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METHODS

Health technology assessment in the era of personalized health care

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Objectives: This article examines the challenges for health technology assessment (HTA) in the light of new developments of personalized health care, focusing on European HTA perspectives.
Methods: Using the example of the Integrated Genome Research Network – Mutanom (IG Mutanom) project, with focus on personalized cancer diagnostics and treatment, we assess the scope of current HTA and examine it prospectively in the context of the translation of basic and clinical research into public health genomics and personalized health care.
Results: The approaches developed within the IG-Mutanom project are based on innovative technology potentially providing targeted therapies for cancer; making

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translation into clinical practice requires a novel course of action, however. New models of HTA are needed that can account for the unique types of evidence inherent to individualized targeted therapies. Using constructive health technology assessment (CTA) models is an option, but further suitable models should be developed.
Conclusions: Integrative, systems biology-based approaches toward personalized medicine call for novel assessment methods. The translation of their highly innovative technologies into the practice of health care requires the development of new HTA concepts.

Keywords: Health technology assessment, Personalized cancer therapy, Public health genomics, Systems biology, Mutanom

Developments in biology, in particular in genomics and systems biology, have given rise to new insights into the mechanisms of human disease and have led to new concepts for diagnosis and therapy. In particular in the field of cancer, rapid progress is being made. The recognition of cancer as a complex genetic disease with disease development and progression differing between individual patients and between individual tumors is a challenge but opens avenues toward new diagnostic approaches and targeted therapies.

The emergence of targeted therapies and of personalized medicine as a new opportunity for health care has major consequences for the route of translation of knowledge and technologies from basic science into point-of-care applications. Health technology assessment (HTA) is one of the main stations on the translational pathway, where the broad scope of the HTA process from multidisciplinary and systematic knowledge integration to policy making includes a tool for bridging the second gap in translation, i.e., a tool for the introduction of methods and products into clinical practice (7). The key question is, whether targeted therapies will require new tools and procedures for effective translation.

In this article, we examine the implications of the developments in the first translational gap—from basic sciences to methods and products—for current HTA. We use the Mutanom project (NGFN-Plus Integrated Genome Research Network-IG Mutanom) as a concrete example (12). This academic research project pursues systems biology-based research into the genomics of complex diseases, in particular of cancer.

METHODS

Using the example of the IG Mutanom project, with focus on personalized cancer diagnostics, prediction of disease progression and treatment, we assessed the scope of current HTA and examined it prospectively in the context of the translation of basic and clinical research into public health genomics and personalized health care. We found that the specific topic of this article has been very little addressed in the current literature. We, therefore, used the material generated through our participation in the Mutanom project (WP-2 Translational Aspects) and the expertise from our international network (co-authors) to delineate the subject. Our broad, transdisciplinary research question and the rapidly changing field of targeted therapies cannot be covered yet through a systematic review of the literature. However, the synergy of knowledge sharing within a multidisciplinary group of collaborators from the fields of systems biology, pharmacogenomics, molecular genetics, philosophy, ethics, law, and HTA resulted in development of the current article.

