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Delivering precision oncology to patients with cancer

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With the increasing use of genomic profiling for diagnosis and therapy guidance in many tumor types, precision oncology is rapidly reshaping cancer care. However, the current trajectory of drug development in oncology results in a paradox: if patients cannot access advanced diagnostics, we may be developing drugs that will reach few patients. In this Perspective, we outline the major challenges to the implementation of precision oncology and discuss critical steps toward resolving these, including facilitation of equal access to genomics tests, ensuring that clinical studies provide robust evidence for new drugs and technologies, enabling physicians to interpret genomics data, and empowering patients toward shared decision-making. A multi-stakeholder approach to evidence generation, value assessment, and healthcare delivery is necessary to translate advances in precision oncology into benefits for patients with cancer globally.

Precision oncology includes the integration of molecular tumor profiles into clinical decision-making in cancer treatment[1]. An increasing number of molecularly guided treatment options (MGTOs) have received regulatory approval on the basis of genomic biomarkers for various tumor types[2]. In some cases, MGTOs have demonstrated clinical activity across multiple tumor types that share the same molecular alteration (for example, *NTRK* fusion, microsatellite instability, DNA mismatch repair deficiency[3]), resulting in broad or even tumor-agnostic approvals. The accelerated development of innovative MGTOs stems from not only advances in our understanding of cancer biology, but also the rapid development of high-throughput technologies, such as massively parallel or next-generation sequencing (NGS)[2,4,5]. Other means for tumor molecular stratification, including transcriptomics, proteomics, and immune profiling, are being developed, but predictive biomarkers that rely on genomic sequencing have enabled most of the recent advances in terms of biomarker-guided therapeutic indications.

This new era of precision medicine has seen several new cancer therapeutics receive regulatory approval every year for biomarker-defined subsets of patients. However, this brings significant challenges for healthcare systems to adapt their infrastructure, methodologies, and reimbursement policies to enable wide access to these drugs for patients. As a result, there is a significant gap between advances in anticancer drug development and delivery of these drugs to patients. This gap risks increasing health disparities in society owing to unequal access to the technology and a lack of knowledge on how to implement advances in the clinic. As an example of how delays in incorporating biomarker testing hamper the delivery of new therapies to patients, a recent large-scale study found that ~23% of patients with newly diagnosed advanced non–small-cell lung cancer (NSCLC) did not receive genomic testing for any of four guideline-recommended therapeutic targets (*ALK*, *BRAF*, *EGFR*, and *ROS1* alterations) before first-line treatment[6].

The magnitude of the problem is expected to increase exponentially as new treatments are approved for relatively narrow populations of patients (Fig. 1). This clearly presents a challenge for implementing precision medicine approaches in clinical practice. Given the rarity of many therapeutic targets, focused testing to investigate each clinically relevant biomarker individually is unlikely to be cost-effective, so broad multigene sequencing panels (also referred to as 'comprehensive genomic profiling' (CGP)) may be needed; national and international guidelines have now incorporated specific recommendations for the use of multigene panel testing in specific settings[7–12]. In the near future, treatment stratification for patients with NSCLC, breast cancer, or colorectal cancer will likely be driven by CGP tests, with many other solid tumor types and hematological malignancies following as clinical value is demonstrated.

Some of the key components for broad and equitable access to precision oncology will depend on the specific situation in various countries and their healthcare systems, as well as the particular patient groups or tumor types in question[13]. However, there exist some globally relevant concepts to help translate advances in precision oncology into improvements in cancer outcomes at the population level. In this Perspective, we analyze these global challenges for the implementation of precision oncology into routine care and discuss ways that healthcare systems may need to respond and adapt to maximize the impact of precision oncology on patient care while carefully considering its impact on healthcare costs.

