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Reviews

The new risk-sharing paradigm in rare cancers: Patient perspective

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ABSTRACT

Advances in understanding the biology of rare cancers and in genomic technologies are reshaping drug development and are fostering patients' hopes because an increasing number of drugs are expected to be made available. However, timely patient access to innovative drugs in rare cancers continues to encounter methodological and regulatory hurdles in an environment more and more characterised by limited resources and health systems under pressure. Decisions on drug pricing and reimbursement often delay access to authorised drugs at national or even regional level. Regulatory and economic issues raise ethical problems. Rare cancer patients have a right to the same quality treatments as all other patients: the higher degree of uncertainty, due to the so-called "intrinsic lack of or defect in evidence" of these diseases, should be addressed by all the different stakeholders to prevent it from being the cause of discrimination against these patients. This challenging goal may be achieved by the adoption of the new ongoing paradigm able to take into consideration both the interdependence of all parties involved, their different drivers and their capability of risk-sharing, starting from the real "core driver," which can be summarised in the words of a patient: "When you are faced with a rare cancer, you really can't wait."

Contents

1. Introduction

Rare cancers account for as many as 20–22% of all new cancers diagnosed [1]. With the ongoing evolution in the understanding of cancer biology and the associated changes in the taxonomy of malignant disease, these numbers probably underestimate the incidence of rare cancers.

New insights into the biology of rare cancers have led to greater knowledge and to the development of new targeted agents [2,3]. This "molecular revolution" has been fostering patients' hopes because it is expected to make an increased number of drugs available to them. Instead, the gap between bench discovery and bedside application appears to be expanding. Despite the tremendous progress made in the last few years, timely patient access to innovative drugs in rare cancers continues to encounter methodological and regulatory hurdles [4]. In addition, it is limited by economic restrictions due to both the cost of large-sized clinical trials and cost-constrained national health systems. Even when marketing authorisation is obtained, health technology assessment (HTA) and decisions on drug pricing and reimbursement often delay access to medicines at national (or even regional) level [5]. Last but not least, economic issues also raise ethical problems, posing the question of rare cancer patient access to drugs in terms of a social trade-off, that is to say, between the needs and expectations of the individual and society.

Here below are some brief considerations on all of these issues and their interdependence, starting from the economic point of view and its relation with the ethical aspects that arise in rare

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cancers, moving through patient needs, drug development, clinical research and decision-making and the regulatory perspective, up to the new approaches aimed at involving the different parties and drivers. The leitmotiv may fundamentally be identified in the following two factors of complexity: the uncertainty that derives from an intrinsic lack of evidence in rare cancers and the consequent manner in which risk management and sharing are handled, the latter of which is inherent in any decision taken in a situation of uncertainty.

However, the advances in the understanding of cancer biology and consequent reclassification of common cancers, based on molecular and genomic markers, are resulting in the creation of new sub-groups, the so-called rare subtypes, which are becoming increasingly common. That is to say, cancers once generically classified as common are now being reclassified as rare, because smaller groups of patients are being identified both for participation in clinical trials and for the decision-making involved in targeting the relevant therapies. This poses a new challenge for the entire oncological community and, more extensively, for society at large, moving towards a new scenario of personalised medicine in an environment characterised by limited resources [6].

2. Economic evaluation and ethical perspective in rare cancers

Rare cancers are a burden and, at the same time, a challenge for society: even if the resources consumed are not easily quantifiable with precision, they are thought to constitute a major public health problem. As highlighted in the 2010 European Society of Medical Oncology recommendations paper on rare cancers, "*Overall health and social costs can be far higher for patients with rare cancers because effective treatments are not always reimbursed, referrals for second opinions within the public health system are not commonplace and many patients must travel long distances to access appropriate care*" [1,7].

Economic evaluation provides a useful tool for several considerations. In a context increasingly characterised by the scarcity of resources and the need for evidence-based decision-making, it enables the costs and results of a new treatment to be compared with other alternatives [8]. The result of this assessment, expressed as an "incremental index" (cost-result increment) is at the basis of drug pricing and reimbursement policies, and, in wider terms, of decision-making in treatment of any kind [9].

The question which therefore arises consists in establishing the threshold value of this cost-effectiveness ratio that the decision-maker is willing to accept [10]. In cost-utility analysis, which is a more sophisticated approach than cost-effectiveness, a new element appears: the "quality of life". Utility is here measured in "*QALY*", the index that assesses benefits both as incremental quantity (years of life gained) and as quality of life obtained [8].