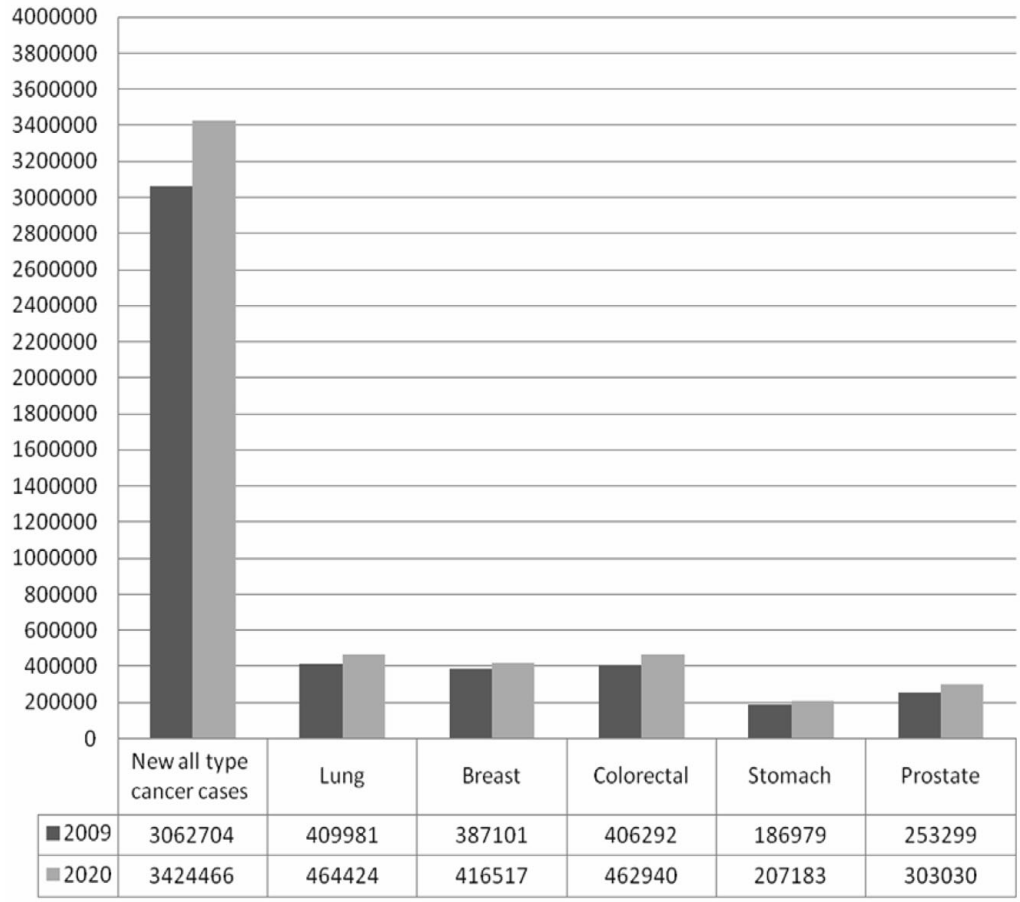
We described the components of current HTA according to the consensus elaborated by European Network for Health Technology Assessment (EUnetHTA), as well as the place and timing of HTA in the process of technology development and diffusion, focusing on European HTA perspectives. We discussed the impact that the approach of personalized health care would have on several aspects, relevant for HTA, in particular the systematic use of primary studies, the design of prospective clinical trials and the regulatory requirements. Finally, we tried to sketch an outline of what type of new HTA may be needed in the near future.

HEALTH TECHNOLOGY ASSESSMENT AND TRANSLATIONAL HEALTH RESEARCH

Current HTA

Current demographic trends, in particular the ageing society in Europe, lead to a continued rise in the incidence of cancer (Figure 1) (8). At the same time, advances in the medical and biological sciences have expanded the range of options for diagnosis and treatment while continuously increasing costs. Throughout Europe, governments are rationalizing healthcare expenditures within their limited budgets by ensuring best value for money. Health Technology Assessment is being used in the decision-making process to assess the cost of the new technologies as compared to their benefits.

There are two frequently used definitions of HTA, one due to the International Network of Agencies for Health Technology Assessment (INAHTA), and a second by EUnetHTA. We will focus on the latter, as it emphasizes that HTA is a *process* (9;13). The role of HTA is to translate basic research into the healthcare decision-making process through rigorous analysis of factual information. Both primary and



	New all type cancer cases	Lung	Breast	Colorectal	Stomach	Prostate
2009	3062704	409981	387101	406292	186979	253299
2020	3424466	464424	416517	462940	207183	303030

Figure 1. The number of new cancer cases in Europe in 2009 and projections for 2020. Source of data: Economist Intelligence Unit (8).

secondary studies can be included in HTA. Moreover, the usually required summary of evidence does not mean that HTA needs to be limited to the synthesis of existing evidence. To make use of the best available evidence, also results of primary, targeted studies can be included, especially in those cases where other information resources are not (yet) available. HTA can also indicate the need for completely new research identified by the HTA process itself. Currently, a most urgent challenge for HTA is the evaluation of new technologies and diagnostics for personalized health care, in particular in cancer, obesity, diabetes, autoimmune, and psychiatric diseases and within a reasonable time frame.

