Beyond One Million Genomes

D5.3

Economic models methodology and case studies

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Document History

Date	Mvm	Who	Description
25/05/2023	0v1	Iñaki Imaz-Iglesia (ISCIII)	Draft circulated to workshop contributors and 1+MG WG6 for feedback
09/06/2023	0v2	Ilse Custers (Lygature)	Draft circulated to the Special Group and the European Commission
05/07/2023	0v3	Nikki Coutts (ELIXIR Hub)	Version circulated to B1MG-OG, B1MG-GB and Stakeholders for feedback
24/07/2023	0v4	Ilse Custers (Lygature), Iñaki Imaz-Iglesia (ISCIII)	Comments addressed.
25/07/2023	1v0	Nikki Coutts (ELIXIR Hub)	Version uploaded to the EC Portal

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1. Executive Summary

Please note that the scope of this Deliverable has been extended following feedback from the reviewers and the title

"**Health Economics Models for Genomics in Healthcare - Recommendations for the application of Health Technology Assessment and Health Economics to genomics in the framework of the 1+MG Initiative**"

best describes the Deliverable after the introduced changes.

The B1MG Work Package 5 (WP5) has among its tasks one dedicated to address health economics aspects of the adoption of genomics in health-care. As a result of the activities performed by the WP5 is this deliverable that tries to contribute to the discussions about a sustainable implementation of genomics in the European countries providing recommendations about Health Technology Assessment and Health Economics and their application to genomics. It is necessary to clarify that the HTA concept includes Health Economics as one of the essential domains to be evaluated.

In order to elaborate this document the WP5 has organised a workshop entitled "Health Technology Assessment and Health Economics of Genomics in Health-care: Key Issues for Implementation". The workshop was organised with the objective of providing insights and facilitating discussion on experiences of national genome initiatives and/or relevant projects from Canada, France, the Netherlands and the United Kingdom. A total of 218 participants from 40 different countries were registered, mainly from academia, governmental organisations and industry. Researchers from ISCIII, Lygature and INSA coordinated the elaboration of this deliverable that is based on the experiences shared and lessons learned in the workshop and during the preparation of the workshop.

This activity has been useful to identify some key challenges for a successful application of the HTA methods to genomics. In addition the activity has served to develop a series of key recommendations, some related to the role of HTA in genomics, others with methodology and others about opportunities for international collaboration.

2. Contribution towards project objectives

With this deliverable, the project has reached or the deliverable has contributed to the following objectives/key results:

[Select 'Yes' (at least one) if the deliverable contributed to the key result, otherwise select 'No'.]

	Key Result No and description	Contributed

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Objective 1 Engage local, regional, national and European stakeholders to define the requirements for cross-border access to genomics and personalised medicine data	**1.** B1MG assembles key local, national, European and global actors in the field of Personalised Medicine within a B1MG Stakeholder Coordination Group (WP1) by M6.	No
	2. B1MG drives broad engagement around European access to personalised medicine data via the B1MG Stakeholder Coordination Portal (WP1) following the B1MG Communication Strategy (WP6) by M12.	No
	3. B1MG establishes awareness and dialogue with a broad set of societal actors via a continuously monitored and refined communications strategy (WP1, WP6) by M12, M18, M24 & M30.	No
	4. The open B1MG Summit (M18) engages and ensures that the views of all relevant stakeholders are captured in B1MG requirements and guidelines (WP1, WP6).	No
Objective 2 Translate requirements for data quality, standards, technical infrastructure, and ELSI into technical specifications and implementation guidelines that captures European best practice	**Legal & Ethical Key Results**	
	1. Establish relevant best practice in ethics of cross-border access to genome and phenotypic data (WP2) by M36	No
	2. Analysis of legal framework and development of common minimum standard (WP2) by M36.	No
	3. Cross-border Data Access and Use Governance Toolkit Framework (WP2) by M36.	No
	Technical Key Results	
	4. Quality metrics for sequencing (WP3) by M12.	No
	5. Best practices for Next Generation Sequencing (WP3) by M24.	No
	6. Phenotypic and clinical metadata framework (WP3) by M12, M24 & M36.	No
	7. Best practices in sharing and linking phenotypic and genetic data (WP3) by M12 & M24.	No
	8. Data analysis challenge (WP3) by M36.	No
	Infrastructure Key Results	
	9. Secure cross-border data access roadmap (WP4) by M12 & M36.	No
	10. Secure cross-border data access demonstrator (WP4) by M24.	No
Objective 3 Drive adoption and support long-term operation by organisations at local, regional, national and European level by providing guidance on phased development (via the B1MG maturity level model), and a	**1.** The B1MG maturity level model (WP5) by M24.	No
	2. Roadmap and guidance tools for countries for effective implementation of Personalised Medicine (WP5) by M36.	Yes
	3. Economic evaluation models for Personalised Medicine and case studies (WP5) by M30.	Yes
	4. Guidance principles for national mirror groups and cross-border Personalised Medicine governance (WP6) by M30.	No

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methodology for economic evaluation	**5.** Long-term sustainability design and funding routes for cross-border Personalised Medicine delivery (WP6) by M34.	No

3. Introduction

The recognition that access to genomic and linked phenotypic data has enormous potential to advance research and implementation of Personalised Medicine, led Europe to launch, in 2018, the 1+Million Genomes (1+MG) initiative[1]. The Declaration of Cooperation "Towards access to at least 1 Million Genomes in the EU by 2022" has now been signed by 24 Member States, the UK and Norway. The 1+MG Initiative seeks to provide cross-border access to genomic and related health data, and it is developing the infrastructure to enable secure genomic data sharing in a trusted environment. For this purpose the Beyond 1 Million Genomes (B1MG)[2] project provides coordination and support to the 1+MG Initiative since 2020, by driving the development of the infrastructure, the legal guidance and the best practices to enable cross-border data sharing.

