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The Molecular Tumor Board Portal supports clinical decisions and automated reporting for precision oncology

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There is a growing need for systems that efficiently support the work of medical teams at the precision-oncology point of care. Here, we present the implementation of the Molecular Tumor Board Portal (MTBP), an academic clinical decision support system developed under the umbrella of Cancer Core Europe that creates a unified legal, scientific and technological platform to share and harness next-generation sequencing data. Automating the interpretation and reporting of sequencing results decrease the need for time-consuming manual procedures that are prone to errors. The adoption of an expert-agreed process to systematically link tumor molecular profiles with clinical actions promotes consistent decision-making and structured data capture across the connected centers. The use of information-rich patient reports with interactive content facilitates collaborative discussion of complex cases during virtual molecular tumor board meetings. Overall, streamlined digital systems like the MTBP are crucial to better address the challenges brought by precision oncology and accelerate the use of emerging biomarkers.

Next-generation sequencing (NGS) assays are a key component of the modern oncology workflow. Beyond on-label drug prescriptions, tumor sequencing results can guide clinical trial enrollment and identify investigational drug opportunities in individual patients. NGS data can also reveal other events of clinical relevance, such as germline pathogenic variants, pharmacogenomics findings and clonal hematopoiesis drivers, which should be recognized and acted upon. However, clinical interpretation of NGS results often relies on manual procedures, which poses considerable challenges to the medical teams undertaking this task. First, variant annotation benefits from numerous resources developed by medical, biological and bioinformatics domains that are not easy to integrate. Second, agreeing on annotation criteria and rules to prioritize actionable findings is critical for consistent clinical decision-making. Third, in the absence of on-label treatment options, patients must be matched with the specific portfolio of investigational therapies and clinical trials available in each hospital (or hospital network), which are subject to continuous changes. Failure to address these issues or the inability to perform them in a clinically acceptable time frame can impair the outcome of individual patients and precision cancer medicine initiatives.

Clinical decision support systems (CDSS) can tackle these challenges by implementing efficient data analysis and reporting processes. Several commercial CDSS software are currently available, but in-house solutions are often used to better accommodate the specific needs of each center. In fact, we believe that the capacity of academic institutions to develop custom CDSS accelerates the use of emerging biomarkers and promotes precision medicine across...
healthcare professionals. We have therefore developed the MTBP, a CDSS that creates a unified framework to interpret sequencing results across the seven comprehensive cancer centers that form Cancer Core Europe (CCE) at present. Importantly, the portal is integrated in the CCE clinical workflows and provides a single platform to distribute the results and support shared discussions at scale. Seamless communication among clinical investigators is essential to leverage the collective expertise of the community in this era of rapidly changing precision-oncology landscape. To our knowledge, this is an unprecedented effort for codeveloping new anticancer therapies and biomarkers under a harmonized infrastructure in Europe. Here, we describe our approach and discuss the results of using the MTBP in a consequent cohort of 500 advanced solid tumors evaluated from January 2019 to January 2021 in the context of the Basket of Baskets (NCT03767075) study, an ongoing CCE multibasket phase 2 clinical trial matching molecular biomarkers with immunotherapies and targeted drugs.

Results

Functional interpretation of cancer variants. Interpretation of NGS data first requires elucidating whether the specific variants observed in the tumor alter the wild-type function of cancer genes, as not all of them have equal biological consequences. Besides the identification of the individual tumor genomic drivers, this analysis enables matching patients to biomarkers defined by functional criteria, such as ‘activating’ mutations in a given oncogene or ‘loss-of-function’ alterations in a given tumor suppressor. Of note, close to one-third of the cancer biomarkers reported at present rely on interpreting the functional effect of variants found in drug targets (Fig. 1a). This number will likely continue to grow as genes involved in more cellular processes, such as DNA damage repair, epigenetics, metabolism and immune regulation, become actionable.

The MTBP interprets the functional relevance of cancer variants under an allele-centric perspective (Fig. 1b). In other words, a given *BRCA1* mutation known to disrupt the activity of the wild-type allele will always be declared as functionally relevant (i.e., loss of function) regardless of tumor-context considerations such as the germline versus somatic origin of the variant, the status of the second allele and/or the cancer type in which it is observed, which are contemplated in the actionability analysis (next section). Multiple genomic knowledge resources can be integrated for a more comprehensive variant functional annotation, but currently there are no well established guidelines on how to do it. Therefore, we agreed on criteria considered to provide strong or very strong supporting evidence (>90% and >99% of certainty, respectively) as extrapolated from previous work and based on three distinct sources of knowledge (Fig. 2a,b). First, the MTBP inspects whether the gene variants observed in the patient’s tumor have an already well-reported effect. Note that different types of assertions can be equally mapped to the context-agnostic notion of a variant being functionally relevant; for example, a given *BRCA1* mutation can be considered as a putative loss-of-function event when it is known to predispose to early breast/ovarian cancer, as well as when it is associated with clinical efficacy of poly-ADP ribose polymerase inhibitors. Therefore, the MTBP queries a number of expert knowledge bases that continuously gather results of clinical, experimental and population genetic studies according to the standard procedures defined for each of their respective scopes (e.g., pathogenicity classification of germline variants), and assertions compatible with the functional relevance (or lack thereof) of the observed variant are matched as appropriate. The aggregation of these different knowledge bases, which are not often used in combination, enables a more comprehensive use of international curation efforts (Fig. 2c).