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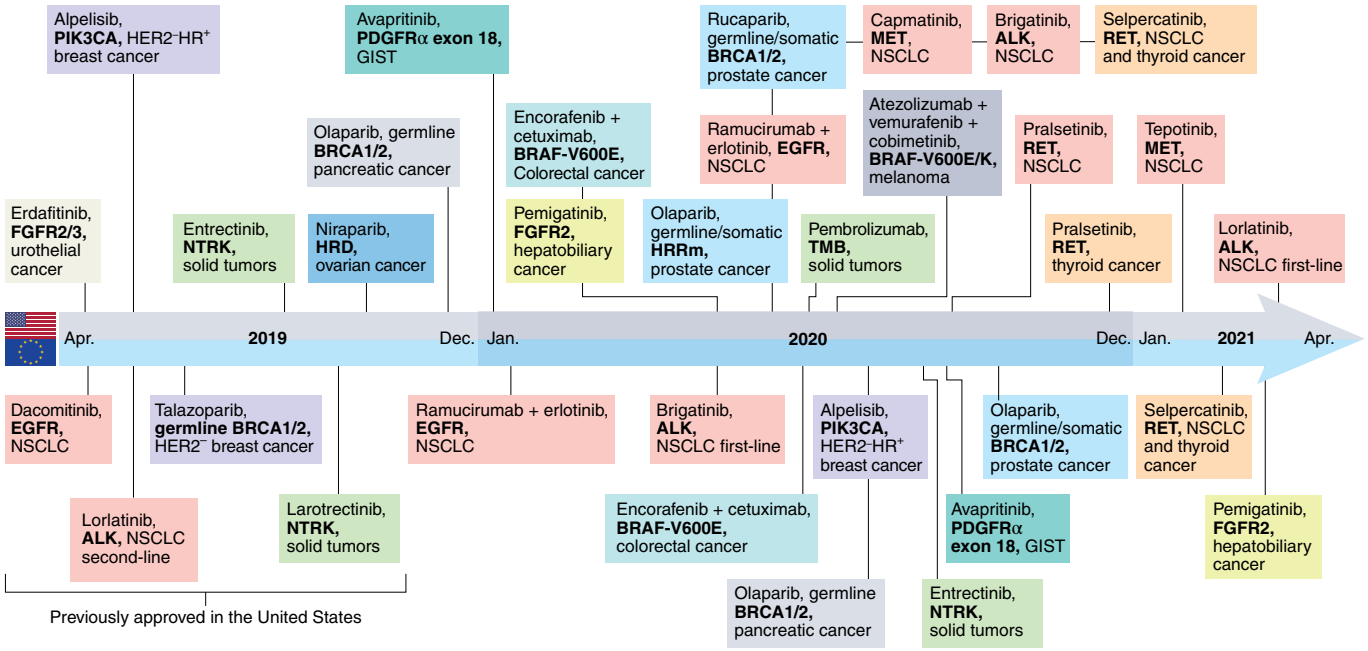

Fig. 1 | Genomic biomarker-driven drug approvals. Recent biomarker-specific solid tumor approvals relevant to comprehensive genomics profiling tests in the United States (Food and Drug Administration) (top half) and EU (EMA) (bottom half) between April 2019 and April 2021, as examples of the rapid advance in the number of available biomarker-driven treatment indications. Approvals related to other means of biomarker testing, such as immunohistochemistry assays, are not included. Each box includes a drug, the relevant biomarker (in bold), and the cancer type or disease setting for which the approval was granted by the relevant regulatory body. ALK, ALK receptor tyrosine kinase; GIST, gastrointestinal stromal tumor; EGFR, epidermal growth factor receptor; FGFR2/3, fibroblast growth factor receptor 2/3; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; HRD, homologous recombination repair deficiency; HRRm, homologous recombination repair gene mutations; MET, MET proto-oncogene, receptor tyrosine kinase; NTRK, neurotrophic tyrosine receptor kinase; PDGFRα, platelet-derived growth factor alpha; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RET, Ret proto-oncogene; TMB, tumor mutational burden.

Ensuring equal access through a patient-centric approach

The past decade has rendered a striking advance in the availability of new technologies for tumor genomic profiling. However, the same amount of time and resources has not been invested into building the backbone elements for practical implementation across institutions. The transition of molecular testing from centers of academic excellence to wider populations receiving care at community practices represents a challenge of a magnitude similar to the inception of such technologies.

