}, Hugh Barr¹⁴³, Elisabet Barrera⁵⁹, John Bartlett^{98,144}, Javier Bartolome⁵⁷, Claudio Bassi¹¹⁵, Oliver F. Bathe^{145,146}, Daniel Baumhoer¹⁴⁷, Prashant Bavi¹⁴⁸, Stephen B. Baylin^{149,150}, Wojciech Bazant⁵⁹, Duncan Beardsmore¹⁵¹, Timothy A. Beck^{152,153}, Sam Behjati⁴⁹, Andreas Behren¹⁵⁴, Beifang Niu³⁵, Cindy Bell¹⁵⁵, Sergi Beltran^{52,61}, Christopher Benz¹⁵⁶, Andrew Berchuck¹⁵⁷, Anke K. Bergmann¹⁵⁸, Erik N. Bergstrom^{101,102}, Benjamin P. Berman^{159,160,161}, Daniel M. Berney¹⁶², Stephan H. Bernhart^{163,164,165}, Rameen Beroukhi^{8,14,82}, Mario Berrios¹⁶⁶, Samantha Bersani¹⁶⁷, Johanna Bertl^{73,168}, Miguel Betancourt¹⁶⁹, Vinayak Bhandari^{6,44}, Shriram G. Bhosle⁴⁹, Andrew V. Biankin^{133,170,171,172}, Matthias Bieg^{42,43}, Darell Bigner¹⁷³, Hans Binder^{163,164}, Ewan Birney⁵⁹, Michael Birrer⁷², Nidhan K. Biswas¹⁷⁴, Bodil Bjerkehagen^{147,175}, Tom Bodenheimer¹³⁴, Lori Boice¹⁷⁶, Giada Bonizzato¹⁷⁷, Johann S. De Bono¹⁷⁸, Arnoud Boot^{179,180}, Moiz S. Bootwalla¹⁶⁶, Ake Borg¹⁸¹, Arndt Borkhardt¹⁸², Keith A. Boroevich^{183,184}, Ivan Borozan⁶, Christoph Borst¹⁸⁵, Marcus Bosenberg¹⁸⁶, Mattia Bosio^{52,53,57}, Jacqueline Boulton¹⁸⁷, Guillaume Bourque^{188,189}, Paul C. Boutros^{6,44,45,46}, G. Steven Bova¹⁹⁰, David T. Bowen^{49,191}, Reanne Bowlby³⁰, David D. L. Bowtell¹⁰³, Sandrine Boyault¹⁹², Rich Boyce⁵⁹, Jeffrey Boyd¹⁹³, Alvis Brazma⁵⁹, Paul Brennan¹⁹⁴, Daniel S. Brewer^{195,196}, Arie B. Brinkman¹⁹⁷, Robert G. Bristow^{44,198,199,200,201}, Russell R. Broaddus⁹⁹, Jane E. Brock²⁰², Malcolm Brock²⁰³, Annegien Broeks²⁰⁴, Angela N. Brooks^{8,24,37,82}, Denise Brooks³⁰, Benedikt Brors^{67,205,206}, Søren Brunak^{207,208}, Timothy J. C. Bruxner^{113,209}, Alicia L. Bruzos^{104,105,106}, Alex Buchanan⁹, Ivo Buchhalter^{43,47,48},

Christiane Buchholz²¹⁰, Susan Bullman^{8,82}, Hazel Burke²¹¹, Birgit Burkhardt²¹², Kathleen H. Burns^{213,214}, John Busanovich^{8,215}, Carlos D. Bustamante^{216,217}, Adam P. Butler⁴⁹, Atul J. Butte²¹⁸, Niall J. Byrne⁷⁶, Anne-Lise Børresen-Dale^{130,219}, Samantha J. Caesar-Johnson²²⁰, Andy Cafferkey⁵⁹, Declan Cahill²²¹, Claudia Calabrese^{59,60}, Carlos Caldas^{222,223}, Fabien Calvo²²⁴, Niedzica Camacho¹⁷⁸, Peter J. Campbell^{49,225}, Elias Campo^{226,227}, Cinzia Cantù¹⁷⁷, Shaolong Cao²¹, Thomas E. Carey²²⁸, Joana Carlevaro-Fita^{229,230,231}, Rebecca Carlsen³⁰, Ivana Cataldo^{167,177}, Mario Cazzola²³², Jonathan Cebon¹⁵⁴, Robert Cerfolio²³³, Dianne E. Chadwick²³⁴, Dimple Chakravarty²³⁵, Don Chalmers²³⁶, Calvin Wing Yiu Chan^{47,237}, Kin Chan²³⁸, Michelle Chan-Seng-Yue¹⁴⁸, Vishal S. Chandan²³⁹, David K. Chang^{133,170}, Stephen J. Chanock²⁴⁰, Lorraine A. Chantrill^{170,241}, Aurélien Chateigner^{76,242}, Nilanjan Chatterjee^{149,243}, Kazuaki Chayama⁹³, Hsiao-Wei Chen^{114,121}, Jieming Chen²¹⁸, Ken Chen⁵⁰, Yiwen Chen²¹, Zhaohong Chen²⁴⁴, Andrew D. Cherniack^{8,82}, Jeremy Chien²⁴⁵, Yoke-Eng Chiew^{246,247}, Suet-Feung Chin^{222,223}, Juok Cho⁸, Sunghoon Cho²⁴⁸, Jung Kyoong Choi²⁴⁹, Wan Choi²⁵⁰, Christine Chomienne²⁵¹, Zechen Chong⁵¹, Su Pin Choo²⁵², Angela Chou^{170,246}, Angelika N. Christ¹¹³, Elizabeth L. Christie¹⁰³, Eric Chuah³⁰, Carrie Cibulskis⁸, Kristian Cibulskis⁸, Sara Cingarlini²⁵³, Peter Clapham⁴⁹, Alexander Claviez²⁵⁴, Sean Cleary^{148,255}, Nicole Cloonan²⁵⁶, Marek Cmero^{257,258,259}, Colin C. Collins⁶², Ashton A. Connor^{255,260}, Susanna L. Cooke¹³³, Colin S. Cooper^{178,196,261}, Leslie Cope¹⁴⁹, Vincenzo Corbo^{138,177}, Matthew G. Cordes^{1,262}, Stephen M. Cordner²⁶³, Isidro Cortés-Ciriano^{264,265,266}, Kyle Covington^{12,23}, Prue A. Cowin²⁶⁷, Brian Craft²⁴, David Craft^{8,268}, Chad J. Creighton²⁶⁹, Yupeng Cun²⁷⁰, Erin Curley²⁷¹, Ioana Cutcutache^{179,180}, Karolina Czajka²⁷², Bogdan Czerniak^{99,273}, Rebecca A. Dagg²⁷⁴, Ludmila Danilova¹⁴⁹, Maria Vittoria Davi²⁷⁵, Natalie R. Davidson^{276,277,278,279,280}, Helen Davies^{49,281,282}, Ian J. Davis²⁸³, Brandi N. Davis-Dusenbery²⁸⁴, Kevin J. Dawson⁴⁹, Francisco M. De La Vega^{216,217,285}, Ricardo De Paoli-Iseppi²¹¹, Timothy Defreitas⁸, Angelo P. Dei Tos²⁸⁶, Olivier Delaneau^{287,288,289}, John A. Demchok²²⁰, Jonas Demeulemeester^{290,291}, German M. Demidov^{52,53,74}, Deniz Demircioğlu^{292,293}, Nening M. Dennis²²¹, Robert E. Denroche¹⁴⁸, Stefan C. Dentre^{49,290,294}, Nikita Desai⁷⁶, Vikram Deshpande⁷², Amit G. Deshwar²⁹⁵, Christine Desmedt^{296,297}, Jordi Deu-Pons^{298,299}, Noreen Dhalla³⁰, Neesha C. Dhani³⁰⁰, Priyanka Dhingra^{301,302}, Rajiv Dhir³⁰³, Anthony DiBiase³⁰⁴, Klev Diamanti³⁰⁵, Li Ding^{1,2,3,20}, Shuai Ding³⁰⁶, Huy Q. Dinh¹⁵⁹, Luc Dirix³⁰⁷, HarshaVardhan Doddapaneni¹², Nilgun Donmez^{62,78}, Michelle T. Dow²⁴⁴, Ronny Drapkin³⁰⁸, Oliver Drechsel^{52,53}, Ruben M. Drews²²³, Serge Serge⁴⁹, Tim Dudderidge^{150,221}, Ana Dueso-Barroso⁵⁷, Andrew J. Dunford⁸, Michael Dunn³⁰⁹, Lewis Jonathan Dursi^{6,7}, Fraser R. Duthie^{133,310}, Ken Dutton-Regester³¹¹, Jenna Eagles²⁷², Douglas F. Easton^{312,313}, Stuart Edmonds³¹⁴, Paul A. Edwards^{223,315}, Sandra E. Edwards¹⁷⁸, Rosalind A. Eeles^{178,221}, Anna Ehinger³¹⁶, Juergen Eils^{54,55}, Roland Eils^{47,48,54,55}, Adel El-Naggar^{99,273}, Matthew Eldridge²²³, Kyle Ellrott⁹, Serap Erkek⁶⁰, Georgia Escaramis^{53,317,318}, Shadrielle M. G. Espiritu⁶, Xavier Estivill^{53,319}, Dariush Etemadmoghadam¹⁰³, Jorunn E. Eyfjord³²⁰, Bishoy M. Faltas²⁸⁰, Daiming Fan³²¹, Yu Fan²¹, William C. Faquin⁷², Claudiu Farcas²⁴⁴, Matteo Fassan³²², Aquila Fatima³²³, Francesco Favero³²⁴, Nodirjon Fayzullaev⁷⁶, Ina Felau²²⁰, Sian Fereday¹⁰³, Martin L. Ferguson³²⁵, Vincent Ferretti^{76,326}, Lars Feuerbach²⁰⁵, Matthew A. Field³²⁷, J. Lynn Fink^{57,113}, Gaetano Finocchiaro³²⁸, Cyril Fisher²²¹, Matthew W. Fittall²⁹⁰, Anna Fitzgerald³²⁹, Rebecca C. Fitzgerald²⁸², Adrienne M. Flanagan³³⁰, Neil E. Fleshner³³¹, Paul Flicek⁵⁹, John A. Foekens³³², Kwun M. Fong³³³, Nuno A. Fonseca^{59,334}, Christopher S. Foster^{335,336}, Natalie S. Fox⁶, Michael Fraser⁶, Scott Frazer⁸, Milana Frenkel-Morgenstern³³⁷, William Friedman³³⁸, Joan Frigola²⁹⁸, Catrina C. Fronick^{1,262}, Akihiro Fujimoto¹⁸⁴, Masashi Fujita¹⁸⁴, Masashi Fukayama³³⁹, Lucinda A. Fulton¹, Robert S. Fulton^{1,3,20}, Mayuko Furuta¹⁸⁴, P. Andrew Futreal³⁴⁰, Anja Füllgrabe⁵⁹, Stacey B. Gabriel⁸, Steven Gallinger^{148,255,260}, Carlo Gambacorti-Passerini³⁴¹, Jianjiong Gao¹²¹, Shengjie Gao⁵⁶, Levi Garraway⁸², Øystein Garred³⁴²,

Erik Garrison⁴⁹, Dale W. Garsed¹⁰³, Nils Gehlenborg^{8,343}, Josep L. I. Gelpi^{57,58}, Joshy George¹¹⁰, Daniela S. Gerhard³⁴⁴, Clarissa Gerhauer³⁴⁵, Jeffrey E. Gershenwald^{346,347}, Mark B. Gerstein^{5,18,19}, Moritz Gerstung^{59,60}, Gad Getz^{8,14,15,16}, Mohammed Ghori⁴⁹, Ronald Ghossein³⁴⁸, Nasra H. Giam³⁴⁹, Richard A. Gibbs¹², Anthony J. Gill^{170,350}, Pelvender Gill³⁵¹, Dilip D. Giri³⁴⁸, Dominik Glodzik⁴⁹, Vincent J. Gnanapragasam^{352,353}, Maria Elisabeth Goebler³⁵⁴, Mary J. Goldman²⁴, Carmen Gomez³⁵⁵, Santiago Gonzalez^{59,60}, Abel Gonzalez-Perez^{298,299,356}, Dmitry A. Gordenin³⁵⁷, James Gossage³⁵⁸, Kunihiro Gotoh³⁵⁹, Ramaswamy Govindan³, Dorte Grabau³⁶⁰, Janet S. Graham^{133,361}, Robert C. Grant^{148,260}, Anthony R. Green³¹⁵, Eric Green²⁷, Liliana Greger⁵⁹, Nicola Grehan²⁸², Sonia Grimaldi¹⁷⁷, Sean M. Grimmond³⁶², Robert L. Grossman³⁶³, Adam Grundhoff^{97,364}, Gunes Gundem⁸⁸, Qianyun Guo⁷⁵, Manaswi Gupta⁸, Shailja Gupta³⁶⁵, Ivo G. Gut^{52,61}, Marta Gut^{52,61}, Jonathan Göke^{292,366}, Gavin Ha⁸, Andrea Haake¹¹¹, David Haan³⁷, Siegfried Haas¹⁸⁵, Kerstin Haase²⁹⁰, James E. Haber³⁶⁷, Nina Habermann⁶⁰, Faraz Hach^{62,63}, Syed Haider⁶, Natsuko Hama¹¹⁸, Freddie C. Hamdy³⁵¹, Anne Hamilton²⁶⁷, Mark P. Hamilton³⁶⁸, Leng Han³⁶⁹, George B. Hanna³⁷⁰, Martin Hansmann³⁷¹, Nicholas J. Haradhvala^{8,72}, Olivier Harismendy^{102,372}, Ivon Harliwong¹¹³, Arif O. Harmanci^{5,373}, Eoghan Harrington³⁷⁴, Takanori Hasegawa³⁷⁵, David Haussler^{24,25}, Steve Hawkins²²³, Shinya Hayami³⁷⁶, Shuto Hayashi³⁷⁵, D. Neil Hayes^{134,377,378}, Stephen J. Hayes^{379,380}, Nicholas K. Hayward^{211,311}, Steven Hazell²²¹, Yao He³⁸¹, Allison P. Heath³⁸², Simon C. Heath^{52,61}, David Hedley³⁰⁰, Apurva M. Hegde³⁸, David I. Heiman⁸, Michael C. Heinold^{47,48}, Zachary Heins⁸⁸, Lawrence E. Heisler¹⁵², Eva Hellstrom-Lindberg³⁸³, Mohamed Helmy³⁸⁴, Seong Gu Heo³⁸⁵, Austin J. Hepperla¹³⁴, José María Heredia-Genestar³⁸⁶, Carl Herrmann^{47,48,387}, Peter Hersey²¹¹, Julian M. Hess^{8,26}, Holmfridur Hilmarsdottir³²⁰, Jonathan Hinton⁴⁹, Satoshi Hirano³⁸⁸, Nobuyoshi Hiraoka³⁸⁹, Katherine A. Hoadley^{134,390}, Asger Hobolth^{75,168}, Ermin Hodzic⁷⁸, Jessica I. Hoell¹⁸², Steve Hoffmann^{163,164,165,391}, Oliver Hofmann³⁹², Andrea Holbrook¹⁶⁶, Aliaksei Z. Holik⁵³, Michael A. Hollingsworth³⁹³, Oliver Holmes^{209,311}, Robert A. Holt³⁰, Chen Hong^{205,237}, Eun Pyo Hong³⁸⁵, Jongwhi H. Hong³⁹⁴, Gerrit K. Hooijer³⁹⁵, Henrik Hornshøj⁷³, Fumie Hosoda¹¹⁸, Yong Hou^{56,396}, Volker Hovestadt³⁹⁷, William Howat³⁵², Alan P. Hoyle¹³⁴, Ralph H. Hruban¹⁴⁹, Jianhong Hu¹², Taobo Hu⁶⁴, Xing Hua²⁴⁰, Kuan-lin Huang^{1,398}, Mei Huang¹⁷⁶, Mi Ni Huang^{179,180}, Vincent Huang⁶, Yi Huang^{65,66}, Wolfgang Huber⁶⁰, Thomas J. Hudson^{272,399}, Michael Hummel⁴⁰⁰, Jillian A. Hung^{246,247}, David Huntsman⁴⁰¹, Ted R. Hupp⁴⁰², Jason Huse⁸⁸, Matthew R. Huska⁴⁰³, Barbara Hutter^{43,67,68}, Carolyn M. Hutter²⁷, Daniel Hübschmann^{48,54,404,405,406}, Christine A. Iacobuzio-Donahue³⁴⁸, Charles David Imbusch²⁰⁵, Marcin Imielinski^{407,408}, Seiya Imoto³⁷⁵, William B. Isaacs⁴⁰⁹, Keren Isaev^{6,44}, Shumpei Ishikawa⁴¹⁰, Murat Iskar³⁹⁷, S. M. Ashiqul Islam²⁴⁴, Michael Ittmann^{411,412,413}, Sinisa Ivkovic²⁸⁴, Jose M. G. Izarzugaza⁴¹⁴, Jocelyne Jacquemier⁴¹⁵, Valerie Jakrot²¹¹, Nigel B. Jamieson^{133,172,416}, Gun Ho Jang¹⁴⁸, Se Jin Jang⁴¹⁷, Joy C. Jayaseelan¹², Reyka Jayasinghe¹, Stuart R. Jefferys¹³⁴, Karine Jegalian⁴¹⁸, Jennifer L. Jennings⁴¹⁹, Seung-Hyup Jeon²⁵⁰, Lara Jerman^{60,420}, Yuan Ji^{421,422}, Wei Jiao⁶, Peter A. Johansson³¹¹, Amber L. Johns¹⁷⁰, Jeremy Johns²⁷², Rory Johnson^{230,423}, Todd A. Johnson¹⁸³, Clemency Jolly²⁹⁰, Yann Joly⁴²⁴, Jon G. Jonasson³²⁰, Corbin D. Jones⁴²⁵, David R. Jones⁴⁹, David T. W. Jones^{426,427}, Nic Jones⁴²⁸, Steven J. M. Jones³⁰, Jos Jonkers²⁰⁴, Young Seok Ju^{49,249}, Hartmut Juhl⁴²⁹, Jongsun Jung⁶⁹, Malene Juul⁷³, Randi Istrup Juul⁷³, Sissel Juul³⁷⁴, Natalie Jäger⁴⁷, Rolf Kabbe⁴⁷, Andre Kahles^{276,277,278,279,430}, Abdullah Kahraman^{431,432,433}, Vera B. Kaiser⁴³⁴, Hojabr Kakavand²¹¹, Sangeetha Kalimuthu¹⁴⁸, Christof von Kalle⁴⁰⁵, Koo Jeong Kang⁹¹, Katalin Karaszi³⁵¹, Beth Karlan⁴³⁵, Rosa Karlič⁴³⁶, Dennis Karsch⁴³⁷, Katayoon Kasaian^{29,30}, Karin S. Kassahn^{113,438}, Hitoshi Katai⁴³⁹, Mamoru Kato⁴⁴⁰, Hiroto Katoh⁴¹⁰, Yoshiiku Kawakami⁹³, Jonathan D. Kay¹¹⁷, Stephen H. Kazakoff^{209,311}, Marat D. Kazanov^{441,442,443}, Maria Keays⁵⁹, Electron Kebebew^{444,445}, Richard F. Kefford⁴⁴⁶, Manolis Kellis^{8,447}, James G. Kench^{170,350,448},

