Building the EU Cancer and Health Genomics Platform

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Contents

1. Summary & Objective

The integration of next-generation sequencing (NGS) into clinical practice represents a profound paradigm shift in the way we approach patient care. This advanced technology offers an unprecedented opportunity to precisely prevent, diagnose, and prognose diseases personalised to the unique genetic makeup of each patient. In the field of oncology, genomic analysis has emerged as a game changer, reshaping our understanding of cancer and its treatment. However, alongside its immense potential, this ground-breaking technology has introduced a new set of challenges for clinicians and oncologists.[1,2]

One of the main challenges lies in the fast-evolving field of cancer drug therapies and the growing number of complex biomarkers, such as microsatellite instability (MSI) and homologous recombination deficiency (HRD). The various combinations between the therapies and the biomarkers are crucial to determining which patients will benefit the most from a specific treatment.[1,2] Additionally, the substantial volume of information generated by sequencing requires expertise to match tumour alterations with approved or experimental therapies. As the number of drug biomarkers with specific targets continues to grow, this could lead to increased variability in clinical recommendations across different centres, potentially impairing patient outcomes and hindering healthcare progress.[2,3]
Although the human brain's ability to synthesise and analyse information is nontrivial for machines to replicate, decision support tools (DST) (also called decision support systems, (DSS)) can effectively ease the cognitive burden faced by clinicians, assisting them in making increasingly complex decisions.[2] These tools are described in the literature as electronic devices designed to assist clinicians in complex decision-making by integrating clinical knowledge, patient information, and other health data. They present patient-specific assessments and recommendations to clinicians, enabling them to combine their expertise with this information at the point of care to make a healthcare decision.[2,4–7]

Modern solutions enhance this process by leveraging advanced data and observations that are otherwise difficult to interpret, thereby reducing uncertainties and improving healthcare delivery. DSTs have been used across various clinical domains, including screening, prevention, diagnosis, and therapy. Their vast application has been deployed for multiple purposes[6,7]:

- **Patient safety:** Reducing medication/prescribing errors and adverse events, providing drug control through computerized alerts and reminders.
- **Clinical management:** Ensuring adherence to clinical guidelines, follow-up, treatment reminders, and disease management systems.
- **Cost containment:** Reducing test and order duplication, suggesting cheaper medication or treatment options.
- **Administrative function/automation:** Automating steps to reduce workloads and automated documentation, note auto-fill, and use of documentation templates.

- **Diagnostics support:** Providing diagnostic suggestions based on patient data (diagnostic code selection), automating output from test results (including imaging, laboratory, and pathology), and supporting diagnosis systems through computerized tools.
- **Patient decision support:** Administering decision support directly to patients through personal health records and other systems.
- **Better documentation and workflow improvement:** Enhancing clinical workflow with patient data reports, and documentation templates.

Overall, the primary contribution of DSTs lies in providing suggestions and recommendations based on knowledge representation systems, including modules created from rules, clinical practice guidelines, and logic algorithms. DSTs can be classified as:

i) knowledge-based, which uses rules (IF-THEN statements) based on literature, practice, or patient-directed evidence, or

ii) non-knowledge-based, which leverages Artificial Intelligence (AI), machine learning (ML), or statistical pattern recognition instead of programmed expert medical knowledge. Despite the rapid growth of non-knowledge-based systems, they face challenges like understanding the AI's logic (black boxes) and data availability, limiting widespread implementation.[6]

Despite evidence of their effectiveness [2,6,7], oncology DST (oncDST) are still emerging, especially those that support variant annotation and interpretation, and the translation of these data into therapy recommendations. A growing number of resources for data curation, including commercial tools and open-source platforms, have been developed. The report they produce summarises key findings and is used as a ground discussion in the Molecular Tumor Board (MTB) meetings.[3,8]. The main goal of the MTB is to provide a collegial multidisciplinary assessment (with expertise in oncology, genomics, pathology and bioinformatics) of clinical evidence and complex genomic data to inform the most appropriate treatment choice including enrolment in innovative clinical trials. The implementation of oncDST could be a game changer for clinicians, particularly for MTB committees, which face complex, time-consuming, and error-prone decisions.[3,8]

A few publications have analysed the performance of oncDSTs by comparing their ability to annotate for pathogenicity and actionability. They illustrate the urgent need for harmonisation of annotation, interpretation and treatment-matching algorithms before clinical implementation.[8–10] With these aspects in mind, we envisaged for this deliverable a comprehensive state-of-the-art of the current oncDSTs that translate NGS data into actionability and support MTB discussion.
Furthermore, this groundwork will be instrumental in shaping the EU-oncDST concept, which aims to introduce the foundational framework for advancing the OncDST field and pave the way for the future implementation of oncDSTs. This report will highlight the strengths, weaknesses, and gaps of current solutions and, will suggest a framework to use them as MTB support in cancer diagnosis and treatment recommendations. By addressing this cooperative and global effort, the Can.Heal Consortium hopes to be one step closer to fully realising the potential of precision oncology.

2. Methodology

Various efforts were launched to map the current oncDST landscape and to elaborate the EU-OncDST concept (Figure 1). All these efforts were performed collaboratively with Can.Heal partners, especially involved in WP8 (molecular tumour board) and WP9 (Treatment and follow-up), experts in the field across Europe and the private sector.

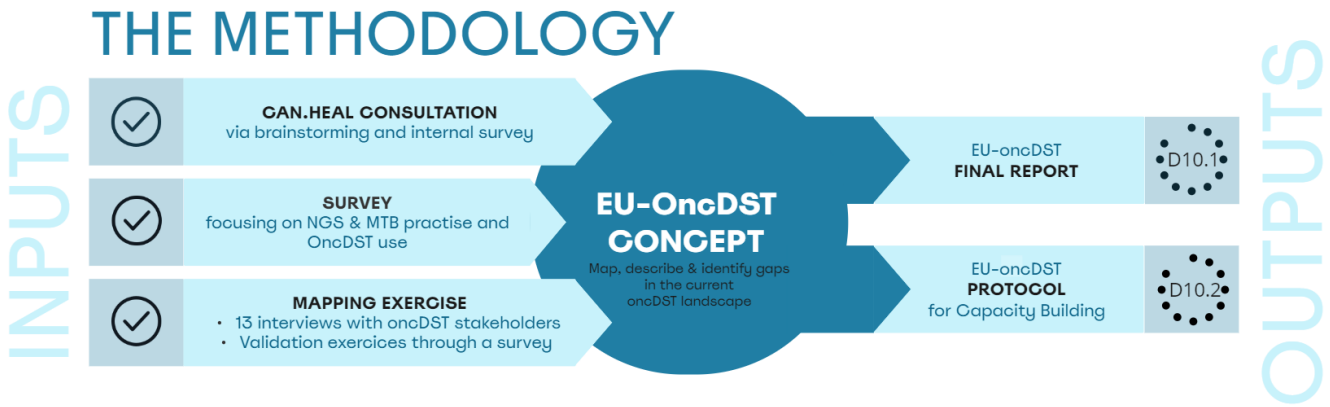

Figure 1: Overview of the methodology on oncDST mapping and EU-oncDST concept development.

2.1 Can.Heal consultation

Virtual meetings with the Can.Heal consortium were organised to collectively brainstorm on the EU-oncDST concept and gather feedback through its development.
As the EU-oncDST concept is also developed to support the MTB, we reached out to the MTB expert community through an internal survey. A question regarding DST use was integrated into WP8's two-page document to collect information on MTB organization across EU countries and was sent to the consortium partners. In addition, WP8 supported us in the organisation of a consultation with MTB members to collect feedback on oncDST requirements.

2.2 Survey

In collaboration with WP8 and WP9, a comprehensive survey, as presented in Figure 2, was developed to collect qualitative and quantitative information mapping the current practices on diagnostic and therapeutic practices of

1. NGS 'wet lab' and 'dry lab',
2. Molecular tumour board (MTB),
3. Decision support tool (DST) and
4. Regulatory, economic and health care policy aspects of NGS in all European countries.

The complete survey results will be presented in an independent, common report between WP8, WP9 and WP10, complementing this deliverable (D10.1), and deliverables D9.2 and D8.4.

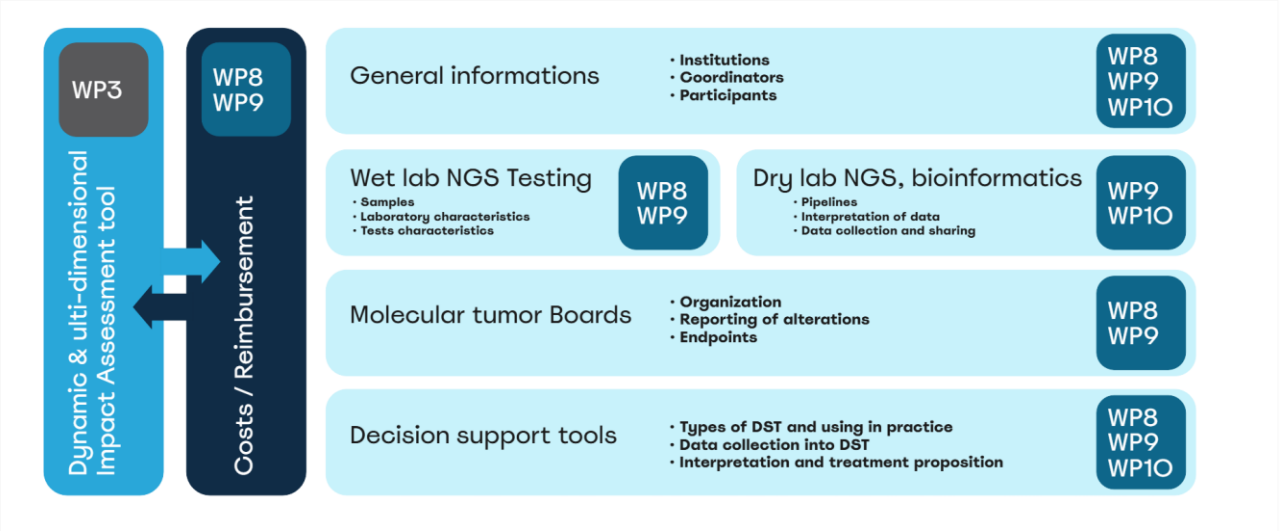

Figure 2: Survey structure: The survey is organized into several sections, encompassing a range of critical domains. These sections include a general information segment, a wet lab NGS testing segment, a dry lab bioinformatics segment, a molecular tumour boards segment, a decision support tools segment, and a cost and reimbursement segment.

2.3 Mapping exercise

To gain insights into the DST landscape, we connected with various stakeholders including hospitals, universities, alternative EU initiatives, and the private sector. All of these entities offer oncDST solutions that support variant annotation and interpretation, as well as the translation of these data into therapy recommendations and/or a platform for supporting MTB discussions. A total of 13 tools were involved in the mapping.

Tools developed by the private sector:

1. Clinical Genomics Workspace (CGW_v6.26.1)
2. Navify (Roche)
3. OncoKDM (OncoDNA_V24.0.2)
4. Oncomine (ThermoFisher_V5.9)
5. QCI Interpret One (Qiagen).

Tools developed within national and European initiatives:

6. BALLETT app (Jessa hospital_V1) developed by the Can.Heal WP9 partner for the BALLETT study[11]
7. Cancer Genome Interpreter[12] (CGI-Clinics_v2)
8. cBioPortal adapted[13–16] for use with an MTB by the MIRACUM MII consortium (cBioPortal adapted_v6)
9. MTB portal[17] (MTBP- Karolinska Institutet).

From 4 tools, no consent was received to mention the tools' names. They will be referred to as others in this work.

For each solution, we organized an hour-long meeting where stakeholders could present their solutions through a slide presentation, a live demonstration, or a combination of both. These interactions provided a deeper understanding of each solution and its capabilities. To objectively evaluate and record the capabilities of each tool, we developed emerging standards based on insights from our various consultation meetings (Annex 1; page 35). These emerging standards represent key aspects that guided our team in comprehensively summarizing and documenting the different exchanges. The summaries were then used to support the analyses provided in the results section. The emerging standards were categorized into five groups, each of them including subcategories presented in Annex 1 (page 35).

Patient Data Management:

the tool should incorporate essential demographic information and have the possibility to interoperate with the electronic health records (EHRs), to include seamlessly patient data, clinical information, pathology reports, haematology reports, imaging results, nuclear medicine and treatment history, etc.

Bioinformatics - Variant Interpretation:

the tool is expected to deliver variant interpretation following secondary bioinformatic analysis by annotating and classifying genomic and transcriptomic alterations that are relevant to treatment recommendations as well as prognosis and diagnosis. In addition, it should be able to identify and prioritize potentially significant variants including driver and germline mutations and actionable alterations.

Clinical Recommendation:

- Diagnosis and Prognosis Interpretation: the tool should be able to make recommendations for diagnosis and prognosis based on genetic data analysis.
- Treatment Recommendations/Theranostics: the tool should be linked to a comprehensive and up-to-date drug-genomic interaction database, including information on drug targets, pharmacogenomics, identified variants, relevant biomarkers, and clinical evidence supporting specifically (targeted) therapy options. These recommendations should be connected to reputable relevant clinical guidelines and evidence-based recommendations in the decision-making process.
- Clinical Trials Availability: The tool should provide information about relevant clinical trials based on the patient's genomic profile, the patient’s electronic health records (EHRs), imaging and pathology reports and the inclusion criteria. It should support the identification of ongoing trials and spot availability that match the patient's molecular characteristics or enable access to potentially novel therapies.

Molecular Tumour Board tool:

the tool should have a module that centralises key information and reports such as EHRs, molecular reports, imaging, and pathology reports to support the MTB in the treatment decision and patient management.

Digital and Interoperability:

- Interoperability: The tool should demonstrate interoperability capabilities for seamless data sharing among partners, facilitating the comparison of individual patient data with a large database of de-identified patient information.
- Digital: the tool should incorporate a system for continuous updates and maintenance of evolving knowledge and technologies. Additionally, the tool should prioritize data privacy and security to safeguard sensitive patient information.

Finally, all DST stakeholders were invited to participate in a validation exercise with a survey. We developed statements based on the EU-oncDST concept and the emerging standards. We asked stakeholders to evaluate how well their solutions aligned with these statements by categorizing their responses as "align", "partially align", or "not align"; and to justify their answers. This survey allowed stakeholders to reflect on their solutions concerning specific emerging standards and enabled us to validate our observations. The survey is available in Annex 2 (page 40). Out of our 13 stakeholders, 9 completed the survey. As stipulated during participation enrolment, individual responses to the survey will remain confidential.

2.4 EU-oncDST concept

The EU-oncDST concept framework was developed using the elaborated emerging standards from the Can.Heal consultations. This framework was subsequently refined and enhanced through survey results and a mapping exercise. Each significant step was presented to the Can.Heal consortium, and feedback was incorporated. The final outcome of this process is detailed in the 'Results' section.

3. Results

3.1 OncDST practice in Europe

a. DSTs practice of Can.Heal MTB members

WP8 evaluated current MTB practices within the Can.Heal consortium through a 2-page document. In this document, the question 'If applicable, which DST does the MTB use?' was included In this report, we will primarily focus on the results of this question; a more detailed overview of the results can be found in deliverable D8.1.

Among the 12 MTB committees located in 10 institutions across 6 countries, it was observed that approximately 42% of the MTBs utilized at least one tool. Interestingly, we noted that participants use knowledge-based, non-knowledge based or a combination of both. An overview of the mentioned DSTs is given in Table 1. Overall we note that these preliminary results already indicate

some disparities in the use (or non-use) of DSTs among the MTBs. The survey in point b provides a more comprehensive understanding of DST utilization in Europe.

Table 1: The table was extracted from the deliverable D8.1 – Local MTB organizations report - Decision support tool section. This summarises the different institutions and their current practice around DST used.

Institutions	DST used
IRE, IT	OncoKB and Oncomine Knowledgebase Reporter from Thermofisher/Life Technologies
Charité, DE	MH Guide (https://www.molecularhealth.com/solutions/mh-guide/)
Curie local MTB, FR	None
Curie national MTB, FR	None
APHP solid tumours, FR	None
APHP acute leukaemias, FR	OncoKB
BSMO, BE	FMI, NAVIFY, custom-designed trial-specific app, OncoKDM and CGW
Antoine Lacassagne, FR	NA
UCCSH, DE	None *cbioportal is used to integrate sequencing data and clinical info. Prioritised recommendations discussed during MTB are manually integrated into cbioportal for a transfer back to the clinical information System*
ICO, ES	NAVIFY and genome databases (Alamut, Franklin)
MUW, PL	None yet
MSCI, PL	None yet

b. Survey

This summary focuses on the DST section analysis of the survey collaboratively run between WP8, WP9, and WP10 and distributed across Europe, involving 116 participants. To guide survey participants in contributing to the DST section, we defined oncDST as “computer systems designed to assist healthcare providers in making complex decisions about individual patients at the point in time when these decisions are required.” The survey reveals that currently the implementation of oncDST is limited (15% of 75 participants), while most (71%) rely on hospital tools like electronic health records (EHRs) or electronic case report forms (eCRFs). Key barriers to DST use include a lack of reimbursement, manual data entry, incomplete integration of data, and concerns about tool reliability and local relevance. Despite these challenges, participants recognize that DSTs provide valuable input for making clinical recommendations in MTB settings.

