

Personalised Health Care, the need for reassessment. A HTA perspective far beyond cost-effectiveness

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ABSTRACT

BACKGROUND: personalised health care has been claimed to play an outstanding role in the future health services. In fact, health care systems will have to face changes in their work flows and processes due to the implementation of personalised technologies. Health Technology Assessment provides information to decision makers at any level on the introduction and exclusion of health technologies from the health care systems.

METHODS: the definition of Health Technology Assessment (HTA) and the concepts and questions raised in the EUnetHTA core model, were used as a framework to analyse the impact of these new services in health care provision.

RESULTS: personalised health care services and products are health technologies, mainly diagnostics, that have a broad impact in the health care systems. Although, safety, clinical effectiveness and economical aspects and consequences have been described, ethical, social and organisational issues raised questions that should be answered before considering their implementation in health systems. Special attention should be paid on new requirements for regulation, data protection and the empowerment of citizen and health professionals.

CONCLUSIONS: the benefits and harms of personalised health care technologies should be decided on a “case by case” rather than a “one size fits all” basis and has to be analysed under its many aspects. The combination of genetic, clinical and environmental factors is crucial for the correct understanding of personalised medicine and its implementation. Personalised health care will require a fine-tuned revision of existing HTA and Pharmacoeconomic’s guidelines to address its characteristics.

Key words: HTA, Personalised Health Care

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INTRODUCTION

Personalised health care has been defined as the use of genetic or other molecular biomarker information to improve the safety, effectiveness and health outcomes of patients by more efficiently targeting risk stratification, prevention and tailored treatment-management approaches (1). Although

it is true that health professionals have attempted to tailor diagnostic and treatment options according to the characteristics of individuals throughout the long history of health care, there have been several recent changes in this context. The main change has been our new-found ability to identify, stratify and treat individuals, thereby avoiding the

previously used trial-error paradigms. This change has had a direct effect on many aspects of the current way in which health care systems are managed. Indeed, it could even lead to a revolution in the management of citizens and populations by diminishing uncertainties and increasing the ability of such systems to predict the impact of different interventions and programs on individuals and the population in general. However, this promising panorama has raised questions that will need to be solved as the continuous evolution of personalized health care produces more evidence and solutions regarding its application to both individuals and groups. These questions include whether current requirements for drug development are sufficient; whether new methods should be used to assess the value of therapies; whether new standards for value need to be defined; whether current mechanisms for treatment surveillance need to be reviewed; how personalized health care may affect regulatory systems; whether reimbursement mechanisms need to be changed to address the requirements of personalized health care; who should pay for the diagnostic tests required to support personalized health care treatments; whether health care systems should reimburse the cost of diagnostic tests not related to a change of management; how personalized health care may affect shared decision-making processes and the patient-health professional relationship; whether there is a need for new regulations regarding the use and collection of personal data; and how personalized health care may affect social inequalities. The more we anticipate and deal with these questions, the easier we will find it to hit upon solutions to most of them.

As the vast majority of these questions are related to health care decision-making processes in both health policy and practice, more information is required to accurately resolve them. In this sense, the International Network of Agencies for Health Technology Assessment (INAHTA) defines Health Technology Assessment (HTA) as the systematic evaluation of the properties, effects and/or impacts of health care technology to inform health care decision-makers in health policy and practice. This process may address the direct, intended consequences of technologies as well as their indirect, unintended consequences (2). Moreover, HTA is a multidisciplinary process that summarizes information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased and robust manner.

The role of HTA in health care decision-making

is expected to increase with the proliferation of new technologies (3) and the funding challenges affecting the sustainability of health care systems.

The challenges that personalized health care pose in the field of HTA will be addressed below and some possible solutions to the questions raised above proposed.

Personalized health care: a health technology

Taking into account that personalized health care covers a broad range of genomic-based products and services that enable tailored approaches to prevention and care to be designed, we can consider it to fall within the broad definition of health technology provided by Goodman in 2004 (4). Thus, health technology covers a sort of methods used to promote health, prevent and treat disease and improve rehabilitation and long-term care and includes drugs, devices, procedures, care settings and screening and prevention programmes. As such, the P4 concept of personalised health care, in other words personalised, predictive, preventive and participatory (5), broadly falls within the scope of HTA. Such personalised health care technologies are mainly included in order to prevent and diagnose and can be found in a wide range of diffusion stages, ranging from future technologies to more established ones. In any case, these health technologies suppose a change in the health care paradigm from provider-driven to consumer-focused health care, where the consumer or citizen will be expected to play a more relevant and active role in his/her health and wealth. This customization of health benefits, with the possibility of “anytime, anywhere” resulting from new, ad hoc health technologies such as telehealth, ambient assisted living (AAL) and web apps, will pose a major organisational and structural challenge to existing health care systems. Furthermore, major organisations such as Cancer Care Ontario, National Health Service Scotland (NHS Scotland) or the US Agency for Health Research and Quality (AHRQ) have started “horizon scanning” initiatives in order to identify current and future developments related to personalised health care and their implications (6-8).