Plans for access to advanced diagnostics need to be designed in a patient-centric, rather than institution-centric, manner. Clearly, it does not seem feasible that every healthcare institution would be able to adopt in-house advanced diagnostic platforms and support teams for data interpretation; thus, access plans should account for the need to deliver testing to patients regardless of where they are receiving care by facilitating patient referrals to centers where the patients can access advanced diagnostics and/or by smoothing the path for efficient transfer of samples and data (rather than patients) across institutions and laboratories in a secure manner, to guarantee equality in access to advanced diagnostics.

A complicating factor is that different regulatory decisions result in different levels of access across countries. For example, although the European Medicines Agency (EMA) is responsible for the evaluation of new medicines in the European Union (EU), EMA regulatory approvals do not necessarily translate into positive access recommendations across all European countries[14], which also affects intercountry heterogeneity in test and drug access and reimbursement[15]. From a global perspective, there is significant variability not only in the regulatory approval process but also in access to testing and access to matched drugs across regions and countries, according to the different healthcare-system characteristics.

Low- and middle-income countries face large inequities in access to new MGTOs and advanced diagnostics, compared with high-income countries. In addition, the latter are where most academic institutions and biopharmaceutical companies develop their research and focus their investments. Unequal access to healthcare is an unfortunate reality for most patients with cancer and other diseases in low- and middle-income countries, but in the field of precision oncology, we face the risk of these inequalities being permanent if low- and middle-income countries are not included in the research and evidence-generation step, even if actions to enhance access are eventually taken.

Genomic testing in clinical-practice guidelines. Clinical-practice guidelines developed by academic and medical societies play a key part in the harmonization of cancer care and the advancement toward equality in access to excellent care. In recent years, several clinical guidelines have endorsed genomic testing for certain routine clinical settings for cancer care. For instance, in 2017, the National Comprehensive Cancer Network (NCCN) guidelines recommended comprehensive genomic profiling of patients with NSCLC to guide appropriate therapy targeting *ALK*, *ROS1*, and *EGFR* alterations[16]. By 2021, the NCCN guidelines had expanded to include recommendations for sequencing of *BRAF*, *KRAS*, *MET*, *RET*, and *NTRK*[7]. In 2020, the European Society for Medical Oncology (ESMO) Precision Medicine Working Group leveraged the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) to evaluate in which settings, among the cancers of higher lethality, multigene NGS could be an attractive alternative to single-biomarker testing[12]. These guidelines should help standardize the use of comprehensive genomic profiling assays in clinical practice. However, there is still a significant disconnect between clinical guidelines and regulatory

decisions for biomarker approval and testing reimbursement across the world, and this can frustrate physicians and patients when discussing treatment plans.

Policy considerations. Access to precision oncology is one of the key priorities included in the EU's new Europe's Beating Cancer Plan, which aims to improve the prevention, detection, treatment, and management of cancer while reducing health inequalities between and within member states[17,18]. The plan includes initiatives to promote the broad and equal use of NGS technologies (Cancer Diagnostic and Treatment for All initiative), to identify priorities in precision medicine research and education (Partnership for Personalised Medicine initiative), and to promote large-scale sharing of genomic data. This plan should help European states to develop harmonized guidelines and recommendations for delivering precision oncology as a healthcare service, following a multi-stakeholder approach[18]. Examples of similar projects focusing on precision medicine are present around the world, including the Precision Medicine Initiative (National Institutes of Health, United States)[19], the Cancer Moonshot program (National Cancer Institute, United States)[20], the Cancer Molecular Screening and Therapeutics program (MoST, Australia)[21], the Center for Cancer Genomics and Advanced Therapeutics (Japan)[22], and the Korea University Medical Applied R&D Global Initiative Center[23].

