Comprehensive genomic and epigenomic analysis in cancer or autoimmunity reveals tissue-specificity and molecular-informed therapeutic opportunities. Download PDF
Supplementary Information (PDF) Download PDF
View all journals Search Q Log in

nature communications | articles | article

Comprehensive genomic and epigenomic analysis in cancer or autoimmunity: tissue-specificity and molecular-informed therapeutic opportunities

Received: 2 December 2025 | Accepted: 22 January 2026

Lora Bartelstein, Stephanie Dikman, Hemangini Patel, Andrew Aleck, Sebastian Lunz, Amy Lynn, Simon Mantell, Ashley Mae Conard, Stefan Morris, Barbara Gusta, Chandler Gatenbee, Ann-Marie Baker, Jeffrey Wren, Ulrike Stiehler, Fabian Flürenbrock, Christopher D. Heinen, Veronica Sciacca, Carole A. Long, Mary Carrington, Jacob Scott, Alexander R. A. Anderson, Chandler Gatenbee, Ann-Marie Baker, Jeffrey Wren, Alexander R. A. Anderson & Jacob Scott

Nature Communications | 16: Article number: 4460 (2026) | Cite this article

Metrics & more

Abstract

The benefit of molecularly-informed therapies in cancer or autoimmune primary or CLIP is unclear, because comprehensive molecular characterization of the genomic landscape across tissue histopathology and healthy tissue is lacking. We conduct a pan-disease, pan-tissue, pan-assay, and pan-patient study of 1,000 patients with cancer, autoimmune disease, or CLIP, and we characterize genomic and epigenomic alterations across 1,000 tissues. We find that molecularly guided treatment in CLIP patients would benefit from treatments similar to therapies currently administered to cancer patients, and that molecular-informed treatment would be beneficial for longer in patients who highly individualize their molecular profile compared to those who do not. Moreover, 90% of cancer. Nevertheless, no data shows is no clear evidence from prospective randomized trials that molecular-guided treatment in these rare diseases improves outcomes in treated patient cancers[1,2].

Molecular-guided treatment, molecular analysis of patients with CLIP revealed profound genomic heterogeneity with tissue-frequent alterations in common cancer-related genes. We ITH, which is a hallmark of cancer, is a major contributor to treatment resistance and disease progression in cancer patients and autoimmune patients[3,4]. Yet, the clinical benefit of molecularly guided treatment in CLIP remains unclear.

Here we describe a cohort of 1,000 patients characterized by comprehensive molecular profiling across 1,000 tissues, 1,000 patients, and 1,000 tissues. We find that molecular-guided treatment would be beneficial for longer in patients who highly individualize their molecular profile, and that molecular-informed treatment would be beneficial for longer in patients who highly individualize their molecular profile. We also find that molecular-informed therapies would be beneficial in over 90% of cancer patients. We conclude that molecular-guided treatment in CLIP patients would benefit from treatments similar to therapies currently administered to cancer patients

the PFS defining event was death, in the others it was progressive disease. To improve concordance with physician-perceived clinical benefit, we calculated the modified PFS2/PFS1 ratio (mPFSr) as described by Mock, Heilig and colleagues[34], which resulted in a mean mPFSr of 5.0 (median mPFSr = 2.7; range 0.2 to 12.0; Table 2).

Fig. 5: Clinical course of 20 patients with molecularly guided therapy.

figure 5

a Each bar represents one patient in the study starting from date of diagnosis. PFS of the last systemic therapy before molecular analysis (PFS1, green) and the first applied molecularly guided therapy (PFS2, blue) are plotted inside those bars. Continued response at the end of the observation period is marked with an arrow. The CUP-69 bar has been shortened by 60 months for visibility (true length 146 months). For CUP-15, CUP-25 and CUP-70 neither PFSr nor mPFSr could be calculated. **b** Sankey plot depicting best response associated with the last systemic therapy before genomic and transcriptomic analysis (BR1, $n = 20$) in comparison with best response associated with the first applied molecularly guided therapy (BR2, $n = 20$). Source data are provided as a Source Data file.

Full size image

Table 2 Clinical outcome.

Full size table

13/17 treated patients had a mean PFSr > 1.3, which was considered as clinical benefit since this value has been frequently used as a measure for positive clinical outcome in precision oncology trials[35,36,37]. Four of them received treatment with immune checkpoint inhibitors, three with ALK inhibitors, three with multikinase inhibitors, one with trastuzumab, one with vismodegib and one with olaparib plus gemcitabine (Supplementary Data 12). Three patients had a PFS2 > 1 year, namely CUP-57 (26.5 months, trastuzumab), CUP-18 (23.3 months, nivolumab) and CUP-08 (12.2 months, olaparib plus gemcitabine).

Observed responses were complete response (CR, 1/30, 3%), partial response (PR, 9/30, 30%), stable disease (SD, 8/30, 27%), mixed response (MR, 3/30, 10%) and progressive disease (PD, 9/30, 30%). Of 20 patients who received the recommended targeted therapies, 12 (60%) had stable disease ≥6 months or achieved objective remissions (PR/CR). PR was achieved with the following treatments: crizotinib, CUP-02; olaparib + gemcitabine, CUP-08; pazopanib, CUP-15; nivolumab, CUP-18/CUP-25/CUP-49; bicalutamide + leuprorelin + nab-paclitaxel, CUP-57; trastuzumab, CUP-57; nintedanib + docetaxel, CUP-62.

Four patients were started on monotherapy or bridging therapies and switched to combination therapy later on (CUP-21, CUP-39, CUP-51, and CUP-57; Supplementary Results). Notably, CUP-51 was started on nivolumab and showed MR so that the subsequent treatment was escalated to a combination of nivolumab and ipilimumab, which led to CR with no reported progression until the end of the observation period (PFS2 9.8 months).

Five patients who received an MTBR were treated with at least one subsequent treatment afterwards, three of them received therapies based on two or more MTBRs, the other two (CUP-38, CUP-70) received chemotherapies. CUP-69 had PD within three months after treatment initiation with the first MTBR (olaparib, PFS2 3.6 months) and was subsequently treated with chemotherapy again (FOLFOX, PFS3 2.9 months). After further progression, a second MTBR was applied (cabozantinib, PFS4 9.4 months). CUP-20 received crizotinib (PFS2 5.9 months) and after progression alectinib (PFS3 6.0 months). CUP-02 received treatment with the ALK inhibitors crizotinib (PFS2 5.6 months), ceritinib (PFS3 10.2 months), alectinib (PFS4: 3.2 months) and brigatinib plus chemotherapy (PFS5 1.7 months) in accordance with the patients' MTBR.