Catherine J. Kennedy^{246,247}, Jules N. A. Kerssemakers⁴⁷, David Khoo²⁷³, Vincent Khoo²²¹, Narong Khuntikeo^{115,449}, Ekta Khurana^{301,302,450,451}, Helena Kilpinen¹¹⁷, Hark Kyun Kim⁴⁵², Hyung-Lae Kim⁷⁰, Hyung-Yong Kim⁴¹⁵, Hyunghwan Kim²⁵⁰, Jaegil Kim⁸, Jihoon Kim⁴⁵³, Jong K. Kim⁴⁵⁴, Youngwook Kim^{455,456}, Tari A. King^{457,458,459}, Wolfram Klapper¹²⁸, Kortine Kleinheinz^{47,48}, Leszek J. Klimczak⁴⁶⁰, Stian Knappskog^{49,461}, Michael Kneba⁴³⁷, Bartha M. Knoppers⁴²⁴, Youngil Koh^{462,463}, Jan Komorowski^{305,464}, Daisuke Komura⁴¹⁰, Mitsuhiro Komura³⁷⁵, Gu Kong⁴¹⁵, Marcel Kool^{426,465}, Jan O. Korbel^{59,60}, Viktoriya Korchina¹², Andrey Korshunov⁴⁶⁵, Michael Koscher⁴⁶⁵, Roelof Koster⁴⁶⁶, Zsafia Kote-Jarai¹⁷⁸, Antonios Koures²⁴⁴, Milena Kovacevic²⁸⁴, Barbara Kremeyer⁴⁹, Helene Kretzmer^{164,165}, Markus Kreuz⁴⁶⁷, Savitri Krishnamurthy^{99,468}, Dieter Kube⁴⁶⁹, Kiran Kumar⁸, Pardeep Kumar²²¹, Sushant Kumar^{5,19}, Yogesh Kumar⁶⁴, Ritika Kundra^{114,121}, Kirsten Kübler^{8,14,72}, Ralf Küppers⁴⁷⁰, Jesper Lagergren^{383,471}, Phillip H. Lai¹⁶⁶, Peter W. Laird⁴⁷², Sunil R. Lakhani⁴⁷³, Christopher M. Lalansingh⁶, Emilie Lalonde⁶, Fabien C. Lamaze⁶, Adam Lambert³⁵¹, Eric Lander⁸, Pablo Landgraf^{474,475}, Luca Landoni¹¹⁵, Anita Langerød¹³⁰, Andrés Lanzós^{230,231,423}, Denis Larsimont⁴⁷⁶, Erik Larsson⁴⁷⁷, Mark Lathrop¹⁸⁹, Loretta M. S. Lau⁴⁷⁸, Chris Lawerenz⁵⁵, Rita T. Lawlor¹⁷⁷, Michael S. Lawrence^{8,72,183}, Alexander J. Lazar^{99,108}, Xuan Le⁴⁷⁹, Darlene Lee³⁰, Donghoon Lee⁵, Eunjung Alice Lee⁴⁸⁰, Hee Jin Lee⁴¹⁷, Jake June-Koo Lee^{264,266}, Jeong-Yeon Lee⁴⁸¹, Juhee Lee⁴⁸², Ming Ta Michael Lee³⁴⁰, Henry Lee-Six⁴⁹, Kjong-Van Lehmann^{276,277,278,279,430}, Hans Lehrach⁴⁸³, Dido Lenze⁴⁰⁰, Conrad R. Leonard^{209,311}, Daniel A. Leongamornlert^{49,178}, Ignaty Leshchiner⁸, Louis Letourneau⁴⁸⁴, Ivica Letunic⁷¹, Douglas A. Levine^{88,485}, Lora Lewis¹², Tim Ley⁴⁸⁶, Chang Li^{56,396}, Constance H. Li^{6,44}, Haiyan Irene Li³⁰, Jun Li²¹, Lin Li⁵⁶, Shantao Li⁵, Siliang Li^{56,396}, Xiaobo Li^{56,396}, Xiaotong Li⁵, Xinyue Li⁵⁶, Yilong Li⁴⁹, Han Liang²¹, Sheng-Ben Liang²³⁴, Peter Lichter^{68,397}, Pei Lin⁸, Ziao Lin^{8,487}, W. M. Linehan⁴⁸⁸, Ole Christian Lingjærde⁴⁸⁹, Dongbing Liu^{56,396}, Eric Minwei Liu^{88,301,302}, Fei-Fei Liu^{201,490}, Fenglin Liu^{381,491}, Jia Liu⁴⁹², Xingmin Liu^{56,396}, Julie Livingstone⁶, Dimitri Livitz⁸, Naomi Livni²²¹, Lucas Lochovsky^{5,19,110}, Markus Loeffler⁴⁶⁷, Georgina V. Long²¹¹, Armando Lopez-Guillermo⁴⁹³, Shaoko Lou^{5,19}, David N. Louis⁷², Laurence B. Lovat¹¹⁷, Yiling Lu³⁸, Yong-Jie Lu^{162,494}, Youyong Lu^{495,496,497}, Claudio Luchini¹⁶⁷, Ilinca Lungu^{144,148}, Xuemei Luo¹⁵², Hayley J. Luxton¹¹⁷, Andy G. Lynch^{223,315,498}, Lisa Lype³⁶, Cristina López^{111,112}, Carlos López-Otín⁴⁹⁹, Eric Z. Ma⁶⁴, Yussanne Ma³⁰, Gaetan MacGrogan⁵⁰⁰, Shona MacRae⁵⁰¹, Geoff Macintyre²²³, Tobias Madsen⁷³, Kazuhiro Maejima¹⁸⁴, Andrea Mafficini¹⁷⁷, Dennis T. Maglinte^{166,502}, Arindam Maitra¹⁷⁴, Partha P. Majumder¹⁷⁴, Luca Malcovati²³², Salem Malikic^{62,78}, Giuseppe Malleo¹¹⁵, Graham J. Mann^{211,246,503}, Luisa Mantovani-Löffler⁵⁰⁴, Kathleen Marchal^{505,506}, Giovanni Marchegiani¹¹⁵, Elaine R. Mardis^{1,193,507}, Adam A. Margolin³¹, Maximillian G. Marin³⁷, Florian Markowetz^{223,315}, Julia Markowski⁴⁰³, Jeffrey Marks⁵⁰⁸, Tomas Marques-Bonet^{61,81,386,509}, Marco A. Marra³⁰, Luke Marsden³⁵¹, John W. M. Martens³³², Sancha Martin^{49,510}, Jose I. Martin-Subero^{81,511}, Iñigo Martincorena⁴⁹, Alexander Martinez-Fundichely^{301,302,451}, Yosef E. Maruvka^{8,26,72}, R. Jay Mashl^{1,2}, Charlie E. Massie²²³, Thomas J. Matthew³⁷, Lucy Matthews¹⁷⁸, Erik Mayer^{221,512}, Simon Mayes⁵¹³, Michael Mayo³⁰, Faridah Mbabaali²⁷², Karen McCune⁵¹⁴, Ultan McDermott⁴⁹, Patrick D. McGillivray¹⁹, Michael D. McLellan^{1,3,20}, John D. McPherson^{148,272,515}, John R. McPherson^{179,180}, Treasa A. McPherson²⁶⁰, Samuel R. Meier⁸, Alice Meng⁵¹⁶, Shaowu Meng¹³⁴, Andrew Menzies⁴⁹, Neil D. Merrett^{115,517}, Sue Merson¹⁷⁸, Matthew Meyerson^{8,14,82}, William U. Meyerson^{4,5}, Piotr A. Mieczkowski⁵¹⁸, George L. Mihaiescu⁷⁶, Sanja Mijalkovic²⁸⁴, Ana Mijalkovic Mijalkovic-Lazic²⁸⁴, Tom Mikkelsen⁵¹⁹, Michele Milella²⁵³, Linda Mileskin¹⁰³, Christopher A. Miller¹, David K. Miller^{113,170}, Jessica K. Miller²⁷², Gordon B. Mills^{33,34}, Ana Milovanovic⁵⁷, Sarah Minner⁵²⁰, Marco Miotto¹¹⁵, Gisela Mir Arnau²⁶⁷, Lisa Mirabello²⁴⁰, Chris Mitchell¹⁰³, Thomas J. Mitchell^{49,315,352}, Satoru Miyano³⁷⁵, Naoki Miyoshi³⁷⁵, Shinichi Mizuno⁵²¹, Fruzsina Molnár-Gábor⁵²², Malcolm J. Moore³⁰⁰, Richard A. Moore³⁰,

Sandro Morganella⁴⁹, Quaid D. Morris^{127,490}, Carl Morrison^{523,524}, Lisle E. Mose¹³⁴, Catherine D. Moser³⁴⁹, Ferran Muiños^{298,299}, Loris Mularoni^{298,299}, Andrew J. Mungall³⁰, Karen Mungall³⁰, Elizabeth A. Musgrove¹³³, Ville Mustonen^{525,526,527}, David Mutch⁵²⁸, Francesc Muyas^{52,53,74}, Donna M. Muzny¹², Alfonso Muñoz⁵⁹, Jerome Myers⁵²⁹, Ola Myklebost⁴⁶¹, Peter Möller⁵³⁰, Genta Nagae⁸⁹, Adnan M. Nagrial¹⁷⁰, Hardeep K. Nahal-Bose⁷⁶, Hitoshi Nakagama⁵³¹, Hidewaki Nakagawa¹⁸⁴, Hiromi Nakamura¹¹⁸, Toru Nakamura³⁸⁸, Kaoru Nakano¹⁸⁴, Tannistha Nandi⁵³², Jyoti Nangalia⁴⁹, Mia Nastic²⁸⁴, Arcadi Navarro^{61,81,386}, Fabio C. P. Navarro¹⁹, David E. Neal^{223,352}, Gerd Nettekoven⁵³³, Felicity Newell^{209,311}, Steven J. Newhouse⁵⁹, Yulia Newton³⁷, Alvin Wei Tian Ng⁵³⁴, Anthony Ng⁵³⁵, Jonathan Nicholson⁴⁹, David Nicol²²¹, Yongzhan Nie^{321,536}, G. Petur Nielsen⁷², Morten Muhlig Nielsen⁷³, Serena Nik-Zainal^{49,281,282,537}, Michael S. Noble⁸, Katia Nones^{209,311}, Paul A. Northcott⁵³⁸, Faiyaz Notta^{148,539}, Brian D. O'Connor^{76,540}, Peter O'Donnell⁵⁴¹, Maria O'Donovan²⁸², Sarah O'Meara⁴⁹, Brian Patrick O'Neill⁵⁴², J. Robert O'Neill⁵⁴³, David Ocana⁵⁹, Angelica Ochoa⁸⁸, Layla Oesper⁵⁴⁴, Christopher Ogden²²¹, Hideki Ohdan⁹³, Kazuhiro Ohi³⁷⁵, Lucila Ohno-Machado²⁴⁴, Karin A. Oien^{523,545}, Akinyemi I. Ojesina^{546,547,548}, Hidenori Ojima⁵⁴⁹, Takuji Okusaka⁵⁵⁰, Larsson Omberg⁵⁵¹, Choon Kiat Ong⁵⁵², Stephan Ossowski^{52,53,74}, German Ott⁵⁵³, B. F. Francis Ouellette^{76,554}, Christine P'ng⁶, Marta Paczkowska⁶, Salvatore Paiella¹¹⁵, Chawalit Pairojkul⁵²³, Marina Pajic¹⁷⁰, Qiang Pan-Hammarström^{56,555}, Elli Papaemmanuil⁴⁹, Irene Papatheodorou⁵⁹, Nagarajan Paramasivam^{43,47}, Ji Wan Park³⁸⁵, Joong-Won Park⁵⁵⁶, Keunchil Park^{557,558}, Kiejung Park⁵⁵⁹, Peter J. Park^{264,266}, Joel S. Parker⁵¹⁸, Simon L. Parsons¹²⁴, Harvey Pass⁵⁶⁰, Danielle Pasternack²⁷², Alessandro Pastore²⁷⁶, Ann-Marie Patch^{209,311}, Iris Pauporté²⁵¹, Antonio Pea¹¹⁵, John V. Pearson^{209,311}, Chandra Sekhar Pedomallu^{8,14,82}, Jakob Skou Pedersen^{73,75}, Paolo Pederzoli¹¹⁵, Martin Peifer²⁷⁰, Nathan A. Pennell⁵⁶¹, Charles M. Perou^{129,518}, Marc D. Perry^{76,77}, Gloria M. Petersen⁵⁶², Myron Peto²², Nicholas Petrelli⁵⁶³, Robert Petryszak⁵⁹, Stefan M. Pfister^{426,465,564}, Mark Phillips⁴²⁴, Oriol Pich^{298,299}, Hilda A. Pickett⁴⁷⁸, Todd D. Pihl⁵⁶⁵, Nischalan Pillay⁵⁶⁶, Sarah Pinder⁵⁶⁷, Mark Pinese¹⁷⁰, Andreia V. Pinho⁵⁶⁸, Esa Pitkänen⁶⁰, Xavier Pivot⁵⁶⁹, Elena Piñero-Yáñez⁹⁵, Laura Planko⁵³³, Christoph Plass³⁴⁵, Paz Polak^{8,14,15}, Tirso Pons⁵⁷⁰, Irinel Popescu⁵⁷¹, Olga Potapova⁵⁷², Aparna Prasad⁵², Shaun R. Preston⁵⁷³, Manuel Prinz⁴⁷, Antonia L. Pritchard³¹¹, Stephenie D. Prokopec⁶, Elena Provenzano⁵⁷⁴, Xose S. Puente⁴⁹⁹, Sonia Puig¹⁷⁶, Montserrat Puiggròs⁵⁷, Sergio Pulido-Tamayo^{505,506}, Gulietta M. Pupo²⁴⁶, Colin A. Purdie⁵⁷⁵, Michael C. Quinn^{209,311}, Raquel Rabionet^{52,53,576}, Janet S. Rader⁵⁷⁷, Bernhard Radlwimmer³⁹⁷, Petar Radovic²⁸⁴, Benjamin Raeder⁶⁰, Keiran M. Raine⁴⁹, Manasa Ramakrishna⁴⁹, Kamna Ramakrishnan⁴⁹, Suresh Ramalingam⁵⁷⁸, Benjamin J. Raphael⁵⁷⁹, W. Kimryn Rathmell⁵⁸⁰, Tobias Rausch⁶⁰, Guido Reifemberger⁴⁷⁵, Jüri Reimand^{6,44}, Jorge Reis-Filho³⁴⁸, Victor Reuter³⁴⁸, Iker Reyes-Salazar²⁹⁸, Matthew A. Reyna⁵⁷⁹, Sheila M. Reynolds³⁶, Esther Rheinbay^{8,14,72}, Yasser Riazalhosseini¹⁸⁹, Andrea L. Richardson³²³, Julia Richter^{111,128}, Matthew Ringel⁵⁸¹, Markus Ringné¹⁸¹, Yasushi Rino⁵⁸², Karsten Rippe⁴⁰⁵, Jeffrey Roach⁵⁸³, Lewis R. Roberts³⁴⁹, Nicola D. Roberts⁴⁹, Steven A. Roberts⁵⁸⁴, A. Gordon Robertson³⁰, Alan J. Robertson¹¹³, Javier Bartolomé Rodríguez⁵⁷, Bernardo Rodríguez-Martin^{104,105,106}, F. Germán Rodríguez-González^{83,332}, Michael H. A. Roehrl^{44,123,148,234,585,586}, Marius Rohde⁵⁸⁷, Hirofumi Rokutan⁴⁴⁰, Gilles Romieu⁵⁸⁸, Ilse Rooman¹⁷⁰, Tom Roques²⁶², Daniel Rosebrock⁸, Mara Rosenberg^{8,72}, Philip C. Rosenstiel⁵⁸⁹, Andreas Rosenwald⁵⁹⁰, Edward W. Rowe^{221,591}, Romina Royo⁵⁷, Steven G. Rozen^{179,180,592}, Yulia Rubanova^{17,127}, Mark A. Rubin^{423,593,594,595,596}, Carlota Rubio-Perez^{298,299,597}, Vasilisa A. Rudneva⁶⁰, Borislav C. Rusev¹⁷⁷, Andrea Ruzzenente⁵⁹⁸, Gunnar Rättsch^{276,277,278,279,280,430}, Radhakrishnan Sabarinathan^{298,299,599}, Veronica Y. Sabelnykova⁶, Sara Sadeghi³⁰, S. Cenik Sahinalp^{62,78,79}, Natalie Saini³⁵⁷, Mihoko Saito-Adachi⁴⁴⁰, Gordon Saksena⁸, Adriana Salcedo⁶, Roberto Salgado⁶⁰⁰, Leonidas Salichos^{5,19}, Richard Sallari⁸, Charles Saller⁶⁰¹, Roberto Salvia¹¹⁵, Michelle Sam²⁷², Jaswinder S. Samra^{115,602}, Francisco Sanchez-Vega^{114,121}, Chris Sander^{276,603,604}, Grant Sanders¹³⁴, Rajiv Sarin⁶⁰⁵,