The Pathway Toward Translation

There are two main gaps within the pathway translating health research into healthcare delivery: (i) the translational gap separating basic and clinical research from new concepts, technologies, and products; and (ii) the gap in the translation of those ideas and products into health care. While bridging the first gap requires preclinical development and early clinical trials, crossing the second gap involves HTA, Health Services Research (HSR) and knowledge management (7;19). The translation of new ideas and products into practice is a multi-step process. Moreover, a wide variety of stakeholders are involved at the various levels in the decision-making process, for example, medical expert societies, patient organizations, HTA agencies, industry, and health insurance providers. Although the procedures involved in the translation differ significantly between countries a common process can be discerned.

In the practice of traditional technology assessment (TA), there are four main procedural steps that lead to the diffusion of new methods and technologies into the European healthcare systems: (i) market authorization (involving the European Medicines Agency (EMA) or national agencies); (ii) process of technology assessment (involving national or regional technology assessment agencies or offices); (iii) process of technology appraisal (by advisory committees or consultative councils); (iv) final coverage decision (by a Ministry of Health or equivalent authority) (21).

The first part of the translational pathway of, for example, drug development ends with the conclusion of clinical

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trials that have been successful with regard to safety and efficacy and led to market approval for the drug, diagnostic, or device (7). The subsequent assessment through HTA methods differs from the assessment-phase before authorization in terms of patient-relevant outcomes, and "real-world" effectiveness in day-to-day practice in comparison with current standard of care. Furthermore, compared with most tools of socioeconomic evaluation which tend to have a single outcome, HTA can produce several outcomes. To evaluate value-for-money aspects, HTA methods also include the assessment of the cost of treatment using cost-effectiveness or cost-utility analysis, similar to the socioeconomic evaluation. In fact, in the case of drug development HTA begins in the course of the second translational gap, at a moment when methods, technologies, or products have obtained approval and reached the market.

This is the usual route for the translation of drug development—from basic to clinically applied research—which provides efficacy and safety assessment at the population level. However, individualized, targeted therapies may well require different strategies for the translation of basic research into health care. As outlined below, new models of HTA are needed that can account for the specific type of evidence that is inherent to these novel therapies (22).

Personalized Health Care and Systems Biology

Personalized medicine and personalized health care are not novel concepts. On the contrary, applying medical knowledge and adjusting diagnostics and therapies to provide the best possible treatment to the individual patient is and has always been at the core of clinical medicine (17). The insight that an individual's state of health is determined by the interaction of a multitude of factors, including age, sex, environment, nutrition, lifestyle, inherited and acquired genetic make-up is not new either (23). So, what is new about personalized medicine and health care today?

The developments in the genomics sciences and related technologies and the application of systems biology to the understanding of human health and disease are drivers behind a truly innovative personalized systems biomedicine. Progress in the genomics sciences goes far beyond the sequencing of DNA—ever faster and cheaper, making individual whole genome sequences clinically available—it involves, for example, the generation of data on gene expression, including transcriptomics, proteomics, and metabolomics, and analysis of the epigenome (2). These data are collected at the level of the individual patient and potentially even compared between healthy and diseased tissue of that individual, or longitudinally in the same tissue (e.g., blood) of an individual. Systems biology analyses of the genomic and proteomic data sets provide insights into genome–environment interactions and they advance our understanding of the development and progression of diseases. Despite terminological discussions and conceptual critique, systems biology appears to provide a comprehensive epistemological framework for the interpretation of the vast amounts of biological data (6).

