

Article

Precision Medicine: From “Omics” to Economics towards Data-Driven Healthcare – Time for European Transformation

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Keywords

Affordable care · Drug development · Omics

Abstract

There is room for improvement for optimally bringing the latest science to the patient while taking into account patient priorities such as quality of life. Too often, regulatory agencies, governments, and funding agencies do not stimulate the integration of research into care and vice versa. Re-engineering the drug development process is a priority, and healthcare systems are long due for transformation. On one hand, patients need efficient access to treatments, but despite precision oncology approaches, efficiently shared screening platforms for sorting patients based on the biology of their tumour for trial access are lacking and, on the other hand, the true value of cancer care is poorly addressed as central questions such as dose, scheduling, duration, and combination are not or sub-optimally addressed by registration trials. Solid evidence on those parameters could potentially lead to a rational and wiser use of anti-cancer treatments. Together, optimally targeting patient population and robust comparative effectiveness data could lead to more affordable and economically sound approaches. The drug development process and healthcare models need to be interconnected through redesigned systems taking into account the full math from drug development into affordable care.

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What Are the Uncertainties for Multidisciplinary Clinical Research and Drug Development?

Clinical research has seen remarkable evolution in the last few years. The growth of knowledge at unprecedented speed with the emergence of new technologies has enabled greater focus on the identification of mechanism-based therapies, changing a number of paradigms. Over a few years, empiric drug development in a single clinically and pathologically defined disease has been challenged by access to specific molecular-defined subsets of patients or histology-agnostic approaches [1]. This is particularly true for cancer clinical research, often referred to as a model for precision medicine, since the understanding of the biology of the tumour and the microenvironment allows more rational drug development. Therefore, clinical research is today a complex cooperation of disciplines, including genomics and imaging, adding to the already multidisciplinary study teams. Despite major progress in various types of cancer, a number of challenges and questions remain, such as understanding the patterns of resistance or relapse and coping with disease heterogeneity. The need to answer such questions has become more obvious since the increasing availability of therapeutic compounds per indication makes optimisation of their use necessary. It has been demonstrated that the evolving complexity of tumour biology during the evolution of the disease makes the process of drug development, including the sequence and combination of anticancer treatments, a much greater endeavour that anyone would have anticipated [2]. Different cancer types are not necessarily driven by similar pathways, while the micro-environment also plays a different role depending on the tumour type and the stage of disease evolution. In addition, immunotherapy has recently further changed the paradigms. While precision medicine treatments have been developed, there is still no cure for most forms of advanced cancer, making continuous or frequent treatment necessary. The long duration of different treatment modalities and compounds expose patients to mechanism-based side effects, including low severity but sustained side effects. Expensive new therapeutic weapons and sub-optimal knowledge on how best to use them and their toxicity profiles impact on the finite resources of our healthcare systems.

All the above changes and observations indicate that our current models for drug development may no longer be suitable to face the next challenge. We have already proposed a new model being referred to as the diabolical shape (Fig. 1) which pleads for a different approach to drug development [3]. Coming from an era of empiric development with clearly separated sequential steps where attrition rate and mainly late attrition of potentially promising agents in their phase of development is frequent, a number of unanswered questions have emerged. Is the classical phase I, II, III process still adequate? How to access efficiently sub-groups of molecularly defined patients? How to optimise translational research in clinical trials? What are the pre-analytical requirements for acquisition, handling, and storage of biological samples? How do biological and imaging biomarkers need to be developed? What are the adequate steps for analytical and clinical validation of a biomarker and the related assay? How to determine cut-off values for the clinical decision process? What is the impact on clinical trial designs and optimal assessment of clinical utility? How will the process of drug registration and access evolve? How will new treatments be valued in light of their true benefit in real life?

These questions are pointing at a significant increase in the complexity of cancer drug development. Therefore, a thorough revisiting of the models of research and development as well as new comprehensive partnerships between and across stakeholders involved in the process of drug development and access to treatments are needed. Addressing inefficiencies and increasing the value of patient-centred drug development need multidisciplinary and inter-professional cross-fertilisation based on new education principles [4] as well as political support.