Iman Sarrafi^{62,78}, Aya Sasaki-Oku¹⁸⁴, Torill Sauer⁴⁸⁹, Guido Sauter⁵²⁰, Robyn P. M. Saw²¹¹, Maria Scardoni¹⁶⁷, Christopher J. Scarlett^{170,606}, Aldo Scarpa¹⁷⁷, Ghislaine Scelo¹⁹⁴, Dirk Schadendorf^{68,607}, Jacqueline E. Schein³⁰, Markus B. Schilhabel⁵⁸⁹, Matthias Schlesner^{47,80}, Thorsten Schlomm^{84,608}, Heather K. Schmidt¹, Sarah-Jane Schramm²⁴⁶, Stefan Schreiber⁶⁰⁹, Nikolaus Schultz¹²¹, Steven E. Schumacher^{8,323}, Roland F. Schwarz^{59,403,405,610}, Richard A. Scolyer^{211,448,602}, David Scott⁴²⁸, Ralph Scully⁶¹¹, Raja Seethala⁶¹², Ayellet V. Segre^{8,613}, Iris Selander²⁶⁰, Colin A. Semple⁴³⁴, Yasin Senbabaoglu²⁷⁶, Subhajt Sengupta⁶¹⁴, Elisabetta Sereni¹¹⁵, Stefano Serra⁵⁸⁵, Dennis C. Sgroi⁷², Mark Shackleton¹⁰³, Nimish C. Shah³⁵², Sagedeh Shahabi²³⁴, Catherine A. Shang³²⁹, Ping Shang²¹¹, Ofer Shapira^{8,323}, Troy Shelton²⁷¹, Ciyue Shen^{603,604}, Hui Shen⁶¹⁵, Rebecca Shepherd⁴⁹, Ruian Shi⁴⁹⁰, Yan Shi¹³⁴, Yu-Jia Shiah⁶, Tatsuhiro Shibata^{118,616}, Juliann Shih^{8,82}, Eigo Shimizu³⁷⁵, Kiyu Shimizu⁶¹⁷, Seung Jun Shin⁶¹⁸, Yuichi Shiraishi³⁷⁵, Tal Shmaya²⁸⁵, Ilya Shmulevich³⁶, Solomon I. Shorser⁶, Charles Short⁵⁹, Raunak Shrestha⁶², Suyash S. Shringarpure²¹⁷, Craig Shriver⁶¹⁹, Shimin Shuai^{6,126}, Nikos Sidiropoulos⁸³, Reiner Siebert^{112,620}, Anieta M. Siewerts³³², Lina Sieverling^{205,237}, Sabina Signoretti^{202,621}, Katarzyna O. Sikora¹⁷⁷, Michele Simbolo¹³⁸, Ronald Simon⁵²⁰, Janae V. Simons¹³⁴, Jared T. Simpson^{6,17}, Peter T. Simpson⁴⁷³, Samuel Singer^{115,458}, Nasa Sinnott-Armstrong^{8,217}, Payal Sipahimalani³⁰, Tara J. Skelly³⁹⁰, Marcel Smid³³², Jaclyn Smith⁶²², Karen Smith-McCune⁵¹⁴, Nicholas D. Succi²⁷⁶, Heidi J. Sofia²⁷, Matthew G. Soloway¹³⁴, Lei Song²⁴⁰, Anil K. Sood^{623,624,625}, Sharmila Sothi⁶²⁶, Christos Sotiriou²⁴⁴, Cameron M. Soulette³⁷, Paul N. Span⁶²⁷, Paul T. Spellman²², Nicola Sperandio¹⁷⁷, Andrew J. Spillane²¹¹, Oliver Spiro⁸, Jonathan Spring⁶²⁸, Johan Staaf¹⁸¹, Peter F. Stadler^{163,164,165}, Peter Staib⁶²⁹, Stefan G. Stark^{277,279,618,630}, Lucy Stebbings⁴⁹, Ólafur Andri Stefánsson⁶³¹, Oliver Stegle^{59,60,632}, Lincoln D. Stein^{6,126}, Alasdair Stenhouse⁶³³, Chip Stewart⁸, Stephan Stilgenbauer⁶³⁴, Miranda D. Stobbe^{52,61}, Michael R. Stratton⁴⁹, Jonathan R. Stretch²¹¹, Adam J. Struck³¹, Joshua M. Stuart^{24,37}, Henk G. Stunnenberg^{396,635}, Hong Su^{56,396}, Xiaoping Su⁹⁹, Ren X. Sun⁶, Stephanie Sungalee⁶⁰, Hana Susak^{52,53}, Akihiro Suzuki^{89,636}, Fred Sweep⁶³⁷, Monika Szczepanowski¹²⁸, Holger Sültmann^{67,638}, Takashi Yugawa⁶¹⁷, Angela Tam³⁰, David Tamborero^{298,299}, Benita Kiat Tee Tan⁶³⁹, Donghui Tan⁵¹⁸, Patrick Tan^{180,532,592,640}, Hiroko Tanaka³⁷⁵, Hirokazu Taniguchi⁶¹⁶, Tomas J. Tanskanen⁶⁴¹, Maxime Tarabichi^{49,290}, Roy Tarnuzzer²²⁰, Patrick Tarpey⁶⁴², Morgan L. Taschuk¹⁵², Kenji Tatsuno⁸⁹, Simon Tavaré^{223,643}, Darrin F. Taylor¹¹³, Amaro Taylor-Weiner⁸, Jon W. Teague⁴⁹, Bin Tean Teh^{180,592,640,644,645}, Varsha Tembe²⁴⁶, Javier Temes^{104,105}, Kevin Thai⁷⁶, Sarah P. Thayer³⁹³, Nina Thiessen³⁰, Gilles Thomas⁶⁴⁶, Sarah Thomas²²¹, Alan Thompson²²¹, Alastair M. Thompson⁶³³, John F. Thompson²¹¹, R. Houston Thompson⁶⁴⁷, Heather Thorne¹⁰³, Leigh B. Thorne¹⁷⁶, Adrian Thorogood⁴²⁴, Grace Tiao⁸, Nebojsa Tijanac²⁸⁴, Lee E. Timms²⁷², Roberto Tirabosco⁶⁴⁸, Marta Tojo¹⁰⁶, Stefania Tommasi⁶⁴⁹, Christopher W. Toon¹⁷⁰, Umut H. Toprak^{48,650}, David Torrents^{57,81}, Giampaolo Tortora^{651,652}, Jörg Tost⁶⁵³, Yasushi Totoki¹¹⁸, David Townend⁶⁵⁴, Nadia Traficante¹⁰³, Isabelle Treilleux^{655,656}, Jean-Rémi Trotta⁶¹, Lorenz H. P. Trümper⁴⁶⁹, Ming Tsao^{124,539}, Tatsuhiko Tsunoda^{183,657,658,659}, Jose M. C. Tubio^{104,105,106}, Olga Tucker⁶⁶⁰, Richard Turkington⁶⁶¹, Daniel J. Turner⁵¹³, Andrew Tutt³²³, Masaki Ueno³⁷⁶, Naoto T. Ueno⁶⁶², Christopher Umbricht^{151,213,663}, Husen M. Umer^{305,664}, Timothy J. Underwood⁶⁶⁵, Lara Urban^{59,60}, Tomoko Urushidate⁶¹⁶, Tetsuo Ushiku³³⁹, Liis Uusküla-Reimand^{666,667}, Alfonso Valencia^{57,81}, David J. Van Den Berg¹⁶⁶, Steven Van Laere³⁰⁷, Peter Van Loo^{290,291}, Erwin G. Van Meir⁶⁶⁸, Gert G. Van den Eynden³⁰⁷, Theodorus Van der Kwast¹²³, Naveen Vasudev¹³⁷, Miguel Vazquez^{57,669}, Ravikiran Vedururu²⁶⁷, Umadevi Veluvolu⁵¹⁸, Shankar Vembu^{490,670}, Lieven P. C. Verbeke^{506,671}, Peter Vermeulen³⁰⁷, Clare Verrill^{351,672}, Alain Viari¹⁷⁷, David Vicente⁵⁷, Caterina Vicentini¹⁷⁷, K. Vijay Raghavan³⁶⁵, Juris Viksna⁶⁷³, Ricardo E. Vilain⁶⁷⁴, Izar Villasante⁵⁷, Anne Vincent-Salomon⁶³⁵, Tapio Visakorpi¹⁹⁰, Douglas Voet⁸, Paresh Vyas^{311,351}, Ignacio Vázquez-García^{49,86,675,676}, Nick M. Waddell²⁰⁹, Nicola Waddell^{209,311}, Claes Wadelius⁶⁷⁷, Lina Wadi⁶

Rabea Wagener^{111,112}, Jeremiah A. Wala^{8,14,82}, Jian Wang⁵⁶, Jiayin Wang^{1,40,66}, Linghua Wang¹², Qi Wang⁴⁶⁵, Wenyi Wang²¹, Yumeng Wang²¹, Zhining Wang²²⁰, Paul M. Waring⁵²³, Hans-Jörg Warnatz⁴⁸³, Jonathan Warrell^{5,19}, Anne Y. Warren^{352,678}, Sebastian M. Waszak⁶⁰, David C. Wedge^{49,294,679}, Dieter Weichenhan³⁴⁵, Paul Weinberger⁶⁸⁰, John N. Weinstein³⁸, Joachim Weischenfeldt^{60,83,84}, Daniel J. Weisenberger¹⁶⁶, Ian Welch⁶⁸¹, Michael C. Wendl^{1,10,11}, Johannes Werner^{47,85}, Justin P. Whalley^{61,682}, David A. Wheeler^{12,13}, Hayley C. Whitaker¹¹⁷, Dennis Wigle⁶⁸³, Matthew D. Wilkerson⁵¹⁸, Ashley Williams²⁴⁴, James S. Wilmott²¹¹, Gavin W. Wilson^{6,148}, Julie M. Wilson¹⁴⁸, Richard K. Wilson^{1,684}, Boris Winterhoff⁶⁸⁵, Jeffrey A. Wintersinger^{17,127,384}, Maciej Wiznerowicz^{686,687}, Stephan Wolf⁶⁸⁸, Bernice H. Wong⁶⁸⁹, Tina Wong^{1,30}, Winghing Wong⁶⁹⁰, Youngchoon Woo²⁵⁰, Scott Wood^{209,311}, Bradley G. Wouters⁴⁴, Adam J. Wright⁶, Derek W. Wright^{133,691}, Mark H. Wright²¹⁷, Chin-Lee Wu⁷², Dai-Ying Wu²⁸⁵, Guanming Wu⁶⁹², Jianmin Wu¹⁷⁰, Kui Wu^{56,396}, Yang Wu^{179,180}, Zhenggang Wu⁶⁴, Liu Xi¹², Tian Xia⁶⁹³, Qian Xiang⁷⁶, Xiao Xiao⁶⁶, Rui Xing⁴⁹⁷, Heng Xiong^{56,396}, Qinying Xu^{209,311}, Yanxun Xu⁶⁹⁴, Hong Xue⁶⁴, Shinichi Yachida^{118,695}, Sergei Yakneen⁶⁰, Rui Yamaguchi³⁷⁵, Takafumi N. Yamaguchi⁶, Masakazu Yamamoto¹²⁰, Shogo Yamamoto⁸⁹, Hiroki Yamaue³⁷⁶, Fan Yang⁴⁹⁰, Huanming Yang⁵⁶, Jean Y. Yang⁶⁹⁶, Liming Yang²²⁰, Lixing Yang⁶⁹⁷, Shanlin Yang³⁰⁶, Tsun-Po Yang²⁷⁰, Yang Yang³⁶⁹, Xiaotong Yao^{408,698}, Marie-Laure Yaspo⁴⁸³, Lucy Yates⁴⁹, Christina Yau¹⁵⁶, Chen Ye^{56,396}, Kai Ye^{40,41}, Venkata D. Yellapantula^{20,86}, Christopher J. Yoon²⁴⁹, Sung-Soo Yoon⁴⁶³, Fouad Yousif⁶, Jun Yu⁶⁹⁹, Kaixian Yu⁷⁰⁰, Willie Yu⁷⁰¹, Yingyan Yu⁷⁰², Ke Yuan^{223,510,703}, Yuan Yuan²¹, Denis Yuen⁶, Takashi Yugawa⁶¹⁷, Christina K. Yung⁷⁶, Olga Zaikova⁷⁰⁴, Jorge Zamora^{49,104,105,106}, Marc Zapatka³⁹⁷, Jean C. Zenklusen²²⁰, Thorsten Zenz⁶⁷, Nikolajs Zeps^{705,706}, Cheng-Zhong Zhang^{8,707}, Fan Zhang³⁸¹, Hailei Zhang⁸, Hongwei Zhang⁴⁹⁴, Hongxin Zhang¹²¹, Jiashan Zhang²²⁰, Jing Zhang⁵, Junjun Zhang⁷⁶, Xiuqing Zhang⁵⁶, Xuanping Zhang^{66,369}, Yan Zhang^{5,708,709}, Zemin Zhang^{381,710}, Zhongming Zhao⁷¹¹, Liangtao Zheng³⁸¹, Xiuqing Zheng³⁸¹, Wanding Zhou⁶¹⁵, Yong Zhou⁵⁶, Bin Zhu²⁴⁰, Hongtu Zhu^{700,712}, Jingchun Zhu²⁴, Shida Zhu^{56,396}, Lihua Zou⁷¹³, Xueqing Zou⁴⁹, Anna deFazio^{246,247,714}, Nicholas van As²²¹, Carolien H. M. van Deurzen⁷¹⁵, Marc J. van de Vijver⁵²³, L. van't Veer⁷¹⁶ & Christian von Mering^{433,717}

⁸⁷Applied Tumor Genomics Research Program, Research Programs Unit, University of Helsinki, 00100 Helsinki, Finland. ⁸⁸Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA. ⁸⁹Genome Science Division, Research Center for Advanced Science and Technology, University of Tokyo, Tokyo 113-8654, Japan. ⁹⁰Department of Surgery, University of Chicago, Chicago, IL 60637, USA. ⁹¹Department of Surgery, Division of Hepatobiliary and Pancreatic Surgery, School of Medicine, Keimyung University Dongsan Medical Center, Daegu, South Korea. ⁹²Department of Oncology, Gil Medical Center, Gachon University, Incheon, South Korea. ⁹³Hiroshima University, Hiroshima 739-8511, Japan. ⁹⁴King Faisal Specialist Hospital and Research Centre, Al Maather, Riyadh, Saudi Arabia. ⁹⁵Bioinformatics Unit, Spanish National Cancer Research Centre (CNIO), 28029 Madrid, Spain. ⁹⁶Bioinformatics Core Facility, University Medical Center Hamburg, 20251 Hamburg, Germany. ⁹⁷Heinrich Pette Institute, Leibniz Institute for Experimental Virology, 20251 Hamburg, Germany. ⁹⁸Ontario Tumour Bank, Ontario Institute for Cancer Research, Toronto, ON M5G 0A3, Canada. ⁹⁹Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA. ¹⁰⁰Laboratory of Pathology, Center for Cancer Research, National Cancer Institute, Bethesda, MD 20814, USA. ¹⁰¹Department of Cellular and Molecular Medicine and Department of Bioengineering, University of California San Diego, La Jolla, CA 92093, USA. ¹⁰²UC San Diego Moores Cancer Center, San Diego, CA 92037, USA. ¹⁰³Sir Peter MacCallum Department of Oncology, Peter MacCallum Cancer Centre, University of Melbourne, Melbourne, VIC 3010, Australia. ¹⁰⁴Centre for Research in Molecular Medicine and Chronic Diseases (CiMUS), Universidade de Santiago de Compostela, 15705 Santiago de Compostela, Spain. ¹⁰⁵Department of Zoology, Genetics and Physical Anthropology, (CiMUS), Universidade de Santiago de Compostela, 15705 Santiago de Compostela, Spain. ¹⁰⁶The Biomedical Research Centre (CINBIO), Universidade de Vigo, 36310 Vigo, Spain. ¹⁰⁷Royal National Orthopaedic Hospital-Bolover, London 36310, UK. ¹⁰⁸Department of Genomic Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA. ¹⁰⁹Quantitative and Computational Biosciences Graduate Program, Baylor College of Medicine, Houston, TX 77030, USA. ¹¹⁰The Jackson Laboratory for Genomic Medicine, Farmington, CT 06032, USA. ¹¹¹Institute of Human Genetics, Christian-Albrechts-University, 24118 Kiel, Germany. ¹¹²Institute of Human Genetics, Ulm University and Ulm University Medical Center, 89081 Ulm, Germany. ¹¹³Queensland Centre for Medical Genomics, Institute for Molecular Bioscience, University of Queensland, St. Lucia, Brisbane, QLD 4072, Australia. ¹¹⁴Salford Royal NHS Foundation Trust, Salford M6 8HD, UK. ¹¹⁵Department of Surgery, Pancreas Institute, University and Hospital Trust of Verona, 37129 Verona, Italy. ¹¹⁶Department of Molecular Oncology, BC Cancer Research Centre, Vancouver, BC V5Z 1L3, Canada. ¹¹⁷University College London, London WC1E 6BT, UK. ¹¹⁸Division of Cancer Genomics, National Cancer Center Research Institute, National Cancer Center, Tokyo 104-0045, Japan. ¹¹⁹DLR Project Management Agency, Bonn, Germany. ¹²⁰Tokyo Women's Medical University, Tokyo 162-8666, Japan. ¹²¹Center for Molecular Oncology, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA. ¹²²Los Alamos National Laboratory, Los Alamos, NM 87545, USA. ¹²³Department of Pathology, University Health Network, Toronto General Hospital, Toronto, ON M5G 2C4, Canada. ¹²⁴Nottingham University Hospitals NHS Trust, Nottingham NG5 1PB, UK. ¹²⁵Epigenomics and Cancer Risk Factors, German Cancer Research Center (DKFZ), 69120 Heidelberg, Germany. ¹²⁶Department of Molecular Genetics, University of Toronto, Toronto, ON M5S, Canada. ¹²⁷Vector Institute, Toronto, ON M5G 1M1, Canada. ¹²⁸Hematopathology Section, Institute of Pathology,

