European Journal of Cancer 187 (2023) 99–104

Available online at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Current Perspective

Do more targets allow more cancer treatments, or not?

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Received 6 March 2023; Received in revised form 31 March 2023; Accepted 31 March 2023
Available online 7 April 2023

KEYWORDS
Mutation;
Genomics;
Next-generation sequencing;
Antineoplastic agents;
Sub iudice;
Access to treatment

Abstract The three current oncology models (histological, agnostic and mutational) mainly differ in clinical, technological and organisational aspects, leading to different regulatory procedures and implications in antineoplastic therapy access by patients. Within the histological and agnostic models, Regulatory Agencies authorise target therapies and define their price, reimbursement, prescription and access based on results from clinical trials including patients affected by the same tumour (histological) or subjects with specific genetic mutations regardless of the tumour site or the histology (agnostic). The mutational model has been developed to identify specific actionable molecular alterations found by next-generation sequencing test-based large platforms on solid and liquid biopsies. Nevertheless, due to the highly uncertain efficacy and possible toxicity of drugs tested within this model, regulatory procedures based on histological or agnostic oncology cannot be followed. Multidisciplinary skills are required (e.g. the molecular tumour board's (MTB) representatives) to identify the best association between the genomic profile and the drug planned to be used, but quality requirements, practices and procedures of these discussions still need to be standardised. Real-world evidence from clinical practice (i.e. genomic findings, clinical data and MTBs' choices) lacks, therefore, it is urgently needed as opposed to limited findings from clinical trials. A potential solution for an appropriate access to the therapy chosen by the mutational model can be the indication-value-based *sub iudice* procedure of authorisation. The access to therapies suggested by extensive molecular profiling could be easily implementable within the Italian national health system, thanks to the existing regulatory procedures, i.e. the managed-

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https://doi.org/10.1016/j.ejca.2023.03.041
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entry agreements and the antineoplastic drug monitoring registries, alongside those granted by conventional studies (phase I, II, III, IV) conducted according to the histological and agnostic models.
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Oncology is experiencing a rapid and radical change and success in cancer treatments due to the evidence of complex and distinct molecular alterations that characterise advanced and metastatic cancers and require matched treatments rather than standard therapies. Despite unavailable evidence on the clinical significance of a specific mutation in a specific tumour, the use of next-generation sequencing (NGS)-based large panels increases alongside decreasing costs of genomic profiling tests [1]. In particular, rather than trying to increase the number of possible therapeutic agents, often devoid of real clinical utility, this information should be properly used, by integrating the authorisation models already available [2,3]. A renewed regulatory strategy is necessary to ensure that patients rapidly receive the best treatment under the optimal access conditions.

To date, the research, market authorisation (MA), access and prescription of cancer drugs are managed within the framework of the histological and agnostic models that involve the use of drugs in the presence of a specific genomic alteration originating from positive results of prospective studies. Whereas, the recent mutational model still lacks of an explicit definition, since it is based on a possible response to targeted therapies, often without any preliminary evidence of activity in a specific type of tumour.

The aim of this report is to describe the main differences between the oncology models in terms of clinical, technological and organisational aspects for moving confidently across the different regulatory issues and their implications in therapy access. Moreover, a possible way to overcome the current barriers in accessing new oncological treatments within the terms of the newest mutational model and the framework of the Italian National Health System (INHS) is suggested.

1. Histological and agnostic model

In the settled histological and agnostic models, similarly to all centrally-approved drugs, the Regulatory Agencies (RAs) evaluate the results of prospective studies and allow the use of a target therapy in a specific clinical context. The Committee for medicinal products for human use (CHMP) of the European Medicines Agency (EMA) provides the MA through European countries; subsequently, national RAs (e.g. the Italian Medicines Agency—AIFA - Agenzia Italiana del Farmaco) define the price and reimbursement (P&R) modalities, and the prescription and access procedures (Fig. 1).

Within the histological model, evidence of MA and P &R come from prospective clinical trials (CTs), where plain or associated antineoplastic drugs are tested for specific cancer sites and tumour stages, according to the treatment lines (i.e. adjuvant, neoadjuvant and metastatic phases). Based on this approach, additional chemotherapies and therapies guided by specific molecular biomarkers linked to the cancer site (e.g. anti-HER2 (Human Epidermal Growth Factor Receptor 2) monoclonal antibodies or HER2 tyrosine-kinase inhibitors for HER2-amplified breast cancer) or immunohistochemical biomarkers (e.g. PD-1/PD-L1—programme cell death-1 and its ligand) [1,4] have been approved.