Second, if no variant effect is reported, or the information is inconclusive and/or supported by weaker evidence (Methods), then the portal evaluates whether bona fide biological assumptions (such as whether a given premature termination codon is likely to trigger nonsense-mediated decay) can be applied (Fig. 2d). These assumptions are largely based on accepted criteria to identify loss-of-function variants in Mendelian disease genes. Of note, the MTBP refines the use of some of these criteria by leveraging the aggregated content of the aforementioned knowledge bases, which for example help to delineate protein regions that are critical for a given tumor suppressor function (Methods). This exemplifies the value of the MTBP for integrating the knowledge available in the community and developing ensembleinformatics models.

Third, if none of these bona fide assumptions can be applied or fulfilled, then computational-based metrics are used as the lowest level of supporting evidence. For example, hotspots of somatic mutations observed across previously sequenced cancer cohorts point out protein sites that are preferentially targeted by tumors and thus relevant for the disease development in both oncogenes and tumor suppressors. To reduce the number of false positives, the MTBP uses methods that consider underlying genomic mutational processes to declare the observed accumulation of mutations as statistically significant. In addition, functional impact predictions can be used to estimate whether other variants drive loss-of-function events. Among all the methods developed with that purpose, we decided to use deleteriousness score calculations, with stringent thresholds exhibiting a 90% predictive value as required for strong supporting criteria, based on the results of our own benchmarking (Fig. 2e).

Variants that cannot be classified as functionally relevant or functionally neutral according to any of the aforementioned criteria appear as ‘of unknown relevance’ in the MTBP reports. For the CCE prospective cohort presented here, composed of 500 solid tumors profiled by NGS panels (from 326 to 350 cancer genes evaluated, depending on the assay; Table 1), the MTBP identified a median of three (interquartile range (IQR), two to four) functionally relevant mutations (single-nucleotide changes and/or small indels) per tumor. Overall, and after excluding mutations assumed to be non-relevant (such as those that do not alter the protein sequence or are common polymorphisms), a total of 26% of the tumor mutations were classified as (putative) functionally relevant, whereas 9% were classified as (putative) neutral (Fig. 3a). One-fourth of these classifications were solely based on bioinformatic predictions, which as discussed is the lowest level of supporting evidence. Even with the comprehensive functional annotation provided by the MTBP, most (65%) of the tumor mutations observed in cancer genes were thus classified as of unknown functional effect (although this number largely varies across genes; Fig. 3b). This illustrates our still-limited ability for interpreting the biological relevance of the genomic alterations that occur in tumor cells. As drug prescriptions progressively move toward a more holistic consideration of the tumor genome (pathway and/or signature centric), we underscore the importance of using interpretation tools that are kept up to date with the knowledge provided by emerging capabilities, such as high-throughput functional assays.

Clinical interpretation of cancer variants. The final objective of the MTBP is to help translate NGS results into the most appropriate therapeutic decisions according to state-of-the-art evidence. Genomic alterations that influence anticancer drug response (sensitivity or resistance) and are of diagnostic or prognostic value are continuously reported in the literature and scientific venues. Several international initiatives gather this information in specific knowledge bases open for the access and feedback of the community. However, these resources follow varying data models, and the accurate aggregation of their content requires an extensive harmonization of the lexicon, ontologies and variant representation syntax used by each. The MTBP implements this process with a semiautomatic pipeline that combines a number of bioinformatic mapping tools.
and manually annotated dictionaries. The adoption of information exchange standards in the community is crucial to mitigate the need for these efforts and facilitate genomic knowledge sharing19–21.

The MTBP matches the cancer biomarkers aggregated across these knowledge bases with the variants observed in the tumor for (i) a specific nucleotide and/or protein amino acid change (e.g., \textit{BRCA1}:c.5468-1G>A or \textit{KIT}:p.D572A); (ii) a variant category (e.g., \textit{EGFR} in-frame deletions in exon 19); or (iii) a functional entity (e.g., \textit{FLT3} oncogenic mutations, as guided by the MTBP functional interpretation) (Fig. 4a). However, as mentioned before, variant actionability must also take into account tumor-context considerations beyond the mere variant match, such as the concordance between the biomarker and patient's cancer type (or a subtype thereof), the presence of co-occurring alterations in the same or other genes and/or the cancer type of the patient's tumor. Questions that are addressed in each step are exemplified here for a given \textit{BRCA1} mutation (HRR, homologous recombination repair; PARPi, poly-ADP ribose polymerase inhibitors).