Christian-Albrechts-University, Kiel 24118, Germany. ¹²⁹Department of Pathology and Laboratory Medicine, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA. ¹³⁰Department of Cancer Genetics, Institute for Cancer Research, Oslo University Hospital, The Norwegian Radium Hospital, 0450 Oslo, Norway. ¹³¹Pathology, Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, 08007 Barcelona, Spain. ¹³²Department of Veterinary Medicine, Transmissible Cancer Group, University of Cambridge, Cambridge CB2 1TN, UK. ¹³³Wolfson Wohl Cancer Research Centre, Institute of Cancer Sciences, University of Glasgow, Glasgow G12 8QQ, UK. ¹³⁴Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA. ¹³⁵Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA 02115, USA. ¹³⁶Department of Pediatrics, Harvard Medical School, Boston, MA 02115, USA. ¹³⁷Leeds Institute of Medical Research at St. James's, University of Leeds, St. James's University Hospital, Leeds LS2 9JT, UK. ¹³⁸Department of Pathology and Diagnostics, University and Hospital Trust of Verona, 37129 Verona, Italy. ¹³⁹Department of Surgery, Princess Alexandra Hospital, Brisbane, QLD 4102, Australia. ¹⁴⁰Surgical Oncology Group, Diamantina Institute, University of Queensland, Brisbane, QLD 4072, Australia. ¹⁴¹Department of Population and Quantitative Health Sciences, Case Western Reserve University School of Medicine, Cleveland, OH 44106, USA. ¹⁴²Research Health Analytics and Informatics, University Hospitals Cleveland Medical Center, Cleveland, OH 44106, USA. ¹⁴³Gloucester Royal Hospital, Gloucester GL1 3NN, UK. ¹⁴⁴Diagnostic Development, Ontario Institute for Cancer Research, Toronto, ON M5G 0A3, Canada. ¹⁴⁵Arnie Charbonneau Cancer Institute, University of Calgary, Calgary, AB T2N 1N4, Canada. ¹⁴⁶Departments of Surgery and Oncology, University of Calgary, Calgary, AB T2N 1N4, Canada. ¹⁴⁷Department of Pathology, Oslo University Hospital, The Norwegian Radium Hospital, Oslo, Norway. ¹⁴⁸PanCuRx Translational Research Initiative, Ontario Institute for Cancer Research, Toronto, ON M5G 0A3, Canada. ¹⁴⁹Department of Oncology, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University School of Medicine, Baltimore, MD 21231, USA. ¹⁵⁰University Hospital Southampton NHS Foundation Trust, Southampton SO16 6YD, UK. ¹⁵¹Royal Stoke University Hospital, Stoke-on-Trent ST4 6QG, UK. ¹⁵²Genome Sequence Informatics, Ontario Institute for Cancer Research, Toronto, ON M5G 0A3, Canada. ¹⁵³Human Longevity Inc, San Diego, CA M5G 0A3, USA. ¹⁵⁴Olivia Newton-John Cancer Research Institute, La Trobe University, Heidelberg, VIC 3086, Australia. ¹⁵⁵Genome Canada, Ottawa, ON K2P 1P1, Canada. ¹⁵⁶Buck Institute for Research on Aging, Novato, CA 94945, USA. ¹⁵⁷Duke University Medical Center, Durham, NC 27710, USA. ¹⁵⁸Department of Human Genetics, Hannover Medical School, 30625 Hannover, Germany. ¹⁵⁹Center for Bioinformatics and Functional Genomics, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA. ¹⁶⁰Department of Biomedical Sciences, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA. ¹⁶¹The Hebrew University Faculty of Medicine, Jerusalem 9112102, Israel. ¹⁶²Barts Cancer Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London E1 4NS, UK. ¹⁶³Department of Computer Science, Bioinformatics Group, University of Leipzig, 04109 Leipzig, Germany. ¹⁶⁴Interdisciplinary Center for Bioinformatics, University of Leipzig, 04109 Leipzig, Germany. ¹⁶⁵Transcriptome Bioinformatics, LIFE Research Center for Civilization Diseases, University of Leipzig, 04109 Leipzig, Germany. ¹⁶⁶USC Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA 90007, USA. ¹⁶⁷Department of Diagnostics and Public Health, University and Hospital Trust of Verona, Verona 37129, Italy. ¹⁶⁸Department of Mathematics, Aarhus University, 8000 Aarhus, Denmark. ¹⁶⁹Instituto Carlos Slim de la Salud, Mexico City, Mexico. ¹⁷⁰Cancer Division, Garvan Institute of Medical Research, Kinghorn Cancer Centre, University of New South Wales (UNSW Sydney), Sydney, NSW 2052, Australia. ¹⁷¹South Western Sydney Clinical School, Faculty of Medicine, University of New South Wales (UNSW Sydney), Liverpool, NSW 2052, Australia. ¹⁷²West of Scotland Pancreatic Unit, Glasgow Royal Infirmary, Glasgow G4 0SF, UK. ¹⁷³The Preston Robert Tisch Brain Tumor Center, Duke University Medical Center, Durham, NC 27710, USA. ¹⁷⁴National Institute of Biomedical Genomics, Kalyani, West Bengal 741251, India. ¹⁷⁵Institute of Clinical Medicine and Institute of Oral Biology, University of Oslo, 0315 Oslo, Norway. ¹⁷⁶University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA. ¹⁷⁷ARC-Net Centre for Applied Research on Cancer, University and Hospital Trust of Verona, Verona 0315, Italy. ¹⁷⁸The Institute of Cancer Research, London SM2 5NG, UK. ¹⁷⁹Centre for Computational Biology, Duke-NUS Medical School, Singapore 169857, Singapore. ¹⁸⁰Programme in Cancer and Stem Cell Biology, Duke-NUS Medical School, Singapore 169857, Singapore. ¹⁸¹Division of Oncology and Pathology, Department of Clinical Sciences Lund, Lund University, Lund, Sweden. ¹⁸²Department of Pediatric Oncology, Hematology and Clinical Immunology, Heinrich-Heine-University, 40225 Düsseldorf, Germany. ¹⁸³Laboratory for Medical Science Mathematics, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan. ¹⁸⁴RIKEN Center for Integrative Medical Sciences, Yokohama, Japan. ¹⁸⁵Department of Internal Medicine/Hematology, Friedrich-Ebert-Hospital, Neumünster, Germany. ¹⁸⁶Departments of Dermatology and Pathology, Yale University, New Haven, CT 06520, USA. ¹⁸⁷Radcliffe Department of Medicine, University of Oxford, Oxford OX1 2JD, UK. ¹⁸⁸Canadian Center for Computational Genomics, McGill University, Montreal, QC H3A 0G4, Canada. ¹⁸⁹Department of Human Genetics, McGill University, Montreal, QC H3A 0G4, Canada. ¹⁹⁰Faculty of Medicine and Health Technology, Tampere University and Tays Cancer Center, Tampere University Hospital, 33520 Tampere, Finland. ¹⁹¹Haematology, Leeds Teaching Hospitals NHS Trust, Leeds LS1 3EX, UK. ¹⁹²Translational Research and Innovation, Centre Léon Bérard, Lyon, France. ¹⁹³Fox Chase Cancer Center, Philadelphia, PA 19111, USA. ¹⁹⁴International Agency for Research on Cancer, World Health Organization, Lyon, France. ¹⁹⁵Earlham Institute, Norwich NR4 7UZ, UK. ¹⁹⁶Norwich Medical School, University of East Anglia, Norwich NR4 7TJ, UK. ¹⁹⁷Department of Molecular Biology, Faculty of Science, Radboud Institute for Molecular Life Sciences, Radboud University, Nijmegen, HB 6525 XZ, The Netherlands. ¹⁹⁸CRUK Manchester Institute and Centre, Manchester M20 4GJ, UK. ¹⁹⁹Department of Radiation Oncology, University of Toronto, Toronto, ON M5S, Canada. ²⁰⁰Division of Cancer Sciences, Manchester Cancer Research Centre, University of Manchester, Manchester M13 9PL, UK. ²⁰¹Radiation Medicine Program, Princess Margaret Cancer Centre, Toronto, ON M5G 2C1, Canada. ²⁰²Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA. ²⁰³Department of Surgery, Division of Thoracic Surgery, The Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA. ²⁰⁴Division of Molecular Pathology, The Netherlands Cancer Institute, Oncode Institute, Amsterdam, CX 1066, The Netherlands. ²⁰⁵Division of Applied Bioinformatics, German Cancer Research Center (DKFZ), 69120 Heidelberg, Germany. ²⁰⁶German Cancer Genome Consortium (DKTK), Heidelberg, Germany. ²⁰⁷Center for Biological Sequence Analysis, Department of Bio and Health Informatics, Technical University of Denmark, 2800 Lyngby, Denmark. ²⁰⁸Novo Nordisk Foundation Center for Protein Research, University of Copenhagen, Copenhagen 1165, Denmark. ²⁰⁹Institute for Molecular Bioscience, University of Queensland, St. Lucia, Brisbane, QLD 4072, Australia. ²¹⁰Federal Ministry of Education and Research, Berlin, Germany. ²¹¹Melanoma Institute Australia, University of Sydney, Sydney, NSW 2006, Australia. ²¹²Pediatric Hematology and Oncology, University Hospital Muenster, 48149 Muenster, Germany. ²¹³Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA. ²¹⁴McKusick-Nathans Institute of Genetic Medicine, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University School of Medicine, Baltimore, MD 21231, USA. ²¹⁵Foundation Medicine, Inc, Cambridge, MA 02141, USA. ²¹⁶Department of Biomedical Data Science, Stanford University School of Medicine, Stanford, CA 94305, USA. ²¹⁷Department of Genetics, Stanford University School of Medicine, Stanford, CA 94305, USA. ²¹⁸Bakar Computational Health Sciences Institute and Department of Pediatrics, University of California, San Francisco, CA 94110, USA. ²¹⁹Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo 0315, Norway. ²²⁰National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA. ²²¹Royal Marsden NHS Foundation Trust, London and Sutton, Sutton SM2 5PT, UK. ²²²Department of Oncology, University of Cambridge, Cambridge CB2 1TN, UK. ²²³Li Ka Shing Centre, Cancer Research UK Cambridge Institute, University of Cambridge, Cambridge CB2 1TN, UK. ²²⁴Institut Gustave Roussy, 94800 Villejuif, France. ²²⁵Department of Haematology, University of Cambridge, Cambridge CB2 1TN, UK. ²²⁶Anatomia Patológica, Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona,

08007 Barcelona, Spain. ^{227c}Spanish Ministry of Science and Innovation, Madrid, Spain. ²²⁸University of Michigan Comprehensive Cancer Center, Ann Arbor, MI 48109, USA. ²²⁹Department for BioMedical Research, University of Bern, 3012 Bern, Switzerland. ²³⁰Department of Medical Oncology, Inselspital, University Hospital and University of Bern, 3012 Bern, Switzerland. ²³¹Graduate School for Cellular and Biomedical Sciences, University of Bern, 3012 Bern, Switzerland. ²³²University of Pavia, 27100 Pavia, Italy. ²³³University of Alabama at Birmingham, Birmingham, AL 35294, USA. ²³⁴UHN Program in BioSpecimen Sciences, Toronto General Hospital, Toronto, ON M5G 2C4, Canada. ²³⁵Department of Urology, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA. ²³⁶Centre for Law and Genetics, University of Tasmania, Sandy Bay Campus, Hobart, TAS 7005, Australia. ²³⁷Faculty of Biosciences, Heidelberg University, 69117 Heidelberg, Germany. ²³⁸Department of Biochemistry, Microbiology and Immunology, Faculty of Medicine, University of Ottawa, Ottawa, ON K1N 6N5, Canada. ²³⁹Division of Anatomic Pathology, Mayo Clinic, Rochester, MN 55905, USA. ²⁴⁰Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA. ²⁴¹Illawarra Shoalhaven Local Health District L3 Illawarra Cancer Care Centre, Wollongong Hospital, Wollongong, NSW 2500, Australia. ²⁴²BioForA, French National Institute for Agriculture, Food, and Environment (INRAE), ONF, Orléans, France. ²⁴³Department of Biostatistics, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD 21218, USA. ²⁴⁴University of California San Diego, San