SUMMARY PAPER

Recommendations from the 1+MG HEOR workshop

European member states • 1+Million Genomes • Whole genome sequencing

Summary

Advances in genomic sequencing technologies have enabled improvements in disease diagnosis, treatment and personalised care and prevention.

As genomic testing is generally regulated at national levels, each jurisdiction in the EU has different financial and infrastructural systems to implement whole genome sequencing (WGS). This could lead to different diagnostic and treatment strategies, and therefore different (unequitable) health outcomes across the EU.

Advances in technology and improvement in health come at a cost, unfortunately society's resources are limited. In order to gain insight in strategies to evaluate WGS and support responsible implementation of WGS in clinical practice, Health Technology Assessment (HTA) could provide information regarding e.g. cost-effectiveness, budget impact, value for patients and citizens, organisational and patient-related issues. Such evaluations are currently performed in many different countries without extensive discussion and collaboration (see appendix 1 for more background on the HTA approach for genomics in Europe). To avoid duplication of efforts and to harmonise methods used in Europe, a workshop (Lisbon, May 23-24 2022) was organised among key experts by B1MG WP5.

1+MG

1+MG HEOR working group

The 1+MG HEOR working group reviewed EU initiatives related to the implementation of whole genome sequencing into clinical practice. The findings were published in a summary paper. As a next step the group formulated recommendations towards the EC and member states. This work is part of B1MG WP5 Personalised Medicine and impact.

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When considering utilisation of WGS, it is likely that what is considered optimal use of health care resources would remain different between jurisdictions. Due to large variations in e.g. level of healthcare spending on a per capita basis and as a share of GDP across Europe, and differences in demographic characteristics, implementation strategies of WGS in healthcare practice will still differ. Transparency about (arguments for or against) policy decisions could help gain insight in lessons learned and distil key points to consider for HTA of WGS. HTA in early stages can steer towards cost-effective solutions.

There is no clear care pathway, nor understanding of a distinct evaluation framework in order to evaluate the use of WGS in each of the 1+MG use cases (oncology, rare diseases, common complex diseases and infectious diseases). In order to accumulate evidence, it is recommended to develop a shared understanding of care pathways across Europe. At present, there is no clear understanding or guidelines of how to evaluate the benefit for patients and citizens of WGS.

Relevant economic evaluation methods for genomics

- **Micro-costing** is a cost estimation methodology employing detailed resource utilisation and unit cost data to generate precise estimates of economic costs.
- **Budget Impact Analysis (BIA)** is an analysis tool that enables to assess the expected changes in the health expenditure of the budget holder (for example, the healthcare system) within a specific health context.
- **Cost Utility Analysis (CUA)** is an economic analysis in which the incremental cost of program from a particular point of view is compared to the incremental health improvement expressed in the unit of quality adjusted life years (QALYs).
- **Cost consequence analysis (CCA)** assesses a wide range of costs and consequences (effects) of the products you are comparing and reports them separately. It includes all types of effects, including health, non-health, negative and positive effects, both to patients and other parties (for example, caregivers).
- **Multi-criteria decision analysis (MCDA)** is a structured decision-making process that offers greater flexibility to incorporate multiple objectives than cost-effectiveness analysis or benefit-cost analysis.

Micro-costing is a so-called partial evaluation method that evaluates only one course of action. Full economic evaluation methods, such as CUA and CCA, provide more valuable information for decision-making. These methods compare the costs and expected consequences of the health intervention to an alternative action. Even if economic evaluations suggest that a health intervention provides good value, its budget impact may be so high that it cannot be adopted. Because of this, BIA is usually performed to estimate the financial consequences of adopting a new intervention.
The aforementioned measures do not indicate whether or not additional resources should be allocated to health care. Cost-benefit analysis, which expresses the net economic benefit in monetary terms, can be used to consider allocative efficiency across sectors of society.

Recommendations to European Commission and Member states

1. Collaboration

- Encourage collaboration between experts, member states, national reimbursement authorities, related programs and other stakeholders.
- Creating a consortium/pool of experts for implementing genomics into healthcare.
- Involve other stakeholders (other than ministries of health), that are involved in introducing technologies to also get their perspective.
- Organise regular meetings.