![Fig. 1 | Clinical relevance of cancer gene variants. a. Overview of gene mutations (single-nucleotide variants and small indels) reported as biomarkers of cancer diagnosis, prognosis and/or drug response by three publicly available knowledge bases (CIViC (Clinical Interpretation of Variants in Cancer), OncoKB (Oncology Knowledge Base) and CGI (Cancer Genome Interpreter)6–8) at the moment of writing. An assertion corresponds to a reported biomarker effect for a given gene variant, in a given cancer type and with a given level of supporting evidence. Assertions supported by weaker or inconclusive evidence (as provided by the knowledge base metadata when appropriate; Methods) are excluded from these results. 1,000g, 1000 Genomes Project; AF, allele frequency. b, Representation of distinct levels of interpretation for cancer gene variants. The functional relevance evaluates the allele-centric effect of the observed variant, whereas context-dependent interpretation factors in additional considerations (such as whether the variant is germline or somatic, co-occurring alterations in the same or other genes and/or the cancer type of the patient’s tumor). Questions that are addressed in each step are exemplified here for a given \textit{BRCA1} mutation (HRR, homologous recombination repair; PARPi, poly-ADP ribose polymerase inhibitors).](image-url)
Fig. 2 | Interpretation of cancer gene variants. a. The MTBP classifies a given cancer gene variant as (putative) functionally relevant or neutral according to three distinct sources of evidence (named A, B and C here) or of unknown relevance if none of these criteria are fulfilled. Note that the knowledge bases listed here are those integrated at the moment of writing, but their usage may be subject to changes depending on evolving needs and preferences. FI, functional impact; OncoKB-mut and OncoKB-biom refer to the biological and predictive relevance annotation of variants in OncoKB, respectively. b. Criteria supporting the variant functional classification are considered to provide strong (>0.9 certainty) or very strong (>0.99 certainty) evidence as extrapolated from the work in variant pathogenicity classification, following the rationale described in the table. c. Aggregated knowledge base assertions (excluding those from genetics population data) at the moment of writing. As expected by the different scopes of each knowledge base and the long tail of lowly recurrent mutations, only a minority of the variants appear curated in more than one knowledge base, which stresses the importance of their aggregation to provide a comprehensive annotation. d. Graphical summary of some of the criteria used for assuming that a variant with null consequence type is disrupting the function of a given tumor suppressor (part of the evidence of type B, a). These are largely based on established rules to identify loss-of-function variants in Mendelian genes (Methods). e. The lowest level of evidence to estimate a given variant effect is based on bioinformatics metrics. For variants that are not located in mutation hotspots, we decided to use the combined annotation dependent depletion (CADD) score to estimate the functional relevance of missense mutations in tumor suppressor genes (TSGs), as functional impact predictions perform worse in other scenarios (data not shown). The method and associated thresholds were selected according to our own benchmarking, based on the performance observed for mutations with curated effects (upper violin plot) and in silico simulations (lower violin plot) (Methods). FN, false negative (given these thresholds); FP, false positive; TN, true negative; TP, true positive.

Unclassified variant (i.e., of unknown functional significance)

Neutral consequence

Malignant or in-frame deletion at a mutation hotspot

TSG missense, very high Fi

Malignant variant (not hotspot) in tumor suppressor gene and very high functional impact

TSG missense, very low Fi

Same than the previous one but for very low functional impact

Missense or indel, hotspot 2D/3D

Missense variant or in-frame deletion at a mutation hotspot

Knowledge base variant aggregation (excluding population genetics data)

| MTBP classification | Evidence A | Evidence B | Evidence C |
|---------------------|------------|------------|------------|
| Pathogenic, likely pathogenic benign, likely benign | Curated variant effect? | Yes | Yes | Yes |
| Pathogenic, likely pathogenic benign, likely benign | No reported effects (or not conclusive) | | | |
| Oncogenic, likely oncogenic | Bona fide assumption? | | | |
| Oncogenic, likely oncogenic | Assumptions are not pertinent/fulfilled | | | |
| Putative functional, putative neutral | Putative functional | Putative functional | Putative functional |
| Noncoding or silent variant | Neutral consequence | Neutral consequence | Neutral consequence |
| Likely disrupting variant in TSG | TSG null consequence | TSG null consequence | TSG null consequence |
| Putative functional | Putative neutral | Putative neutral | Putative neutral |
| Putative functional | Putative functional | Putative functional | Putative functional |
| Putative functional | Putative functional | Putative functional | Putative functional |
| Putative functional | Putative functional | Putative functional | Putative functional |
| Putative functional | Putative functional | Putative functional | Putative functional |

The molecular tumor board discussion (Fig. 5a). These were mostly associated with the use of immune checkpoint inhibitors in the presence of loss-of-function events in DNA damage repair genes, as estimated by the MTBP variant interpretation (Methods). However,
the majority (60%) of these patients were not finally enrolled in the Basket of Baskets trial, mostly because of the deterioration of their clinical condition or subsequent screening failures. This further emphasizes the importance of deploying systems that can support an efficient and rapid trial recruitment at the point of clinical decision-making.

