Deliverable

D3.2 Publication: Synthesis of existing studies assessing cost effectiveness and clinical utility of WES/WGS	
Version | Status	V2 | final
Work package	WP3
Lead beneficiary	DIJON
Due date	31.12.2019 (M24)
Date of preparation	21.11.2022
Target Dissemination Level	Public
Author(s)	Christine Peyron, Aurore Pélissier, Camille Level (all Uni Bourgogne)
Reviewed by	Laurence Faivre (CHU Dijon)
Approved by	Gisèle Bonne (INSERM CRM)

The Solve-RD project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 779257.

Université de Bourgogne Franche-Comté

EA 7437

Synthesis of existing studies assessing the cost effectiveness and clinical utility of WES/WGS

Based on a literature review and the scientific contributions presented at the ECOgenomics conference (Dijon, May 2021)

Christine Peyron, Aurore Pélissier, Camille Level

[2022 – October]

Contents

Foreword

This document presents a synthesis of the issues involved in the economic evaluation of genetic tests and more particularly of whole exome and whole genome sequencing (WES/WGS). It is based on a literature review of published health economics evaluations but also presents the issues and methods of economic analyses presented at the EcoGenomics conference (Dijon, May 2021).

The aim is to highlight the advances but also the difficulties encountered by economic evaluation in the specific field of WES/WGS tests and which economists have yet to overcome.

In the first part, after recalling what medico-economic evaluations are and their uses in terms of decision making, we will summarise evaluations on genetic tests that predate the development of WES/WGS. The synthesis of this research allows to approach the general evaluation challenges in the field of genetics.

We then synthesis how the WES/WGS reinforces some of the methodological difficulties highlighted for genetic testing and produces new ones. Recent literature reviews show that economists have, however, made real progress in terms of methodological and costs and benefits assessment of these new sequencing technologies.

The presentations and debates that took place during the EcoGenomics conference made it possible, in the second part of this synthesis, to complete this literature review with the contributions of the research in progress at the time of the conference and to produce some analysis conducive for scientific projects to be developed about assessing cost effectiveness and clinical utility of WES/WGS.

I – Health economic evaluation and its use for genetic and genomic testing

1. Health economics evaluation

The increasing use of economic calculation in health care decision making responds to the need to rationalise collective expenditures: the aim is to guarantee that the best possible use is made of resources. It also corresponds to a search for transparency: any decision involving collective resources must be justified and everyone must be able to examine the use made of them.

Consequently, the question that is posed, and which economic calculation aims to answer, is the following: "How can we judge that it is economically justified to use collective resources to implement a given therapeutic option rather than to use these resources for an alternative use? The answer to this question has two dimensions: a scientific dimension on the methodological quality of the evidence and a normative dimension on the interpretation of the evidence. Methods for health economic evaluation (HEE) respond to these two dimensions. They have developed rigorous methodological frameworks and define rules for decision making.

HEE is a comparative analysis of alternative diagnostic, therapeutic or preventive strategies based on their costs and health outcomes. It is structured around 5 main steps (Drummond *et al*., 2015).

The first is choosing the assessment method. The choice of the primary outcome criterion determines the HEE method. Cost-minimisation analysis can only be used when the equivalence of medical consequences between the two strategies to be compared has been established beforehand. For *cost-effectiveness evaluation*, a quantitative and unidimensional clinical effectiveness criterion is chosen that is validated as close as possible to the benefit for the patient, such as morbidity criteria (number of new cases of a disease diagnosed, number of lesions detected) or mortality criteria (number of deaths avoided or number of years of life gained). The most commonly used unit of measurement in a *cost-utility evaluation* is the QALY (Quality-Adjusted Life-Year). Finally, in a *cost-benefit evaluation*, the various consequences of the strategies are measured in the same (monetary) measure, which allows them to be directly compared with the costs.