The aim in defining the threshold value is that of allocating the available resources, beginning with those treatments generating a minimum-cost *QALY* and ending with those that present the greatest cost–*QALY* ratio. The premises for adopting a threshold value for this incremental ratio are fundamentally the following:

- a fixed-budget requirement,
- a maximisation of health outcomes as the main criterion for resource allocation,
- the availability of comprehensive information regarding costs and results [9,10].

According to an evaluation of this kind, it is the size of the fixed budget that determines the threshold value. The focus is on allocative efficiency rather than equity, in particular if defined with regard to access to treatments.

When economic evaluation is carried out on orphan drugs, such as those for rare cancers, the incremental cost utility ratio may however be unfavourable, beyond the acceptable threshold. Other criteria may then be used to make a decision, such as the absence of alternative life-saving treatments and patient inability to sustain, on his own, the cost of a new drug [11]. The NICE for example, in spite of an unfavourable ratio, authorised the use of a new drug to treat CML in the absence of efficacious alternative therapies (with the exception of bone-marrow transplants).

How can the characteristic complexity of rare cancer drugs be reconciled? That is to say, how can a balance among this tendentially high incremental ratio, the "weakness" of significant clinical evidence and the absence of alternative life-saving therapies be reached?

A multicriteria evaluation would allow a variable threshold value to be adopted in relation to the specific disease, the drug itself and the decision-making context, instead of using a fixed threshold value [9,12]. The question which therefore arises is: how much is society willing to pay for a "QALY" in a patient affected by a rare cancer? In short, what value does society assign to a further year of life, weighted for quality of life, for such a patient?

If the decision-making criteria applied are of a utilitarian nature, interpreted as the maximisation of the benefits for society, it is hardly ethical to allocate resources for rare diseases in general, regardless of the cost of the treatment, for a simple question of cost opportunity: in short, their use in an alternative activity would be of greater benefit to society.

It is not by chance that EU legislation [13] has established that patients affected by rare diseases have a right to the same quality treatments as all other patients, affirming an approach based on fairness and not utilitarianism.

Social research reveals that the acceptable threshold value of an incremental cost–utility ratio is generally higher for those treatments to which society attributes a greater social value, in relation to the severity of the disease. Society, that is to say, attributes a higher value to an improvement in health if the number of cases is limited, in conditions of severe illness and the lack of life-saving alternatives, thus evidencing a non-neutral system of preferences [14].

Several elements must be contemplated at this point:

- rare cancers, taken altogether, comprise about 20–22% of all cancers;
- rare cancers and common cancers are in any case cancers, that is to say severe, life-threatening diseases;
- in the economic evaluation of rare tumours, the major problem is the difficulty of measuring effectiveness rather than unfavourable incremental ratio, due to the higher degree of uncertainty inherent in these diseases.

This uncertainty, compounded by the dimensions of the problem, is the key issue. How can it be "measured objectively" in order to allow an appropriate evaluation of costs and results for incremental evaluations, at the same time preventing it from becoming a discriminating factor in the decision-making on resource allocation? The assumption, however, is that "a Qaly remains a Qaly" both for a patient with a common cancer and for one with a rare tumour.

But exactly what does uncertainty mean? How can it be dealt with by all the players/stakeholders involved in rare cancers, so as fundamentally to avoid these patients being discriminated against?

3. Uncertainty in rare cancers: from clinical research to clinical practice

Rare cancers are affected by a so-called "intrinsic lack of or defect in evidence" due, on the one hand, to the limited number of patients, and on the other, to both conventional clinical research methodologies and regulatory constraints. That is to say, a higher uncertainty renders study and, consequently, accumulation of clinical evidence more problematic than in frequent cancers.

The scarcity of patients for each type or sub-type makes it hard to demonstrate the benefit of new drugs in compliance with conventional methodologies, which require large numbers of patients, by definition difficult to put together in rare cancers. The main consequences are therefore two: an elevated risk of failing to gather enough evidence to get a new drug approved and the limited interest in developing new drugs determined by the high costs to the pharma industry of running small trials. The risk of discrimination is therefore much higher for rare cancer patients.