Transparency in the data sources used by DSTs is essential to build user trust. Some participants were unaware of the datasets integrated into the tools, highlighting the need for better communication. DSTs currently fall short in areas like methylomics or transcriptomics data analysis and lack features like automated treatment recommendations and prioritization, which would require the implementation of AI and enhanced interoperability.

The survey also highlights that DST-generated case reports vary in format, with some institutions using PDF or Word documents and others using interactive digital reports. Each format has its advantages, though interactive reports could better facilitate MTB discussions.

The complete survey report on the DST section is available in Annex 3 (page 51).

c. DST practice conclusion

Overall, both the survey and the 2-page document consistently reveal a significant gap in the adoption of oncDST across Europe, as most institutions continue to rely on hospital tools such as EHRs or eCRFs to support MTB discussions. A critical barrier to the implementation of oncDST is the lack of reimbursement, which limits its widespread use. Notably, participants often reported using a combination of tools (knowledge-based and non- knowledge-based), highlighting the absence of a comprehensive solution that adequately addresses all their needs.

The survey specifically highlighted that the current strength of oncDST lies in NGS data analysis and interpretation, while its main weaknesses are the manual entry of information, labour-intensive processes, and the lack of automated treatment recommendations and prioritization. This lack of automation could hinder the development of interoperability. A key takeaway from the survey is that all participants unanimously agreed that the recommendations provided by DSTs are beneficial in MTB discussions.

3.2 The concept

Through the development of the EU oncDST concept, we aim to tackle many of the challenges identified in point 3.1 and support all involved stakeholders by suggesting a system that envisions centralizing patient data, offering personalized treatment recommendations, facilitating clinical trial enrollment, and improving interoperability across institutions.
Based on the consultation sessions, the Can.Heal consortium defined that the EU-oncDST concept should be modular, transparent, interoperable and ever-growing, as illustrated in Figure 3.

This concept is envisioned as a comprehensive system composed of multiple modules including patient data, bioinformatics with variant interpretation, clinical recommendation, MTB and interoperability, each serving distinct yet interconnected purposes to support decision-making within MTBs (Figure 4). These modules are designed to:

I. centralise both historical and current patient medical data,
II. select actionable molecular alteration of interest,
III. provide personalized treatment recommendations tailored to individual patient cases,
IV. streamline patient enrolment in clinical trials,
V. centralise patient and genomic data and clinical evidence to support decision-making within MTBs,
VI. allow continuous patient follow-up, and
VII. promote interoperability among diverse national and international medical centres.

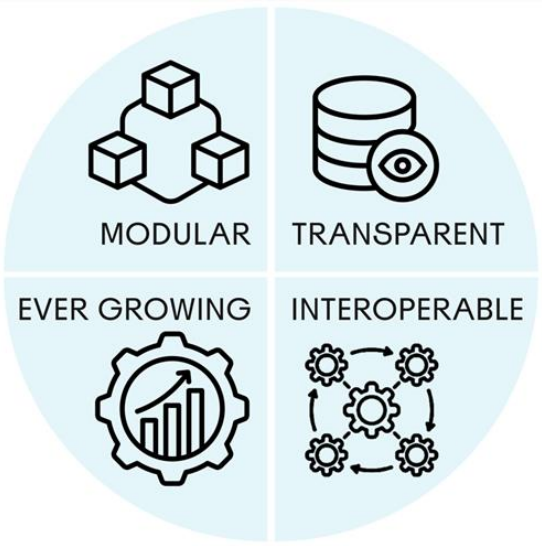

Figure 3: EU-oncDST concept definition.

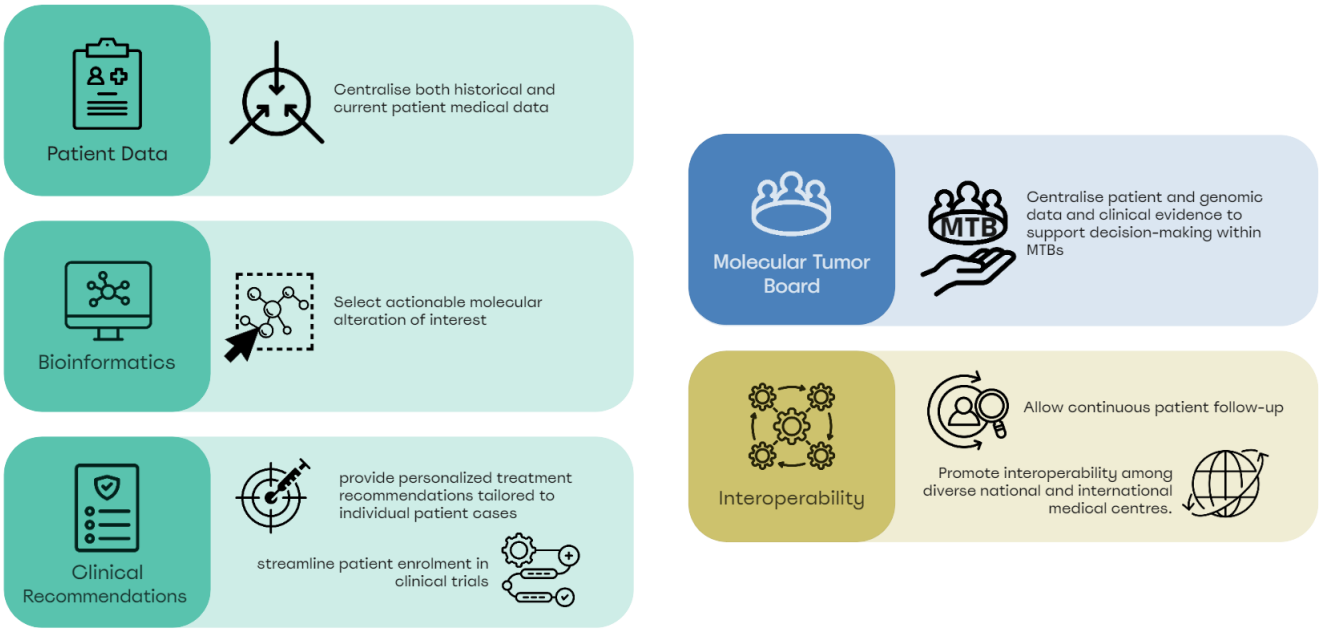

Figure 4: EU-oncDST concept modules.

The workflow of this modular concept is illustrated in Figure 5. The patient data, MTB, and interoperability modules are linked to the local Electronic Health Record (EHR) or Laboratory Information Management (LIM) system. The EHR/LIM system should automatically transfer key patient data to the relevant module and be updated through the MTB structured report, which summarizes the key MTB recommendations. The MTB module is also connected to the interoperability module which is composed of patient follow-up and previous case repositories.

In the subsequent sections, we explore in-depth how each module integrates with the concept, examine the mapping results associated with each module, and identify gaps and opportunities for enhancing each module.

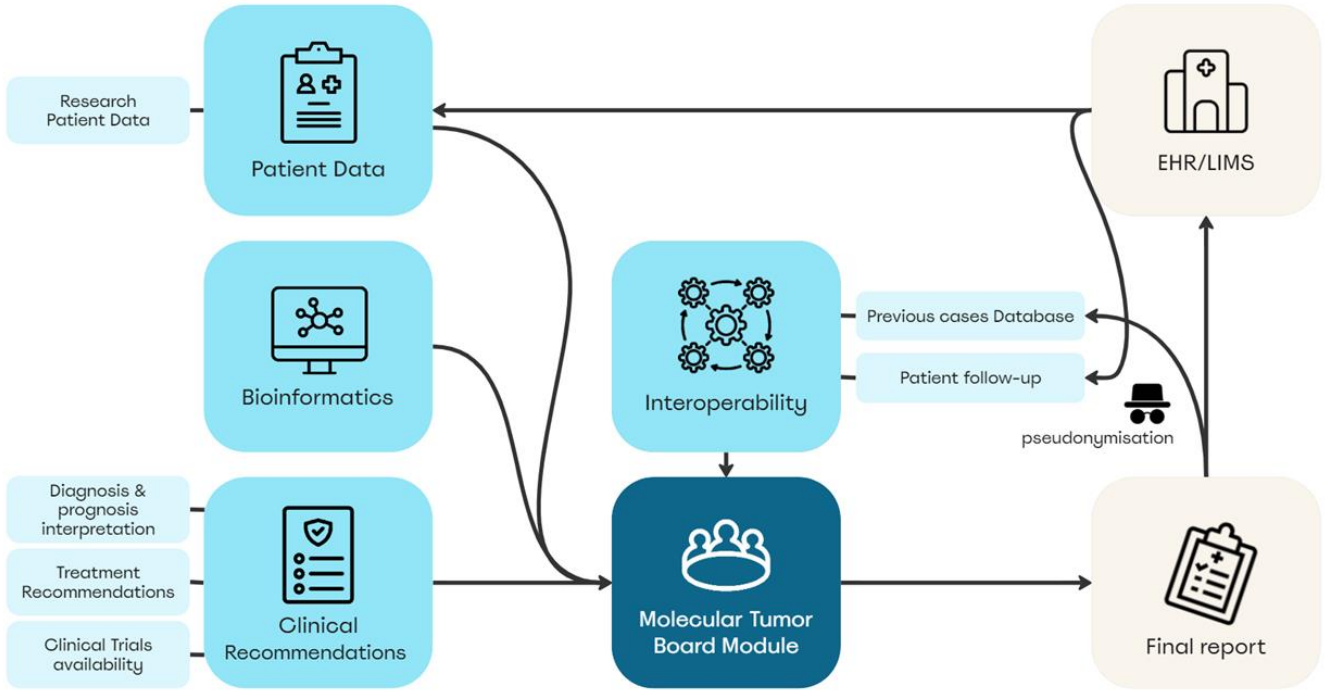

Figure 5: Workflow of the EU-oncDST concept according to the Can.Heal consortium vision.

a. Modules

1. Patient data module

Concept description

The patient data module of the EU-oncDST concept should be compatible with local EHR or LIM systems. This module should include a minimal data set of highly structured information to define patients' characteristics, such as demographics (gender, age), medical and treatment history, cancer type, age at diagnosis, staging (if applicable), co-morbidities, smoking status and vital status. While this list is not exhaustive, it covers the essential fields a clinician might need to analyse a case making well-informed and personalized decisions without requiring additional effort to gather patient information. The data entry format should comply with the European EHR exchange format.[18] Additionally, institutes should also have the possibility to customize some fields according to their specific needs. In addition to the demographic data, a section should be dedicated to the integration and visualization of complementary test results that support treatment recommendations, such as pathology and haematology data, with corresponding imaging results.

The research patient data submodule allows the incorporation of patient data that are still considered in the research phase. It is worth considering the incorporation of germline alteration data results, including pharmacogenomics data, polygenic risk score (PRS) analysis, and other pertinent omics analyses. This will bridge public health genomics and valuable insights into the patient's susceptibility to specific cancer types and potential response to treatments. For instance, the research patient data submodule could be connected to a risk prediction model such as CanRISK used to calculate future breast and ovarian cancer risks in women.[19–21]. With this addition, healthcare providers can include genetic factors when formulating treatment plans, thereby enhancing the precision and effectiveness of interventions. AI-based DST using genetic and

environmental data to predict cancer are further studied in WP5 (PR and DST) of the Can.Heal project.

Results from the mapping exercise

We have observed that essential patient information is manually entered into oncDSTs. The automatic implementation currently requests case-by-case adjustment due to the large variety of local EHR/LIM systems. Nevertheless, if the oncDST is used in the frame of a clinical trial it seems easier to create an automatic incorporation due to the standardisation of the collected data. We observed that incorporating patient-specific data is currently optional when using oncDSTs. This means that, at this stage, the system can generate clinical recommendations based solely on the specified cancer type, without requiring additional patient information. . In addition, this makes data less valuable for second-use purposes such as building a learning cancer system.

The integration of test results previously performed such as imaging (CT, PET CT scans, pathology slide), blood tests, tumour markers, prognostic indicators, bone marrow assessments, kidney and liver function tests, and biopsy results can be available in some solutions. However, the test results that can be integrated vary according to the solution and only a limited number of solutions allow the visualisation of imaging results.

Overall, the mapping shows that most tools have a section where patient demographic information can be introduced and customised according to the preference of the institution. None of the tools show the opportunity to integrate these data in the analysis for clinical recommendation. Finally, some of the tools incorporate additional test results and in some cases allow their visualisation.

Recommendations

The following recommendations aim to improve the current patient data modules and to align more to the user needs and facility interoperability:

- Facilitate the review of patient information within the MTB module.
- Ensure that key patient information is included in the MTB structured report.
- Enhance interoperability between systems, including EHR/LIM systems.
- Follow the European Electronic Health Record (EHR) exchange format.
- Integrate a unified Common Data Model (CDM) for oncology by leveraging insights from initiatives like OMOP CDM, mCODE, OSIRIS, and the 1+ Million Genomes Initiative to ensure standardized data collection and facilitate harmonized analyses across different research settings.[22–25].
- Align with the Unified Medical Language System (UMLS), which integrates and distributes essential terminologies, classifications, coding standards, and related resources to enhance the development of more efficient and interoperable biomedical information systems, including electronic health records;[26].
- Allow the automatic and seamless integration of patient clinical data into clinical recommendations.

- Incorporate and visualize test results (radiology, pathology) to support well-informed treatment decisions, as these tests are crucial in the diagnostic work-up for most cancers. While the incorporation of test results is often possible, their visualization is neither systematic nor easy to manage within current solutions. Additionally, the outcomes of these tests should be automatically integrated into the clinical recommendations to streamline decision-making.

These points will ensure that patient data are properly identified and collected without burdening clinicians. Establishing a centralized and interoperable patient data system is crucial for supporting treatment decisions. This requires collaborative development efforts between DST, relevant research data, and EHR providers, to achieve automated integration across these systems.

2. Bioinformatics module

Concept description

The bioinformatics module involves variant interpretation following secondary bioinformatic analysis by annotating and classifying genomic and transcriptomic alterations that are relevant to treatment recommendations as well as prognosis and diagnosis. In addition, it should be able to identify and prioritize significant variants including driver and actionable alterations and flag potential germline mutations.

Specifically, the EU-oncDST concept should make use of databases recognized for their accuracy, reliability, and comprehensiveness in variant annotation and classification, such as ClinVar, OncoKB, cBioPortal, JAX CKB and/or COSMIC. It should have the capacity to analyse diverse genomic variations, including single-nucleotide variants (SNVs), insertions and deletions (indels), copy number variations (CNVs), gene fusions, exon skipping events, and various biomarkers like microsatellite instability (MSI), tumour mutational burden (TMB), homologous recombination deficiency (HRD), mutation signatures, transcriptional signatures, methylomics or transcriptomics alterations.

To ensure seamless integration with secondary bioinformatic analysis, the EU-oncDST concept should be versatile in accepting different formats, such as VCF, BAM, FASTQ, BED, etc independent of used NGS platform. Users should have the flexibility to customize the tool by selecting or adding recognized guidelines and specific resources for variant classification and interpretation. This adaptability empowers users to tailor the tool to their specific requirements, ensuring access to the most pertinent and up-to-date sources and aligning with national guidelines for harmonised variant interpretation.

Transparency is the foundation of the EU-oncDST concept. It should be evident in the incorporation of guidelines, databases, and resources, with clear indications of the sources used for variant classification and interpretation. This transparency will facilitate clinicians' access and verification of the sources and instil confidence in the tool's outputs, promoting informed decision-making.

The bioinformatics module should also be equipped with a query functionality for previous cases to enhance the learning cancer system. This feature will enable users to analyze the frequency of

specific variants in certain cancer types or target populations. Additionally, in the case of rare or novel variants, it will facilitate the initiation of learning about their unique characteristics.

Results from the mapping exercise

Our mapping exercise revealed that the bioinformatics module emerges as the most developed module on the market. The tools consistently reference relevant and appropriate databases within the bioinformatics modules. Each solution has its own system for variant annotation and classification, often referencing one or more international databases such as ClinVar, OncoKB, cBioPortal, JAX CKB, CIVIC or COSMIC, as well as national databases e.g. database with variants collected according to the Belgian ComPerMed guidelines.[27,28] These annotations are supported by computational methods, such as machine learning or AI, and are complemented by manual curation. The curation process involves independent review by at least two scientists, combined with geographic adaptation based on local drug regulations.