A number of general concepts about health policy, drug access, and precision oncology should be noted[17]. First, policy initiatives should involve stronger collaboration between regulators and those working in healthcare, to harmonize basic principles for access to new drugs. Second, new policies should encourage streamlined and predictable regulatory procedures for precision oncology — for example, in the consideration of new trial designs and alternative modes of evidence generation (such as real-world evidence (RWE)). Third, policies should promote investment in research that accelerates the translation of laboratory-based findings into affordable medicines, new molecular diagnostic standards, and infrastructure. Building and supporting large biobanks and high-quality clinical genomic data registries could not only accelerate the development of precision-oncology strategies but also transform routine clinical practice outside academic centers.

Assessing the value of precision oncology

Affordability of new therapeutic strategies, such as precision oncology, is a requirement for ensuring the sustainability of healthcare systems. Various assessment frameworks play an important role here, by providing a set of methods and processes to evaluate the benefits and risks, and, in some instances, the costs and added value, of healthcare interventions[24]. Some frameworks (for example, those of ESMO, the American Society of Clinical Oncology, and NCCN) are intended for use mainly by patients and physicians to inform treatment decision-making and hence focus on clinical and patient outcomes. Other frameworks (for example, those by the Institute for Clinical and Economic Review and the Professional Society for Health Economics and Outcomes Research) aim to inform policymakers and payers on coverage and reimbursement decisions and therefore consider aspects such as costs, cost-effectiveness, and/or budget impact.

Differences between frameworks' definitions of benefit or, when costs are considered, of value, as well as the type of decision they intend to inform, indicate that the assessment of precision oncology is not standardized[25]. There are valid reasons for this lack of standardization — for instance, not all countries require cost-effectiveness analyses to inform reimbursement decisions — but it can nevertheless contribute to variations in patient access to, and implementation of, precision oncology. However, when considering, for example, budget impact (the financial consequences of adopting a new intervention) or cost-effectiveness (the cost of an intervention relative to patient outcomes), it is important to clarify first which costs and outcomes are considered and second that budget impact and cost-effectiveness are heavily context dependent.

In some cancers, comprehensive genomic profiling may improve turnaround times and time to therapy initiation compared with pursuing multiple single-biomarker tests[26], which may streamline the delivery of precision oncology and potentially enhance cost-effectiveness[27], when treatment costs are commensurate with the benefit they provide. However, the mere implementation of CGP tests is not necessarily linked to improved overall survival[28]. Presley et al., for example, showed that only a small fraction of patients with NSCLC undergoing testing were candidates for targeted therapies, and hence their potential benefit would be diluted across the broad cohort of patients with NSCLC[28]. This obviously affects the cost-effectiveness evaluation. Using the same clinical data, an expanded analysis of the incremental cost-effectiveness ratio in patients with advanced NSCLC compared multigene panel sequencing with single-marker tests and found multigene panel sequencing to be only moderately cost-effective on the basis of overall survival, testing costs, and the proportion of patients who received a matched therapy[29]. However, this modeling-based study suggested that, all else being equal, cost-effectiveness could improve with greater availability of, and patient access to, targeted therapies[29].

Multiple systematic reviews have analyzed the cost-effectiveness of genomic tests; in one of these systematic reviews, which included four studies that examined the cost-effectiveness of using NGS to identify targeted therapeutic options, only one study showed that NGS improved outcomes at lower total costs of care. The other three studies found incremental cost-effectiveness ratios of >US$100,000 per (quality-adjusted) life year gained[30]. These studies included the costs of applying both NGS and subsequent targeted treatments in their economic evaluation, and the result may reflect the high level of decision uncertainty involved when applying nonstandard targeted treatments. Another review found that the cost-effectiveness of CGP was limited mainly by the cost of treatment[31]. Therefore, in addition to appropriate implementation of testing in the patient pathway, cost-effectiveness of broad genomics panels is tied to the cost-effectiveness of new MGTOs[29].