Whereas, within the agnostic model, evidence for MA and P&R come from specific genetic mutations regardless of the tumour site or the histology [5].

In Europe, for both models, the MA is granted by the EMA and P&R is defined by national RAs (Fig. 1), which establish also the prescription rules of antineoplastic drugs (i.e. by oncologists). In Italy, the prescription of several new antineoplastic drugs is monitored by registries, with the aims of ensuring the appropriateness of drug use, monitoring the effectiveness and safety outcomes of a new drug and allowing the payment according to the Managed Entry Agreements (MEAs), whether they are financial or outcome-based.

By now, in Europe, following the (tissue-) agnostic model, larotrectinib and entrectinib are authorised based on the inhibition of the oncogenic fusions involving the neurotrophin receptor tyrosine kinase (NTRK), while pembrolizumab as monotherapy for the treatment in adults of some microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumours [1] (i.e. cancers that are advanced, have spread or returned, are not responding to other treatments or cannot be removed by surgery [6]).

Finally, these two models are based, at least for some tumours (e.g. NSCLC - Non-Small Cell Lung Cancer - or biliary tract carcinoma), not only on the identification of few predictive factors of response to targeted drugs through several single gene testing, but more frequently on the use of small NGS panels. The latter are able to detect genomic alterations that allow the use of molecular targeted drugs that are previously authorised or otherwise available, for example, in

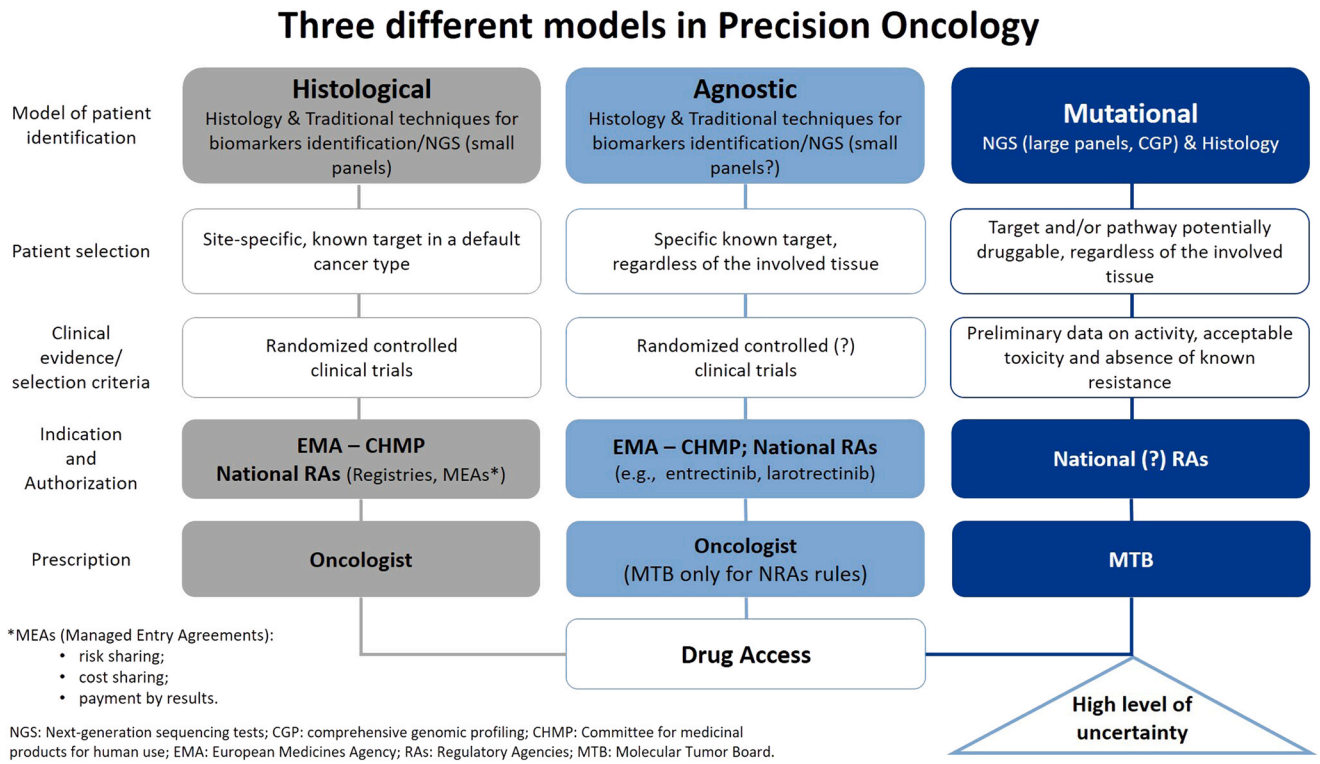


Fig. 1. The main differences between histological, agnostic and mutational models in oncology.

compassionate use programmes or in clinical trials performed in the same country of use or in Europe.