There are, essentially, two ways of dealing with the uncertainty of these diseases:

- one is by using all the available strategies which may enable the application of conventional clinical trial design to rare cancer populations;
- the second is by working on alternative methodologies of clinical research to address the specific challenges posed by rare cancers, aiming to potentially change clinical practice [15].

With regard to the first point, the main strategies consist in:

- maximisation of patient recruitment by organising large-sized clinical trials. For these, extensive international collaborative networks, consistent amounts of funding and engagement of specialist centres that centralise the rare cancer population are needed. These large collaborations are increasingly being performed by Research Consortia [16], such as the ongoing Euro Ewing Consortium [17] and the EuroSARC [18], which are in charge of creating and implementing clinical research programmes and in which, in an innovative manner, Patient Advocacy Groups (PAGs) are key partners, contributing both to disseminate information and support several activities, including patient recruitment [19]. The specific challenges to mounting rare cancer trials, low recruitment and higher costs, are also addressed by some research organisations, like the International Rare Cancers Initiative [20], which helps with development of international, large-sized trials.
- minimisation of sample size or maximisation of the usefulness of evidence. The genetic and molecular alterations, or tumour profiling, in addition to histological subtypes, are allowing smaller selected populations to be identified and are increasingly becoming inclusion criteria for clinical trials for selected treatments. Clinical studies pursuing large benefits should be encouraged by regulatory bodies even where target populations are small, possibly accepting the greater degree of uncertainty due to the paucity of the latter. When large benefits are expected, studies on small selected populations should always have the precedence over large studies on unselected patient groups where only moderate-to-small benefits are anticipated. Research on new drugs should also consider biomarkers as a constituent element, as it could pinpoint those patient populations that would derive remarkable benefits from a specific medicine, thus achieving a reduction in the time and expense involved in the trials [21].

In addition, selection of new surrogate endpoints, external rather than internal controls and adaptive trials may all be instrumental to support conventional trials in the rare cancer population. Adaptive trials, in particular, afford a special benefit, given the difficulty in finding patients for clinical studies and the long recruitment timelines that necessarily follow [22]. In rare cancers, even more than elsewhere, adaptive mechanisms enable new drugs to be developed more easily and faster.

The choice of which strategy is to be used depends on the position of the cancer on a sliding scale of rarity.

Working on alternative methodologies means, instead, looking for the so-called "unconventional" but "pragmatic" ways to conceive the study design, data analysis and result evaluation that are instrumental in obtaining evidence. Bayesian statistics, basket trials, umbrella and n-of-1 study designs are all examples of these [15]. In particular, Bayesian-design trials employing a methodology that consider evidence available outside the trial itself in the various steps of trial planning, analysis and interpretation may help optimise the low patient enrolment in rare cancer clinical studies. There is, in fact, no predetermined number of patients: it is the desired precision of the summary estimate of treatment effect – the range width of its plausible values – that dictates the target number of patients. Statistical significance alone ought never to be the sole determinant considered in regulatory/reimbursement or clinical purposes [15,21].

Basket and umbrella trials increase efficiency by providing opportunities to assess several drugs simultaneously within cohorts of patients with histologically- and molecularly-defined cancers. These novel trial designs are based on the advances in new technologies, like Next-Generation Sequencing (NGS), the so-called molecular profiling of tumours, which has revealed that tumours with specific mutations have the potential to respond to a treatment targeted to that mutation. In basket clinical trials, thus named because their focus is on a defined tumour mutation (or mutations) instead of a tumour type, patients, who all manifest a specific tumour mutation, but with varying tumour types, are enrolled in the study and put into individual study arms, or "baskets" by tumour type. These types of studies are often devised for newly-defined or rare tumour mutations, where finding a large enough population in one tumour type with that specific mutation would be very difficult and time-consuming [23,24].

Moreover, innovative ways of summarising available evidence should be considered in rare cancers, ranging from observational studies to the analysis of retrospective case series or anecdotal cases, up to preclinical studies, with a strong rationale for evidence coming from the treatment of biological equivalence in similar diseases. When establishing the efficacy of an intervention, all available data should assume greater importance in trials of rare cancers than in those of common cancers. Thus, rather than classifying interventions as efficacious or non-efficacious in a binary fashion on the basis of one pre-specified endpoint or definition of success, several relevant outcomes should be investigated collectively to determine how the study results should be applied to clinical practice as well as the will to accept post-marketing assessments to generate additional safety and effectiveness data [15].