Access to comprehensive genomic profiling could also lead to the identification of targetable tumor alterations for which drugs are already available but not formally indicated (that is, 'off-label' use)[32] — but without systematic data collection, it is difficult to understand the merit of this practice in particular patient populations and to provide support for extension of the label. For example, in the EU, no structured framework exists for the use of medicinal products outside their formal or approved indication, and there is heterogeneity in the approach to such use of MGTOs in European healthcare[33,34]; indeed, this divergence also occurs at a global level, with different healthcare systems and approaches to access and reimbursement. Nevertheless, there is a clear need for structured data collection, preferably in the context of clinical studies and registries, when MGTOs are used outside their formal labels to assess the risks and benefits of drugs in such settings. Ongoing studies, such as DRUP (NCT02925234), TAPUR (NCT02693535), or MoST (ACTRN12616000908437), could aid in reaching this end. Collaborative, multi-stakeholder frameworks (including regulatory bodies, academia, patient organizations, and pharmaceutical companies) could help streamline and standardize data collection in order to assess potential benefits, risks, and health economic value; these data could eventually be used to inform further precision-oncology studies that can then generate the necessary evidence to embrace new therapeutic strategies[34].

Evidence generation in precision oncology

Clinical trials. Advanced diagnostics, such as NGS, progressively identify new biomarker-defined tumor subtypes that can be targeted

with MGTOs; however, the need to recruit more precisely defined populations renders traditional clinical trials of MGTOs costly and time-consuming[35], which delays their translation into real-world benefits. To achieve adequate power in clinical trials, it will be necessary to screen large populations, which requires multi-institutional and frequently multinational efforts. This challenge, however, should not result in lower standards for drug approval, but rather in innovative clinical-trial designs that generate the necessary evidence efficiently. These approaches include enrichment trials (for example, MINDACT), basket trials (for example, BASKET), umbrella (for example, ALCHEMIST), and adaptive trials (for example, BATTLE-1)[35], as well as combinations of these (for example, DRUP; Box 1(ref. [36])). Anticipating the future need for combination strategies, the I-PREDICT study used an '*n* of one' approach to test distinct therapeutic combinations based on individual molecular profiles, which was associated with better outcomes in this highly selected population[3,37]. Harmonized annotation and sharing of the individual patient-level biomarker data from clinical trials should be a priority. This will allow the use of clinical genomics data beyond the biomarker of interest for a particular trial to determine the natural history of the disease characterized by that biomarker.

Real-world evidence. RWE studies use data collected in routine clinical care[38]; these can not only identify treatment gaps and describe quality of care[39], but also complement clinical trials by generating supporting evidence for new precision-oncology biomarkers and therapies. One clear example involves the generation of confirmatory efficacy data after accelerated/provisional approval of an MTGO, or post-approval safety evaluations in diverse populations. RWE can be collected from numerous sources, including electronic health records, registries, and patient-reported data that can be complemented through mobile technologies and wearables[40]. Technical and logistical barriers to effective RWE generation include limitations in cross-study data comparability; heterogeneity in data storage, collection, and representation; difficulties in the storage and transfer of large datasets; and ethical, regulatory, and legal issues related to achieving broad patient consent and data sharing[41]. Challenges also exist in curating, standardizing, and structuring RWE so that data can be extracted and translated to evidence. Akin to clinical trials, RWE studies need to evolve with the rapid development of precision oncology. For example, payers report concerns with RWE quality and comprehensiveness, data standardization, lack of methodological transparency, and failure to collect or prioritize data relevant to decision-making in healthcare[17,42]. Regulatory bodies describe challenges with drug-approval packages that include RWE, particularly in the context of data quality and methodological issues[43]. Consensus guidelines are needed to standardize the methodology of RWE-based studies and best practices for data sharing according to data-protection regulations[42]. Medical and scientific journals should contribute to such guidelines when publishing results of RWE-based studies[44]. At present, few journals provide specific recommendations for authors to follow when conducting, reporting, or submitting manuscripts on RWE studies[44].