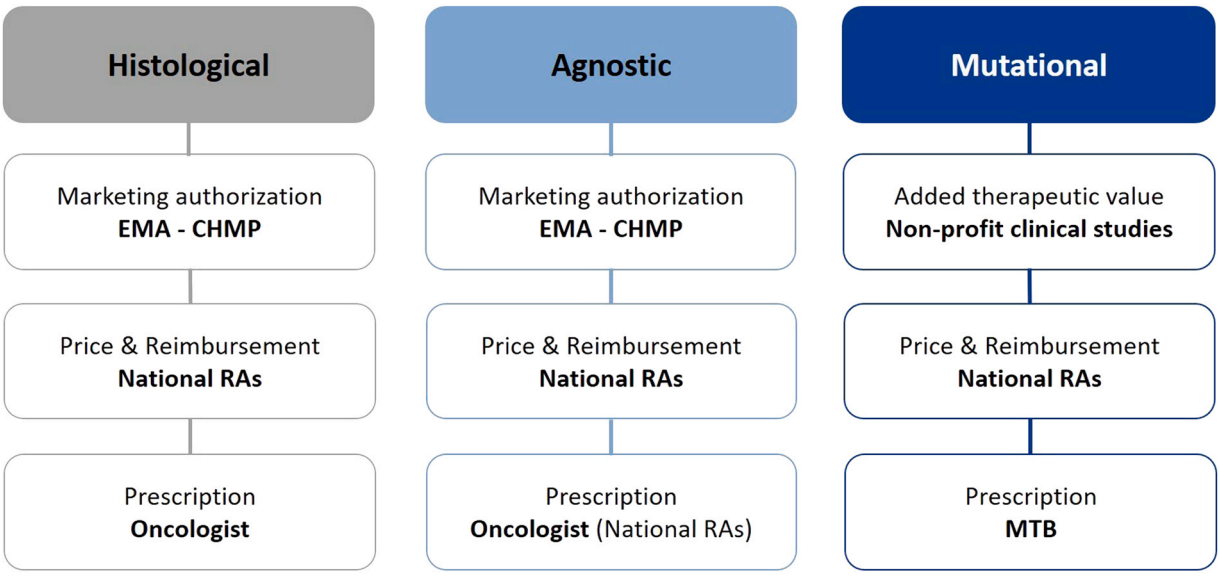
2. Mutational model

The need for more comprehensive tests to guide the therapeutic choices has brought to the development and spread of NGS tests based on ever larger panels. Given the considerable number of different tumours, NGS-based large panels were also useful to identify some predictive response factors to choose the most specific antineoplastic drugs that are already authorised in other clinical context [1].

Within this panorama, the most recent mutational model, which is based on the identification of specific *actionable* molecular alterations found by NGS-based large platforms on solid and liquid biopsy (i.e. WGS - whole genome sequencing, WES - whole exome sequencing, CGP - comprehensive genomic profiling), has been developed [1]. However, the effectiveness of the chosen drug could depend not only on the identified *actionable* mutation, but also on the tumour site and presence of resistance mechanisms; the case of the lower overall response rate (ORR) achieved in patients treated with vemurafenib and affected by BRAF (v-raf murine sarcoma viral oncogene homolog B1) V600-mutant colorectal cancers (5% ORR) [7] compared with those affected by BRAF V600E-mutant melanoma (~50% ORR) [8] or non-small cell lung cancer (38% ORR) [9] is emblematic. Therefore, given the high level of uncertainty of both the efficacy and the possible toxicity of the drugs within the mutational model, the MA and P&R procedures based on histological and agnostic models (Fig. 2) cannot be followed. In this regard, the ROME (Road to Personalize Target Therapy and Immunotherapy) Trial has preliminarily analysed 1319 patients enrolled from 40 Italian sites, showing that 316/721 (44%) subjects with relevant genomic alterations and discussed by the Molecular Tumor Board (MTB) were treated without any approved and reimbursed therapy for their specific mutation or cancer site [10].