Variants are typically classified according to guidelines from the American College of Medical Genetics and Genomics (ACMG), the Association for Molecular Pathology (AMP), ESCAT, or custom tier systems. The tier system put in place by AMP/ASCO/CAP organizes variants based on the level of evidence supporting their clinical relevance, such as pathogenicity. The incorporation of (inter)national guidelines into these tools varies. The sources used for variant interpretation and classification can often be easily changed when the tools provide this option. When a desired option is not available, collaboration with tool providers is often necessary, which may require additional costs.

The prevalent file type recognized across the solutions is the VCF, with BAM and FASTQ formats on a less frequent basis. Additionally, most tools are independent of used sequencer platforms. Nearly all tools can handle single nucleotide variants, small indels, copy number variations, fusions, splice variants, tumour mutational burden (TMB), microsatellite instability (MSI), and homologous recombination deficiency (HRD). Research is ongoing to integrate the missing types of genomic alterations for the solution that doesn't cover them all. However, none of the tools currently support methylomic or transcriptomic alterations. Finally, variants of unknown significance (VUS) are generally flagged.

Accessibility via hyperlinks to relevant literature and guidelines is generally provided offering clinicians the opportunity to review the original source. However, it is notable that the attribution of sources for variant interpretation is not consistently motivated.

Recommendations

Although it is the most advanced module on the market, it would be interesting to consider:

- The integration of the ClinGen initiative.[29] This initiative is a National Institutes of Health (NIH)-funded resource dedicated to building an authoritative central resource that defines the clinical relevance of genes and variants for use in precision medicine and research. They aim to build a genomic knowledge base to improve patient care. They have established a partnership with ClinVar to improve their knowledge of clinically relevant genomic variation. This partnership includes significant efforts in data sharing, data archiving, and collaborative curation to characterize and disseminate the clinical relevance of genomic variation.[30] They

also have a partnership with the Clinical Pharmacogenetics Implementation Consortium (CPIC®)[31] and PharmGKB[32] to expand ClinGen's valuable clinical genetics resource to include pharmacogenetics (PGx). ClinGen's expert panels evaluate gene-disease relationships but do not cover gene-drug interactions. In contrast, CPIC and PharmGKB concentrate on gene-drug and variant-drug associations. CPIC offers evidence-based clinical practice guidelines for pharmacogenetics implementation and determines the clinical actionability of gene-drug pairs. PharmGKB provides expertly curated summaries of variant-drug phenotypes based on peer-reviewed publications, including associations that may not yet meet the evidence threshold required for implementation guidelines.[33]

- AI combined with manual curation contributes to the creation of high-quality databases. However, users should still have the option to access hyperlinks for reviewing the underlying information. This capability builds trust in the tool and ensures that users remain up-to-date with the latest knowledge.

- The assessment of VUS needs improvement. The OncodriveMUT schema, developed by CGI, is a rule-based tool that evaluates the oncogenic potential of VUS by analyzing key features such as gene role, mutation type, location, and predicted impact. By integrating data from large sequenced cohorts, it effectively classifies VUS as either driver or passenger mutations and provides detailed outputs to assist users in reviewing and interpreting these variants' roles in cancer.[12]

- For our concept, we focused on oncDST for somatic testing and not on DST for non-tumor testing. However we believe it is crucial that there should be a connection with non-tumor testing e.g. germline and pharmacogenomic testing. In our concept, we integrated these into the research submodule of the patient module, however we realize that this is also clinical practice and not only research and that it could be integrated through another module.

3. Clinical recommendation module

The clinical recommendation has been organized into three submodules to simplify the description. These submodules encompass diagnosis and prognosis interpretation, treatment recommendations, and clinical trial availability. Each submodule can be presented differently depending on the specific oncDST solution applied. Leveraging AI and advanced machine learning systems, the module will automatically generate a structured case report that summarizes the outcomes of all submodules. This report integrates actionable biomarkers identified in the bioinformatics module with patient data and alternative test results from the patient data module. Designed for use in MTB discussions, the report will include sections linking to all submodules, with specific sections summarising the patient and bioinformatics data. The following section details the key aspects of these submodules.

Concept description

Diagnosis and prognosis interpretation

The EU-oncDST should demonstrate the capability to interpret genomic data, thereby providing precise and dependable diagnostic and prognostic information that aligns with relevant classification and scoring systems. This means that the tool should not only offer diagnostic suggestions but also refine existing diagnoses. The tool should make the supporting evidence available via hyperlinks for its diagnosis and prognosis recommendations, including comprehensive documentation and references supporting these suggestions. This transparency empowers clinicians and MTB members to critically evaluate the reliability and pertinence of the information presented.

Treatment recommendation

For treatment recommendation, the EU-oncDST should be linked to a comprehensive and up-to-date drug repository database. The recommendations should be connected with well-established and precise clinical guidelines, drug-genomic interaction databases, and evidence-based suggestions. These sources may include respected organizations such as the National Comprehensive Cancer Network (NCCN), the European Society for Medical Oncology (ESMO) with the ESCAT scale, the American Society of Clinical Oncology (ASCO), the Food and Drug Administration (FDA), European Medicines Agency (EMA), OncoKB™, The Jackson Laboratory Clinical Knowledgebase (JAX CKB), among others. By adhering to such sources, the tool can guarantee that its treatment recommendations are grounded on solid evidence and comply with the highest standards of oncology practice. Furthermore, the tool should permit flexibility and customisation by regional or institutional clinical guidelines. This adaptability empowers healthcare institutions and regions to tailor the oncDST to their specific clinical practices and protocols, ensuring alignment with their unique healthcare needs and preferences. As for the previous module, it should ensure transparency of treatment recommendations, providing articulate explanations and justifications for suggested treatments, accompanied by references to the supporting evidence from clinical trials, research studies, and established guidelines. This approach empowers clinicians and MTB members to make well-informed decisions regarding each patient's most suitable treatment options. The tool should strive to create personalized treatment recommendations by combining clinical information from the patient data module and genomic data from the bioinformatic module. This integration gives a comprehensive view of the patient's medical history, pathology reports, treatment responses, and genomic profile, including mutations, biomarkers, and molecular characteristics. Considering these essential factors, the tool supports clinicians and the MTB in recommending the most suitable and effective treatment options for individual patients. To achieve this, the tool may utilize AI and/or machine learning algorithms.

Clinical Trials

The clinical trials submodule is designed to provide detailed information about pertinent clinical trials tailored to the patient's unique profile. It suggests trials based on insights derived from the patient's genomic profile, patient data, imaging and pathology reports, and the specific trial inclusion criteria. Its primary function is to streamline the identification of ongoing trials where the

patient meets eligibility requirements and can be enrolled. The interface eases the process of matching patient-specific cases to clinical trials by connecting to an extensive database containing relevant clinical trials. The tool should highlight and provide information about ongoing trials, including eligibility criteria, locations, enrolment contact details, and available slots for patient participation, thereby highlighting trials actively seeking participants. These features help clinicians identify the most suitable clinical trial options for each patient and consider viable opportunities for participation in ongoing studies.

Results from the mapping exercise

Diagnosis and prognosis interpretation

Our research revealed that tools are equipped to support diagnosis by giving clinical information from guidelines and by the Tier classification of variants that can help in refining or reframing diagnosis. However, none of these tools appear to provide a definitive diagnosis suggestion. The DSTs require the specification of the tumour type to perform the analysis from the sequencing file, and therefore, cannot conduct in our knowledge the analysis independently or in an agnostic manner. Furthermore, no tool can provide meaningful insights at this stage regarding the prognostic aspect.

Treatment recommendation

Accurate guidelines and curated genomic datasets, such as ESCAT, OncoKB or JAX CKB, are currently in use. The solutions offer regional customizability by allowing users to select the relevant regulatory body associated with their institution. For example, users may choose from agencies like EMA , NICE (UK's National Institute for Health and Care Excellence), Health Canada, ESMO , NCCN, Swissmedic, and others. However, national drug regulations are not automatically integrated into these platforms. Incorporating them is possible in certain solutions after collaboration with the tool's engineering team.

References supporting the recommendations are typically embedded within the curated databases, so they are not always explicitly highlighted or accessible through the module. A list of references is usually provided and can be appended to reports. This list is not definite to a specific recommendation, requiring users to review the suggested references themselves. These lists can sometimes be extensive and overload the user with information.
Currently, the evaluated solutions offer treatment prioritization through the level of evidence but do not automatically take into account patient-specific clinical information and genomic data to create personalized treatment plans.

Clinical Trials

Most solutions have integrated Clinical.org, highlighting trials based on the variants found in genomic files, along with the patient's diagnosis, gender, and age. Trials can generally be further filtered by specific genes, trial phases, geographic location, or other criteria. Some tools preselect trials by focusing on those that have reached at least phase 2 or are marked as open for recruiting at the time of search. The list of proposed clinical trials is often extensive, requiring the user to have

some level of tool literacy to effectively filter and highlight the most relevant options regarding eligibility and availability for enrolment.

Recommendations

- Where needed, include submodules for essential prognostic information to support the MTB to provide better treatment recommendations.
- Enhance diagnostic interpretation by allowing NGS results to be analyzed without specifying the tumour type. For instance, in the case of cancers of unknown primary (CUP), Institut Curie (France) is leading a national initiative that implemented a national MTB and has developed the TransCUPtomics AI tool designed to improve CUP diagnosis and treatment. TransCUPtomics harnesses molecular profiling technologies to analyze tumour transcriptomic data, helping to identify the tissue of origin and develop personalized treatment strategies.[34,35]
- Improve current solutions by increasing flexibility in the integration of national drug regulatory data or national clinical trial registries.
- Strive for an integrated multimodal approach by developing advanced AI and machine learning systems that combine patient data, results of alternative testing (e.g., MRI, CT scans, pathology data) and genomic actionability, to better support MTB recommendations for more precise and personalized treatment strategies, better-informed clinical decisions and optimized patient care.[36]
- Develop systems that automatically match patients with clinical trials based on patient and genomic data. The volume of patient sequencing data and the complexity of clinical trial eligibility have made matching patients to precise trials challenging, time-consuming and required significant resources. Currently, the MatchMiner initiative[37] from the Dana-Farber Cancer Institute (DFCI) helps address this challenge as an open-source platform that computationally matches genomically profiled cancer patients to appropriately define the matching patient trials. A similar initiative was launched by the European-wide foundation to accelerate data-driven cancer research (EOSC4Cancer) initiative where the MTBP solution is used. They have focused on the enhancement of interoperability between clinical trial databases and clinical DST for oncology. Connected to MTBP, the TrialMatchAI automates the matching of patient profiles with clinical trials focusing on genomic biomarkers and other relevant patient data to generate tailored clinical trial recommendations.[38] It is also worth noting that commercial groups like MassiveBio and Tempus offer cancer clinical trial-patient matching services.

4. MTB module

MTBs are composed of multidisciplinary clinicians and specialists. who leverage expertise in clinical oncology genomics pathology and bioinformatics to interpret complex genomic data and translate them into actionable therapeutic recommendations for individual patients, taking into account the

global patient history. Today, the main element that they are taking into consideration is the specific molecular alteration regardless of tumour histology.[39]

Concept description

The MTB module is designed to support MTB discussions by centralizing and visualizing essential patient data. This module serves as a data hub, allowing the reviewing of the patient case report, encompassing clinical information, genomic profiles, treatment recommendations, and clinical trial availability. By consolidating these elements into a single, centralized location, clinicians within the MTB can seamlessly access and review all pertinent information. This accessibility empowers them to make well-informed decisions concerning patient care and treatment options. However, it is important to note that the final decision regarding treatment plans ultimately rests with the referring physician.

The MTB module should also include features that enhance decision-making and data analysis. These include hyperlinks for easy access to clinical guidelines and relevant literature, as well as a query functionality that enables users to connect with an interoperable network to analyze previous cases and evaluate the impact of MTB. This capability allows clinicians and researchers to gain insights from past patient data, compare treatment outcomes, and identify trends to inform current decisions. In addition, a connection to the follow-up module further streamlines the tracking of patients' treatment progress, responses, and changes in clinical or genomic profiles, supporting continuous care and improving long-term patient management.

The outcome of MTB discussions should be compiled into a standardized and structured report, summarizing key findings and providing an overall treatment recommendation that can support referent physicians for treatment orientation This format ensures that all essential information is clearly presented and can be easily integrated into the interoperable network for both research and clinical purposes. Additionally, a patient-friendly summary should be generated for use during patient consultations.

Finally, some of the conceptual recommendations are further elaborated in the MTB guideline published by WP8 (Diagnosis and treatment decision via MTB). Among these recommendations is the integration of specific functionalities into the MTB platform to meet the needs of virtual MTB sessions and accommodate various clinical disciplines.[39]

Results from the mapping exercise

The MTB module currently offers limited fully operational solutions, with some still in development. The most advanced solutions provide a clear overview of patient data to support MTB discussions. Some systems provide consistent access to past patient cases, but many still don't. Query features in the follow-up module aren't available yet, though some groups are starting to consider adding them.

Additionally, there appears to be confusion between the patient case report, which informs the MTB with relevant information from previous modules, and the MTB report, which documents the MTB recommendations and informs the patient's clinician. Although these reports could be combined, a specific section on the MTB recommendation and justification should be present.

Recommendations

- Develop the MTB module in close collaboration with MTB representatives to address specific needs such as clinical trials, internal MTB workflows, and the requirements for a structured MTB report format. The module is a central component of the EU-oncDST concept, designed to assist the MTB in making well-informed and thoroughly documented decisions on complex cancer cases. The partnership will ensure that the next-generation MTB module is tailored to the MTB's requirements and aligned with the operational level of the MTB, whether institutional, national, or European. Pallocca et al. (2024) reinforce our approach by emphasising the importance of tailored digital tools and standardized frameworks to align MTB operations across different operational levels.[40]

5. Interoperability module

Concept description

The EU-oncDST concept promotes interoperability by adhering to the FAIR principles, ensuring that critical information is findable, accessible, interoperable, and reusable.[41] This fosters enhanced collaboration among clinicians, researchers, and healthcare providers. Developing this module will contribute to the creation of a European learning cancer system, advancing knowledge about cancer and addressing the disease's complexity.

This module is designed to facilitate the exchange of de-identified, structured MTB reports, including case details, genomic profiles, treatment decisions, and potential clinical trial enrolments. It will enable the comparison of individual patient data with a comprehensive database of de-identified patient information, thereby facilitating MTB recommendations. Additionally, it will support tracking patient progress and treatment responses by bridging the EHR systems with a patient follow-up submodule. AI and machine learning technologies will enable seamless sharing and interpretation of these data among stakeholders. The module will include a query functionality, allowing the MTB to search for complementary information from previous cases and learn about treatment outcomes in similar cases through the MTB module.

The concept needs to be compatible with various healthcare systems, ensuring efficient sharing and utilization of patient data, treatment recommendations, and clinical insights. By promoting data sharing and standardization, the module enhances communication and decision-making, ultimately leading to improved patient outcomes.

Results from the mapping exercise

The infrastructure supporting interoperability as outlined in the EU-oncDST concept is currently limited although some solutions can connect with existing EHR or LIMS systems through Application Programme Interface. Additionally, some include multiple institutions within a large geographic area. Achieving full interoperability requires close collaboration among all stakeholders.

Recommendations

- Build on current initiatives that adress the challenge of promoting data harmonisation and interoperability. From cancer prevention to diagnosis to treatment, the European-wide Foundation to Accelerate Data-driven Cancer Research (EOSC4Cancer) initiative formulates standard operating procedures (SOPs) for several data types widely used in cancer research. This includes exposome, cancer registry, screening, clinical, genomic, radiology, and pathology data. These SOPs aim to provide more general considerations and guidelines to a broader community on how the interoperable platform should be implemented. This work highlights a real need for data standardisation.[42]

- The query functionality could be developed based on insights gained from the 1+M genome project on how to secure cross-border data access.[43]

- Consider converting data into the OMOP or FHIR common data models to enhance interoperability and support future federated learning initiatives.