External validity of genomic studies. Clinical trials, and most genomic landscape studies investigating the prevalence of a given biomarker, focus on highly selected populations receiving care mainly at academic institutions, which are not necessarily representative of the wider patient population. Patients with comorbidities, particularly older people, and those receiving care at community practices are often not included in clinical trials; moreover, various ethnic or socio-economic groups are repeatedly under-represented in clinical trials. Indeed, many of these databases include a disproportionately large share of white patients.

As a result, the data supporting the adoption of a new biomarker test or a new therapy may be misleading because of poor generalizability of data to the wider society. This problem of 'external validity' of genomics datasets jeopardizes strategic decisions to allocate resources to implementation of new drugs or implementing new tests in clinical practice. Investigating the genomics of real-world populations enriching for those groups under-represented in clinical trials, as well as clinico-genomics registries in specific territories, can expand our knowledge of the true prevalence of infrequent precision-oncology targets, support local regulatory decisions, and inform allocation of resources. These data could also increase confidence among clinicians and patients in interpreting the results of comprehensive genomics profiling[45].

Validation of genomic profiling technologies. Discrepant results between NGS assays can be the result of different tests' having different sensitivities and specificities for specific genetic alterations, as well as differences in panel design. Results, however, also depend on the source of genomic material and its relation to the natural history of the disease; for example, the use of archival versus contemporaneous tumor biopsies or primary tumor versus metastasis has complex implications when spatial heterogeneity and tumor evolution are taken into account over time[46,47]. The availability of different options for comprehensive genomic profiling can improve patient access; however, a minimum of common test features needs to be standardized to ensure comparability of results and equal confidence in guiding treatment decisions. To maximize the impact of genomic profiling for patients, it is crucial to understand the possibilities and limitations of a test in each clinical setting, encompassing the technology and the source of material.

Unlike other medical devices, comprehensive genomic profiling assays cannot define a priori all potential findings of the test, because new genetic variants, or even meaningful alterations in non-coding DNA, are continually identified through scientific insights and as more patients and tumor types are tested[48–52]. This challenges the standard regulatory approach to approving new devices and requires continuous reclassification of genomic events as new data are generated. Notably, this reclassification is likely to result in increased value per test over time as new therapies linked to genomic features are identified. Revisiting actionability

Box 1 | The Drug Rediscovery Protocol

The Drug Rediscovery Protocol (DRUP) is an ongoing multi-drug, pan-tumor trial (NCT02925234) in the Netherlands that aims to identify signals of clinical benefit of approved drugs used outside their label in rare, molecularly defined subsets of patients with cancer while generating real-world evidence for precision-oncology strategies[36]. Patients with advanced or metastatic solid tumors, multiple myeloma, or B cell non-Hodgkin lymphomas are matched to one of the drugs available in the study, and patient cohorts are refined on the basis of signals of drug activity[36]. Up to 24 patients are enrolled per cohort, and a drug is deemed to warrant further investigation if at least 5 of 24 patients experience clinical benefit (complete response, partial response, or stable disease beyond 16 weeks)[36]. Analysis of patients recruited in the first 2 years of the study indicated an overall clinical benefit rate of 34% ($n = 74/215$) across all cohorts, with a median duration of 9 months (95% confidence interval, 8–11 months)[36]. As a consequence of this trial, the Dutch Healthcare Institute and insurance agencies have now embraced a personalized reimbursement model for certain molecularly guided treatment options, such as nivolumab in patients with MSI-high tumors (clinical benefit rate: $n = 19/30$ (63%)), thus enhancing patient access to this drug[36].

assessments and keeping patients informed about the clinical relevance of their results has significant ethical and clinical-practice implications. Making raw data and bioinformatics pipelines for clinical genomics tests accessible to researchers would facilitate re-analysis of data and cross-test comparisons; these actions may not only accelerate research in the field and support decision-making by regulatory authorities, but can also impact individual patients. It is therefore key to build infrastructure that brings data together and that invests in future analyses. Beyond tumor panel testing, clinical implementation of wider whole-exome or whole-genome sequencing approaches can significantly contribute to care by unlocking clinically relevant findings for patients[47,53,54]. Moreover, the advent of liquid biopsies may facilitate longitudinal testing of wider populations[55–57]. Taken together, collection, analysis, and storage of these clinical genomics data may create a critical resource to refine precision treatment of patients with cancer.