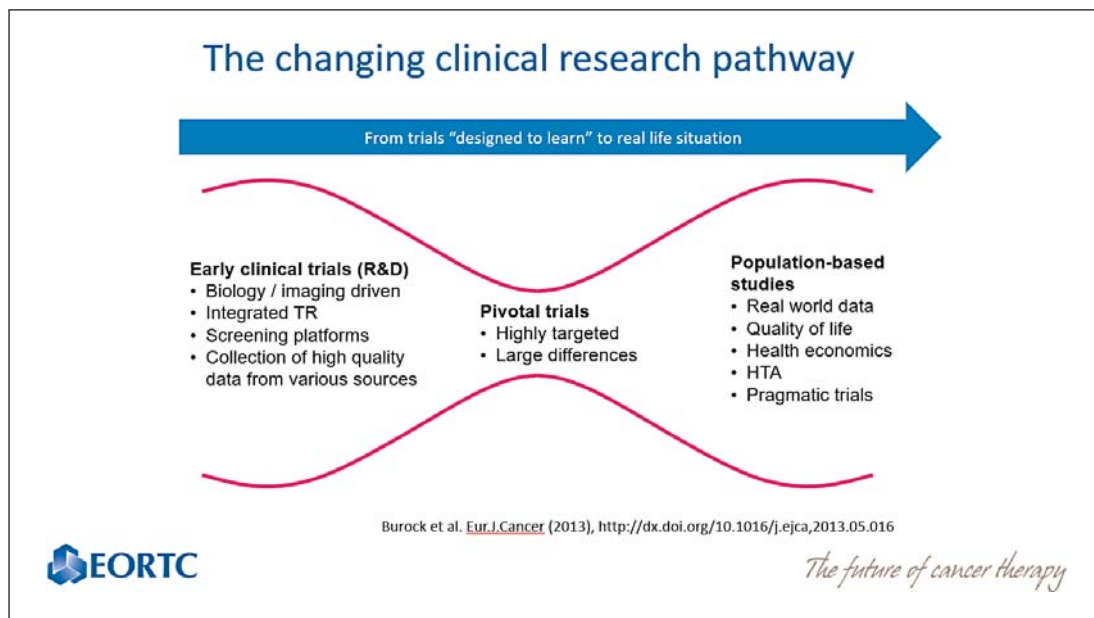


Fig. 1. New developmental schemes based on the understanding of the disease leading to informed pivotal trial designs and opening up to real-life issues. The diaboloid shape indicates the magnitude of efforts and methods to understand the mechanisms of action of treatments and illustrates the need for the understanding of real-life issues. R&D, research and development; HTA, health technology assessment.

The Next Challenges: Taking a Holistic Approach along the Continuum of the Disease

Patient management and care, rather than drug development, should be the centre of the process as we move into patient-centred clinical research. Patients must remain the focus throughout the process as streamlined solutions from research into healthcare are developed. Patient needs are multiple and most commonly do not depend on a single drug at any point in time and certainly not along the evolution of the disease. Therefore, the concept that drugs are developed with the sole purpose of market access, not anticipating the open questions beyond registration, needs to be revisited. Indeed, in the case of cancer, but largely applicable to other diseases, a single agent will not suffice to treat the disease. Questions such as combinations and sequence of new and old drugs or other therapeutic modalities need to be addressed, so that the strategies for the implementation of a new agent in the therapeutic armamentarium are optimised. This highlights the need for profound transformation of the drug development cycle.

The Continuum of Care and the Continuum of Disease Evolution: New Math

There is room for improvement for optimally bringing the latest science to the patient [5] while taking into account patient priorities such as quality of life. Avoiding exposure to treatments from which patients are not expected to benefit, looking at the dose and scheduling and defining optimal duration of treatments for instance are critical aspects which are not priorities of drug developers. Too often, regulatory agencies, governments, and funding agencies

do not stimulate the integration of research into care and vice versa. Similarly, the pharmaceutical drug development process remains protected during the competitive phase, placing drug development priorities before public health issues when the continuum of care would require early consideration, a broader view, and a more comprehensive approach. While preserving the interest and needs of all stakeholders, a substantial waste of knowledge and resources must be avoided. For instance, the MINDACT trial [6] has demonstrated that a specific genomic signature can avoid undue exposure to toxic chemotherapy for early breast cancer while not compromising therapeutic outcome. This obviously impacts on the quality of life of a patient not experiencing in vain the toxicity of chemotherapy while decreasing prescriptions and costs of treatments. These types of public health trials are currently given attention in the drug development process.

