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Commentary

The Molecular Tumor Board Turns 10: The Age of Complexity

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Abstract

Gene sequencing has brought a titanic of complex data into clinical precision oncology. Deciphering this complexity for practice requires new constructs. In 2014, the Molecular Tumor Board (MTB) was introduced into the literature by a publication in *The Oncologist*. Ten years later, MTBs have become globally established vehicles that integrate rapidly emerging "omic" information, helping to transform cancer management.

Sequencing of the human genome was a monumental scientific achievement that revolutionized oncology. The draft of the first human genome sequence was finalized in 2001 after work that spanned a decade and cost about 3 billion dollars. However, a key technological breakthrough—next-generation sequencing (NGS)—resulted in plummeting sequencing costs and time, allowing NGS to be democratized. By 2012, NGS was being performed in a clinical-grade setting at an affordable price and completed within a few days, permitting the dawn of its clinical exploitation to understand the underpinnings of cancer in individual patients (Figure 1).

Because NGS generates massive amounts of data quickly and cost-effectively, a tectonic shift in cancer diagnosis and treatment emerged. Initially, it seemed that the abundance of new molecular data and the exploding granularity of genomic portraits of malignancy were a mere extension of increasing diagnostic resolution since the light microscope. It soon became apparent, however, that modern oncology needed to create new constructs in order to decipher the complicated molecular portfolios that were being presented to oncologists in day-to-day patient care. Indeed, NGS unveiled an unexpected reality about cancer, ie, that each metastatic tumor is both tremendously complex and distinct. Honing this new understanding of the molecular underpinnings of cancer, accompanied by the ability to address molecular alterations therapeutically, counterintuitively made therapeutic decision-making immensely more difficult.[1] Therefore, complexity-reducing, interdisciplinary clinical infrastructures capable of informing cancer care decisions derived from high throughput sequencing became necessary.

Precision oncology implies that patients and their tumors are treated in a "precise" way with drugs that match the molecular portfolio of each cancer and the host environment. However, suppose every tumor and every patient is unique and complicated in their underlying molecular landscape. In that case, it becomes evident that combinations of agents may often be necessary to optimize therapy. Moreover, in order to be precise, treatment must be personalized. In other words, optimal therapy requires that each patient receive an N-of-1 individualized treatment or combination of drugs matched to the patient and their cancer.

With the aim of precise and personalized biomarker-driven treatment in mind, the "*Molecular Tumor Board*" (MTB) was first published in 2014,[2] describing the MTB at the University of California San Diego. The goal of the MTB was to create the multidisciplinary input required to decipher the complexity of NGS's output. Its ultimate purpose was to discuss and synthesize knowledge that would translate to better care in the N-of-1 molecular era.[2] The MTB team included clinicians (medical, surgical, and radiation oncologists, pathologists, and radiologists) with expertise in various cancer types, basic scientists, geneticists, and bioinformatics/pathway specialists. Molecular tests were performed in a Clinical Laboratory Improvement Amendments (clinical-grade) environment.

Today, 10 years after its coining, we note that the MTB swiftly became part of many oncology departments worldwide, creating a blueprint for leveraging innovative therapeutic approaches. The MTB proved to be an efficient venue for addressing complexity arising from expanding diagnostic and pharmacological concepts, and it intercalated itself into the landscape of vehicles that generate evidence for patients. In the context of the MTB, testing or generating hypotheses coexist as two sides of the same coin. The MTB deliberations link the technologies able to detect pharmacologically tractable targets with the possibility of testing the hypothesis of whether or not targeting these anomalies produces clinical benefit. Moreover, the MTB may integrate existing data and discuss novel, potentially druggable molecular targets, while connecting them with the presumed best course of treatment in individual patients, ultimately generating new hypotheses.

