Cancer is a complex process, and its progression involves diverse processes in the patient's body. Consequently, the cancer research community generates massive amounts of molecular and phenotypic data to study cancer hallmarks as comprehensively as possible. The rapid accumulation of omics data catalysed by breakthroughs in high-throughput technologies has given rise to the notion of 'big data' in cancer, which we define as a dataset with two basic properties; first, it contains abundant information that can give novel insights into essential questions, and second, its analysis demands a large computer infrastructure beyond equipment available to an individual researcher — an evolving concept as computational resources evolve exponentially following Moore's law. A model example of such big data is the dataset collected by The Cancer Genome Atlas (TCGA). TCGA contains 2.5 petabytes of raw data — an amount 2,500 times greater than modern laptop storage in 2022 — and requires specialized computers for storage and analysis. Further, between its initial release in 2008 to March 2022, at least 10,242 articles and 11,054 NIH grants cited TCGA according to a PubMed search, demonstrating its transformative value as a community resource that has marked advances in our basic understanding of cancer biology and translational advancements. Further advances will require a concerted effort among data scientists, clinicians, biologists and policymakers. Here, we review the current state of the art and future challenges for harnessing big data to advance cancer research and treatment.

Big data in basic and translational cancer research

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Abstract | Historically, the primary focus of cancer research has been molecular and clinical studies of a few essential pathways and genes. Recent years have seen the rapid accumulation of large-scale cancer omics data catalysed by breakthroughs in high-throughput technologies. This fast data growth has given rise to an evolving concept of ‘big data’ in cancer, whose analysis demands large computational resources and can potentially bring novel insights into essential questions. Indeed, the combination of big data, bioinformatics and artificial intelligence has led to notable advances in our basic understanding of cancer biology and to translational advancements. Further advances will require a concerted effort among data scientists, clinicians, biologists and policymakers. Here, we review the current state of the art and future challenges for harnessing big data to advance cancer research and treatment.
Table 1 | Common molecular omics data types in cancer research

| Data type          | Technology                          | Description                                                                                                                                 |
|--------------------|-------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| DNA mutations      | Whole-exome/whole-genome sequencing | Reveals DNA nucleotide mutations, such as single-nucleotide missense mutations, frameshift insertions or deletions, nonsense mutations, copy number alterations, DNA non-coding variations in regulatory regions that may impact the gene regulatory network and large structural variants, such as genome rearrangements and chromothripsis. Whole-exome sequencing can provide focused readouts if only protein-coding alterations are needed. Single-cell genome sequencing is possible on a few cells. |
| Chromatin accessibility | ATAC-seq or DNase I-seq | Reveals accessible chromatin regions in bulk cells, a hallmark of active DNA regulatory elements. Coupled with cell barcoding techniques, ATAC-seq technologies can reveal chromatin accessibility at the single-cell level. |
| Histone modification | ChiP–seq                           | Identifies the genome-wide location of DNA-binding proteins or histones with diverse modifications. Single-cell ChiP–seq can reveal chromatin states for hundreds of cells. |
| DNA methylation    | Bisulfite sequencing and BeadChip   | Bisulfite conversion of unmethylated cytosine to uracil, coupled with sequencing or BeadChip, enables genome-wide profiling of DNA methylation patterns. Single-cell bisulfite sequencing can provide methylation readout at up to 50% of CpG dinucleotides on the genome scale. |
| Transcriptomics    | Microarrays                         | Reveals gene expression level or transcript isoforms from diverse patient sample types. Microarrays can profile more than 30 protein antibody intensities in a tissue slice with spatial and single-cell resolution. |
| Proteomics         | Mass spectrometry                   | Profiles protein expression and phosphorylation in bulk samples on the genome scale. Mass spectrometry can profile more than 30 protein antibody intensities in a tissue slice with spatial and single-cell resolution. |
| Metabolomics       | NMR spectroscopy                    | Reveals metabolites from samples on the basis of resonance frequencies of atoms and their immediate chemical environment in the magnetic field. NMR spectroscopy can profile more than 30 protein antibody intensities in a tissue slice with spatial and single-cell resolution. |

By default, most technologies work on bulk samples. When applicable, single-cell or spatial solutions are discussed in the description. ATAC-seq, assay for transposase-accessible chromatin using sequencing; ChiP–seq, chromatin immunoprecipitation followed by sequencing; CODEX, co-detection by indexing; DNase I-seq, DNase I hypersensitive site sequencing; FISSEQ, fluorescent in situ sequencing; RNA-seq, RNA sequencing.

Common data types

There are five basic data types in cancer research: molecular omics data, perturbation phenotypic data, molecular interaction data, imaging data, and textual data. Molecular omics data describe the abundance or status of molecules in cellular systems and tissue samples. Such data are the most abundant type generated in cancer research from patient or preclinical samples, and include information on DNA mutations (genomics), chromat in or DNA states (epigenomics), protein abundance (proteomics), transcript abundance (transcriptomics) and metabolite abundance (metabolomics) (TABLE 1). Early studies relied on data from bulk samples to provide insights into cancer progressions, tumour heterogeneity and tumour evolution, by using well-designed computational approaches. Following the development of single-cell technologies and decreases in sequencing costs, current molecular data can be generated at multi-sample and single-cell levels and reveal tumour heterogeneity and evolution at a much higher resolution. Furthermore, genomic and transcriptomic readouts can include spatial information, revealing cancer clonal evolutions within distinct regions and gene expression changes associated with clone-specific aberrations. Although more limited in resolution, conventional bulk analyses are still useful for analysing large patient cohorts as the generation of single-cell and spatial data is costly and often feasible for only a few tumours per study.