Why Our Current Systems Have Reached Their Limit

Neither individual clinical expertise nor unstructured research is enough in isolation to inform good clinical practice [7]. The emerging treatment complexity makes clinical trials narrowly targeting drug registration inadequate to inform practice, and therefore clinical practice is necessarily simplified to a set of more or less coarse guidelines. A revisited model of development to tackle the issues described here for a new continuum of drug development would need to integrate a second dimension into the first one, taking into account disease evolution reflecting real life. Rather than a snapshot clinical stage/treatment allocation, patterns of relapse and evolution of the biology need to be taken into consideration, and a rational approach of successive treatments needs to be built in our systems.

This proposed principle takes into account the following facts:

- For the first drug-oriented dimension, different models of drug development approaches planning early on for the real-life impact are gradually becoming possible, alongside the proposed diabolical shape model, through which pragmatic questions for daily implementation of a new agent into the standards of care are an integral part of the process.
- The second dimension focusing on the patient and the disease evolution is closer to the art of medicine. It requires that questions central to patient care are being addressed early on to optimise the use of treatments in real life. A number of questions central to patients and healthcare providers are not addressed during the drug development process such as, but not limited to, treatment duration or combinations. These are critical issues for health technology assessment of the true added medical value of new treatments. Efficient comparative effectiveness research which could be referred to as applied clinical research [8] is needed to bridge drug development and real life, offering a tighter link into real life as well as ensuring long-term patient safety and monitoring long-term outcome.

Innovative mechanisms are greatly needed globally and in particular in Europe to ensure that patient dimension becomes one of the key drivers, as well as ensuring synergies, notably for rare entities. Indeed, innovation is no longer the issue; access to innovation is the next challenge. New rules [9] and frameworks need to be re-engineered.

Methodology and Alignment of Competencies: An Opportunity Not to Be Missed!

The next challenge is to ensure a healthy alignment of competencies, which will help in identifying those research findings which will lead to better and affordable health. Solutions that bring the latest science from research to care will require new partnership models where

stakeholders work on a more open agenda even in the early stage process of development [10] and greater sharing of information [11–13]. Approaches to integrate early stage research and pragmatic research aiming to improve effectiveness and public health values are being proposed [14, 15].

High-technology clinical trials to define the role of biomarkers [16] and new statistical and study designs are emerging [17–19], but the needs of the ultimate users, i.e. the patients, must remain the driving force. The European Medicines Agency has been creating new solutions such as Medicine Adaptive Pathways for Patients (MAPP) and thinking into solutions to address effectiveness [20–25]. It may be claimed that these approaches remain drug centred. A number of issues remain unaddressed such as optimal access to clinical trials for small groups of patients, level of certification for cut-off values of biomarkers, and external validity of clinical trials. Siloed drug development mostly remains oriented to market access and does not take into account clinical management, access, or affordability. Therefore, while new regulatory approaches are part of the solutions, they may not have taken into account the broader view of patient needs.

Protocols are written to develop a certain agent and/or answer a certain question. When ready, they are activated to find eligible patients to match often very complex eligibility criteria, leading to clinical trial populations that differ significantly from the intended patient population. It seems intuitive that having as much information as possible about the patient and the disease would allow efficient allocation of these patients to appropriate therapeutic protocols. This can be achieved through models such as clearing house type of platforms integrated into healthcare systems, sorting patients as scientific knowledge develops. Patients in real-life settings would therefore be better targeted towards an appropriate match between disease biology and treatment.

Is Europe Ready to Move to Patient-Centred Research?