We practice medicine at a time when the volume of data has reached an unprecedented level and is moreover

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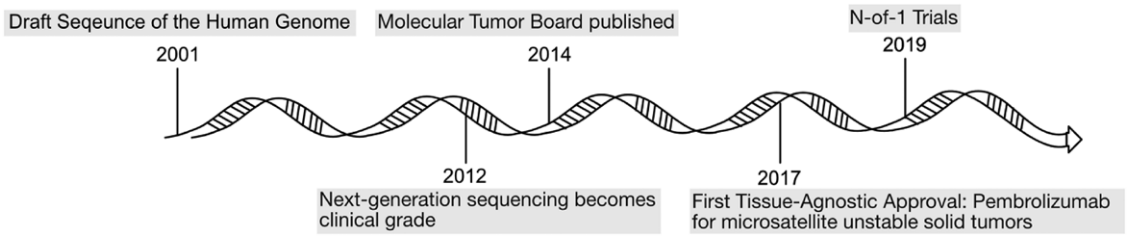

Figure 1. Milestone events leading to and following the emergence of the Molecular Tumor Board.

growing at an accelerating and breathtaking rate. Translating the resulting findings into clinical actionability and generating new evidence in a timely fashion constitutes an important challenge. As such, the MTB also serves as an attractive springboard to trailblaze new therapeutic concepts. Moreover, beyond somatic tumor DNA sequencing, the complexity arising from transcriptomic, proteomic, immunomic, microbiomic, and metabolomic cues, as well as host genomics—with hypothetical clinical actionability—requires an interdisciplinary filter as well as decision support generated from machine learning/artificial intelligence tools. The importance of the synthesis of this immense amount of knowledge, previously almost unimaginable, still requires testing in clinical trials, but the underlying question is now often generated and discussed in an MTB. This contextualization yields an insight that proved to be a most valuable, yet unexpected, result of the abundance of new data—an insight that is still difficult to reconcile. In essence, the MTB and any of its decision support tools attempt to optimize therapy for each individual based on rapidly evolving knowledge. Moreover, the resultant personalized, N-of-1 therapies may be given under the umbrella of an MTB-related, internal review board-approved clinical trial and consent. The therapies can be evaluated based on the degree to which they match each individual cancer's (patho)biology, assessing the ability of corresponding drugs to interfere with disease-driving cues. This type of trial and practice is very different from the classic gold standard randomized phase III trials in multiple ways: (i) therapy is individualized rather than the same for all patients[3,4]; (ii) therapeutic decision-making is not locked down but rather evolves as new scientific information about molecular anomalies and their targets rapidly emerges; and (iii) the ultimate evaluation of the therapy is not based on how well it serves a group of patients as compared to another control group, but rather by the cumulative benefit (or lack thereof) of N-of-1 personalized matched therapies for each individual. As such, matching of genomic architecture using DNA[3] or RNA[4] sequencing and unraveling complexity[5] yielded the insight that, indeed, clinical benefit was engrained in higher levels of molecular matching. In parallel, evidence is also being generated on an individual patient's level, embracing the concept of N-of-1 trials.

Additional aspects may be of crucial importance in regard to MTB deliberations. Imperatively, a question imposes itself onto the calibrating nature of the MTB, incorporating novel diagnostic layers or therapeutic concepts into the reality of real-world oncology. While doing so, it finds itself at the vantage point of revisiting old—previously unshaken—paradigms. Among these, the most brazenly heralded shift was the notion of questioning the tissue-specific nature of some features of cancer (eg, *NTRK* fusions or mismatch repair defects) and thus, their narrow—or for that matter broadened—scope of action. Emblematic of this new paradigm was the first tissue-agnostic approval of pembrolizumab, an anti-PD-1 antibody, against microsatellite instability-high (mismatch repair-deficient) tumors in 2017.[6]

