Precision oncology: separating the wheat from the chaff

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ABSTRACT

Precision oncology based on next-generation sequencing (NGS) test is growing in daily clinical practice. However, the real impact of this strategy in patients’ outcome on a large scale remains uncertain. In this review, we summarise existing literature on this topic, limitations for broad NGS implementation, bottlenecks in genomic variant interpretation and the role of molecular tumour boards.

The magnitude of the challenge that cancer management poses is alarming, with close to 50% of projected increases of new cases from 2012 to 2030 worldwide. However, patient prognosis has also changed significantly over the last decades with a gradual decrease in cancer-related mortality, reflecting dramatic improvements in cancer care. These advances are explained in part by increased understanding of the heterogeneous genomic landscape of both common and rare cancer types, which contributed with the development of new targeted therapeutic strategies and positively impacted on patient survival.

In oncology, precision medicine refers to the use matched therapies that are expected to confer benefit to a subset of patients whose cancers display specific genomic events that can be either directly targeted or molecular alterations that lead to dysregulation of a pathway for which there are potential targets. Technological advances in molecular profiling tools paired with development of novel targeted therapies have changed cancer care landscape. The proportion of patients with cancer whose tumours harbour a targetable molecular alteration is increasing overtime and there are at least currently 11 genomic events across 11 different cancer types with matched agents approved by European Medicines Agency and Food and Drug Administration (FDA). Genetic alterations in EGFR, ALK, ROS1, HER2, KIT, BRAF and germline BRCA1/BRCA2 mutations have been validated as powerful predictive biomarkers in the management of diverse solid tumours such as non–small cell lung cancer (NSCLC), breast and gastric cancer, gastrointestinal stromal tumours, melanoma and breast along with ovarian cancer. For this reason, in selected tumour types, gene sequencing is now part of routine cancer care. More recently, emerging biomarkers have been linked to response to targeted agents irrespective of tumour type, such as NTRK family fusions. The recent approval of an immunotherapeutic agent with microsatellite instability as a tissue-agnostic biomarker suggests that in the precision oncology era, evidence for new drug approvals may come from small patient cohorts with diverse tumour types and a common genomic event. It is expected that tissue-agnostic biomarker approvals will increase in the coming years, which may trigger a shift from the traditional classification of cancer by site of origin to a genomics-based model. Unfortunately, approvals may happen before clinical validation of the marker across all tumour types, leading to widespread molecular testing and drug adoption by the community prior to a clear understanding of which patients should get tested, treated and at which time point in the evolution of the disease.

As previously stated, only 11 out of more than 400 genomic alterations known to drive tumour progression can be directly matched with approved targeted therapies. But there is a myriad of rare genomic events in multiple cancer types that represent enrichment biomarkers for experimental therapies in clinical trials or can be matched to approved drugs in off-label indications, which has promoted the adoption DNA next-generation sequencing (NGS) gene panels across all tumour types with the aim of improving patients’ treatment options and outcomes (please refer to Gagan and Van Allen for a technical review on the technology). For this reason, many large-scale initiatives for prospectively performing tumour sequencing analysis and enrolling patients on genomically guided clinical trials were initiated. However, the real impact of this strategy in patients’ outcome on a broad scale remains uncertain. Nowadays, whether medical oncologists should restrict tumour NGS adoption to selected cancer types where validated
biomarkers are available or should recommend its use across all tumours as an investigational tool with the goal of matching patients to clinical trials is still debatable, and the line between clinical care and clinical investigation is constantly shifting.22

Before broad adoption of molecular profiling for precision oncology, some questions need to be considered. First, what is the real proportion of cancer patients eligible to tumour NGS who benefit from a matched therapy selection? Can we translate this benefit to the overall population of cancer patients or are physicians impelled to overestimate the potential benefit of molecularly guided cancer drugs? Also, what is an acceptable turnaround time from tumour DNA sequencing to therapy initiation in patients with advanced cancer? Should we perform molecular screening upfront at the time of diagnosis or is there any value for sequential testing to identify emergent genomic alterations in patients whose tumours progress on targeted therapies? Importantly, how to interpret all the information provided by large NGS panels in aggregate and not as isolated genomic events? How to prioritise therapies when multiple targetable alterations co-occur, including tumour mutation burden as an emerging predictive marker for immunotherapy selection? Finally, what is the psychological impact of this strategy to patients and families, particularly when combined germline DNA sequencing is performed? Will we ever be able to implement precision oncology on a global scale?