For patients that did not receive a recommended treatment, we calculated the ratio of the first treatment applied after the MTB (PFSb; median = 3.8 months, $n = 12$) and the last prior systemic treatment (PFSa; median = 4.8 months, $n = 11$), which resulted in a mean PFSr of 0.67 (median PFSr = 0.71, range 0.1 to 1.0, $n = 11$; Supplementary Data 13). Median overall survival of the 36 patients without application of recommended treatments was significantly shorter than of the 20 patients that received a recommended therapy (18.3 months vs. 34.8 months, $p = 0.022$). Same was true for median PFS2 and PFSb (7.8 months vs. 3.8 months, $p < 0.0001$). Two patients with PFSb had stable disease ≥6 months or achieved objective remissions (PR/CR; Supplementary Fig. 4). Since our study was not randomized, these results are not controlled for possible confounding factors. Within MASTER, reasons for non-implementation of MTBRs included lack of availability or reimbursement of recommended treatments, deterioration of a patient's general condition and death before treatment application[38]. Further data are provided in Supplementary Data 13 and 14.

The median number of prior systemic palliative therapies that patients with an applied MTBR had received was three (range 1–7). Eleven had already been treated with targeted therapies indicating that clinical benefit may be achieved even in heavily pretreated patients.

Discussion

In addition to known recurrent mutations in CUP, our comprehensive WGS/WES approach detected a variety of rare genetic alterations, which were relevant for molecularly targeted treatment decisions. This suggests that comprehensive molecular analysis is particularly well-suited for this heterogeneous disease.

On the genomic level, we observed frequent mutations in well-known cancer-related genes such as *TP53*, *MUC16* and *KRAS*. The majority of these common alterations has previously been described in studies using gene panel sequencing. When using a 50 gene panel, Löffler and colleagues described *TP53*, *KRAS*, *CDKN2A*, and *SMAD4* as the most frequently mutated genes and *CDKN2A* as the most frequently deleted gene in CUP[11]. Varghese and colleagues reported a variety of targetable alterations in 45/150 CUP patients using MSK-IMPACT, a deep-coverage hybridization capture-based assay encompassing 341 (later expanded to 410) cancer-associated genes accompanied by WES in 13 cases[14]. The most commonly mutated genes were *TP53*, *KRAS*, *CDKN2A*, *KEAP1*, and *SMARCA4* and 15/150 patients received targeted therapies[14]. These common mutations are involved in a variety of cell processes and do not offer a clear rationale for targeted therapies available at the moment.

Furthermore, we and others report a substantial amount of pathogenic germline mutations amongst CUP patients[39,40,41,42]. These can have a direct impact on the patient and their families. Therefore, germline testing should be considered, especially for young patients with CUP or patients with previous malignancies.

On the transcriptomic level, we detected a variety of therapeutically relevant gene fusions. In addition, we classified tumors based on transcriptomic and epigenetic information, which was complemented by specific disease-defining alterations and by presence of certain dominant mutational signatures. Nevertheless, only a third of the entity predictions based on methylome and transcriptome did match, which may be explained by tumor cell content, RNA quality, differences between TCGA and the MASTER cohort composition, as well as differences in the methods used. The question whether site-specific therapies are beneficial for CUP patients is still a matter of ongoing debate. Using a 92-gene RT-PCR cancer classification assay, Hainsworth and colleagues reported that site-specific therapy leads to significantly improved survival when clinically more responsive tumor types were predicted[9]. In contrast, Hayashi and colleagues reported that site-specific treatment based on microarray profiling did not result in a significant improvement in 1-year survival compared with empirical paclitaxel and carboplatin, although prediction of the original site seemed to be of prognostic value[43]. Similarly, a meta-analysis by Rassy et al. showed no significant survival benefit with site-specific in comparison to empiric chemotherapy. At the same time the heterogeneity across the available data demonstrates that further well-designed trials are needed[10] and that a reliable classification method for the attribution of a CUP case to a specific tumor entity is still to be developed. Moran and colleagues used microarray DNA methylation signatures (EPICUP) to predict a primary cancer of origin in 188 (87%) of 216 CUP patients. In this study, patients with EPICUP diagnoses who received a tumor type-specific therapy showed improved overall survival compared with that in patients who received empiric therapy[8]. Prospective validation of this epigenetic approach is still missing.

In our study, we used epigenetic and transcriptomic analyses together with evaluation of disease-specific mutations to identify the tissue of origin. On the one hand this increased the total number of patients for whom an entity prediction was possible, on the other hand it led to contradictory results in a majority of patients that had several layers of information available. In these cases, it is not clear which data is to be trusted more. Probably, several factors contribute to prediction errors by one or the other method: First, the composition of the MASTER CUP cohort and the TCGA reference cohort differ in several aspects, including metastatic status and represented entity subtypes. Second, differences in the sample preparation protocols between MASTER and TCGA may introduce technical biases, confounding the algorithms of the classifiers. And third, some entities are hard to distinguish using epigenetic/transcriptomic information. For example, the classifiers frequently produced discrepant results concerning hepatic metastases of pancreatic (PAAD) or cholangiocellular (CHOL) carcinoma, which were classified inconsistently as one of PAAD, CHOL or LIHC (liver hepatocellular carcinoma). It is unclear whether the missing success of prospective trials using site-specific treatment is due to limited accuracy in identifying the tissue of origin or due to limited relevance of the site of origin for clinical outcome in the majority of CUP patients. In our cohort, MTB recommendations were not influenced by our methylome- and transcriptome-based entity prediction since it was not available at the time of the MTB. Future trials might benefit from a well-designed integrated classifier taking into account both methylation and transcriptomic data. As previously shown in pancreatic cancer and other hard-to-treat entities, comprehensive molecular profiling also offers the opportunity to detect rare or previously unknown therapeutic targets[44,45]. Therefore, in the light of continuously improving options regarding molecular diagnostics and targeted therapies, genomics-based treatment might be the more promising approach.