2. Data and information sharing

- Support a website where information can be shared (e.g. relevant publications, events, recommendations).
- Understand the evidence required by countries for implementation of genomics into healthcare.
- Share implementation and uptake models.
- Share data on a healthcare consumption, how is it used in various EU countries?
- Develop a platform for sharing health economic data.
- Merging clinical, genomic and social data may pose major GDPR challenges. Solutions for data collection should be found and shared.

3. Increase understanding of costs & benefits

- Identify the direct and indirect costs associated with WGS (e.g., data storing and analysing costs).
- Explore countries' perspectives on which societal benefits need to be taken into account for evaluating WGS.
- To truly understand the direct and indirect (clinical) benefits of WGS.
- To obtain credible information on the benefits, more research is needed to enable causal interpretation.

4. Modelling

- Stimulate collaboration of national reimbursement authorities to harmonise economic evaluation requirements.
- Develop methodology to evaluate the innovation and economic benefit of WGS.
- Consider using multi-criteria decision analysis and decide on what is needed (type of data/models) to more efficiently make decisions.
- Conduct pilot studies to compare models, indicators.

5. Implementation

- Identify whether, and if so how, adopting WGS would impact the care pathway.
- Finding a sustainable shared path towards an universal evaluation framework for genetic/genomic technologies is a priority.

Related European initiatives & programs

- ICPerMed provides a platform to initiate and support communication and exchange on personalised medicine research, funding and implementation. EPPerMed is a European Partnership for Personalised Medicine in collaboration with ERA PerMed
- HEcoPerMed stands for Healthcare- and pharma-economics in support of the International Consortium for Personalised Medicine.
- PERMIT develops recommendations for robust and reproducible personalised medicine research.
- Europe's Beating Cancer Plan sets out a new EU approach to cancer prevention, treatment and care. It will tackle the entire disease pathway, from prevention to quality of life of cancer patients and survivors, focusing on actions where the EU can add the most value.
- EUnetHTA supports collaboration between European HTA organisations that brings added value to healthcare systems at the European, national, and regional level.

Appendix 1

THE HTA APPROACH FOR GENOMICS

Thanks to research and innovation, new technologies with the potential to improve the health of populations through more effective care are continuously being introduced. However, not every technological development results in net health gains. There are several examples of technologies that did not produce the expected benefits or even proved harmful. On the other hand, health technologies of proven effectiveness pose a continuous challenge for health systems since their application may require the mobilisation of additional resources or redistribution of existing funds within the healthcare system. Therefore, to optimise available resources, it is necessary to ensure that health technologies are evaluated properly. The most effective technologies should be promoted while taking into consideration organisational, societal, and ethical issues[1].

Health Technology Assessment (HTA) is a multidisciplinary process that summarises information about medical, economic, social, and ethical issues related to the use of a given health technology. The main purpose of HTA is to provide policymakers with evidence-based information, so they can formulate health policies that are safe, effective, patient-focused, and cost-effective. In the context of rising healthcare expenditure and increasing budgetary constraints, HTA is considered a key tool to ensure the accessibility, quality, and sustainability of their healthcare systems. By determining the added value of a given health technology compared to others, HTA helps allocate national resources to effective health interventions[2]. The importance of implementing such an analytical approach is twofold: on the one hand, it avoids the uncontrolled implementation of technologies without proven benefits, which can lead to inappropriate management of patients, detrimental effects on patient health, waste of resources, and loss of public confidence in the medical profession; on the other hand, in line with the requirement for public health programs to maximise population health benefits, it supports the implementation of those currently available technologies that have proven effectiveness and cost-effectiveness[3].