- Cloud computing, AI, and machine learning will be essential for developing an EU-learning cancer system that integrates with the MTB module to assist clinicians in their decision-making. Investigating how digital twins can support this initiative will be crucial for the system's development. A digital twin is a virtual replica of a tangible entity or process, such as a patient, their anatomical structure, or a healthcare environment (e.g., hospital setting). These digital twins dynamically reflect various data sources, including electronic health records (EHR), -omics data, physical indicators, demographic information, and lifestyle factors. By continuously adapting to real data, digital twins can help predict future scenarios and provide valuable insights for MTBs, enhancing diagnostics, prognosis, and treatment recommendations. Additionally, this system will empower patients by giving them access to their digital twin data, including personalized health insights, treatment plans, and progress tracking, enabling them to take a more active role in managing their health and facilitate their engagement with healthcare providers.[44]

6. Additional aspects of EU-oncDST digital and data management

Concept description

As previously noted, the EU-oncDST concept should remain modular, allowing for customization to fit various clinical settings and workflows. This flexibility enables healthcare providers to tailor the tool to their specific needs, ensuring that only relevant functionalities and components are integrated. This approach enhances versatility and usability, facilitating smooth integration into existing clinical workflows. Additionally, the tool features an intuitive and user-friendly interface, which simplifies navigation and interaction for clinicians and users, ensuring an efficient and effective experience within the system.

The EU-oncDST concept is designed with modules that not only ensure continuous updates and maintenance of evolving knowledge and technologies but also align for data management by applying the FAIR principle, meaning that the data are Findable, Accessible, Interoperable, and

Reusable.[41] Regular updates are prioritized to integrate the latest scientific advancements, treatment options, and guidelines, thereby providing clinicians with the most current, evidence-based information is crucial.
In parallel, a strong emphasis should be placed on data privacy and security, implementing rigorous measures to safeguard patient information. These measures include compliance with relevant regulations and standards, encryption, secure transmission methods, and comprehensive data storage and access policies. By prioritizing data privacy and security, the tool procures confidence in users and patients, encouraging responsible handling and protection of their personal health information. Finally, some of these modules will follow under the new EU IVDR/MDR regulation and the AI Act. Therefore alignment following these regulations will be needed.

Results from the mapping exercise

All solutions place significant emphasis on data safeguarding, often incorporating GDPR and other certifications to ensure compliance with appropriate data management practices. Data storage frameworks vary across solutions, with some offering internal tool storage and others utilizing cloud-based servers. In most cases, a cloud-based server located within an EU member state is available to meet national and institutional requirements. Additionally, access to the tool can be managed with restrictions based on user groups. Finally, each solution has its protocol for user notifications and database updates that ranges from daily to every 3 months.

Recommendations

- Recognizing the FAIR principle as a fundamental foundation for achieving optimal data management.
- Some modules of the EU-oncDST concept, such as bioinformatics and clinical recommendations modules, will require certification and accreditation. EU initiatives are working to homogenise and simplify these processes, but it remains challenging to generalize recommendations for implementation, as this varies by facility and member state. A collaboration with the institution's DPO department is recommended to address the exact legal framework for data storage, retention, and disposal and ensure secure storage, regulatory compliance, and appropriate data disposal in alignment with the current EU regulations, including GDPR, IVDR, MDR, and the AI Act.. Some of these challenges will be covered in the Omics network of expertise included in the Joint Action of Network of Expertise which aims to implement a hub to support and guide legal questions.
- Establish a guideline for timely database updates to ensure oncDSTs provide clinicians with the most current and accurate information and avoid disparity between the solutions used.

4. Discussion

The main aim of this deliverable was to provide a comprehensive state-of-the-art of the current oncDST landscape and to define a concept of a European oncDST (Figure 8). Methods that were used are consultation meetings with CAN.HEAL partners, a survey on current practices in DST use and a

mapping exercise of currently available DSTs. With this process, valuable insights into the field, highlighting the latest innovations and their practical applications in clinical settings were provided as a list of strengths and areas of improvement (Figure 6) and some recommendations regarding each module (Figure 7).

4.1 Strengths and areas of improvement

Strengths:

- Several oncDSTs developed by the private sector or national & European initiatives, are already available.
- Bioinformatics modules with variant interpretation are well developed and are utilising various databases.
- The case reports produced by oncDSTs are considered vital support for MTB discussions. Recommendations made by the tool are always taken into account by the MTB.
- OncDST providers consider user and institutional requests and flexibility is integrated in the solutions e.g. integration of national guidelines or databases, support in connection with the EHR/LIM systems. This indicates the willingness to fulfil the user's needs, which is required for the effective implementation of oncDST.
- Optimal implementation of oncDSTs provides the opportunity for a learning cancer system to advance cancer diagnosis and treatment and improve patient outcomes.

Areas of improvement

- OncDSTs are still poorly implemented in the EU: The main barriers are manual, labour-intensive data entry, incomplete data integration, along with the cost and reliability of tools, and the lack of locally relevant output.
- Enhancing workflow with access to complete and comprehensive data: This includes automating data entry and integration, ensuring interoperability and connectivity, and providing flexibility for various healthcare environments and platforms to enhance usability and scalability. Furthermore, for complete and comprehensive data, all alterations should be considered in the data analysis including methylomic and transcriptomic data. Alternative testing options should be accessible, and datasets should encompass all communities, such as solid tumours, haematological conditions, and pediatric cases.
- To improve clinical implementation and minimize disparities in treatment recommendations, it is essential to establish standardized, harmonized processes for annotation, interpretation, and treatment-matching algorithms. Although AI and machine learning support clinical decision-making, variability in outputs from current oncDST solutions has led to inconsistent classifications. These findings emphasize the need for a consistent approach in annotation and interpretation, as inconsistency in Tier variant

classification remains significant. Such discrepancies arise not only from differences in software algorithms and evidence sources but also from subjective language in AMP/ASCO/CAP guidelines, which allows for interpretive variations that can impact patient outcomes. Aligning tiering criteria and harmonizing variant classification standards across platforms, along with establishing objective guidelines for assessing complex biomarkers, is essential for ensuring consistent results and equitable clinical decision-making.

- Improve support to MTB discussions and reporting to come to uniform, reliable and transparent recommendations: This requires multiple challenging actions:
    - a clear visualization of all data (also alternative testing results)
    - the development of an agnostic diagnostic approach and the inclusion of prognostic information in the clinical recommendation module
    - a multimodal approach by integrating AI and machine learning
    - the implementation of automated clinical trial matching systems
    - Include the national context in the oncDST outputs
    - the creation of structured MTB reports
- Ensure uniformity and reliability: This requires besides a common language and standardized data formats, also clear guidelines for software features, AI and manual curation processes, database maintenance and updates. Transparency is also crucial; users need straightforward access to original sources to enhance the reliability of the tools and empower and engage them effectively.
- Face complex regulatory challenges: Leveraging innovative frameworks like regulatory sandboxes could help ease GDPR, MRD/IVR and emerging AI law certification.
- oncDST implementation impact: The implementation of the EU-oncDST concept will require substantial new resources, including financial investments, infrastructure, and specialized personnel, such as an oncDST coordinator and consultation services for patients. Supporting this data-sharing initiative also demands significant resources for database maintenance, cybersecurity, quality control, scalability, and robust access control and data monitoring. However, it should also be considered that the implementation of oncDST can reduce costs by optimizing treatment and diagnostic testing and by optimizing workforce productivity.

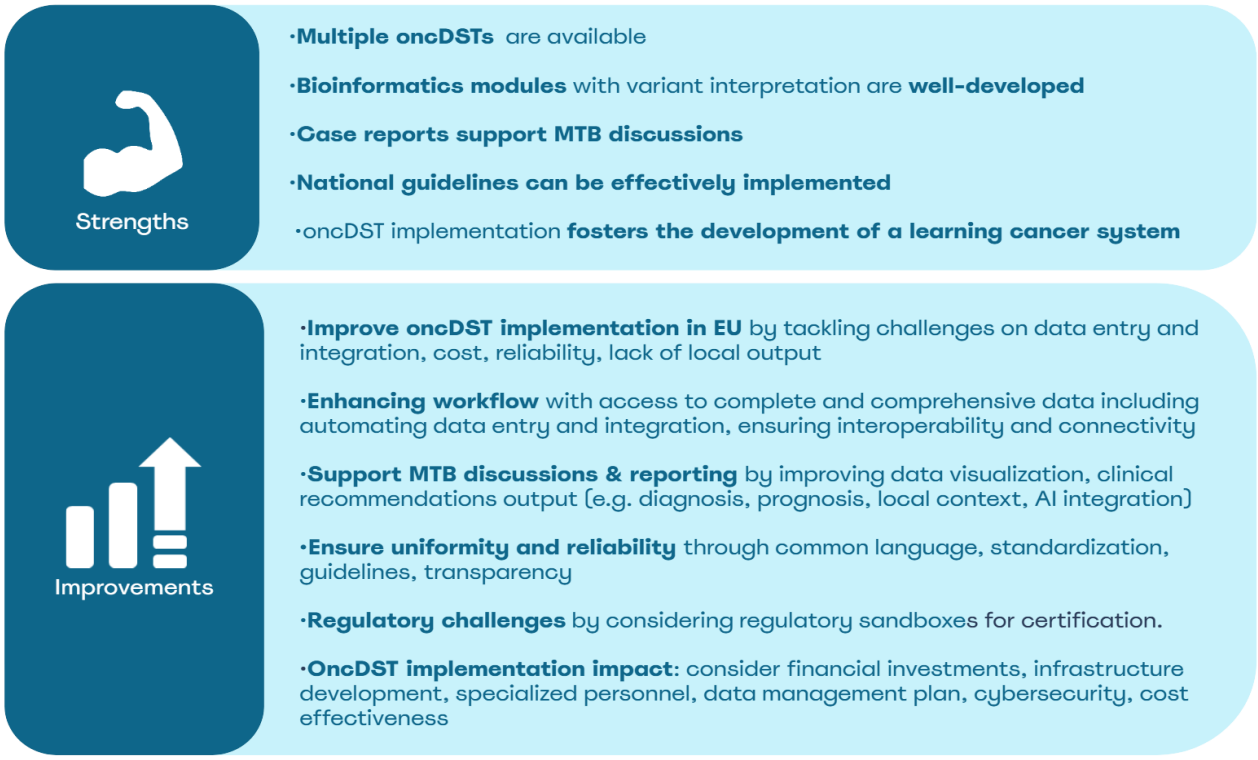

Figure 6 Strengths and areas of improvement

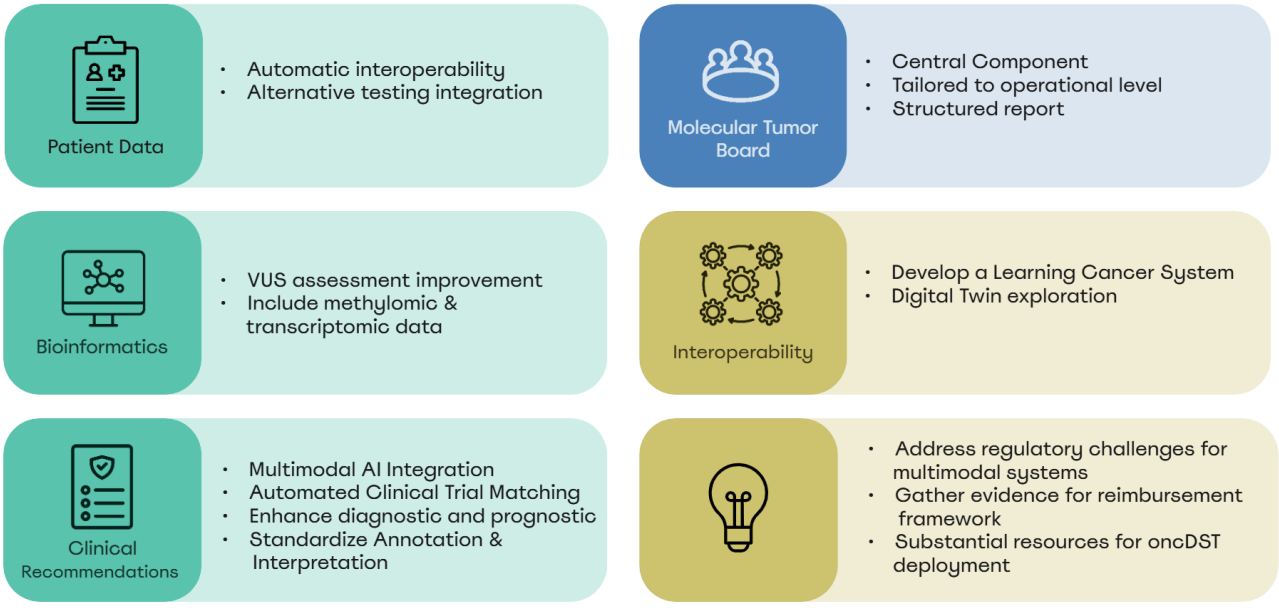

Figure 7 Recommendations per module

To effectively tackle the challenges in the oncDST field, interdisciplinary collaboration among clinicians, MTB members, data scientists, IT professionals, and the private sector is essential for the successful implementation of MTB platforms at various levels and for developing a learning cancer system. Centralizing patient information is crucial for ensuring accessibility and interoperability with electronic health records (EHRs), which supports informed treatment decisions. Deliverable 10.2 will explore capacity-building opportunities and outline recommended pathways for advancing the implementation of the EU-oncDST concept.

	Patient Data	Bioinformatics	Clinical Recommendations				Molecular Tumor Board Module	Interoperability
			Diagnosis & prognosis	Treatment	Clinical trials	Case Report		
Concept	• System compatibility • Key patient information • Clinical data integration • Automatic interoperability	• Variant annotation & classification • Prioritisation • Comprehensive variant analysis • Datbase reliance • Guidleines customability • Format versatility • Transparency • Learning cancer system intergration	• Alignment with Accurate Guidelines & Databases • Refinement of Diagnosis • Combined Recommendations • Transparency	• Drug repository integration • Personalized treatement recommendations • Flexibility & customisation • Transparency	• Patient -Specific clinical trials matching • Reliable and extensive trial database • Streamlined trial identification	• Case reports summarizing outcomes of Bioinformatics and Clinical recommendations including essential patient data information	• Centralized Key Data • Decision -support features • Learning cancer system intergration • Standardized report generation • Refer to MTB guidlines edited by the CanHeal consortium	• FAIR Principles • Learning Cancer System • Query Functionality • Patient Progress Tracking (follow-up submodule) • De-Identified Data Exchange
Mapping Results	• Manual data entry • Variable & customisable patient information • Variable clinical data integration • Limited interoperability	• Advanced module • Comprehensive variant analysis • Dependable database • Common guideline adherence • Flexible file format recognition • Source accessibility	• Support diagnosis suggestions & refinement • Limited agnostic approach • Option for unknown origin • No prognosis insight	• Acurate guidlines and curated databases • REgional cusomisability • Possible National Drug Regulations integration • Lack of treatment prioritization • treatement recommendation based on genmic data • Limited transparency	• Broad integration with Clinical.org • Advance filtering capabilitites • no automatic patient - specific clincila tiral matching • Preselected trial phase	• Pre-PDF Customizability • Lack of report Harmonization • MTB used	• Limited operational solutions • Facilitate MTB discussion • follow-up query not yet available • MTB reporting framework	• Limited Interoperability Infrastructure
Areas of Improvement	• Regulatory interoperability • Automatic interoperability • Data standardization • Report support • Alternative testing integration • Terminology alignment	• Expanded dabatase integration • VUS assessment improvement • Trust through transparency	• Develop Prognostic insight • Diagnostic interpretation enhancement • Increase flexible regulatory integration • Multimodal AI integration • Automated clinical trial matching				• Central Component • Collaborative development with MTB members • Support the development of the learning cancer system • Tailored to operational level • Support patient consultation	• Development of a learning cancer system • Digital twin exploration • Patient empowerment • Enhance query functionality • Building on data harmonisation initiatives • Callaboative development

Figure 8 Overall Mapping exercises

5. Conclusion

In conclusion, the integration of NGS into clinical practice signifies a transformative shift in patient care. This powerful technology offers unprecedented opportunities to personalize disease prevention, diagnosis, prognosis and therapy according to each patient's unique genetic makeup. However, while this technology holds immense promise, it also presents new challenges for healthcare providers.

The EU-oncDST concept addresses the evolving field of NGS data interpretation, actionable biomarker identification, and personalized treatment recommendations by harmonizing workflows and enhancing current systems. It supports the implementation of the Molecular Tumor Board (MTB) platform, facilitating data visualization, case overviews, and structured reporting. Additionally, the concept emphasizes the creation of a continuously learning cancer system built on data interoperability, as illustrated in Figure 9, aiming to advance cancer diagnosis and treatment while improving patient outcomes. However, challenges like AI implementation and interoperability must be overcome through collaboration to fully realize the potential of this innovative approach.