These different strategies to obtain evidence in rare cancers are outlined in the recent "Consensus paper on the new methodology of clinical trials in rare cancers" released last year by Rare Cancers Europe [25], a multi-stakeholder initiative representing medical societies, industry but also patient representatives, and discussed with the EMA (European Medicines Agency) regulators, constituting an important milestone in the dialogue among all the parties involved and their different perspectives [21].

Following this event, there was another important workshop on chordoma, a very rare cancer occurring in the skull base or in the spine and affecting only one person in a million per year, that was held at the EMA to discuss the challenges in developing drugs and to identify possible new methodological solutions that could work for this and other very rare cancers [26].

All of these constitute significant steps forward in the joint effort to develop and assess new therapies in response to specific unmet needs, involving the disease-oriented communities (of both patients and researchers) in the field of rare cancers.

4. Risk sharing and stakeholder drivers

Uncertainty is directly connected to the concept of risk, which, in its general meaning, is the "combination of the probability of occurrence of harm and the severity of that harm" [27].

But exactly what kind of risk and consequent harm are involved here? For whom and under whose responsibility?

In the healthcare field, risk can basically be defined, under the principle of the Hippocratic Oath *Primum non nocere*, as a "potential unfavourable effect that can be attributed to the clinical use of a drug and is of concern to the patient", chiefly with regard to the drug's safety profile rather than to its efficacy [28,29].

However, patient needs and requests are increasingly concerning early or, at least, timely access to new drugs; they can be summarised in the words of a patient representative: "The safest drug that no one can afford or that arrives too late is of no benefit to a patient" [30]. This statement, the so-called patient-driver, all the more applicable to life-threatening diseases, highlights two critical issues from the patient perspective: the growing pressure to obtain timely access benefitting not only future but also current generations of patients and, at the same time, the awareness of increasingly constrained healthcare budgets.

Therefore, how can patient needs be met? Which stakeholders/players, then, are involved in handling uncertainty? What is the nature and the degree of risk that each of them would be willing to accept and share?

Considering the higher uncertainty of rare cancers, ascribable to the reasons described above, understanding how much of it can be accepted and handled is crucial. This means identifying the "reasonable risk" in terms of a minimisation of the same, in relation to the potential benefits expected and the assurance that continuous surveillance, monitoring and assessment will be performed [4]. But for whom is this risk "reasonable"?

Patients affected by rare cancers live in the hope that effective therapies will be discovered and are willing to accept risks. "For us," they say, "doing nothing is the biggest risk of all. Time is our enemy" because "When you are faced with a rare cancer, you really can't wait."

This desperate need should be the "core driver" leading all the others. Listening to and including it, as early as possible, in the entire research and development process of a new treatment up to its availability, starting from clinical trial design to the regulatory pathway, is fundamental. This is the reason why even closer interaction between PAGs and other stakeholders is crucial, in terms both of partnership, as presently evidenced within the Research Consortia for clinical trials, and/or consultation, as seen with regulators.

The individual patient will often rationally opt to take the new drug, as from his perspective, the risk of potential side effects is preferable to the certainty of progressive cancer. This patient attitude should also be taken into consideration by regulatory authorities, for whom the safety and efficacy evaluation of any new drug is, instead, both the primary concern and mandatory. "*Access versus evidence*" [31] is consequently "the conundrum" that drug regulators are already facing and which will become even more pressing in the future, as the convergence of advancing understanding of cancer biology, the ability to routinely carry out increasingly sophisticated tumour profiling, and the rapidly rising numbers of targeted and immunological drugs is defining a new scenario in oncology that fosters patient hope, bringing closer the promise of a more precise oncologic approach and personalised care. It refers to the delicate trade-off between patient needs for rapid access to promising therapies and the assurance that patients, clinicians and regulators have adequate information on benefits and risks/harms at the time of marketing authorisation. All of this requires an innovative regulatory approach, revising many of the conventional paradigms for regulatory evidence required in clinical trials [32–34,48].

5. Risk sharing and regulatory tools for early access to innovative medicines.

In recent years, regulators have typically responded to the challenges posed by innovative drugs by introducing early access tools for conditions in which "*the benefits of immediate availability outweigh the risks inherent in the fact that additional data are still required*" [35]. These measures comprise flexible licensing pathways, including accelerated assessment, compassionate use, conditional marketing authorisation/approval (in the EU) as well as other regulatory tools, such as patient registries and pharmacovigilance allowing the collection of real-life data and the development of risk management plans [35–37].