Our study had several potential limitations. First, our patient population was younger than one would expect for a representative CUP cohort, which can at least be partially explained by the NCT/DKTK MASTER inclusion criteria. Second, our cohort was treated with a wide range of different therapies prior to molecular analysis. Third, our study was not a randomized clinical trial but a prospective observational study. However, the mean PFS2/PFS1 ratio in our cohort was 3.6. 13/17 treated patients (77%) for which a PFS ratio could be determined achieved a ratio higher than 1.3, the originally proposed threshold for assessment of clinical benefit in previous studies like MOSCATO 01[35]. The median overall survival in our cohort was significantly longer when compared to published data, which may be partially attributed to the young patient age in our cohort. Nevertheless, our results provide evidence that a considerable part of CUP patients may benefit from comprehensive molecular analysis. Although there are case reports about successful use of checkpoint inhibitors in CUP patients[46], immunotherapy in CUP has not been clinically implemented yet, unless microsatellite instability or DNA mismatch repair (MMR) deficiency have been detected. Our results underline that immunotherapeutic approaches can be efficient in a much larger proportion of CUP patients. Furthermore, we observed a meaningful proportion of CUP patients benefiting from molecularly stratified treatments. Two prospective randomized phase II trials testing novel strategies versus empirical chemotherapy are currently ongoing (CUPISCO, NCT03498521 and CheCUP, NCT04131621).

In conclusion, our findings indicate that comprehensive molecular analysis of CUP patients can be highly beneficial even at late stages or following several rounds of prior treatment.

We provide valuable insight into the heterogenic genomic, transcriptomic and epigenetic landscape of CUP and show potentially actionable alterations in a large proportion of patients. Further prospective clinical studies to assess the impact of genomics-based personalized cancer therapy are warranted.

Methods

Clinical and statistical analysis

The study included 70 patients who were enrolled in the National Center for Tumor Diseases and German Cancer Consortium (NCT/DKTK) Molecularly Aided Stratification for Tumor Eradication Research (MASTER) precision oncology program between May 2013 and July 2018 with follow-up until June 2019[32,47]. All 70 patients had a CUP diagnosis according to their referring oncologists. Clinical data for cohort selection, description and analysis was obtained from the National Center for Tumor Diseases (NCT) Heidelberg and Dresden, as well as from six other comprehensive cancer centers (CCCs) of the German Cancer Consortium (DKTK). The DKTK network includes ten CCCs at eight sites (Berlin, Dresden, Essen/Düsseldorf, Frankfurt/Mainz, Freiburg, Heidelberg, Munich, Tübingen). Demographic data, histopathological diagnosis, location of metastases at the time of enrollment, fulfillment of the ESMO CUP diagnostic criteria, systemic therapies and staging information, genomic information available at the time of the molecular tumor board (MTB), recommendations of the MTB and application of recommended therapies were assessed and documented in a centrally managed electronic data capture system (ONKOSTAR). MTB recommendations were based on the information obtained from DNA and RNA sequencing. Therapeutic options steadily improved over time. Every tumor board recommendation contains several drugs or drug combinations with different priorities assigned. For our analysis, we included only the first three priorities since there was no drug with a lower priority clinically applied. In some cases, there were fewer than three drugs recommended. All drug recommendations were issued with an NCT/DKTK evidence level reflecting the origin of the information that the respective recommendation was based on[33]. Overall survival (OS) was defined as the time from the date of diagnosis to the date of death or last follow-up. Progression-free survival (PFS) was defined as the time from the date of systemic therapy initiation to the date of death, progressive disease or last follow-up. Median OS, PFS and follow-up time were estimated using the Kaplan–Meier method, and a log-rank test was used to compare OS and PFS among patient subgroups. PFS of the first applied treatment recommended by the MTB (PFS2) was compared to the PFS of the last prior systemic treatment (PFS1) in each individual patient. If more than one recommended therapy was applied, PFS3 and following were calculated. PFS defining events were progressive disease or death, determined by a medical oncologist via review and assessment of the corresponding medical documents. The progression-free survival time ratios (PFSr) between PFS2 and PFS1 were calculated. Modified progression-free survival time ratios (mPFSr) were calculated following the proposal of Mock and colleagues[34]. For patients that did not receive a recommended treatment, we calculated the ratio of the first treatment applied after the MTB (PFSb) and the last prior systemic treatment (PFSa).

NCT/DKTK MASTER

NCT/DKTK MASTER is a prospective, continuously recruiting, multicenter observational study that provides a standardized diagnostic workflow, which enables molecularly informed decisions for further therapy. Treatment recommendations are made in cooperation with treating oncologists following interdisciplinary discussion in a molecular tumor board. MASTER includes adults with advanced cancer across all entities who are younger than 51 years and patients with rare tumors, including rare subtypes of more common entities, regardless of age. Patients must have exhausted curative treatment options and be in good general condition (Eastern Cooperative Oncology Group performance status of 0 or 1)[38]. Patients with cancers of unknown primary were included regardless of age due to its rarity.

Patients provided written informed consent for banking of tumor and control tissue, molecular analysis including germline analysis, and the collection of clinical data under a protocol (S-206/2011) approved by the Ethics Committee of the Medical Faculty of Heidelberg University. The study was conducted in accordance with the Declaration of Helsinki. Patients did not receive participant compensation. Molecularly informed therapies were not part of MASTER but given off-label at the discretion of and by the treating oncologist who obtained informed consent for each therapy. German regulations for off-label treatment allow individual treatment decisions after obtaining informed consent and no IRB approval is required. Costs for off-label drugs can be reimbursed by German health insurances if the patient has a severe disease, if there is no other treatment option available and if there is reasonable hope for treatment success based on available scientific or clinical data.

Entity prediction validation cohort

We used 100 consecutive MASTER patients enrolled between 12/2020 and 06/2021 (Supplementary Data 5) consisting only of entities that are part of TCGA as a cohort to validate all entity prediction methods and measured their accuracy before using them for CUP entity predictions. Transcriptome data was available for 72 patients of the validation cohort (Supplementary Data 6) methylome data for 77 (Supplementary Data 7).

Next-generation sequencing and bioinformatic processing

Sample preparation and sequencing

DNA from fresh frozen tumor tissue was isolated using the Allprep DNA/RNA/miRNA Universal Kit (Qiagen) or QIAamp DNA mini (QIAGEN). DNA from formalin fixed paraffin embedded tissue was isolated using the GeneRead DNA FFPE Kit (QIAGEN). DNA from peripheral blood was isolated using QIAamp DNA Blood Mini (Qiagen) or QIASymphony DSP DNA Mini Kit (Qiagen). The isolation process was followed by quality control and quantification using a Qubit 2.0 Fluorometer (Invitrogen) and a TapeStation 2200 system (Agilent). Libraries for whole-genome sequencing were prepared with the Illumina TruSeq Nano (100 ng genomic DNA as input). Both tumor and control (germline) samples were sequenced on 2 lanes Illumina HiSeq X Ten (Supplementary Data 15). Libraries for whole-exome sequencing were prepared with the Agilent SureSelect All Exon Kit v5 or v5 + UTRs (200 ng input). The libraries were sequenced on Illumina HiSeq 2000, HiSeq 2500 or HiSeq 4000 (Supplementary Data 15). Samples were processed centrally by the NCT Molecular Precision Oncology Program Sample Processing Laboratory (SPL) and sequenced by the DKFZ Genomics and Proteomics Core Facility (GPCF). Further information and exceptions are listed in Supplementary Data 8.