Diego, CA 92093, USA. ²⁴⁵Division of Experimental Pathology, Mayo Clinic, Rochester, MN 55905, USA. ²⁴⁶Centre for Cancer Research, The Westmead Institute for Medical Research, University of Sydney, Sydney, NSW 2006, Australia. ²⁴⁷Department of Gynaecological Oncology, Westmead Hospital, Sydney, NSW 2145, Australia. ²⁴⁸PDXen Biosystems Inc, Seoul, South Korea. ²⁴⁹Korea Advanced Institute of Science and Technology, Daejeon, South Korea. ²⁵⁰Electronics and Telecommunications Research Institute, Daejeon, South Korea. ²⁵¹Institut National du Cancer (INCA), Boulogne-Billancourt, France. ²⁵²Division of Medical Oncology, National Cancer Centre, Singapore 169610, Singapore. ²⁵³Medical Oncology, University and Hospital Trust of Verona, Verona 37129, Italy. ²⁵⁴Department of Pediatrics, University Hospital Schleswig-Holstein, 23562 Kiel, Germany. ²⁵⁵Hepatobiliary/Pancreatic Surgical Oncology Program, University Health Network, Toronto, ON M5G 1L7, Canada. ²⁵⁶School of Biological Sciences, University of Auckland, Auckland 1010, New Zealand. ²⁵⁷Department of Surgery, University of Melbourne, Parkville, VIC 3010, Australia. ²⁵⁸The Murdoch Children's Research Institute, Royal Children's Hospital, Parkville, VIC 3052, Australia. ²⁵⁹Walter and Eliza Hall Institute, Parkville, VIC 3052, Australia. ²⁶⁰Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, ON M5G 1X5, Canada. ²⁶¹University of East Anglia, Norwich NR4 7TJ, UK. ²⁶²Norfolk and Norwich University Hospital NHS Trust, Norwich NR4 7UY, UK. ²⁶³Victorian Institute of Forensic Medicine, Southbank, VIC 3006, Australia. ²⁶⁴Department of Biomedical Informatics, Harvard Medical School, Boston, MA 02115, USA. ²⁶⁵Department of Chemistry, Centre for Molecular Science Informatics, University of Cambridge, Cambridge CB2 1TN, UK. ²⁶⁶Ludwig Center at Harvard Medical School, Boston, MA 02115, USA. ²⁶⁷Peter MacCallum Cancer Centre, University of Melbourne, Melbourne, VIC 3010, Australia. ²⁶⁸Physics Division, Optimization and Systems Biology Lab, Massachusetts General Hospital, Boston, MA 02114, USA. ²⁶⁹Department of Medicine, Baylor College of Medicine, Houston, TX 77030, USA. ²⁷⁰University of Cologne, 50923 Cologne, Germany. ²⁷¹International Genomics Consortium, Phoenix, AZ 85004, USA. ²⁷²Genomics Research Program, Ontario Institute for Cancer Research, Toronto, ON M5G 0A3, Canada. ²⁷³Barking Havering and Redbridge University Hospitals NHS Trust, Romford, UK. ²⁷⁴Children's Hospital at Westmead, University of Sydney, Sydney, NSW 2006, Australia. ²⁷⁵Department of Medicine, Section of Endocrinology, University and Hospital Trust of Verona, 37129 Verona, Italy. ²⁷⁶Computational Biology Center, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA. ²⁷⁷Department of Biology, ETH Zurich, Zürich, Switzerland. ²⁷⁸Department of Computer Science, ETH Zurich, Zurich, Switzerland. ²⁷⁹SIB Swiss Institute of Bioinformatics, Lausanne, Switzerland. ²⁸⁰Weill Cornell Medical College, New York, NY 10021, USA. ²⁸¹Academic Department of Medical Genetics, University of Cambridge, Addenbrooke's Hospital, Cambridge CB2 1TN, UK. ²⁸²MRC Cancer Unit, University of Cambridge, Cambridge CB2 1TN, UK. ²⁸³Departments of Pediatrics and Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA. ²⁸⁴Seven Bridges Genomics, Charlestown, MA 02129, USA. ²⁸⁵Annai Systems, Inc, Carlsbad, CA 92013, USA. ²⁸⁶Department of Pathology, General Hospital of Treviso, Department of Medicine, University of Padua, 35122 Treviso, Italy. ²⁸⁷Department of Computational Biology, University of Lausanne, 1015 Lausanne, Switzerland. ²⁸⁸Department of Genetic Medicine and Development, University of Geneva Medical School, 1205 CH Geneva, Switzerland. ²⁸⁹Swiss Institute of Bioinformatics, University of Geneva, 1205 CH Geneva, Switzerland. ²⁹⁰The Francis Crick Institute, London NW1 1AT, UK. ²⁹¹University of Leuven, 3000 Leuven, Belgium. ²⁹²Computational and Systems Biology, Genome Institute of Singapore, Singapore 138672, Singapore. ²⁹³School of Computing, National University of Singapore, Singapore 119077, Singapore. ²⁹⁴Big Data Institute, Li Ka Shing Centre, University of Oxford, Oxford OX1 2JD, UK. ²⁹⁵The Edward S. Rogers Sr. Department of Electrical and Computer Engineering, University of Toronto, Toronto, ON M5S, Canada. ²⁹⁶Breast Cancer Translational Research Laboratory JC Heuson, Institut Jules Bordet, 1000 Brussels, Belgium. ²⁹⁷Department of Oncology, Laboratory for Translational Breast Cancer Research, KU Leuven, 3000 Leuven, Belgium. ²⁹⁸Institute for Research in Biomedicine (IRB Barcelona), The Barcelona Institute of Science and Technology, 08036 Barcelona, Spain. ²⁹⁹Research Program on Biomedical Informatics, Universitat Pompeu Fabra, 08002 Barcelona, Spain. ³⁰⁰Division of Medical Oncology, Princess Margaret Cancer Centre, Toronto, ON M5G 2C1, Canada. ³⁰¹Department of Physiology and Biophysics, Weill Cornell Medicine, New York, NY 10065, USA. ³⁰²Institute for Computational Biomedicine, Weill Cornell Medicine, New York, NY 10065, USA. ³⁰³Department of Pathology, UPMC Shadyside, Pittsburgh, PA 15232, USA. ³⁰⁴Independent Consultant, Wellesley, USA. ³⁰⁵Department of Cell and Molecular Biology, Science for Life Laboratory, Uppsala University, 752 36 Uppsala, Sweden. ³⁰⁶Hefei University of Technology, Anhui, China. ³⁰⁷Translational Cancer Research Unit, GZA Hospitals St.-Augustinus, Center for Oncological Research, Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp 2000, Belgium. ³⁰⁸University of Pennsylvania, Philadelphia, PA 19104, USA. ³⁰⁹The Wellcome Trust, London NW1 2BE, UK. ³¹⁰Department of Pathology, Queen Elizabeth University Hospital, Glasgow G51 4TF, UK. ³¹¹Department of Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, QLD 4006, Australia. ³¹²Department of Oncology, Centre for Cancer Genetic Epidemiology, University of Cambridge, Cambridge CB2 1TN, UK. ³¹³Department of Public Health and Primary Care, Centre for Cancer Genetic Epidemiology, University of Cambridge, Cambridge CB2 1TN, UK. ³¹⁴Prostate Cancer Canada, Toronto, ON M5C 1M1, Canada. ³¹⁵University of Cambridge, Cambridge CB2 1TN, UK. ³¹⁶Department of Laboratory Medicine, Translational Cancer Research, Lund University Cancer Center at Medicon Village, Lund University, Lund, Sweden. ³¹⁷CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, Spain. ³¹⁸Research Group on Statistics, Econometrics and Health (GRECS), UdG, Barcelona, Spain. ³¹⁹Quantitative Genomics Laboratories (qGenomics), Barcelona, Spain. ³²⁰Icelandic Cancer Registry, Icelandic Cancer Society, Reykjavik, Iceland. ³²¹State Key Laboratory of Cancer Biology, and Xijing Hospital of Digestive Diseases, Fourth Military Medical University, Shaanxi, China. ³²²Department of Medicine (DIMED), Surgical Pathology Unit, University of Padua, 35122 Padua, Italy. ³²³Department of Cancer Biology, Dana-Farber Cancer Institute, Boston, MA 02215, USA. ³²⁴Rigshospitalet, Copenhagen, Denmark. ³²⁵Center for Cancer Genomics, National Cancer Institute, National Institutes of Health, Bethesda, MD 20814, USA. ³²⁶Department of Biochemistry and Molecular Medicine, University of Montreal, Montreal, QC H3T 1J4, Canada. ³²⁷Australian Institute of Tropical Health and Medicine, James Cook University, Douglas, QLD 4811, Australia. ³²⁸Department of Neuro-Oncology, Istituto Neurologico Besta, Milano, Italy. ³²⁹Bioplatforms Australia, North Ryde, NSW, Australia. ³³⁰Department of Pathology (Research), University College London Cancer Institute, London WC1E 6DD, UK. ³³¹Department of Surgical Oncology, Princess Margaret Cancer Centre, Toronto, ON M5G 2C1, Canada. ³³²Department of Medical Oncology, Josephine Nefkens Institute and Cancer Genomics Centre, Erasmus Medical Center, 3015 GD Rotterdam, The Netherlands. ³³³The University of Queensland Thoracic Research Centre, The Prince Charles Hospital, Brisbane, QLD 4032, Australia. ³³⁴CIBIO/InBIO-Research Center in Biodiversity and Genetic Resources, Universidade do Porto, 4099-002 Vairão, Portugal. ³³⁵HCA Laboratories,

London, UK. ³³⁶University of Liverpool, Liverpool L69 3BX, UK. ³³⁷The Azrieli Faculty of Medicine, Bar-Ilan University, Safed 5290002, Israel. ³³⁸Department of Neurosurgery, University of Florida, Gainesville, FL 32611, USA. ³³⁹Department of Pathology, Graduate School of Medicine, University of Tokyo, Tokyo 113-8654, Japan. ³⁴⁰National Genotyping Center, Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan. ³⁴¹University of Milano Bicocca, Monza 20126, Italy. ³⁴²Department of Pathology, Oslo University Hospital Ullevål, 0450 Oslo, Norway. ³⁴³Center for Biomedical Informatics, Harvard Medical School, Boston, MA 02115, USA. ³⁴⁴Office of Cancer Genomics, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA. ³⁴⁵Cancer Epigenomics, German Cancer Research Center (DKFZ), 69120 Heidelberg, Germany. ³⁴⁶Department of Cancer Biology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA. ³⁴⁷Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA. ³⁴⁸Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA. ³⁴⁹Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN 55905, USA. ³⁵⁰University of Sydney, Sydney, NSW 2006, Australia. ³⁵¹University of Oxford, Oxford OX1 2JD, UK. ³⁵²Cambridge University Hospitals NHS Foundation Trust, Cambridge CB2 0QQ, UK. ³⁵³Department of Surgery, Academic Urology Group, University of Cambridge, Cambridge CB2 0QQ, UK. ³⁵⁴Department of Medicine II, University of Würzburg, 97070 Würzburg, Germany. ³⁵⁵Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL 33146, USA. ³⁵⁶Institut Hospital del Mar d'Investigacions Mèdiques (IMIM), Barcelona, Spain. ³⁵⁷Genome Integrity and Structural Biology Laboratory, National Institute of Environmental Health Sciences (NIEHS), Durham, NC 27709, USA. ³⁵⁸St. Thomas's Hospital, London SE1 7EH, UK. ³⁵⁹Osaka International Cancer Center, Osaka, Japan. ³⁶⁰Department of Pathology, Skåne University Hospital, Lund University, Lund, Sweden. ³⁶¹Department of Medical Oncology, Beatson West of Scotland Cancer Centre, Glasgow G12 0YN, UK. ³⁶²Centre for Cancer Research, Victorian Comprehensive Cancer Centre, University of Melbourne, Melbourne, VIC 3010, Australia. ³⁶³Department of Medicine, Section of Hematology/Oncology, University of Chicago, Chicago, IL 60637, USA. ³⁶⁴German Center for Infection Research (DZIF), Partner Site Hamburg-Borstel-Lübeck-Riems, Hamburg, Germany. ³⁶⁵Department of Biotechnology, Ministry of Science and Technology, Government of India, New Delhi, Delhi 110016, India. ³⁶⁶National Cancer Centre