The MTBP retrieves the trials’ eligibility criteria from in-house databases gathering clinical, pathological and molecular requisites. This information is curated following an ad-hoc syntax adapted to the growing complexity of cancer biomarkers, which are defined by the presence (or absence) of a given combination of genomic alterations and/or genomic signatures. This syntax also defines prioritization rules in case that the allocation to multiple trials is possible, as well as variant interpretation nuances to be used by the MTBP interpretation framework. One example of the latter is the evidence required for considering variants in a given actionable gene as functionally relevant; in general, we only match clinical trials with tumor variants whose effect is based on well-curated studies or bona fide biological assumptions, but lower evidence, such as bioinformatic predictions, is also considered for emerging biomarkers associated with less characterized genes. Upfront agreement on these details enables the MTBP to refine the actionability flags issued in the reports, which facilitates efficient discussions during the molecular tumor board meetings and increases the consistency of the clinical decision-making.

Importantly, the MTBP can be used to automate the detection of other events of potential clinical relevance. For example, and in collaboration with the CCE genetic counseling task force, we have established unified criteria to flag germline variants requiring genetic specialist referral (Methods). As a result, the MTBP issued genetic counseling alerts for 49 germline variants in 48 individuals (57 ± 13 years) of the CCE cohort, which represent 13% of those with paired tumor/normal samples sequencing available (with a cancer type distribution similar to that of the overall cohort; Table 1). Incidentally, three (6%) of these variants showed a low variant allele frequency in the tumor sample, and thus, they would not have been contemplated as of potential germline origin with tumor-only sequencing data, as per published criteria. Genetic counselor review deemed these findings as of clinical relevance in all the cases, although close to half (44%) of the variant carriers did not meet personal criteria for clinical germline testing. Moreover, a considerable (18%) proportion of these pathogenic germline variants were found in genes not associated with the patient’s index cancer, which further complicates their discovery via standard guidelines-directed genetic testing. These results illustrate the importance of the oncology setting for screening hereditary cancer susceptibility variants and the value of the MTBP to streamline that task.

The MTBP technology. The MTBP provides a single unified framework for sharing and harnessing NGS data across CCE centers. Deidentified patient clinical and pathological information is fetched from a centralized electronic case report forms system, whereas sequencing data files are retrieved from different institutional and external laboratories. Data transfer, storage and access are implemented by a set of technical measures in accordance with the European legal framework under compliance with data protection regulation (Methods). After data capture, the system triggers a technical assessment.

Table 1 | Characteristics of the 500 tumors in the CCE prospective cohort

| Characteristics | Values |
|-----------------|--------|
| Age (y), median (IQR) | 59 (49–67) |
| Female sex, n (%) | 300 (60%) |
| Paired samples, n (%) | 375 (75%) |
| Primary tumor sample, n (%) | 270 (54%) |
| Tumor purity, median (IQR) | 60% (35–80) |
| Primary cancer type, n (%) | 100 (20%) |
| Breast carcinoma | 100 (20%) |
| Colorectal adenocarcinoma | 65 (13%) |
| Ovarian epithelial tumor | 55 (11%) |
| Esophageal adenocarcinoma | 30 (6%) |
| Cholangiocarcinoma | 25 (5%) |
| Pancreatic adenocarcinoma | 20 (4%) |
| Cancer of unknown primary | 15 (3%) |
| Prostate adenocarcinoma | 10 (2%) |
| Salivary carcinoma | 10 (2%) |
| Pleural mesothelioma | 10 (2%) |
| Gallbladder cancer | 10 (2%) |
| Other | 150 (30%) |

Patients with advanced/refractory disease considered for CCE clinical trials from January 2019 to January 2021. Note that the cohort is biased toward those cancer types that were more suited to the Basket of Baskets treatment arms opened during that time period. All samples were profiled by targeted NGS panels. *Sequencing of paired white blood cells and tumor tissue samples identifying germline versus tumor somatic variants; only the tumor sample was sequenced otherwise. **Sequenced tumor sample obtained from the primary tumor; sample was from a metastatic site otherwise. †Percentage of tumor content in the tumor sample as reported by the pathology assessment.