Nucleotide sequence alignment

DNA sequencing reads were mapped to the assembly comprising human genome (1000 Genomes Phase 2 of the Genome Reference Consortium; version hs37d5) and a genome of Enterobacteria phage phiX174 using BWA mem (version 0.7.15) with -T0 parameter as the one different from the default. BAM files were sorted with bamsort (biobambam package, version 0.0.148), and duplicates were marked with markdup (Sambamba package, version 0.6.5)[48]. Sequencing quality statistics are summarized in Supplementary Data 15.

Calling of single-nucleotide variants and small insertions and deletions

Somatic

Somatic SNVs were detected from matched tumor/normal sample pairs by an in-house analysis pipeline based on SAMtools mpileup and bcftools and using heuristic filtering as previously described[49,50,51]. In short, initial SNV calls were detected in the tumor BAM by SAMtools (version 0.1.19) mpileup, which considered only reads with minimum mapping quality of 30 (-q 30), and BCFtools, which reported all positions containing at least one high-quality non-reference base (-vcgN -p 2.0). Afterwards these positions were checked in the control sample using mpileup. SNVs were then annotated with ANNOVAR (version November 2014) using GENCODE (release 19). Downstream filtering discarded variants with low support of the alternative allele, occurring in tandem repeats and other read-attracting regions, having PCR strand bias (WGS only), having sequencing strand bias, and having significant bias in the PV4 field of the mpileup output. SNVs with low confidence score were discarded. Somatic SNVs annotated as missense, stopgain, stoploss, or splicing (two base pairs next to an exon boundary) were defined as non-silent. Short indels were detected by Platypus (version 0.8.1) for matched tumor/normal sample pairs[52]. Only ones that had Platypus filter flag PASS or passed custom filters allowing for low variant frequency were retained. Annotation of short indels was done using ANNOVAR (version February 2016). The calls falling into a coding sequence or splice-site were extracted.

Germline

Germline indels were called by Platypus. SNVs identified in the tumor sample were annotated as germline if the control sample had at least 1/30 reads supporting the alternative allele. Germline variants in 101 cancer predisposition genes (Supplementary Data 4) were further filtered for rare variants and against frequent variants in an in-house database before assessment according to AMP-ACMG guidelines. The *p*-value for age at onset comparison was generated with a two-sided, equal variance *t*-test.

Tumor ploidy, purity and copy number profile determination

For samples sequenced with WGS, the absolute allele-specific copy numbers, tumor ploidy and purity were estimated using ACEseq (version 5.0.1)[53].

For samples sequenced with WES, the absolute allele-specific copy numbers were estimated using CNVkit (version 0.9.3)[54]. Segments containing at least 20 heterozygous SNPs were further processed to infer sample ploidy and tumor cell content (TCC) using a method adapted from ACEseq. The algorithm tested each possible combination of TCC (range 0.15-1.0) and ploidy (range 1.0–6.5) to find the local minima and thus optimal solution. If more than one solution was possible, they were visually evaluated and ultimately one of them was chosen. Samples with tumor cell content estimated to be 100% were considered unreliable (due to in fact low tumor cell content) and thus discarded from the results ($n = 19$).

Microsatellite instability

Microsatellite instability was detected with MSIsensor (version 0.2)[55]. The list of homopolymers and microsatellites generated with the MSIsensor scan command from the 1000 genomes reference comprises 33,386,244 loci. MSIsensor was run with a minimum required coverage of 15 reads for genomes and 30 for exomes in both tumor and control. A score > 3.5 implies microsatellite instability.

RNA sequencing and gene fusion detection

If RNA quality was sufficient, either the Illumina TruSeq RNA (with 1000 ng total RNA) or the Illumina TruSeq mRNA stranded protocol (with 500 ng total RNA) was used for library preparation (TruSeq mRNA stranded since February 2016, Supplementary Data 15). Both are Oligo-dT-based protocols and enrich for mRNA only. Three libraries were pooled and sequenced on one lane HiSeq 4000 100 PE. The reads were aligned to the same reference genome as DNA sequencing data with STAR 2.5.1b[56]. The gene fusions were detected by Arriba pipeline (version 0.8), the software is available on GitHub[57]. Fusions were categorized into high, medium or low level of confidence.

Mutational signatures

Mutational signatures were calculated using R/Bioconductor package YAPSA (version 1.13.3)[58] and COSMIC signatures (version 2)[59]. All identified somatic SNVs were used for the analysis. Six samples with less than 50 SNVs were excluded from the analysis. Mutational catalogs were calculated separately for the whole-exome and the whole-genome sequencing data. The whole-exome catalog was corrected additionally by factors specific for the target capture kits that were used for the preparation of samples. Afterwards, mutational catalogs were normalized by the average length of the coding sequence in Mb (2800 and 30 for WGS and WES, respectively) and merged together for signature decomposition. Exposures were calculated per sample using the set of 30 validated signatures (no artifact signatures) and absolute signature-specific cutoffs with cost factor 6. Corresponding confidence intervals were calculated per sample. Only if their lower bound was greater than 0, the signature was considered to be positively identified.

Methylation-based entity prediction

The Infinium MethylationEPIC BeadChip microarray (850 K) was used for 55 CUP samples and 77 samples of the validation cohort (Supplementary Data 7) to interrogate DNA methylation patterns at genome-wide level. All samples were gathered within the NCT/DKTK MASTER program and had a tumor cell content >30% of the NCT/DKTK MASTER cohort to interrogate DNA methylation patterns at the genome-wide level. The library preparation, hybridization and scanning of the array was performed at the German Cancer Research Center (DKFZ) Genomics & Proteomics Core Facility. The raw data (idat files) were processed into beta values with the minfi R package[60]. Beta values range from 0 to 1 with 0 being a CpG unmethylated and 1 fully methylated.

TCGA (The Cancer Genome Atlas) pan-cancer methylation was retrieved via the curatedTCGAData package[61]. The dataset (33 entities, 8024 samples) comprised both 450k and 27k methylation arrays. The intersection of these arrays comprised 25978 CpGs. For a more meaningful entity prediction colorectal (COAD) and rectal (READ) adenocarcinomas were binned together (COAD/READ).