There are multiple challenges for MTBs. They include interpretation of increasingly complicated results, timeliness, scalability, and fit into a global health care system wherein regulations that govern patient care privacy and the use of approved medications as well as access to clinical trials differ from country to country.[7-10] First, interpretation of the molecular anomalies in each patient's cancer is a complicated undertaking that necessitates a deep understanding of their contextual functional impact and pathogenicity, including whether alterations are drivers or passengers, as well as associations with sensitivity or resistance to specific therapies.[7] Moreover, many drugs such as small-molecule inhibitors have numerous targets, and a deep knowledge of target impact is essential. Multi-omic expertise accompanied by the use of advanced decision support, perhaps with artificial intelligence-based algorithms, may be needed to optimize therapeutic suggestions. Because of varying levels of expertise and thresholds, MTBs can determine that anywhere from ~20% to over 90% of patients have deleterious or actionable alterations.[7-10] Timeliness is another challenge. Patients with metastatic disease often have rapid progression and cannot wait long for a treatment shift.

We have found that, in addition to in-person or virtual MTBs, a just-in-time electronic MTB, wherein a templated outline of the patient's history and molecular features is emailed using a secured system to the MTB members by a coordinator who curates the replies, with the attending physician included in the distribution list, is necessary for patients whose tumors are aggressive and cannot wait for the next scheduled MTB, even if it is weekly. In our experience, the deliberations for electronic MTBs can be completed within 72 hours or less. However, timeliness also applies to getting the sequencing results back. Our experience is that it often takes about 4 weeks to have tissue results returned (with about half that time spent finding and retrieving the tissue from the pathology laboratory and the other half for the actual sequencing). Hence, we do liquid biopsies for NGS on all our patients; blood is drawn in the clinic and results are returned to the physician within about 10 days. It is also important for physicians to request molecular testing and an MTB deliberation early in the course of the disease, and certainly before progression has already occurred. Scalability is also an important obstacle. Cancer is one of the most common diseases, and individual MTBs

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for every patient in need are ultimately not feasible. A plethora of electronic decision support tools are now available and will eventually become more sophisticated and accessible. Navigating and understanding the global health care logistical, regulatory, and therapeutic ecosystem is also a major challenge. For instance, in the WINTHER precision medicine trial,[4] which involved 5 countries across multiple time zones, simply finding a suitable time for an MTB was a daunting task; one solution is to have MTBs alternate times on a weekly basis to negotiate the various time zones, as well as electronic MTBs as mentioned earlier. Health data security and privacy laws also vary across countries,[9] meaning that international MTBs must be set up to comply with the strictest laws. Finally, access to clinical trials varies from country to country and even from center to center and must be considered. Moreover, drugs approved by regulatory agencies differ from country to country as do laws around the possibility of off-label use of drugs and the affordability of such use. Additionally, countries have different payor systems. Medication accessibility is a significant barrier to the success of MTBs and their therapeutic suggestions. In our MTBs, we found that access could be enhanced by having a master protocol for which patients signed consent as well as a medication acquisition specialist and clinical study coordinator who attended every MTB and followed up regarding patients meeting eligibility for specific trials as well as by providing specialized assistance for accessing approved, off-label medications in the United States.

It is of note that broad access to comprehensive genomic profiling, liquid biopsies, and early testing integration is available to only a restricted group of cancer centers around the globe, and hence, our experiences and conclusions are applicable only to centers with such resources.[11,12]

In summary, embracing the complexity of cancer[5] through the lens of a well-carried-out MTB permits readjusting and, most importantly, reclassifying cancer subtypes, therapies, and, ultimately, patient groups. Nonetheless, overcoming the vagaries of translating molecular profiles into clinical practice may not just benefit from reducing their inherent complexity to make insights tangible. Indeed, we may instead consider the MTB as the midwife facilitating the birth of new concepts in clinical oncology. To date, most patients presented to the MTB have advanced refractory disease. As such, the critical issue of early treatment—ie, before tumor evolution restrains efficient targeting of oncogenic liability—still warrants addressing. The next decade may also witness the broad incorporation of functional assays and computer (in silico/artificial intelligence) modeling of innovative strategies in real-time for individual patients.

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Conflicts of interest

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