Singapore, Singapore 169610, Singapore. ³⁶⁷Brandeis University, Waltham, MA 02453, USA. ³⁶⁸Department of Internal Medicine, Stanford University, Stanford, CA 94305, USA. ³⁶⁹The University of Texas Health Science Center at Houston, Houston, TX 77030, USA. ³⁷⁰Imperial College NHS Trust, Imperial College, London, INY SW7 2BU, UK. ³⁷¹Senckenberg Institute of Pathology, University of Frankfurt Medical School, 60323 Frankfurt, Germany. ³⁷²Department of Medicine, Division of Biomedical Informatics, UC San Diego School of Medicine, San Diego, CA 92093, USA. ³⁷³Center for Precision Health, School of Biomedical Informatics, The University of Texas Health Science Center, Houston, TX 77030, USA. ³⁷⁴Oxford Nanopore Technologies, New York, NY OX4 4DQ, USA. ³⁷⁵Institute of Medical Science, University of Tokyo, Tokyo 113-8654, Japan. ³⁷⁶Wakayama Medical University, Wakayama 641-8510, Japan. ³⁷⁷Department of Internal Medicine, Division of Medical Oncology, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA. ³⁷⁸University of Tennessee Health Science Center for Cancer Research, Memphis, TN 38163, USA. ³⁷⁹Department of Histopathology, Salford Royal NHS Foundation Trust, Salford M6 8HD, UK. ³⁸⁰Faculty of Biology, Medicine and Health, University of Manchester, Manchester M13 9PL, UK. ³⁸¹Peking University, 100871 Beijing, China. ³⁸²Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA. ³⁸³Karolinska Institute, 171 77 Stockholm, Sweden. ³⁸⁴The Donnelly Centre, University of Toronto, Toronto, ON M5S, Canada. ³⁸⁵Department of Medical Genetics, College of Medicine, Hallym University, Chuncheon, South Korea. ³⁸⁶Department of Experimental and Health Sciences, Institute of Evolutionary Biology (UPF-CSIC), Universitat Pompeu Fabra, 08002 Barcelona, Spain. ³⁸⁷Health Data Science Unit, University Clinics, Heidelberg, Germany. ³⁸⁸Hokkaido University, Sapporo 060-0808, Japan. ³⁸⁹Department of Pathology and Clinical Laboratory, National Cancer Center Hospital, Tokyo 104-0045, Japan. ³⁹⁰Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA. ³⁹¹Computational Biology, Leibniz Institute on Aging-Fritz Lipmann Institute (FLI), 07745 Jena, Germany. ³⁹²University of Melbourne Centre for Cancer Research, Melbourne, VIC 3010, Australia. ³⁹³University of Nebraska Medical Center, Omaha, NE 68198, USA. ³⁹⁴Syntekabio Inc, Daejeon, South Korea. ³⁹⁵Department of Pathology, Academic Medical Center, Amsterdam, 1105 AZ, The Netherlands. ³⁹⁶China National GeneBank-Shenzhen, Shenzhen, China. ³⁹⁷Division of Molecular Genetics, German Cancer Research Center (DKFZ), 69120 Heidelberg, Germany. ³⁹⁸Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA. ³⁹⁹AbbVie, North Chicago, IL 60064, USA. ⁴⁰⁰Institute of Pathology, Charité - University Medicine Berlin, Berlin, Germany. ⁴⁰¹Centre for Translational and Applied Genomics, British Columbia Cancer Agency, Vancouver, BC V8R 6V5, Canada. ⁴⁰²Edinburgh Royal Infirmary, Edinburgh EH16 4SA, UK. ⁴⁰³Berlin Institute for Medical Systems Biology, Max Delbrück Center for Molecular Medicine, 13125 Berlin, Germany. ⁴⁰⁴Department of Pediatric Immunology, Hematology and Oncology, University Hospital, Heidelberg, 69120 Heidelberg, Germany. ⁴⁰⁵German Cancer Research Center (DKFZ), 69120 Heidelberg, Germany. ⁴⁰⁶Heidelberg Institute for Stem Cell Technology and Experimental Medicine (HI-STEM), 69120 Heidelberg, Germany. ⁴⁰⁷Institute for Computational Biomedicine, Weill Cornell Medical College, New York, NY 10021, USA. ⁴⁰⁸New York Genome Center, New York, NY 10013, USA. ⁴⁰⁹Department of Urology, James Buchanan Brady Urological Institute, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA. ⁴¹⁰Department of Preventive Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo 113-8654, Japan. ⁴¹¹Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, TX 77030, USA. ⁴¹²Department of Pathology and Immunology, Baylor College of Medicine, Houston, TX 77030, USA. ⁴¹³Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX 77030, USA. ⁴¹⁴Technical University of Denmark, 2800 Lyngby, Denmark. ⁴¹⁵Department of Pathology, College of Medicine, Hanyang University, Seoul, South Korea. ⁴¹⁶Academic Unit of Surgery, School of Medicine, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow Royal Infirmary, Glasgow G12 8QQ, UK. ⁴¹⁷Department of Pathology, Asan Medical Center, College of Medicine, Ulsan University, Songpa-gu, Seoul, South Korea. ⁴¹⁸Science Writer, Garrett Park, MD, USA. ⁴¹⁹International Cancer Genome Consortium (ICGC)/ICGC Accelerating Research in Genomic Oncology (ARGO) Secretariat, Ontario Institute for Cancer Research, Toronto, ON M5G 0A3, Canada. ⁴²⁰University of Ljubljana, 1000 Ljubljana, Slovenia. ⁴²¹Department of Public Health Sciences, University of Chicago, Chicago, IL 60637, USA. ⁴²²Research Institute, NorthShore University HealthSystem, Evanston, IL 60201, USA. ⁴²³Department for Biomedical Research, University of Bern, Bern 3012, Switzerland. ⁴²⁴Centre of Genomics and Policy, McGill University and Génome Québec Innovation Centre, Montreal, QC H3A 0G4, Canada. ⁴²⁵Carolina Center for Genome Sciences, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA. ⁴²⁶Hopp Children's Cancer Center (KiTZ), Heidelberg, Germany. ⁴²⁷Pediatric Glioma Research Group, German Cancer Research Center (DKFZ), 69120 Heidelberg, Germany. ⁴²⁸Cancer Research UK, London NG34 7SY, UK. ⁴²⁹Indivumed GmbH, Hamburg, Germany. ⁴³⁰University Hospital Zurich, 8091 Zurich, Switzerland. ⁴³¹Clinical Bioinformatics, Swiss Institute of Bioinformatics, 1015 Geneva, Switzerland. ⁴³²Institute for Pathology and Molecular Pathology, University Hospital Zurich, 8091 Zurich, Switzerland. ⁴³³Institute of Molecular Life Sciences, University of Zurich, 8091 Zurich, Switzerland. ⁴³⁴MRC Human Genetics Unit, MRC IGMM, University of Edinburgh, Edinburgh EH8 9YL, UK. ⁴³⁵Women's Cancer Program at the Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA. ⁴³⁶Department of Biology, Bioinformatics Group, Division of Molecular Biology, Faculty of Science, University of Zagreb, 10000 Zagreb, Croatia. ⁴³⁷Department for Internal Medicine II, University Hospital Schleswig-Holstein, 23562 Kiel, Germany. ⁴³⁸Genetics and Molecular Pathology, SA Pathology, Adelaide, SA 5011, Australia. ⁴³⁹Department of Gastric Surgery, National Cancer Center Hospital, Tokyo, Japan. ⁴⁴⁰Department of Bioinformatics, Division of Cancer Genomics, National Cancer Center Research Institute, Tokyo, Japan. ⁴⁴¹A.A. Kharkevich Institute of Information Transmission Problems, Moscow, Russia. ⁴⁴²Oncology and Immunology, Dmitry Rogachev National Research Center of Pediatric Hematology, Moscow, Russia. ⁴⁴³Skolkovo Institute of Science and Technology, Moscow, Russia. ⁴⁴⁴Department of Surgery, The George Washington

University, School of Medicine and Health Science, Washington, DC 20052, USA. ⁴⁴⁵Endocrine Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA. ⁴⁴⁶Melanoma Institute Australia, Macquarie University, Sydney, NSW 2109, Australia. ⁴⁴⁷MIT Computer Science and Artificial Intelligence Laboratory, Massachusetts Institute of Technology, Cambridge, MA 02139, USA. ⁴⁴⁸Tissue Pathology and Diagnostic Oncology, Royal Prince Alfred Hospital, Sydney, NSW 2050, Australia. ⁴⁴⁹Cholangiocarcinoma Screening and Care Program and Liver Fluke and Cholangiocarcinoma Research Centre, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand. ⁴⁵⁰Controlled Department and Institution, New York, NY, USA. ⁴⁵¹Englander Institute for Precision Medicine, Weill Cornell Medicine, New York, NY 10065, USA. ⁴⁵²National Cancer Center, Gyeonggi, South Korea. ⁴⁵³Health Sciences Department of Biomedical Informatics, University of California San Diego, La Jolla, CA 92093, USA. ⁴⁵⁴Research Core Center, National Cancer Centre Korea, Goyang-si, South Korea. ⁴⁵⁵Department of Health Sciences and Technology, Sungkyunkwan University School of Medicine, Seoul, South Korea. ⁴⁵⁶Samsung Genome Institute, Seoul, South Korea. ⁴⁵⁷Breast Oncology Program, Dana-Farber/Brigham and Women's Cancer Center, Boston, MA 02215, USA. ⁴⁵⁸Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA. ⁴⁵⁹Division of Breast Surgery, Brigham and Women's Hospital, Boston, MA 02115, USA. ⁴⁶⁰Integrative Bioinformatics Support Group, National Institute of Environmental Health Sciences (NIEHS), Durham, NC 27709, USA. ⁴⁶¹Department of Clinical Science, University of Bergen, 5007 Bergen, Norway. ⁴⁶²Center For Medical Innovation, Seoul National University Hospital, Seoul, South Korea. ⁴⁶³Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea. ⁴⁶⁴Institute of Computer Science, Polish Academy of Sciences, Warsaw, Poland. ⁴⁶⁵Functional and Structural Genomics, German Cancer Research Center (DKFZ), 69120 Heidelberg, Germany. ⁴⁶⁶Laboratory of Translational Genomics, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA. ⁴⁶⁷Institute for Medical Informatics Statistics and Epidemiology, University of Leipzig, 04109 Leipzig, Germany. ⁴⁶⁸Morgan Welch Inflammatory Breast Cancer Research Program and Clinic, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA. ⁴⁶⁹Department of Hematology and Oncology, Georg-Augusts-University of Göttingen, 37073 Göttingen, Germany. ⁴⁷⁰Institute of Cell Biology (Cancer Research), University of Duisburg-Essen, 47057 Essen, Germany. ⁴⁷¹King's College London and Guy's and St. Thomas' NHS Foundation Trust, London WC2R 2LS, UK. ⁴⁷²Center for Epigenetics, Van Andel Research Institute, Grand Rapids, MI 49503, USA. ⁴⁷³The University of Queensland Centre for Clinical Research, Royal Brisbane and Women's Hospital, Herston, QLD 4029, Australia. ⁴⁷⁴Department of Pediatric Oncology and Hematology, University of Cologne, 50923 Cologne, Germany. ⁴⁷⁵University of Düsseldorf, 40225 Düsseldorf, Germany. ⁴⁷⁶Department of Pathology, Institut Jules Bordet, Brussels 1000, Belgium. ⁴⁷⁷Institute of Biomedicine, Sahlgrenska Academy at University of Gothenburg, 413 90 Gothenburg, Sweden. ⁴⁷⁸Children's Medical Research Institute, Sydney, NSW 2145, Australia. ⁴⁷⁹ILSbio, LLC Biobank, Chestertown, MD, USA. ⁴⁸⁰Division of Genetics and Genomics, Boston Children's Hospital, Harvard Medical School, Boston, MA 02115, USA. ⁴⁸¹Institute for Bioengineering and Biopharmaceutical Research (IBBR), Hanyang University, Seoul, South Korea. ⁴⁸²Department of Statistics, University of California Santa Cruz, Santa Cruz, CA 95064, USA. ⁴⁸³Department of Vertebrate Genomics/Otto Warburg Laboratory Gene Regulation and Systems Biology of Cancer, Max Planck Institute for Molecular Genetics, 14195 