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PERSPECTIVE

Position paper: new insights into the immunobiology and dynamics of tumor–host interactions require adaptations of clinical studies

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ABSTRACT

Introduction: Prospective double-blind placebo-controlled randomized clinical trials (RCTs) are considered standard for the proof of the efficacy of oncologic therapies. Molecular methods have provided new insights into tumor biology and led to the development of targeted therapies. Due to the increasing complexity of molecular tumor characteristics and of the individuality of specific anti-tumor immune reactivity, RCTs are unfortunately only of limited use.

Areas covered: The historical methods of drug research and approval and the related practices of reimbursement by statutory and private health insurance companies are being questioned. New, innovative methods for the documentation of evidence in personalized medicine will be addressed. Possible perspectives and new approaches are discussed, in particular with regard to glioblastoma.

Expert opinion: Highly specialized translational oncology groups like the IOZK can contribute to medical progress and quick transfer 'from bench to bedside.' Their contribution should be acknowledged and taken into account more strongly in the development of guidelines and the reimbursement of therapy costs. Methodological plurality should be encouraged.

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Cancer immunotherapy; guidelines; conflict of interest; randomized trials; tumor immunology; evidence-based medicine; dendritic Cells; newcastle Disease Virus

1. Introduction

The field of clinical research aimed to generate evidence-based medicine becomes complicated due to the remarkable gain in knowledge in basic science and translational research. The well-established methodology of phase I toward phase III trials and post-marketing vigilance is challenged, and the difficulties around randomized clinical trials are openly debated, as exemplified by the Symposium 'Are randomized trials obsolete? Brussels April 2020' organized by the International Drug Development Institute. The Immune-oncologic Center in Köln (IOZK) is a small-medium enterprise which was granted a drug manufacturing license in May 2015 to produce IO-Vac®. This is an approved personalized medicinal product consisting of autologous mature dendritic cells (DC) loaded with autologous tumor antigens and matured with danger signals involving cytokine cocktail and Newcastle Disease Virus (NDV). As a private nonprofit organization focused on translational oncology in the domain of multimodal immunotherapy for patients with solid cancers and brain tumors, we aim to contribute to the current debate.

2. Efficacy testing and evidence-based medicine

Modern medicine has a high claim to quality, which is reflected in the concept of evidence-based medicine. The term refers to the use of the best available evidence in the decision-making process for patient care. The practice of evidence-based medicine involves combining individual clinical experience with the best available external clinical evidence from systematic research[1].

For the evaluation of external evidence, the Oxford Center for Evidence-Based Medicine has developed a scheme to which medical guidelines usually refer. It evaluates the quality of treatment recommendations according to certain criteria and assigns them a 'Level of Evidence' (LOE). Systematic reviews of randomized controlled trials (RCTs) are regarded as the highest level (LOE 1a), expert opinions, fundamental pathophysiological models or results from basic research as the lowest (LOE 5). LOE 5 means that scientific evidence is inherently acknowledged for innovations derived from basic research and long-standing medical experience with novel clinical applications, and hence should not be underestimated. Such gain of knowledge and relevant medical innovation can come from single clinics and treatment centers, and can occur outside the pharma industry.

At the beginning of the twentieth century, statistical methods gained importance in science. In the 1940s the first Randomized Controlled Trial was undertaken to appraise the effects of Streptomycin. In 1964 the World Medical Association issued the 'Helsinki Declaration,' a guideline for medical research. The introduction of control groups, blinding, and randomization is a means of reducing bias. RCTs were successfully established as a gold standard in oncologic research by the 1980ies.

University clinics are capable of conducting large clinical studies and often participate in pharma industry-initiated RCTs. RCTs are a valuable tool of evidence if they are adequately conducted and interpreted without bias. However, their value and significance are often overestimated. RCTs determine the mean treatment effect and provide a general

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Article highlights

- New insights into tumor biology and 'OMICS' technologies have led to the development of personalized therapies that are only effective for a fraction of patients.
- Some immunological approaches aim at the induction of an anti-tumor immune response, the modulation of the pattern of cytokines and of the tumor microenvironment.
- Development of cancer drugs is expensive and time-consuming. Clinical translation of promising technologies is hampered. Spending on oncologic pharmaceuticals keeps rising with minimal clinical advances.
- The primacy of RCTs and the established methodology of phase I toward phase III trials are being challenged.
- The approval of cancer drugs and the development of guidelines are often based on fragile data and can be associated with considerable conflicts of interest.
- Small translational clinics can contribute valuable clinical insights and methodologic innovation.
- The establishment of large databases of results from individual patients and the development of innovative study designs could lower expenditures and enable clinical translation of scientific findings.

statistical estimate of efficacy for the study population under investigation. An example is the Kaplan–Meier curve of survival probability of a group of patients over time. RCTs have only limited significance for the single patient. The transferability of the results to other populations is questionable [2] but is very common in clinical practice.