Perturbation phenotypic data describe how cell phenotypes, such as cell proliferation or the abundance of marker proteins, are altered following the suppression or amplification of gene levels or drug treatments. Common phenotyping experiments include perturbation...
Cross-cohort data aggregation. Integration of datasets from multiple centres or studies can achieve more robust results and potentially new findings, especially where individual datasets are noisy, incomplete or biased with certain artefacts. A landmark of cross-cohort data aggregation is the discovery of the **TMPRSS2–ERG** fusion and a less frequent **TMPRSS2–ETV1** fusion as oncogenic drivers in prostate cancer. A compendium analysis across 132 gene-expression datasets representing 10,486 microarray experiments first identified **ERG** and **ETV1** as highly expressed genes in six independent prostate cancer cohorts; further studies identified their fusions with **TMPRSS2** as the cause of **ERG** and **ETV1** overexpression. Another example is an integrative study of tumour immune evasion across many clinical datasets that revealed that **SERPINB9** expression consistently correlates with intratumoural T cell dysfunction and resistance to immune checkpoint blockade. Further studies found **SERPINB9** activation to be an immune checkpoint blockade resistance mechanism in cancer cells and immunosuppressive cells.

A general approach for cross-cohort aggregation is to obtain public datasets that are related to a new research topic or have similar study designs to a new dataset. However, use of public data for a new analysis is challenging because the experimental design behind each published dataset is unique, requiring labour-intensive expert interpretation and manual standardization. A recent framework for data curation provides natural language processing and semi-automatic functions to unify datasets with heterogeneous meta-information into a format usable for algorithmic analysis (Framework for Data Curation in **Table 3**).

Although data aggregation may generate robust hypotheses, batch effects caused by differences in laboratories, individual researcher’s techniques or platforms or other non-biological factors may mask or reduce the strength of signals uncovered, and correcting for these effects is therefore a critical step in cross-cohort aggregations. Popular batch effect correction approaches include the ComBat package, which uses empirical Bayes estimators to compute corrected data, and the Seurat package, which creates integrated single-cell clusters anchored on similar cells between batches. Despite the availability of batch correction methods, analysis of both original and corrected data is essential to draw reliable conclusions as batch correction can introduce false discoveries.

Cross-modality data integration. Cross-modality integration of different data types is a promising and productive approach for maximizing the information gained from data as the information embedded in each data type is often complementary and synergistic. Cross-modality data integration is exemplified by projects such as TCGA, which provides genomic, transcriptomic, epigenomic and proteomic data on the same set of tumours (**Table 2**). Cross-modality integration has led to many novel insights regarding factors associated with cancer progression. For example, the phosphorylation status of proteins in the EGFR signalling pathway — an indicator of EGFR signalling activity — is
highly correlated with the expression of genes encoding EGFR ligands in head and neck cancers but not receptor expression, copy number alterations, protein levels or phosphorylations\textsuperscript{41}, suggesting that patients should be stratified to receive anti-EGFR therapies on the basis of ligand abundance instead of receptor status.

A recent example of cross-modality data integration used single-cell multi-omics technologies that allowed genome-wide transcriptomics and chromatin accessibility data to be measured together with a handful of proteins of interest\textsuperscript{42}. The advantages of using cross-modality data were clear as during cell lineage clustering, CD8\textsuperscript{+}

