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Precision oncology platforms: practical strategies for genomic database utilization in cancer treatment

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Abstract

In recent years, the expansion of molecularly targeted cancer therapies has significantly advanced precision oncology. Parallel developments in next-generation sequencing (NGS) technologies have also improved precision oncology applications, making genomic analysis of tumors more affordable and accessible. Targeted NGS panels now enable the rapid identification of diverse actionable mutations, requiring clinicians to efficiently assess the predictive value of cancer biomarkers for specific treatments. The urgency for timely and accurate decision-making in oncology emphasizes the importance of reliable precision oncology software. Online clinical decision-making tools and associated cancer databases have been designed by consolidating genomic data into standardized, accessible formats. These new platforms are highly integrated and crucial for identifying actionable somatic genomic biomarkers essential for tumor survival, determining corresponding drug targets, and selecting appropriate treatments based on the mutational profile of each patient's tumor. To help oncologists and translational cancer researchers unfamiliar with these tools, we review the utility, accuracy, and comprehensiveness of several commonly used precision medicine software options currently available. Our analysis categorized selected genomic databases based on their primary content, utility, and how well they provide practical guidance for interpreting somatic biomarker data. We identified several comprehensive, mostly open-access platforms that are easy to use for genetic biomarker searches, each with unique features and limitations. Among the precision oncology tools we evaluated, we found MyCancerGenome and OncoKB to be the first choice, offering comprehensive, accurate up-to-date information on the clinical significance of somatic mutations. To illustrate the application of these precision oncology tools in clinical settings, we evaluated three case studies to see how use of the platforms could have influenced treatment planning. Most of the precision oncology software evaluated could be easily streamlined into clinical workflows to provide updated information on approved drugs and clinical trials related the actionable mutations detected. Some platforms were very intuitive and easy to use, while others, often developed in smaller academic settings, were more difficult to navigate and may not be updated consistently. Future enhancements, incorporating artificial intelligence algorithms, are likely to improve integration of the platforms with diverse big data sources, enabling more accurate predictions of potential therapeutic responses.

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Background

Cancer is a leading cause of mortality worldwide, representing a significant public health challenge. The year 2022 witnessed a staggering incidence of close to 20 million new cases reported, with 9.7 million fatalities, contributing to nearly one-sixth of total deaths, which emphasizes the profound global impact of this disease [1]. These figures underscore the critical need for ongoing cancer research and innovative therapeutic approaches to combat the disease.

The evolution of cancer research into the field of precision medicine has led to a greater understanding of the genomic underpinnings of cancer. Advances in genomic profiling have enabled researchers to identify key cancer-driving mutations that influence cancer risk, prognosis, and treatment responses [2]. This rapid increase in the availability of genomic data has driven progress in tumor classification and the development of personalized therapeutic strategies [3].

Advances in precision medicine have been greatly facilitated by next-generation sequencing (NGS) technologies, which have become more accessible and cost-effective. Various targeted NGS panels enable comprehensive genomic profiling of tumors to provide timely identification of diverse actionable mutations [4]. Other promising new developments include applications of liquid biopsies, which allow for real-time detection of mutations in circulating tumor DNA, revealing clinical information about tumor dynamics and potential acquired resistance mechanisms [5]. The development of patient-derived tumor organoid cultures is accelerating the discovery of new anti-cancer therapies by enabling in vitro testing of novel drugs on cells derived from the patient's own tumor [6]. Recent progress in treatments include immunotherapy, which has shown remarkable success in various tumors by activating the natural anticancer immune system [7]. These innovations have transformed the landscape of cancer treatment, offering new avenues for targeted therapies and improving patient outcomes. As oncologists gain access to detailed molecular profiling reports, they face several key tasks to translate this wealth of new information into actionable clinical interventions.

Initially, clinicians must determine the tumor tissue and type of genomic analysis they will use and assess the reliability of the test results. Afterward, they need to identify actionable gene alterations and determine how these acquired changes might impact tumor gene function. The challenge lies in interpreting which somatic molecular alterations are clinically significant, as only a subset represents actionable cancer driver mutations [8]. For actionable somatic changes, oncologists must have an up-to-date evaluation of all the therapeutic implications, considering drugs that target these genetic mutations or copy number changes, both approved and in development.

Despite notable advances in the development and approval of molecularly targeted cancer therapies, there remains a lack of standardized processes for somatic mutation analysis and NGS sequencing reports. Clinicians must assess the evidence supporting a cancer biomarker's predictive value for a specific treatment, while also considering other approved or investigational therapeutic options. Given the limited time available to oncologists for decision-making, these steps must be completed efficiently in a timely and accurate way. To address this challenge, reliable cancer databases and associated precision oncology platforms have emerged to aid clinical decision-making by consolidating data from multiple sources into a standardized and accessible format.

Precision oncology platforms must efficiently identify the actionable somatic mutations essential for tumor survival, determine the drugs that can target these mutations, and identify the most appropriate treatments based on the mutational profile of the tumor. In this review, we evaluate the utility, accuracy, and comprehensiveness of some of the commonly used precision medicine support tools available to oncologists and cancer researchers. We provide practical guidance on their use to facilitate better interpretation of cancer mutation panel results. By assessing these aspects, we aim to identify the most effective web-based tools for integrating cancer genomic data into clinical practice. These platforms will also be invaluable for translational cancer researchers investigating preclinical therapies related to mutations, while also offering critical insights into emerging biomarkers such as gene expression data (RNA-seq), copy number variation (CNV), and structural aberrations. Additionally, we present three case studies from the literature to illustrate how clinicians can take advantage of these precision medicine tools to decide on potential treatment options based on tumor mutations. Ultimately, our goal is to provide oncologists with practical insights and recommendations to optimize the use of genomic medicine for personalized cancer treatment.

Methods

To facilitate a comprehensive analysis, a review of genomic databases was conducted. The selected databases were identified by searching existing literature, and

each platform was categorized based on its primary content and utility (detailed in Supplementary Table 1). The databases were divided into three distinct categories:

- "*Clinical Reasoning Guiding Genomic Databases*": these platforms allow users to search for a gene mutation and obtain relevant information on its association with cancer types and corresponding therapies. They provide valuable data on the clinical significance of drugs (including currently available and those drugs under clinical trials).
- "*Therapy Guiding Genomic Databases with Limitations*": these platforms allow users to search for a gene mutation and obtain relevant information on its association with cancer types and corresponding therapies. However, they have certain limitations, such as requiring paid memberships, relying on data about the clinical significance of therapies from other platforms, or having variable completeness of data.
- "*Cancer Research Guiding Databases*": these platforms allow users to search for a gene mutation and get relevant clinical information. However, these platforms do not focus on providing information to guide clinical reasoning and are likely to be of more use for translational cancer research.

Each identified database was systematically assessed and categorized according to the above criteria. The platform classifications are shown in Table 1. Our categorization process involved evaluating the databases' scope, primary purpose, the type of genomic information provided, and a detailed description of the functionality and ease of navigation. In Fig. 1 we provide a flowchart to illustrate the process of genomic data navigation, from data upload/analysis through to searching in research and clinical contexts. For each genomic platform, we also describe the various metrics used to estimate levels of evidence for the observations made. Our database summaries also include a description of the primary focus, the intended user base, and the specific types of genomic data evaluated.

To better understand the utility of the platforms under review, we chose three clinical cases from the literature that illustrate how mutational findings could be used to guide treatment. Each case involved a treatment modification based on the discovery of a new mutation through NGS. The mutations were then investigated using the platforms to evaluate the available information and exemplify how they could have helped to plan treatment.

Table 1 Databases and their respective websites. Databases are separated into three categories described in methods (left column)

	Name of database	Site
Category 1	MyCancerGenome	www.mycancergenome.org
	OncoKB	www.oncokb.org/
	VICC Variant Interpretation of Cancer Consortium	https://search.cancervariants.org
	CIViC	https://civicdb.org/welcome
	Personalized Cancer Therapy (MD Anderson)	https://pct.mdanderson.org/
	The Jackson Laboratory Clinical Knowledgebase (JAX)	https://ckb.jax.org
	Catalog of Somatic Mutations in Cancer (COSMIC): Cancer gene census	https://cancer.sanger.ac.uk/census
Category 2	Precision Medicine Knowledgebase	https://pmkb.weill.cornell.edu
	Molecular Match, Inc	https://www.molecularmatch.com/solutions/mmportal-clinical-decision-support.html
	cBioPortal for cancer genomics	https://www.cbioportal.org
	GCD Data Portal	https://portal.gdc.cancer.gov/
	BBG Lab - Cancer Genome Interpreter/Cancer Biomarker Database	https://www.cancergenomeinterpreter.org/home and https://www.cancergenomeinterpreter.org/biomarkers
Caterogy 3	Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer	https://mitelmandatabase.isb-cgc.org/
	Cancer Therapeutic Drug Portal	https://portals.broadinstitute.org/ctrp.v2.1/
	Cancer Cell Line Encyclopedia (CCLE) in Depmap Portal	https://depmap.org/portal/
	intOGen	https://www.intogen.org/
	DriverDBv4	http://driverdb.bioinfomics.org/
	European Variation Archive	https://www.ebi.ac.uk/eva
	GTEX portal	https://gtexportal.org/home/gene
	DoCM and DGIdb	http://docm.info and https://www.dgidb.org
	Tumor Portal	http://www.tumorportal.org/
	Genecards	https://www.genecards.org
	Cancer Driver Log	https://candl.osu.edu
	Genomics of drug sensitivity	https://www.cancerrxgene.org/