Last month, for example, under accelerated assessment, the EMA granted a conditional marketing authorisation to olaratumab, the first immunotherapic drug in soft tissue sarcoma (STS). It is a monoclonal antibody to PDGFRa, a protein present in high levels or overactive in patients with advanced STS. Olaratumab was previously assigned an "orphan drug designation", that is, the key instrument available in the European Union to encourage the development of medicines for patients with rare diseases and qualify medicines for ten years' market exclusivity. As part of the conditional marketing authorisation, based on the results of the Phase II study, the company must provide results from an ongoing Phase III study in order to confirm the previous results [38].

Another example is pazopanib, a drug for the treatment of adults with selective subtypes of advanced STS, which was originally given "conditional approval" then switched to "full approval" after additional information was provided by the company [39].

Moreover, the example of mifamurtide, an immunomodulator which treats high-grade non-metastatic osteosarcoma, assigned as "orphan drug designation", whose marketing authorisation was renewed on the basis of the review of additional data on quality, safety and efficacy, since the marketing authorisation was granted [40].

Moreover, in the last two years, EMA has launched its so-called "Adaptive pathways", a pilot project [2014–2016], not a new route for marketing authorisation but a new "approach" or "pathway" for drugs under development, based on the existing regulatory tools, to bring multiple stakeholders together for early shared decisions and risk assumption. Under this approach, the medicine will first be authorised in a small patient population in which it is expected to reap the greatest benefits. Additional evidence is then gathered over time, resulting in progressive licensing adaptations to extend or restrict its previously-authorised indications [37].

This year EMA has furthermore launched Priority Medicine (PRIME), a scheme designed to enhance support for the development of medicines that target an unmet medical need. It is a voluntary programme based on enhanced interaction and early dialogue with developers of promising drugs – specifically academia and SMEs – to optimise development plans and speed up evaluation in order to reach patients earlier [41].

It should be stressed that none of these early access tools are mutually exclusive. Therefore, irrespective of their individual headings, their underlying concepts are similar and can be summarised in the following definition of Adaptive Licensing (AL) "*Adaptive*

licensing is a prospectively planned, flexible approach to regulation of drugs and biologics. Through iterative phases of evidence-gathering to reduce uncertainties followed by regulatory evaluation and license adaptation, AL seeks to maximise the positive impact of new drugs on public health by balancing timely access for patients with the need to assess and to provide adequate evolving information on benefits and harms so that better-informed patient-care decisions can be made." [37,42]

Three criteria must be considered for drug eligibility to adaptive pathways [42–44]:

1. Iterative development. This is either:
   - staggered approval from an initial restricted patient population in which the benefit outweighs the risk, to increasingly wider populations (expansion of the indication); or
2. confirmation of the benefit/risk balance of a product authorised under Conditional Marketing Authorisation with early or surrogate endpoints;
3. Gathering of evidence through real-world data to supplement clinical trial data;
4. Involvement of patients and health technology assessment (HTA) bodies in the discussion of the product development programme.

With reference to the second point, it may be useful to point out the difference between drug efficacy, generally intended as an average effect observed under ideal conditions, *i.e.*, in a clinical trial, and its effectiveness, which may well be different from what happens in real conditions, *i.e.*, in actual clinical practice. In this sense, an issue may arise regarding the generalisability of a trial on a new treatment, namely, to what extent the efficacy demonstrated in the trial can be converted into effectiveness in real life [45]. However, clinical research is undertaken to improve clinical practice, which then should incorporate these new results. Therefore, when a trial has shown the superiority of a new treatment, its lack of generalisability should be properly addressed by finding ways for it to be transferred into clinical practice and not viewed, in principle, as an obstacle to the introduction of the new treatment. This is all the more true of rare cancers, where the expertise is less accessible and the driving force of the market is lower to attract for-profit players [21].

With regard to point 3, and considering the patient perspective, which issues are relevant and/or may require patient inputs? The following might serve as examples [37,43]:

- Are surrogate/early endpoints acceptable?
- What Quality of Life (QoL) data and scales are needed?
- Does a Patient Reported Outcome (PRO) need to be developed?
- Can existing disease registries, indirect analysis of comparators and outcomes, and off-label use be employed?