The MTBP patient reports are HTML web-based documents accessible for the clinical investigators via a secure online platform. These reports are discussed in weekly virtual molecular tumor board meetings, in which members of each CCE center connect from different locations and agree on clinical recommendations. As discussed before, genomic alterations are flagged in the MTBP report according to predefined expert actionability criteria, and all the results appear systematically organized in a user-friendly, readily interpretable view (Fig. 5c). In addition, further information and variant annotation details are accessible via interactive elements of the HTML report, which empowers an in-depth revision of the content and supporting evidence. Although the MTBP can also distribute simplified reports in PDF format, we believe that working with interactive data-rich documents is more appropriate in the context of academic medical centers, in which molecular tumor boards discuss complex cases and serve as a venue for continued education in genomics-driven oncology. Of note, we observed a learning curve to use the MTBP system lasting for approximately 25 patients (Fig. 5d). After that, the amount of time devoted to discussing each case averaged less than three minutes, which is key for scaling the process to a large number of patients.

At the moment of writing, the MTBP system used by CCE initiatives supports the interpretation of genomics data (mutations, copy-number alterations, structural variants and mutational signatures) and has recently incorporated gene expression analysis. In addition, and in the context of ongoing efforts to implement new clinical trial designs, we are currently working on the incorporation of emerging tumor profiling technologies such as proteomics, ex vivo drug screening and digital pathology. Ultimately, we envision the MTBP as a catalyst for systems-based precision oncology, capable of integrating
multiple levels of molecular and imaging data and inform treatment decisions throughout the patient's disease course. In addition, we have also created an open website (https://mtbp.org) that provides access to a lightweight version of the MTBP analytical framework. This public resource is intended for research purposes and only supports a general interpretation of gene variants that may be of interest for investigators outside our network (Extended Data Fig. 1).

**Discussion**

The MTBP provides a unified platform for implementing precision oncology strategies in a truly collaborative manner. As the complexity of cancer biomarkers continues to grow, automating the interpretation and reporting of sequencing results decreases the need for manual procedures and facilitates rapid, comprehensive and consistent clinical decision-making. In addition, the MTBP creates the infrastructure to systematically gather the molecular and clinical information in a ‘biorepository’ of data, which supports the discovery of new biomarkers and insights for future trial designs. However, deploying the MTBP across the CCE network raised multiple challenges, such as (i) ensuring the interoperability with the information technology systems of each connected center; (ii) automating the retrieval of clinical, pathological and sequencing data provided by different facilities; (iii) developing user-friendly interfaces for distinct user types, such as medical practitioners, project managers and data analysts; (iv) coordinating the efforts to agree on variant interpretation criteria and actionability prioritization; and (v) creating the associated resources, such as a database with up-to-date information of the clinical trials open for recruitment across the network. These tasks require expertise from domains...
such as medical software regulation, cybersecurity and front-end development, which is not easily available in the academic setting and thus creates needs for collaboration with industry partners. In conclusion, we believe that streamlining digital systems like the MTBP at the point of care is key to better address the challenges of delivering biomarker-driven oncology at scale, but the success of these initiatives relies on the long-term investment needed to develop and maintain the technology.

Methods

Ethical regulation. The Vall d’Hebron Institute of Oncology is the sponsor of the Basket of Baskets trial. The protocol was submitted through the Voluntary Harmonization Procedure and approved by the Medicines & Healthcare products Regulatory Agency in the United Kingdom. Subsequently, the competent authorities in Spain (Agencia Española de Medicamentos y Productos Sanitarios), France (Agence nationale de sécurité du médicament et des produits de santé), Germany (Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel), the Netherlands (Centrale Commissie Meegebroken Onderzoek) and Sweden (Läkemedelsverket) provided local approval. Ethics committee approvals have been obtained in Spain, the United Kingdom, France, the Netherlands and Sweden under EducaCT project number 2018-005108-89. All patients signed an informed consent form for preregistration and another for the trial in the case of recruitment. The clinical and sequencing data transfer, storage and access complies with European legal and ethical regulations as appropriate.

Statistics and reproducibility. This article includes a description of a consecutive cohort of advanced tumor patients preregistered in the Basket of Baskets (NCT03767075) trial during a 2-yr period. No statistical method was used to predetermine sample size. No data were excluded from the analyses. The experiments were not randomized. The investigators were not blinded to allocation during experiments and outcome assessment. The article describes general tumor genomic
findings aggregated at the cohort level, and the resulting descriptive numbers (no statistic tests were necessary) are available in the text, tables and figures.