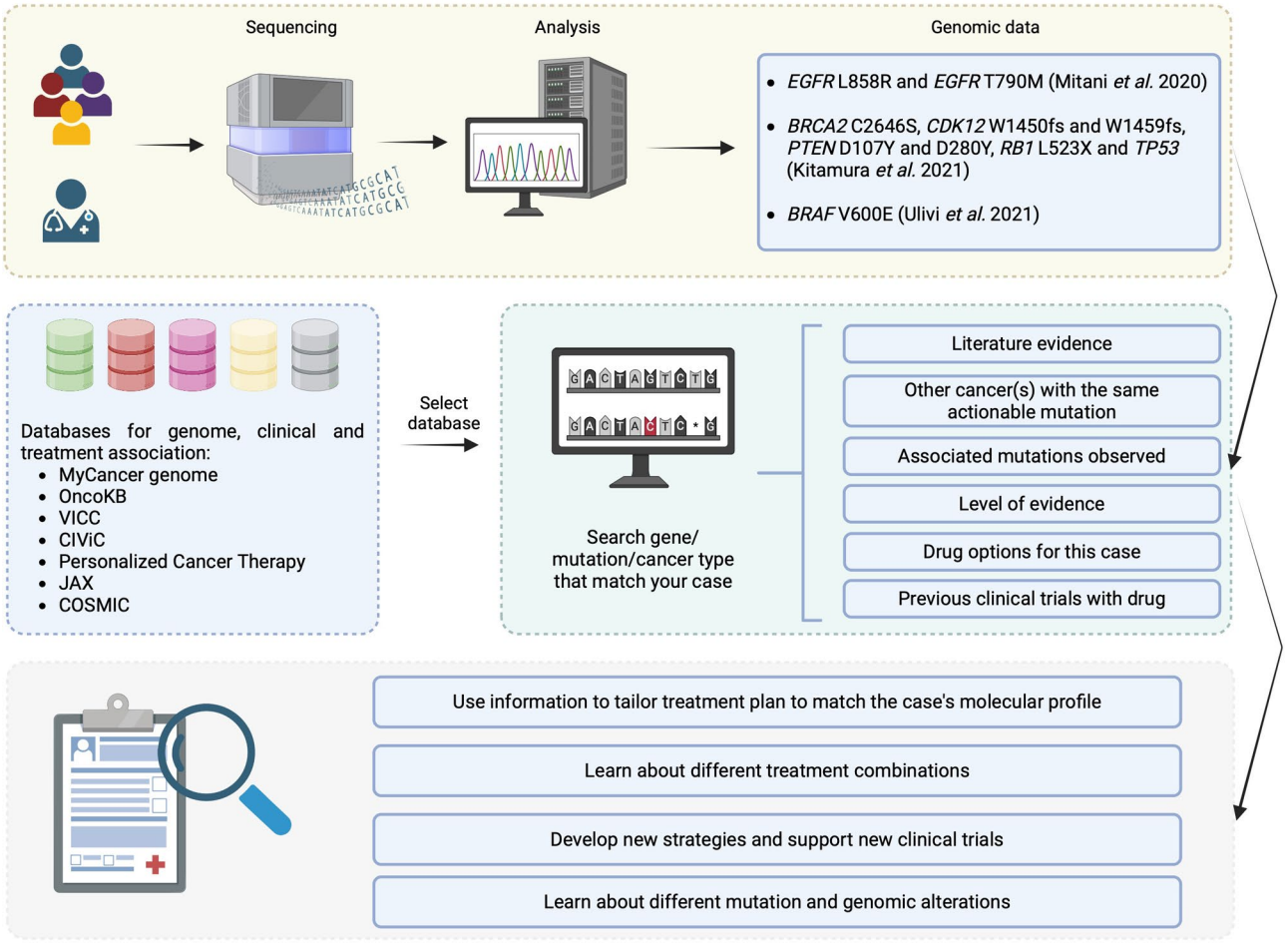

Fig. 1 Flowchart of a genomic database navigation. Yellow: contains an infographic representation of how the data is uploaded to the platforms. Usually, researchers sequenced data, analyzed it, and later included it in the platforms. Blue: represents the genomic databases, with examples. Green: users should search for a gene, mutation, or cancer type and get result data from the platforms. Grey: represents the several usages of the data provided by the platforms

Results

Clinical reasoning guiding genomic databases

My Cancer Genome

My Cancer Genome (www.mycancergenome.org) is an extensive online academic platform supported by Vanderbilt University (USA), which was designed to provide detailed information on genomic alterations in cancer, with a focus on their potential clinical implications. The platform automatically updates new information populating the web pages using their source knowledge base [9]. The resource is intended to be used by clinicians and researchers, facilitating a deeper understanding of the genomic landscape of cancer to support informed treatment decisions. The platform encompasses a broad range of molecular biomarkers, including chromosomal markers, structural alterations, and copy number variations (CNVs), with an emphasis on how these biomarkers impact drug responses and correlate with various cancer types.

This platform analyzes data from 16,871 molecular biomarkers and offers clinical recommendations for the use of 2,861 drugs across 955 cancer types. Additionally, My Cancer Genome contains data from nearly 100,000 tumor samples and almost 90,000 patients, sourced from the AACR Project GENIE database, which helps illustrate the prevalence of these biomarkers. This information is curated from a variety of authoritative sources, including the U.S. Food and Drug Administration (FDA) drug labels, National Comprehensive Cancer Network (NCCN) guidelines, other professional society guidelines, and primary literature, more than 9,800 clinical trials, and a broad range of peer-reviewed publications. By analyzing cancer genomic information derived from these databases, the platform provides detailed insights that are annotated to provide the key clinical implications associated with observed genomic alterations.

My Cancer Genome's search tool allows users to directly query the database for specific mutations, genes,

drugs, diseases, or clinical trials. The platform organizes search results into five categories: biomarkers, diseases, drugs, clinical trials, and pathways. When querying a somatic variant, for example, the platform offers a range of information including details about the genetic alteration and its associated cancer types, data on the prevalence of this alteration, information on past and current clinical trials related to this mutational variant and any potential clinical significance and therapeutic implications across various cancer types. The platform details the biomarker criteria for each drug and its predictive response, which is useful for choosing the best available option of treatment. The platform plans to include more assertions, such as prognostic and diagnostic assertions to the online platform and implement a level of evidence system in future updates [9].

MyCancerGenome platform is very intuitive, making it an ideal starting point for beginners exploring cancer-related genomic information. The platform is easy to navigate with comprehensive up-to-date information needed to guide clinical reasoning. MyCancerGenome also supports integration with applications outside its web interface, such as landscape analyses and interpretive reports for pathologists, clinical trial planning, and molecular tumor board reports [9]. This flexibility highlights the platform's application not only for individual patient care but also for broader clinical and research applications.

OncoKB

OncoKB™ (www.oncokb.org/) is a precision oncology knowledge base developed by Memorial Sloan Kettering Cancer Center (MSKCC) that integrates biological and clinical information related to genomic alterations in cancer [10, 11]. The platform analyses combined data from a range of sources, including PubMed, the National Comprehensive Cancer Network (NCCN), and FDA. OncoKB encompasses information on over 800 genes and more than 7,800 genomic alterations, with content guided by the MSK Clinical Genomics Annotation Committee.

The OncoKB database is structured to annotate the biologic and oncogenic effects, as well as the prognostic and predictive significance, of somatic molecular alterations (Additional Fig. 2). To facilitate its use in clinical settings, the database classifies the treatment implications of specific genomic alterations into levels, based on the evidence supporting their predictive value for drug response. The stratification of evidence encompasses FDA labeling, NCCN guidelines, recommendations from disease-focused expert groups, and data from the scientific literature. The categorization of therapeutic implications is as follows:

- *Level 1*: Biomarkers recognized by the FDA as predictive of response to FDA-approved drugs for a specific indication.
- *Level 2*: Standard care biomarkers recommended by NCCN or other professional guidelines that are predictive of response to FDA-approved drugs for a specific indication.
- *Level 3 A*: Compelling clinical evidence that biomarker is predictive of response to a drug in a certain indication.
- *Level 3B*: Standard care or investigational biomarker predictive of response to an FDA-approved or investigational drug in another indication.
- *Level 4*: Biomarker predictive of response based on compelling biological evidence.
- *R1*: Standard care biomarker predictive of resistance to an FDA-approved drug in this indication.
- *R2*: Biomarker predictive of resistance to a drug based on compelling clinical evidence.

OncoKB annotations are publicly accessible through its website and are also integrated into the cBioPortal for Cancer Genomics, enabling easy interpretation of genomic alterations by researchers and clinicians [12–14]. Users can search for specific genes, alterations, cancer types, drugs, or genomic variants using the platform's searcher. Upon querying a somatic variant, for example, the platform provides detailed information on the gene's function, the type of mutation, whether the mutation is oncogenic, and a list of cancer type-specific targeted therapies associated with the alteration, along with the corresponding level of evidence indicating clinical actionability and specific FDA level of evidence, assigning clinical significance.

Overall, it is a very thorough, user-friendly platform that contains the necessary information to guide clinicians. When using the platform for the first time, users have limited information, because there is a need to register to access a more detailed description of drug associations and clinical findings. After registration, the account needs to be accepted, so users might have delayed access to the complete platform. Information on the platform is frequently updated and users can subscribe to receive them via email notifications.

VICC

The Variant Interpretation for Cancer Consortium (VICC) (https://search.cancervariants.org) is an initia tive under the Global Alliance for Genomics & Health (GA4GH) framework, aiming to develop a comprehensive meta-knowledgebase of biomarkers related to cancer's response to drugs [15]. The consortium gathers data from several well-known sources focused on somatic variants in cancer, including CIViC, JAX-CKB,

MMatch, OncoKB, and PMKB. VICC's primary objective is to address the challenges of representing and sharing curated interpretations across the cancer research community. To achieve this, it integrates interpretations from various knowledge bases into a single platform, providing a unified view of cancer biomarkers and their associated clinical implications.