Recognizing the role that HTA plays in supporting healthcare decision-making, European Union (EU) Member States have been introducing HTA processes at the national and/or regional levels over the past 20 years, but with major differences in the procedural framework and methodologies[4]. To help address this fragmentation, cooperation on HTA at EU level was promoted through Directive 2011/24/EU (the Cross-border Healthcare Directive), which provided for the establishment of a voluntary network of Member States' HTA bodies to support cooperation and exchange of scientific information among Member States. Following on from the directive, the HTA Network (as the strategic arm of EU cooperation on HTA) was established in 2013. This work was complemented by three joint actions on HTA (as the scientific and technical arm of the cooperation), carried out by the European network for HTA (EUnetHTA). In 2018, to further boost cooperation

Appendix 1

amongst EU Member States when assessing health technologies, the European Commission published a legislative proposal. This regulation, formally endorsed by the European Parliament in 2021, establishes a legal framework and procedures for the cooperation of Member States at EU level and promotes convergence toward the use of HTA tools and methodologies already developed by the EUnetHTA Joint Actions[4,5].

The HTA Core Model is the methodological framework for the production and sharing of HTA information developed within these Joint Actions. It has been developed to meet the most relevant aspects of all technologies through the presence of applications, each focusing on the assessment of specific types or uses, namely medical and surgical interventions, diagnostic technologies, screening technologies, and pharmaceuticals. Its structure consists of standardised assessment items grouped into nine domains of HTA, four of which are clinical (i.e., description of the health problem addressed by the health technology and the current use of other technologies addressing that health problem, description and technical characterization of the health technology, relative clinical effectiveness, and relative clinical safety of the technology) and five non-clinical (i.e., costs and economic evaluation of the health technology, ethical, organisational, social and legal aspects related to its use)[6].

The completion of the Human Genome Project in 2001 has generated enthusiasm for translating genome discoveries into testing applications that have the potential to improve healthcare. The resulting increased availability of genetic tests has made the assessment of their performance crucial for clinical and public health practice. However, the assessment of the risk and benefits of the resulting genetic and genomic tests is not straightforward. Given their complexity, rapid development and marketing, widespread impact on families and society, and the lack of standardised outcomes, one of the main challenges for their evaluation is the lack of scientific evidence on which to base such evaluations[3]. Several ad hoc evaluation methods have been proposed in the past, mostly based on the ACCE model, a framework named after the included dimensions (i.e., Analytic validity, Clinical validity, Clinical utility, Ethical, legal, and social implications), whereas only a minority were tailored adjustments of the HTA approach. However, while the ACCE-based models are strongly focused on the technical aspects of genetic and genomic tests, they generally lack a systematic analysis of the economic and organisational aspects of the delivery of the genetic testing program as a whole[3]. On the other hand, while HTA-based approaches have the advantage of integrating genetic test-specific evaluation dimensions within a traditional HTA structure, their extensive adoption has been undermined by their lack of validation and generalizability[3].

Therefore, finding a sustainable, shared path toward a universal evaluation framework for genetic and genomic tests is still a priority. Within this context, the EUnetHTA Core Model could serve as a reference tool for the assessment of these technologies. It is built

on solid theoretical and methodological principles, validated, capable of a comprehensive assessment of all the technical, clinical and delivery aspects of the technology and commonly shared across EU[7]. This would also help in the application of the new European regulation, which advocates the conduction of joint assessments of the clinical aspects of the most innovative health technologies[4], and genomic applications make no exception. According to this regulation, the HTA aspects that will be the object of joint assessments between Member States are the clinical domains included in the so called EUnetHTA Core Model for Rapid Relative Effectiveness Assessment (Rapid REA), a type of simplified assessment that is limited to the clinical, more transferable, aspects of health technologies[8]. The EUnetHTa core model also allows to analyse more broader values then only cost-effectiveness.

Such collaboration between Member States in the collection and sharing of information on the clinical domains could also alleviate some of the problems related to the evaluation of genetic and genomic technologies. Precisely, it could facilitate the evaluation of prognostic and presymptomatic genetic or genomic tests, as well as pharmacogenetic tests, whole genome sequencing (WGS) and whole exome sequencing (WES) testing, that often suffer from the lack of direct evidence of efficacy and economic, organisational, and patient management aspects [9,10,11].

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