Sharing of genomic and linked phenotypic data has the potential to have a high impact in advancing the implementation of genomic medicine in health-care systems. Citizens and patients can benefit from genomic data for accurate and timely diagnosis, more effective treatments with less adverse events, and accurate profiling for disease prevention. Research outcomes will likely expand the application of genomics in medicine exponentially in the coming years. However, implementation of genomics in health-care is complex, and requires adjustments in the governance, structure and organisation of health services, as well as dedicated investments.

The B1MG Work Package 5 (WP5) "Delivering Personalised Medicine cross-borders: Implementation in health-care systems and societal impact" is addressing the adoption of genomics in health-care systems, ensuring sustainability and equity in access. European countries are at variable stages of maturity regarding genomic medicine programmes, and have diverse health-care system infrastructures, processes and legislation. For implementation of genomics in health-care, it is therefore crucial that we understand what are the challenges faced by health-care systems regarding the use of genomics, how best practices can be shared, and how economic viability can be addressed.

Capacity building has been a priority in this context, and for this purpose WP5 organised three country exchange visits to countries with advanced implementation of the genomics in health-care. This resulted in the Policy Brief entitled "Genomics in health-care: Key issues for implementation"[3], which provides recommendations for addressing main aspects of genomics in the clinic: the engagement and trust of citizens and patients, health-care infrastructure, ethical and legal frameworks, synergies between the clinic, research and industry, and capacity building for health professionals.

To drive adoption of genomic medicine, WP5 also developed a Maturity Level Model (MLM) as a tool for health-care systems to self-assess the maturity of their genomic medicine practices(1). This MLM provides a common matrix for optimization of genomic practices in eight main domains, thus promoting equitable access to personalised medicine across Europe. The MLM addresses eight main domains, including Governance, Investment, ELSI, Public awareness,

[1] https://digital-strategy.ec.europa.eu/en/policies/1-million-genomes
[2] https://b1mg-project.eu/
[3] https://b1mg-project.eu/images/pdf/Policy_Brief_Genomics_in_Healthcare_2022.pdf

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Workforce, Clinical organisation, Clinical infrastructure and Data management. The maturity of multiple indicators for each of these domains is assessed by selecting one of five pre-defined maturity levels, which are indicative of maturity progression, from a non-existent or ad hoc level of implementation to an optimised level of maturity characterised by a system adaptable to opportunity and change, and in support of international cooperation. This allows not only the understanding of the maturity of practices for the use of genomics in health-care, but also the definition of a path towards optimization.

The MLM was piloted in eight European countries, providing important information about the common strengths, weaknesses and asymmetries of genomic medicine practices across Europe. Of particular relevance for the subject addressed in this deliverable, the pilot showed that there were many asymmetries in practices related to investment and economic models for genomics in health-care. This suggests that there is work to do to improve and homogenise Health Technology Assessment (HTA) and Health Economics models for genomics in Europe, and that best practice sharing is crucial for this purpose.

The WP5 performed a series of activities to progress on this topic:

1. A review of European initiatives about the implementation of Whole Genome Sequencing (WGS) in clinical practice, which resulted in the publication of a summary paper[4].

2. A workshop about harmonisation of HTA and health economics for genomics in Europe. It was a two-half day workshop held both online and in person (Lisbon, May 23th-24th, 2022), with participation of 25 experts of the 1+MG Working Group 6. The workshop resulted in the publication of a summary paper entitled "Recommendations from the 1+MG HEOR workshop"[5].

3. A second workshop with the aim to exchange experiences on HTA and health economics models and its application for genomics. It was a virtual workshop entitled "Health Technology Assessment and Health Economics of Genomics in Health-care: Key Issues for Implementation", that took place online on 18th April 2023. The workshop was organised with the objective of providing insights and facilitating discussion on experiences of national genome initiatives and/or relevant projects from Canada, France, the Netherlands and the United Kingdom.

In the light of the presentations and discussion held in the second workshop, the WP5 has written this document that aims to provide with recommendations about key elements of HTA and Health Economics that can facilitate a sustainable implementation of genomics in the health-care system and to support a harmonised approach across Europe.

HTA and Health Economics are not synonyms. HTA has been recently defined in an international consensus(2) as a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle. The purpose is to inform decision-making in order to promote an equitable, efficient, and high-quality health system. The definition includes also the following clarifying notes that are highly relevant:

Note 1: A health technology is an intervention developed to prevent, diagnose or treat medical conditions; promote health; provide rehabilitation; or organise health-care delivery. The intervention can be a test, device, medicine, vaccine, procedure, program or system[6].

[4] https://b1mg-project.eu/images/pdf/1+MG-HEOR-Summary-paper.pdf
[5] https://b1mg-project.eu/images/pdf/1+MG%20HEOR%20workshop%20summary%20brief.pdf
[6] http://htaglossary.net/health+technology

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Note 2: The process is formal, systematic, and transparent, and uses state-of-the-art methods to consider the best available evidence.

Note 3: The dimensions of value for a health technology may be assessed by examining the intended and unintended consequences of using a health technology compared to existing alternatives. These dimensions often include clinical effectiveness, safety, costs and economic implications, ethical, social, cultural and legal issues, organisational and environmental aspects, as well as wider implications for the patient, relatives, caregivers, and the population. The overall value may vary depending on the perspective taken, the stakeholders involved, and the decision context.

Note 4: HTA can be applied at different points in the lifecycle of a health technology, i.e., pre-market, during market approval, post-market, through to the disinvestment of a health technology.

The note 3 clarifies that HTA includes among the dimensions of value costs and economics implications. So, HTA is a discipline that includes Health Economics. Therefore, throughout this document, when we refer to HTA, we will also be including Health Economics.