In addition to MAPP, the EU commission has released the PerMed report [26], and the European Council has published conclusions on personalised medicine [27]. Finally, the Innovative Medicine Initiative [28] (IMI) has successfully piloted pre-competitive partnership models which have embraced the challenges of personalised medicine. Europe can build on these initiatives which all point out to the needs of integrating data through all the omics disciplines, provide solutions for European-wide biomarker assessments and ensure longitudinal studies in line with the continuum of the disease.

Cancer represents the group of diseases where precision medicine has probably contributed the most so far. Existing cancer-specific infrastructures such as the European Organisation for Research and Treatment of Cancer (EORTC) have more than 50 years of track record in clinical research and therapeutic progress. Such infrastructure able to collect and analyse data should be seen as a tremendous asset to build solid innovative solutions that will address the challenges and fragmentation depicted hereto [29]. In addition, solid infrastructure with appropriate auditable procedures allows partnership with other similar organisations, a key element for benchmarking quality assurance procedures for all types of large-scale omics testing platforms which have been mapped by the Global Alliance for Genomics and Health [30], e.g. the EORTC Screening Patient for Effective Clinical Trial Access (SPECTA) [31].

A Proposal for Building a Large-Scale Interconnected Platform: The Centre of the Transformative Process for Precision Medicine

The evolution of more effective clinical research requires a completely different approach to address feasibility in dealing with multiple small subsets of patients. Planning for such trials in silo will lead to failure. Similarly, the feasibility of multiple large-scale omics platforms is uncertain due to their costs, the multiplicity of technologies, and the rapidly evolving science. Actually, the number of clinical trials they have been able to facilitate so far is rather low compared to the investment [32]. Working on complex platforms, which are centred on the biology of the disease is challenging, as the current regulatory field in Europe is not ready to optimally accommodate them [33, 34]. Europe should give consideration to developing solutions to efficiently sort patients and screen and provide access to European biology-based clinical trials which would be plugged into such coordinating infrastructure [35]. Multiplication of screening programs is inefficient and is currently one of the major contributors to waste.

A substantial benefit to be enforced is that patient-centric approaches would allow biological material to be only accessible and collected for entry in clinical trials through independent and collaborative platforms such as SPECTA, whose mission would be generating knowledge and structuring data facilitating data sharing and partnerships. It would be ensured that patients have access to the most suitable trial for their disease with regard to the choice of the drug but also for technological measurement of the target [36].

Partnership and Business Models of the Future

There has always been a delicate balance between pharmaceutical innovation and access [37] to drugs, but principles of new business models taking into account the interest and the needs of all stakeholders have been proposed [38]. Today, such business models must optimally anticipate effectiveness and real-life issues. This is why early drug development from access to patients to implementation in the healthcare systems must be profoundly transformed with optimisation of the skills of all partners and be patient centric. Drug development is no longer in the sole remit of the industry and regulators. Addressing the questions we have postulated cannot be done when multiple new drugs are made available on the market. Optimal therapeutic options are not limited to a single agent, and patients will face a different disease each time it recurs. New frameworks are desperately needed to be able to profit from the emerging complexity [39] and progress in very specific clinical situations [40] as well as specific issues such as optimal combinations and duration of treatments. If the dose, schedule, and duration of treatment of expensive anticancer treatments were optimised, the impact on value and economics would be tremendous. But registration trials presented to regulatory agencies are unlikely to address such questions, which are however of primary concern to healthcare providers. Evidence has to be shown, as such knowledge will not emerge from routine practice, and real-life programs have so far not turned into convincing natural experiment.

Impact and Expected Deliveries of Innovative Platforms

At a time when pricing is an issue, placing first critical real-life questions will allow to anticipate quality of care and affordability and may possibly sustain a pay-for-performance approach. For instance, a permanently functioning omics clearing house could not only

allocate patients to clinical trials but also be a unique source of knowledge development for biomarkers and assays. Patients not entering a clinical trial, in a real-life setting could be equally monitored and help benchmarking new treatments, hence ensuring surveillance of the continuum from research to care. This has proven to be an attractive model for the commercial sector [41, 42]. Regulators would also benefit from solutions that bring MAPP closer if not integrated into platforms that would help qualify and validate biomarkers [43]. Patient-centred and continuum of care solutions will inevitably lead to patient empowerment as highlighted in the PerMed report and now recognised as an asset for both therapeutic progress [44] and evolution of the regulatory framework [45].