Data from clinical trials and cohorts of patients testing precision oncology clearly suggest that broad tumour genomic sequencing is not feasible to all patients and matched therapy rates according to NGS results remain suboptimal in diverse solid tumours,21 23–40 as summarised in table 1. Tumour molecular profiling is challenging as up to 30% of patients lack archived cancer tissue material or existing samples fail quality control and proper DNA yield.23 For example, tumour mutation burden could be calculated in only 57% of the tissue samples from patients enrolled in a landmark clinical trial assessing an immune-checkpoint inhibitor combination in NSCLC.41 Also, the identification of gene fusion transcripts, some representing critical oncogenic drivers with therapeutic implications across different cancers,42 43 poses many technical difficulties. Either when inferred from DNA sequencing tests or when identified through gold-standard RNA sequencing assays, bioinformatic pipelines for gene fusion detection are quite complex.45 Across different studies displayed in table 1, after median turn-around time of 3 weeks, on average 40% of the patients had at least one potentially targetable genomic alteration in tumour NGS. However, access to a matched drug is the pre-requisite for a potential benefit from precision oncology. In practice, no more than 25% of the patients were ultimately enrolled onto genotype-matched trials, even in highly specialised reference institutions with broad access to experimental therapies. For instance, of more than 6000 and 11 000 patients with advanced or refractory solid tumours screened in NCI-MATCH40 and MSK-IMPACT trial,21 only 18% and 11% were paired with targeted therapy, respectively. Similarly, in a retrospective cross-sectional study, the percentage of patients with advanced cancer who were eligible for FDA-approved genome-driven therapy increased from 10.5% in 2006 to 15.4% in 2018.44 More recently, in a real-world study of 5688 patients with advanced NSCLC treated in the community oncology setting, among those who received broad-based genomic sequencing (15% of the population had any multigene panel sequencing assay examining more than 30 genes prior to third-line treatment), less than 5% eventually received non-approved targeted treatments based on testing results, which did not independently associate with better 12-month survival outcomes.45 Several challenges may limit access to genomically matched trials: nearly 30% of the patients did not return to the reference institution where the molecular test was performed or finally decided to be treated closer to home, and others did not initiate a new treatment as a result of declining performance status or strict inclusion criteria in clinical trials.25 These estimates suggest that molecular profiling should be carefully indicated in patients with heavily pre-treated or aggressive cancers, particularly when clinical-laboratory findings and logistical issues may complicate access to drugs. Availability of slots in early clinical trials with matched therapies can also negatively impact recruitment rates. Moreover, misinterpretation of complex genomic data is another challenge for the clinician implementation of precision oncology as one-third of physicians describe difficulties for making treatment recommendations or clinical trial matching when reading standard static NGS reports.46 Despite extensive use of tumour NGS, prospective evidence for community implementation of precision oncology strategies over standard regimens is still missing.44 45 47 For instance, in the SHIVA study, the only randomised clinical trial that tested this strategy with a control arm of palliative unmatched therapy, off-label use of molecularly targeted agents according to a predefined treatment algorithm did not translate into improved progression-free survival (PFS) estimates.24 However, the targets and drug matches in the SHIVA trial were considered non-optimal considering current knowledge on drivers and targetability.24 In another study examining the impact of NGS and targeted therapies in patients with cancer of unknown primary, which associates with dismal prognosis, investigators reported a median overall survival (OS) of 13 months, similar to historical data of patients treated with cytotoxic chemotherapy.48 On the other hand, different meta-analyses evaluating precision oncology in an early clinical trial setting reported higher response rates (RRs) and longer survival among patients treated with targeted therapies compared with those with non-personalised approach.49–51 However, these reports might be biased given the selection of medically fit individuals who were more likely to do well as a consequence of more indolent tumour behaviour,52 53 and some of these studies miss important information about the key
Table 1 Clinical trials and cohorts of patients evaluating matched therapies according to genomic alterations

