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# Advancing molecular tumour boards: highly needed to maximise the impact of precision medicine

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Nine per cent of patients with metastatic cancer harbour genomic alterations that are recognised as biomarkers for optimal treatment selection in current standard of care. An additional 27% carries genomic aberrations for which compelling clinical evidence exists supporting the use of these alterations as predictive biomarkers for drug response outside the registered indication.[1] As novel molecular and genomic treatment indications are explored in rapid pace, the generation and correct interpretation of molecular tumour profiles are quickly becoming a necessity for offering optimal cancer treatment.

The complexity and vast amounts of data generated through molecular profiling techniques, like next-generation sequencing, make expert review an absolute requirement in order to translate molecular profiles into clinical benefit for our patients. Leading cancer care providers are currently trying to address this by developing the so called 'molecular tumour boards' (MTBs), which comprise experts of various disciplines who help clinicians to interpret the molecular profiles of their patients. This is a challenging task and many uncertainties about the optimal implementation of these boards remain. Among different institutions, implementations can differ on various grounds: technically (eg, the used sequencing techniques, bioinformatics pipelines), composition wise (eg, which types of specialists are involved) or organisationally (eg, centralised vs localised). Recently, Moore and colleagues share how they implemented an MTB in the UK: the Sarah Cannon Research Institute (SRCI) UK/UCL Genomics Review Board (GRB).

The paper describes the molecular profiling results, given recommendations and clinical trial enrolment of 895 patients reviewed by the GRB. In addition to these prospective data, the authors share the challenges encountered during the establishment of the GRB.

A multidisciplinary team comprising physicians, a molecular oncologist, clinical geneticist and molecular pathologist evaluated each individual GRB submission, taking clinical history of the patient and (technical) details of the tumour specimen into account. The latter included examination of the tumour fraction and variant allele frequency, which could help in identifying germline variants that may be clinically relevant. In 117 cases (13.1%), this led to referral to a clinical geneticist for genetic counselling, which, importantly, would in some cases seriously affect patients' lives or that of their relatives.

For all patients discussed in the GRB, an individual report was generated in seven to eight working days that summarised all actionable genomic aberrations and matched treatment and/or clinical trial recommendations. A comprehensive, but easy to read patient report can assist healthcare providers in understanding molecular profiles of patients and may increase awareness of the availability of potentially effective genomics-guided therapies (either off-label or in context of a clinical trial). As pointed out by the authors, 22% of the physicians in a tertiary cancer centre reported on the lack of confidence in their genomic knowledge.[2] This clearly stresses the need for education of oncologists in interpreting genomics data. Such improvement in molecular knowledge can only be achieved if all hospitals providing oncological care have access to MTBs that interpret sequencing data.

Van der Velden *et al*[3] showed results of a survey among hospitals in the Netherlands pointing out that less than 50% of hospitals and only 5% of non-academic hospitals had access to an MTB. Multiple hospitals indicated that they would like to participate in an MTB, but that logistical barriers hampered them from doing so. Facilitating entry to

MTBs for all hospitals will be challenging, but is essential to create equality in precision oncology care and should therefore be highly prioritised during implementation of MTBs in a country or region.

During the first 45 active months of the GRB, 180 patients (20%) of the 895 reviewed cases were provided with a genomics-based therapeutic advice that led to referral for off-label drug use or clinical trial screening. In the end, only 62 (7%) received trial therapy. However, this also included patients that received trial treatment based on clinical characteristics. In total, about 5% was treated on a molecular basis. The actual number of patients benefitting from the MTB review process is therefore rather low compared with what is reported in literature. Basse *et al* published in European Society for Medical Oncology Open in 2018 about their experience with an MTB at the Institute Curie.[4] The authors showed that 17% (74 out of 442 patients) of the initial study population with available molecular analyses were enrolled in a clinical trial with matched targeted agents. In yet another study, conducted at the Johns Hopkins Hospital, 15% (24 out of 155) of the patients received off-label treatment or were enrolled in clinical trial based on their molecular profile.[5] This exposes that, apart from expert interpretation of molecular profiles, interesting additional challenges remain in order to exploit the full potential of precision oncology.

First, approved drugs are often inaccessible to biomarker-positive patients due to the absence of reimbursement for drugs beyond their labelled indication. This requires that these patients are treated within clinical trials or via compassionate access programmes. However, clinical trials only cover a minority of potential genomic treatment indications and often have strict inclusion criteria. An improved infrastructure to increase patient access to drugs matched to their genomic profile is highly needed. In addition, regulators and health insurances need to redefine how they operate in a world of precision medicine in which they cannot depend on guidelines because every patient is unique. Prospective multi-drug and pan-cancer trials, such as the Dutch Drug Rediscovery Protocol (NCT02925234), could serve as an example of how these barriers can be overcome.

Second, the systematic charting of successful and unsuccessful molecular treatment indications has only just begun. Continuing efforts in data collection linking biomarkers to drug and/or tissue type are needed in order to expand the number of patients for which a molecular profile can be linked to a potentially effective drug. These data need to be made public, in order to make sure that all MTBs across the globe are ever well informed and up to speed.

Perhaps, the application of more extensive sequencing approaches (eg, whole-exome sequencing and whole-genome sequencing) would also have helped Moore *et al*[6] in identifying more actionable targets for therapy. The focused nature of the sequencing panels used for review in the GRB at SRCI potentially attributes to the relatively low number of patients receiving genomic-based trial therapy in the current study of Moore *et al*. Namely, 94 patients needed further molecular testing, of whom it is unclear whether they eventually received a study treatment matched to their molecular profile. The cost-effectiveness of whole-exome or whole-genome sequencing programme still needs to be demonstrated, but there is clearly need for a comprehensive test that can keep up with the rapidly evolving landscape of new biomarkers and treatments.

Third, it is likely that future MTBs are increasingly going to be exposed to novel molecular profiling techniques. For example, high-dimensional characterisation of the immune infiltrate, or functional experimentation with patient-derived organoids and/or immune cells might guide personalised immunotherapy treatment in the years to come. This expanded use of different molecular profiles might increase the number of patients who can be linked to an effective therapeutic regimen.

Taken together, the development of MTBs is a highly needed but dynamic and challenging process in a rapidly evolving field. Moore *et al*[6] make an important contribution by sharing and discussing their implementation of an MTB with the oncological community. Sharing experiences on the implementation of MTBs will undoubtedly accelerate the quality of care in this area.

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