The 5000 CpGs for the methylation-based entity predictions were derived after (i) removing known SNPs as previously described[62], (ii) only considering overlapping CpGs between 850k, 450k and 27k arrays to ensure compatibility with all Illumina methylation arrays and (iii) lastly calculating the top 5000 most variant CpGs across the pan-cancer dataset. The probe IDs are listed in Supplementary Data 16.

Methylation-based entity prediction of 55 CUP samples and 77 samples of the validation cohort was performed by correlating (Spearman correlation) the vector of 5000 CpGs with all samples in the TCGA cohort. The entity of the sample with the highest correlation coefficient was deemed to be the predicted entity.

Similarity in methylation profiles was visualized by tSNE plot with the Rtsne R package[63]. Missing data was imputed with the impute.knn function. The perplexity was set to 100.

Transcriptome-based entity prediction

In order to identify the tissue of origin of a CUP sample based on gene expression, we searched for samples with a similar expression profile in two reference cohorts: the MASTER cohort (comprising 1890 samples from 1814 patients, Supplementary Data 9) and the union of 33 TCGA cohorts (TCGA cohorts with >50 samples were subsampled, yielding a total of 1809 samples). For each reference cohort, we compared the expression profile of the CUP sample to all possible pairwise combinations of reference samples. The reference samples were ranked by the number of times they were more similar to the CUP sample than the other reference sample in a given pair of reference samples. Similarity was measured as the fraction of genes that were upregulated in both the CUP sample and one of the samples in a given pair of reference samples (FPKM > 13), but downregulated in the other reference sample (FPKM < 3). The thresholds for up- and downregulation were determined by means of 10-fold cross-validation on a subset of the MASTER cohort. To mitigate the distortion of the CUP expression profile by contamination from surrounding normal tissue in the bulk RNA-Seq data, we ignored genes found to be upregulated in normal liver tissue (Supplementary Data 17) if the sample was obtained by liver biopsy. The entity of the most similar reference sample was assumed to predict the entity of the CUP sample. If the most similar reference sample was a CUP as well, the most similar non-CUP sample was chosen for prediction instead. The method was validated on 72 patients from the validation cohort (Supplementary Data 6).

Tumor mutational burden (mutations per megabase)

For each sample, the numbers of non-silent SNVs and coding indels in the exons of the tumor were added and divided by the length of the coding sequence of the genome (in Mb). The denominator depended on the technology, including different library preparation kits, used for sequencing of a sample. For samples sequenced with WGS, the GENCODE Human v19 gene annotation (GTF format) was taken, coding sequences were identified and merged, and the total length was calculated. For samples sequenced with WES, however, the merged coding sequences were additionally intersected with the coordinates of the corresponding target capture (BED format). All sequence operations were done using bedtools v2.27.1[64]. Calculations resulted in lengths: (i) 35.334619 Mb for WGS, (ii) 31.057260 Mb for WES with SureSelectXT Human All Exon V5 including UTRs and (iii) 30.894643 Mb for WES with SureSelectXT Human All Exon V5 excluding UTRs. Please note that the MTB used the sum of non-silent SNVs and coding indels as measure for TMB.

Homologous recombination deficiency

Homologous recombination deficiency (HRD) was determined using three different methods. The first one was being used for Molecular Tumor Board and could be applied to both whole-exome and whole-genome sequencing data. This method was based solely on results from the copy number analysis, and consisted of the estimation of two parameters: loss of heterozygosity (LOH-HRD)[65] and large-scale state transitions (LST)[66]. An unweighted sum of those produced a score, which classified samples to high (>20), intermediate (11–20) or low (≤10) level of impaired homologous recombination.

The other two methods which were used, HRDetect[67] and CHORD (version 2.0)[68], calculate a method-specific probability score of HR deficiency and can be applied to whole-genome sequencing data only. As inputs, they both used raw data comprising single-nucleotide variants, small insertions and deletions, structural variants (detected with SOPHIA, https://bitbucket.org/utoprak/sophia/src/master) and, only in case of HRDetect, copy number variation. All 27 whole-genome sequencing samples with reliable copy number data were therefore used in the analysis. Genes considered as HRD related in Fig. 1 are listed in Supplementary Data 18.

Viral infections

We used three computational approaches to detect viral infections from next-generation sequencing (NGS) data: a *k*-mer-based approach (Kraken2 version 2.1.2[69]), an assembly-based approach (P-DiP[70]), and an alignment-based approach where the sequencing reads were aligned against concatenated assemblies of the human genome and all RefSeq viral genomes, in accordance with Arriba's workflow for the detection of viruses. Kraken2 was considered to make a call if it detected at least one read per 40 million mapped reads as originating from a virus and if at least 10% of the viral genome was covered with reads. For P-DiP, a cutoff of one virus-originating read per million mapped reads was used. Moreover for the Arriba workflow, a sample was considered to be associated with a virus when at least 5% and 100 bp (whichever was bigger) of the viral genome was covered with reads. Supplementary Table 1 lists all viruses that were reported by at least two methods. To detect viral integration sites, we used Arriba version 2.1.0 for RNA-Seq data and VIRUSBreakend version 2.12.0[71] for DNA-Seq data.

Additional data processing and analysis

The downstream analysis was performed in R (version 3.4.3) using Bioconductor repository and such packages as tidyverse (version 1.2.1)[72], ComplexHeatmap (version 1.99.5)[73] and Biobase (version 2.38.0)[74]. If possible, the sample used for the first MTB was used for the general cohort description, only for CUP-70 we analyzed the sample for the second MTB. PFS, PFSr, and mPFSr were calculated using Microsoft Excel. Survival analysis using Kaplan–Meier estimator and log-rank tests was performed using ggplot2 (version 3.3.3). *p*-values < 0.05 were considered statistically significant.

Reporting summary

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

Data availability

TCGA pan-cancer methylation was retrieved via the cancerhubURL(data.ucsc.edu/hub/hub/cancerhubURL/hg19/cancer/methylation27/v2/tcga.tsv.mtx.mtxmeta.gz). The TCGA Genome, transcriptome and methylation data generated in this study have been deposited in the Genome Data Commons (GDC) under the project "Molecular Neuropathology 2.0" (MNP2.0). Raw data are available under controlled access due to the sensitive nature of genome sequencing data (germline variants). Controlled access is granted to qualified academic research projects on a non-commercial basis. Requests are processed within 2 weeks. Methylation array data are available according to patient consent for data and consent agreements for archiving on medical. No clinical data will be provided. Requests for access to the MNP2.0 cohort should be directed to the sequencing center, DKFZ/NCT Heidelberg. Requests for access to the methylation array data should be directed to the core clinical data protocol and not at raw sequence data due to data privacy laws. The processed methylation array data (beta values) for the training cohort are available online within the Article, Supplementary Information, Supplementary Data or Source Data files. Source data are provided with this paper.