| Series                  | N     | Patients with a molecular profile obtained | Patients with 1+ actionable mutation from the whole population included | Patients included in matched clinical trials from the whole population included | Turnaround time (days) | Patients’ outcome* |
|-------------------------|-------|--------------------------------------------|-------------------------------------------------|--------------------------------------------------------------------------|------------------------|------------------|
| Clinical trials         |       |                                            |                                                 |                                                                          |                        |                  |
| MOSCATO                 | 1035  | 81%                                        | 40%                                             | 18%                                                                      | 21                     | 37% PFS2/PFS1>1.3 RR: 11%; OS: 11.9 months |
| SAFIR01†                | 423   | 71%                                        | 46%                                             | 13%                                                                      | NR                     | RR: 9%            |
| SHIVA phase II‡         | 741   | 67%                                        | 40%                                             | 26%‡                                                                     | ~60§                    | PFS: 2.3 vs 2.0 months, HR 0.88, p=0.41 |
| Longitudinal cohorts with nested trials—all tumours |       |                                            |                                                 |                                                                          |                        |                  |
| MSK-IMPACT              | 11 369| 91%                                        | 36.7%                                           | 11%                                                                      | 21                     | NR               |
| PROFILER†               | 2676  | 73%                                        | 37%                                             | 5.3%                                                                     | NR                     | 3-year OS: 54% vs 46%¶ |
| NCI-MATCH39 40          | 5963  | 93%                                        | NR                                              | 18%                                                                      | 27                     | NR               |
| MDACC                   | 2601  | 77%                                        | 24% (excluding KRAS)                            | 3.2%                                                                     | 26                     | NR               |
| MDACC                   | 1283  | 89.2%                                      | 36%                                             | 16.4% if 1 molecular alteration 2.8% if 2–3 molecular alterations       | NR                     | Patients with 1 molecular alteration: RR: 27% vs 55%, p<0.0001 TTF: 5.2 vs 2.2 months, p<0.0001 OS: 13.4 vs 9.0 months, p=0.017 |
| MDACC                   | 500   | 67.8%                                      | 64.4%                                           | 24.4%                                                                    | NR                     | TTF: 2.8 vs 1.9 months, p<0.001. No correlation with OS (p=0.087) |
| IMPACT/COMPACT          | 1893  | 87%                                        | <1%–31%**                                       | 5%                                                                       | 32                     | RR: 19% vs 9%, p=0.026 OS: 16 vs 13 months, p=0.10 |
| PREDICT                 | 347   | NR                                         | NR                                              | 25%                                                                      | NR                     | SD ≥6 months: 34.5% vs 16.1%, p=0.02 PFS: 4.0 vs 3.0 months, p=0.039 |
| CLEVELAND               | 250   | 82.2%                                      | 86%                                             | 10%                                                                      | 18                     | NR               |
| VANDERBILT              | 103   | 94%                                        | 83%                                             | 17%                                                                      | NR                     | NR               |
| JOHNSON§                | 1197  | 97%                                        | 45%                                             | 9.2%                                                                     | NR                     | NR               |
| BOLAND                  | 500   | 84%                                        | 30%                                             | NR                                                                      | 17                     | NR               |
| ARANGO/MDA              | 1200  | NR                                         | 44%                                             | 1%                                                                       | 25                     | NR               |
| Longitudinal cohorts with nested trials—tumour type-specific       |       |                                            |                                                 |                                                                          |                        |                  |
| MSKCC Lung27            | 1537  | 72%                                        | 46%                                             | 18%                                                                      | NR                     | OS: 3.5 years vs 2.4 years, p=0.006 |
| IFCT Group              | 17 664| 79%                                        | −50%                                            | NA                                                                       | 11                     | PFS: 10.0 vs 7.1 months, p<0.0001 OS: 16.8 vs 11.8 months, p<0.0001 |
| Vanderbilt Melanoma cohort | 150  | 100%                                       | 60%                                             | 15% (or 28% with metastatic disease)                                      | NR                     | NR               |

*Benefit obtained with matched therapies.
†Breast cancer patients only included.
‡Only included patients with some of these alterations: hormone receptor, PI3K/AKT/mTOR, RAF/MEK.
§From the biopsy to randomisation.
¶Survival patients received matched therapies (N=143) vs patients who did not receive the recommended targeted therapy (n=502) (exploratory analysis).
**According to three molecular profile assays (MALDI-TOF, TSACP, ASCP).
NA, not applicable; NR, not reported; OS, overall survival; PFS, progression-free survival; R, Retrospective study; RR, response rate; TTF, time to failure.