MTBP in CCE (CCE-MTBP). Patient clinical and tumor pathological information is gathered in pseudo-anonymized electronic case report forms (ALEA system; https://www.aleaclinical.eu/). Molecular assay results are provided by CCE institutional facilities and commercial laboratories. Data is automatically transferred to the CCE-MTBP through secure protocols as appropriate. Upon receipt of each data file the CCE-MTBP checks the integrity of the content and (if no issues are detected) several analytical pipelines are triggered to process the results and create the corresponding patient-centric report, which is made available to clinical investigators via an online secure platform.

Public instance of the MTBP (public-MTBP). Access to a lightweight version of the MTBP genomics analytical pipeline has been made freely available at https://mtbp.org. At the moment of writing, the public-MTBP supports the analysis of single-nucleotide variants and small indels, which can be manually uploaded via a VCF file (hg19/GRCh37 and hg38/GRCh38 coordinates supported) or through a free text box for genomic, cDNA and/or protein-based mutations (HGVS syntax supported). The public-MTBP provides a general public-MTBP.

The logs of each CCE-MTBP pipeline run are manually reviewed by the MTBP developers as part of our standard operating procedures, and email alerts are sent as appropriate when new results are available.

Public instance of the MTBP (public-MTBP). Access to a lightweight version of the MTBP genomics analytical pipeline has been made freely available at https://mtbp.org. At the moment of writing, the public-MTBP supports the analysis of single-nucleotide variants and small indels, which can be manually uploaded via a VCF file (hg19/GRCh37 and hg38/GRCh38 coordinates supported) or through a free text box for genomic, cDNA and/or protein-based mutations (HGVS syntax supported with several reference systems supported). The public-MTBP provides a general interpretation of the functional and predictive relevance of the uploaded variants but does not issue actionability flags (such as potential eligibility for clinical trials here).
Genomic alterations considered for the Basket of Baskets study. Genomic alterations considered for the use of atezolizumab in the first treatment module opened for the Basket of Baskets (NCT03767075) study opened during the evaluation of the CCE patient cohort described here are the following: BRCA1 or BRCA2 loss-of-function mutations (arm 1A); MEH1, MSH6, and PMS2 loss-of-function mutations (arm 1B); POLE or POLD1 switch-of-function mutations (arm 1C); intermediate or high tumor mutation burden without an apparent mechanism for DNA damage repair malfunction (arm 1D); loss of function observed in other DNA damage repair genes (arm 1E); and CD274 (PD-L1) copy-number amplifications (arm 1F). Note that the Basket of Baskets is a dynamic protocol trial in which new treatment modules are progressively opened or closed through the corresponding amendments.

List of genes evaluated for germline variants conferring inherited cancer risk. These are the genes recommended by the American College of Medical Genetics and Genomics for cancer predisposition testing, plus some others (marked with an asterisk) agreed to be clinically actionable by the CCE Genetic Counseling Task Force. Of note, the MTBP issues genetic counseling alerts only if the germline variants observed in these genes are estimated to be loss of function based on well-curated evidence and/or bona fide biological assumptions, regardless of their clinical relevance: APC, ATM, ATM*, BRCA1, BRCA2, CDH1*, CHEK2, MEN1, MLH1, MSH2, MSH6, MUTYH (only reported for homozygous or compound heterozygous MUTYH mutations), NF2, PALB2*, PMS2, PTEN, RAD51C*, RAD51D*, RB1*, RET, SDHB, SDHC, SDHD, SMAD3, SMAD4, STK11, TGFBR1, TGFBR2, TP53, TSC1, TSC2, VHL, and WT1.