METHODS

We should analyse the possible consequences of these so-called personalised health care technologies from an HTA perspective. For that purpose, we will include medical (safety, clinical

effectiveness and organisational aspects), social, legal, economic (costs and economic evaluation) and ethical aspects of these technologies and their possible impact on existing health care systems. In each domain we will partly use the structure of the European network of HTA (EUnetHTA) core model to aid us in the analysis (9).

RESULTS

The information will be structured based on the domains that are considered by HTA bodies when assessing a health technology, that is: safety, clinical effectiveness, costs and economic evaluation, ethical issues, organisational aspects, social and legal aspects.

Safety

The products and services, mainly diagnostics, covered by the umbrella of personalised health care increase, by definition, the safety profile of treatments by providing a more accurate and tailored establishment of indications. This affects both novel therapeutics and current research and development of new drugs, as well as existing ones, to the extent that personalised diagnosis could provide the basis for a better indication of existing treatments. Thus, on the basis of new evidence, HTA bodies will have to reassess existing technologies on their life cycle (Figure 1) and help to identify subpopulations of patients in which the safety profile of treatments allows their use. Post-marketing follow-up of health technologies, mainly drugs, will play a crucial role in this reassessment process by providing prospective data regarding the safety of treatments (10). Furthermore, HTA bodies will have to recommend the review of existing regulatory and reimbursement measures for the approval of treatments whose safety and risk-benefit profile is no longer appropriate (11). As a result, progress in the field of personalised medicine could lead to the modification and tightening of existing legal frameworks and requirements for the approval of treatments based on new evidence regarding their safety profiles. In any case, the definition of subpopulations with an admissible safety profile should be based on robust evidence, including both individual genomic data and clinical and demographical data. Health care systems should ensure that these mechanisms are adopted and implemented as quickly as possible in order to minimise their

possible impact on individuals (safety concerns), service providers (legal concerns) and health-technology manufacturers (legal concerns and delay in the approval of new treatments).