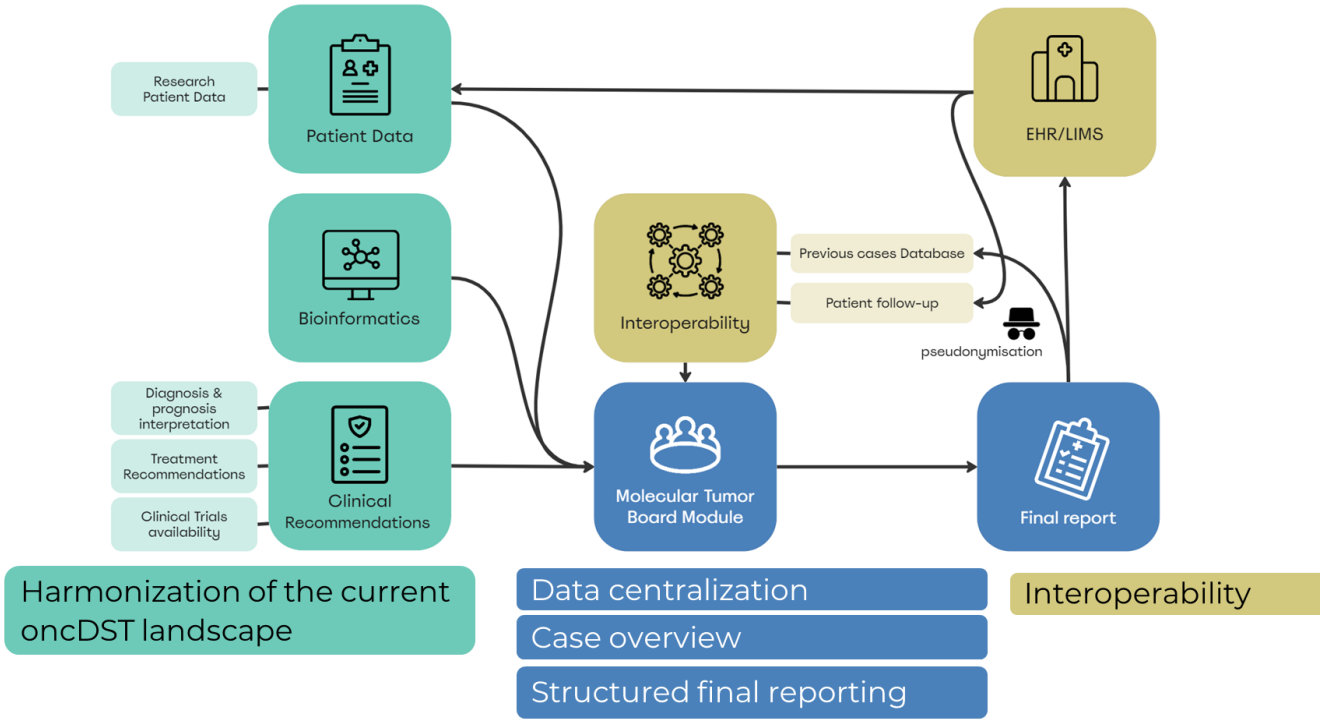

Figure 9 : EU-oncDST concept outcome

6. Bibliography

1. Edsjö, A. *et al.* Current and emerging sequencing-based tools for precision cancer medicine. *Mol. Aspects Med.* **96**, 101250 (2024).
2. Walsh, S. *et al.* Decision Support Systems in Oncology. *JCO Clin. Cancer Inform.* 1–9 (2019) doi:10.1200/CCI.18.00001.
3. Tamborero, D. *et al.* Support systems to guide clinical decision-making in precision oncology: The Cancer Core Europe Molecular Tumor Board Portal. *Nat. Med.* **26**, 992–994 (2020).
4. Nafees, A. *et al.* Evaluation of clinical decision support systems in oncology: An updated systematic review. *Crit. Rev. Oncol. Hematol.* **192**, 104143 (2023).
5. Hak, F., Guimarães, T. & Santos, M. Towards effective clinical decision support systems: A systematic review. *PLOS ONE* **17**, e0272846 (2022).
6. Sutton, R. T. *et al.* An overview of clinical decision support systems: benefits, risks, and strategies for success. *Npj Digit. Med.* **3**, 1–10 (2020).
7. Wright, A. & Sittig, D. F. A Four-Phase Model of the Evolution of Clinical Decision Support Architectures. *Int. J. Med. Inf.* **77**, 641–649 (2008).
8. Perakis, S. O. *et al.* Comparison of three commercial decision support platforms for matching of next-generation sequencing results with therapies in patients with cancer. *ESMO Open* **5**, e000872 (2020).
9. Khalife, R. *et al.* Comparing Classifications from Multiple Variant Annotation Software Solutions Using Real-World Next Generation Sequencing Data from Oncology Testing. *J. Mol. Pathol.* **5**, 81–95 (2024).
10. Sakai, K. *et al.* A comparative study of curated contents by knowledge-based curation system in cancer clinical sequencing. *Sci. Rep.* **9**, 11340 (2019).

11. BSMO. Precision intiative “Two ongoing comprehensive genomic profiling studies from BSMO: GeNeo and BALLETT”. *BSMO* https://www.bsmo.be/news/precision-intiative-two-ongoing-comprehensive-genomic-profiling-studies-from-bsmo-geneo-and-ballett/ (2021).
12. Tamborero, D. *et al.* Cancer Genome Interpreter annotates the biological and clinical relevance of tumor alterations. *Genome Med.* **10**, 25 (2018).
13. Metzger, P. *et al.* MIRACUM-Pipe: An Adaptable Pipeline for Next-Generation Sequencing Analysis, Reporting, and Visualization for Clinical Decision Making. *Cancers* **15**, 3456 (2023).
14. Unberath, P. *et al.* Searching of Clinical Trials Made Easier in cBioPortal Using Patients’ Genetic and Clinical Profiles. *Appl. Clin. Inform.* **13**, 363–369 (2022).
15. Reimer, N. *et al.* Challenges and Experiences Extending the cBioPortal for Cancer Genomics to a Molecular Tumor Board Platform. *Stud. Health Technol. Inform.* **287**, 139–143 (2021).
16. Ustjanzew, A. *et al.* cbpManager: a web application to streamline the integration of clinical and genomic data in cBioPortal to support the Molecular Tumor Board. *BMC Med. Inform. Decis. Mak.* **21**, 358 (2021).
17. Tamborero, D. *et al.* The Molecular Tumor Board Portal supports clinical decisions and automated reporting for precision oncology. *Nat. Cancer* **3**, 251–261 (2022).
18. Recommendation on a European Electronic Health Record exchange format.pdf.
19. Carver, T. *et al.* CanRisk Tool-A Web Interface for the Prediction of Breast and Ovarian Cancer Risk and the Likelihood of Carrying Genetic Pathogenic Variants. *Cancer Epidemiol. Biomark. Prev. Publ. Am. Assoc. Cancer Res. Cosponsored Am. Soc. Prev. Oncol.* **30**, 469–473 (2021).

20. Archer, S. *et al.* Evaluating clinician acceptability of the prototype CanRisk tool for predicting risk of breast and ovarian cancer: A multi-methods study. *PLOS ONE* **15**, e0229999 (2020).
21. Lee, A. *et al.* BOADICEA: a comprehensive breast cancer risk prediction model incorporating genetic and nongenetic risk factors. *Genet. Med.* **21**, 1708–1718 (2019).
22. Osterman et al. - 2020 - Improving Cancer Data Interoperability The Promis.pdf.
23. Riba, M. *et al.* The 1+Million Genomes Minimal Dataset for Cancer. *Nat. Genet.* **56**, 733–736 (2024).
24. Ahmadi, N., Peng, Y., Wolfien, M., Zoch, M. & Sedlmayr, M. OMOP CDM Can Facilitate Data-Driven Studies for Cancer Prediction: A Systematic Review. *Int. J. Mol. Sci.* **23**, 11834 (2022).
25. Guérin, J. *et al.* OSIRIS: A Minimum Data Set for Data Sharing and Interoperability in Oncology. *JCO Clin. Cancer Inform.* 256–265 (2021) doi:10.1200/CCI.20.00094.
26. Bodenreider, O. The Unified Medical Language System (UMLS): integrating biomedical terminology. *Nucleic Acids Res.* **32**, D267–D270 (2004).
27. Froyen, G. *et al.* Standardization of Somatic Variant Classifications in Solid and Haematological Tumours by a Two-Level Approach of Biological and Clinical Classes: An Initiative of the Belgian ComPerMed Expert Panel. *Cancers* **11**, 2030 (2019).
28. *Exigences Particulières Pour l'accréditation Des Laboratoires Médicaux Qui Réalisent Des Analyses de Tumeurs Hématologiques et Solides Selon La Méthode NGS (Next Generation Sequencing)*. https://www.compermed.be/cms/public/compermed/assets/pg40r9bbgmoswks4 (2023).
29. Welcome to ClinGen. https://clinicalgenome.org/.

30. ClinGen & ClinVar Partnership. https://www.clinicalgenome.org/about/clingen-clinvar-partnership/.
31. The Clinical Pharmacogenetics Implementation Consortium (CPIC®). https://cpicpgx.org/.
32. PharmGKB. https://www.pharmgkb.org/.
33. ClinGen, CPIC and PharmGKB Partnership. https://clinicalgenome.org/about/clingen-cpic-pharmgkb/.
34. Vibert, J. *et al.* Identification of Tissue of Origin and Guided Therapeutic Applications in Cancers of Unknown Primary Using Deep Learning and RNA Sequencing (TransCUPtomics). *J. Mol. Diagn. JMD* **23**, 1380–1392 (2021).
35. Jacquin, N. *et al.* Metastatic renal cell carcinoma with occult primary: a multicenter prospective cohort. *Npj Precis. Oncol.* **8**, 1–6 (2024).
36. Boehm, K. M., Khosravi, P., Vanguri, R., Gao, J. & Shah, S. P. Harnessing multimodal data integration to advance precision oncology. *Nat. Rev. Cancer* **22**, 114–126 (2022).
37. Klein, H. *et al.* MatchMiner: an open-source platform for cancer precision medicine. *Npj Precis. Oncol.* **6**, 1–9 (2022).
38. Nikolski, M. & Tamborero, D. D3.1 Molecular Tumour Board Portal Interoperability. (2024).
39. Ciliberto, G. *et al.* Can.Heal D8.3-Molecular Tumour Board Guidelines.pdf. (2024).
40. Pallocca, M. *et al.* Clinical bioinformatics desiderata for molecular tumor boards.
41. Pugliese, P., Knell, C. & Christoph, J. Exchange of Clinical and Omics Data According to FAIR Principles: A Review of Open Source Solutions. *Methods Inf. Med.* **59**, e13–e20 (2020).
42. Kabdullayeva, T., Navest, R., Aguilo, S., Starmans, M. & Royo, R. D2.1 - SOPs for minimal clinical, image and omics data exchange. (2024) doi:10.5281/ZENODO.10829318.

43. Spalding, D., Nyrönen, T. & Riski, R. Beyond 1 Million Genomes (B1MG) D4.3 Secure cross-border data access roadmap - 2v0. (2023).

44. Vallée, A. Digital twin for healthcare systems. *Front. Digit. Health* **5**, 1253050 (2023).

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Funded by the European Union. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or HaDEA. Neither the European Union nor the granting authority can be held responsible for them.

7. Annexes

7.1 Annex 1: State of the art document with emerging standards

One of the aims of the Can.Heal project is to map and define tools for clinical and genomic data integration and decision support for the Molecular Tumour Board and treatment decision. To achieve this goal a state of the art of available decision support tool (DST) is proposed and realised by WP10.

The key standard outlined below has been established based on discussions within the Can.Heal consortium, focusing on the development of the EU-OncoDST concept (a deliverable of WP10).

Through this assessment, WP10 aims to identify the strengths and existing gaps in the current DST landscape. The findings from this assessment will contribute to advancing the development of effective decision support tools for precision oncology and improve patient care.

For each criterion the definition of what is considered as an emerging standard (ES) by the Can.Heal consortium has been described in **Table 2-Table 6**. Then the canvas of the DST assessment is represented.

Table 2 : Patient data management emerging standards

Patient data management emerging standards	
1.	**Patient data: the tool should incorporate essential demographic information and have the possibility to interoperate with the electronic health records (EHRs), to include seamlessly patient data, clinical information, pathology reports, haematology reports, imaging results, nuclear medicine and treatment history, etc**
1.A	**The essential clinical and demographic information**
ES	The essential clinical and demographic information that should be included comprises the following: Gender, Age, Medical and treatment history, Cancer type, Staging (if applicable), Co-morbidities, Smoking status, and Others (precise which one).
1.B	**The capability to integrate test results, such as pathology or haematology information, with the corresponding imaging data.**
ES	Test results encompass a range of factors, including blood tests, tumour markers, prognostic indicators, bone marrow assessments, kidney and liver function tests, and biopsies. Additionally, they encompass outcomes from imaging studies such as CT or PET CT scans. Note that this list is not exhaustive.
1.C	**Possible interoperability with the EHR system.**
ES	The ideal system will offer access to and integrate relevant clinical data from the patient's EHR in the different DST modules. This interoperability suggests also data compatibility between the EHR system and DST tool and real-time up-to-date patient data. Ideally, this will operate automatically.

Table 3 Bioinformatic emerging standards

Bioinformatic emerging standards	
2.	**Variant Interpretation: The tool is expected to deliver variant interpretation following secondary bioinformatic analysis by annotating and classifying genomic and transcriptomic alterations that are relevant to treatment recommendations as well as prognosis and diagnosis. In addition, it should be able to identify and prioritize potentially significant variants including driver and germline mutations and actionable alterations**
2.A	**Accuracy, reliability and comprehensiveness of variant annotation and classification databases.**

ES	The tool should refer to databases that are accurate, reliable and comprehensive for the variant interpretation such as ClinVar, OncoKB, cBioPortal, COSMIC
2.B	**Capability to process diverse types of genomic alterations.**
ES	Able to analyse single-nucleotide variants (SNVs), insertions and deletions (indels), copy number variations (CNVs), gene fusions, and exon skipping events, as well as various biomarkers like microsatellite instability (MSI), tumour mutational burden (TMB), homologous recombination deficiency (HRD), mutation signatures, transcriptional signatures, and germline mutations.
2.C	**Can be used with sequencing results from any platform using formats compliant with international standards.**
ES	The tool should be able to connect with the primary bioinformatic analysis through different formats such as VCF, BAM, FASTQ, BED, GTF/GFF, MA, etc.
2.D	**The flexibility of the incorporation of internationally & nationally recognised guidelines, databases and resources for variant classification and interpretation.**
ES	The tool should provide customizable options for users to select which recognized guidelines they want to incorporate and allow the addition of specific resources for variant classification and interpretation (e.g., ComperMed). This flexibility enables users to modify the tool to their specific needs and preferences, ensuring that they can utilize the most relevant and up-to-date sources for accurate variant interpretation.
2.E	**Transparency and availability of supporting evidence for variant interpretations.**
ES	The tool should ensure transparency in the incorporation of guidelines, databases, and resources, providing clear indications of the sources used for variant classification and interpretation. This enables clinicians to easily access and verify the utilized sources, promote confidence in the tool's output and facilitate informed decision-making.