Accordingly, the drugs approved on this basis are only effective for some of the patients receiving them. This means that many patients are treated with a therapy that offers them no benefit but may cause side effects. The measure for the number of patients who need to be treated with a drug to avoid an additional event (e.g. tumor progression or death) is the 'number needed to treat' (NNT). In view of the possibly considerable side effects of conventional cytotoxic cancer drugs, this represents a major burden for patients. In the case of endometrial carcinoma, for example, a statistically significant survival advantage is confirmed following additional chemotherapy after hysterectomy and radiotherapy. However, the NNT is still 33 to allow an additional patient to survive for 5 years [3]. In turn, this means that 32 patients will receive this potentially toxic therapy and will have no or less benefit from it.

Renowned scientists criticize that most doctors and decision makers are not able to safely assess the credibility and benefit of medical evidence. The poor quality of clinical evidence can contribute significantly to overuse, underuse, avoidable side effects, and waste of health-care resources [4].

3. New insights into tumor biology suggest approaches of personalized and individualized medicine

The development of new molecular biological and mass spectroscopic techniques, such as Next-Generation Sequencing (NGS), has led to a remarkable new insight into tumor biology. 'OMICS' technologies allow the study of genome, epigenome, transcriptome, proteome, peptidome, ligandome, and metabolome and are used to uncover the molecular features underlying complex cellular phenotypes. They provide new features about the pathogenesis and course of cancer, which in turn is important for the development of new therapies [5]. For instance, targeted therapies are aimed specifically at individual molecular features. Their effectiveness depends on the expression of the respective target by the tumor cells. Hence, targeted cancer therapy is only effective for a fraction of patients but is extremely effective for this subgroup. Personalized medicine, therefore, is useful and can provide considerable patient benefit [6].

An innovative method of identifying the patients who benefit from personalized medicine is termed 'theranostics.' Specific tumor biomarkers that have been developed for imaging with either Single Photon Emission Computed Tomography (SPECT-CT) or Positron Emission Tomography (PET-CT) can be used as vectors for therapeutic radionuclides. Suitable patients can be identified with the imaging techniques to ensure a targeted and specific therapy [7].

Immunological approaches, such as DC vaccination or oncolytic virus (OV) therapy, do not primarily aim at defined molecular targets of the tumor cells, but rather at the induction of specific T cell-mediated anti-tumor immune responses. OV-induced immunogenic cell death (ICD) can induce cytotoxic T-cell responses against a large number of tumor antigens. These do not need to be specifically identified. In addition, the modulation of the pattern of cytokines and of the tumor microenvironment is important for clinical success. Therefore, in addition to monitoring the molecular characteristics of the tumor cells, the monitoring of the patient's immune function is essential. New findings demonstrate intra- and inter-individual heterogeneity of tumors with regard to their molecular signature. Such signature can also change significantly over time through genetic and/or epigenetic mechanisms, for example, during the time of therapeutic intervention. As a result, tumor cell variants are generated and selected, which are resistant to the therapeutic intervention [8].

If therapy resistance develops in a patient, the therapeutic strategy has to be changed. A multimodal therapy approach reduces the risk of development of therapy resistance [9]. If an oncolytic virus such as NDV which induces ICD [10] is included in the therapy, its capacity to break therapy resistance is of further advantage [11].

Tumor neoantigens and the corresponding immune response to them are individually specific. The neoantigens have to be bound by MHC-I or MHC-II molecules to enable CD8+ and CD4+ immune responses, respectively. MHC molecules are highly polymorphic in the human population, i.e., one individual hardly resembles another. The repertoire of spontaneous immune reactions against tumors is therefore individually distinct.