Interpretations are split across five different elements: gene, variant, disease, drugs, and evidence. Each element is color-coded to indicate its originating knowledge base, allowing users to identify the source of the data. In the platform, a gene or variant can be searched, and the platform will give a list of findings including the data source, the gene and the variant, the associated diseases and drugs with their response levels, their evidence labels, and the source URL and links to publications showing the findings. The search will also give a result count, an interactive source pie graph with the percentage of findings from each source, and an interactive evidence pie graph with the distribution of results by normalized evidence level (A-D) based on the Association for Molecular Pathology, the American Society of Clinical Oncology, and the College of American Pathologists (AMP/ASCO/CAP) guidelines. Users can apply filters to refine their search, such as focusing on findings with a specific evidence level (e.g., Level A). The platform also has an interactive gene/drug heatmap, to help visualize the frequency of results describing a gene/drug pair, and a gene/disease heatmap, to help visualize the frequency of results describing a gene/disease pair.

The metrics of evidence used by VICC follow the guidelines published by the AMP/ASCO/CAP. Evidence levels are normalized based on these guidelines:

- *Level A* (tier I): evidence from professional guidelines or FDA-approved therapies relating to a biomarker and disease.
- *Level B* (tier I): evidence from clinical trials or other well-powered studies in clinical populations, with expert consensus.
- *Level C* (tier II): evidence for therapeutic predictive markers from case studies, or other biomarkers from several small studies. Also, evidence for biomarker therapeutic predictions for established drugs for different indications.
- *Level D* (tier II): Preclinical findings or case studies of prognostic or diagnostic biomarkers. Also, includes indirect findings.

The VICC platform serves as a valuable resource for cancer researchers and clinicians, providing a consolidated view of biomarkers and drug response information from multiple sources. The platform is straightforward and user-friendly, and the graphic information facilitates the understanding of the results. Because this platform aggregates information from several platforms, it is a good place to do the first search and then be redirected to the platform that contains more information about the specific mutation of interest, in case more details are needed [15].

Additionally, there are other interesting tools in VICC´s website, such as the Standard Operation Procedure (SOP) that was developed in conjunction with the Interpretation Standards (KCIS) working group (WG) and the ClinGen Somatic Clinical Domain WG. VICC SOP (https://cancervariants.org/research/standards/onc_path_sop/) is an important tool for classification of somatic variants and assessment of oncogenicity of a therapeutic target that follows a systematic and comprehensive set of standards and rules. Together with the AMP/ASCO/CAP somatic guidelines, VICC SOP allows users to clinically evaluate SNVs and small insertions or deletions. Access can be made from VICC´s website. (Horak et al. Genetics in Medicine 2022, PMID: 35101336).

CIViC

Clinical Interpretation of Variants in Cancer (CIViC) (https://civicdb.org/welcome*)* is an open-source platfo rm designed to provide a comprehensive resource for the clinical interpretation of cancer genome alterations hosted by Washington University [15]. It offers detailed information about the associations between specific cancer variants and clinical outcomes, including data on therapies, clinical trials, and diseases. The primary objective of CIViC is to facilitate the interpretation of genomic data for precision oncology, helping researchers, clinicians, and patients make informed treatment decisions.

Users can search for a specific gene variant to view its association with diseases, therapeutic implications, and related clinical trials. Users can also search for a specific drug or therapy and find associated variants, diseases, and clinical trial outcomes. One can find information on clinical trials related to specific variants or therapies and discover variants associated with cancer types. Variants associated with cancer or drugs will be ranked by level of evidence, evidence type, significance, variant origin, and evidence rating. The latter is a quality-of-evidence metric that evaluates the individual components of evidence extracted from the source, taking into account factors such as study size, study design, orthogonal validation, and reproducibility. CIViC classifies the strength of evidence as follows:

- *05 stars*: Strong evidence from reputable sources, well-controlled experiments, and reproducible results.
- *04 stars*: Strong evidence with minor discrepancies or limited reproducibility.

- *03 stars*: Moderate evidence, generally from smaller studies or novel results with limited follow-up.
- *02 stars*: Weak evidence, with low sample size, lacking proper controls, or from lower-impact journals.
- *01 star*: Very weak evidence, often lacking reproducibility or strong experimental support.

The evidence level indicates the strength of the association between a variant and a clinical outcome. The quality of evidence metrics is classified as follows:

- *Level A*: Validated association.
- *Level B*: Clinical evidence.
- *Level C*: Case study.
- *Level D*: Preclinical evidence.
- *Level E*: Inferential association.

While exploring CIViC, the platform is not as user-friendly as the platforms above, requiring a little bit more time to understand it. The platform does not clearly distinguish between heritable rare variants and acquired somatic variants, which could be a source of confusion in determining the significance of acquired genomic alterations. Also, information is not as visually accessible. For example, after searching a mutation, a list will be provided with therapies per cancer type. However, for further details on a drug of interest, the user might need to access that drug´s page, search the mutation and cancer type on the list provided there, and then hover the mouse above the columns for further details on the drug and its evidence. Despite not being visually the best option, the platform is very complete, being a valuable resource for exploring the clinical relevance of cancer variants, and providing insights into therapy and clinical trial outcomes, while offering a robust framework for assessing evidence based on both quality and strength. The platform appears to be updated on a monthly basis.

MD anderson - personalized cancer therapy

The Personalized Cancer Therapy (PCT) platform (https://pct.mdanderson.org/) was developed at MD Anderson Cancer Center [16, 17]. It aims to bridge the gap between molecular alteration detection and the identification of appropriate cancer therapies. This platform provides detailed information on gene alterations and their potential therapeutic implications.

Access to the PCT platform requires registration and approval. After approval, users can explore various sections of the platform, including gene overview, genetic alterations, frequencies and outcomes, therapeutic implications, drugs, and clinical trials. The platform allows users to search for specific genes or genetic variants. The search results provide comprehensive information, including an overview of the gene and its known alterations, frequencies, and outcomes associated with those alterations, functional significance and actionability of each alteration, a list of potential therapies and drugs with corresponding levels of evidence and FDA links, a list of genomically matched clinical trials.

Levels of evidence metrics are as follows:

- *1 A*: FDA-approved drugs for a specific biomarker in specific tumor types or histology-agnostic indication.
- *1B*: Evidence suggestive that biomarker predicts tumor response to the drug or that drug is clinically effective in a biomarkers-selected cohort.
- *2 A*: Large-scale retrospective study demonstrating that biomarker is related to tumor response to the drug.
- *2B*: Clinical data indicative that the biomarker predicts tumor response to the drug in a different tumor type.
- *3 A*: Unusual responders showing biomarkers are related to response to the drug and are supported by a scientific rationale.
- *3B*: Preclinical data demonstrating that a biomarker predicts the response of cells or tumors to drug treatment.

The PCT platform is continuously updated with new information, curated by healthcare professionals and scientists. Nevertheless, it is important to check the date of the last update, considering some findings might have been recently updated, while others might have been updated a few years before the search. Generally, the platform is easy to navigate, with a good visual display of information. It contains a good amount of significant information to help guide clinical decisions. However, the search is limited to the list of genes offered by the platform, leaving some genes without the option of search. The registration and approval for an account do not take long, allowing users to start using their accounts on the same day of registration.

Clinical knowledgebase – the Jackson Laboratory (JAX-CKB)

The Jackson Laboratory has been a pioneer in the use of genetically defined mouse models to advance the understanding of human genetics and disease. They host the Jackson Laboratory Clinical Knowledgebase (JAX-CKB) (https://ckb.jax.org), which is an interactive digital resource for interpreting complex cancer genomic profiles, providing clinical context to genomic and protein data [18, 19]. The platform helps researchers and clinicians identify any evidence related to the clinical implications of specific gene variants in cancer and presents potential treatment decisions. The platform is divided into three subscription plans. CKB CORE is

the open-access, free version of the platform, allowing access to data on 50 oncology-related genes. It requires registration for access. CKB BOOST provides additional content and data compared to CKB CORE but requires a paid subscription. The CKB FLEX allows users to download information for offline use, in addition to providing expanded data content and features.

The platform contains data on gene and variant descriptions, drug indication status, clinical trials, treatment approaches, efficacy evidence supporting the response to treatment approaches by indication and resistance evidence supporting resistance to treatments by indication. It allows users to start their search by gene or variant. The search results provide a wealth of information, including details about the specific variant, its clinical significance, information on molecular profiles that include the variant, additional data sources supporting the variant's relevance, and clinical trials that are linked to the variant, including their recruitment status.

The platform will list molecular profiles, associating them with a tumor type and therapy name, including response type, approval status, evidence type, and actionability. The efficacy evidence section provides more analytical depth for users, in the form of clinical trials and literature results with external reference links for further details. If clinical trials exist the portal will also give further details into it, including recruitment status. Each gene page contains a list of variants with descriptions and their potential associations with drug resistance. Users can navigate from a gene to specific variants to find relevant clinical information.

Evidence types in JAX-CKB are divided into various categories, such as actionable, diagnostic, prognostic, risk factor, emerging, and not active. Response types include sensitive, predicted-sensitive, resistance, predicted-resistance, decreased response, conflicting, no benefit, and not applicable.

The platform is semi-automated and manually curated, which increases the update frequency. The open-access subscription is very complete regarding the 50 genes that it encompasses, however, users might need to use other platforms to search for some genes not available in the open-access version. The platform is easy to navigate.