oncological history. There is also heterogeneity in the primary endpoint chosen for estimating the benefit of precision oncology strategy: RR, PFS and PFS ratio between matched and previous unmatched therapy. These are all surrogate endpoints that sometimes have limited impact in OS, which should be the optimal endpoint in clinical trials assessing precision oncology in advanced solid tumours. For example, the within-patient PFS ratio used in some precision medicine trials (PFS under molecularly guided therapy over PFS under previous unmatched treatment) is highly influenced by the natural course of the disease. In addition, the magnitude of clinical benefit achieved with this strategy should also be estimated according to European Society
for Medical Oncology (ESMO) and American Society Clinical Oncology (ASCO) scales. The ‘spectrum’ of targetability with matched drugs has a wide range, from on-label approved agents to experimental drugs that have limited preclinical evidence of activity in molecularly stratified models. Indeed, studies assessing precision oncology should not restrict matching to approved targeted drugs in off-label indications despite its broad endorsement. The Achilles heel of precision oncology is to induce oncogene de-addiction, such as in EGFR-mutant and ALK-rearranged patients with NSCLC with a deep RR that leads to prolonged PFS and (in some cases) OS benefit with targeted therapies compared with standard chemotherapy regimens. However, achieving such a large RR with matched therapies across different tumour types is not a trivial task. Both biomarker redundancy and/or targeted agents not able to induce oncogene de-addiction may explain the high failure rate of genomically targeted drugs in the clinics. In addition, most studies evaluating precision oncology, such as the SHIVA trial, assessed multiple treatment arms composed of many molecular alterations in patients with various tumour types, thereby introducing an important source of variability into the analysis. Despite the excitement with tissue-agnostic predictive biomarkers, the same level of antitumour activity with personalised therapies will hardly occur across different malignancies, such as vemurafenib in BRAF V600E mutated non-melanoma cancers, which has been reported as a targetable oncogene in melanoma but not in colorectal cancer or the different outcomes achieved with trastuzumab/TDM1 in HER2-positive breast cancer compared with HER2-positive NSCLC. Also, patients enrolled in studies evaluating precision oncology approaches were largely refractory to standard therapies, and this setting is likely associated with higher genomic heterogeneity and clonal selection, limiting the efficacy of targeted therapies as single agents. In this scenario, given the capability of liquid biopsies to capture dynamic intrapatient genomic heterogeneity and provide a molecular portrait for the tumour at the time of treatment selection, it seems reasonable to further evaluate this tool as a surrogate of tumour tissue NGS. Furthermore, the early assessment of synergistic molecularly targeted drugs in combination regimens is an appealing way to counteract primary or acquired resistance; however, substantial toxicity has been reported in many trials, which might limit clinical benefit.

Another critical aspect in precision oncology is the definition of standardised bioinformatics procedures and development of algorithms to define which driver gene alterations or pathway changes must guide targeted therapy selection. With the shift from single gene tests and small hotspot panels to larger gene panels and whole exome and genome platforms, interpretation and prioritisation of the genomic alterations with clinical significance across individual tumours (and matched germline DNA) has become a major challenge. There are multiple manually curated precision oncology knowledge databases in public domain designed to help cancer researchers on this task, each with different data input and output formats and levels of evidence for targetability. These resources do not substitute expert-guided decisions: they have no clear rules for variant prioritisation when multiple alterations coexist and when more than one matched drug or trial exists for a given alteration. Additionally, annotation on resistance biomarkers is limited and functional assessment of rare gene variants is sometimes missing. In this context, greater harmonisation of data capture processes is needed to support effective and reliable interpretation of molecular and linked clinical data. However, we should keep in mind that the level of evidence for targetability of cancer variants is dynamic, varying significantly over time. One example is KRAS mutation in NSCLC as predictive biomarker for multiple different drugs and combinations including MEK inhibitors, which has not been confirmed in a randomised phase III clinical trial. Therefore, it is critical to continuously update the resources used for clinical interpretation of cancer variants with emerging drugs. Similarly, recent studies have linked mutational signatures rather than single gene alterations as predictive biomarkers of response to immunotherapies. At the end of the day, multidisciplinary molecular tumour boards are crucial for providing objective evidence-based translation of observed molecular alterations into patient-centred clinical action. Despite these complexities, community adoption of tumour NGS tests for patient care is increasing and physicians’ perception of the benefit of precision oncology is sometimes biased, with a tendency to overestimate its value and underestimate the harms. In daily clinical practice of a reference institution, physicians reported that sequencing results altered patients’ management in approximately 20% of cases. Among patients whose treatment was not altered, physicians indicated the presence of an actionable alteration in 55% of the cases; however, only 45% of them had a genomic variant annotated as targetable by expert curators. The use of interactive genomic reports and molecular tumour boards empowered by cognitive computing have been assessed as tools to improve comprehensive data analysis and physicians’ ability to accurately interpret genomic results. In this scenario, the clinical application of ESCAT (ESMO Scale of Clinical Actionability for molecular Targets), a standardised six-level evidence-based classification system of genomic alterations with direct implications for patient management and selection for targeted therapies, will certainly facilitate interpretation of NGS results. ESCAT level I represents targets ready for implementation in routine clinical decisions; level II, investigational targets that likely define a patient population that benefits from a matched drug but additional data are needed; level III, when clinical benefit was previously demonstrated in other tumour types or for molecular targets with similar functionality; level IV, limited preclinical evidence of actionability; level V, evidence
supporting that co-targeting approaches (combination regimens) are needed; and level X, lack of evidence for actionability.84