Systems biology aims to understand the principles governing how biological functions arise from the interactions of components of biological systems (26). It addresses the complexity of living systems and attempts to integrate all levels of organization from molecules, cells, tissues, and organs to the whole organism. Systems biology integrates disparate, so-called "omics" data sets (see Table 1) and gives them meaning in terms of mechanisms of network behavior. Cancer is a "systems biology disease," in which molecular defects lead to malfunctioning (perturbation) of regulatory and signaling networks at the cellular level, leading to a disease that affects the whole organism (11). Indeed, recent insights have led to a reclassification of the disease: cancer is no longer defined in terms of the affected organ (lung cancer, breast cancer, colon cancer) but increasingly characterized by the molecular networks that are involved in the individual patient. This means that therapies targeting cancer pathways need to be selected based on individual disease features relative to the individual healthy tissues of the patient, thereby necessitating "personalized systems biomedicine" in cancer treatment. Examples of drugs that have become an established part of cancer therapy are monoclonal antibodies (mAbs), like trastuzumab which interferes with HER2/neu receptor or bevacizumab which recognizes and blocks vascular endothelial growth factor A (VEGF-A), and small molecules, like imatinib, targeting several tyrosine kinase receptors such as the platelet derived growth factor receptor (PDGF-R). Currently, a few hundred mAbs and small molecules are in the cancer-drug development pipeline (1).

Requirements for Systems Biology-Based Personalized Medicine

There are many requirements for systems biology technologies in the context of personalized medicine. Fully automated high-throughput systems for molecular analysis are needed, accurate in terms of sensitivity and specificity, able to deal with large amounts of heterogeneous micro-scale samples and linked with a computational platform that recognizes meaningful signal among noise, integrates and thereby reinforces various types of information and turns the integral into useful knowledge on function and malfunction of the various molecular networks in the diseased individual.

Apart from the molecular information, systems biology-based personalized medicine needs a comprehensive concept for the collection and management of both genotype and phenotype data, including health information on family history and environmental exposures. Patient-centric, longitudinal, and cross-institutional electronic health records (EHRs)—with provision of data encryption and privacy protection—should enable full interpretation of integrated genetic and genomic testing results (25). Information on relevant

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Table 1. Definitions of the Key Concepts as Used in This Article

Personalized health care	Health care tailored to individual patient's need, based on the molecular analysis of gene expression, transcriptomics, proteomics, metabolomics, and analysis of the epigenome in individual patient, increasingly amplified with systems biology models.
Targeted therapy	A type of treatment that uses drugs or other substances, such as monoclonal antibodies or small molecule inhibitors, that target a specific pathway in the growth and development of a cell, mostly but not exclusively in cancer.
Pharmacogenomics	The study of drug response in the context of the entire genome. (http://www.pharmgkb.org)
Systems biology	Systems biology aims to understand how biological functions arise from the interactions of the components of biological systems (26).
Disruptive innovation	Innovation which is able to fully disrupt the market by fundamental change in the system (24).
Omics	*Omics* is a general term for a broad discipline of science and engineering for analyzing the interactions of biological information objects in various 'omes.' These include genome, proteome, metabolome, expressome, and interactome. The main focus is on: (i) mapping information objects such as genes, proteins, and ligands; (ii) finding interaction relationships among the objects; (iii) engineering the networks and objects to understand and manipulate the regulatory mechanisms; and (iv) integrating various omes and omics subfields (Omics Wiki, http://omics.org).
Micro-scale samples	Sample preparation processes developed for micro-scale volumes in miniaturized formats.

subpopulations is needed to put the data into perspective (14). Realistic mathematical models and bioinformatics platforms with adequate privacy protection in place are essential to help draw things together for each patient (5).

Toward Personalized Cancer Treatment

There are several research projects based on systems biology and aiming at the discovery of tumor biomarkers, relying on next generation sequencing and high throughput molecular analysis techniques (16). Potentially, these projects will lead to the development of personalized biomarkers, enabling sensitive and specific tumor monitoring and targeted therapies based on the specific biological features of the disease of the individual patient. Data on ongoing basic research in academia or industry are hard to obtain. The NIH Clinical Trial registry provides information about research projects in academia and industry that have reached the stage of initial clinical trials. To date, by the end of 2010, the number of clinical studies using molecular biomarkers as a guidance to individualized targeted cancer drug therapy is still relatively small: only two studies similar to Mutanom could be identified.