Catalog of Somatic Mutations in Cancer (COSMIC)

The Catalog of Somatic Mutations in Cancer (COSMIC) (https://cancer.sanger.ac.uk/census) is a comprehensive database managed by the Wellcome Sanger Institute that focuses on cataloging somatic gene mutations in cancer. It provides insights into mutation frequency, distribution, and functional impact across a wide range of cancer types. A recent update now includes functional and mechanistic descriptions of how each gene contributes to disease progression in terms of the key cancer hallmarks and the impact of mutations on gene and protein function [20].

Users can search for specific genes or mutations to retrieve a list of associated cancer types. The platform provides details on these associations, including links to PubMed articles for further information on the discovery and characterization of these mutations. COSMIC connects with the Genomics of Drug Sensitivity in Cancer (GDSC) platform to provide information on potential drug associations with specific mutations, including those related to drug sensitivity and resistance [21]. Users can also search by cancer type to obtain a list of related mutations, along with the number of cases reported and links to relevant PubMed articles. The Cancer Gene Census feature provides a list of genes that are frequently implicated in cancer, helping users identify key cancer-related genes.

COSMIC's latest update, the "COSMIC Mutation Actionability in Precision Oncology," is designed to offer insights into available therapies or clinical trials for specific somatic mutations in cancer. To access this product, users must download the data from the COSMIC website after registering. Commercial users require a paid license. The downloaded data is presented in spreadsheet format, which can be filtered for specific information. Each row contains data on a gene and its associated mutations, a cancer type, actionability ranking, associated drugs, and information on the drug's development phase and trial status. One limitation to note is that COSMIC does not include guidelines on therapeutic approaches. It primarily provides information on the frequency and distribution of somatic mutations, allowing users to explore associations with specific cancer types and drug sensitivities.

In summary, COSMIC is a rich resource for exploring somatic mutations in cancer, offering detailed data on gene mutations and their associations with cancer types and potential drug associations. However, to access more advanced features like the COSMIC Mutation Actionability in Precision Oncology, users must register and, for commercial use, obtain a paid license. Also, data needs to be downloaded which makes it harder to navigate. The platform is constantly updated.

Therapy guiding genomic databases with limitations

Open-access category 2 databases

Precision Medicine Knowledgebase (PMKB)

Developed by the Englander Institute for Precision Medicine (EIPM) at Weill Cornell Medicine, the Precision Medicine Knowledgebase (https://pmkb.weill.cornell.edu) is an online, interactive, open-access resource for collaborative editing, maintenance, and sharing of clinical-grade interpretations on cancer genes, connecting its

variants to tumor-specific and tissue-specific interpretations [22]. Key features of PMKB include support for all major variant types, standardized authentication, distinct user roles including high-level approvers, and detailed activity history. As of this review, PMKB contained 2,247 variant descriptions with 1,766 clinical-grade interpretations.

The platform allows users to search for specific genes, variants, and cancer types, as well as submit and edit existing entries for the continued growth of the knowledge base. Each gene entry is associated with primary sites and tumor types, providing a list of variants. These primary sites include an interpretation paragraph with scientific data and literature references, potentially including treatment information. Each variant page contains detailed descriptions, and potential interpretations, and might include a hyperlink to COSMIC for further details (another platform described above).

Variant evidence metrics are ranked by clinical significance into three tiers:

- *Variants with strong evidence of clinical utility* (tier 1): Variants with strong evidence of clinical actionability for the tumor type, including FDA-approved targeted therapies and prognostic significance, as well as those recognized by WHO guidelines.
- *Variants with potential clinical relevance* (tier 2): Variants with strong evidence of clinical actionability in the specified or different tumor types, and those under investigational studies. These variants are characteristic of tumor types but do not meet tier 1 criteria.
- *Variants of undetermined clinical significance* (tier 3): Variants with currently undetermined relevance, provided for future potential clinical utility if new evidence emerges.

PMKB is easy to navigate and a valuable resource for clinicians and researchers, providing a dynamic platform for cancer genomic data interpretation and informed decision-making based on insights, with the option of downloading all data interpretations and variants. All changes undergo review by molecular pathologists and oncologists, however, because information is being constantly added by specialists in "interpretation" format, some genes might have less information available, and data might be incomplete concerning potential treatment associations and trials. Users need to verify the date of the last update to make sure information remains current because the "interpretation" dates for each genomic alteration vary considerably, having information from several years.

cBioPortal

The cBioPortal for Cancer Genomics (https://www.cbioportal.org) is an open-access platform designed to host and analyze large-scale cancer genomics datasets [12]. It provides a comprehensive collection of genomic information, including data on mutated genes, genetic variants, and alteration frequencies, derived from over 5,000 patients across more than 20 published sequencing projects, each containing data from individual tumor samples. The platform aggregates data from multiple sources, including The Cancer Genome Atlas (TCGA) [23], and various literature datasets, offering a centralized resource for cancer genomics research. Through cBioPortal, users can also access data from the AACR Project GENIE upon access request. This project is a data-sharing consortium integrating clinical-grade cancer genomic and clinical outcome data from thousands of patients from several institutions worldwide, with a focus on creating an evidence base for precision cancer medicine [24].

The cBioPortal platform supports and stores diverse types of genomic data, including non-synonymous mutations, DNA copy-number variations, mRNA and microRNA expression data, protein-level and phosphoprotein-level data, DNA methylation data, and de-identified clinical data [12, 13]. Upon accessing cBioPortal, users can select from a list of cancer studies, with options to explore datasets related to drug development or other research areas. The platform offers various tools for data visualization and analysis. After selecting a study, users can view infographic summaries of reported mutations and patient profiles, as well as a detailed list of individual cases within the study. The platform allows users to filter information by specific criteria, such as copy-number variations, or to search for a specific gene. When searching for a particular gene, cBioPortal provides a list of cancer cases containing mutations in that gene among the selected studies, along with the mutation type and associated cancer type for each case. cBioPortal provides access to processed clinical data from TCGA studies and allows researchers to visualize mutations in 3D protein structures by integrating data from the Protein Data Bank (PDB), which is valuable for studying the biological effects of specific mutations.

However, data on the clinical relevance of specific genomic alterations comes from cBioPortal's integration with the OncoKB platform. The OncoKB symbol, displayed next to relevant cases, provides direct access to additional insights regarding the potential therapeutic implications of specific genomic alterations. By clicking the symbol, users are redirected to the OncoKB platform, where they can explore detailed information on biomarkers, targeted therapies, and levels of evidence for clinical actionability.

This integration makes cBioPortal particularly useful for oncologists and researchers, allowing them to quickly identify similar cases already reported in the literature and obtain clinically relevant information to support treatment decisions. It eliminates the need to manually search through individual studies and provides a more streamlined approach to exploring the connections between genomic alterations and clinical outcomes. The platform contains an extensive dataset of data from studies; however, it is not the easiest to navigate requiring a few steps to finalize the search and an understanding of the filtering options. The platform is frequently updated. When reviewing the platform, it had just been updated the days before.

NIH genomic data commons data portal

The NIH Genomic Data Commons (GDC) Data Portal (https://portal.gdc.cancer.gov/) is a centralized platf orm designed to collect, integrate, and share large-scale genomic data from various cancer research projects [25]. The platform allows researchers to explore a wealth of genomic information, including data on specific mutations, cancer cases, and clinical outcomes. The portal hosts information from 22 major projects, with some of the most significant being:

- *Therapeutically Applicable Research to Generate Effective Treatments (TARGET)*: a collaborative effort that focuses on characterizing and studying the genomic changes in childhood cancers.
- *Cancer Genome Atlas Program (TCGA)*: a large-scale project that molecularly characterized over 20,000 primary cancers and matched normal samples across a wide array of cancer types. TCGA provides one of the most extensive genomic resources for cancer research, spanning more than 30 cancer types.
- *Molecular Analysis for Therapy Choice (NCI-MATCH)*: a precision medicine clinical trial designed to test whether targeted therapies based on specific genetic alterations in a patient's tumor can be effective across multiple cancer types. NCI-MATCH seeks to match patients with targeted treatments according to their unique genomic profile.

Users can search the GDC Data Portal for specific genes or genomic alterations and retrieve information on cases reported in each project, along with their characteristics, such as tumor type, mutation type, and associated clinical data. The portal provides links to external resources like COSMIC (Catalogue of Somatic Mutations in Cancer) and CIViC (Clinical Interpretation of Variants in Cancer), which offer further information on clinical significance, targeted therapies, and other relevant data. While most data are publicly available, some raw data from the TCGA and TARGET databases may require additional authorizations to access via dbGaP, which can delay access to certain subsets of data for researchers.

In summary, the GDC Data Portal serves as a central hub for genomic data from numerous cancer studies, allowing researchers to explore and analyze comprehensive datasets. Data on clinical significance is from external sources. The platform is easy to navigate and very frequently updated. When reviewing the platform, it had been updated three months before.

Barcelona biomedical genomics lab (BBG Lab) - cancer genome interpreter and cancer biomarker database

The Cancer Genome Interpreter (CGI) (https://www.cancergenomeinterpreter.org/home) was developed by an academic research group in Barcelona, designed to facilitate the identification of tumor alterations that act as cancer drivers or are therapeutically actionable [26, 27]. CGI uses computational methods and public domain knowledge to analyze newly sequenced tumor genomes and annotate alterations according to various levels of evidence indicating their role in oncogenesis or therapeutic response.

CGI analyzes a list of genomic alterations in a tumor or across multiple samples to identify likely cancer drivers using computational tools such as BoostDM [28] and OncodriveMut. It also annotates alterations that serve as biomarkers for response to cancer therapies by integrating information from multiple databases, including OncoKB, the Cancer Biomarkers Database, the Variant Interpretation for Cancer Consortium (VICC), and CIViC.