| Table 2 | Large-scale projects generating cancer genomic datasets |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Project         | Samples         | Data type             | Size            | Description |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| TCGA            | Primary cancers, matched normal samples, some metastatic samples | Gene expression, DNA mutations, DNA methylation, chromatin accessibility, CNA, protein expression, histopathology images | 11,315 cancer genomes from 33 cancer types | Joint effort between the US National Cancer Institute and the US National Human Genome Research Institute |
| ICGC            | Primary cancers, matched normal samples, some metastatic samples | Gene expression, DNA mutations, DNA methylation, CNA, protein expression | 25,000 cancer genomes from 22 cancer types | A global cancer genomics effort for documenting somatic mutations that drive common tumour types |
| PCAWG           | Samples from TCGA and ICGC | DNA variations from whole-genome sequencing | 2,658 cancer genomes from 38 tumour types | Revealed 288,457 structural variations across topologically associated domains\textsuperscript{12} |
| LINCS           | Human cell lines | Differential expression upon treatment or genetic perturbations | 1.4 million gene expression profiles in 50 cell types, focused on approximately 1,000 landmark genes | Probes how cell models respond to chemical or genetic perturbations through use of microarrays focused on approximately 1,000 genes that are most representative of variations in the transcriptome\textsuperscript{12} |
| CCLE            | Human cancer cell lines | Gene expression, DNA mutations, promoter methylation, CNA, metabolomics, drug sensitivity, CRISPR/RNAi genome-wide screens, protein expression for a few targets | 1,072 cell lines | Provides a data encyclopedia of human cancer cell lines\textsuperscript{178} |
| CPTAC           | Human cancers and normal tissue | Protein expression and post-translational modifications | Almost 4,000 samples from 14 tumour sites | A national effort to understand the molecular basis of cancer through large-scale proteome genomics |
| Human Protein Atlas | Human cancers, normal tissues, cell models | IHC images, gene expression | 3.1 million annotated IHC tissue images for most protein-coding genes, spanning 17 cancer types | Aims to map all human proteins in tumours and tissues using IHC\textsuperscript{179} |
| GENIE           | Human cancers | Exome mutations focused on common cancer-related genes | 136,096 cases from 110 cancer sites | A registry assembled through 19 cancer centres worldwide, aggregating sequencing data obtained during routine medical practice from patients with cancer |
| CAMELYON        | Sentinel lymph nodes of patients with metastatic breast cancer | H\textsubscript{\textsc{\textit{E}}}-stained slides | 1,399 whole-slide images with pathology annotations of metastases regions | A challenge to evaluate new and existing algorithms for automated detection and classification of breast cancer metastases in whole-slide images of lymph nodes\textsuperscript{119} |
| TARGET          | Paediatric cancers | Gene expression, DNA mutation (whole-genome and whole-exome sequencing), DNA methylation | 6,196 cancer genomes spanning 9 cancer types | Applies a comprehensive genomic approach to determine molecular changes that drive childhood cancers |

CCLE, Cancer Cell Line Encyclopedia; CNA, copy number alteration; CPTAC, Clinical Proteomic Tumour Analysis Consortium; H\textsubscript{\textsc{\textit{E}}}, haematoxylin and eosin; ICGC, International Cancer Genome Consortium; IHC, immunohistochemistry; PCAWG, Pan-Cancer Analysis of Whole Genomes; TARGET, Therapeutically Applicable Research to Generate Effective Treatments; TCGA, The Cancer Genome Atlas.
T cell and CD4+ T cell populations could be clearly separated in the protein data but were blended when the transcriptome was analysed. Conversely, dendritic cells formed distinct clusters when assessed on the basis of transcriptomic data, whereas they mixed with other cell types when assessed on the basis of cell-surface protein levels. Chromatin accessibility measured by assay for transposase-accessible chromatin using sequencing (ATAC-seq) further revealed T cell sublineages by capturing lineage-specific regulatory regions. For each cell, the study identified neighbouring cells through similar methods. Then, the study defined the weights of the different data modalities in the lineage classification as their accuracy for predicting molecular profiles of the target cell from the profiles of neighbouring cells. The resulting cell clustering, using the weighted distance averaged across single-cell RNA, protein and chromatin accessibility data, was then shown to improve cell lineage separation.

Another common type of multimodal data analysis involves integrating molecular omics data and data on physical interaction networks (typically those involving protein–protein or protein–DNA interactions) to understand how individual genes interact with each other to drive oncogenesis and metastasis. For example, an integrative pan-cancer analysis of TCGA detected 407 master regulators organized into 24 modules, partly shared across cancer types, that appear to canalize heterogeneous sets of mutations. In another study, an analysis of 2,583 whole-tumour genomes across 27 cancers by the Pan-Cancer Analysis of Whole Genomes Consortium revealed rare mutations in the promoters of genes with many interactions (such as TP53, TLE4 and TCF4), and these mutations correlated with low downstream gene expression. These examples of integrating networks and genomics data demonstrate a promising way to identify rare somatic mutations with a causal role in oncogenesis.

**Knowledge transfer through data reuse.** Existing data can be leveraged to make new discoveries. For example, cell-fraction deconvolution techniques can infer the composition of individual cell types in bulk-tumour transcriptomics profiles. Such methods typically assemble gene expression profiles of diverse cell types from many existing datasets and perform regression or signature-enrichment analysis to deconvolve cell fractions or lineage-specific expression in a bulk-tumour expression profile.

Other data reuse examples come from single-cell transcriptomics data analysis. As single-cell RNA sequencing (scRNA-seq) has a high number of zero counts (dropout), analyses based on a limited number of genes may lead to unreliable results, and genome-wide signatures from bulk data can therefore complement such analyses. For example, the transcriptomic data atlas collected from cytokine treatments in bulk cell cultures has enabled the reliable inference of signalling activities in scRNA-seq data, further, single-cell signalling activities inferred through bulk data have been used to reveal therapeutic targets, such as FIBP, to potentiate cellular therapies in solid tumours and molecular programmes of T cells that are resistant to immunosuppression in cancer. In another example, the analysis of more than 50,000 scRNA-seq profiles from 35 pancreatic adenocarcinomas and control samples revealed edge cells among non-neoplastic acinar cells, whose transcriptomes have drifted towards malignant pancreatic adenocarcinoma cells; TCGA bulk pancreatic adenocarcinoma data were then used to validate the edge-cell signatures inferred from the single-cell data.
Data reuse can assist the development of new experimental tests. For example, existing tumour whole-exome sequencing data were used to optimize a circulating tumour DNA assay by maximizing the number of alterations detected per patient, while minimizing gene and region selection size\(^8\). The resulting circulating tumour DNA assay can provide a comprehensive view of therapy resistance and cancer relapse and metastasis by detecting alterations in DNA released from multiple tumour regions or different tumour sites\(^7\).