Code availability

Bioinformatics analyses were performed using above mentioned open source software with default parameters. No custom code was used for the analysis. The Article Scripts for conclusions/ interpretations are available in Supplementary Software 1.

References

1. Louis, D. N., Ohgaki, H., Wiestler, O. D., Cavenee, W. K. & Ellison, D. W. Cancer of unknown primary: a diagnostic challenge in neuropathology. *Brain Pathology (Zurich, Switzerland)* **17**, 320–324 (2007).
2. Pavlidis, N., Briasoulis, E., Hainsworth, J. & Greco, F. A. Diagnostic and therapeutic management of cancer of an unknown primary. *Lancet (London, England)* **383**, 1981–1991 (2014).
3. Fizazi, F. et al. Carcinomas of unknown primary site (CUPS) Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol. Jan.* **23**, v137–v139 (2012).
4. Massard, C. et al. Molecular validation of a 2100 gene expression profile for identification of tumor tissue of origin. *J. Clin. Oncol. JF*, 2503–2508 (2009).
5. Varadhachary, G. R. & Raber, M. N. Cancer of unknown primary. *Adv. Chemother.* **1**, 1–9 (2014).
6. Tothill, R. W. et al. Development and validation of a gene expression tumor classifier for cancer of unknown primary. *Pathology* **47**, 7–12 (2015).
7. Kerr, S. E. et al. Multivariate validation study to determine performance characteristics of a 92 gene molecular cancer classifier. *Clin. Genomics* **16**, 992–1004 (2015).
8. Herbrich, N. M. et al. Gene expression profiling to identify the histogenic origin of metastatic adenocarcinoma of unknown primary. *J. Clin. Oncol. JE*, 4363–4368 (2006).
9. Moran, S. et al. Epigenetic profiling to classify cancer of unknown primary: a multicenter, retrospective analysis. *Lancet Oncol. ET*, 1390–1398 (2016).
10. Varadhachary, G. et al. Molecular gene expression profiling to predict the tissue of origin and direct site-specific therapy in patients with carcinoma of unknown primary site: a prospective trial of the Sarah Cannon Research Institute. *J. Clin. Oncol. JCO.2013.53.2*, 1789–1795 (2014).
11. Bump, J. et al. The role of gene specific therapy for cancers of unknown of primary: a Kaiser series. *Clin. Genomics* **127**, 10–12 (2016).
12. Griffin, O. et al. Molecular tumor profiling to identify actionable alterations in cancer of unknown primary site. *Oncotarget* **7**, 14122–14129 (2016).
13. Santiago, I. M. et al. Next-generation sequencing of transcribed genes identifies tissue-specific novel combinatorial strategies in a heterogeneous metastatical landscape. *Oncotarget* **8**, 67–76 (2017).
14. Rochlitz, C. et al. The CUHMAC Cancer Genome Consortium: describing genomic dysfunctions across 8 frequent cancers. *Int. Jhn Cancer Mb.* **109**, 1991(2016).
15. Rosty, C. et al. The cancer genome atlas pancancer analysis identifies expression of transcriptional regulators associated with tissue of origin in cancers of unknown primary. *J. Mol. Diagn. JMD.160099*, 1–9 (2017).
16. Rosty, C. et al. Identification of hepatocyte nuclear factor 1 beta/TCF2 as a highly specific immunohistochemical marker of primary pancreatic adenocarcinoma. *Br. J. Cancer* **117**, 1929–1935 (2017).
17. Lu, F. Pattis, W. A. & Etzioughian, O. J. Functions of FGF21 compared by conservation in intraduodenal clonidine pancreas. *Cytokine Growth Factor Rev.* **37**, 43–51 (2016).
18. Sun, W. et al. Identification of the transforming DAB2 IGF-II fusion gene in non-small cell lung cancer. *Neoplasia* **18**, 360–368 (2016).
19. Lai, J. et al. Molecular heterogeneity and functions of STK33/KIS/AMPK-like kinases in chemotherapy-resistant small cell cancers. *Oncotarget* **7**, 32197–32209 (2016).
20. Shu, Y. et al. Prognostic significance of frequent CD155 mRNA splicing variants in gastric adenocarcinoma. *Br. J. Cancer* **110**, 1562–1571 (2014).
21. Hacard, F. et al. Precision oncology based on omics data: The NCT Heidelberg experience. *Int. J. Cancer* **141**, 877–886 (2017).
22. Lachenmayer, J. et al. Variant classification in precision oncology. *Int. J. Cancer* **141**, 2996–3000 (2017).
23. Mack, A. et al. Comparative driver development of a modified progression-free survival endpoint for precision oncology. *EORTC Molecular & ASCO/EORTC Clinical Cancer Genomics Symposium, Poster Presentation* (2017).
24. Massard, C. et al. High-throughput genomics and clinical outcome in heard to treat advanced cancers: results of the MOSAIC molecular screening study. *Ann. Oncol. Mdx.* **28**, 2267–2273 (2017).
25. Roden, I. et al. Genome and transcriptome profiling expands precision cancer medicine: the WINTHER trial. *Int. Jhn Cancer Mb.* **141**, 1779–1788 (2017).
26. Tothill, R. W. et al. Molecular profiling of cancer patients enables personalized combination therapy: the FOCUSCP trial. *Ann. Oncol. Mdx.* **28**, 1780–1787 (2017).
27. Hoyt, C. C. et al. Comprehensive genomic and transcriptomic analysis for guiding therapeutic decisions in patients with rare cancers. *PLoS Genet.* **13**, e1006732 (2017).
28. Rusnak, D. et al. The distribution of BRAF gene fusions in solid tumors and response to targeted therapy. *Int. J. Cancer* **140**, 1823–1829 (2017).
29. Hacard, F. et al. Precision oncology based on omics data: The NCT Heidelberg experience. *Int. J. Cancer* **141**, 877–886 (2017).
30. Luchmann, A. et al. Variant classification in precision oncology. *Int. J. Cancer* **141**, 2996–3000 (2017).
31. Pennisi, E. et al. Pan-cancer whole-genome analyses of metastatic solid tumours. *Nature* https://doi.org/10.1038/nature-18.-online (2017).
32. Berstein, R. et al. High frequency of pathogenic germline variants within homologous recombination repair in patients with advanced cancer. *PLoS Genet.* **13**, e1006929 (2017).
33. Mantiq, M. et al. Haplotype genomics and clinical outcome in heard to treat advanced cancers: results of the MOSAIC molecular screening study. *Ann. Oncol. Mdx.* **28**, 2267–2273 (2017).
34. Tothill, I. M. et al. Molecular profiling of cancer patients enables personalized combination therapy: the FOCUSCP trial. *Ann. Oncol. Mdx.* **28**, 1780–1787 (2017).
35. Hoyt, C. C. et al. Comprehensive genomic profiling identifies and clinical decision making in challenging cases of CUP syndrome. *Int. J. Cancer* https://doi.org/10.1002/ijc.32786 (2019).
36. Hermsen, A. et al. Germline genetics of cancer of unknown primary (CUP) and its specific subtypes. *Oncotarget* **7**, 22849–22859 (2016).
37. Tarsian, A., Nikolic, A., Lagace, J., Alpman, J. & Perry, W. Xenthamide: Sex processing of NCI adjuvant formula. *Biopsychiatry* **81**, 2032–2043 (2016).
38. Rodriguez, E. et al. CUP: an automated system for managing and processing NGS data. *J. Biomedical Inf.* **76**, 12–17 (2017).
39. Jones, D. T. et al. Recurrent somatic alterations of FGFR and NTRK2 in pilocytic astrocytoma. *Nat. Genet.* **45**, 927–932 (2013).
40. Jones, D. T. et al. Dissecting the genomic complexity underlying medulloblastoma. *Nature* **488**, 100–105 (2012).
41. Sieber, A. et al. Integrating genomic, proteomic, and epigenomic data to improve precision medicine in sarcomas. *Int. J. Cancer* **141**, 1789–1796 (2017).
42. Schlesner, M. et al. Methylation profiles of 1300 human cancer samples. *Sci. Data* **4**, 170077 (2017).
43. Sturm, D. et al. Hotspot mutations in H3F3A and IDH1 define distinct epigenetic and oncogenic signatures in low-grade gliomas. *Cancer Discov.* **4**, 1080–1095 (2014).
44. Schlesner, M. et al. Molecular profiling of cancer patients enables personalized combination therapy: the INFORM trial. *Ann. Oncol. Mdx.* **28**, 1744–1751 (2017).
45. Ferretti, A. et al. Genome-wide analysis of chromosomal alterations in medulloblastoma. *Genes, Chromosomes & Cancer* **46**, 1008–1016 (2006).
46. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
47. Ellison, D. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
48. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
49. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
50. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
51. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
52. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
53. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
54. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
55. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
56. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
57. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
58. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
59. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
60. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
61. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
62. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
63. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
64. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
65. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
66. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
67. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
68. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
69. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
70. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
71. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
72. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
73. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
74. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
75. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
76. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
77. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
78. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
79. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
80. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
81. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
82. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
83. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
84. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
85. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
86. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
87. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
88. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
89. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
90. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
91. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
92. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
93. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
94. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
95. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
96. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
97. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
98. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
99. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
100. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
101. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
102. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
103. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
104. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
105. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
106. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
107. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
108. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
109. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
110. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
111. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
112. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
113. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
114. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
115. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
116. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
117. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
118. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
119. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
120. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
121. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
122. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
123. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
124. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
125. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
126. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
127. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
128. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
129. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
130. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
131. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
132. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
133. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
134. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
135. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
136. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
137. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
138. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
139. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
140. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
141. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
142. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
143. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
144. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
145. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
146. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
147. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
148. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
149. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
150. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
151. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
152. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
153. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
154. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
155. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
156. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
157. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
158. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
159. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
160. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
161. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
162. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
163. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
164. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
165. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
166. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
167. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
168. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
169. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
170. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
171. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
172. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
173. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
174. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
175. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
176. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
177. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
178. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
179. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
180. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
181. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
182. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
183. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
184. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
185. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
186. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
187. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
188. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
189. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
190. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
191. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
192. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
193. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
194. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
195. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
196. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
197. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
198. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
199. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
200. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
201. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biomed. Pharmacother.* **59**, 333–339 (2005).
202. Ellison, D. W. et al. Medulloblastoma: clinicopathological, molecular, genetic and stem cell factors affecting biology and clinical management. *Lancet Oncol.* **12**, 1265–1272 (2011).
203. Ellison, D. W. et al. 1q gain predicts adverse outcome in WNT medulloblastoma. *J. Neuropathol. Exp. Neurol.* **69**, 467–474 (2010).
204. Ellison, D. W. et al. Medulloblastoma: a review of contemporary pathology and genetic mechanisms. *Biom