The output will be divided into two sections called "alterations" (mutations and copy number alterations) and "*prescriptions*". The "alterations" section will give a list of samples from studies for each gene, with information on the protein changes, oncogenicity, mutation details, consequences, and transcripts. The "*prescription*" section will give a list of samples from a study and give information on the gene alterations and associated biomarkers, along with data on related diseases, drugs, response status, evidence level and external references for further details. The relevance of alterations as biomarkers of drug response is evaluated using data from the Cancer Biomarkers Database, CIViC, and OncoKB. Evidence levels for therapeutic actionability can range from guideline-based standard-of-care to preclinical assay evidence, including clinical practice, clinical trials (Phases I-IV), case reports, and preclinical studies.

It is free and simply requires registration to use but is not easy to navigate, requiring some time to fully understand how to use the platform and how to correctly write the input for the platform to accept your search query.

The platform is frequently updated. If the user is willing to find information to guide clinical decisions about a mutation, it might be easier and faster to search directly into Cancer Biomarkers Database, which is also part of BBG Lab.

The Cancer Biomarkers Database (https://www.cancergenomeinterpreter.org/biomarkers) contains a list of genomic biomarkers classified by cancer type, response status (sensitivity, resistance, or severe toxicity), and levels of clinical evidence supporting these associations. The database also includes an inventory of validated oncogenic mutations derived from published experimental assays, DoCM, ClinVar, and OncoKB databases. This inventory provides information on genes, mutations, protein changes, transcripts, context, and tumor type associations. Moreover, there is a list of genes driving tumorigenesis, with specific alterations, based on the Cancer Gene Census and manually curated information, called Catalog of Cancer Genes, and a downloadable cancer bioactivities database containing various cancer-related biological activities.

The database access also requires users to create an account, but this procedure only takes a few minutes. The platform's objective is to provide a resource for researchers and clinicians to interpret cancer genomics data, identify potential therapeutic targets, and guide personalized cancer therapy. It is straightforward to search, and data was last updated in 2022. Although the database provides external references from the literature for further exploration, detailed descriptions of the associations are not provided in the platform. Hence, users need to check other platforms to complement their search and get more details on the association.

Category 2 platforms with a paid subscription

MolecularMatch Inc

MolecularMatch Inc. (https://www.molecularmatch.com/solutions/mmportal-clinical-decision-support.html) is a paid resource that aims to provide updated information and recommendations on clinical trials and drugs, with corresponding evidence levels and details from the literature. It contains a keyword searcher that allows users to search for a mutation. The platform will correlate the search with clinical trials, publications, and drugs, giving information on those for users to read further.

Evidence-level metrics are as follows:

- *1 A*: FDA-approved drugs or professional guidelines.
- *1B*: Clinical trial (phase II or above).
- *2 C*: FDA approval in other conditions or multiple small, published studies.
- *2D*: Pre-clinical or case reports.
- *3*: Mutation prevalence in cancer is zero.
- *4*: Pop freq max of the variant is greater than 0.05.
- *Ind*: Further specification is required to recommend this drug.
- *NE*: Supporting evidence for this therapy is not present.

This platform integrates numerous data sources including clinical trials, targeted drug treatments, mutation databases, scientific abstracts, and publications. MolecularMatch's search approach offers greater depth by mining the scientific literature using Natural Language Processing (NLP) algorithms. The company claims that in comparison to public domain database mining their NLP search approach can identify significantly more relevant variants and mutations. However, to access the platform users must contact the company to subscribe.

To get to know the platform before paying for a subscription, it offers a thirty-day free trial. Despite this limitation, the platform is frequently updated, easy to navigate, and can be used to guide clinical reasoning, offering valuable insights and information on drugs and clinical trials for different genes and mutations, with filtering options per cancer type.

VarSome

VarSome (https://varsome.com) is a comprehensive genomic knowledge base that aggregates data from over 140 genomic databases. It features a search bar for querying variants, copy number variations (CNVs), genes, transcripts, publications, and diseases, with advanced filtering options available for more specific searches. Users can begin using the platform without signing up, though registration provides access to additional features. Upon searching for a variant, VarSome presents detailed information, including the variant's classification (e.g., pathogenic), graphical visualizations, and links to relevant publications or external references.

Some information on VarSome, such as drug data, clinical trials, and more extensive genomic insights, is restricted to paid subscribers under the Premium, Clinical, or API plans. The paid version is particularly useful for clinicians and researchers, offering resources that support clinical decision-making when combined with other platforms. VarSome Clinical, a paid tool, allows for the processing, annotation, and classification of next-generation sequencing (NGS) data. It integrates information from multiple databases, helping with the identification of genetic variants and their annotation based on recognized guidelines, although it does not provide direct clinical recommendations [29].

Cancer research guiding databases

Genomic databases are critical tools in modern biological and medical research, contributing to research in several ways. These databases aggregate and organize

data and make them accessible, facilitating researchers to find associations, to collaborate and to share data. Some platforms provide standardized formats for data storage and retrieval, helping with the consistency of data interpretation across different studies. Some platforms also contain bioinformatics tools for data analysis and visualization tools to help cancer researchers interpret complex genomic data and somatic mutation findings in more graphical formats.

The third category is platforms we consider to be helpful for cancer research purposes. Various platforms provide information on gene mutations and variants and their cancer associations, being useful for hypothesis generation and cancer research purposes. Even though they might contain information on mutation-related treatments, these platforms are not focused on guiding clinical treatments. Each platform has its strengths and limitations, contributing to different aspects of cancer research and treatment development.

The platforms classified in this category are the following:

- *Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer*: a database focused on cytogenetic abnormalities in cancer and their associations with various cancer types, helping to identify patterns of cytogenetic alterations in different cancers. It is not so easy to navigate but data is constantly updated [30]. (https://mitelmandatabase.isb-cgc.org/)

The Cancer Therapeutics Response Portal (CTRP): is a valuable tool for exploring the connections between cancer cell line characteristics and drug sensitivity, being a useful source to identify potential therapeutic targets and to understand the mechanistic basis for drug response [31–33]. It is user-friendly but not frequently updated (https://portals.broadinstitute.org/ctrp.v2.1/).

- *The Cancer Cell Line Encyclopedia (CCLE)*: a comprehensive resource designed to catalog and characterize a large collection of human cancer cell lines, including data on genomic profiles, lineage information, gene expression patterns, and pharmacological responses to anticancer drugs. DepMap, short for "Dependency Map," is a platform that offers systematic datasets, analytical tools, and visualization capabilities based on CCLE and other related projects [34]. It is user-friendly and will be updated soon (https://depmap.org/portal/).
- *Integrative OncoGenomics (intOGen)*: a comprehensive resource that compiles a list of cancer driver mutations identified through a systematic analysis of several large-scale genomic cohorts, offering insights into their roles in tumorigenesis and potentially guiding therapeutic hypothesis [26]. The platform displays data visually with graphics. It is user-friendly and was updated in 2023 (https://www.intogen.org/).
- *DriverDBv4*: a useful tool for identifying cancer driver genes and mutations, with a focus on CNV analysis, offering a range of features for exploring genomic data, particularly through its gene search functionality and heatmaps depicting CNV trends [35]. It was recently updated and is user-friendly with infographic data (http://driverdb.bioinfomics.org/).
- *European Variation Archive*: a rich resource for genetic variation data from multiple species, allowing users to explore a wide array of projects that study structural variations and other genetic changes [36]. It contains a search bar for SNPs and a variant browser that can be filtered by chromosomal location, variant ID or gene symbol per organism. Data can be added by users of the platform (https://www.ebi.ac.uk/eva).
- *Adult Genotype Tissue Expression (GTEx) Project*: a large-scale public repository of expression quantitative trait loci (eQTLs) and histological data from various sampled tissues, primarily focusing on healthy individuals. Their aim is to enhance the understanding of human biology and disease by elucidating the relationship between genetic variation and gene expression in diverse tissues. The platform contains a search bar for genes or SNP ID, with graphical results for interpretation (https://gtexportal.org/home/gene).
- *Database of curated mutations (DoCM) and the Drug Gene Interaction Database (DGIdb)*: DoCM (http://docm.info) is an open-access platform that provides a curated collection of somatic mutations with established relevance to cancer biology based on prognostic, diagnostic, predictive, or functional roles. DoCM contains a search filter by mutation type, gene (from a list of options), disease, tags, amino acid, chromosome, publications and reference. Each variant's page has an option to check for drug interactions, leading to the DGIdb platform (https://www.dgidb.org) that enables the user to explore potential drug-gene interactions related to a specific somatic mutation and the potentially druggable genome. DGIdb contains a straightforward search bar by gene graphics and interactive list results. Platforms are easy to navigate. DoCM has had several versions since its release and DGIdb was recently updated in 2024 [37, 38].
- *Tumor Portal*: a useful resource for exploring genes associated with various cancer types, along with related statistical data and figures or graphical

representations from cancer studies, allowing users to visualize gene mutation patterns and other statistical information [39]. There is no date of recent updates available on the platform. The search query is by gene and not by mutation, with infographical results (http://www.tumorportal.org/).