4. Methods

A half-day workshop was held on-line on 18th April 2023, entitled "HTA and Health Economics of genomics in health-care: key issues for implementation". The objective of the workshop was to promote the exchange of experiences on assessment and implementation of genomics in health-care systems, as well as, to establish recommendations regarding key elements related with HTA that may facilitate a sustainable implementation of genomics in health-care systems. The organisers of the workshop were Lygature (The Netherlands), INSA (Portugal) and ISCIII (Spain).

We selected experts from countries with advanced HTA processes applied on genomics in their respective countries. The selected experts were:

- Prof. Isabelle Durand-Zaleski, Université de Paris, CRESS, INSERM, INRA. France.
- Dr. James Buchanan, University of Oxford. United Kingdom.
- Prof. Deborah Marshall, University of Calgary. Canada.
- Prof. Valesca Retèl, Netherlands Cancer Institute, Erasmus University Rotterdam. The Netherlands.

The experts were contacted in advance by email. The organisers of the workshop presented the workshop and exchanged with the participating experts a series of documents discussing the most important topics of interest for the WG. Those were the following:

- How is the HTA methodology applied to genomics in your country? What are the HTA domains used to evaluate genomics in your country?
- How the economic domain is taken into account within the HTA methodology used to evaluate genomics in your country?
- Are there differences between the HTA framework used for genomics and the routine HTA framework? If so, explain those differences.

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- How is the decision-making system to approve a list of genomic technologies to be reimbursed and how is the list updated?
- What is the financing/reimbursement model applied to genomics into your public health-care system?
- Main facilitators and barriers you found relevant in your country regarding a successful application of a HTA approach in genomics

The agenda of the workshop was agreed by the organisers. The workshop included an introduction to the B1MG project by Astrid Vicente (Instituto Nacional Saúde Doutor Ricardo Jorge, Portugal), followed by a brief introduction to WP 5.3 by Ilse Custers (Lygature, The Netherlands) and four presentations from the external experts. A roundtable focused on debating experiences was moderated by Iñaki Imaz (ISCIII, Spain) and Ilse Custers. The total duration of the workshop was three hours, with a 15-minutes break.

Researchers from ISCIII, Lygature and INSA coordinated the elaboration of this deliverable that is based on the experiences and lessons learned shared in the workshop and during the preparation of the workshop. The content of the workshop cannot be disseminated publicly because it includes some confidential data and presenters did not give us permission to disseminate it. This deliverable has also received comments from the participants in the 1+MG Working Group 6 and from the four selected experts who participated in the workshop.

A registration form had to be completed by those interested in participating in the workshop. This form included information about the participant's country as well as her/his background. According to the information gathered during the registration process the following figures were obtained:

- The total number of registered participants was 218 from 40 different countries representing the five continents of the world.
- Italy, Spain, Estonia, the United Kingdom and Portugal were the five countries with the highest number of registered participants in the workshop. Figure 1.
- Background profile: Most of the participants were from academia (40.1%) and governmental organisations (32.8%). Participants belonging to the industry (13.05), consultancy companies (9.4%), patient organisations (1.0%) and others (3.7%) were also registered. Figure 2.

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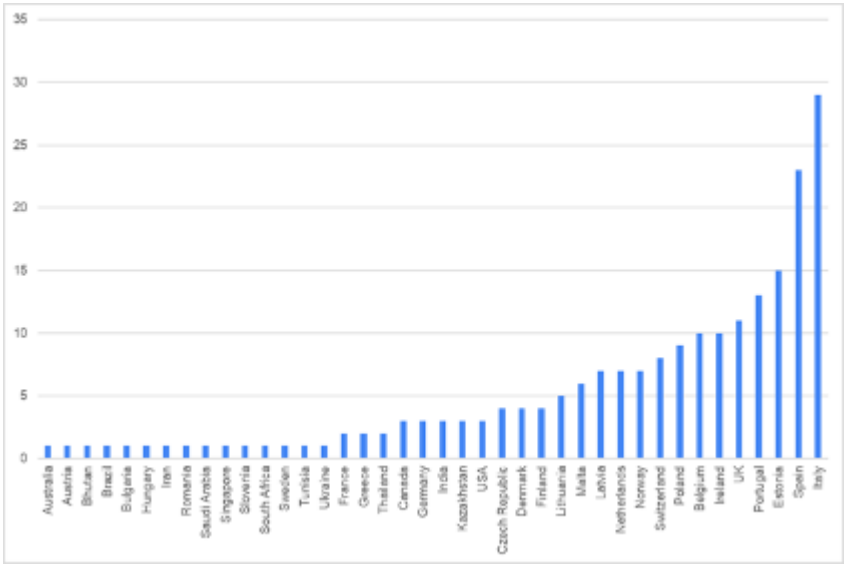

Figure 1: Participants in the workshop by country.

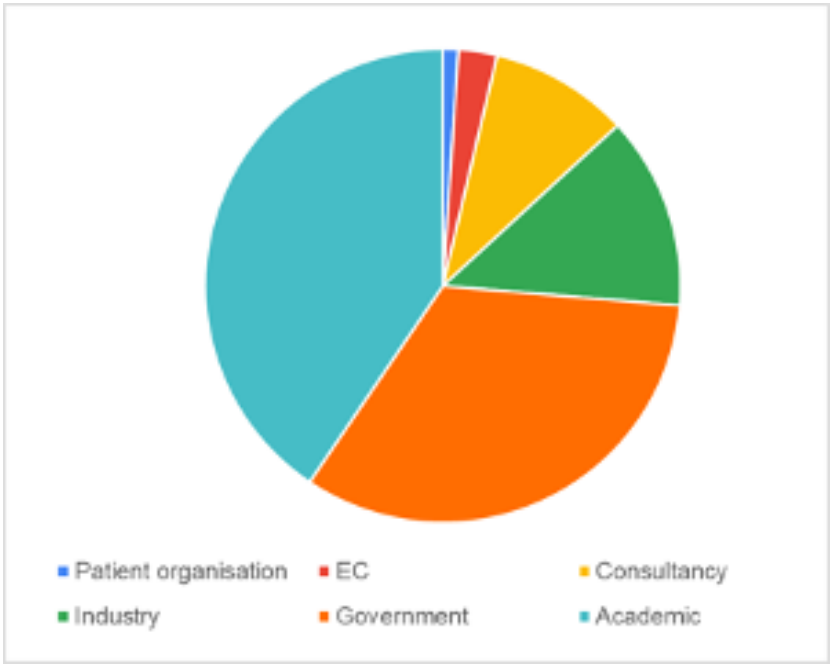

Figure 2: Participants in the workshop by background.