MTBP annotation. The MTBP uses a combination of in-house and publicly available bioinformatic tools to transform the different formats produced by the CCE-MTBP data providers and the different variant nomenclatures accepted by the public-MTBP into a single unambiguous representation system. The MTBP annotates these data with multiple resources based on the classification schemes shown in Fig. 2 (functional relevance) and Fig. 1 (predictive relevance). Among these resources, the MTBP uses third-party knowledge bases that (i) formalize information about the variants’ effect by using predefined processes, (ii) are based on published biomedical literature and (iii) are committed to periodical updates. Variant nomenclature, terminology and taxonomy systems used to annotate the data are also unified across knowledge bases with a seminar on MTBP methodology regularly updated. Additional filtering distinguishes knowledge base assertions supported by weaker or inconclusive evidence, as extracted from the corresponding metadata as appropriate (e.g., less than two or three stars in the ClinVar or CIViC evidence rating, respectively). Only resources open for academic research purposes are used in the public-MTBP. The MTBP also implements bona fide biological assumptions to estimate the relevance of variants without conclusive curated effects, which are largely based on established rules to identify loss-of-function variants in Mendelian genes and subsequent refinements. In the case of tumor suppressors (see Fig. 2d), these include canonical splice site disruptions and variants leading to a premature stop codon (likely) triggering nonsense-mediated decay mechanisms, which are considered very strong criteria (so-called ‘PVS1’). Variants truncating/disrupting protein regions that are crucial for the tumor suppressor function, which are considered strong supporting criteria (PVS1_Strong) (of note, the identification of these essential protein regions is refined by analyzing location and consequence type of known loss-of-function variants, as gathered from the knowledge bases aggregated by the MTBP (manuscript in preparation)), and variants truncating/disrupting more than 10% of the wild-type tumor suppressor protein, which are considered strong supporting criteria (PVS1_Strong). Finally, if none of the previous evidence is conclusive, then the MTBP evaluates variants’ relevance with computational methods selected according to our own benchmarking (next section). On the other hand, the MTBP factors in additional tumor-context considerations to classify the actionable relevance of variants as functionally relevant following the European Society for Medical Genetics and Genomics and the Association for Molecular Pathology. Genet. Med. 17, 405–424 (2015). Abou Tayoun, A. N. et al. Recommendations for interpreting the loss of function PSVI ACMG/AMP variant criterion. Hum. Mutat. 39, 1517–1524 (2018). Tchegnabegu, D., Gonzalez-Perez, A. & Lopez-Rivas, N. OncodriveCLUST: exploiting the positional clustering of somatic mutations to identify cancer genes. Bioinformatics 29, 2238–2244 (2013). Chang, M. T. et al. Identifying recurrent mutations in cancer reveals widespread lineage divergence and frames insertional mutational specificity. Nat. Biotechnol. 34, 155–163 (2016). Gao, J. et al. 3D clusters of somatic mutations in cancer reveal numerous rare mutations as functional targets. Genome Med. 9, 1 (2017). Kircher, M. et al. A general framework for estimating the relative pathogenicity of human genetic variants. Nat. Genet. 46, 310–315 (2014). Zhou, W. et al. TransVar: a multilevel variant annotator for precision genetics. Nat. Methods 12, 1902–1903 (2015). McLaren, W. et al. The Ensembl variant effect predictor. Genome Biol. 17, 122 (2016).

Data availability. Sequencing data have been deposited to the European Genome–phenome Archive, which is hosted by the European Bioinformatics Institute and the Centre for Genomic Regulation. Because of patient privacy constraints, the data are under controlled access and available upon reasonable request to the CCE Basket of Baskets Data Access Committee (bob@vhio.net) based on European Genome–phenome Archive terms (see accession number EGAS00001005893 for further details). Source data are provided with this paper.
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Characteristics

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Author contributions

The project was conceived and supervised by D.T. and J.L. The MTBP analytical pipeline, from end-system and data infrastructure were developed by D.T., M.H.R., J. Boekel, M.J. and R.D. The results shown in this article were prepared by D.T., A.L.-F. and J. Balmaña. X.V. Project coordination, clinical review and scientific input were provided by D.T., M.H.R., J. Boekel, M.J. and C.C. Additional information

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Gene variants analysis in the public MTBP website

Extended Data Fig. 1 | Public version of the Molecular Tumor Board Portal. **a**, The public MTBP is an open resource for research purposes that provides a lightweight version of the MTBP analytical pipeline. This public resource is accessed via a website (https://www.mtbp.org/) that offers an interface to upload the gene variants to analyze. At the moment of writing this manuscript, the public MTBP only supports the analysis of single-nucleotide variants and small indels. **b**, The public version of the MTBP does not issue actionability flags that require information that cannot be inferred from the generic input employed here and/or require interpretation nuances that may differ across investigators/institutions (such as matching with a given portfolio of clinical trials or the identification of germline incidental findings). Instead, the public MTBP provides a general interpretation of the functional and predictive relevance of the uploaded variants, with the aim of supporting a detailed review of the user according to his/her specific needs. **c**, Public MTBP website activity from the date of its release until the moment of writing this manuscript.
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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection
Clinical, pathology and sequencing data files are collected and subsequently analysed by the MTB portal by using appropriate secure transfer protocols and data access security measures (not disclosed here). Additional regulation details can be found in the manuscript.

Data analysis
MTB variant annotation and interpretation combines multiple resources following expert-consensus criteria as described in detail in the manuscript. The analytical pipeline to interpret the data is built in Python (>=3.0), with versions spanning from that available for the patient n=1 (pipeline v1.0) to that available for the patient n=500 of this present cohort (pipeline v4.8), and aggregating several publicly available bioinformatics tools (TransVar v2.5 and VEP v94-101) and knowledgebases [ClinVar, BRCAXchange, CincoXB, CIVIC CGI, 1000g. gnomAD]. More details and references can be found in the manuscript.