- *GeneCards*: a gene database with detailed information on human genes, is helpful for investigating genes, their functions, associated disorders, drug interactions, and pathways, among other characteristics [40]. It is free and user-friendly (https://www.genecards.org).
- *Cancer Driver Log (CanDL)*: is a catalog of driver mutations that are potentially actionable, with a classification by evidence level. There are external links with information on potential therapies associated with those driver mutations [41]. However, data was last updated in 2015 and is limited to a small list of genes provided by the platform (https://candl.osu.edu).
- *Genomics of Drug Sensitivity in Cancer (GDSC)*: the platform provides information on the relationship between genes, cell lines, and drugs in cancer, offering genomic markers of sensitivity and resistance for various cancer types, based on studies conducted in cancer cell lines, and giving insights into which compounds might be effective or ineffective for specific genetic profiles [21, 42]. Specific mutations cannot be searched. Despite its extensive characterization of cell lines, the number of available compounds is limited, so users might not always find associations with known medications. It is user-friendly (https://www.cancerrxgene.org/).
- *CancerHotspots.com*: this platform contains a list of significant mutations, including single residue and in-frame indel mutation hotspots, identified on two scientific studies from more than twenty-four thousand tumor samples. Users can search the list by gene or variant. (https://www.cancerhotspots.org/#/home)
- *drugbank.org*: this drug bank contains a straightforward search bar by drug, gene or mutation that will give a list of drugs related to the search and details on the drug and components. Information on clinical trials, drug interactions, adverse effects and some other clinical data is available through a subscription to the platform´s Clinical Drug Data API plan, but the platform is more focused on the drugs itself and allows advanced drug searching features instead of focusing on providing clinical information for somatic variant searches. (https://go.drugbank.com/)
- *UCSC Xena Browser*: this platform allows visualization and exploration of large public and private genomic and biomedical datasets, with special focus on cancer research datasets. Users can select studies and search specific genes and variants (https://xenabrowser.net/).
- *University of Alabama at Birmingham Cancer (UALCAN)*: this platform allows users to analyze cancer omics data from publicly available databases, particularly from TCGA, with visualization tools. Users can select a study, and search by gene/gene class and cancer type (https://ualcan.path.uab.edu/index.html).
- *Gene Expression Profiling Interactive Analysis (GEPIA)*: this platform allows users to perform analysis and visualization of gene expression data with data from studies like TCGA and GTEx (http://gepia.cancer-pku.cn/).
- *ClinVar*: it is a freely available, public database that provides interpretations of the clinical significance of genomic variants for conditions and serves as a repository for sharing interpretations of variants among the clinical and research communities. However, it has a stronger focus on germline variants. Efforts to include more somatic variant data are ongoing, with some of the information currently accessible through ClinVar's GitHub repository (ncbi.nlm.nih.gov/clinvar/).
- *Atlas of Genetics and Cytogenetics in Oncology and Haematology*: this is an atlas of genes and variants associated with cancer with their characterization and description, linked to literature references (atlasgeneticsoncology.org).

Platform evaluations and recommendations

Based on our evaluation and personal perceptions during the review process of the platforms, MyCancerGenome and OncoKB would be the first-choice Category 1 platforms for guiding clinical decisions. Both are user-friendly, visually pleasing, open access, with comprehensive accurate, and frequently updated data on the clinical significance of somatic mutations, available inside the platform.

VICC is interesting because it aggregates data from multiple platforms, providing a graphical representation that shows which platform contains more data about a certain genomic alteration. Thus, while users can find information by checking external sources, VICC also indicates the original platform for further details if needed. CIViC is a thorough and accurate platform, though it might not be as straightforward to use initially as some other platforms. However, once users learn how to navigate it, it becomes a great option. Information on treatment indications and criteria may not be as detailed as on other platforms. PCT-MD Anderson and JAX are

frequently updated, user-friendly, and have an intuitive interface, but open-access data is limited to a certain number of genes. JAX offers the option to expand the available data with a paid subscription. In general, both are good options as well.

COSMIC is one of the larger researcher-oriented Category 1 platforms, offering a comprehensive amount of data. However, the main limitation is that the clinical actionability data is only available after registration in a downloadable spreadsheet format. Therefore, users need to know how to download and open data to access the clinical information. In general, the data from the spreadsheet is thorough and frequently updated, but users might have to download it several times to ensure they are using the latest version. It is a good option for accessing data without the internet.

PMKB is an interesting Category 2 platform that contains information on therapies associated with genomic alterations in expert-written paragraphs that are later reviewed by a team of specialists. Besides being complete, open-access, and easy to navigate, the decision was made to consider it a Category 2 platform mainly because of the variability of data (in terms of the date of the last update and quantity of information on each variant). Because data is manually curated, some gene variations might lack data while others might have a very complete interpretation with enough information on potential therapies, not necessarily being the best representation of reality. So, users might find it excellent to guide clinical reasoning for some gene variations and not enough for others.

Differently from PMKB, cBioPortal for Cancer Genomics, GDC Data Portal and BBG Lab - Cancer Genome Interpreter are in Category 2 because data on clinical significance is from external sources. Although users can start their search on those platforms, they will ultimately be led to another platform to finish their search if their goal is to find guidance for clinical decision-making. Although the BBG Lab also contains the Cancer Biomarker Database that contains more information on therapies and their significance, the user might still need to use other platforms or search the literature further to complement their searches with more detailed descriptions of the association.

Molecular Match Portal is in Category 2 mainly because it is paid. In general, it is a very comprehensive platform that is constantly updated. VarSome is a thorough platform that aggregates data from several genomic databases, but clinical data is mostly accessible through the paid subscription. Their VarSome Clinical plan is very interesting because it allows users to have human DNA sequencing data processed, annotated, and classified based on guidelines, which is a differential feature from this platform. Not being an open-access platform can be a limitation for some users. However, among the Category 2 platforms, Molecular Match Portal and VarSome (paid subscription plans) might be the most comprehensive for clinical actionability data.

Most of the Category 3 portals are of more use to translational cancer researchers as their focus is not directed to clinical users seeking information on gene mutations and their responses to therapies. The platforms, however, can be valuable for preclinical and clinical research, providing information that can potentially help generate new hypotheses. Genomic databases in Category 3 focus on guiding therapy decisions can also be used in research settings for information on genes, gene mutations, therapies, and diseases. With these platforms, researchers can become updated on drug-mutation associations, which can help identify trends and gaps in current knowledge, inspire new research questions, and generate hypotheses for new studies aimed at drug development or repurposing existing drugs.

Researchers can use these types of databases to discover new therapeutic targets by studying the effects of mutations on disease progression and response to treatment. This information can enhance understanding of underlying mechanisms of action, helping to optimize therapies and develop more effective and specific drugs. Additionally, researchers can learn about variants reported in certain tumor types or diseases that may not have been previously studied or associated with therapies. These data can generate ideas for new preclinical studies (e.g.: in vitro cancer studies, animal models) to identify new tumor targets or mechanisms of drug-variant associations, potentially leading to new clinical studies. For example, researchers can induce a certain mutation in an animal model and study its effect on tumor development and progression. In general, most of these Category 3 platforms facilitate translational cancer research and preclinical studies, serving as a bridge between patient data and the laboratory, allowing clinical findings to be applied to experimental studies.

Case studies

To better understand the platforms under review, we selected some historical cancer cases from literature. Each case involved a treatment modification based on the discovery of a new mutation through NGS. The mutations were then investigated using the platforms to evaluate how guidance information provided by the platforms could have influenced treatment planning.

Case 1 In 2020, Mitani et al. [43] published a case study of a patient with metastatic cancer of unknown primary (CUP). Without knowing the origin of a primary tumor, it is challenging to determine the most effective treatment protocols. This case highlights the practical application

of NGS that can inform treatment decisions through the identification of actionable mutations. They described a case of a metastatic CUP that underwent empiric chemotherapy. Due to the absence of a detected primary tumor, comprehensive genomic analysis with an NGS-based multiplex assay was conducted, revealing an *EGFR* mutation c.2573 T>G p.Leu858Arg (L858R). Given that this mutation is a known biomarker for *EGFR* tyrosine-kinase inhibitors (TKI) in non-small-cell lung carcinoma (NSCLC), the treatment was adjusted to include *EGFR* tyrosine-kinase, Erlotinib. The patient exhibited a good response for fifteen months until the disease progressed. Subsequently, a cell-free circulating tumor DNA liquid biopsy showed an additional *EGFR* mutation, c.2369 C>T p.Thr790Met (T790M), which is known to confer acquired resistance to *EGFR* TKIs. The patient was then started on Osimertinib and responded for 2 years and 9 months until a late adverse event of radiotherapy occurred.

In this case, after the NGS-based multiplex assay pointed out an EGFR alteration (L858R), the physician could have first opened the OncoKB platforms and searched it, for example. According to the OncoKB database, the *EGFR* L858R mutation is classified as an oncogenic alteration. This platform provides detailed information about the mutation´s association with TKIs and Ex20ins-active inhibitors. It gives information on level 1 evidence drugs, Afatanib, Dacomitinib, Erlotinib, Erlotinib+Ramucirumab, Gefitinib, Osimertinib, and level 3 A evidence drug, Patritumab Deruxtecan, for *EGFR*-mutated NSCLC that progressed after *EGFR* TKI therapy and platinum-based chemotherapy. Furthermore, if access to the paid VarSome Clinical plan is available at the professional´s institution, one can benefit from processing the NGS results through their platform and getting an analysis based on several genomic databases.

Later, when the patient was found to have an additional EGFR mutation (T790M), the same platform could have been used to search new therapy options that are sensitive to this new finding. Moreover, it is would be interesting to explore other platforms to complement the search. The *EGFR* T790M mutation is recognized by OncoKB and by the Cancer Biomarker Database as an oncogenic alteration, associated with response to Osimertinib (level 1 evidence) and predictive of resistance to Afatanib, Erlotinib, and Gefitinib. Similarly, the CIViC database provides information on the association of L858R with TKIs and the association of Osimertinib in the presence of EGFR T790M mutation. My Cancer Genome provides additional insights into the association of L858R with pembrolizumab (based on PD-L1 expression level), with a potential response when *EGFR* T790M is mutated, as well on the potential response to Afatinib in combination with Cetuximab in *EFGR* T790M-mutated cases. If the patient had not experienced the adverse event related to radiotherapy, potential new treatment options could have included combination therapy with Afatinib and Cetuximab targeting the *EGFR* T790M mutation or immunotherapy with Pembrolizumab if the tumor expressed PD-L1. Additionally, participation in clinical trials for novel agents targeting *EGFR* mutations, like Patritumab Deruxtecan, could have been considered. As mentioned during this review, some platforms contain updated information on clinical trials, but one can also find them on the website clinicaltrials.gov [43].