Table 4 Clinical recommendation emerging standards

Clinical recommendation emerging standards	
3.	**Diagnosis and prognosis interpretation: The tool should have the capability to analyze genomic data to provide accurate and reliable diagnosis and prognosis information linked with relevant classification and scoring systems.**
3.A	**Ability to suggest diagnosis and prognosis based on bioinformatic results.**
ES	The tool should possess the capability to offer suggestions for both diagnosis and prognosis based on genomics. This feature can assist clinicians and the Molecular Tumor Board (MTB) in making informed decisions regarding the patient's condition and potential treatment options.
3.B	**Transparency and availability of supporting evidence on the diagnosis and prognosis.**
ES	The tool should exhibit transparency and make available the supporting evidence for the diagnosis and prognosis suggestions it provides. This includes clear documentation of the sources and scientific basis behind the tool's recommendations, allowing clinicians and the Molecular Tumor Board (MTB) to assess the reliability and relevance of the information presented.
4.	**Treatment Recommendations/ Theranostics: the tool should be linked to a comprehensive and up-to-date drug-genomic interaction database, including information on drug targets, pharmacogenomics, identified variants, relevant biomarkers, and clinical evidence supporting specifically targeted therapy options. These recommendations should be connected to reputable relevant clinical guidelines and evidence-based recommendations in the decision-making process.**
4.A	**Alignment with established and accurate clinical guidelines and drug genomic interaction databases and evidence-based recommendations. (eg. NCCN, ESMO, OncoKB)**
ES	The tool should align with well-established and accurate clinical guidelines, drug-genomic interaction databases, and evidence-based recommendations, such as those from reputable organizations like the National Comprehensive Cancer Network (NCCN), the European Society for Medical Oncology (ESMO),

	and others. By adhering to these sources, the tool can ensure that its treatment recommendations are evidence-based and in line with best practices in oncology.
4.B	**Customizability to regional or institutional clinical guidelines**
ES	The tool should offer the flexibility to be customized according to regional or institutional clinical guidelines. This adaptability allows healthcare institutions or regions to tailor the decision support tool to their specific practices and protocols, ensuring that it aligns with their unique healthcare requirements and preferences.
4.C	**Transparency and availability of supporting treatment recommendations based on the available evidence.**
ES	The tool should demonstrate transparency and make treatment recommendations based on available evidence readily accessible. This includes providing clear explanations and justifications for the suggested treatments, along with references to the supporting evidence from clinical trials, research studies, and established guidelines. By doing so, the tool empowers clinicians and the Molecular Tumor Board (MTB) to make informed decisions about the most appropriate treatment options for each patient.
4.D	**Besides the level of evidence, the tool provides a suggestion for treatment prioritisation.**
ES	In addition to considering the level of evidence, the tool should take into account various factors such as tumour type and stage, genomic characteristics, treatment efficacy, toxicity, comorbidities, availability of clinical trials, previous treatment history, and prognostic factors. By evaluating these critical elements, the tool can provide preferred or recommended treatment choices, guiding clinicians and the Molecular Tumor Board (MTB) in selecting the most suitable and effective treatment options for each patient.
4.E	**Possibility to make recommendations combining clinical information (EHRs) and genomic data to generate personalized treatment.**
ES	The tool should have the capability to generate personalized treatment recommendations by integrating both clinical information from Electronic Health Records (EHRs) and genomic data. This integration can enable a comprehensive understanding of the patient's medical history, pathology reports, and treatment responses, along with their genomic profile, which includes relevant mutations, biomarkers, and molecular characteristics. To achieve this, the tool may use Artificial Intelligence (AI) and/or machine learning algorithms.
5.	**Clinical Trials availability: The tool should provide information about relevant clinical trials based on the patient's genomic profile, the patient's electronic health records (EHRs), imaging and pathology reports and the inclusion criteria. It should support the identification of ongoing trials and spot availability that match the patient's molecular characteristics or enable access to potentially novel therapies.**
5.A	**Access to a comprehensive database of relevant clinical trial accessibility.**
ES	The tool should provide access to a comprehensive database containing relevant clinical trials and their accessibility information. This database should include details about ongoing trials, eligibility criteria, trial locations, contact information for enrolment, and other pertinent data to facilitate informed decision-making and patient access to potentially beneficial clinical trials.
5.B	**Matching patient-specific cases to clinical trials.**
ES	The tool should have the capability to match patient-specific cases to relevant clinical trials. It should consider the patient's genomic profile, clinical information, and eligibility criteria for various trials. By doing so, the tool can efficiently identify and present the most suitable clinical trial option(s) for each patient.
5.C	**Highlight if the trial has some availability.**
ES	The tool should prominently indicate whether the clinical trials have available slots for enrolment. This feature will draw attention to trials that are actively accepting participants, helping clinicians and patients identify and consider viable options for participation

Table 5 Molecular tumour board tool standards

Molecular tumour board tool standards	
6.	**Molecular tumour board (MTB): *the tool should have a module that centralises key information and reports such as EHRs, molecular reports, imaging, and pathology reports to support the molecular tumour board in the treatment decision and patient management*.**
6.A	**Centralisation of key patient information (EHRs, clinical, diagnosis and prognosis interpretation genomic profile, treatment recommendation, clinical trial availability….)**
ES	The MTB module should centralize essential patient information, including clinical data, genomic profiles, treatment recommendations, and clinical trial availability. By consolidating this critical data in one centralized location, clinicians of the Molecular Tumor Board (MTB) can easily access and review all relevant information to make well-informed decisions regarding patient care and treatment options.
6.B	**Query functionality for previous cases (in-house analytics)**
ES	The tool should have a query functionality that allows users to access and analyze previous cases through in-house analytics. This feature enables clinicians and researchers to retrieve valuable insights from past patient data, compare treatment outcomes, and identify patterns or trends that can inform current decision-making processes.
6.C	**Connection for reviewing clinical guidelines and literature to motivate the decision.**
ES	The tool should provide transparency in accessing and reviewing clinical guidelines and relevant literature to support decision-making. This includes clear visibility of the sources used for treatment recommendations, along with links or references to established guidelines and reputable scientific publications. By offering easy access to this information, the tool empowers clinicians and the Molecular Tumor Board (MTB) to critically evaluate and validate the basis of the recommendations, ensuring they are well-informed and evidence-based
6.D	**The generation of a standardised/ structured report with a summary of the findings and overall recommendations.**
ES	The system shall support clinicians in generating a standardized and structured report that includes a summary of the findings and an overall treatment recommendation. This feature aids in creating a consistent and organized report, ensuring that all essential information is presented clearly and ready to share among healthcare providers.
6.E	**Availability of a follow-up module that interoperates with the EHRs module**
ES	The tool should include an integrated follow-up module that interoperates seamlessly with the Electronic Health Records (EHRs) module. This feature enables clinicians to easily track and manage patient progress, treatment responses, and any changes in the clinical or genomic profile over time. This will ensure continuous and up-to-date monitoring of the patient's journey, supporting ongoing care decisions and improving long-term patient management.

Table 6 Digital and interoperability standards

Digital and interoperability standards	
7.	**Interoperability: The tool should demonstrate interoperability capabilities for seamless data sharing among partners, facilitating the comparison of individual patient data with a large database of de-identified patient information**
7.A	**The interoperability system should allow sharing of the DST information and the structured MTB report with the key elements that describe the case and the aligned decision.**

ES	The interoperability system should enable the seamless sharing of DST information and the structured Molecular Tumor Board (MTB) report, which includes key elements describing the case and the aligned treatment decision. This feature ensures that relevant information is easily accessible and transferable between different healthcare systems, facilitating collaboration among clinicians, researchers, and healthcare providers. By promoting data sharing and standardization, the interoperability system enhances communication and decision-making, ultimately leading to improved patient outcomes.
7.B	**Ability and compatibility to exchange data with other healthcare systems or decision support tools.**
ES	The tool should possess the ability and compatibility to exchange data with other healthcare systems or decision support tools. This feature ensures seamless integration and interoperability between different systems, enabling the efficient sharing and utilization of patient data, treatment recommendations, and clinical insights
8.	**Digital: the tool should incorporate a system for continuous updates and maintenance of evolving knowledge and technologies. Additionally, the tool should prioritize data privacy and security to safeguard sensitive patient information**
8.A	**Regular updates to incorporate new scientific knowledge, treatment options, and guidelines.**
ES	The tool should undergo regular updates to incorporate the latest scientific knowledge, treatment options, and guidelines. By staying current with advancements in oncology, the tool can provide clinicians with the most up-to-date and evidence-based information, ensuring that treatment recommendations are based on the latest research and clinical insights.
8.B	**Ensure data privacy and security**
ES	The tool should prioritize data privacy and security, implementing robust measures to safeguard sensitive patient information. This includes compliance with relevant regulations and standards, the use of encryption and secure transmission methods, and the establishment of appropriate policies for data storage and access. By ensuring data privacy and security, the tool gives confidence in users and patients, encouraging the responsible handling and protection of their personal health information.
8.C	**Well-defined policies and practices for data storage, retention, and disposal.**
ES	The tool should have well-defined policies and practices for data storage, retention, and disposal. These policies ensure that patient data is stored securely, retained for an appropriate duration based on regulatory requirements, and properly disposed of when no longer needed. By adhering to these practices, the tool maintains data integrity, privacy, and compliance, promoting responsible data management and promoting trust among users and patients.
8.D	**The modularity of the decision support tool ensures that capabilities can be tailored to different clinical settings and workflows.**
ES	The modularity of the decision support tool allows for the customization of capabilities to suit various clinical settings and workflows. This feature enables healthcare providers to adapt the tool to their specific needs, integrating only the relevant functionalities and components necessary for their practice. By offering modularity, the tool enhances its versatility and usability, accommodating different healthcare environments and ensuring seamless integration into existing clinical workflows.
8.E	**Intuitive and user-friendly interface**

ES	The tool should feature an intuitive and user-friendly interface, making it easy for clinicians and users to navigate and interact with the system.

7.2 Annex 2: Mapping exercise: survey for oncDST developers

SURVEY MAPPING INTRODUCTION

Dear Participant,

We trust that this year has well started.

We would like to thank you once more for your support in the decision support tool (DST) mapping exercise for the Can.Heal project (https://canheal.eu/).

We are at the finalization stage of this exercise. To validate our observation and give you a final opportunity to comprehend the information you provided, we have compiled this survey. The statements in the survey are based on the EU-oncDST concept developed within the Can.Heal project. Please note that your answers will remain confidential and will be handled by the team with whom you had the interview.
These answers will be used solely to validate the observations made during the exercise.

Disclaimers :

The Can.Heal consortium, represented by experts from Sciensano, is presently involved in mapping analysis focused onthe utilization of Decision Support Tool (DST) solutions within the European Union. It's crucial to emphasize that neither Sciensano nor the CanHeal project advocates prefer any specific solution over others. Their role is to offer expert opinions derived from the assessment conducted, aiming to provide informed perspectives without endorsing the exclusive use of any particular solution or tool

The Can.Heal project is funded by the European Union. Views and opinions expressed are however those of the authorsonly and do not necessarily reflect those of the European Union or HaDEA. Neither the European Union nor the granting authority can be held responsible for them.

There are 46 questions in this survey.

GENERAL INFORMATION

IDENTIFICATION FORM & CONSENT *

Choose one of the following answers

Please choose **only one** of the following:

◯ Yes, I consent having my company or institution's name mentioned in publications related to the EU-oncDST.

◯ No, I do not wish for my company or institution's name to be mentioned in publications related to the EU-oncDST.

Please specify how you would like your company or institution to be referenced : *

Please write your answer here:

PARTICIPATION TO THIS SURVEY *

Choose one of the following answers

Please choose **only one** of the following:

◯ Yes, I am willing to assist in finalizing the mapping by completing the survey.

◯ No, I believe I have provided all necessary information and will not participate in the survey.

DISCLAIMER :

The personal data you provide will be processed by Sciensano (controller) (https://www.sciensano.be/en (https://www.sciensano.be/en)), based on the legal ground of informed consent, with the purpose of answering the deliverables of the Can.Heal project and related EU initiatives (e.g. The Networks of Expertise, the CCC networks, the JRC Knowledge Centre on Cancer, the ERN's, the EHDS, etc), and will be stored for 5 years.

You have the right to request Scienano to access, correct, delete and transfer (copy) your personal data, or limit its use. You also have the right to withdraw consent at any time (without affecting the lawfulness of processing before its withdrawal).
To exercise these rights, you can contact the Can.Heal study coordinator by email : CAN.HEAL@sciensano.be, or by phone : 0032 (0)2 642 51 11. Or you can contact the Data Protection Officer by email : dpo@sciensano.be, or by phone : 0032 (0)2 642 51 02. In addition, you have the right to lodge a complaint with a supervisory authority. In Belgium this is the Data Protection Authority (GBA, Drukpersstraat 35, 1000 Brussels or contact@apd-gba.be).

*Please choose **only one** of the following:

◯ I provide my informed consent for the processing of my personal data for the purpose of answering the deliverables of the Can.Heal project and related EU initiatives.

PATIENT DATA MODULE

How does your tool align with the following statements?

INCORPORATION OF PATIENT DATA

Please choose the appropriate response for each item:

	Totally	Partially	Not align
The tool allows the possibility of adding the essential clinical and demographic information on the patient, comprising at least, the following: Gender, Age, Medical and treatment history, Cancer type, Staging (if applicable), Comorbidities, and Smoking status. ***If others, please precise which one.***			

- "Totally" means that your tool aligns with the entire statement.
- "Partially" means that your tool aligns with certain criteria of the statement but not all.
- "Not align" means that your tool does not align with the statement.

Justify your answer

Please write your answer here:

INCORPORATION OF TEST RESULTS

Please choose the appropriate response for each item:

	Totally	Partially	Not align
The tool offers the possibility of adding test results such as imaging studies (CT or PET CT scans), blood tests, tumour markers, prognostic indicators, bone marrow assessments, kidney and liver function tests, and biopsies. Note that this list is not exhaustive. ***Please precise which test.***			

- "Totally" means that your tool aligns with the entire statement.
- "Partially" means that your tool aligns with certain criteria of the statement but not all.
- "Not align" means that your tool does not align with the statement.

Justify your answer

Please write your answer here:

BIOINFORMATICS MODULE

How does your tool align with the following statements?

VARIANT INTERPRETATION

Please choose the appropriate response for each item:

	Totally	Partially	Not align
The tool performs variant interpretation allowing annotation and classification of genomic and transcriptomic alterations that are relevant in cancer.			

- Totally" means that your tool aligns with the entire statement.
- "Partially" means that your tool aligns with certain criteria of the statement but not all.
- "Not align" means that your tool does not align with the statement.

Justify your answer

Please write your answer here:

QUERY FUNCTIONALITY FOR PREVIOUS CASES (IN-HOUSE ANALYTICS) *

Please choose the appropriate response for each item:

	Totally	Partially	Not align
The bioinformatics module has a in-house analytic functionality that allows users to access and analyse previous variant interpretations.			

- "Totally" means that your tool aligns with the entire statement.
- "Partially" means that your tool aligns with certain criteria of the statement but not all.
- "Not align" means that your tool does not align with the statement

Justify your answer

Please write your answer here:

TRANSPARENCY AND AVAILABILITY OF SUPPORTING EVIDENCE FOR VARIANT INTERPRETATION

Please choose the appropriate response for each item:

	Totally	Partially	Not align
The tool ensures transparency in the incorporation of guidelines, databases, and resources with clear indications of the sources used for variant classification and interpretation. ***Please, precise sources that can be consulted.***			

- "Totally" means that your tool aligns with the entire statement.
- "Partially" means that your tool aligns with certain criteria of the statement but not all.

- "Not align" means that your tool does not align with the statement.

Justify your answer
Please write your answer here:

CUSTOMIZABILITY IN VARIANTS INTERPRETATION *
Please choose the appropriate response for each item:

	Totally	Partially	Not align
The tool provides customisable options for users such as selecting which recognised guidelines they want to incorporate to allow the adjustment of variant classification and interpretation according to national or internal guidelines or the possibility to modify the variant classification. **These changes are tracked and can be collected on a user knowledge base.** ***Please, precise what your tool can provide.***			

- "Totally" means that your tool aligns with the entire statement.
- "Partially" means that your tool aligns with certain criteria of the statement but not all.
- "Not align" means that your tool does not align with the statement.

Justify your answer
Please write your answer here:

CLINICAL RECOMMENDATION MODULE

How does your tool align with the following statements?

DIAGNOSIS INTERPRETATION
Please choose the appropriate response for each item:

	Totally	Partially	Not align
The tool provides clear and transparent diagnostic recommendations based on genomic data in line with existing scoring classification systems.			

- Totally" means that your tool aligns with the entire statement.
- "Partially" means that your tool aligns with certain criteria of the statement but not all.

- "Not align" means that your tool does not align with the statement.

Justify your answer
Please write your answer here:

TREATMENT RECOMMENDATIONS
Please choose the appropriate response for each item:

	Totally	Partially	Not align
The tool is linked to a comprehensive and up-to-date drug-genomic interaction database, including information on drug targets and clinical evidence, supporting specifically targeted therapy options.			

- Totally" means that your tool aligns with the entire statement.
- "Partially" means that your tool aligns with certain criteria of the statement but not all.
- "Not align" means that your tool does not align with the statement.

Justify your answer
Please write your answer here:

TRANSPARENCY AND AVAILABILTY OF SUPPORTING EVIDENCE FOR CLINICAL RECOMMENDATION
Please choose the appropriate response for each item:

	Totally	Partially	Not align
The treatment recommendations are done transparently connected to reputable relevant clinical guidelines and evidence-based recommendations in the decision-making process. This includes providing readily clear explanations and justifications for the suggested recommendations, along with references to the supporting evidence from clinical trials, research studies, and established guidelines. ***Please, precise type of evidence provided.***			

- Totally" means that your tool aligns with the entire statement.
- "Partially" means that your tool aligns with certain criteria of the statement but not all.
- "Not align" means that your tool does not align with the statement.

Justify your answer

Please write your answer here:

CLINICAL TRIAL RECOMMENDATIONS

Please choose the appropriate response for each item:

	Totally	Partially	Not align
The tool provides access to a comprehensive database containing recruiting clinical trials and accessibility information. This database includes detailed eligibility criteria, trial locations, and other pertinent data to facilitate informed decision-making and patient access to potentially beneficial clinical trials.			