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Sequencing data has been deposited at the European Genome-phenome Archive (EGA), which is hosted by the European Bioinformatics Institute and the Centre
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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size

This paper describes the deployment of an academic clinical decision support system across a network of European Cancer Centers. To illustrate its results, we also present the results (aggregated at the cohort level) of using the system in a prospective, consecutive cohort of cancer patients pre-registered to the Basket of Baskets trial (NCT03767075) during two years, summing up a total of 500 evaluated tumors. Such number of tumors and time span are considered large enough to illustrate the performance of the system and the experience of using it, which is the aim of the present manuscript, and thus no other sample size calculations apply here.

Data exclusions

No sample of the aforementioned cohort was excluded in the results presented here.

Replication

Sequencing results were interpreted using the MTB portal analytical framework developed under the Cancer Core Europe umbrella. The MTBP analytical framework was systematically applied by an automated workflow across the whole cohort presented here. The pipeline code and the resources employed to annotate the patients’ results are under version control in the corresponding software and data repositories employed by the system, respectively. Before releasing any code and/or data update, the system is tested in a stage server by semi-automatic workflows based on predefined test input data according to our standard operating procedures.

Randomization

This manuscript includes the results of using the MTB portal in a prospective, consecutive cohort of cancer patients pre-registered to the Basket of Baskets trial (NCT03767075) during two years. The Basket of Baskets allocates tumors with pre-defined molecular profiles to treatment arms testing different targeted drugs and immune therapies (no patient randomization). However, this manuscript describes the results of interpreting the genomics data (aggregated at the cohort level), but no clinical outcomes connected to the trial are reported here.

Blinding

This manuscript includes the results of using the MTB portal in a prospective, consecutive cohort of cancer patients pre-registered to the Basket of Baskets trial (NCT03767075) during two years; the trial arms opened during this time use no blinding, but note that (as stated in the previous section), the paper describe the results of interpreting the genomics data (aggregated at the cohort level), but no clinical outcomes connected to the trial are reported here.

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|    | Eukaryotic cell lines |
|    | Palaeontology and archaeology |
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|    | Human research participants |
|    | Clinical data         |
|    | Dual use research of concern |

Methods

| n/a | Involved in the study |
|-----|-----------------------|
|    | ChIP-seq              |
|    | Flow cytometry        |
|    | MRI-based neuroimaging |

Human research participants

Policy information about studies involving human research participants

Population characteristics

Results of interpreting the NGS tumor data of a total of 500 patients (median 59y, 60% female) with advanced solid cancers pre-registered to the Basket of Baskets (NCT03767075) study during a 2-years period are presented in this manuscript (results aggregated at the cohort level; characteristics of the cohort detailed in Table 1 of the manuscript).

Recruitment

Patients pre-registered in the Basket of Baskets trial (NCT03767075) during 2 years. Further inclusion/exclusion trial criteria available at https://clinicaltrials.gov/ct2/show/NCT03767075 . All included patients signed the corresponding informed consent for molecular profiling and (when pertinent) trial participation (more details in the manuscript).
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## Clinical data

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### Clinical trial registration

| Clinical trial registration | NCT03767075 |
|----------------------------|-------------|

### Study protocol

The manuscript reports general genomic findings of patients preregistered to the Basket of Baskets trial [https://clinicaltrials.gov/ct2/show/NCT03767075](https://clinicaltrials.gov/ct2/show/NCT03767075) during a 2-years period

### Data collection

Patient clinical and tumor pathological information (e.g., sex, age, diagnosis, tumor sample characteristics and patient's previous treatments) are gathered by members of the clinical teams in each patient's medical institution in pseudo-anonymised electronic case report forms (AI FA system, [https://www.aleadclinical.eu/](https://www.aleadclinical.eu/)). Molecular assay results (cancer gene NGS panels) are provided by the institutional facilities of Cancer Core Europe and commercial laboratories as required by each Basket of Baskets study module. Data transfer, storage and sharing is performed by the MTB portal by implementing a number of measures complying with Cancer Core Europe ethical/legal/cybersecurity framework, as described in the manuscript. This manuscript includes the results of interpreting the data of 500 consecutive patients preregistered to the Basket of Baskets trial (NCT03767075) during a 2-years period (January 2019 to January 2021).

### Outcomes

The Global objective of this Basket of Basket study is to evaluate the antitumor activity of each matched therapies that will be evaluated through the study in small molecularly selected populations. The primary objective of module 1 is to determine the overall response rate by RECIST 1.1 after 3 weeks of treatment with atezolizumab in several arms selected according to predefined molecular alterations. Secondary outcomes include: mean progression free survival (PFS by RECIST 1.1; Time Frame: through study completion); progression Free Survival (PFS by RECIST 1.1; Time Frame: 6 months); mean overall survival; Time Frame: through study completion). However, note that this manuscript present the results of interpreting the NGS data of 500 consecutive tumors registered for the Basket of Baskets study (aggregated at the cohort level), but this manuscript does not report outcomes of the clinical interventions associated to the trial study.