Case 2 In 2021, Kitamura et al. [44] reported a case of an adenocarcinoma of prostate treatment initially with androgen deprivation therapy (ADT) and Bicalutamide. Upon systemic progression, a new histological finding was revealed, squamous cell carcinoma. This tumor may arise after endocrine or radiation treatment. It has a poor response to conventional treatment resulting in an unfavourable prognosis. The patient then underwent chemotherapy. Before the patient´s death, an NGS was performed, showing several mutations, including mutations on the genes: *BRCA2*, *CDK12*, *TP53*, *PTEN*, *APC*, and *RB1*.

If the patient had not been deceased, after receiving the NGS results from this case, one could start by choosing a Category 1 platform to search the mutation findings and define a treatment strategy based on the search results. When searching the mutated genes in MyCancerGenome, OncoKB, and PCT MD Anderson platforms, for example, it was found that the FDA approved the use of the drug Olaparib in combination with Abiraterone for patients with metastatic castration-resistant prostate cancer (mCRPC) who are eligible for Abiraterone and have deleterious or suspected deleterious *BRCA*-mutation. The TRITON 3 [45] trial confirmed the effectiveness of Rucaparib for *BRCA*-mutated mCRPC in patients who have been treated with ADT. Additionally, in 2023, the second-generation androgen-receptor pathway inhibitor Talazoparib with Enzalutamide was approved for patients with Homologous Recombination Repair gene-mutated (e.g.: *CDK12* or *BRCA2*) mCRPC who had no previous therapy for this stage of the disease. Niraparib in combination with abiraterone plus Prednisone was also approved in 2023 for *BRCA*-mutated mCRPC according to the platforms. In this case, the *BRCA2* mutation allele frequency was >30% of the sample, suggesting that a treatment targeting this mutation could have been beneficial.

Regarding *TP53*, OncoKB explains that there are no therapies for prostate cancers targeting the *TP53* mutation variants found in this case´s tumor analysis. The platform explains that the missense variants P151A and V274A are likely oncogenic, likely leading to a loss of function. Concerning the *PTEN* variants found in

the tumor analysis, there was no specific data found on CIViC about them. However, CIViC gives information on a combination of drugs with preclinical evidence for prostate cancer with *PTEN* mutations, PI3Kbeta Inhibitor AZD8186, Enzalutamide and Alpelisib, that in the future might become a potential treatment combination. Regarding *RB1* mutation in prostate cancer, data is limited, but on MyCancerGenome and the COSMIC Actionability spreadsheet, users can find information on some clinical trials for prostate cancer with *RB1* mutation as an inclusion criterion.

Not all the mutations identified in the NGS had significant studies or trials associated with them on these platforms. Furthermore, the rarity of adenosquamous carcinoma of the prostate limits the availability of data on this specific tumor histology. However, these platforms are a valuable resource for accessing updated literature on each mutation and identifying relevant clinical trials to determine the best treatment options.

Case 3 In 2021, Ulivi et al. [46] described a male patient in his forties diagnosed with advanced colorectal carcinoma (CRC) with multiple metastatic lesions to the liver and peritoneal carcinomatosis. At diagnosis, the primary tumor tissue MassARRAY Sequenom analysis showed a *RAS* and *BRAF* wild-type status. First-line treatment was FOLFOXIRI and panitumumab, with disease progression. A liquid biopsy was obtained and analyzed by Real-Time PCR, showing the presence of a *BRAF* V600E mutation. The patient then underwent FOLFIRI with aflibercept, but, due to rapid progression and decline, died a month after starting second-line chemotherapy. The authors speculated that the *BRAF* mutation was either present at a low level in the heterogeneous primary tumor tissue or was acquired during treatment, inducing a secondary resistance mechanism.

When searching potential drug associations related to *BRAF* V600E-mutated metastatic CRC, CKB-JAX and MyCancerGenome indicate a potential decreased sensitivity/resistance to cetuximab and panitumumab, and theoretical primary resistance or no response to vemurafenib. Thus, the mutation may have contributed to the patient's lack of response during chemotherapy with panitumumab. MyCancerGenome and OncoKB show a predicted primary sensitivity to cetuximab associated with encorafenib (a *BRAF* inhibitor) after prior therapy (FDA-approved), and to encorafenib associated with panitumumab (NCCN) in cases of metastatic CRC with *BRAF* V600E mutation. Considering the above, these regimens could have been considered treatment options if the patient's performance status allowed it and searching one or some of these platforms would probably have helped to choose the best therapy strategy. CKB-JAX shows predicted sensitivity to a triple therapy with encorafenib, binimetinib, and cetuximab, based on results of a published phase III trial (2022) for metastatic CRC that progressed after one or two previous regimens (ClinicaTrials: NCT02928224). The COSMIC Actionability spreadsheet lists several phase III trials that are still open and could be considered if approved therapies do not show good response (e.g. Tunlametinib + Vemurafenib for *BRAF* V600E mutant metastatic CRC whose disease has progressed after 1 or more prior regimens in the metastatic setting, which is planning to be recruiting and to be open until 2026). CIViC and CKB-JAX both show that a combination of vemurafenib and cobimetib might be effective, according to a phase II basket trial (clinical evidence – B) [47], making it a potential future treatment option.

As take-home messages, the health professionals can start by choosing a Category 1 platform, like OncoKB for example, to search the NGS or DNA liquid biopsy findings to guide clinical reasoning. Also, users might benefit from searching a second platform either, like MyCancerGenome, CIVIC or even a Category 2 platform, if possible, to complement their findings and be able to best tailor the patient´s therapy plan. If available, the paid VarSome NGS result processing can be an interesting tool. Apart from clinical trial data available in some of the platforms, the Clinicaltrials.gov website is a good option to find clinical trials.

Conclusions and future directions

In this review, we identified several comprehensive, mostly open-access, platforms for searching genetic biomarkers, each exhibiting advantages and limitations. A detailed description of these platforms was provided, highlighting their capabilities for clinical and translational cancer research. Some of them contain information on treatment options and clinical evidence, aiding in clinical decision-making. The incorporation of these platforms in a clinician's routine can facilitate and accelerate searching a genomic profile result and provide updated information on approved drugs and clinical trials. Platform improvement incorporating artificial intelligence (AI) will soon greatly enhance ease of use by integrating diverse big data sources, enabling real-time genomic analysis, with more precise predictive modeling of therapeutic responses [48]. This will lead to better personalized treatment plans and more comprehensive clinical decision support. Additionally, AI's continuous learning capabilities will refine recommendations over time, continually enhancing the modeling of likely patient outcomes [49]. Also, some platforms are starting to incorporate multi-omics data, such as transcriptomic data [50, 51], which are becoming a valuable tool for defining targeted therapy strategies for each patient and represent a future challenge for precision oncology databases.

Supplementary Information

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Supplementary Material 1: Supplementary Table 1 contains a list of genomic databases and respective websites reviewed in this paper, divided by categories (left column), according to characteristics evaluated during the review process described in the columns. The columns classify platforms on whether they are user-friendly and open-access or not, whether they contain clinical significance data, how frequently data is updated, and how complete data to guide clinical decisions is. *BBG Lab - Cancer Biomarker Database contains data on clinical significance but does not detail their associations.