5. Results

France. “Assessing the impact of WGS on care pathways and health-care costs”. Prof. Isabelle Durand-Zaleski, on behalf of the Seqogen group.

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Prof. Isabelle Durand-Zaleski presented the France Genomic Medicine Plan 2025 (FGMP)[7], which includes the Seqogen project. This project is aimed to evaluate the impact of WGS on care pathways and health-care costs in France with real world data. The FGMP selected in 2017 two sequencing platforms to be financed by the French Ministry of Health. Those platforms cover the whole French territory providing genomic information to physicians of the French Health System. The platforms are located in Paris (SeqOIA) and Lyon (AURAGEN).

The FGMP establishes currently over 60 pre-indications for which physicians can obtain genomic information, but the list is regularly updated. Cancer and rare diseases are the main areas covered by the pre-indications. The Seqogen project aims to study costs, organisational issues, impact on care pathways (clinical benefits) and economic evaluation. The project is in progress and has the following challenges:

- Difficulties to establish a control group in order to assess clinical benefit and cost-effectiveness.
- Privacy issues are demanding and time consuming. Particularly important is the task of re-contact patients to obtain consent for the reuse of data.
- The linkage with databases or medical records to obtain cost data is a challenge.
- No quality of life data are available to be included in the project so cost per Quality Adjusted Life Years (QALYs) can not be calculated.
- Difficulties to agree with clinicians, researchers and payers about the performance indicators to be used to evaluate the platforms.

The issue about indicators to be used is particularly important for rare diseases. Some process indicators were agreed about rare diseases and cancer (delays, volume, case mix, type of sequencing). However outcomes indicators were agreed only in cancer but not in rare diseases (Off label drug use, actionable, vital status).

The presenter proposed some actions to do in order to progress in the international setting:

- An exchange of experiences and discussions between countries would make us progress and learn from each other.
- Participate in the International Consortia for Personalised Medicine (ICPerMed)[8] as a useful platform where to share experiences and discuss solutions.
- If the FGMP Board agrees the protocols and methods could be shared with other countries.
- An international collaboration and discussion is necessary in the future in order to avoid duplicating same problems, exchange tips on practical issues (ie. patients' consent), and adopt the best practices.

[7] https://pfmg2025.aviesan.fr/en/
[8] https://www.icpermed.eu/

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United Kingdom. "Use of health economic evidence to inform the implementation of genome sequencing in clinical practice in the NHS in England". Dr. James Buchanan, Health Economics Research Centre, University of Oxford, UK.

Dr. James Buchanan described the HTA framework in England, which is coordinated by NICE (National Institute for Health and Care Excellence[9]), and particularly its application to genomics. NICE evaluates many of the new health-care interventions that are introduced in England, with diagnostics primarily being evaluated via the Diagnostic Assessment Programme (DAP)(3). The DAP has performed 40 evaluations since 2011, but few of these have considered genetic or genomics interventions, with exceptions such as tumour profiling tests for breast cancer. Instead, genetic and genomic diagnostic tests often emerge into clinical practice via the development of "Gene Dossiers". Those dossiers contain limited information on clinical validity/utility, and sometimes test costs, but rarely present the robust health economic evidence that would appear in a typical NICE appraisal.

Although there is no clear HTA framework used for genomics in England, there is also no consensus that a specific assessment framework for genomics is required. Indeed, there are arguments for and against genomics being a special case for HTA. Genomics does pose challenges for standard HTA methods (related to the rapid evolution of testing technology and genomic knowledge, the lack of robust cost data, weak effectiveness data, and the use of outcome measures may not capture all relevant dimensions of outcomes) but the relative significance of these challenges is debated.

Dr. Buchanan then presented his experience conducting health economic analyses using data from the the Genomics England 100,000 Genomes Project (100KGP)[10]. As part of the 100KGP, a health economics clinical interpretation partnership was established in 2016 to apply/develop health economic methods to better understand the economic impact of genome sequencing in clinical practice and the incentives for evidence generation.

This partnership is working on different activities, including:

- Estimating the costs of genomics in cohorts of rare disease patients.
- Estimating diagnostic yield of genomic sequencing in rare diseases(4).
- Estimating cost-effectiveness of sequencing in exemplar disorders.
- Calculating the secondary care resource use of cancer patients undergoing genome sequencing.
- Quantifying the extent of inequalities in access and outcomes related to genomics(5).
- Using the above health economic evidence to inform the design of the forthcoming newborn sequencing programme.

Regarding cancer, the preliminary results of a 100KGP study suggest that sequenced patients experience fewer and shorter hospital episodes compared to non-sequenced patients. These effects vary over time and across cancer types (results not published yet).

[9] https://www.nice.org.uk/
[10] https://www.genomicsengland.co.uk/initiatives/100000-genomes-project

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Regarding rare diseases, preliminary results indicate that genomic testing has the potential to reduce the diagnostic odyssey and also reduce the costs per person.