Traditionally, the classification of tumors and the corresponding treatment is based on histological features. Since the development of targeted therapies, it has become clear that each type of tumor has a multitude of molecular subtypes. In the future, the recognition of further target structures can be expected. It has been observed that certain genetic aberrations occur in tumors of different origins. For the

efficacy of new therapeutic strategies, the molecular target structures could, therefore, become more meaningful than histological classification [12]. The classic paradigm of clinical studies, in which inclusion criteria are based on clinical-pathological parameters, is increasingly being abandoned in favor of the detection of specific molecular aberrations [13].

Furthermore, many additional variables have been defined that influence the interaction between the immune system and tumor growth as well as the effectiveness of an immunotherapy. These include the tumor microenvironment and host-related factors such as age, HLA, nutrition, metabolism, infections, and microbiome [14]. The increased complexity caused by genetic, immunological, and host-related heterogeneity poses a challenge for the determination of an optimal treatment combination.

New knowledge about tumor biology and immunology and about the importance of tumor–host interactions challenges the traditional paradigm of tumor-focused treatments. Since many personalized treatment methods are only effective in a small proportion of patients, classical phase III studies with broad approval criteria are inefficient. Given the great variability of individual markers, tumor characteristics, microenvironment, comorbidities, and other co-variables, even the best RCTs cannot account for all differences in the randomized arms. Furthermore, due to the large and increasing number of new drugs, it is neither timely nor financially feasible to conduct randomized trials for all these substances. In addition, conceptual deficits can limit the significance of RCTs in oncology, making their results of limited relevance to clinical practice [15]. Table 1 provides an overview of the important shortcomings of RCTs.

The fragility index is a statistical measure to evaluate the reliability of study results. It identifies the number of events required to change statistically significant results to non-significant results. For example, an index of 2 means that statistical significance is lost if two patients in the intervention group had an 'event' instead of 'no event.' Thus, the lower the index, the more fragile the outcome of the study. Many randomized-controlled phase III studies which led to the approval of cancer drugs by the FDA between 2014 and 2018 have only a low fragility index [16]. The critical number of patients in whom 'no event' rather than an 'event' would have to occur for the loss of statistical significance is often less than 1% of the study group or lower than the number of study participants lost to follow up [17]. This means that the approval of many cancer drugs is based on fragile data. Accordingly, only less than half of the RCTs that led to FDA approval meet the criteria for clinically relevant benefit [18]. An evaluation of new cancer drugs approved by the FDA in 2015 and 2016 showed that many substances only offer a marginal benefit [19]. Another survey shows that most drugs approved by the EMA between 2009 and 2013 had no benefit with regard to survival or quality of life and only marginal improvements compared to existing treatment options or placebo [20].

Table 1. Important shortcomings of RCTs

Important shortcomings of RCTs
Depend on large cohorts
Associated with high costs
Associated with long duration
Can only be financed by large pharmaceutical companies
Prone to conflicts of interest
Aim primarily at market introduction not at patient benefit
Limited significance for the single patient
No benefit for patients in control group
Prone to misinterpretation and overestimation
Limited transferability of results to other populations
Not suitable for assessing various parameters
Not suitable to identify a small proportion of patients that respond to therapy
Mostly directed to surrogate parameters

Most of the 54 admission studies between 2014 and 2016, which led to the approval of new cancer drugs by the EMA, were RCTs. In only 26% of these studies was overall survival the primary endpoint, the other studies investigated surrogate parameters. Almost half of all the approval studies were classified as highly biased [21]. The bias in the study results is due to methodological shortcomings. These often overestimate the benefit of the therapy under investigation [22].

Traditional definitions, including dose-limiting toxicity (DLT: toxicity that is considered severe enough to limit further dose escalation) and maximum tolerated dose (MTD: this is the dose at which no more than 30% of patients treated will experience DLT), are based on the empirical linear relationship between dose, efficacy, and toxicity found in chemotherapy. These have low specificity and high toxicity, while many immunotherapeutic approaches have high specificity and low toxicity [23]. With monoclonal antibodies, for example, there is no linear relationship between dose, toxicity, and efficacy and in many Phase I studies no DLT has been achieved. This challenges the usual sequence of Phase I–III clinical trials, in which the early phases serve to determine dosage and tolerability [24].

The new findings and therapeutic options thus make it necessary to change methods of clinical studies [25,26,27]. The aim is to make as many new and effective treatments as possible available to cancer patients in a safe, fast, and effective way. This will require a joint effort by researchers, translational institutions, clinicians, and regulatory authorities [28].