As to this last question, it should be mentioned that there have been patient-driven efforts to feed the data bases of studies and cancer registries, which may become formidable tools for the acquisition of new knowledge in rare conditions.

In any case, regardless of the specific regulatory tool used, systematic consultations between regulatory bodies and the rare cancer-based communities (both patient- and physician-driven) would be vital to tailor the way new drugs are developed in rare cancers, given the key role played by the scientific advice the former impart to pharmaceutical companies embarking on the development of new cancer drugs. Even if in these last few years, several important successes have been achieved in the registration of new drugs in selected rare tumour types, there nonetheless remain challenges for the upcoming years. The fragmentation of cancers in small entities could increase the number of trials and their costs unless new, less expensive clinical research methods are shared and accepted by regulators.

Undoubtedly, systematic consultations and close dialogue represent important tools to provide better patient access to drugs but many challenges are yet to be addressed and some of these refer to the legislative framework itself. This is the case of the new European Resolution, just adopted by the European Parliament (15th December, 2016), on the Paediatric Medicines Regulation. This Regulation (Reg. 1901/2006/EC), launched in 2007, has changed the landscape for drug development for children [46]. Many childhood diseases have benefitted from it, but, to date, not sufficiently cancer, which remains one of the most urgent human, social and public health issues in Europe, taking also into consideration that childhood cancers are rare, and many of them very rare. This is the reason why the pan-European childhood cancer community and beyond called on the European Institutions to support the urgent revision of the Paediatric Medicines Regulation and modernise the current legislation in order to better address the needs of children and adolescents with life-threating-disease, cancers included, facilitating a more rapid development and access to innovative medicines [47].

6. Risk-sharing and economic assessment

What, then, should be said about the involvement of HTA bodies? What is their role?

In the current healthcare environment, the regulatory approval of medicinal products, even if necessary, is not sufficient to ensure timely patient access because of the pressing economic constraints on national and/or regional healthcare systems. In general terms, only a small fraction of treatments in the EU is fully paid out-of-pocket by patients. It follows that the decision made by the so-called third-party payer whether or not and how to reimburse is becoming more and more crucial to both patients and pharmaceutical companies. Like regulators, third-party payers, or the HTA bodies that advise them, cannot escape the conundrum "*access versus evidence*" and the uncertainty of clinical evidence related to it [48]. If the availability of full information on a drug's performance is required for the first coverage/reimbursement decision to be made, then patient access, above all in rare cancers, is limited and these patients are discriminated against by definition.

A further question is posed by the need to define the "evidence" data required, as finalities do not exactly coincide [49]. While the centralised procedure (Reg. 726/2004/EC) [50] establishes that the regulatory body – in this case, the European Medicines Agency (EMA) – is responsible for the marketing authorisation of fixed typologies of medicines, including oncological drugs, Health Technology Assessment (HTA) bodies, at national or regional level, issue recommendations regarding medicines and other health technologies that can be financed or reimbursed by the healthcare system in a particular Member State or region. This means that following regulatory approval, subsequent decisions on coverage (reimbursement) and price of an authorised drug are made at national level. Therefore, HTA assessments have a strong influence on market access and consequently on patient "inequalities" across Europe, as confirmed in 2009 in the Comparator Report on Patient Access to Cancer Drugs in Europe [51].

HTA provides evidence-based information for decision-making on how to allocate resources in accordance with the sustainability of national/regional healthcare systems and their threshold values. In countries where health technology assessment is in place, payers, pricing and reimbursement agencies or HTA bodies depend on these assessments to:

- determine reimbursement status;

– provide information on benefits and risks of new treatments compared to available treatment options;
– support the price negotiation process [52].

This is the reason why, since 2010, the EMA has undertaken a pilot project called "Parallel HTA-regulatory scientific advice and protocol assistance", conducted with the participation of several HTA bodies, that allows drug developers (pharmaceutical companies first of all) to receive simultaneous feedback from both regulators and national HTA bodies at any point in the developmental lifecycle of medicines. This is a multi-stakeholder procedure that amounts to a support tool to help the parties establish the evidence that each of them will need to determine a medicine's benefit–risk balance and value as efficiently as possible. This close interaction between regulators, HTA bodies and other relevant bodies early on is fundamental in enabling patient access to new medicines. The aim is to reduce developmental resources by re-shaping and focusing drug development programmes in order to obtain data valuable for regulators, HTA bodies and other stakeholders. Parallel Advice covers a variety of therapeutic areas, including rare conditions [52,53].