More generally, Dr. Buchanan noted that the extent to which health economic evidence has informed clinical practice in England is unclear. The evidence base on the value of sequencing is sparse, and there are few relevant economic evaluations in England and abroad. However, sequencing is still being implemented in clinical practice, which suggests that broader considerations (including political priorities) may be informing implementation rather than clinical or economic evidence. In the UK, for example, it is a priority to position the UK as an international leader in life sciences. Consequently, it may be the case that macroeconomic evidence returns to investment in national sequencing programmes is valued more highly by decision-makers than evidence from more narrowly-defined cost-effectiveness studies.

Dr. Buchanan also outlined some key challenges, lessons and next steps. Performing a robust cost-effectiveness analysis of a genomic intervention is demanding in terms of resources, skills and expertise. It requires a multidisciplinary approach, with health economists involved from the early design stages of a study onwards. A key early task is to identify appropriate comparators of counterfactual populations (e.g. people who have not undergone genome sequencing) and ensure appropriate data is also available for these populations. There are also no shortcuts when undertaking high quality health economic analyses; the time required to clean genomic data for these analyses can be lengthy, and this should be incorporated into planning.

Some elements of the health economic analyses conducted in England may be transferable to other countries, such as patterns of care and clinical benefit results. However, estimates of costs and costs-effectiveness may be more context specific. It is also crucial to share best practice in health economics between countries to avoid repeat problems or mistakes. Finally, there is value in exploring the possibility of establishing a common core of datasets that can be shared across countries.

Canada. Challenges in Assessing the Value and Impact of Genomics in Health-care Systems. Prof. Deborah Marshall, University of Calgary, Canada.

Prof. Deborah Marshall started her presentation discussing about the concept of value and its evaluation applied to genomics and personalised medicine. There is a rapid rise in the availability of new personalised medicines and genetic tests on the market in the last 15 years(6). However, at the same time the concern about the increased cost for health systems related with the advance of personalised medicine and genetics already expressed in 2002 by Harold Varmus, the former Director of the NIH in the US, still persists or it is even higher today(7). Personalised medicine and genomics are fields where it is especially important to assess value and find the right frameworks to do so. The classical HTA framework that includes clinical effectiveness, safety, cost-effectiveness, budget impact analysis and patient values perhaps is not enough when we are measuring value in personalised medicine.

In Canada, the drugs assessment process is well established, and it is based on the “Common Drug Review” (CDR), which is coordinated by the Canadian Agency for Drugs and Technology in Health (CADTH), with final reimbursement decisions depending on regional/local

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administrations. However, the field of personalised medicine includes other technologies with a less clear assessment and regulatory pathway.

The laboratory developed tests are an example, which assessment process has been examined recently in Canada(8). The authors of this study concluded that the recent expansion of the molecular diagnostics industry has revealed weaknesses in Canada's regulatory system for laboratory-developed tests, which are not subject to statutory regulations on medical devices. However, diagnostics developed as "test kits" and sold to hospitals are considered to be in vitro diagnostics devices under Medical Devices Regulation.

Treatments with Companion Diagnostics have been recently addressed in a specific guidance of economic evaluation in Canada(9). The guidance recommends best practices for conducting economic evaluations including the formulation of the study question, the target population, the comparators, modelling, diagnostic effectiveness, and other issues. However, it is still early to see results from the implementation of this guidance in the health system.

The CADTH publishes yearly a list of the top precision medicine issues and the 2023 Watch List identifies the current issues that could limit the health systems from realising the full potential of precision medicine technologies(10). Aspects mentioned as key issues were an increasing complexity related to interpreting test results and challenges in regulating and evaluating precision medicine technologies. Those are key issues that likely warrant more attention and will influence the wider adoption, diffusion, and implementation of precision medicine technologies.

A recent article of Prof Marshall and her team discussed the most important challenges in assessing the economic value of next generation sequencing tests(11). They could be summarised in three main categories:

1. Model structure and study questions. This category includes aspects such as the complexity of the models that have to incorporate multiple pathways, results and testing because multiple genes are evaluated. Other aspects included in this category are the time frame, the secondary findings, the type of analysis and comparators used, the identification of costs and outcomes directly attributable to next generation sequencing.

2. Measuring costs and outcomes. It includes aspects such as the need of quantifying a broad range of outcomes (psychological benefit from having a diagnosis, impact on family members or societal outcomes, among others).

3. Data availability and quality. It includes challenges related with the lack of evidence and data variability, and statistical issues such as integration of data sources and using value of information analysis.

The presenter indicated that there is a need to broaden our view of value and extend the cost-effectiveness framework in personalised medicine. An interesting proposal is the ISPOR Value Framework that go beyond the impact on the individual, and look at broader effects as value of hope, spillover effects, work productivity and value of information among others(12).

Personalised medicine is a field that highlights the need for analyses beyond traditional cost-effectiveness analysis and QALY to support decision-making in an effective way. The

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preference for positive aspects as benefits or aversion to negative aspects as harms should be taken into account in personalised medicine.

Some other papers of her team have addressed some of the challenges regarding the evaluation of genomics proposing some methodological tools that could partially overcome some of the problems such as the valuation of non-health outcomes or preferences elicitation(11,13). The use of cost-benefit analysis, net monetary benefit, discrete choice experiment or methods to ascertain the willingness to pay are tools useful to advance in methodology. An example, it is a study conducted with parents of children with suspected rare genetic diseases showed that parents were willing to pay ~CAD$6,500 for Whole Exome Sequencing (WES) and other genetic tests, compared with other procedures(14).

Another issue is the translation of genomics research findings in clinical practice. Health systems need consistent regulatory and assessment frameworks to incorporate the best but affordable technologies into the systems. However, the pathway to move from genome discoveries into health-care and disease prevention remains uncertain and reveals access inequities(15,16). Implementation research studies are needed to ascertain the real impact of using genomics in routine practice.

