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For Precision Oncology, the Molecular Tumor Board Portal Facilitates Clinical Choices and Automated Reporting

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Commentary

Systems that efficiently support the work of medical teams at the precision-oncology point of care are in high demand. The Molecular Tumor Board Portal (MTBP), an academic clinical decision support system established under the aegis of Cancer Core Europe that establishes a uniform legal, scientific, and technological platform for sharing and using next-generation sequencing data, is presented here [1]. The requirement for time-consuming and error-prone manual operations is reduced by automating the interpretation and reporting of sequencing findings. The use of a process agreed upon by experts to systematically link tumour molecular profiles to clinical interventions enhances uniform decision-making and structured data collection across the connected sites [2]. During virtual molecular tumour board meetings, the inclusion of information-rich patient reports with interactive content improves collaborative discussion of complex cases. Overall, streamlined digital systems such as the MTBP are critical for better addressing precision oncology's problems and accelerating the application of developing biomarkers.

Assays for Next-generation Sequencing (NGS) are an important part of the current oncology process. Tumor sequencing findings can drive clinical trial enrolment and reveal exploratory treatment options in particular patients, in addition to on-label medicinal prescriptions [3]. Other clinically relevant events revealed by NGS data include germline pathogenic mutations, pharmacogenomics results, and clonal hematopoiesis drivers, all of which should be recognised and addressed. Clinical interpretation of NGS results, on the other hand, frequently relies on manual processes, posing significant obstacles to medical teams tasked with this task. For starters, variant annotation makes use of a variety of resources provided by the medical, biological, and bioinformatics sectors that are difficult to combine. Second, consistent clinical decision-making requires agreement on annotation criteria and guidelines to prioritise actionable discoveries. Third, in the absence of off-label choices, patients must be matched with the unique portfolio of experimental medicines and clinical trials accessible in each institution (or hospital network), which is always changing. Individual patient outcomes and precision cancer treatment projects can be harmed if these concerns are not addressed, or if they are not addressed in a clinically appropriate time frame.

By establishing effective data analysis and reporting processes, Clinical Decision Support Systems (CDSS) can address these issues. Although there is commercial CDSS software available, in-house solutions are frequently employed to better meet the unique demands of each centre [4]. Indeed, we believe that academic institutions' ability to design custom CDSS accelerates the application of developing biomarkers and encourages healthcare practitioners to practise precision medicine. As a result, we created the MTBP, a CDSS that unifies the interpretation of sequencing results among the seven comprehensive cancer centres that currently make up Cancer Core Europe (CCE). Importantly, the portal is fully linked with the CCE clinical procedures, providing a single platform for disseminating data and facilitating large-scale discussions. In this era of quickly evolving precision-oncology landscape, seamless communication across clinical investigators is critical for leveraging the community's combined expertise. To our knowledge, this is the first time in Europe that a standardised infrastructure has been used to co-develop novel anticancer medicines and biomarkers.

The results of using the MTBP in a consecutive cohort of 500 advanced solid tumours evaluated from January 2019 to January 2021 in the Basket of Baskets (NCT03767075) study, an ongoing CCE multibasket phase 2 clinical trial matching molecular biomarkers with immunotherapies and targeted drugs, are presented here. Because not all of the variants seen in the tumour have the same biological consequences, interpreting NGS data requires first determining whether the specific variants observed in the tumour modify the wild-type function of cancer genes. This approach allows patients to be matched to biomarkers specified by functional criteria, such as 'activating' mutations in a particular oncogene or 'loss-of-function' abnormalities in a specific tumour suppressor, in addition to identifying the individual tumour genetic drivers. It's worth noting that about a third of the cancer biomarkers currently in use are based on evaluating the functional effect of medication target variations. The MTBP uses an allele-centric approach to determine the functional significance of cancer mutations. In other words, regardless of tumor-context considerations like the germline versus somatic origin of the variant, the status of the second allele, and/or the cancer type in which it is observed, a given BRCA1 mutation known to disrupt the activity of the wild-type allele will always be declared as functionally relevant [5] .

For a more extensive variant functional annotation, many genetic information resources can be combined, although there are currently no well-established recommendations on how to do so. As a result, we agreed on criteria that we regarded to give strong or very strong supporting evidence (>90 percent and >99 percent of certainty, respectively) based on earlier work and three different sources of information. First, the MTBP checks to see if the gene variations found in the patient's tumour have been previously shown to have an effect. Second, if no variant effect is provided, or if the information is equivocal and/or backed by weaker evidence, the gateway assesses if legitimate biological assumptions (such as whether a certain premature termination codon is likely to induce nonsense-mediated decay) can be applied. These assumptions are based on well-established criteria for detecting loss-of-function variations in Mendelian disease genes. The MTBP refines the application of some of these criteria by combining the material of the aforementioned knowledge bases, which can help to identify protein areas that are crucial for a tumour suppressor's function, for example. This demonstrates the utility of the MTBP in incorporating community information and generating ensemble bioinformatics models.

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