Although the data scale in cancer research is typically much smaller than in other fields, the number of input features, such as genes or imaging pixels, can be extremely high. Training a machine learning model with a high number of input dimensions (a large number of features) and small data size (a small number of training samples) is likely to lead to overfitting, in which the model learns the noise from training data and cannot generalize on new data\(^4\). Transfer learning approaches are a promising way of addressing this disparity related to data reuse. These approaches involve training a neural network model on a large, related dataset, and then fine-tuning the model on the smaller, target dataset. For example, most cancer histopathology artificial intelligence (AI) frameworks start from pretrained architectures from ImageNet — an image database containing 15 million images with detailed hierarchical annotations\(^1\) — and then fine-tune the framework on new imaging datasets of smaller sizes. As a further example of this approach, a few-shot learning framework enabled the prediction of drug response using data from only several patient-derived samples and a model pretrained using in vitro data from cell lines\(^9\). Despite these successful applications, transfer learning should be used with caution as it may produce mostly false predictions when data properties are markedly different between the pretraining set and the new dataset. Training a lightweight model\(^8\) or augmenting the new dataset\(^7\) are alternative solutions.

Table 4 | Web applications that enable interactive analysis of cancer datasets

| Web application | Data sources integrated | Functions |
|-----------------|------------------------|-----------|
| cBioportal      | 344 cancer omics data cohorts from large-scale projects, such as TCGA and GENIE, and many homogenized datasets from individual studies\(^1\) | Interactive analysis and visualization modules to find associations among different data types and clinical outcomes |
| UCSC Xena       | 139 omics data cohorts from large-scale projects, such as TCGA, ICGC and GTEx, and many homogenized datasets from individual studies\(^2\) | Interactive data analysis and visualization modules to identify cancer immune evasion regulators, predict immune checkpoint blockade response from pretreatment transcriptomic profiles and evaluate new immunotherapy biomarkers in public cohorts |
| PRECOG          | 166 gene expression datasets, collected from GEO and ArrayExpress | Query associations between gene expression and survival outcomes\(^7\) |
| RABIT           | 686 ChIP--seq profiles representing 150 transcription factors with 7,484 TCGA tumour profiles in 18 cancer types | Presents transcription factors and RBPs shaping gene expression patterns in diverse cancer types by integrating ChIP--seq data from diverse cell models, with information on transcription factor and RBP motifs and tumour gene expression profiles\(^3\) |
| TISCH           | 79 public single-cell RNA-seq datasets, including 2,045,746 cells | Shows gene expression levels in diverse cell populations in tumours\(^4\) |
| DepMap          | Genome-wide CRISPR screen data from 1,086 cell lines and RNAi screen data from 710 cell lines, paired with omics profiles and drug sensitivities of cell models | Queries the effects of perturbing genes on cell line fitness. Also presents a cell line's gene expression, copy number alterations and DNA mutations |
| Tres            | 36 single-cell RNA-seq datasets from 168 tumours spanning 19 cancer types, 8 T cell transcriptomics datasets from immunotherapy response studies and 8 genome-wide genetic screens in T cells | Uses single-cell transcriptomic data from solid tumours to identify signatures of T cells that are resilient to immunosuppressive signals\(^5\). Users can query whether a gene is a positive or a negative marker of tumour-resilient T cells, or input gene expression profiles of T cells or T cell-enriched samples to predict the clinical efficacies of T cells in immune checkpoint blockade and adoptive cell transfer |

ChIP--seq, chromatin immunoprecipitation followed by sequencing; GEO, Gene Expression Omnibus; GTEx, Genotype-Tissue Expression Project; ICGC, International Cancer Genome Consortium; RBP, RNA-binding protein; RNA-seq, RNA sequencing; TCGA, The Cancer Genome Atlas.

Data-rich translational studies

Many clinical diagnoses and decisions, such as histopathology interpretations, are inherently subjective and rely on interpreters’ experience or the availability of standardized diagnostic nomenclature and taxonomy. Such subjective factors may bring interpretive error\(^6\) and diagnostic discrepancies, for example when senior stature
can have an undue influence on diagnostic decisions — the so-called big-dog effect\(^a\). Big-data approaches can provide complementary options that are systematic and objective to guide diagnosis and clinical decisions.

**Diagnostic biomarkers trained from data cohorts.** A major focus of translational big-data studies in cancer has been the development of genomics tests for predicting disease risk, some of which have already been approved by the US Food and Drug Administration (FDA) and commercialized for clinical use\(^a\). Distinct from biomarker discoveries through biological mechanisms and empirical observations, big-data-derived tests analyse genome-scale genomics data from many patients and cohorts to generate a gene signature for clinical assays\(^b\). Such predictors mainly help clinicians determine the minimal therapy aggressiveness needed to minimize unnecessary treatment and side effects. The success of such tests depends on their high negative predictive value — the proportion of negative tests that reflect true negative results — so as not to miss patients who need aggressive therapy options\(^a\).