Finally, it is the challenge of sharing genomic information across countries and jurisdictions. There are barriers which could be summarised in the following(17–19):

- Technical barriers. Interoperability, standardisation, harmonisation, terminology, data access.
- Ethical and legal. Broad Informed Consent needed, Barrier to sharing individual patient data, Siloed legal and ethical regulations (by institutions, countries), privacy and security.
- Cultural. Language (e.g., ethical and legal documents in different languages), cultural diversity, socio-cultural expectations regarding data sharing.
- Motivational. Incentives for data sharing.

Personalised medicine does not require a complete new HTA paradigm but poses some particular challenges that require advances in new methods and processes to ascertain the real value and impact on patients and health systems.

The Netherlands. “Towards a Tipping Point for broad molecular diagnostics in oncology”. Prof. Valesca P. Retèl, Netherlands Cancer Institute (NKI), Erasmus University Rotterdam.

Prof. Valesca Retèl focused her presentation in oncology and molecular diagnostics. She started pointing out the increase in the number of EMA-approved medicines and the costs associated with cancer medicines in the EU since 1995. There are several challenges from the HTA perspective in this area such as tougher budgetary decisions and uncertainty in evidence. On the other hand, nowadays new opportunities appear with advanced information systems and learning health-care systems but at the same time it is a field with large differences between countries.

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The presenter showed a series of studies performed within the framework of the TANGO project "Technology Assessment of Next Generation Sequencing in Personalized Oncology" (20). This project included amongst others an assessment of the consequences of potential implementation in the Netherlands of WGS compared to the standard diagnosis (the current clinical practice of molecular diagnosis in the Netherlands) for advanced cancer (patients with inoperable stage IIIB,C/IV non squamous non-small-cell lung cancer)(21). The design of this study was a cost-effectiveness model based on an iterative decision tree that represents the diagnostic pathway (fig. 3) and the data to populate the model came from a network meta-analysis that used data from the literature(22). The presenter discussed that despite that RCTs are the ideal design, they are hard to achieve in personalised medicine, so this type of alternative design allows evaluating effectiveness and long-term outcomes and not only the concordance between the two groups, which is a short-term outcome usual in personalised medicine studies.

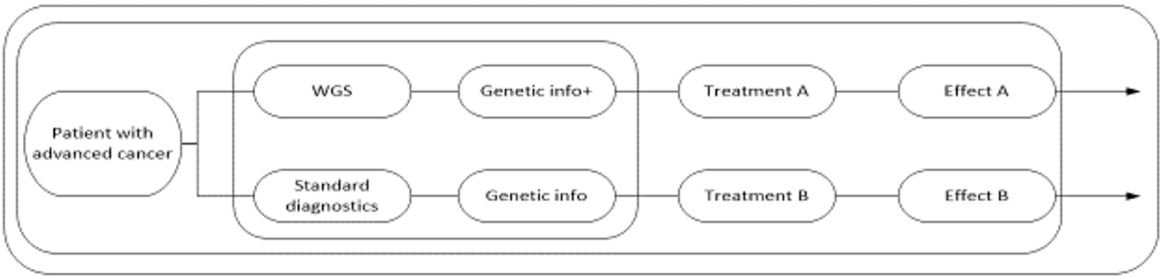

Figure 3. Conceptual scheme of the decision tree used in (20,21).

The TANGO studies provided HTA information using three different approaches:

- Cost-effectiveness models based on literature data(23).
- Cost-effectiveness studies based on real world data(24).
- Health systems models that include workflows, organisational pathways among other parameters complementing cost-effectiveness models(25).

To populate those models it is necessary gathering different data and inputs, i.e. microcosting, real world data, time to treatment data, and although difficult, preferable RCT data.

Within the framework of the TANGO project, ethical and legal issues related to the duty to recontact patients were also analysed. Three papers have been elaborated summarising those ethical and legal issues found along the project, and also providing a decision tool to help health-care professionals to deal with those problems in the clinical setting(26–28).

A study of the real implementation in the Dutch health-care system was also presented during the workshop(29). The WIDE study is an observational study that compared WGS with the standard molecular diagnosis in patients with (suspected) stage IV solid tumours of all occurring tumour types. They found positive results for WGS in terms of feasibility, validity and clinical value(30).

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All of those studies provided HTA information to authorities in the Netherlands but molecular diagnostics reimbursement is still under discussion and recently the Dutch House of Representatives approved a motion to request the Ministry of Health, Welfare and Sport to examine the quality, accessibility and affordability of molecular diagnostics in a broad way in the health-care system. The motion established that molecular diagnostics must be arranged for advanced cancer patients in good condition, who exhausted all treatment options. They found that molecular diagnostics could be reimbursed under special conditions, potentially accepting other arguments besides effectiveness and cost-effectiveness.

In reply to this request the Dutch Health-care Institute (ZIN) has recently started the Tipping Point Project. The project is divided into three parts: 1) Organisational care, 2) Macro-costs, 3) Effectiveness and the placing of molecular diagnostics in patient's trajectories. The project aims to ascertain the tipping point of small versus broad molecular diagnostics in the health-care system, in terms of added value. Within this project, the NKI-team is currently in the first phase, performing literature review about relevant "other" determinants that could play a role in the choice for small or broad molecular diagnostics, besides clinical benefit and costs. The HTA frameworks considered to establish those determinants are the EUnetHTA Core Model(31) and the ISPOR Value framework(12).

Subsequently, interviews were performed with stakeholders to provide insight into these "other" determinants. Finally, they work towards a "Tipping Point" model, integrating clinical benefit, cost-effectiveness and the "other" determinants, in order to make a comprehensive policy decision upon (broad) molecular diagnostics- for oncology.