One example of systems biology-based basic research that is on the verge of entering initial clinical trials is the Integrated Genome Research Network (IG) Mutanom project.

The Mutanom Project as an Example

The IG Mutanom project was launched in June 2008 and is supported by the German National Genome Research Network (NGFN) (12). Its main goal is to understand the effects of cancer related mutations at the level of the molecule, the cell, and the organism. Research is conducted on human cell lines and in mouse models using functional genomics approaches and next-generation sequencing platforms. It is expected that the integration of the experimental results through a modeling approach and translation to the clinical and the Public Health sector will lead to the development and introduction of a highly innovative, mutational profiling tool for use in routine diagnostics.

The early stage, basic research in Mutanom includes: (i) identification of cancer-related somatic mutations by means of database mining, high-throughput sequencing analysis of cancer tissues and established cancer cell lines, with the focus on cancer of prostate, stomach, colon, and breast; (ii) characterization of these mutations and genetic (somatic) alterations both on a functional level and in a molecular pathway level, in cells and mouse knockout models; (iii) determination of cellular parameters: protein levels, protein modifications, mRNA and in cell lines; (iv) integration of these data with patient data, tissue parameters (protein & mRNA expression, mutations) and clinical parameters (metabolism, disease progression; drug response efficacy); (v) modeling of quantitative parameters obtained from the experimental and clinical data in terms of their expected effect on the main

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cellular signaling pathways; (vi) identification of new molecular targets for the development of site-specific chemotherapies.

This early stage research, is located at the very beginning of the translational pathway, that is, in the first translational gap, see also Figure 2. It is quite distant from the later stage where established HTA is currently used. In the next section we will consider the feasibility of some type of "precursor" HTA-related activities that could be applied in this early phase.

RATIONALE FOR EARLY HTA METHODS

HTA Revisited

Currently, HTA agencies base their recommendation on nine main HTA domains: (i) current use of the technology (implementation level), (ii) description and technical characteristics of the technology, (iii) safety, (iv) effectiveness, (v) cost, economic evaluation, (vi) ethical aspects, (vii) organizational aspects, (xiii) social aspects, and (ix) legal aspects.

One of the most important questions is whether current HTA methods are appropriate for technologies that will be used in personalized diagnostics and treatment. A similar problem did occur during the assessment of orphan drugs for rare diseases with a market of limited application. If there are very few patients globally, and for as long as systems biology-based knowledge is limited, it is impossible to give recommendations based on the highest level of evidence. Until now, evidence gained from large randomized controlled trials (RCTs) showing consistent impressive benefits combined with few adverse events and minimal inconvenience and cost, is regarded the "golden standard." The evidence hierarchy, with RCTs on top and expert opinions on the lowest level, was originally created to rank evidence according to its quality. The aim was to raise awareness that some forms of evidence are more trustworthy than other. Although high quality evidence does not automatically lead to strong recommendations, expert reports, case reports and other uncontrolled clinical observations are still explicitly labeled as very low quality evidence (10).

Mutanom: Disruptive Innovation?

Approaches like the one being developed in the Mutanom project have the potential to change cancer diagnostics and treatment profoundly, therefore they can be classified as a highly innovative technology. When successful, such technologies will initiate the process called disruptive innovation (24). That will be the case if the new approach of diagnostics and treatment ultimately results in the replacement of current cancer management methods with personalized methods. This potentially disruptive innovation, as a consequence, calls for new strategies in HTA and for the rethinking of the HTA process as a whole.

Looking Forward: Very Early HTA

HTA methods were originally created to compare technologies that have already been used in health care with new and emerging technologies like those developed by Mutanom. The typical HTA report consists of safety, efficacy, cost, and cost-effectiveness analyses. Ethical, organizational, social, and legal aspects of the technology are claimed to be part of the assessment and to impact the decision-making process. Substantial progress in the latter areas made in the past decade, is all too often neglected in classical HTA reports. Nevertheless, these non-technical aspects are highly relevant for the assessment of technologies, already in very early stages of development, and for the assessment of innovative technologies, such as those currently being developed within the IG Mutanom.