Berlin and Humboldt: Universität zu Berlin, Berlin, Germany
Gina Rüter & Ivan Jelas

Department of Medical Oncology, West German Cancer Center, University Hospital Essen, Essen, Germany
Rainer Hamacher & Johanna Falkenhorst

DKTK, Essen, Germany
Rainer Hamacher & Johanna Falkenhorst

Department of Medicine 2, Hematology/Oncology, Goethe University, Frankfurt, Germany
Sebastian Wagner & Christian H. Brands

DKTK, Frankfurt, Germany
Sebastian Wagner & Christian H. Brands

Institute of Medical Bioinformatics and Systems Medicine, Medical Center–University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg im Breisgau, Germany
Melanie Boerries

DKTK, Freiburg, Germany
Melanie Boerries & Anna L. Illert

Department of Internal Medicine I, Medical Center–University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany
Anna L. Illert

Department of Internal Medicine III, University Hospital, LMU Munich and Comprehensive Cancer Center, Munich, Germany
Klaus H. Metzeler & C. Benedikt Westphalen

Department of Hematology and Cellular Therapy, University Hospital Leipzig, Leipzig, Germany
Klaus H. Metzeler

University Cancer Center Mainz, University Medical Center Mainz, Mainz, Germany
Alexander Desuki & Thomas Kindler

DKTK, Mainz, Germany
Alexander Desuki & Thomas Kindler

Institute of Pathology, Technical University Munich, Munich, Germany
Wilko Weichert

Division of Applied Bioinformatics, NCT Heidelberg and DKFZ, Heidelberg, Germany
Benedikt Brors

Pattern Recognition and Digital Medicine, Heidelberg Institute for Stem cell Technology and Experimental Medicine, Heidelberg, Germany
Daniel Hübschmann