Some early examples of diagnostic biomarker tests trained from big data include prognosis assays for patients with oestrogen receptor (ER)- or progesterone receptor (PR)-positive breast cancer, such as Oncotype DX\(^a,b\), MammaPrint\(^c,d\), EndoPredict\(^e\) and Prosigna\(^f\). These tests are particularly useful as adjuvant endocrine therapy alone can bring sufficient clinical benefit to ER/PR-positive, HER2-negative patients with early-stage breast cancer\(^g\). Thus, patients stratified as being at low risk can avoid unnecessary additional chemotherapy. Predictors for other cancer types include Oncotype DX biomarkers for colon cancer\(^h\) and prostate cancer\(^i\) and Pervenio for early-stage lung cancer\(^j\).

In the early applications discussed above, large-scale data from genome-scale experiments served in the biomarker discovery stage but not in their clinical implementation. Owing to the high cost of genome-wide experiments and patent issues, the biomarker tests themselves still need to be performed through quantitative PCR or NanoString gene panels. However, the rapid decline of DNA sequencing costs in recent years could allow therapy decisions to be informed directly by genomics data and bring notable advantages over conventional approaches\(^k\). Gene alterations relevant to therapy decisions could involve diverse forms, including single-nucleotide mutations, DNA insertions, DNA deletions, copy number alterations, gene rearrangements, microsatellite instability and tumour mutational burden\(^\ell, m-o\). These alterations can be detected by combining hybridization-based capture and high-throughput sequencing. The MSK-IMPACT\(^n\) and FoundationOne CDx\(^o\) tests profile 300–500 genes and can use DNA from formalin-fixed, paraffin-embedded tumour specimens to detect oncogenic alterations and identify patients who may benefit from various therapies.

Variant interpretation in clinical decisions is still challenging as the oncogenic impact of each mutation depends on its clonality\(^p\), zygosity\(^q\) and co-occurrences with other mutations\(^r\). Sequencing data can uncover tumorigenic processes (such as DNA repair defects, exogenous mutagen exposure and prior therapy histories\(^s\)) by identifying underlying mutational signatures, such as DNA substitution classes and sequence contexts\(^t\). Future computational frameworks for therapy decisions should therefore consider many dimensions of variants and inferred biological processes, together with other clinical data, such as histopathology data, radiology images and health records.

Data-rich assays that complement precision therapies currently focus on specific genomic aberrations. However, epigenetic therapies, such as inhibitors that target histone deacetylases\(^u\), have a genome-wide effect and are typically combined with other treatments, and therefore current genomics assays may not readily evaluate their therapeutic efficacy. We could not find any clinical datasets of histone deacetylase inhibitors deposited in the NCBI GEO database when writing this Review, indicating there are many unexplored territories of data-driven predictions for this broad category of anticancer therapies.

**Clinical trials guided by molecular data.** Genome-wide and multimodal data have begun to play a role in matching patients in prospective multi-arm clinical trials, particularly those investigating precision therapies. For example, the WINTER trial prospectively matched patients with advanced cancer to therapy on the basis of DNA sequencing (arm A, through Foundation One assays) or RNA expression (arm B, comparing tumour tissue with normal tissue through Agilent oligonucleotide arrays) data from solid tumour biopsies\(^v\). Such therapy matches by omics data typically lead to off-label drug use. The WINTER study concluded that both data types

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**Fig. 1** Considerations for using big data in translational applications and basic research. Clinical decisions, basic research and the development of new therapies should consider two orthogonal dimensions when leveraging big-data resources: integrating data across many data modalities and integrating data from different cohorts, which may include the transfer of knowledge from pre-existing datasets.
were of value for improving therapy recommendations and patient outcomes. Furthermore, there were no significant differences between DNA sequencing and RNA expression with regard to providing therapies with clinical benefits, which was corroborated by a later study.

Other, similar trials have demonstrated the utility of matching patients for off-label use of targeted therapies on the basis of genome-wide genomics or transcriptomics data (Fig. 2). In these studies, the fraction of enrolled patients who had therapies matched by omics data ranged from 19% to 37% (WINTHER, 35%; POG, 37%; MASTER, 31.8%; MOSCATO 01, 19.2%; CoPPO, 20%). Among these matched patients, about one third demonstrated clinical benefits (WINTHER, 25%; POG, 46%; MASTER, 35.7%; MOSCATO 01, 33%; CoPPO, 32%). Except for the POG study, all studies used the end point defined by the Von Hoff model, which compares progression-free survival (PFS) for the trial (PFS2) with the PFS recorded for the therapy preceding enrolment (PFS1) and defines clinical benefit as a PFS2/PFS1 ratio of more than 1.3 (REF 3).

A recent study demonstrated the feasibility and value of an N-of-one strategy that collected multimodal data, including immunohistochemistry data for multiple protein markers, RNA levels and genomics alterations in cell-free DNA from liquid biopsies (Fig. 2). A broad multidisciplinary molecular tumour board (MTB) then made personalized decisions using these multimodal omics data. Overall, patients who received MTB-recommended treatments had significantly longer PFS and overall survival than those treated by independent physician choice. Similarly, another study also demonstrated overall survival benefits brought by MTB recommendations.