After an adaptive licensing, such as a conditional marketing authorisation and HTA assessment, in some healthcare environments "Managed Entry Agreements" (MEAs) are concluded, at operational level, between payers and manufacturers with the aim of sharing the financial risk due to uncertainty around the clinical and cost-effectiveness of new technologies at the time of introduction. MEAs can take different forms, including clinical performance-based agreements. In order to realise their full potential, these arrangements need to have the flexibility to allow new information on a drug's performance to trigger price change. Post-authorisation safety and/or efficacy studies imposed by regulators could be prospectively planned and aligned with post-licensing evidence generation foreseen by payers under an MEA scheme—provided that a "learning healthcare system" is in place [47].

Last but not least, from a strictly payer point of view, the impact of a new drug should not in any case be assessed exclusively with regard to a specific threshold drug budget, but to "multiple" budgets covering patient treatment pathways in their entirety as well, so as to evaluate whether and to what degree resource consumption is affected. In this sense, it must be stressed that any clinical decisions regarding the administration of innovative drugs should be made in reference centres in order to allow appropriate treatment to be determined and, at the same time, new evidence generated. This is therefore essential for the interests not only both of the patient and of clinicians, but also of the third-party payer and pharmaceutical companies. Inappropriate prescribing diminishes the benefit–risk ratio and the value of treatments under any licensing or coverage.

The rare cancer focus on national Reference Networks and even more on the European Reference Networks (ERNs) should further strengthen this approach, not only because these networks can provide the most appropriate treatment, improving clinical outcomes and the quality of life for rare cancer patients, but also because Member States have the responsibility for the organisation and sustainability of their healthcare, in consideration of the fact that rare cancers account for 20–22% of all cancers. This is the reason for which they will need to recognise centres of expertise and endorse them, preventing vulnerable citizens from being discriminated against.

7. Conclusions

According to T. Kuhn "when a prevailing paradigm fails to make productive predictions, then the difficulty may lie with the paradigms on which the research is based". In this case, the new paradigm is the adoption of a new approach able to take into consideration the interdependence of all parties involved and their different drivers, as early as possible [48,54]. Fundamentally, this approach is based on the following main features:

– Early engagement of all stakeholders involved in drug development.
– Focus on patient access: information needs of all stakeholders have to be considered from the very start of drug development in order to enable timely patient access.
– Regulatory early access toolkit and repeated learning-cycles: of "learning-confirming-(re)licensing, allowing both timely access and knowledge accumulation.
– *Evidence generation toolkit: not only conventional clinical trials, and* all the available strategies which may enable their application, but also alternative methodologies of clinical research; in addition real world data to gain post initial licensing evidence
– *Innovation and sustainability*, stimulating the research, development and bringing to the market of appropriate medicines by the pharmaceutical industry, *avoiding discrimination and inequity "a priori"*.

Patients, researchers and clinicians, pharma investors, regulators and payers are driven by different expectations and needs, but all of them concur to achieve a common goal: better patient treatments, according to a new emerging "revolutionary" understanding in science and technologies, allowing, on the one hand, timely patient access and, on the other, the sustainability, both for investors and payers, of innovative drugs. Clinical drug development, including new clinical research methodologies, licensing, reimbursement, utilisation in clinical practice and monitoring of treatment outcomes should be viewed as a continuum and, to the greatest extent possible, should be planned in a prospective and integrated way, with input from all these stakeholders, starting as early as possible.

The above-described "intrinsic lack of or defect in evidence" in rare cancers elevates the uncertainty to be faced by each stakeholder and consequently poses the question of correlated risk assumption. This is leading to a challenging new scenario in which a greater degree of risk-sharing among all the stakeholders is required to avoid discrimination against rare cancer patients. In this scenario, the involvement of PAGs – or the disease-oriented communities (of both patients and researchers) – is crucial and needs to be increasingly implemented in a systematic manner, allowing a continuous improvement in understanding needs and sharing decisions, at all different levels, including awareness campaign actions to revise the current legislative and regulatory framework.

Finally considering the complexity of rare cancers, the present and future successes achieved in their management will very likely enhance the development of therapies for patients affected by malignancies of any kind, both rare and common.

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