Support systems to guide clinical decision-making in precision oncology: The Cancer Core Europe Molecular Tumor Board Portal

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To the editor: the optimal management of cancer patients is increasingly dependent on individualized treatments guided by tumor sequencing data. As comprehensive genomic tests become routine in many disease settings and academic centers promote *omics*-guided clinical trial recruitment, accurate and scalable data interpretation represents a major challenge. The meticulous task of matching tumor alterations with approved or experimental therapies relies heavily on the expertise of each center. Unsurprisingly, we see similar sequencing results leading to different clinical recommendations[1]. While the number of drug biomarkers with target specificities is constantly growing, these disparities are likely to escalate, which may ultimately impair patients' outcomes and research progress. Access to commercial test results does not simplify decision-making, as they often deliver generic reports that lack the

necessary information to prioritize emerging therapies. In addition, data interpretation must also contend with incidental germline findings, which further complicates the process. Medical teams face the extra burden of manually searching for the latest scientific evidence associated with detected gene alterations, which is a complex, time consuming and error-prone task. Here we argue for the need to streamline expert-driven genomic data interpretation and reporting workflows and employ user-friendly decision support tools that foster interactive treatment planning.

In response, we have developed the Molecular Tumor Board Portal (MTBP), a clinical decision support system that unifies the analysis of sequencing results across seven European comprehensive cancer centers under the umbrella of the Cancer Core Europe (CCE) network[2]. The portal is used to select candidates for the Basket of Baskets trial (NCT03767075), a modular multi-arm study for genomically-defined populations, as well as other clinical studies with active recruitment across CCE sites. Following a process agreed among CCE experts, the system automates *omics* data capture, interpretation and reporting, and creates a framework to share and harness results (Figure). MTBP reports are discussed during weekly virtual meetings where multidisciplinary representatives from each CCE center decide on clinical interventions. These reports are patient-centric web-based documents with the annotations supporting a given variant classification and the complete provenance of all assertions readily accessible through interactive elements. This approach, as opposed to “black box” static documents, empowers intuitive decision-making and case discussion, which may require an in-depth revision of the available information. Variants of clinical interest, such as those qualifying for genetic counseling referral or clinical trial allocation, appear automatically flagged according to CCE predefined criteria. Oncologists acknowledge the advantages of reports with modern user interface design, systematically structured and tailored to the needs of ongoing clinical initiatives, in a system that enables sharing the responsibility of treatment allocation with experts in a truly collaborative manner. Of note, we observed a learning curve to use the portal lasting for approximately 25 reviewed patients. After that, the amount of time devoted to discussing each patient’s case (more than 500 at the moment of writing this manuscript) rarely exceeds four minutes, which is key to scale the process.

A precision oncology decision support tool must give access to the latest clinical actionability evidence and computational analytical tools. Data interpretation can benefit from a variety of publicly available genomics resources, but as variant information exchange standards have not yet been adopted by the community[3], the MTBP implements an extensive data format harmonization to ensure their accurate aggregation. We interpret the patient’s germline and tumor variants in terms of both functional and predictive relevance, two distinct and complementary analyses required for the full range of decision-making of a molecular tumor board. First, the variants’ functionality informs the need for genetic counselling referral when deleterious (pathogenic) germline events in actionable disease-causing genes are detected[4–6]. Importantly, this analysis also provides the necessary information for patient matching to clinical trials with “categorical” inclusion criteria – those that rely on estimating the functional effect of

variants observed in drug targets, such as “activating” mutations in a given oncogene or “loss-of-function” alterations of a tumor suppressor. The MTBP classifies a variant as functionally relevant by integrating up-to-date evidence from multiple expert-curated knowledgebases, *bona fide* biological assumptions and bioinformatics predictions. Second, the predictive interpretation matches functionally relevant variants to biomarkers of disease diagnosis, prognosis and drug response reported at present[7–9]. In addition to on-label prescribing, this informs off-label and experimental drug opportunities to be considered according to current knowledge. Decision support tools are especially useful for target-drug prioritization in complex molecular scenarios, such as tumors with co-occurring alterations known to interact and modify the efficacy of a given drug. The portal ranks the variants’ predictive relevance according to the ESMO’s Clinical Actionability of Molecular Targets scale[10], which factors in the scientific evidence supporting the biomarker effect and gene-drug-disease interactions. As a resource to investigators outside of our network, we recently launched an open access version of the MTBP genomics interpretation pipeline (https://mtbp.org), which provides a general framework to classify the functional and predictive relevance of a given list of variants.