With these initial successes, emerging clinical studies aim to collect additional data beyond bulk-sample sequencings — such as tumour cell death response following various drug treatments or scRNA-seq data collected on longitudinal patient samples — to study therapy response and resistance mechanisms. Besides omics data generated from tumour samples, cross-modality data integration is a potential strategy to improve therapy recommendations. One such promising direction involves the study and application of synthetic lethal interactions, which, once integrated with tumour transcriptomic profiles, can accurately score drug target importance and predict clinical outcomes for many anticancer treatments, including targeted therapies and immunotherapies. We foresee that new data modalities and assays will provide additional ways to design clinical trials.

**Artificial intelligence for data-driven cancer diagnosis.** Genomics datasets, such as gene expression levels or mutation status, can typically be aligned to each other on gene dimensions. However, data types in clinical diagnoses, such as imaging data or text reports, may not directly align across samples in any obvious way. AI approaches based on deep neural networks are an emerging method for integrating these data types for clinical applications.

The most popular application of AI for analysing imaging data involves clinical outcome prediction and tumour detection and grading from tissue stained with haematoxylin and eosin (H&E). In September 2021, the FDA approved the use of the AI software Paige Prostate to assist pathologists in detecting cancer regions from prostate needle biopsy samples (Fig. 3a). This approval reflects the accelerating momentum of AI applications on histopathology images to complement conventional pathologist practices and increase analysis throughput, particularly for less experienced pathologists. The CAMELYON challenge for identifying tumour regions provided 1,399 manually annotated whole-slide H&E-stained tissue images of sentinel lymph nodes from patients with breast cancer for training AI algorithms. The top performers in the challenge used deep learning approaches, which achieved similar performance in detecting lymph node metastasis as expert pathologists. Other studies have trained deep neural networks to predict patient survival outcomes, gene mutations or genomic alterations, on the basis of analysing a large body of H&E-stained tissue images with clinical outcome labels or genomics profiles.

Besides histopathology, radiology is another application of AI imaging analysis. Deep convolutional neural
networks that use 3D computed tomography volumes have been shown to predict the risk of lung cancer with an accuracy comparable to that of predictions by experienced radiologists\textsuperscript{114}. Similarly, convolutional neural networks can use computed tomography data to stratify the survival duration of patients with lung cancer and highlight the importance of tumour-surrounding tissues in risk stratification\textsuperscript{115}. AI frameworks have started to play an important role in analysing electronic health records. A recent study evaluating the effect of different eligibility criteria on cancer trial outcomes using electronic health records of more than 60,000 patients with non-small-cell lung cancer revealed that many patient exclusion criteria commonly used in clinical trials had a minimal effect on trial hazard ratios\textsuperscript{25}. Dropping these exclusion criteria would only marginally decrease the overall survival and result in more inclusive trials without compromising patient safety and overall trial success rates\textsuperscript{25}. Besides images and health records, AI trained on other data types also has broad clinical applications, such as early cancer detection through liquid biopsies capturing cell-free DNA\textsuperscript{116,117} or T cell receptor sequences\textsuperscript{118}, or genomics-based cancer risk predictions\textsuperscript{119,120}. Additional examples of AI applications in cancer are available in other reviews\textsuperscript{40,121}. New AI approaches have started to play a role in biological knowledge discovery. The saliency map\textsuperscript{122} and class activation map\textsuperscript{123} can highlight essential portions of input images that drive predicted outcomes. Also, in a multisample cohort, clustering data slices on the basis of deep learning-embedded similarities can reveal human-interpretable features associated with a clinical outcome. For example, clustering similar image patches related to colorectal cancer survival prediction revealed that high-risk survival predictions are associated with a tumour–adipose feature, characterized by poorly differentiated tumour cells adjacent to adipose tissue\textsuperscript{124}. Although the molecular mechanisms underlying this association are unclear, this study provided an example of finding imaging features that could help cancer biologists pinpoint new disease mechanisms. Despite the promising results described above, few AI-based algorithms have reached clinical deployment due to several limitations\textsuperscript{26}. First, the performance of most AI predictors deteriorates when they are applied to test data generated in a setting different from that in which their training data are generated. For example,