Berlin, Germany. ⁴⁸⁴McGill University and Genome Quebec Innovation Centre, Montreal, QC H3A 0G4, Canada. ⁴⁸⁵Gynecologic Oncology, NYU Laura and Isaac Perlmutter Cancer Center, New York University, New York, NY 10003, USA. ⁴⁸⁶Division of Oncology, Stem Cell Biology Section, Washington University School of Medicine, St. Louis, MO 63110, USA. ⁴⁸⁷Harvard University, Cambridge, MA 02138, USA. ⁴⁸⁸Urologic Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA. ⁴⁸⁹University of Oslo, 0315 Oslo, Norway. ⁴⁹⁰University of Toronto, Toronto, ON M5S, Canada. ⁴⁹¹School of Life Sciences, Peking University, Beijing, China. ⁴⁹²Leidos Biomedical Research, Inc, McLean, VA, USA. ⁴⁹³Hematology, Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, 08007 Barcelona, Spain. ⁴⁹⁴Second Military Medical University, Shanghai, China. ⁴⁹⁵Chinese Cancer Genome Consortium, Shenzhen, China. ⁴⁹⁶Department of Medical Oncology, Beijing Hospital, Beijing, China. ⁴⁹⁷Laboratory of Molecular Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital and Institute, Beijing, China. ⁴⁹⁸School of Medicine/School of Mathematics and Statistics, University of St. Andrews, St. Andrews, Fife KY16 9AJ, UK. ⁴⁹⁹Department of Biochemistry and Molecular Biology, Faculty of Medicine, University Institute of Oncology-IUOPA, Oviedo, Spain. ⁵⁰⁰Institut Bergonié, Bordeaux, France. ⁵⁰¹Cancer Unit, MRC University of Cambridge, Cambridge CB2 1TN, UK. ⁵⁰²Department of Pathology and Laboratory Medicine, Center for Personalized Medicine, Children's Hospital Los Angeles, Los Angeles, CA 90027, USA. ⁵⁰³John Curtin School of Medical Research, Canberra, ACT 2601, Australia. ⁵⁰⁴MVZ Department of Oncology, PraxisClinic am Johannisplatz, Leipzig, Germany. ⁵⁰⁵Department of Information Technology, Ghent University, Ghent, Belgium. ⁵⁰⁶Department of Plant Biotechnology and Bioinformatics, Ghent University, Ghent, Belgium. ⁵⁰⁷Institute for Genetic Medicine, Nationwide Children's Hospital, Columbus, OH 43205, USA. ⁵⁰⁸Department of Surgery, Duke University, Durham, NC 27708, USA. ⁵⁰⁹Institut Català de Paleontologia Miquel Crusafont, Universitat Autònoma de Barcelona, Barcelona, Spain. ⁵¹⁰University of Glasgow, Glasgow G12 8QQ, UK. ⁵¹¹Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain. ⁵¹²Department of Surgery and Cancer, Imperial College, London, INY SW7 2BU, UK. ⁵¹³Applications Department, Oxford Nanopore Technologies, Oxford OX4 4DQ, UK. ⁵¹⁴Department of Obstetrics, Gynecology and Reproductive Services, University of California San Francisco, San Francisco, CA 94110, USA. ⁵¹⁵Department of Biochemistry and Molecular Medicine, University California at Davis, Sacramento, CA 95616, USA. ⁵¹⁶STARR Innovation Facility, Princess Margaret Cancer Centre, Toronto, ON M5G 2C1, Canada. ⁵¹⁷Discipline of Surgery, Western Sydney University, Penrith, NSW 2150, Australia. ⁵¹⁸Department of Genetics, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA. ⁵¹⁹Departments of Neurology and Neurosurgery, Henry Ford Hospital, Detroit, MI 48202, USA. ⁵²⁰Institute of Pathology, University Medical Center Hamburg-Eppendorf, 20251 Hamburg, Germany. ⁵²¹Department of Health Sciences, Faculty of Medical Sciences, Kyushu University, Fukuoka, Japan. ⁵²²Heidelberg Academy of Sciences and Humanities, Heidelberg, Germany. ⁵²³Department of Clinical Pathology, University of Melbourne, Melbourne, VIC 3010, Australia. ⁵²⁴Department of Pathology, Roswell Park Cancer Institute, Buffalo, NY 14203, USA. ⁵²⁵Department of Computer Science, University of Helsinki, 00100 Helsinki, Finland. ⁵²⁶Institute of Biotechnology, University of Helsinki, 00100 Helsinki, Finland. ⁵²⁷Organismal and Evolutionary Biology Research Programme, University of Helsinki, 00100 Helsinki, Finland. ⁵²⁸Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Washington University School of Medicine, St. Louis, MO 63110, USA. ⁵²⁹Penrose St. Francis Health Services, Colorado Springs, CO 80923, USA. ⁵³⁰Institute of Pathology, Ulm University and University Hospital of Ulm, Ulm 89081, Germany. ⁵³¹National Cancer Center, Tokyo, Japan. ⁵³²Genome Institute of Singapore, Singapore 138672, Singapore. ⁵³³German Cancer Aid, Bonn, Germany. ⁵³⁴Programme in Cancer and Stem Cell Biology, Centre for Computational Biology, Duke-NUS Medical School, 169857 Singapore, Singapore. ⁵³⁵The Chinese University of Hong Kong, Shatin, NT, Hong Kong, China. ⁵³⁶Fourth Military Medical University, Shaanxi, China. ⁵³⁷The University of Cambridge School of Clinical Medicine, Cambridge CB2 1TN, UK. ⁵³⁸St. Jude Children's Research Hospital, Memphis, TN 38105, USA. ⁵³⁹University Health Network, Princess Margaret Cancer Centre, Toronto, ON M5G 1L7, Canada. ⁵⁴⁰Center for Biomolecular Science and Engineering, University of California Santa Cruz, Santa Cruz, CA 95064, USA. ⁵⁴¹Department of Medicine, University of Chicago, Chicago, IL 60637, USA. ⁵⁴²Department of Neurology, Mayo Clinic, Rochester, MN 55905, USA. ⁵⁴³Cambridge Oesophago-gastric Centre, Cambridge University Hospitals NHS Foundation Trust, Cambridge CB2 0QQ, UK. ⁵⁴⁴Department of Computer Science, Carleton College, Northfield, MN 55057, USA. ⁵⁴⁵Institute of Cancer Sciences, College of Medical Veterinary and Life Sciences, University of Glasgow, Glasgow G12 8QQ, UK. ⁵⁴⁶Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL 35294, USA. ⁵⁴⁷HudsonAlpha Institute for Biotechnology, Huntsville, AL

35806, USA. ⁵⁴⁸O'Neal Comprehensive Cancer Center, University of Alabama at Birmingham, Birmingham, AL 35294, USA. ⁵⁴⁹Department of Pathology, Keio University School of Medicine, Tokyo, Japan. ⁵⁵⁰Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Tokyo, Japan. ⁵⁵¹Sage Bionetworks, Seattle, WA, USA. ⁵⁵²Lymphoma Genomic Translational Research Laboratory, National Cancer Centre, Singapore 98121, Singapore. ⁵⁵³Department of Clinical Pathology, Robert-Bosch-Hospital, 70376 Stuttgart, Germany. ⁵⁵⁴Department of Cell and Systems Biology, University of Toronto, Toronto, ON M5S, Canada. ⁵⁵⁵Department of Biosciences and Nutrition, Karolinska Institutet, 171 77 Stockholm, Sweden. ⁵⁵⁶Center for Liver Cancer, Research Institute and Hospital, National Cancer Center, Gyeonggi, South Korea. ⁵⁵⁷Division of Hematology-Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea. ⁵⁵⁸Samsung Advanced Institute for Health Sciences and Technology, Sungkyunkwan University School of Medicine, Seoul, South Korea. ⁵⁵⁹Cheonan Industry-Academic Collaboration Foundation, Sangmyung University, Cheonan, South Korea. ⁵⁶⁰NYU Langone Medical Center, New York, NY 10016, USA. ⁵⁶¹Department of Hematology and Medical Oncology, Cleveland Clinic, Cleveland, OH 44195, USA. ⁵⁶²Department of Health Sciences Research, Mayo Clinic, Rochester, MN 55905, USA. ⁵⁶³Helen F. Graham Cancer Center at Christiana Care Health Systems, Newark, DE 19713, USA. ⁵⁶⁴Heidelberg University Hospital, 69120 Heidelberg, Germany. ⁵⁶⁵CSRA Incorporated, Fairfax, VA, USA. ⁵⁶⁶Research Department of Pathology, University College London Cancer Institute, London WC1E 6DD, UK. ⁵⁶⁷Department of Research Oncology, Guy's Hospital, King's Health Partners AHSC, King's College London School of Medicine, London WC2R 2LS, UK. ⁵⁶⁸Faculty of Medicine and Health Sciences, Macquarie University, Sydney, NSW 2109, Australia. ⁵⁶⁹University Hospital of Minjoo, INSERM UMR 1098, Besançon, France. ⁵⁷⁰Spanish National Cancer Research Centre, Madrid 28029, Spain. ⁵⁷¹Center of Digestive Diseases and Liver Transplantation, Fundeni Clinical Institute, Bucharest, Romania. ⁵⁷²Cureline, Inc, South San Francisco, CA, USA. ⁵⁷³St. Luke's Cancer Centre, Royal Surrey County Hospital NHS Foundation Trust, Guildford, UK. ⁵⁷⁴Cambridge Breast Unit, Addenbrooke's Hospital, Cambridge University Hospital NHS Foundation Trust and NIHR Cambridge Biomedical Research Centre, Cambridge CB2 0QQ, UK. ⁵⁷⁵East of Scotland Breast Service, Ninewells Hospital, Aberdeen, UK. ⁵⁷⁶Department of Genetics, Microbiology and Statistics, University of Barcelona, IRSJD, IBUB, Barcelona, Spain. ⁵⁷⁷Department of Obstetrics and Gynecology, Medical College of Wisconsin, Milwaukee, WI 53226, USA. ⁵⁷⁸Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, GA 30322, USA. ⁵⁷⁹Department of Computer Science, Princeton University, Princeton, NJ 08544, USA. ⁵⁸⁰Vanderbilt Ingram Cancer Center, Vanderbilt University, Nashville, TN 37235, USA. ⁵⁸¹Ohio State University College of Medicine and Arthur G. James Comprehensive Cancer Center, Columbus, OH 43210, USA. ⁵⁸²Department of Surgery, Yokohama City University Graduate School of Medicine, Kanagawa 236-0027, Japan. ⁵⁸³Research Computing Center, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA. ⁵⁸⁴School of Molecular Biosciences and Center for Reproductive Biology, Washington State University, Pullman, WA 99163, USA. ⁵⁸⁵Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON M5S, Canada. ⁵⁸⁶Department of Pathology, Human Oncology and Pathogenesis Program, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA. ⁵⁸⁷University Hospital Giessen, Pediatric Hematology and Oncology, Giessen, Germany. ⁵⁸⁸Oncologie Séniologie, ICM Institut Régional du Cancer, Montpellier, France. ⁵⁸⁹Institute of Clinical Molecular Biology, Christian-Albrechts-University, Kiel, Germany. ⁵⁹⁰Institute of Pathology, University of Wuerzburg, 97070 Wuerzburg, Germany. ⁵⁹¹Department of Urology, North Bristol NHS Trust, Bristol, UK. ⁵⁹²SingHealth, Duke-NUS Institute of Precision Medicine, National Heart Centre Singapore, Singapore 169609, Singapore. ⁵⁹³Bern Center for Precision Medicine, University Hospital of Bern, University of Bern, Bern 3012, Switzerland. ⁵⁹⁴Englander Institute for Precision Medicine, Weill Cornell Medicine and New York Presbyterian Hospital, New York, NY 10065, USA. ⁵⁹⁵Meyer Cancer Center, Weill Cornell Medicine, New York, NY 10065, USA. ⁵⁹⁶Pathology and Laboratory, Weill Cornell Medical College, New York, NY 10065, USA. ⁵⁹⁷Vall d'Hebron Institute of Oncology: VHIO, Barcelona, Spain. ⁵⁹⁸General and Hepatobiliary-Biliary Surgery, Pancreas Institute, University and Hospital Trust of Verona, Verona, Italy. ⁵⁹⁹National Centre for Biological Sciences, Tata Institute of Fundamental Research, Bangalore 560065, India. ⁶⁰⁰Department of Pathology, GZA-ZNA Hospitals, Antwerp, Belgium. ⁶⁰¹Analytical Biological Services, Inc, Wilmington, DE 19801, USA. ⁶⁰²Sydney Medical School, University of Sydney, Sydney, NSW 2050, Australia. ⁶⁰³Bio Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA 02115, USA. ⁶⁰⁴Department of Cell Biology, Harvard Medical