Constructive technology assessment (CTA) is an example of a new approach in HTA that has been put into practice already (20). CTA focuses on design, development, and implementation of innovative technologies and represents the reasonable alternative tool to the usual cost-effectiveness analyses within the HTA reports. This method of CTA does not exclude HTA, but is based on it. It may be seen as the early phase of the technology assessment process, hence as part of the wider whole HTA process. The great advantage of CTA is that it can be applied already before the new technology has been put into practice, while the usual cost-effectiveness analysis can only start after the market position of the technology has been established.

POLICY IMPLICATIONS

Some concluding remarks on the future potential of the outcomes of the projects based on systems biology approaches are due. If successful, the future models for diagnostics and treatment of cancer will have a broad impact on individual and public health. The same approach is also increasingly used in the development of models for other complex diseases, for example, infectious diseases, diabetes mellitus, autoimmune, neurodegenerative, and psychiatric diseases.

Systems biology-based research projects offer new options for pharmacogenomics, not only by facilitating the prediction of drug efficacy and of potential adverse events and by allowing an optimization of choice among existing therapies, but also through the development of new therapeutic strategies and diagnostics. However, for any of these applications the key question arises of how to prove—on the individual level—the efficacy and safety of new individualized diagnostics and treatment technologies, as well as their cost-effectiveness, in terms of the requirements of current evidence-based medicine (EBM) and HTA methods on the population level. Regulatory agencies at the national level, but also the FDA on the international and the EMA on the European level, are used to base their decisions on high level evidence gained from randomized controlled trials. Such trials, however, may be extremely complex and costly, may

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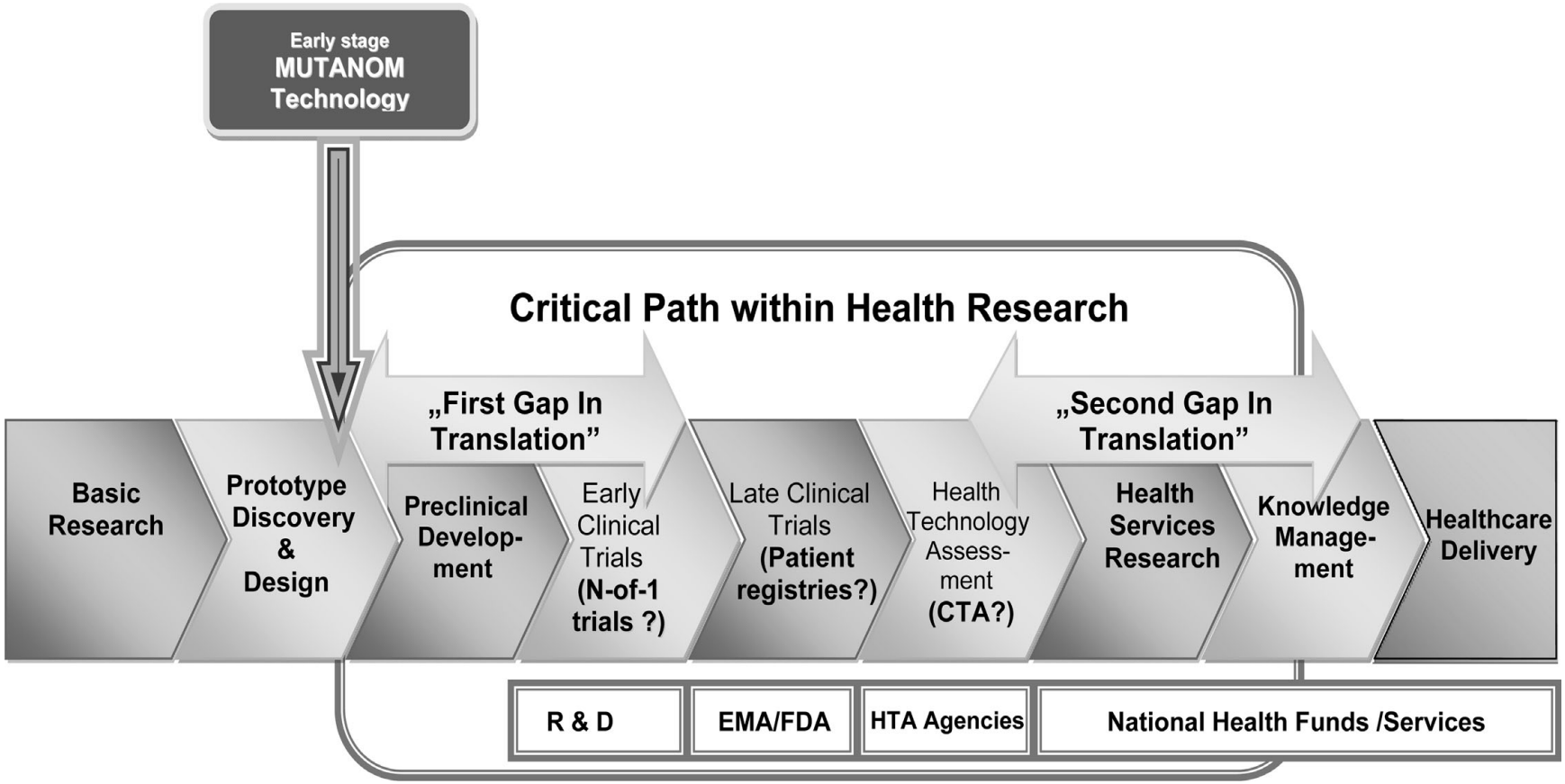