Fig. 3 | Data-driven artificial intelligence to support cancer diagnosis. a | A common artificial intelligence (AI) framework in cancer detection uses a convolutional neural network (CNN) to detect the presence of cancer cells from a diagnostic image. CNNs use convolution (weighted sum of a region patch) and pooling (summarize values in a region to one value) to encode image regions into low-dimensional numerical vectors that can be analysed by machine learning models. The CNN architecture is typically pretrained with ImageNet data, which is much larger than any cancer biology imaging dataset. To increase the reliability of the AI framework, the input data can be augmented through rotation or blurring of tissue images to increase data size. The data are separated into non-overlapping training, tuning and test sets to train the AI model, tune hyperparameters and estimate the prediction accuracy on new inputs, respectively. False-positive predictions are typically essential data points for retraining the AI model. b | An example of the application of AI in informing clinical decisions, as per the US Food and Drug Administration-approved AI test Paige Prostate. From one needle biopsy sample, the pathologist can decide whether cancer cells are present. If the results are negative (‘no cancer’) or if the physician cannot make a firm diagnosis (‘defer’), the Paige Prostate AI can analyse the image and prompt the pathologist with regard to potential cancer locations if any are detected. The alternative procedure involves evaluating multiple biopsy samples and performing immunohistochemistry tests on prostate cancer markers, independently from the AI test\textsuperscript{185}. 
the performance of top algorithms from the CAMELYON challenge dropped by about 20% when they were evaluated on the basis of data from other centres. Such a gap may arise from differences in image scanners (if imaging data are being evaluated), sample collection protocols or study design, emphasizing the need for reliable data homogenization. Second, supervised AI training requires a large amount of annotated data, and acquiring sufficient human-annotated data can be challenging. In imaging data, if a feature for a particular diagnosis is present in only a fraction of image regions, an algorithm will need many samples to learn the task. Furthermore, if features are not present in the training data, the AI will not make meaningful predictions; for example, the AI framework of AlphaFold2 can predict wild type protein structures with high accuracy, but it cannot predict the impact of cancer missense mutations on protein structures because the training data for AlphaFold2 do not contain altered structures of these mutated proteins.

Many studies of AI applications that claim improvements lack comparisons with conventional clinical procedures. For example, the performance study of Paige Prostate evaluated cancer detection using an H&E-stained tissue image from one needle biopsy sample. However, the pathologist may make decisions on the basis of multiple needle biopsy samples and immunohistochemistry stains for suspicious samples instead of relying on one H&E-stained tissue image. Therefore, rigorous comparison with conventional clinical workflows is necessary for each application before the advantage of any AI framework is claimed.

**New therapy development aided by big-data analysis.**

Developing a new drug is costly, time-intensive and suffers from a high failure rate. The development of new therapies is a promising direction for big-data applications. To our knowledge, no FDA-approved cancer drugs have been developed primarily through big-data approaches; however, some big data-driven preclinical studies have attracted the attention of the pharmaceutical industry for further development and may soon make impactful contributions to clinics.

Big data have been used to aid the repurposing of existing drugs to treat new diseases and the design of synergistic combinations. By creating a network of 1.2 billion edges among diseases, tissues, genes, pathways and drugs by mining more than 40 million documents, one study revealed that the combination of vandetanib and everolimus could inhibit ACVR1, a drug efflux transporter, as a potential therapy for diffuse intrinsic pontine glioma. Recent studies have combined pharmacological data and AI to design new drugs. A deep generative model was used to design new small molecules inhibiting the receptor tyrosine kinase DDR1 on the basis of information on existing DDR1 inhibitors and compound libraries, with the lead candidate demonstrating favourable pharmacokinetics in mice. Deep generative models are neural networks with many layers that...
learn complex characteristics of specific datasets (such as high-dimensional probability distributions) and can use them to generate new data similar to the training data\textsuperscript{10}. For each specific drug design application, such a framework can encode distinct data into the neural network parameters and thus naturally incorporate many data types. A network aiming to find novel kinase inhibitors, for example, may include data on the structure of existing kinase inhibitors, non-kinase inhibitors and patent-protected molecules that are to be avoided\textsuperscript{106}.

AI can also be used for the virtual screening of bioactive ligands on target protein structures. Under the assumption that biochemical interactions are local among chemical groups, convolutional neural networks can comprehensively integrate training data from previous virtual screening studies to outperform previous docking methods based on minimizing empirical scores\textsuperscript{139}. Similarly, a systematic evaluation revealed that deep neural networks trained using large and diverse datasets composed of molecular descriptors and drug biological activities could predict the activity of test-set molecules better than other approaches\textsuperscript{139}.

**Big data in front of narrow therapeutic bottlenecks.** During dynamic tumour evolution, cancers generally become more heterogeneous and harbour a more diverse population of cells with different treatment sensitivities. Drug resistance can eventually evolve from a narrow bottleneck of a few cells\textsuperscript{135}. Furthermore, the difference between a treatment dose with antitumour effects and toxicity leading to either clinical trial failure or treatment cessation is small\textsuperscript{136}. These two challenges are common reasons for anticancer therapy failures as increasing drug combinations to target rare cancer cells will quickly lead to unacceptable toxic effects. An essential question is whether big data can bring solutions to overcome heterogeneous tumour evolution towards drug resistance while avoiding intolerable toxic effects.

Ideally, well-designed drug combinations should target various subsets of drug-tolerant cells in tumours and induce robust responses. Computational methods have been developed to design synergistic drug pairs\textsuperscript{131,141}; however, drug synergy may not be predictable for certain combinations even with comprehensive training data. A recent community effort assessed drug synergy prediction methods trained on AstraZeneca’s large drug combination dataset, consisting of 11,576 experiments from 910 combinations across 85 molecularly characterized cancer cell lines\textsuperscript{136}. The results showed that none of the methods evaluated could make reliable predictions for approximately 20% of the drug pairs whose targets independently regulate downstream pathways.