Conclusion

The issues of drug development are too complex to be tackled in isolation. It has been emphasised that an international approach of healthcare systems embracing the challenges of all stakeholders would be more efficient [46]. Big data and optimised information technology solutions through more centralised platforms would help manage the efforts to maintain such goals for the patients [47]. Decisions taken exclusively from real-life data carry uncertainty and have been demonstrated to overestimate treatment effects. Healthcare systems cannot afford such uncertainty and therefore are prone to sustain continued solutions from research into care, which is the only way to improve efficiency and reduce waste [48, 49].

It is critical that independent information is captured for all types of clinical, biological, and imaging data and records alongside biomarker test results and all therapies received in databases which are constantly maintained for high quality. Developing such knowledge is only feasible through highly centralised platforms which ensure high quality for qualification and validation of biomarkers. This would allow not only optimal access to forefront clinical trials but would also enable benchmarking clinical research and real life. It is urgent that European bodies which have the capacity to stimulate such happening get their acts together if we want to make precision medicine a given rather than a fortuitous happening, generating false hope for the patients and the scientific community.

Our current systems are based on protocols searching for specific patient groups, but we need to turn to solutions where patients can be screened based on the latest science for treatment/protocol entry matching their disease. This can be best achieved through the alignment of competencies which reside in different stakeholders. We propose to re-discuss the architecture of the process from “omics” to health technology assessments and economics based on outcome-focused systems, which anticipate the real-life questions early on in the development. Using anticancer treatments wisely will inevitably impact on the value of cancer care and healthcare systems. The points highlighted in this paper can be best summarised by the 10 statements developed in the Appendix.

Appendix

1. Access to patients for clinical research needs new set-ups for rapid identification of patients by sub-groups in a pre-competitive manner for rapid assignment according to target, treatment, and/or trials in the best interest of the patient.
2. Patients need to be informed about the latest scientific advances, and Europe also needs a new set-up to ensure high-quality biomarker identification to allow secured treatment access.

3. New solutions are needed for optimal benchmarking of emerging technologies across and within classes of agents. The concept one drug, one target, one protocol is no longer the way forward.
4. Key questions anticipating the real-life implementation of new drugs need to be addressed early on, i.e. combinations, duration of treatments, type of questions, etc., need to be implemented to optimize optimal delivery and economically efficient use of new drugs with no delay beyond registration.
5. Long-term toxicity monitoring of mechanism-based therapies needs a new set-up beyond registration of drugs and into real life for prolonged time. Clinical research data sets representing a selection of the population provide robust and systematic longitudinal access to data for learning which must then be confirmed in real-life settings.
6. There is no integrated European solution to optimally learn, across cohorts of patients, patterns of resistance and relapse as patients receive treatments and/or enter clinical trials during the evolution of their disease. This is a major limiting factor in addressing one of the key oncology challenges: tumour heterogeneity.
7. Integrated solution would be key in addressing regulatory end-points linked to the current scenario by which the evolution of the disease driven by clonal heterogeneity selection is at stake.
8. Independent data capture for all types of clinical, biological, and imaging data and records alongside biomarker test results and all therapies received, in databases which are constantly curated and annotated, would be critical for benchmarking and validating new clinical trial methodology, as well as benchmarking clinical situations when randomisation may not be possible.
9. Solutions taking the continuum of drug development for optimal access to the forefront clinical trials but that would also enable benchmarking clinical research and real life could be integrated into new processes, where applied comparative effectiveness research supports the decisions taken by Health Technology Assessment bodies and payers, rather than often too artificially designed registration trials.
10. A major transformation of clinical research building on the strengths and complementarity of stakeholders working alongside new business models must be tackled.

Disclosure Statement

The authors declare no conflicts of interest.

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