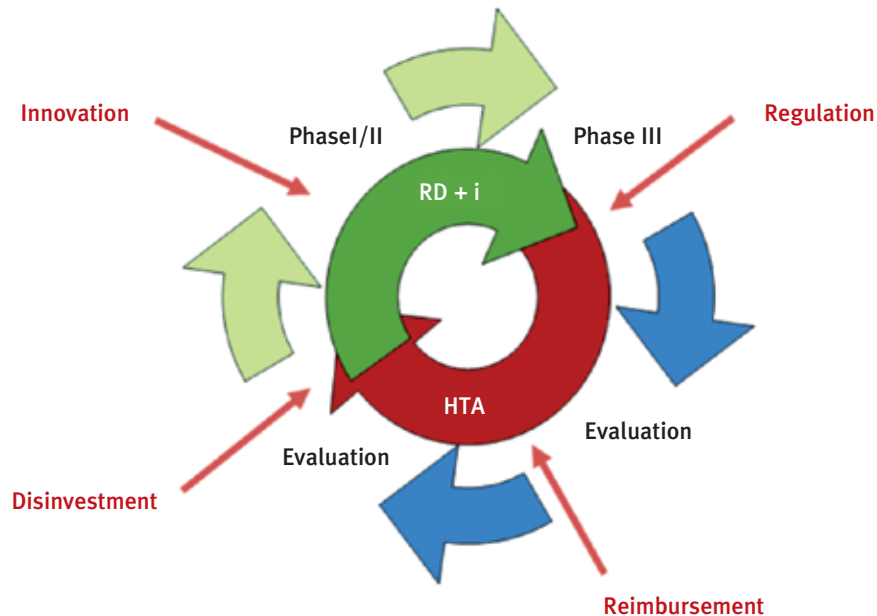
Clinical effectiveness

It has been claimed that personalised health care solutions increase the clinical effectiveness of treatments in a similar manner as safety aspects, in other words by allowing treatments to be tailored to those patients that are more likely to benefit from them (12). Clear examples could be found in existing cancer therapies and related diagnostic tools, such as: Human Epidermal Growth Factor Receptor 2 (HER2/neu)-Herceptin; KRas protein/Epidermal Growth Factor Receptor (KRAS/EGFR) - Panitumumab and Cetuximab; OncoType D - breast cancer chemotherapy; or anticoagulant therapy: PGx Predict - warfarin. As a result, the continual implementation of personalised health care services will decrease the uncertainties that arise when indicating treatments and provide invaluable information to health professionals for use when reaching decisions together with their patients. Despite this, the evidence that some treatments fail to benefit subgroups of patients has been claimed to change the randomized controlled trials (RCTs) paradigm currently used to demonstrate treatment efficacy (12). Moreover, some authors have proposed that the introduction of personalised health care solutions will increase the number of rare diseases by identifying subgroups that would not benefit from new or existing drugs for a concrete disease or condition (13). However, this does not mean that the trustworthiness of these sources of evidence will necessarily change.

One of HTA bodies' strengths is that they provide recommendations for reaching decisions on the basis of existing evidence, irrespective of what that evidence is. As such, new methods for grading the quality of evidence and strength of recommendations, such as the working group on Grading of Recommendations Assessment, Development and Evaluation (GRADE) (14), have been explored by HTA bodies (15). According to these methods, high-quality evidence, such as that obtained from RCTs, does not automatically lead to strong recommendations, and expert reports, case reports and other uncontrolled clinical observations could lead to strong recommendations for treatment indications (16).

FIG. 1

HEALTH TECHNOLOGIES IN THEIR LIFE CYCLE. THE ROLE OF HTA.



Some barriers for the incorporation of personalised health care services are not inherent to such services or their effectiveness but are common to diagnostic health technologies (17). Indeed, diagnostic technologies provide data regarding surrogate outcomes and HTA bodies are in agreement that a cautious approach must be taken as regards the use of such outcomes in technology assessment (18). Thus, the success of personalised health care diagnostic products is closely related to their link to changes in the management of patients for their benefit and not just to identifying risks or susceptibilities with no associated treatments or interventions that could change the prognosis or the course of the conditions. Furthermore as it occurs in other diagnostic technologies, the effectiveness should be measured on the basis of final outcomes on health and wealth of the citizens and not just on the change of intermediate clinical parameters or outcomes. In this sense, R&D activities of drugs will have to run in parallel with genomic diagnostic tools that enable health care systems and professionals to provide the treatments to those who benefit more.

The correct implementation of personalised health care services will require the combination of genomic, clinical and environmental data. This combination of sources of evidence is a challenge

that should be kept in mind when translating such evidence into recommendations on health practice and policy. On the one hand, some European initiatives such as Information and Telecommunication for the Future of Medicine (ITFoM; <http://www.itfom.eu>) are trying to bridge this gap by providing reliable evidence that combines such different sources. On the other hand, there is a chance for the impact measurement of primary prevention interventions based on life style changes including nutrition (19).

Costs and economic evaluation

The cost of genome-sequencing services has decreased dramatically over the past two decades (20) from a level that was unaffordable even for health care systems (95 Million US\$ per genome in 2001) to one which can be paid by individual customers (7000 US\$ per genome in 2012). Despite this, their use in clinical practice isn't as widespread as it perhaps should be in light of their promising implications for patients' health (safety and clinical effectiveness). Possible barriers to their implementation include a lack of strong scientific evidence in some fields and lack of a clear reimbursement system for related services (21). One of the main issues when analysing the implementation of a health

technology is who will pay for it and how the reimbursement mechanisms will be established. For example, a Public Health Service provider will not pay for a technology that does not change the management of a patient, although financial incentives could be discussed if the outcomes may encourage them to assume a more active role in their own health care.

Some authors have stated that personalised health care may decrease the budgetary impact of the introduction of new health technologies, mainly drugs, by indicating treatments only for those patients who would benefit the most, as has been seen for the recently introduced diagnostic tests for the indication of certain novel chemotherapy solutions (12). Despite this, various questions, such as those relating to who should assume the costs of diagnostic tests or how new reimbursement mechanisms for drugs associated with a more tailored indication should affect pricing policies, remain to be solved. In light of this, discussions should take place between policy makers, health care service providers and health-technology manufacturers in order to define whether the co-development of drugs and genome-based diagnostics that help to tightly define indications will be required for approval or as an incentive for reimbursement.

With respect to the cost-effectiveness of personalised health care, it must be said that other authors have analyzed this aspect partially (22) and admit that personalised health care impacts on the Quality Adjusted Life years calculation, sensitivity analysis and discounting, due to the inherent characteristics of the technology, its accuracy and predictive values and related clinical utility. Thus, existing Pharmacoeconomic guidelines should be revised accordingly to address these issues.