Interpretation of clinical genomics data: education and decision-support tools

As the complexity and scale of data generated through comprehensive genomics profiling increases[53], the task of matching tumor alterations with optimal therapies relies heavily on the expertise of caregivers, who may not be experts in clinical genomics. A survey of 1,281 US oncologists found that only 38.2% felt very confident in using NGS, and that confidence directly influenced the translation of the test into patient care[58]. Furthermore, a survey of clinicians across 19 countries in Europe found that 39% were concerned with the turnaround times for NGS tests, the reliability of samples, and the interpretation of results[59]. Physician uncertainty exposes patients to risks and holds back the implementation of new diagnostic and therapeutic strategies. Education of healthcare professionals, development of decision-support tools, and access to multidisciplinary teams including members with expertise in interpreting molecular data are key pillars in the improved clinical use of CGP assays.

Education. Understanding the basic principles and limitations of comprehensive genomics profiling and other molecular testing modalities used in clinical practice should be part of the global training curricula for physicians involved in the management of patients with cancer, and particularly for oncologists and pathologists. This concept would also apply to continuous education programs for practicing physicians, in order to ensure that all patients have equal access to high-quality care when it comes to the use of these tests and interpretion of their results. The joint ESMO–ASCO initiative for a global oncology training curriculum already acknowledges this need and describes specific knowledge and skills to be acquired[60].

Decision-support tools. Documenting the clinical relevance or 'actionability' of a biomarker in clinical genomics reports is critical for assisting in the interpretation of these data in clinical practice. With the increasing availability of comprehensive genomic profiling assays, prioritization of targets has become essential. OncoKB is among the most relevant precision-oncology knowledgebases, comprising catalogs of pathogenic mutations in cancer[61], ranked on the basis of evidence of clinical actionability. The Molecular Tumor Board Portal is another example of a publicly available support system for clinical genomic decisions, supported by seven European comprehensive cancer centers united in Cancer Core Europe[62]. One of the key challenges for these knowledgebases is keeping pace with emerging genomics and clinical-trial data and providing regular updates in their annotations and assessments of actionability. Areas for further development include the integration of data from different knowledgebases and harmonization of actionability assessments — toward which there are ongoing efforts, such as those from the Variant Interpretation for Cancer Consortium — and the need for standardized terminology for evaluating clinical actionability of targets. To the latter point, ESMO's ESCAT[63–65] was developed as a classification system that provides shared language for the reporting of clinical genomics data or the communication of new clinical research data. Importantly, the clinical utility of many of these frameworks has yet to be established[66]. Another challenge for these decision-support tools, as more correlative data for patients undergoing multigene panel testing emerge, is the need to refine predictive value assignments according to co-occurrence of alterations and evaluation of more complex patterns of alterations; to that end, using sophisticated algorithms and embracing artificial-intelligence approaches may merit evaluation.

Precision oncology and the multidisciplinary team. Multidisciplinary inputs help clinicians to interpret and give context to genomic results, which aids in the translation into clinical benefit[50]. Integration of expertise in clinical genomics, data science, and genetic counseling in tumor-type-directed multidisciplinary teams would be ideal; however, specific molecular tumor boards (MTBs) can be an alternative tool to complement the education of clinicians and to facilitate practical implementation of precision oncology[67]. MTB discussions should systematically integrate molecular alterations within a clinical context (for example, performance status, comorbidities, prior treatments), generating a report that complements or adds to the genomics test report with a concise and clear presentation of findings and clinical interpretation of results — including therapeutic recommendations, if relevant[67]. On the basis of the best available evidence, the report should clearly differentiate between recommendations of approved therapies versus suggestions to consider experimental treatments and appropriate clinical trials[68]. This effort needs to be synchronized with a drug-access infrastructure and well-defined pathways to connect the patient with professionals who can consider their suitability for clinical trials[69]. The obvious obstacles for the implementation of MTBs are difficulties in obtaining multidisciplinary expertise, as well as logistical challenges in community practices, particularly at small institutions. Accurate annotation of actionability in clinical genomics reports and the previously discussed genomic knowledgebases could optimize the clinical interpretation of genomics data at the level of the individual patient at the point of care; these are critical steps toward the implementation of precision medicine at institutions that may not have access to in-house expertise in clinical genomics. Other innovative solutions, such as remote participation in virtual MTBs of reference institutions, could also partially resolve this limitation and facilitate the referral of patients with low-prevalence biomarkers to drug-access programs and clinical trials[70].