Too often the first question asked when discussing NGS is 'Who pays for the test?', while the correct question should be 'What is the clinical utility of large panel NGS in this patient?' Considering the continuous decrease in the costs of extensive NGS profiling, it would be probably sufficient to reallocate economic resources available from an improvement of the diagnostic therapeutic process. Moreover, an economic coverage of NGS tests could also be discussed and agreed with the pharmaceutical companies that produce drugs with a molecular target, also through a specific national fund, if this is of benefit to a better use of targeted therapies.

To achieve the goal of tailoring treatments to patients based on their genomic profile, multidisciplinary skills are required, such as those represented in the MTB (i.e. oncology, pathology, pharmacy, clinical genetics,



CHMP: Committee for medicinal products for human use; EMA: European Medicines Agency; RAs: Regulatory Agencies; MTB: Molecular Tumor Board

Fig. 2. Marketing authorisation, price and reimbursement, prescription and drug access within the three models in oncology.

molecular biologists, translational research, scientists, bioinformatics and data scientists) [11]. MTBs aim to identify the best association between the genomic profile and the drug planned to be used, considering the highly complex assessment of the NGS results, in terms of types and number of alterations, MSI, and tumor mutational burden (TMB) combined with histological evaluations (e.g. HER2 low or PD-L1 status). In particular, the MSI and TMB values can address to an immunological therapy [12,13]. Interestingly, it has been reported better ORR, time to treatment failure (TTF), progression-free survival, or overall survival in patients receiving an MTB-recommended therapeutic strategy than in subjects treated without an MTB-guided choice [3].

Despite the increasing use of NGS-based large panels (i.e. WGS, WES and CGP) [1,2,14], eligibility criteria for patients' access to NGS tests and MTBs' discussions are still not standardised [12]. Usually, panels encompassing roughly 300/500 genes allow to capture most potential biomarkers for targeted drugs, the TMB and the MSI. Contrarily, WES and WGS are not likely to enter the clinical practice soon and, for the time being, are limited to research setting. Eligibility criteria can be life expectancy of > 6 months, acceptable performance status (0–2 ECOG - Eastern Cooperative Oncology Group - Scale) and absence of any available and reimbursed treatments according to histological or agnostic models, if adequately explored, as previously explained [11–13,15]. The recently defined ESMO (European Society for Medical Oncology) scale for clinical actionability of molecular targets (ESCAT) should also be included as a rational and evidence-based decision-making support to identify genomic alterations with respect to their potential targeted anticancer therapies [16].

The uncertainty at the basis of mutational model's therapeutic strategies and the absence of standardised quality requirements, practices and procedures of MTBs call for evidence from clinical practice (real-world evidence—RWE). In this scenario, genomic findings, clinical data and related MTBs' therapeutic choices represent real-world data (RWD) extremely important for building and implementing the knowledge and for addressing future researches.

A major criticism of the clinical research is that CTs do not represent the 'real-world' population, given their restrictive criteria and the limited analyses framed to answer specific questions that often do not apply to real-world patients. Attempts have been made to close the gap between CTs and the real life. It is, however, important to distinguish between the RWD generated by daily clinical practice and standard cares, and the RWE originating from RWD (e.g. regarding the potential use of a product). In particular, RWE is produced by pragmatic trials and prospective and/or retrospective observational studies.

Finally, new strategies should be introduced to ensure the appropriate therapy access within the framework of the mutational model. In this regard, RWD sets may represent the key to address the uncertainties of the mutational model and to overcome the current barriers of the histological and agnostic models' MA and P&R procedures, which are instead based on evidence from CTs [17].

3. The antineoplastic therapeutic value-based governance

Based on the mutational model, variations of the expected benefit and the cost of the same antineoplastic treatment for different indications (i.e. molecular alterations) [18] are challenging in terms of access and P&R, which are already variously but insufficiently addressed by European countries [19]. To date, only the universal-coverage INHS has developed a pharmaceutical governance approaching (despite still not completely) an indication-based pricing (IBP) system, which applies differential pricing when the value of a drug for each indication is reflected (I-VBP, Indication Value-Based Pricing) [20], particularly efficient for antineoplastics. The I-VBP system can make easier drug access, more appropriate prescriptions, fairer and more sustainable health systems (from the payers' point of view), and foster more studies on new drug indications [20].

The I-VBP system is based on two pillars [21] included in the currently implemented INHS regulatory procedures:

- MEAs: pharmaceutical company and payer (AIFA in Italy) agree that the MA of some new medicines and their P&R are closely related to the evidence on therapeutic benefits and consumption volumes;
- AIFA Monitoring Registries: an IT platform accessible by prescribers and pharmacists, which collects information about appropriateness, clinical and therapeutic follow-up of new drugs.