Ethical issues

The consequences of personalised health care are difficult to predict as a whole. It is, however, clear that new genomic-based diagnostic approaches may have far-reaching consequences in the field of health care by changing the concepts of disease and diagnosis used to date. Despite this, they raise other questions relating to the information itself, its collection, its protection and its ownership. Although we would need a full article to

discuss the ethical consequences that these services could have for the general public, we will nevertheless attempt to mention some of the most important ones, especially whether we have a sufficient understanding to justify population-based genome sequencing; who will own the information collected; who will collect it; how the information will be safeguarded, whether all patients have a sufficient understanding of this field to be able to reach a reasoned decision based on genomic information; whether personalised health care services are likely to be fully accessible to the population as a whole; or whether they will result in further inequalities, such as access to diagnostic technologies at unaffordable prices and to their related tailored treatments. The consequence would be that the gap among subgroups of citizens will increase.

Although personalised health care has been claimed to increase patients' and/or the public's autonomy, it has also been claimed that not even professionals have a sufficiently in-depth understanding to be able to clearly explain the consequences of genomic information to their patients (23). Similarly, increasing patients' autonomy could affect the current status of health professionals by forcing them into uncomfortable situations where they have to admit their lack of knowledge or share uncertainties.

Personalised health care could also affect human dignity by labelling people and defining subgroups that could be excluded from society, stigmatised or even discriminated against when applying for employment or requesting life or health insurance. Likewise, the impact of personalised health care on human integrity should also be considered as it could affect moral convictions, preferences and commitments, including the right not to be tested or diagnosed. This question should be considered with particular care when promoting population screening and population genome sequencing programmes as such programmes are likely to directly impact human rights.

Finally, the benefits and harms of personalised health care technologies should be decided on a "case by case" rather than a "one size fits all" basis. In light of the above-mentioned ethical aspects, current legislation should be analysed carefully in order to make it clear that all possible consequences have been considered.

Organisational aspects

Personalised health care services create a new concept in the field of health care provision by placing particular emphasis on wellness and disease prevention (23, 24). Thus, whereas current health care services are mostly based on a hospital-centred concept of provision, this new paradigm goes back to models where primary care and public health play an outstanding role (Figure 2). A change in work- and patient-flow processes will therefore be needed to fulfil these new requirements. Similarly, as patients' autonomy will be empowered and shared decision-making will become possible, the tasks and time dedicated to patients, especially in primary health care, will have to be carefully rescheduled. In light of this, special effort should be dedicated to staff training on genomics, management of genomic information and its consequences, and the acquisition of shared decision-making skills, and to this end, providers should include health literacy as part of their commitments.

Patient stratification by risks profile and status has been claimed to be a key measure for increasing the efficiency of health care systems and ensuring their sustainability (25). In this respect, personalised health care solutions could provide evidence to reduce the uncertainties when stratifying the population by more accurately establishing these subgroups.

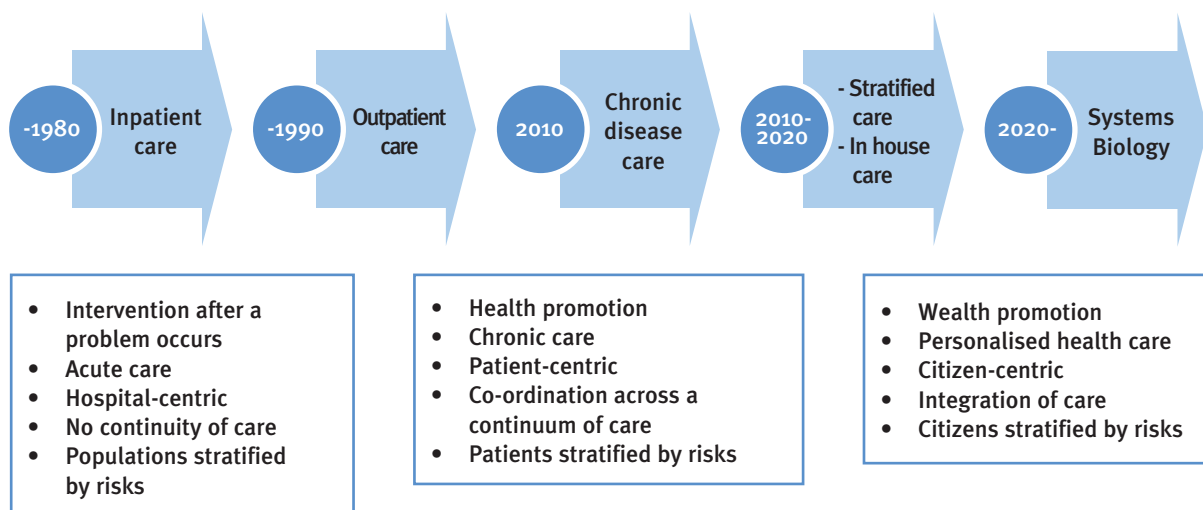
Decisions regarding the centralisation of diagnostic services and decentralisation of decision-making processes will be needed, and funds must be made available for personal data protection and supercomputing systems to treat genome, clinical and environmental data. It is true that, from a Public Health Services provision and citizens' perspective, the new paradigm is an opportunity that should not be wasted. As such, both patients and Public Health Systems should be empowered to ensure that information is used in a proper way and that it remains the property of the patient. Systems should also be put into place to ensure the acceptance of the new decision-making process (shared decisions) by both professionals and patients. The participation of the different stakeholders involved in this process should be a requirement when it comes to reorganising these services.