- Totally" means that your tool aligns with the entire statement.
- "Partially" means that your tool aligns with certain criteria of the statement but not all.
- "Not align" means that your tool does not align with the statement.

Justify your answer

Please write your answer here:

CUSTOMIZABILITY OF CLINICAL RECOMMENDATIONS *

Please choose the appropriate response for each item:

	Totally	Partially	Not align
The tool offers the flexibility to be customized according to regional or institutional clinical guidelines.			

- Totally" means that your tool aligns with the entire statement.
- "Partially" means that your tool aligns with certain criteria of the statement but not all.
- "Not align" means that your tool does not align with the statement.

Justify your answer

Please write your answer here:

REPORT

Please choose the appropriate response for each item:

	Totally	Partially	Not align
The tool provides a standardised, structured and editable report with a summary of the findings and overall recommendations from the bioinformatic analysis.			

- Totally" means that your tool aligns with the entire statement.
- "Partially" means that your tool aligns with certain criteria of the statement but not all.
- "Not align" means that your tool does not align with the statement.

Justify your answer

Please write your answer here:

MOLECULAR TUMOR BOARD (MTB) MODULE

How does your tool align with the following statements?

PLATFORM

Please choose the appropriate response for each item:

	Totally	Partially	Not align
The tool has an MTB platform that centralizes and allows visualization of essential patient information and test results, including clinical data, genomic profiles, treatment recommendations, and clinical trial availability			

- Totally" means that your tool aligns with the entire statement.
- "Partially" means that your tool aligns with certain criteria of the statement but not all.
- "Not align" means that your tool does not align with the statement.

Justify your answer

Please write your answer here:

QUERY FUNCTIONALITY FOR PREVIOUS CASES (IN-HOUSE ANALYTICS)

Please choose the appropriate response for each item:

	Totally	Partially	Not align
The MTB platform has a query functionality that allows users to access and analyze previous cases through in-house analytics to support current decision-making.			

- Totally" means that your tool aligns with the entire statement.
- "Partially" means that your tool aligns with certain criteria of the statement but not all.
- "Not align" means that your tool does not align with the statement.

Justify your answer

Please write your answer here:

MTB REPORT

Please choose the appropriate response for each item:

	Totally	Partially	Not align
The tool integrates the MTB recommendation into a standardized and structured report with a concise summary of the findings and an overall treatment recommendation.			

- Totally" means that your tool aligns with the entire statement.
- "Partially" means that your tool aligns with certain criteria of the statement but not all.
- "Not align" means that your tool does not align with the statement.

Justify your answer

Please write your answer here:

INTEROPERABILITY MODULE

How does your tool align with the following statements?

INTEROPERABILITY WITH PARTNERS

Please choose the appropriate response for each item:

	Totally	Partially	Not align
The tool demonstrates interoperability capabilities for seamless data sharing among partners, facilitating the comparison of individual patient data with a large database of de-identified patient information.			

- Totally" means that your tool aligns with the entire statement.
- "Partially" means that your tool aligns with certain criteria of the statement but not all.
- "Not align" means that your tool does not align with the statement.

Justify your answer

Please write your answer here:

INTEROPERABILITY WITH ELECTRONIC HEALTH RECORD (EHR)

Please choose the appropriate response for each item:

	Totally	Partially	Not align
The tool integrates relevant patient data from the EHR system into different modules. Moreover, the tool facilitates bidirectional exchange between different healthcare systems facilitating collaboration. ***Please, precise if the tool is bidirectional or the specific direction.***			

- Totally" means that your tool aligns with the entire statement.
- "Partially" means that your tool aligns with certain criteria of the statement but not all.
- "Not align" means that your tool does not align with the statement.

Justify your answer

Please write your answer here:

DATA MANAGEMENT

How does your tool align with the following statements?

PRIVACY AND SECURITY

Please choose the appropriate response for each item

	Totally	Partially	Not align
The tool prioritizes data privacy and security, implementing robust measures to safeguard sensitive patient information. This includes compliance with relevant regulations and standards, the use of encryption and secure transmission methods, and the establishment of appropriate policies for data storage and access. ***Please, precise where the data are stored.***			

- Totally" means that your tool aligns with the entire statement.
- "Partially" means that your tool aligns with certain criteria of the statement but not all.
- "Not align" means that your tool does not align with the statement.

Justify your answer

Please write your answer here:

UPDATES

Please choose the appropriate response for each item:

	Totally	Partially	Not align
The tool undergoes regular updates to incorporate the latest scientific knowledge, treatment options, and guidelines. The updates are notified to the user. ***Please precise how often.***			

- Totally" means that your tool aligns with the entire statement.
- "Partially" means that your tool aligns with certain criteria of the statement but not all.
- "Not align" means that your tool does not align with the statement.

Justify your answer

Please write your answer here:

ADDITIONAL COMMENT

Feel free to add comments to complement the survey answers :

Please write your answer here:

Thank you very much for your involvement.

7.3 Annex 3: Survey report on the DST section

In the frame of this survey, we defined oncology DST as "computer systems designed to support healthcare providers facing a complex decision about individual patients at the point in time that these decisions are made." Therefore, the survey focuses on tools that translate NGS and relevant clinical data from individual patients to support the MTB in making decisions for the management and treatment of individual patients.

Results

Among the 119 participants, 75 reached the DST section. Only 15% (11) indicated that they are using a DST, while 71% (53) use a hospital tool such electronic health record (EHR) or electronic case report form (eCRF), and finally, 15% (11) have no solution yet in place to support MTB discussion (Table 7)

Table 7 : Type of tool that supports MTB discussions

MTB discussion supported by tool	Participants
DST	11
Hospital tools (e.g. EHR, eCRF)	53
None of them	11

From this point, our analysis will focus on the 11 responses which use an oncDST in supporting MTB discussions.

Among these 11 participants, most of them are clinicians, molecular biologists involved in diagnostics and specialist in laboratory medicine (Table 8).

Table 8 Role of the DST responders

Role of the DST responders	Number
Clinician	4
Molecular biologist involved in diagnostics	2
Specialist in Laboratory Medicine	2
Chief Medical Officer	1
Scientific Director and Coordinator of the local MTB	1
Bioinformatician involved in molecular diagnostics	1

As illustrated in Figure 10, various types of tools or combinations of them are implemented within institutions using DST. These include commercial tools, academic/publicly available tools and custom-designed/local-use tools. We decided to examine the practices involving single or combined tools for our analysis. In our opinion, this approach accurately reflects current practices and highlights some challenges and gaps surrounding the use of DSTs. We can notice that when tools are combined they always involve commercial solutions with either academic/publicly available or custom-design solutions.

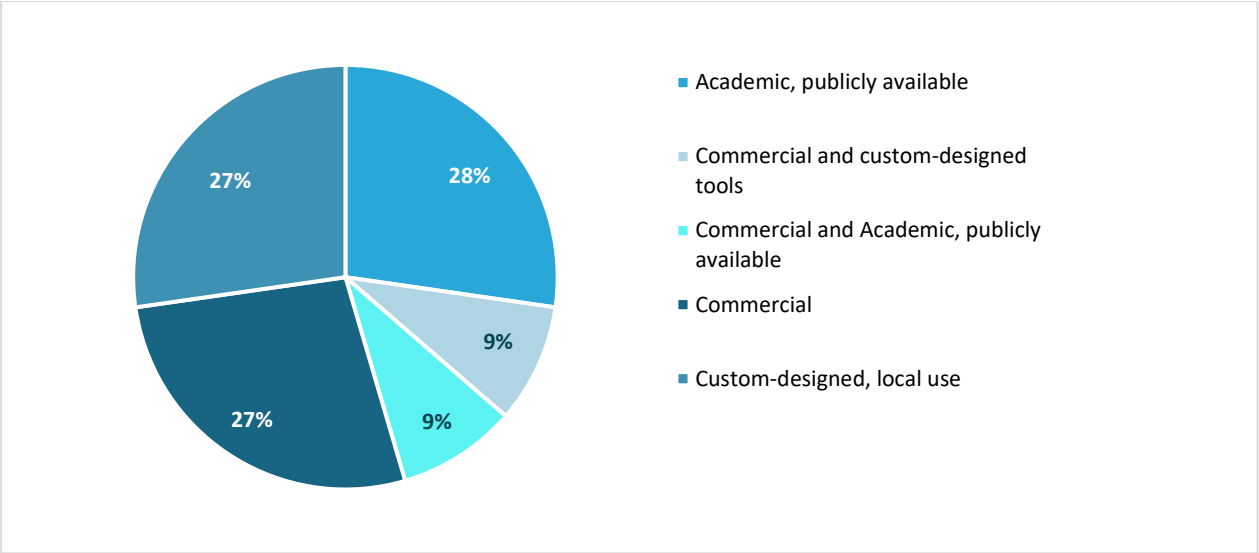


Figure 10: Type of DST used

Table 9 provides an overview of the types of DST implemented in various institutions more specifically in the EU countries Belgium, Italy, Germany and France. The two participants from Germany are from the same institution. After contacting them, it was agreed to combine their entries regarding tool characteristics. In Belgium, several institutions have been using the same combination of tools due to their participation in the BALLETT clinical trial, a PRECISION initiative with comprehensive genomic profiling. After consulting with the Principal Investigator (PI) of the trial, answers of institutions involved in the trial were merged. To simplify the reading, the last column of the table summarizes which institutions were pooled and provides a short common DST name.

It was specifically asked to precise which type of alterations and NGS biomarkers can be analysed by the DST (Table 10). Almost all of the tools can handle single nucleotide variants and small indels, copy number variations, fusions, splice variants, tumour mutational burden (TMB), microsatellite instability (MSI) and homologous recombination deficiency (HRD). However, none of the tools can consider methylomis or transcriptomics alterations.
Furthermore, participants were asked to indicate the features of the used DST (Table 11). The list of proposed features were
i) Data analysis and interpretation such as :

- Variant clinical classification
- NGS data analysis (eg. variant annotation and biological classification)
- Integrated reference to expert treatment guidelines (eg. NCCN, ESMO, …)
- Clinical interpretation and treatment recommendation for genome-wide biomarkers (TMB, MSI)

ii) Data visualization and management such as

- Specific format for visualisation of patient data during the MTB

- Integrated data repository of historical cases and querying for similar cases (eg. based on mutation profile, cancer type…)
- Clinical follow-up module

iii) Diagnostic and prognostic support such as:

- Support for determining the diagnosis
- Support for determining the prognosis
- Support for determining the need for additional testing/examinations

iv) Automated treatment recommendations and prioritization such as :

- Automated treatment recommendation(s)
- Automated treatment prioritization in cases of more than one treatment option
- Artificial Intelligence for multimodal searching of databases and automated treatment recommendation

According to the participants' answers, we noticed that most DST provide support for data analysis and interpretation by referring to expert databases and guidelines. The support for diagnosis and prognosis varies between the different solutions or a combination of them. Data visualization and management also show variability among the different options. Finally, the automation of treatment recommendations and prioritization is almost non-existent in the various options described in this report.

Table 9 : DST and Tool users

	COUNTRY	INSTITUTE CODE	INSTITUTE NAME	TYPE OF DST	DST NAME provided by the user	INSTITUTE POOLING+ SHORT DST NAME
1	BELGIUM	BE09	Jessa hospital	Custom-designed, local use	BALLETT-app (+ OncoKDM, OncoDNA, CGW, Velsera)	BALLETT
2		BE09	Jessa hospital	Custom-designed, local use	BALLETT-app (+ OncoKDM, OncoDNA, CGW, Velsera)	
3		BE07	IPG	Custom-designed, local use	BALLETT-app (+ OncoKDM, OncoDNA, CGW, Velsera)	
4		BE10	UZLeuven	Commercial and custom-designed	Roche Navify MTB module + BALLETT-app (+ OncoKDM, OncoDNA, CGW, Velsera)	NAVIFY MTB + BALLETT
5		BE05	GHDC	Commercial	OncoKDM (OncoDNA) + CGW (PierianDX)	OncoKDM + CGW
6		BE08	Institut Jules Bordet	Commercial	Roche Navify MTB module + BALLETT-app MTB module	NAVIFY MTB + BALLETT MTB
7	ITALY	IT10	Oncologia IRCCS	Commercial	Roche Navify	NAVIFY
8		IT08	IRCCS Regina Elena Istituto Europeo di	Commercial and Academic, publicly available	OKR (Oncomine Knowledgebase Reporter Thermofisher), OncoKB, CIVIC, cBioportal	OKR
9	GERMANY	DE04	UKSH	Academic, publicly available	MIRACUM- (Cbioportal, Cosmic, OnkoKB, VEP)	cBioPortal adapted
10		DE04	UKSH	Academic, publicly available	MIRACUM- Cbioportal, Cosmic, OnkoKB, VEP)	
11	FRANCE	FR06	CHU Limoges	Academic, publicly available	CHU Limoges	CHU Limoges

Table 10 genetic alterations and NGS biomarkers that are introduced in the DST. According to the users, V indicates that the alteration is treated and X indicates that the alteration is not treated by the tool.

Institute code	DST name	SNV and small INDELS	CNV	Fusions	Splice variants	TMB	MSI	HRD
BE05	OncoKDM + CGW	V	V	V	V	V	X	V
BE08	NAVIFY MTB + BALLETT MTB	V	V	V	V	V	V	V
BE09, BE07, BE09	BALLETT	V	V	V	V	V	V	V
BE10	NAVIFY MTB + BALLETT	V	V	V	V	V	V	V
DE04, DE04	cBioPortal adapted	V	V	V	X	V	V	V
FR06	CHU Limoges	V	V	V	V	V	V	V
IT08	OKR	V	V	V	X	V	V	X
IT10	NAVIFY	V	V	V	V	V	V	V

Table 11 Features included in the DST: According to the users, V indicates that the feature is included and X indicates that the feature is not included

		Data Analysis and Interpretation				Data Visualization and Management			Diagnostic and Prognostic Support			Automated Treatment Recommendations and Prioritization		
Institute code	DST name	Variant clinical classification	NGS data analysis	Integrated reference treatment guidelines	Clinical interpretation & treatment recomm.	MTB Visualization Format	Integrated data repository of historical cases and querying	Clinical follow-up module	Diagnosis Support	Prognosis Support	Support for determining need for additional testing	Automated treatment recomm.	Automated Treatment Prioritization	AI Multimodal Search
BE05	OncoKDM + CGW	V	X	X	X	X	X	X	X	X	X	V	X	X
BE08	NAVIFY MTB + BALLETT MTB	V	V	X	X	X	X	X	X	X	X	X	X	X
BE09, BE07, BE09	BALLETT	X	X	V	X	V	V	X	X	X	X	X	X	X
BE10	NAVIFY MTB + BALLETT	V	V	V	V	V	V	V	V	V	V	X	X	X
DE04, DE04	cBioPortal adapted	V	V	V	V	V	X	X	X	X	X	X	X	X
FR06	CHU Limoges	V	V	V	V	X	X	V	V	V	V	V	V	X
IT08	OKR	V	V	V	X	V	X	V	X	X	X	X	X	X
IT10	NAVIFY	X	X	V	X	V	V	V	X	X	X	V	X	V

The Can.Heal consortium identified elements essential for the effectiveness of DSTs such as

i) clinical and demographic data,
ii) pathology information,
iii) digital pathology images,
iv) NGS variants,
v) other NGS biomarkers,
vi) MTB recommendations, and
vii) patient outcome follow-ups.

We inquired how this information is integrated into the used DSTs, specifically whether it is implemented manually, automatically, or not at all to evaluate the labour intensity of incorporating this information. According to Figure 3, DST users primarily input information manually. However, it is interesting to note that NGS variants are automatically introduced in half of the cases. Additionally, pathology digital images are not included in half of the tools.