Some researchers recommend the establishment of databases of results from individual patients treated with immunotherapies for early identification of effective drugs in a large patient population [29]. However, the establishment of such data collection is likely to be difficult. Sharing of information between many investigators and multiple companies is not usual. Various study designs are being discussed. These include basket trials (a drug is tested simultaneously in different 'baskets', i.e., subgroups of different tumor types) or umbrella trials (evaluation of several targeted therapies for a single disease) [30]. Another strategy is N-of-1 trials, or single-patient trials. These could, if planned prospectively and combined with larger amounts of data, be a suitable means of gaining insights into cancer diseases, especially rare diseases or if RCTs are not possible. Of course, they are not feasible in all conditions and need very careful planning and execution [31,3233].

In N-of-1 trials, the acquisition of knowledge is coupled with an individual benefit for the single patient, in contrast to RCT, where the patients in the control arm have no personal benefit. This could lead to improved recruitment and

adherence. Furthermore, such a study design could lead to a significant reduction in costs [34].

4. Research financing and financeability

The costs of developing a drug to market entry are considerable and have increased since the turn of the millennium [35]. Only large corporations with enormous resources can afford such studies. The development of new therapies is a risky, cost-intensive, and long-term undertaking. The success rate of the clinical approval of cancer drugs is estimated at 13.4% for the entire study process [36], for the first phase even below 6% [37].

The number of promising active substances is small and the few drugs that make it to the market must cover the research costs of all other drugs in development. Because the costs are so high, pharmaceutical companies pass the costs on to consumers. This is not possible for medium-sized companies or translational centers that work with personalized drugs and treatments. They have a serious competitive disadvantage, although they can potentially contribute important innovations for society.

Partly due to the passing on of development costs, health expenditure on cancer has risen steadily from 35.7 billion euro in 1995 to 83.2 billion euro in 2014 in the EU, and expenditure on cancer drugs from 7.6 billion euro in 2005 to 19.1 billion euro in 2014. While expenditure on oncological drugs has increased in both absolute and relative terms over this period, other cancer-related expenditure has remained stable or decreased [38].

As a result, the costs of newly approved cancer drugs, in particular, are so high – up to over 100,000 USD per year – that they are hardly in any reasonable relation to their often modest additional benefits [39]. Another factor driving the costs is the fact that high prices exclude independent comparative efficacy trials aimed at establishing equivalent but cheaper alternatives. High drug prices thus protect the market share of expensive drugs [40].

Al-Badriyeh *et al*. presented the first systematic analysis of the influence of industrial financing on the results of studies on chemotherapy. Five hundred and seventy-four publications were examined. The paper shows that industrial funding is associated with a positive outcome for the sponsor and that the sources of funding are not sufficiently disclosed at the time of publication [41].

5. Potential conflicts of interest in the development of guidelines and in the approval of oncological pharmaceuticals

In view of the financial implications and particular commercial interests outlined above, possible conflicts of interest in the development of guidelines and in the approval of pharmaceuticals must be discussed. This debate is largely neglected, as the associated insights are questioning the self-image of the scientific community: 'It is difficult to get a man to understand something, when his salary depends on his not understanding it.', as Upton Sinclair so aptly pointed out [42].

Guidelines have a significant and increasing influence on clinical decisions. They are also frequently used as a reference for the reimbursement of treatment costs by statutory and private health insurance companies. They are considered dependable and trustworthy by clinicians, although they can be distorted by economic interests and fundamental conceptual limitations [43,44]. A review of the oncology guidelines published by the National Comprehensive Cancer Network found that 71.9% of the recommendations were based on weak evidence and 87.1% of the authors received payments from the industry [45]. Financial conflicts of interest are not necessarily obvious and often difficult to trace. The content of conventional guidelines is dominated by a few 'key opinion leaders' who are likely to have conflicts of interest [46]. According to a scholarly survey of international gynecological guidelines, these recommend chemotherapy even in diseases where the effect of chemotherapy is controversial and the recommendations are based on scant evidence. Medical associations are probably not inclined to advise against treatment forms that are particularly profitable for their members [47].

As outlined above, the registration studies for newly approved oncological drugs are often fragile and their additional benefit questionable. The circumstance that 65% of the FDA's budget for regulatory drug approval is covered by industry fees [48] and 86% of the EMA's budget [49] sheds particular light on these facts. Individual financial conflicts of interest of commission members can also lead to bias [50]. Further insights into conflicts of interest in medicine have been described, including their definitions and backgrounds as well as possible solutions [51,52,53].