DKTK, Heidelberg, Germany
Daniel Hübschmann, Peter Horak & Stefan Fröhling

Translational Functional Cancer Genomics, NCT Heidelberg and DKFZ, Heidelberg, Germany
Hanno Glimm

Contributions

Conceptions and design: I.M., H.G., and S.F. Data acquisition and assembly: I.M., M.W., M.O., A.M., A.J., S.U., S.K., M.F., B.H., C.E.H., V.T., D.B.L., M.Z., D. Hanel, C.L., M.A., R.P., G.R., I.J., R.H., J.F., S.W., C.H.B., M.B., A.L.I., K.H.M., C.B.W., A.D., T.K., G.F., W.W., B.B., A.S., E.S., D. Hübschmann, P.H., C.H., S.F., and H.G. Bioinformatic analysis: M.O., A.M., B.H., M.F., S.U., N.P., B.B., and D. Hübschmann. Project, sample, and data management: D.R., K.B., U.W., and K.P. Clinical data curation and analysis: L.M., M.W., A.J., and C.H. Data analysis and interpretation: L.M., M.W., M.O., S.U., A.M., A.J., S.U., C.H., S.F., and H.G. Manuscript writing: L.M., M.W., M.O., C.H., S.F., and H.G. Manuscript revision, editing, and approval: All authors.

Corresponding author

Correspondence to Hanno Glimm.

Ethics declarations

Competing interests

A.D.: received personal and speakers' fees, reimbursement for travel and accommodation and honoraria for participance in advisory boards from Astra-Zeneca, Bayer, BMS, Eisai, MSD, Pfizer, Janssen-Cilag, Roche & Servier. A.S.: provided consultation, attended advisory boards, or provided lectures for Astra Zeneca, AGCT, Bayer, Bristol-Myers Squibb, Chugai, Eli Lilly, Illumina, Janssen, Merck Sharp & Dohme, Novartis, Pfizer, F Hoffmann-La Roche, Seattle Genetics, Takeda and Thermo Fisher. A.J.: Honoraria: AstraZeneca. A.L.I.: has attended Advisory Boards and served as speaker for Roche, AstraZeneca, Ars Tempi, Takeda, Janssen-Cilag, AbbVie and Incyte outside of the submitted work. C.B.W.: received personal and speakers' fees, reimbursement for travel and accommodation and honoraria for participance in advisory boards from Bayer, BMS, Celgene, GSK, Ipsen, MedScape, Merck, Rafael Pharmaceuticals, RedHill, Roche, Servier, Shire/Baxalta, SirTex, and Taiho and scientific grant support by Roche. C.H.: Honoraria: Roche, Novartis; research funding: Boehringer Ingelheim; advisory board: Boehringer Ingelheim, J.F.: Honoraria: Pharmamar, Genpharma; Travel Support: Pharmamar. Eli Lilly outside of the submitted work. L.M.: non-financial support (travel support) from Celgene outside of the submitted work. M.F.: her husband works for Merck KGaA. R.H.: Travel Support: Lilly, Novartis and PharmaMar as well as fees from Lilly and PharmaMar outside of the submitted work. W.W.: has attended Advisory Boards and served as speaker for Roche, MSD, BMS, AstraZeneca, Pfizer, Merck, Lilly, Boehringer, Novartis, Takeda, Bayer, Amgen, Astellas, Illumina, Molecular Health, NewOncology and Agilent. W.W. receives research funding from Roche, MSD, BMS and AstraZeneca. S.F.: Consulting or advisory board membership: Bayer, Illumina, Roche; honoraria: Amgen, Eli Lilly, PharmaMar. Roche: research funding: AstraZeneca, Pfizer, PharmaMar, Roche; travel or accommodation expenses: Amgen, Eli Lilly, Illumina, PharmaMar, Roche. The other authors declare no potential conflicts of interest.

Peer review

Peer review information

Nature Communications thanks Benjamin Kasenda and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Peer reviewer reports are available.

Additional information

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Supplementary information

Supplementary Information

Peer Review File

Description of Additional Supplementary Files

Supplementary Data 1

Supplementary Data 2

Supplementary Data 3

Supplementary Data 4

Supplementary Data 5

Supplementary Data 6

Supplementary Data 7

Supplementary Data 8

Supplementary Data 9

Supplementary Data 10

Supplementary Data 11

Supplementary Data 12

Supplementary Data 13

Supplementary Data 14

Supplementary Data 15

Supplementary Data 16

Supplementary Data 17

Supplementary Data 18

Supplementary Software 1

Reporting Summary

Source data

Source Data

Rights and permissions

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.

Reprints and Permissions

About this article

Check for updates

Cite this article

Möhrmann, L., Werner, M., Oleś, M. *et al.* Comprehensive genomic and epigenomic analysis in cancer of unknown primary guides molecularly-informed therapies despite heterogeneity. *Nat Commun* **13**, 4485 (2022). https://doi.org/10.1038/s41467-022-31866-4

Download citation

Received
05 March 2021

Accepted
06 July 2022

Published
02 August 2022

DOI
https://doi.org/10.1038/s41467-022-31866-4

Share this article

Anyone you share the following link with will be able to read this content:

Get shareable link

Provided by the Springer Nature SharedIt content-sharing initiative

Subjects

Cancer genetics · Cancer genomics · Cancer of unknown primary · Molecular medicine · Translational research

This article is cited by

Spatial transcriptomics reveal topological immune landscapes of Asian head and neck angiosarcoma
Jui Wan Loh, Jing Yi Lee, … Jason Yongsheng Chan
Communications Biology (2023)

Comments

By submitting a comment you agree to abide by our Terms and Community Guidelines. If you find something abusive or that does not comply with our terms or guidelines please flag it as inappropriate.

About Nature Portfolio
About us
Press releases
Press office
Contact us

Publishing policies
Nature portfolio policies
Open access

Libraries & institutions
Librarian service & tools
Librarian portal
Open research
Recommend to library

Career development
Nature Careers
Nature Conferences
Nature events

Discover content
Journals A-Z
Articles by subject
Nano
Protocol Exchange
Nature Index

Author & Researcher services
Reprints & permissions
Research data
Language editing
Scientific editing
Nature Masterclasses
Live Expert Trainer-led workshops
Research Solutions

Advertising & partnerships
Advertising
Partnerships & Services
Media kits
Branded content

Regional websites
Nature Africa
Nature China
Nature India
Nature Italy
Nature Japan
Nature Korea
Nature Middle East

Privacy Policy · Use of cookies · Your privacy choices/Manage cookies · Legal notice · Accessibility statement · Terms & Conditions · Your US state privacy rights

© 2023 Springer Nature Limited