Social aspects

As has been described in the EUnetHTA core model, the social domain takes the patient as the starting point for its analysis of the manifold social implications of health technology (9). Thus, when applying personalised health care, we should consider positive aspects, such as the empowerment and increasing autonomy of patients and their relatives, alongside the possible consequences of stigmatisation of certain subpopulations according to their genomic, clinical and environmental data.

FIG. 2

TRENDS IN HEALTH SYSTEMS' FOCUS AND THEIR CHARACTERISTICS. THE DYNAMICS OF CHANGE.



Current technology makes internationalisation of the data possible.

Policies designed to promote the implementation of personalised health services should consider the consequences of these services from a social point of view, including the people involved, the support required and the costs involved, as well as people's reaction for or against such services. The assumption of value and the empowerment of patients may not always be seen as positive by all groups as they could affect a person's working ability, social relationships, the way in which they cope with illness and the treatment of, or attitudes towards, a labelled subgroup of citizens. Who will pay? And for which services? Will incentives for those who take care of their own health be promoted? Is genome sequencing a mandatory requirement to obtain health insurance? These questions and many others will influence the social perception of personalised health care products.

Legal aspects

The main legal consequences related to personalised health care concern the maintenance of citizens' autonomy, legal liability and protection of the information generated (26). In many cases, professional ethical guidelines become statutes or mandatory guidelines that must be adhered to. Health care is no exception to this, and as such legal issues are a fundamental part of a full HTA analysis. Taking into account that personalized health care is based on the decentralization of decisions and the centralization of data and analysis, one of the main risks could be the lack of harmonisation of laws in different contexts (3). The multicentric and international sharing of information allows researchers and citizens to manage increasing amounts of data that could be processed, thus allowing conclusions to be reached more quickly. However, although patients' autonomy, the collection of biological and clinical data and data protection are regulated by law in Europe (27), this is not always the case in other countries.

Careful attention should therefore be paid to the legal barriers concerning different

reimbursement and pricing policies throughout the world and their impact on the implementation of personalised health care services and products resulting from inequities and unequal access to them. HTA could play an outstanding role in this case as it was stated by Trostman et al, 2011 for private payers in the US (3). At the same time, legal liability, marketing authorisation, advertising and free movement of services should be harmonised in order to reduce both citizens' misconceptions and unlawful practices that could lead to fraud and abuse.

CONCLUSIONS

Personalised health care proposes a new via for the reorganisation of health care services and products, redefines the role of the patient/citizen in their relation with the health professional and bridges a gap to the understanding of health and disease. Its many sides and consequences should be carefully and profoundly analysed, including ethical, organisational, legal and social aspects. HTA, Health Outcomes Research and Health Impact Assessment could play a crucial role in this analysis. Furthermore, the benefits and harms of personalised health care technologies should be decided on a "case by case" rather than a "one size fits all" basis. HTA should be aware that the combination of genetic, clinical and environmental factors (including life style) is crucial for the planning of the future health care services. It will have an implication in: a) R&D activities, need of a combined development of diagnostic and treatment solutions; b) regulation, new requirements for treatments approval linked to a better definition of indicated population, and c) reimbursement, existing and future health technologies should be assessed along their life cycle. Although acute disease management (inpatient care), chronic disease management (outpatient care) and wellness management (in house care) continue being fundamental in health care provision, personalised health care supposes a change in the health systems paradigm and prioritises and emphasises the role of primary prevention, tailored to the citizen, in the health agenda. Thus, the investment dedicated to each parcel of the health care provision should be reoriented to answer to these new requirements.

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