6. The glioblastoma treatment as an example for the discussion of the issues involved

Glioblastoma is the most frequent brain tumor in adults and has the worst prognosis of brain tumors [54,55]. It is considered incurable and has a mean survival time of 14.6 months despite standard treatment [56,57]. Standard treatment provides a combination of surgery with subsequent radiochemotherapy and maintenance chemotherapy. Although the results of the underlying study were published 15 years ago, it is still considered the standard worldwide.

It became clear early on that there are molecular biological determinants that influence the prognosis and the response to therapy. For example, the effectiveness of chemotherapy depends on the methylation status of the MGMT promoter [58]. It was therefore selected as a criterion for the randomization of new studies. On the basis of further analyses, at least six subtypes of GBM could be identified, each with different characteristics and prognosis [59]. For the treatment of the different subtypes, different targeted therapies were developed. These were tested as a single agent in recurrent disease or as an addition to the therapy standard [60,61,62,63,64,65]. The availability of molecular diagnostics and corresponding therapy options enabled personalized medicine: for the first time, a specific tumor entity was no longer treated according to defined treatment or study protocols, but the treatment could be adapted to the individual tumor biological profile of each patient. A stratification of study participants by subtypes became necessary to ensure comparability between patients in an experimental arm and those in a control arm. Due to the

resulting need for larger cohorts, recruitment took longer and costs increased significantly. This development poses a major challenge to the validity and feasibility of RCTs [66]. The rapid introduction of new drugs forced clinical researchers to find innovative statistical designs for clinical trials [67].

To date, most studies on the use of individual targeted therapies in GBM have not been successful. This is probably, among others, due to the fact that GBM consists of different tumor cell clones, including glioma cancer stem cells. These can change in the course of the disease through mutation and selection, e.g., after therapeutic intervention. Maintaining an unalterable treatment protocol for a dynamically changing lethal tumor over a longer period of time, e.g., in a clinical trial, no longer seems appropriate in view of the new findings.

High hopes are set on immunological therapies [68,69], especially vaccination strategies [70]. A personalized combination of different therapeutic measures is considered promising [71,72]. These types of immunotherapy do not primarily target the molecular biological characteristics of the tumor cells, but rather their immunological profile, including known and unknown tumor antigens [73], immune-costimulatory, and -inhibitory molecules [74,75,76] and the production of cytokines that have an influence on the antitumor immune response. Accordingly, studies to prove the efficacy of immunotherapy must not only consider the clinical risk profile, the intracellular molecular biological and epigenetic profile of tumor cells, but also the surface of the tumor cells, the tumor–host interaction, the micro-environment of the tumor and the immunological condition of the patient, all variables subsequently being in evolution during treatment. Finally, one should take into account the interaction between the different modes of treatment [77]. All these facts make appropriate double-blind placebo-controlled RCTs with numerous stratifications for a risk-adapted control group impossible. Outside the multiple clinical and statistical challenges, financial issues affected the conduction of larger Phase IIb or phase III DC vaccination RCTs for GBM [78], or caused ultimate suspension of the trial (NCT02546102).

7. Conclusion

Since the 1980 s, RCTs have been considered a valuable tool of evidence and gold standard in medical science. In recent years, however, limitations are being discussed of RCTs as a basis for developing treatment guidelines. This position paper explains why new insights into the complexity of the immunobiology of tumor–host interactions require adaptations of clinical study design.

Immunological agents such as vaccines and antibodies show bell-shape dose–effect relationships in contrast to chemotherapeutic drugs with their linear dose–effect relationship. RCTs in oncology are based on histopathologically defined cancers. New technologies from molecular biology revealed many different subgroups within classically defined cancer types. In addition, tumor neoantigens, which are important for immune rejection, were shown to be distinct for each individual cancer. There are also many additional variables such as the tumor microenvironment, the HLA type, or the gut microbiome. Even the best RTCs cannot account for all such differences in the randomized arms.

Personalized treatment methods such as targeted therapies focus on a small proportion of patients and thus achieve higher effectivity. N-of-1 trials like individualized immunotherapy offer benefit for each individual patient. With RCTs, patients in the control arm have no personal benefit. A database of results from individual patients can lead to the acquisition of new knowledge.