Starting from this advanced Italian context, a new regulatory approach to govern the timesaving decision, an early and wide access and the reimbursement of an MTB-recommended treatment not already authorised for a specific molecular aberration, can be imagined.

This should consider the uncertainty of conclusions based on few patients, short observational periods, possible phase-1 CTs, case reports, mutations in different tumour sites or even the absence of any CT, and incomplete predictive drug response with respect to the morphological characteristics and mutational profile of cancer. In case of scarce or even absent evidence, also the price cannot be defined a priori.

Therefore, the *sub iudice* authorisation procedure can represent a potential solution, according to the following suggested regulatory steps:

- Step 1—The drug access is totally charged to the pharmaceutical company for an acceptable number of patients during the observation time period resulting from Step 2, because of the absence of the MA dossier and the inability to apply for P&R. However, it is not definitive, since strictly dependent on Step 2;
- Step 2—The added therapeutic value can be assessed through the supply to pharmaceutical companies of findings from non-profit CTs (e.g. ROME Trial [10]) and observational studies (e.g. SMARTCare Project - Soluzioni e Metodi Avanzati di Riorganizzazione Territoriali in Sanità, or the Italian MTB Virtual Consultation System—MTB VCS ITA Project) used for MA purposes. Ongoing and future studies on genomic profiling should produce outcomes on ORR or TTF and consider a case-control methodology based on which a patient is the control of him/herself in respect of his/her previous treatment;
- Step 3—Pharmaceutical companies can apply to national RAs for P&R with a dossier built on findings from non-profit CTs and observational studies performed for MA purposes (e.g. in Italy according to a specific Decree of the Italian Ministry of Health for facilitating non-profit studies [22]). Collected data from the use in the real life would provide useful cut-offs to help the national RAs to determine effectiveness and safety for the MA dossier.

The *sub iudice* procedure could be implemented at national level. In particular, in Italy, the already existing I-VBP system, based on MEAs and AIFA Monitoring Registries, would easily enable its implementation.

Moreover, the suggested methods of recruitment, and assessment and use of genetics-guided antineoplastic therapies not yet authorised, should run in parallel with a systematic collection of RWD on effectiveness, resource consumption and safety, which should be shared to be interpreted and translated in clinical guidelines, and then in RWE useful to regulatory MA, access and P&R procedures. The development of at least one national platform (e.g. the one currently in use in Italy within the MTB-VCS-ITA Project) where all data could be merged, could build a clinical wisdom that would become a unique therapeutic opportunity [2,11].

Finally, the suggested model of governance presents cost-saving opportunities that could be larger when considering the societal perspective.

4. Conclusions

The mutational model may represent a challenge to the already established histological and agnostic models in oncology. The *sub iudice* procedure could overcome the actual barriers, enable the access to the target treatments, and generate a huge amount of RWD useful for a renewed patient-centred pharmaceutical governance.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Paolo Marchetti: Conceptualisation; Writing – original draft; Writing – review & editing. **Giuseppe Curigliano**: Writing – review & editing. **Silvia Calabria**:

Visualisation; Writing – original draft; Writing – review & editing. **Carlo Piccinni**: Visualisation; Writing – original draft; Writing – review & editing. **Andrea Botticelli**: Writing – review & editing. **Nello Martini**: Conceptualisation; Writing – original draft; Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **PM** declares grants to his Institution from Roche, BMS, Pfizer, Incyte, Novartis, Takeda, MSD, Pierre Fabre; Personal payments from Roche, BMS, MSD, Novartis, Pfizer, Pierre Fabre; Personal support for congress attendance from BMS, Roche; is President of the Italian Foundation of Personalized Medicine, of AIOM Servizi s.r.l., of the Steering and Verification Board of the 'Regina Elena' National Cancer Institute. **GC** declares grants from Merck; consulting fees from BMS, Roche, Pfizer, Novartis, Lilly, Astra Zeneca, Daichii Sankyo, Merck, Seagen, Ellipsis, Gilead; payment for lectures from Lilly, Pfizer, Relay; support for attending meetings from Daichii Sankyo. **AB** declares grants, consulting fees and payment for lectures from BMS, Pfizer, Roche, Lilly, Novartis, Msd, Seagen, Gilead; participated on a Data Safety Monitoring Board or Advisory Board for BMS, Pfizer, Roche, Lilly, Novartis, Msd, Seagen, Gilead. All remaining authors have declared no conflicts of interest.

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