Roundtable

The roundtable began with a discussion about HTA frameworks and their applicability when evaluating the implementation of genomics in health-care systems. Should we apply standard HTA approaches to inform health-care decision-makers, or should we revise the standard HTA framework? Several comments were received, as follows:

- There are arguments for and against modifying the standard HTA framework for the particular case of genomics, but it is important to recognise that this framework has not yet been widely applied to evaluate genomic interventions. Furthermore, HTA frameworks reflect broader population preferences about how health-care resources should be allocated. Consequently, changes should not be driven by the preferences or beliefs of HTA experts.
- There is currently insufficient high-quality evidence to populate HTA models, but ways of overcoming those problems were discussed. These include the use of a combination of approaches using different inputs (i.e. Prof. Retel presentation). However, the authorities do not necessarily trust these methods. Obtaining more preferential data, using more patient-centric methods, and holding constructive discussions with key stakeholders are important to advance in this challenge.

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- The huge amount of data available in hospitals or industry, for example, is an opportunity to advance in this field. The European Health Data Space (EHDS) or the Horizon Europe projects are good examples of future possibilities.
- It would be useful to explore the potential to share data across jurisdictions and establish a common core dataset that can provide useful information to decision-makers in different countries.

Regarding establishing a common core dataset the following comments were made:

- There is a large community of researchers in this field that could join efforts in harmonising or proposing a common core of set of information to gather. Elements to agree on would be: what to measure, definitions, in which populations and how frequent should data collection take place, among others. Exercises are being done in European projects of Rare Diseases that could be shared.
- The B1MG Demo – Federated Data Access for Rare Diseases[11], was mentioned as an interesting tool. However, it is useful to search genomic information as variants but is not useful to collect evidence for HTA.
- On one hand it was mentioned that it would be really interesting to collaborate in agreeing and collecting data in the same way across countries, but on the other hand it was argued that it will be difficult to establish a common agreement accepted by different governments on the required data and the method to use them.
- Different types of data will require different levels of sharing. For example, costs are very setting-dependent and not necessarily comparable, but sharing how to collect data on costs and outcomes is possible and useful.
- There is room for collaboration and advance on shareable data and transferable results.
- On the other hand, sometimes genomic data are not generalizable because they are not representative of the general population. The Genomics England Diverse Data[12] is currently exploring potential solutions to this problem.

Other discussions considered the following points:

- Attendees asked for general recommendations for a country that is just beginning to design a genomics sequencing programme. It was noted that first it is a political decision regarding whether it is worthwhile to invest in genomics compared with budgetary priorities (e.g. education). If the answer is yes, at that point it is appropriate to involve HTA and health economics experts, and to learn from how other countries have collected data and undertaken analyses, established comparator groups and dealt with other methodological issues.
- There were also discussions about the lack of evidence about the clinical utility of genomic tests and associated interventions. The need for high-quality evidence on the safety and effectiveness of genomic tests was mentioned as a necessary first step in order to determine the clinical utility of genomic technologies.

[11] https://youtu.be/6MtIJA4xXdU
[12] https://www.genomicsengland.co.uk/initiatives/diverse-data

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- It was also mentioned the relevance of including the carbon footprint impact in projects about efficiency and utility of research and health-care investments.

6. Discussion

The workshop and its preparatory work have allowed to extract some relevant results regarding challenges and solutions about the application of HTA and Health Economics to genomics. We have obtained results in topics as the HTA frameworks applicable to genomics, methodological advances needed to determine the value of genomic technologies and proposals on potential collaborations in methodological harmonisation. Some of the questions asked when organising the workshop, however, were covered in a limited way, i.e. decision-making systems or the financing and reimbursement models applicable to genomics.

The need to perform more HTA and Health Economics studies in the area of genomics is a shared view, but on the other hand it was also shared that the standard HTA methods are not enough to reply to all of the assessment questions relevant to genomics. There is a need to incorporate aspects not sufficiently covered by standard methodologies, such as patient preferences, stakeholder deliberation, non-health outcomes evaluation, modelization including the clinical complexity of genomics, among others. Another relevant result was a common positive view about the possibilities of building joint data schemes that could be shared among jurisdictions.

Regarding the **HTA framework**, the content of the recent international consensus about the HTA definition is remarkable(2). It states a theoretical framework which is broad enough to cover complex fields such as genomics. It includes the social, ethical, organisational and cultural dimensions of value, as well as wider implications of the patient, relatives, caregivers and the population. It considers multidisciplinarity, and its orientation to inform decision-making. This theoretical framework would be valid to genomics. Nevertheless, it is also important to highlight that the definitions do not establish specific methodologies for particular technologies.

It has been also discussed if genomics should be considered a special case for HTA. The need for new HTA frameworks for special cases has been mentioned many times, but the number of cases is so large that it calls into question the qualifier “special”. It has been argued for e-health, medical devices, public health interventions, complex technologies, biotechnologies, personalised medicine and genomics among others(32–38). Pharmaceutical technologies would be the ones with the most common assessment standards at the international level.

In Europe, the harmonisation of HTA processes has achieved a relevant milestone with the recent approval of the European Regulation on HTA(39). The Regulation harmonises the assessment of the relative (comparative) safety and clinical effectiveness, leaving the non-clinical domains to the national level. The Regulation will start with new cancer drugs and advanced therapy drugs in January 2025, and states a calendar for pharmaceutical medicines but it is vague regarding medical devices and other complex technologies, which affects the genomic technologies.

The European harmonisation is based mainly on the results of the EUnetHTA Joint Actions and projects(40), which provide with a widely accepted HTA framework (the HTA Core Model®(31)) that has been extensively used by the European countries (298 of 27 joint clinical assessments uses reported by European countries)(41). While the HTA Core Model® includes applications for diagnostic, medical and surgical interventions, pharmaceuticals and screening technologies, it

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was designed to assess a broad spectrum of health technologies and does not include specific considerations for genomic technologies.