Supplementary Material 2

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Author contributions
A.A.G. and J.A.S. curated the platforms. A.A.G. gained proficiency in their use, documented their functionalities, and categorized them. A.A.G. and J.A.S. wrote the review text, including, the abstract, background, platform's review, case studies, wrap-up section, and conclusion. W.L.D. contributed to the curation of case reports, writing, and review text. L.F.A. and R.B.R. provided supplementary input to the manuscript. All authors participated in conceptualizing the review. J.A.S. supervised and reviewed all aspects of the work. All authors reviewed and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74:229–63.
2. Waarts MR, Stonestrom AJ, Park YC, Levine RL. Targeting mutations in cancer. J Clin Invest. 2022;132.
3. Murciano-Goroff YR, Suehnholz SP, Drilon A, Chakravarty D. Precision Oncology: 2023 in review. Cancer Discov. 2023;13:2525–31.
4. Casolino R, Beer PA, Chakravarty D, Davis MB, Malapelle U, Mazzarella L, et al. Interpreting and integrating genomic tests results in clinical cancer care: overview and practical guidance. CA Cancer J Clin. 2024;74:264–85.
5. Lone SN, Nisar S, Masoodi T, Singh M, Rizwan A, Hashem S, et al. Liquid biopsy: a step closer to transform diagnosis, prognosis and future of cancer treatments. Mol Cancer. 2022;21:79.
6. Zhao Z, Chen X, Dowbaj AM, Sljukic A, Bratlie K, Lin L, et al. Organoids Nat Reviews Methods Primers. 2022;2:94.
7. Waldman AD, Fritz JM, Lenardo MJ. A guide to cancer immunotherapy: from T cell basic science to clinical practice. Nat Rev Immunol. 2020;20:651–68.
8. Malone ER, Oliva M, Sabatini PJB, Stockley TL, Siu LL. Molecular profiling for precision cancer therapies. Genome Med. 2020;12:8.
9. Holt ME, Mittendorf KF, LeNoue-Newton M, Jain NM, Anderson I, Lovly CM et al. My Cancer Genome: Coevolution of Precision Oncology and a molecular Oncology Knowledgebase. JCO Clin Cancer Inf. 2021;995–1004.
10. Suehnholz SP, Nissan MH, Zhang H, Kundra R, Nandakumar S, Lu C, et al. Quantifying the Expanding Landscape of clinical actionability for patients with Cancer. Cancer Discov. 2024;14:49–65.
11. Chakravarty D, Gao J, Phillips S, Kundra R, Zhang H, Wang J et al. OncoKB: a Precision Oncology Knowledge Base. JCO Precis Oncol. 2017;1–16.
12. Gao J, Aksoy BA, Dogrusoz U, Dresdner G, Gross B, Sumer SO et al. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Sci Signal. 2013;6.
13. Cerami E, Gao J, Dogrusoz U, Gross BE, Sumer SO, Aksoy BA, et al. The cBio Cancer Genomics Portal: an Open platform for exploring Multidimensional Cancer Genomics Data. Cancer Discov. 2012;2:401–4.
14. de Bruijn I, Kundra R, Mastrogiacomo B, Tran TN, Sikina L, Mazor T, et al. Analysis and visualization of longitudinal genomic and clinical data from the AACR Project GENIE Biopharma Collaborative in cBioPortal. Cancer Res. 2023;83:3861–7.
15. Wagner AH, Walsh B, Mayfield G, Tamborero D, Sonkin D, Krysiak K, et al. A harmonized meta-knowledgebase of clinical interpretations of somatic genomic variants in cancer. Nat Genet. 2020;52:448–57.
16. Johnson A, Zeng J, Bailey AM, Holla V, Litzenburger B, Lara-Guerra H, et al. The right drugs at the right time for the right patient: the MD Anderson precision oncology decision support platform. Drug Discov Today. 2015;20:1433–8.
17. Dumbrava EI, Meric-Bernstam F. Personalized cancer therapy—leveraging a knowledge base for clinical decision-making. Mol Case Stud. 2018;4:a001578.
18. Patterson SE, Statz CM, Yin T, Mockus SM. Utility of the JAX Clinical Knowledgebase in capture and assessment of complex genomic cancer data. NPJ Precis Oncol. 2019;3:2.
19. Patterson SE, Liu R, Statz CM, Durkin D, Lakshminarayana A, Mockus SM. The clinical trial landscape in oncology and connectivity of somatic mutational profiles to targeted therapies. Hum Genomics. 2016;10:4.
20. Sondka Z, Dhir NB, Carvalho-Silva D, Jupe S, Madhumita, McLaren K, et al. COSMIC: a curated database of somatic variants and clinical data for cancer. Nucleic Acids Res. 2024;52:D1210–7.

21. Yang W, Soares J, Greninger P, Edelman EJ, Lightfoot H, Forbes S, et al. Genomics of Drug Sensitivity in Cancer (GDSC): a resource for therapeutic biomarker discovery in cancer cells. Nucleic Acids Res. 2013;41:D955–61.
22. Huang L, Fernandes H, Zia H, Tavassoli P, Rennert H, Pisapia D, et al. The cancer precision medicine knowledge base for structured clinical-grade mutations and interpretations. J Am Med Inform Assoc. 2017;24:513–9.
23. Weinstein JN, Collisson EA, Mills GB, Shaw KRM, Ozenberger BA, Ellrott K, et al. The Cancer Genome Atlas Pan-cancer analysis project. Nat Genet. 2013;45:1113–20.
24. André F, Arnedos M, Baras AS, Baselga J, Bedard PL, Berger MF, et al. AACR Project GENIE: Powering Precision Medicine through an International Consortium. Cancer Discov. 2017;7:818–31.
25. Grossman RL, Heath AP, Ferretti V, Varmus HE, Lowy DR, Kibbe WA, et al. Toward a Shared Vision for Cancer genomic data. N Engl J Med. 2016;375:1109–12.
26. Martínez-Jiménez F, Muiños F, Sentís I, Deu-Pons J, Reyes-Salazar I, Arnedo-Pac C, et al. A compendium of mutational cancer driver genes. Nat Rev Cancer. 2020;20:555–72.
27. Tamborero D, Rubio-Perez C, Deu-Pons J, Schroeder MP, Vivancos A, Rovira A, et al. Cancer Genome Interpreter annotates the biological and clinical relevance of tumor alterations. Genome Med. 2018;10:25.
28. Muiños F, Martínez-Jiménez F, Pich O, Gonzalez-Perez A, Lopez-Bigas N. In silico saturation mutagenesis of cancer genes. Nature. 2021;596:428–32.
29. Kopanos C, Tsiolkas V, Kouris A, Chapple CE, Albarca Aguilera M, Meyer R, et al. VarSome: the human genomic variant search engine. Bioinformatics. 2019;35:1978–80.
30. Mitelman F, Johansson B, Mertens F. Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer [Internet]. 2024 [cited 2024 Jul 9]. https://mitelmandatabase.isb-cgc.org
31. Basu A, Bodycombe NE, Cheah JH, Price EV, Liu K, Schaefer GI, et al. An interactive resource to identify Cancer Genetic and Lineage dependencies targeted by small molecules. Cell. 2013;154:1151–61.
32. Seashore-Ludlow B, Rees MG, Cheah JH, Cokol M, Price EV, Coletti ME, et al. Harnessing connectivity in a large-scale small-molecule sensitivity dataset. Cancer Discov. 2015;5:1210–23.
33. Rees MG, Seashore-Ludlow B, Cheah JH, Adams DJ, Price EV, Gill S, et al. Correlating chemical sensitivity and basal gene expression reveals mechanism of action. Nat Chem Biol. 2016;12:109–16.
34. Nusinow DP, Szpyt J, Ghandi M, Rose CM, McDonald ER, Kalocsay M, et al. Quantitative proteomics of the Cancer Cell Line Encyclopedia. Cell. 2020;180:387–e40216.
35. Liu C-H, Lai Y-L, Shen P-C, Liu H-C, Tsai M-H, Wang Y-D, et al. DriverDBv4: a multi-omics integration database for cancer driver gene research. Nucleic Acids Res. 2024;52:D1246–52.
36. Cezard T, Cunningham F, Hunt SE, Koylass B, Kumar N, Saunders G, et al. The European variation archive: a FAIR resource of genomic variation for all species. Nucleic Acids Res. 2022;50:D1216–20.
37. Ainscough BJ, Griffith M, Coffman AC, Wagner AH, Kunisaki J, Choudhary MN, et al. DoCM: a database of curated mutations in cancer. Nat Methods. 2016;13:806–7.
38. Cannon M, Stevenson J, Stahl K, Basu R, Coffman A, Kiwala S, et al. DGIdb 5.0: rebuilding the drug–gene interaction database for precision medicine and drug discovery platforms. Nucleic Acids Res. 2024;52:D1227–35.
39. Lawrence MS, Stojanov P, Mermel CH, Robinson JT, Garraway LA, Golub TR, et al. Discovery and saturation analysis of cancer genes across 21 tumour types. Nature. 2014;505:495–501.
40. Stelzer G, Rosen N, Plaschkes I, Zimmerman S, Twik M, Fishilevich S et al. The GeneCards suite: from Gene Data Mining to Disease Genome sequence analyses. Curr Protoc Bioinf. 2016;54.
41. Damodaran S, Miya J, Kautto E, Zhu E, Samorodnitsky E, Datta J, et al. Cancer driver log (CanDL). J Mol Diagn. 2015;17:554–9.
42. Iorio F, Knijnenburg TA, Vis DJ, Bignell GR, Menden MP, Schubert M, et al. A Landscape of Pharmacogenomic interactions in Cancer. Cell. 2016;166:740–54.
43. Mitani Y, Kanai M, Kou T, Kataoka S, Doi K, Matsubara J, et al. Cancer of unknown primary with EGFR mutation successfully treated with targeted therapy directed by clinical next-generation sequencing: a case report. BMC Cancer. 2020;20:1177.
44. Kitamura J, Taguchi S, Okegawa T, Honda K, Kii T, Tomida Y, et al. Genomic analysis of circulating tumor cells in adenosquamous carcinoma of the prostate: a case report. BMC Med Genomics. 2021;14:217.
45. Fizazi K, Piulats JM, Reaume MN, Ostler P, McDermott R, Gingerich JR, et al. Rucaparib or Physician's choice in metastatic prostate Cancer. N Engl J Med. 2023;388:719–32.
46. Ulivi P, Passardi A, Marisi G, Chiadini E, Molinari C, Canale M et al. Case Report: the added value of Liquid Biopsy in Advanced Colorectal Cancer from Clinical Case experiences. Front Pharmacol. 2021;12.
47. Klute KA, Rothe M, Garrett-Mayer E, Mangat PK, Nazemzadeh R, Yost KJ, et al. Cobimetinib Plus Vemurafenib in patients with colorectal Cancer with BRAF mutations: results from the targeted Agent and profiling utilization Registry (TAPUR) study. JCO Precis Oncol. 2022;6:e2200191.
48. Ferber D, El Nahhas OSM, Wölflein G, Wiest IC, Clusmann J, Leßman M et al. Autonomous Artificial Intelligence Agents for Clinical Decision Making in Oncology. ArXiv. 2024.
49. Zhang C, Xu J, Tang R, Yang J, Wang W, Yu X, et al. Novel research and future prospects of artificial intelligence in cancer diagnosis and treatment. J Hematol Oncol. 2023;16:114.
50. Tsakiroglou M, Evans A, Pirmohamed M. Leveraging transcriptomics for precision diagnosis: lessons learned from cancer and sepsis. Front Genet. 2023;14.
51. Wei L, Niraula D, Gates EDH, Fu J, Luo Y, Nyflot MJ et al. Artificial intelligence (AI) and machine learning (ML) in precision oncology: a review on enhancing discoverability through multiomics integration. Br J Radiol. 2023;96.

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