RCTs can limit innovations because of their high costs and their long duration. Their results may lead to drug approval but they may be of little value for the clinical practice if the given medication or intervention highly depends on individual effects. To achieve fast approval, a majority of RCTs investigate surrogate parameters rather than overall survival. They often have a low fragility index as a sign of poor reliability. Potential conflicts of interest and bias are further problems of pharmaceutical company-controlled studies that influence drug approval and development of guidelines. The reimbursement of therapy costs should therefore not be so exclusively dependent on guidelines. Our position is that assessment of clinical efficacy needs new concepts and adaptations for including personalized and individualized treatment results and for dealing with fast continued progress in innovations and knowledge translatable into clinical reality.

8. Expert opinion

For the aforementioned causes, the clinical translation of promising technologies in the field of immunotherapy is often lengthy and inefficient. How can the gain in scientific knowledge from oncologic research be best translated to the patient? Various strategies are under discussion to improve the situation [79]. Conventional RCTs are lengthy, extremely expensive, and methodologically only conditionally suitable for testing the efficacy of individualized cancer therapies. Smaller translational research groups are not predestined for the conduct of classical large RCTs due to their infrastructure. So what are the key competences of these institutions and how can they make a valuable contribution to the acquisition of scientific knowledge and progress of treatment?

The gain in knowledge of classical RCTs is based on the acquisition of only a few influencing factors and data in as many patients as possible. The individual medical judgment and personal knowledge are thereby eliminated. Many studies serve primarily to obtain drug approval, not to cure the patient.

In single-case studies, in contrast, as many influencing factors and data as possible are measured in a limited number of patients. Individual medical knowledge and clinical experience are explicitly considered. This strategy serves both to gain experience by the medical community and to cure the individual patient.

This position paper is not just based on theoretic considerations how to translate findings from basic research into clinical practice. It also provides with IOZK an example as to how this can be done. Of course, there are also other concepts and ways how to do this. Highly specialized translational oncology groups like the IOZK are particularly suited for high-

quality single case studies due to their organizational structure, the individually optimized application of a multimodal concept and the comprehensive recording of immunological parameters before and during treatment. An institutional strength is the flexibility that underlies the concept. At the personalized level it enables a continuous optimization and adaptation of the treatment mode on the basis of the individual evolution of each patient. It also allows for a continuous optimization and adaptation of the global treatment concepts on the basis of newly published research data and experience. Innovations can thus be made available to patients and clinical evaluation in a prompt manner. An example is IO-VAC®, a DC vaccine modified by loading the cells with oncolysate from patient-derived tumor cells infected with an oncolytic strain of NDV. For an approved immunologic drug, such as Provenge®, and for investigational drugs like DCVax [78] or ICT-107 (NCT02546102) an adaptation of the personalized drug production process to the actual state-of-the-art over time is excluded.

It is worth quoting once again one of the pioneers of evidence-based medicine who pointed out that without clinical experience there is a risk that clinical practice will be 'tyrannized' by external evidence. Even excellent external evidence may not be applicable or inappropriate for the individual patient. Evidence-based medicine requires a fundamental approach that combines the best external evidence with individual clinical experience and the consent of the patient. Thus, it cannot lead to 'slavish cookbook approaches.' Sometimes the external evidence will even need to come from basic research.[1].

To this end, translational institutes such as the IOZK should make their wealth of experience and the data they collect available to the scientific community in the most appropriate way. This can take the form of publications in relevant journals, participation in conferences or even the organization of symposia. The IOZK takes on this task alongside its therapeutic work and endeavors to constantly improve the corresponding infrastructure.

Modern science and the institutionalized regulatory control and approval of drugs are a blessing for the safety and medical care of patients. However, they can only preserve their credibility if they are prepared to face the new challenges. The limitations of scientific knowledge gained by RCTs must be acknowledged and taken into account when assessing the value of study results and establishing guidelines. A meta-analysis of newly approved anti-cancer drugs revealed not only high costs [52] but also high risks of associated toxicities [53]. Cancer vaccines and oncolytic viruses were found to exert profoundly lower side effects than the FDA-approved new drugs [80]. Examples of therapeutic benefits from immunotherapy with virus-modified cancer vaccines in comparison to controls have recently been summarized and new insights into mechanisms of function provided [81].

Methodological plurality should be encouraged. Experiences of translational institutions must be recognized in their value and taken into account more strongly in the reimbursement of therapy costs. If this does not succeed, Ivan Illich's gloomy statement will come true: 'Modern medicine is a negation of health. It isn't organized to serve human health, but only itself, as an institution' [82].

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