Another HTA framework that was considered particularly relevant for genomics in the workshop is the ISPOR Value Framework(12). This is an academic proposal that has not been officially adopted by HTA bodies or authorities, but that complements the EUnetHTA framework proposing a broader list of value assessment elements for medical technologies, which has interest for genomics. A summary of both frameworks could be showed if we would join both frameworks, as in the following list of dimensions to be evaluated:

- Health problem, severity of disease, status & characteristics of technologies (EUnetHTA and ISPOR)
- Safety, Efficacy, effectiveness, QALY (EUnetHTA and ISPOR)
- Costs, economic, productivity (EUnetHTA and ISPOR)
- Family and scientific spillovers (ISPOR)
- Value of knowing (ISPOR)
- Value of hope (ISPOR)
- Insurance value: financial and health (ISPOR)
- Fear of contagion and disease (ISPOR)
- Real option-value (ISPOR)
- Equity (ISPOR)

In addition to the discussion on HTA domains or value assessment elements, it was highlighted that the application of HTA to genomics still faces some **methodological challenges**. The implementation of genomics in clinical practice involves many different pathways and organisational issues that make complex the design of good evaluation studies. The rapid evolution of genomics and the increasing amount of genomic discoveries with potential application in health-care, which make it difficult for an HTA system to provide timely and updated relevant HTA information. The regulatory and assessment processes are less clear for diagnostic, medical devices and other technologies compared with pharmaceuticals, which particularly affects genomics. There are also methodological difficulties related with the comparators, modelization, availability of data, measuring the relevant outcomes, and other issues.

The discussion about **solutions and recommendations** was motivating and provided with some interesting insights. The most relevant proposal was regarding a potential international collaboration of proposing a core data set that could be shared and useful across jurisdictions. There have been experiences in specific fields such as rare diseases, oncology(42) or clinical outcomes(43). However, those papers are located more in the academic debate than in the decision-making arena. The experience explained in the French health system indicates that establishing common indicators to evaluate such complex technologies is a challenge. It is common for the initial introduction, and sometimes also the expansion, of these technologies to be done without assessment. Partly because of that, the real use of evaluation indicators is sometimes difficult to impose.

In the workshop, it was also mentioned the importance of overcoming ethical and legal barriers, particularly the need to recontact patients because of informed consent. However, the ESLI issues have not been used to formulate recommendations in this deliverable because they

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belong to other B1MG groups. The need to also consider the environmental impact among the HTA dimension was also raised. This is already included in the international consensus about the HTA definition and it is being incorporated by some HTA bodies(44).

7. Key challenges

The most important challenges identified in relation with the application of HTA in genomics were the following:

- The rapid evolution of genomics and the increasing amount of discoveries with potential application in health-care poses major issues to the HTA bodies to provide timely and updated relevant HTA information.
- The unclear regulatory and assessment frameworks for diagnostic, medical devices and other technologies different from pharmaceuticals particularly affect genomics.
- Modelling applied to a field as complex as genomics, with multiple clinical trajectories, abundant genetic information, among other complexity factors is a big challenge.
- Lack of high quality data about costs and outcomes to populate HTA models in genomics make it difficult to reply to assessment questions relevant in this field.
- Classical outcomes measures do not capture all dimensions of outcomes that are relevant for genomics as the psychological benefit from having a diagnosis, the impact on family members, and impact on productivity, among others.
- Managing complex and multiple sources of information, difficulties regarding interoperability, standardisation, harmonisation of terminology or data access are relevant challenges in this field.
- Reaching agreements between researchers, authorities and stakeholders on the essential indicators to evaluate technology is a great challenge.
- Establishing common HTA standards and harmonising HTA methods across countries and jurisdictions is a big challenge among other reasons because the HTA processes are a national competence and context dependent.
- Limitations in the transferability of data and evaluations between different jurisdictions which is particularly relevant about costs.
- Limitations in the generalizability of the genomic information, because the cohorts sometimes are not representative of the general population.

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8. Key recommendations

Recommendations about the role of HTA in genomics:

- Perform more HTA studies in genomics, including HTA reports and primary studies that generate evidence to be included in HTA Reports. They can provide rigorous scientific information to support decision-making in the adoption and funding of genomic technologies in health systems.
- Conduct high quality HTA studies (reports and primary studies) in genomics with a multidisciplinary approach, with good planning of the necessary resources and skills, and involving stakeholders in formal discussions about methodological requirements and decision criteria.
- Assess genomic technologies with a broad view of the components of the value assessment, including among other components the spillover effects, value of hope, value of knowing and work productivity.

Recommendations on methodology:

- Research on modelling methods that incorporate the complexity of genomics and its application into clinical practice, considering the issue of finding good comparators, consider the multiple clinical pathways and multiple genes in the models, include secondary findings among the outcomes and design models with appropriate time frames among other issues.
- Research on methods to advance in valuation of non-health outcomes using preference-based approaches (i.e. discrete choice experiment and contingent valuation).
- Use of a mix of methodological designs to complement the information needs (i.e. cost-effectiveness models based on real world data, models based on literature, randomised clinical trials, health system and macroeconomic models, among others).
- Research on implementation barriers and facilitating factors that can provide real world information and help to understand how to navigate within the complexity of the health systems.
- Advances in data management, integration of data sources and big data. Take advantage of the increased availability of a big amount of data.

Recommendations on international collaboration

- Continue collaborating in forums such as those established in the 1+MG initiative for the exchange of experiences and share best practices, avoiding duplication of problems in countries and developing joint international projects where to advance in finding common solutions.
- To develop plans of sharing data and establishing a common core dataset able to provide useful information to decision-makers in countries. Elements to agree on would be: what to measure, definitions, in which populations and how frequent should be measured, among others.

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- Collaborate in the design and conduct of studies on the safety and effectiveness of genomic tests in order to provide high-quality data to evaluate the clinical utility of genomic technologies.

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