Figure 2. Pathway for translation of MUTANOM technology into healthcare delivery. Figure adapted from Cooksey (7).

pose serious ethical dilemmas, and, eventually, the results may not be applicable for developing personalized therapies. A clinical trial where a large number of patients would be treated using individually targeted therapies and a control group would receive standard care, requires a highly unusual study protocol. The study arms would not compare drugs (or drug and placebo), but series of subgroups consisting of single or few patients each with an individually targeted drug. If this will be the case, do we need to reconsider our "golden standard" of large numbers, and instead think in terms of "personal evidence"? We believe that other models of clinical trials must be considered. Exploring the usefulness of Phase 0 trials, N-of-1 trials, and new models of adaptive clinical trials will be part of our further research (4;15;18). Trial evidence may have to be convoluted with systems biology modeling, such that multiple trials validate the mathematical model which then subsequently can be used to predict treatment effect for a variety of individual patients and their individual tumors. Only this approach can be cost-effective. When entering the stage of clinical trials, ethical and legal aspects become particularly relevant. Each new trial model will require appropriate consent protocols and must meet all relevant legal criteria.

Furthermore, incorporating electronic health records (EHRs) into the healthcare system will be invaluable when assessing personalized medicine interventions. EHRs can transform the research infrastructure through supporting secondary use of health data including analysis, research, quality, and safety measurements. EHRs can be the source of so called real-world patient data, and replace today's patient registries, as they will be comprehensive with respect to clinical and environmental details on the individual level. Thus, EHRs may be kept by the individual allowing the health management by the person her- or himself ("personal health management"), assisted perhaps by user-friendly systems biology models. However, EHR data can also be used for monitoring and surveillance on the population level (3). The introduction and use of EHRs has a wide scope of societal implications. Suitable legislation and oversight must be put in place. Moreover, conditions for acceptability by potential patients and by the healthcare professionals need to be fulfilled.

CONCLUSIONS

From the regulatory and reimbursement system's point of view, it is now the right moment to raise questions about current HTA methods to adapt or change them just in time for the moment that personalized diagnostics and treatments will be ready for use in routine practice, in particular for cancer. Such a process should start soon, using models of very early "precursor" HTA methods, to not delay patients' access to potentially highly effective methods for diagnosis and therapy. It is the right moment also for the public health policy planning of countries, given the increased projected healthcare expenditures over the coming decades, due to the ageing society of Europe and other parts of the world, and the resulting increase in cancer incidence.

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CONFLICT OF INTEREST

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