We believe that adoption of cancer type-focused treatment guidelines or access to medical records equipped with clinical pathways are insufficient to meet the full potential of *omics*-guided precision oncology. Instead, the use of stand-alone health technology tools that can provide patient-centered predictive analyses moving beyond generic rules-based criteria will be increasingly important. We advocate that decision support systems driven by academic networks such as the MTBP facilitate the cross-institutional development of clinical trials and real-world data repositories, and accelerate the translation of biomarker discoveries to the clinics. In this regard, we are currently working to incorporate data from emerging biomarkers such as proteomics and digital pathology in our portal. In the near future, these systems will become learning platforms where novel data-to-decision models can be properly assessed and improved. For this to happen, healthcare stakeholders must collaborate to create seamlessly integrated “precision oncology information technologies” and invest in the assets necessary to maintain them.

Competing interests:

David Tamborero reports consultant/advisory fees from Roche. Rodrigo Dienstmann reports receiving honoraria for speaker activities from Roche, Ipsen, Amgen, Sanofi, Servier Laboratories, Merck Sharp & Dohme; advisory role from Roche and Boehringer Ingelheim; and research grants from Merck and Pierre Fabre. Richard Baird reports consultant or advisory roles (with funding to institution) for AstraZeneca, Daiichi-Sankyo, Lilly, Molecular Partners, Novartis, Roche, Shionogi; principal/sub-Investigator of clinical trials for Astex, AstraZeneca, Boehringer-Ingelheim, Boston Therapeutics, Genentech/Roche, Johnson&Johnson, Lilly, Molecular Partners, PharmaMar, Roche, Sanofi-Aventis, Shionogi and Taiho; and research grants from AstraZeneca, Boehringer-Ingelheim and Genentech. Irene Braña reports consultant or advisory role for Orion Pharma; speaker activities for BMS; travel grants from AstraZeneca and Merck Serono; principal investigator of clinical trials for AstraZeneca, BMS, Celgene, Gliknik, GSK, Janssen, KURA, MSD, Novartis, Orion Pharma, Pfizer, Shattuck, Northern Biologics, Rakutan Aspirian and Nanobiotics. Christophe Massard reports consultant/advisory fees from Amgen, Astellas, Astra Zeneca, Bayer, BeiGene, BMS, Celgene, Debiopharm, Genentech, Ipsen, Janssen, Lilly, MedImmune,

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Figure Legend

The Molecular Tumor Board Portal automates a common NGS data capture, interpretation and reporting process across Cancer Core Europe centers, currently formed by the Cancer Research UK Cambridge Centre (Cambridge), German Cancer Research Center & National Center for Tumor Diseases

(Heidelberg), Institut Gustave Roussy (Paris), Karolinska Institutet (Stockholm), National Cancer Institute (Milan), Netherlands Cancer Institute (Amsterdam) and Vall d'Hebron Institute of Oncology (Barcelona).

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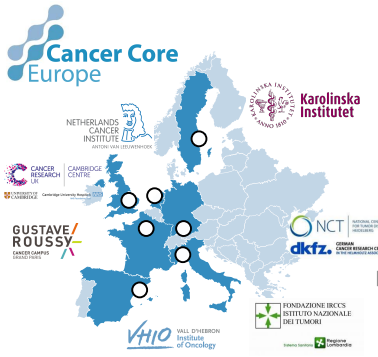

Molecular Tumor Board Portal

Patient data (screening & follow-up)

clinical, pathological and *omics* profiling

Automated data analysis

- data integrity
- data harmonization
- variant annotation
- variant classification
- report generation

In-house and public resources

- knowledgebases
- bioinformatic tools
- expert consensus criteria
- ongoing clinical trials databases

Data repository

Virtual molecular tumor board

- on-label prescription
- clinical trials allocation
- investigational drug opportunities
- genetic counselling referral

novel biomarkers, drug efficacy endpoints and predictive models

Data science