There could be a theoretical limitation of the power of drug combinations in killing heterogeneous tumour cells while avoiding toxic effects on normal tissues. A recent study mining 15 single-cell transcriptomics datasets revealed that inhibition of four cell-surface targets is necessary to kill at least 80% of tumour cells while sparing at least 90% of normal cells in tumours\textsuperscript{142}. However, a feasible drug-target combination may not exist to kill a higher fraction of tumour cells while sparing normal cells.

An important challenge accompanying therapy design efforts is the identification of genomic biomarkers that could predict toxicity. A community evaluation demonstrated that computational methods could predict the cytotoxicity of environmental chemicals on the basis of the genotype data of lymphoblastoid cell lines\textsuperscript{143}. Further, a computational framework has been used to predict drug toxicity by integrating information on drug-target expression in tissues, gene network connectivity, chemical structures and toxicity annotations from clinical trials\textsuperscript{144}. However, these studies were not explicitly designed for anticancer drugs, which are challenging with regard to toxicity prediction due to their extended cytotoxicity profiles.

**Challenges and future perspectives**

While many big-data advancements are encouraging and impressive, considerable challenges remain regarding big-data applications in cancer research and the clinic. Omics data often suffer from measurement inconsistencies between cohorts, marked batch effects and dependencies on specific experimental platforms. Such a lack of consistency is a major hurdle towards clinical translation. Consensus on the measurement, alignment and normalization of tumour omics data will be critical for each data type\textsuperscript{145}. Besides these technical challenges, structural and societal challenges also exist and may impede the progress of the entire cancer data science field. We discuss these in the following subsections.

**Less-than-desirable data availability.** A key challenge of cancer data science is the insufficient availability of data and code. A recent study found that machine learning-based studies in the biomedical domain compare poorly with those in other areas regarding public data and source code availability\textsuperscript{146}. Sometimes, the clinical information accompanying published cancer genomics data is not provided or complete, even when security and privacy issues are resolved. One possible reason for this bottleneck is related to data release policies and data stewardship costs. Although many journals require the public release of data, such requirements are often met by deposition of data into repositories that require author and institutional approval-of-access requests due to intellectual property and various other considerations. Furthermore, deposited data may be missing critical information, such as missing cell barcodes for single-cell sequencing data or low-resolution images in the case of histopathology data.

In our opinion, the mitigation of these issues will require the enforcement of policies regarding public data availability by funding agencies and additional community efforts to examine the fulfilment of open data access. For example, a funding agency may suspend a project if the community readers report any violations of data release agreements upon publication of articles. The allocation of budgets in grants for patient de-identification upon manuscript submission and financial incentives for checking data through independent data stewardship services upon paper acceptance could markedly help facilitate data and code availability. One notable advance in data availability through industry-academia
alliances has come in the form of data-sharing initiatives; specifically, making large repositories of patient tumour sequencing and clinical data available for online queries to researchers in partner institutions. Such initiatives typically involve query-only access (that is, without allowing downloads), but are an encouraging way to expand the collaborative network between academia and industry entities that generate massive amounts of data.

**Data-scale gaps.** As mentioned earlier, the datasets available for cancer therapeutics are substantially smaller than those available in other fields. One reason for such a gap is that the generation of medical data depends on professionally trained scientists. To close the data-scale gap, more investments will be required to automate the generation of at least some types of annotated medical data and patient omics data. Rare cancers especially suffer from a lack of preclinical models, clinical samples and dedicated funding. Moreover, the usability of biomedical data is typically constrained by the genetic background of the population. For example, the frequency of actionable mutations may differ among East Asian, European and American populations.

A further reason for the data-scale gap is a lack of data generation standards in cancer clinical and biology studies. For example, most clinical trials do not yet collect omics data from patients. With the exponential decrease in sequencing cost, collection of omics data in clinical trials should, in our opinion, be markedly expanded, and possibly be made mandatory as a standard requirement. Further, current data repositories, such as ClinicalTrials.gov and NCBI GEO, do not have common metagenealogy standards, whose incorporation would markedly improve the development of algorithms applied to their analysis. Although semi-automated frameworks are becoming available to homogenize metadata, the foundational solution should be establishing common vocabularies and systematic meta-information standards in critical fields.

**Conclusion**

Data science and AI are transforming our world through applications as diverse as self-driving cars, facial recognition and language translation, and in the medical world, the interpretation of images in radiology and pathology. We already have available tumour data to facilitate biomedical breakthroughs in cancer through cross-modality integration, cross-cohort aggregation and data reuse, and extraordinary advancements are being made in generating and analysing such data. However, the state of big data in the field is complex, and in our view, we should acknowledge that ‘big data’ in cancer are not yet so big. Future investments from the global research community to expand cancer datasets will be critical to allow better computational models to drive basic research, cancer diagnostics and the development of new therapies.

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P.J. and E.R. designed the scope and structure of the Review, assembled write-up components and finalized the manuscript. C.S. wrote the text on tumour evolution and heterogeneity. S.H. wrote the text on transcriptional dysregulation. P.J. wrote the sections related to spatial genomics and artificial intelligence. P.J., E.R. and K.A. wrote the section on cancer diagnosis and treatment decisions. S.S. and P.J. prepared Tables 1–4.

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