Likewise, there are still major technical and ethical barriers that need to be overcome when implementing NGS tests in the clinics. The results of commercially available tests run in parallel may be discordant in one-third of the cases, both in terms of mutations detected and their clinical interpretation or drug matches.47 In addition, it is still unknown what is the appropriate number of genes to be screened in tumour type-specific gene panels or as universal tissue-agnostic tests. Whether larger gene panels improve the chances of finding targetable alterations may depend on tumour type. In a prospective analysis for mutations in  $>$300 cancer-associated genes in advanced lung adenocarcinoma, investigators found that 37% of patients received a matched therapy guided by their tumour molecular profile. When excluding alterations linked to standard-of-care therapies, this number fell to 14%.82 The added value of larger gene panels may reside in identifying a ‘hypermutation’ or DNA damage repair signatures with increased predictive value for immunotherapies over existing clinical and a pathological selection criteria. If large NGS panels are used, the question of whether paired germline sequencing adds value to the variant functional interpretation and clinical management remains critical. Besides, physicians report an ethical dilemma when disclosing secondary or incidental germline results that are not actionable in practical terms,83 knowing the psychological impact for the patients and family members.84

Another major issue is the financial toxicity of NGS tests. In a recent study, a decision analytic model showed that NGS was cost-effective over sequential single-gene testing modalities for newly diagnosed advanced NSCLC in the USA, without introducing delays in patient management.85 However, the same model could give contrary results if applied in patients with NSCLC from a different region, such as Asian population, where the incidence of EGF mutation is higher than Caucasians (50% vs 11%), and a sequential approach could be more cost-effective than NGS test upfront.86 Despite the limited evidence of cost-efficacy of precision oncology approach,22 47 FDA has recently approved the first comprehensive NGS test as a companion diagnostic in solid tumours. This decision confronts two profiles of physicians: the ‘conservative’ ones, who accept this strategy only as an investigational tool as a part of clinical trials and prospective cohorts; and the ‘believer’ ones, who anticipate that the approval and widespread use of a NGS companion diagnostic may help identify rare patients that can get substantial benefit for specific targeted therapies, as described among patients with NTRK-fusion cancer.

We are in favour of NGS for precision oncology in controlled environments or clinical trials like some of those displayed in table 1, where off-label administration of expensive drugs based on limited biological evidence is restricted to prospective patient registry cohorts.87 Medical oncologists need to be educated on the interpretation of genomic tests through molecular tumour boards and structured dynamic reports, with prioritisation rules for matched therapies in case more than one targetable alteration is found. Most importantly, clinical outcome of patients treated under this approach need to be published or shared with the research community in order to advance collective knowledge on targetability of cancer variants. Indeed, not only the absolute number of patients who benefited from this strategy is relevant: the denominator of the equation (number of patients screened and ultimately enrolled in a matched therapy clinical trial) is also crucial. In this context, the TAPUR (NCT02693535) phase II study aims to test in a real-world setting the efficacy of FDA-approved drugs for specific alterations irrespective of tumour type. In fact, the development and validation of therapeutic agents that target molecular drivers requires innovation in clinical-trial designs,88 such as basket trials like NAVIGATE phase II study (NCT02576431), and umbrella trials like the ongoing randomised SAFIRO2_breast and SAFIRO2_lung cancer trials (NCT02299999 and NCT02117167, respectively), for quantifying the impact of such approach in larger populations.

In conclusion, although physicians continue to obtain increasing amount of information about genomic molecular alterations, only a minority of patients with cancer derive clear benefit from matched targeted treatment opportunities, suggesting that NGS for precision oncology based on emerging biomarkers remains an investigational strategy. The results of ongoing clinical trials may help elucidate the long-term outcome of this intervention. Also, the current model for precision oncology usually matches single agents to patients with late-stage disease, refractory to different therapies, with molecularly complex diseases, and this approach is suboptimal. In the near future, combinations of immunotherapies and targeted agents may become new standard strategies in some tumours, and predictive biomarkers for both treatments may increase the demand of NGS tests in clinical practice. The balance between the cost of precision oncology strategy and patient benefit according to defined scales is also needed. Undoubtedly, today’s era of precision medicine brings with it as many challenges as it does opportunities. It is our job to continuously advance this field of research.

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