School, Boston, MA 02115, USA. ⁶⁰⁵Advanced Centre for Treatment Research and Education in Cancer, Tata Memorial Centre, Navi Mumbai, Maharashtra 400012, India. ⁶⁰⁶School of Environmental and Life Sciences, Faculty of Science, The University of Newcastle, Ourimbah, NSW 2308, Australia. ⁶⁰⁷Department of Dermatology, University Hospital of Essen, 45147 Essen, Germany. ⁶⁰⁸Martini-Clinic, Prostate Cancer Center, University Medical Center Hamburg-Eppendorf, 20251 Hamburg, Germany. ⁶⁰⁹Department of General Internal Medicine, University of Kiel, 24118 Kiel, Germany. ⁶¹⁰German Cancer Consortium (DKTK), Partner site Berlin, Berlin, Germany. ⁶¹¹Cancer Research Institute, Beth Israel Deaconess Medical Center, Boston, MA 02215, USA. ⁶¹²University of Pittsburgh, Pittsburgh, PA 15260, USA. ⁶¹³Department of Ophthalmology and Ocular Genomics Institute, Massachusetts Eye and Ear, Harvard Medical School, Boston, MA 02115, USA. ⁶¹⁴Center for Psychiatric Genetics, NorthShore University HealthSystem, Evanston, IL 60031, USA. ⁶¹⁵Van Andel Research Institute, Grand Rapids, MI 49503, USA. ⁶¹⁶Laboratory of Molecular Medicine, Human Genome Center, Institute of Medical Science, University of Tokyo, Tokyo, Japan. ⁶¹⁷Japan Agency for Medical Research and Development, Tokyo, Japan. ⁶¹⁸Korea University, Seoul, South Korea. ⁶¹⁹Murtha Cancer Center, Walter Reed National Military Medical Center, Bethesda, MD 20814, USA. ⁶²⁰Human Genetics, University of Kiel, 24118 Kiel, Germany. ⁶²¹Department of Oncologic Pathology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA 02115, USA. ⁶²²Oregon Health and Science University, Portland, OR 97239, USA. ⁶²³Center for RNA Interference and Noncoding RNA, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA. ⁶²⁴Department of Experimental Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA. ⁶²⁵Department of Gynecologic Oncology and Reproductive Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA. ⁶²⁶University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK. ⁶²⁷Department of Radiation Oncology, Radboud University Nijmegen Medical Centre, Nijmegen 6525 GA, The Netherlands. ⁶²⁸Institute for Genomics and Systems Biology, University of Chicago, Chicago, IL, USA. ⁶²⁹Clinic for Hematology and Oncology, St.-Antonius-Hospital, 60637 Eschweiler, Germany. ⁶³⁰Computational and Systems Biology Program, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA. ⁶³¹University of Iceland, Reykjavik, Iceland. ⁶³²Division of Computational Genomics and Systems Genetics, German Cancer Research Center (DKFZ), Heidelberg, Germany. ⁶³³Dundee Cancer Centre, Ninewells Hospital, Dundee, UK. ⁶³⁴Department for Internal Medicine III, University of Ulm and University Hospital of Ulm, Ulm, Germany. ⁶³⁵Institut Curie, INSERM Unit 830, Paris, France. ⁶³⁶Department of Gastroenterology and Hepatology, Yokohama City University Graduate School of Medicine, Kanagawa, Japan. ⁶³⁷Department of Laboratory Medicine, Radboud University Nijmegen Medical Centre, Nijmegen 6525 GA, The Netherlands. ⁶³⁸Division of Cancer Genome Research, German Cancer Research Center (DKFZ), Heidelberg, Germany. ⁶³⁹Department of General Surgery, Singapore General Hospital, Singapore, Singapore. ⁶⁴⁰Cancer Science Institute of Singapore, National University of Singapore, Singapore, Singapore. ⁶⁴¹Department of Medical and Clinical Genetics, Genome-Scale Biology Research Program, University of Helsinki, Helsinki, Finland. ⁶⁴²East Anglian Medical Genetics Service, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK. ⁶⁴³Irving Institute for Cancer Dynamics, Columbia University, New York, NY 10027, USA. ⁶⁴⁴Institute of Molecular and Cell Biology, Singapore, Singapore. ⁶⁴⁵Laboratory of Cancer Epigenome, Division of Medical Science, National Cancer Centre Singapore, Singapore, Singapore. ⁶⁴⁶Universite Lyon, INCa-Synergie, Centre Léon Bérard, Lyon, France. ⁶⁴⁷Department of Urology, Mayo Clinic, Rochester, MN 55905, USA. ⁶⁴⁸Royal National Orthopaedic Hospital-Stanmore, Stanmore, Middlesex, UK. ⁶⁴⁹Giovanni Paolo II / I.R.C.C.S. Cancer Institute, Bari, BA, Italy. ⁶⁵⁰Neuroblastoma Genomics, German Cancer Research Center (DKFZ), Heidelberg, Germany. ⁶⁵¹Fondazione Policlinico Universitario Gemelli IRCCS, Rome, Italy, Rome, Italy. ⁶⁵²University

of Verona, Verona, Italy. ⁶⁵³Centre National de Génotypage, CEA-Institute de Génomique, Evry, France. ⁶⁵⁴CAPHRI Research School, Maastricht University, Maastricht, ER, The Netherlands. ⁶⁵⁵Department of Biopathology, Centre Léon Bérard, Lyon, France. ⁶⁵⁶Université Claude Bernard Lyon 1, Villeurbanne, France. ⁶⁵⁷Core Research for Evolutional Science and Technology (CREST), JST, Tokyo, Japan. ⁶⁵⁸Department of Biological Sciences, Laboratory for Medical Science Mathematics, Graduate School of Science, University of Tokyo, Yokohama, Japan. ⁶⁵⁹Department of Medical Science Mathematics, Medical Research Institute, Tokyo Medical and Dental University (TMDU), Tokyo, Japan. ⁶⁶⁰University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK. ⁶⁶¹Centre for Cancer Research and Cell Biology, Queen's University, Belfast, UK. ⁶⁶²Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA. ⁶⁶³Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA. ⁶⁶⁴Department of Oncology-Pathology, Science for Life Laboratory, Karolinska Institute, 171 77 Stockholm, Sweden. ⁶⁶⁵School of Cancer Sciences, Faculty of Medicine, University of Southampton, Southampton, UK. ⁶⁶⁶Department of Gene Technology, Tallinn University of Technology, Tallinn, Estonia. ⁶⁶⁷Genetics and Genome Biology Program, SickKids Research Institute, The Hospital for Sick Children, Toronto, ON M5G 1X8, Canada. ⁶⁶⁸Departments of Neurosurgery and Hematology and Medical Oncology, Winship Cancer Institute and School of Medicine, Emory University, Atlanta, GA 30322, USA. ⁶⁶⁹Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway. ⁶⁷⁰Argmix Consulting, North Vancouver, BC, Canada. ⁶⁷¹Department of Information Technology, Ghent University, Interuniversitair Micro-Electronica Centrum (IMEC), Ghent, Belgium. ⁶⁷²Nuffield Department of Surgical Sciences, John Radcliffe Hospital, University of Oxford, Oxford OX1 2JD, UK. ⁶⁷³Institute of Mathematics and Computer Science, University of Latvia, Riga, LV 1586, Latvia. ⁶⁷⁴Discipline of Pathology, Sydney Medical School, University of Sydney, Sydney, NSW 2006, Australia. ⁶⁷⁵Department of Applied Mathematics and Theoretical Physics, Centre for Mathematical Sciences, University of Cambridge, Cambridge 10027, UK. ⁶⁷⁶Department of Statistics, Columbia University, New York, NY, USA. ⁶⁷⁷Department of Immunology, Genetics and Pathology, Science for Life Laboratory, Uppsala University, 752 36 Uppsala, Sweden. ⁶⁷⁸Department of Histopathology, Cambridge University Hospitals NHS Foundation Trust, Cambridge CB2 0QQ, UK. ⁶⁷⁹Oxford NIHR Biomedical Research Centre, University of Oxford, Oxford OX1 2JD, UK. ⁶⁸⁰Georgia Regents University Cancer Center, Augusta, GA 30912, USA. ⁶⁸¹Wythenshawe Hospital, Manchester M23 9LT, UK. ⁶⁸²Wellcome Centre for Human Genetics, University of Oxford, Oxford OX1 2JD, UK. ⁶⁸³Thoracic Oncology Laboratory, Mayo Clinic, Rochester, MN 55905, USA. ⁶⁸⁴Institute for Genomic Medicine, Nationwide Children's Hospital, Columbus, OH 43205, USA. ⁶⁸⁵Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Mayo Clinic, Rochester, MN 55905, USA. ⁶⁸⁶International Institute for Molecular Oncology, Poznań 60-203, Poland. ⁶⁸⁷Poznan University of Medical Sciences, 61-701 Poznań, Poland. ⁶⁸⁸Genomics and Proteomics Core Facility High Throughput Sequencing Unit, German Cancer Research Center (DKFZ), 69120 Heidelberg, Germany. ⁶⁸⁹NCCS-VARI Translational Research Laboratory, National Cancer Centre Singapore, Singapore 169610, Singapore. ⁶⁹⁰Edison Family Center for Genome Sciences and Systems Biology, Washington University, St. Louis, MO 63130, USA. ⁶⁹¹MRC-University of Glasgow Centre for Virus Research, Glasgow G61 1QH, UK. ⁶⁹²Department of Medical Informatics and Clinical Epidemiology, Division of Bioinformatics and Computational Biology, OHSU Knight Cancer Institute, Oregon Health and Science University, Portland, OR 97239, USA. ⁶⁹³School of Electronic Information and Communications, Huazhong University of Science and Technology, 430074 Wuhan, China. ⁶⁹⁴Department of Applied Mathematics and Statistics, Johns Hopkins University, Baltimore, MD 21218, USA. ⁶⁹⁵Department of Cancer Genome Informatics, Graduate School of Medicine, Osaka University, Osaka 565-0871, Japan. ⁶⁹⁶School of Mathematics and Statistics, University of Sydney, Sydney, NSW 2006, Australia. ⁶⁹⁷Ben May Department for Cancer Research and Department of Human Genetics, University of Chicago, Chicago, IL 60637, USA. ⁶⁹⁸Tri-Institutional PhD Program in Computational Biology and Medicine, Weill Cornell Medicine, New York, NY 10065, USA. ⁶⁹⁹Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Shatin, NT, Hong Kong, China. ⁷⁰⁰Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA. ⁷⁰¹Duke-NUS Medical School, Singapore 169857, Singapore. ⁷⁰²Department of Surgery, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China. ⁷⁰³School of Computing Science, University of Glasgow, Glasgow G12 8QQ, UK. ⁷⁰⁴Division of Orthopaedic Surgery, Oslo University Hospital, 0450 Oslo, Norway. ⁷⁰⁵Eastern Clinical School, Monash University, Melbourne, VIC 3800, Australia. ⁷⁰⁶Epworth HealthCare, Richmond, VIC 3121, Australia. ⁷⁰⁷Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA 02215, USA. ⁷⁰⁸Department of Biomedical Informatics, College of Medicine, The Ohio State University, Columbus, OH 43202, USA. ⁷⁰⁹The Ohio State University Comprehensive Cancer Center (OSUCCC-James), Columbus, OH 43202, USA. ⁷¹⁰BIOPIIC, ICG and College of Life Sciences, Peking University, 100871 Beijing, China. ⁷¹¹The University of Texas School of Biomedical Informatics (SBMI) at Houston, Houston, TX 77030, USA. ⁷¹²Department of Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA. ⁷¹³Department of Biochemistry and Molecular Genetics, Feinberg School of Medicine, Northwestern University, Chicago, IL 60208, USA. ⁷¹⁴Faculty of Medicine and Health, University of Sydney, Sydney, NSW 2006, Australia. ⁷¹⁵Department of Pathology, Erasmus Medical Center Rotterdam, 1066 CX Rotterdam, GD, The Netherlands. ⁷¹⁶Division of Molecular Carcinogenesis, The Netherlands Cancer Institute, 1066 CX Amsterdam, The Netherlands. ⁷¹⁷Institute of Molecular Life Sciences and Swiss Institute of Bioinformatics, University of Zurich, 8006 Zurich, Switzerland.