Precision oncology and the patient journey

Physicians have a valuable role in guiding patients who are navigating their disease journeys. However, the challenges that healthcare professionals face in interpreting molecular and genomics test results could impact interaction with patients, potentially raising reservations on the patient's side about innovative approaches. Beyond physician education, there needs to be investment in understanding and improving the patient's experience in the delivery of precision oncology in clinical practice.

When discussing genomic testing with patients, it is important to communicate accurate information in language that is accessible, helping to set reasonable expectations and build confidence for shared decision-making. Information empowers patients to express their preferences and evaluate their options; in this setting, discussions should include details about the test procedure, potential risks and benefits, limitations, and possible consequences of the results[71,72]. Patients should be made aware of potential challenges in accessing drugs that could be indicated on the basis of their test results, particularly when access to a certain treatment

may be restricted to clinical trials; in that setting, patients may need to consider additional factors before making an informed decision. Potential repercussions of testing include the identification of variants that can have implications beyond treatment selection, some of which may point to inherited alterations that require confirmatory germline DNA testing and can be relevant not just to the patient but to their family members as well. All these issues raise ethical and practical questions about whether and how these results should be reported[71,72]. It is important to have a management plan for these 'incidental findings' in place when introducing a CGP test in clinical practice, and to discuss it with patients upfront. This will require consensus with cancer-genetics experts and ethics committees, and access to those interventions or consultations that may be triggered by incidental findings must be ensured.

Patient information and engagement in shared decision-making become even more critical for patient groups under-represented in precision-oncology research studies. Ideally, patient advocates and patient support groups should be involved along the development, validation, and clinical-implementation pipeline of new precision-oncology strategies, as well as in the later stages of regulatory discussions, budget decisions, and the design of clinical-service infrastructures for delivery of these strategies. Advocates and support groups can help disseminate advances in clinical practice, critically raising patients' awareness of advances in, limitations of, and access to precision medicine.

Information about genomics-data ownership and adherence to personal-data-protection legislation need to be properly presented to patients, particularly as patients may receive care from different professionals and institutions along their treatment journey. At present, most electronic health-record systems are poorly prepared for the integration of genomics data, and this negatively affects the patient when the information needs to be shared with other healthcare professionals, or when a patient fairly aims to seek additional opinions about the management of their disease.

Conclusions

Precision oncology is advancing rapidly as a research field, resulting in a plethora of new therapeutic options based on genomic and molecular biomarkers. Although the impact on treatment guidelines has already materialized, the delivery of its full potential and impact on clinical practice depends greatly on ensuring wide and equal patient access to diagnostic technologies and therapeutics, beyond a few academic centers in privileged countries.

Progress toward this goal fundamentally requires ways to fast-track research advances into routine clinical practice, to dedicate resources to transform healthcare infrastructures to embrace new resources without increasing health disparities, and to empower patients in shared decision-making. Investing in new assets for healthcare systems, such as clinicogenomic data repositories, and promoting the education of multidisciplinary teams and the development of validated decision-support tools will be critical.

A favorable policy environment that promotes harmonized, fully transparent, validated, and multi-stakeholder-based value-assessment frameworks is also critical; it will inform budget decisions regarding advanced diagnostics and MGTOs and facilitate global implementation of precision oncology, culminating in improved patient outcomes.

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