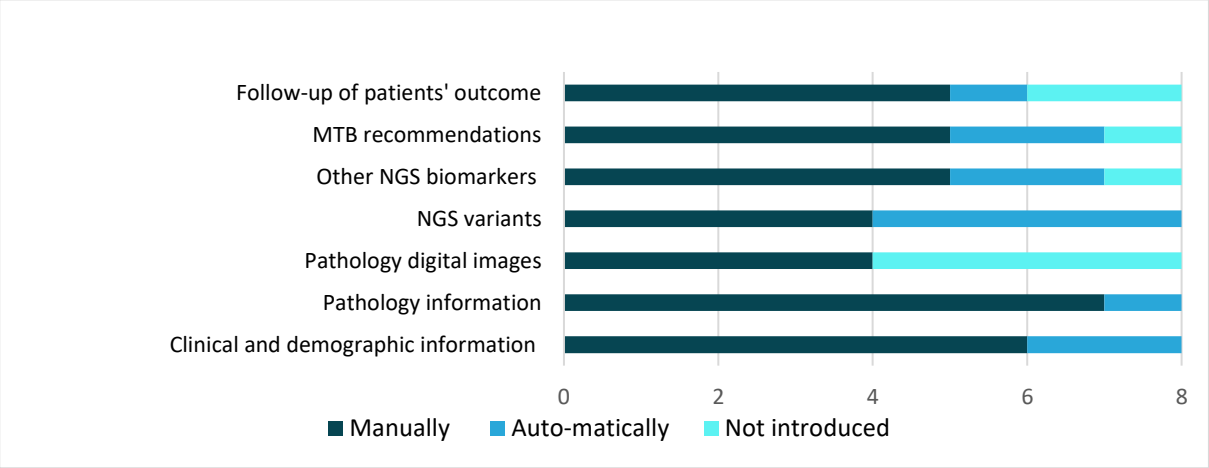


Figure 11: Information introduction in DST

We also inquired about the sources from which data is automatically transferred within the institution, considering that while the tool may support automatic transfers, this functionality might not have been implemented at the institutional level. Table 12 shows that the main source was the NGS report. In addition, some institutions use also automatic transfer from EHR/LIMS or VCF files.

Table 12: Type of source from where the data are automatically transferred

	EHR	LIS	eCRF	VCF-files	NGS report	No automatic transfer
BE05	X	X	X	V	X	X
BE08	X	X	X	X	X	V
BE09, BE07, BE09	X	X	X	X	X	V
BE10	X	X	V	X	X	X
DE04, DE04	V	X	X	V	V	X
FR06	X	V	X	X	V	X
IT08	X	X	V	X	V	X
IT10	V	V	V	X	V	X

According to Figure 12 and participant answers, DSTs refer mainly to publicly available academic resources as integrated databases of matched drugs and also to FDA/EMA databases. Participants selected 'Other' when they were uncertain about which database was integrated or when a commercially curated database was available through the solution they used. Regarding the integration of a clinical trial application, ClinicaTrials.gov is mainly integrated. Similarly, participants selected 'Other' when they were uncertain about which database was integrated or when a commercially curated database was available through the solution they used (Figure 13). Finally, for both the matched drug and clinical trial databases, there is no integration of local or national databases.

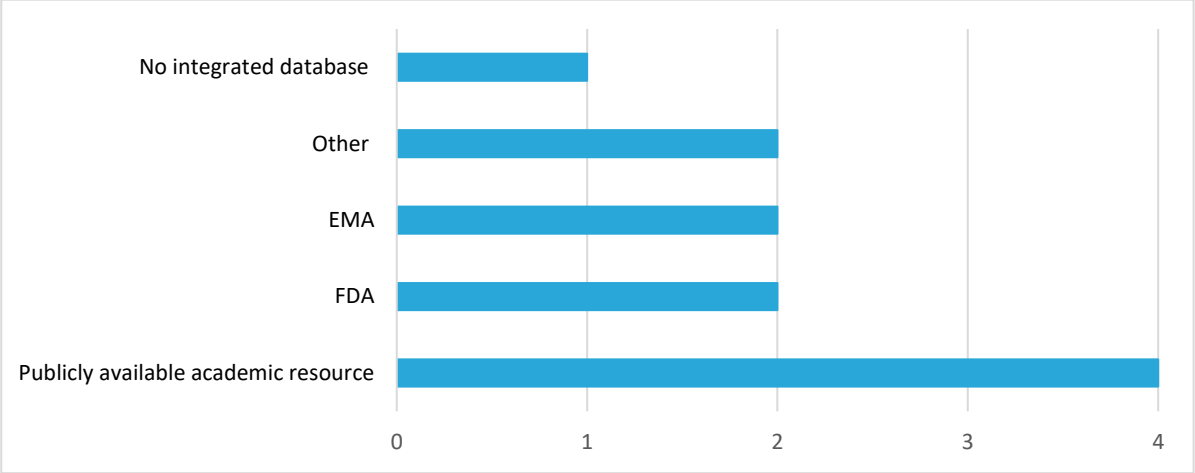


Figure 12: Integrated database of matched drugs in DST

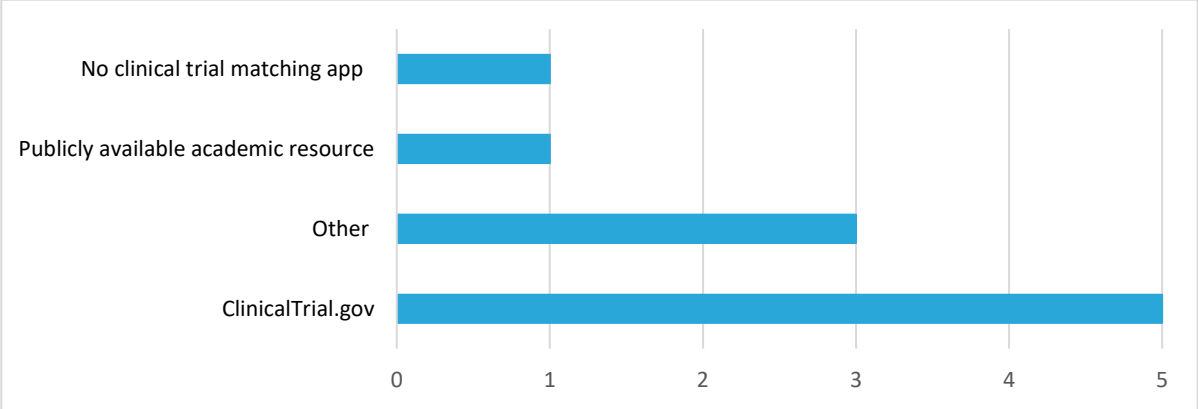


Figure 13: Integrated Clinical Trial Application in DST

All of the participants agree unanimously that the suggestion made by the DST is taken into account for patient management but it is the MTB that makes the final recommendation. Case reports are created mostly as PDF or Word (63%) or through an interactive digital report accessible via the dedicated MTB platform (37%) (Table 13).

As indicated in Figure 14, access to the DST is in most cases given to the MTB coordinator or all MTB members. Some institutions also give access to physicians submitting a case. No participants indicated that external parties have access to the institute's DST

Table 13 Report format

PDF or Word for Download		Interactive Digital Report	
BE05	OncoKDM + CGW	DE04, DE04	MIRACUM
BE08	NAVIFY MTB + BALLETT MTB	FR06	CHU Limoges
BE09, BE07, BE09	BALLETT	IT08	OKR
BE10	NAVIFY MTB + BALLETT		
IT10	NAVIFY		

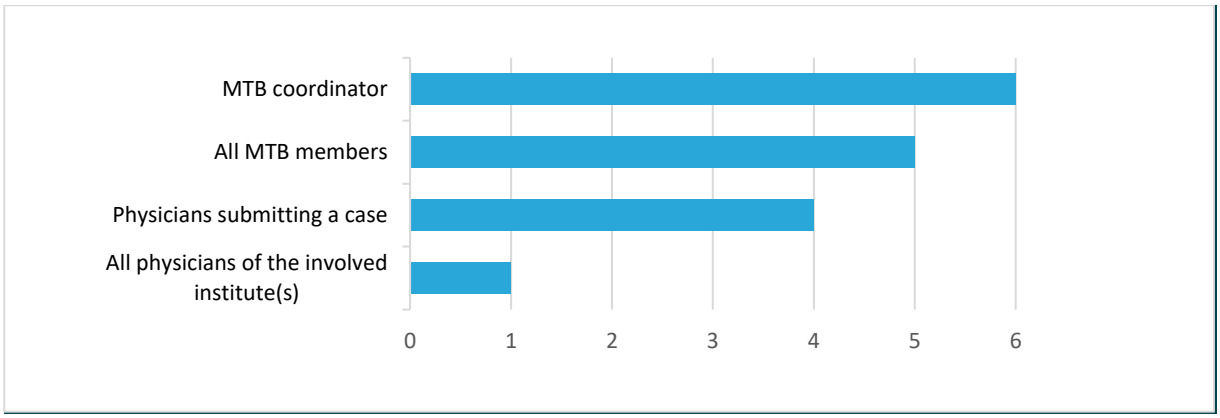
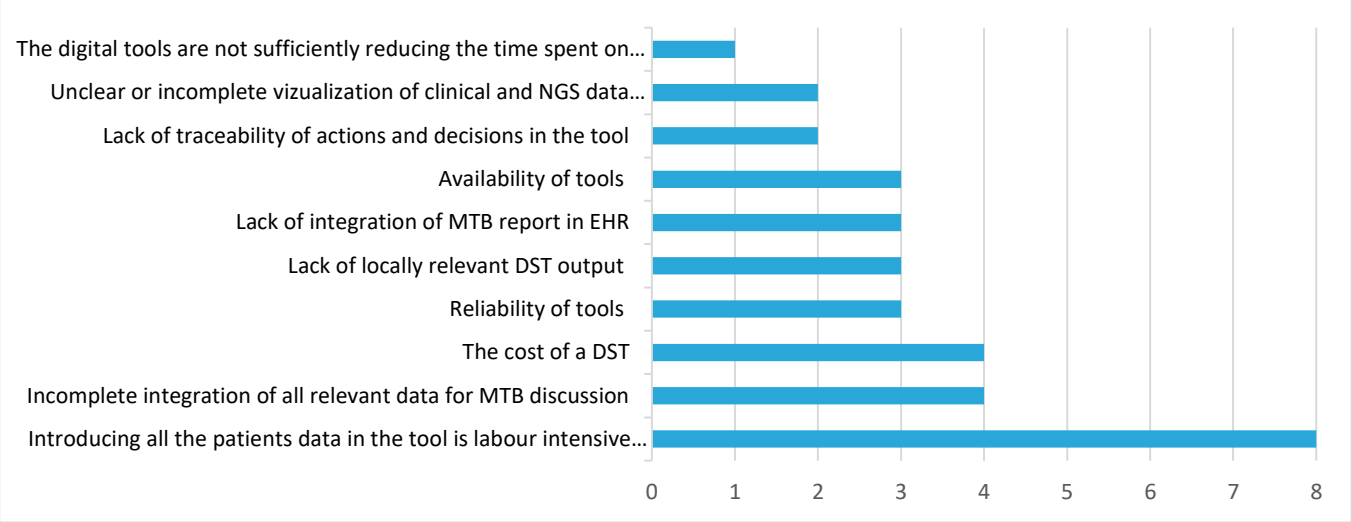


Figure 14: DST access

Participants were asked about the reimbursement of DST use and also their opinion on a given list of possible key barriers that could hamper access to and optimal use of DSTs. In none of the participating countries, the use of DST is reimbursed by the healthcare system. As indicated in Table 10, the most significant barrier indicated is the labour-intensive and error-prone process of introducing all patient data into the tool. The cost of DSTs and incomplete integration of relevant data for MTB discussions are also major concerns. Additionally, the reliability of tools, lack of locally relevant output (such as nearby clinical trials), lack of integration of MTB reports with EHR, and limited availability of tools are significant barriers. Some potential barriers do not seem to significantly affect the use of DSTs: lack of regulation for DSTs, restrictions on manual editing of final reports by MTB experts, lack of treatment prioritization in cases of multiple actionable findings, infrequent updates of integrated knowledgebases, and ethical considerations and privacy issues (e.g., GDPR).

Table 14: Barriers hampering the access and optimal use of DST



Discussion & conclusion

The survey on oncologic DSTs reveals a significant gap in their adoption across Europe. Among the 119 participants, 75 (63%) of them reach the DST section and only 15% of these participants actively use a DST while most (n= 64;71%) rely on hospital tools like EHRs or eCRFs to support MTB discussions. This low adoption rate could be correlated to several aspects that participants highlighted. First, due to the lack of reimbursement for DSTs, none of the participating countries supported the use. However, participants unanimously indicated that the DST suggestions are beneficial in MTB discussions to make a final recommendation. Secondly, the most significant barriers to optimal DST use include the labour-intensive process of data entry, incomplete integration of relevant data, and concerns about tool reliability and local relevance.

Addressing these issues will require a multifaceted approach by advocating for policy changes to include DST reimbursement in healthcare systems and support their integration into routine clinical practice. Also, enhancing integration capabilities, by improving automated integration processes interoperating with ERH, LIS or eCRF will decrease the time dedicated to data integration and by extension reduce the possibility of mistakes. Additionally, allowing a wider range of information introduced in a DST such as pathology digital images could be beneficial to support a better overview of the case and the integration of this type of information in clinical recommendations could be easier.

While DSTs often rely on public academic resources and regulatory databases (such as FDA, EMA, and clinicalTrials.gov), they commonly lack integration with local and national databases, which limits their relevance to specific patient populations or local clinical practices. To allay concerns about the tool's reliability, it is essential to demonstrate regular updates and incorporate local clinical trials and databases, as these are crucial for enhancing the functionality of DSTs. Incorporating these local resources could improve the accuracy and applicability of DST recommendations. Custom-designed tools can help address this issue by tailoring solutions to specific institutional needs, though they may require significant resources to develop and maintain. Academic tools tend to be more affordable but may lack certain functionalities. Therefore, it is common to use a combination of DSTs, including commercial solutions that offer strong support at

a higher cost, alongside either academic/publicly available tools or custom-designed options, underscoring the fact that no single tool can meet all the needs of MTBs.

To increase trust in the use of these devices the transparency of which database and how they are potentially curated should be well disseminated to the user. Some of the participants were not aware of what datasets were integrated. Ensuring transparency of the information's origin can enhance trust in the tool, empower community knowledge, and prevent associations with a black-box system.

According to the participant's answer, DSTs primarily handle key genetic alterations such as single nucleotide variants, fusion or small indels but they fall short in methylomics or transcriptomics data interpretation. This limitation can impact the comprehensiveness of patient assessments and treatment recommendations. In addition, DSTs do not support automated treatment recommendations and prioritization in cases of more than one available treatment option or suggest additional testing. Support for either diagnosis or prognosis decisions is limited. All of these features request artificial intelligence, highlighting the fact that collecting data will be necessary to develop them. Therefore, an emphasis should be put on interoperability through, for instance, an integrated data repository of historical cases with query and a patient clinical follow-up module. Both seem essential to improve DSTs' suggestions to the MTB.

An important objective of a DST is to provide a case overview by generating a report to be discussed by the MTB. Case reports generated are primarily in PDF or Word formats, with some institutions using interactive digital reports. Each format has its advantages, interactive reports could be more dynamic for the MTB discussion, while PDF and Word formats could be easily added to the patient's EHR hospital folder and even sent to his general practitioner. Although the final report should be accessible to most of the case contributors, it seems that an MTB interface summarising the case for discussion could offer more dynamics and ease the creation of interoperability modules. Currently, access to DSTs is typically restricted to MTB coordinators and MTB members with some exceptions for clinicians that follow the case. The survey reveals that DST users encompass a range of professionals including clinicians, molecular biologists, and specialists in laboratory medicine. This diversity reflects the multidisciplinary nature of cancer care but also presents challenges in terms of training and utilization. Different roles require specific functionalities from DSTs, and varying levels of expertise mean that user interfaces and training programs must be tailored accordingly.

The future of DSTs lies in their ability to adapt to the needs of diverse healthcare settings and to provide comprehensive, accurate, and actionable insights. However, a harmonisation and clear frame around DST is still needed. The Can.Heal consortium has actively contributed to this issue by elaborating on the EU oncDST concept. This concept is envisioned as a comprehensive system composed of multiple modules, each serving distinct yet interconnected purposes to support decision-making within MTBs. These modules are designed to

i) centralise both historical and current patient medical data,
ii) select actionable molecular alteration of interest,
iii) provide personalized treatment recommendations tailored to individual patient cases,

iv) streamline patient enrolment in clinical trials,

v) centralise patient and genomic data and clinical evidence to support decision-making within MTBs, iv) allow continuous patient follow-up, and

vi) promote interoperability among diverse national and international medical centres.

(See “Deliverable D10.1 – D30 – EU-oncDST-v4” released in November 2024).

Finally, the responses to the survey are based on the current usage and knowledge of the participants. Consequently, some discrepancies may arise regarding the full capabilities of the tool, as participants may not be aware of all its features or may not utilize them to their fullest extent. This gap in understanding can lead to varied perceptions of the tool's effectiveness and potential.

In conclusion, the survey gives an overview of the use of DST across Europe and its challenges to support MTBs in oncologic care. DSTs could offer significant advantages in data analysis and decision-making, but currently their implementation is limited and hampered by a lack of clear standardized frameworks, reimbursement support, interoperability, and automation. By addressing these issues and focusing on their implementation in clinical settings, MTBs could potentially leverage their recommendation through the use of DSTs to improve patient outcomes and streamline clinical workflow in oncology.

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