The second step deals with the methodological choices for cost assessment. The various cost items must be identified and listed according to the perspective adopted for the study. There are three categories of costs: *direct medical costs* are those directly linked to the medical management of the

disease (drugs, consultations, laboratory tests, hospitalisation, re-hospitalisation) ; *direct non-medical costs* concern the impact in time and expenses for the patient and his entourage (most often the family): transportation costs to get to the hospital, expenses for home improvements for example ; *indirect costs* correspond to the impact of interventions on the activity of the population of the analysis (loss of productivity due to illness, temporary or permanent sick leave, presenteeism, household help).

The third step concerns the methodological choices for evaluating outcomes and costs. The perspective or point of view to be adopted directly guides the accounting of the resources consumed by the strategies compared and their valuation. The population to be analysed represents all the individuals whose health is directly or indirectly affected by the interventions. The choice of comparator(s) varies according to the context, but the innovation must always be compared with the current and/or recommended practice that it is likely to replace. The time horizon corresponds to the duration of the study, which must allow the main effects of the strategies evaluated to be covered in terms of costs and consequences. Both costs and consequences should be studied over the same time period. It depends on the natural history of the disease as well as the expected consequences and the choice of the outcome criteria. Finally, the discounting method makes it possible to make the costs and consequences occurring in different years comparable. This reflects the fact that costs and consequences do not have the same value in the past, in the present and in the future.

The fourth step checks the robustness of the results. The model developed is subject to a sensitivity analysis that allows to consider the uncertainty of the parameters, the structure of the model and the methodological choices.

Finally, **the fifth step** deals with the presentation and interpretation of the economic evaluation findings. In a *cost-effectiveness analysis*, incremental cost-effectiveness ratios (ICERs) are calculated. ICER allows for the comparative analysis of the costs and outcomes of alternative health strategies. It gives the additional cost or saving to achieve one additional unit of outcome with strategy 1 compared to strategy 2. The most efficient strategy will be the most cost-effective.

Depending on the country, the HEE is an informational tool or a decision-making tool with a threshold value to decide to finance or reimburse a technology or a health product. Today, some countries like the United Kingdom or the Netherland use an explicit threshold for generating these health decisions. Other countries use an implicit threshold as a criterion for health benefit basket decisions or, like France, have no explicit threshold for inclusion in the benefit basket. Decision is then essentially based on the improvement of the medical service rendered.

These methods, whether they are used directly to decide or only contribute to that decision, have largely shown their value in objectifying choice criteria and quantifying the relative benefits of health decisions.

In the field of genetics and even more so in the field of genomics, these methods come up against difficulties present in almost all the preceding steps. In particular, they are about the choice of outcome, the evaluation of the cost, the choice of comparator, the time horizon of the study, the robustness of the results... Moreover, HEEs require data, which in the field of genetics and genomics, presents weaknesses in terms of availability and reliability.

The following summary details both these difficulties and the development of HEE in these fields.

2. Health economics evaluation for genetic tests

As soon as genetic testing became widely used in health care, economists developed economic evaluations and tried to specify criteria for cost-effective testing. This first work dates back to the early 2000s, and thus before WES/WGS.

Criteria for evaluating a genetic test have been defined by some authors (Higashi and Veenstra, 2003; Flowers and Veenstra, 2004). According to these authors, a genetic test is of interest and can be financially supported by the community if the following conditions are met:

- the variant being tested for is common in the population, and its prevalence may vary between ethnic groups. The definition of the target population is of primary importance from an economic point of view;
- the polymorphism has a high penetrance (association between phenotype and genotype). Penetrance is equivalent to the positive predictive value of a test. The positive predictive value depends on both the sensitivity of the test and the prevalence of the disease;
- the genetic test is sensitive and specific (note that genetic tests are very often near perfect tests). The sensitivity and specificity of the testing procedure depend not only on the qualities of the test itself but also, and more importantly, on the penetrance of the polymorphism sought;
- the test is available at a reasonable cost compared to other existing means (clinical monitoring, biological tests);
- the disease is serious and can be treated;

- the knowledge of the test result makes it possible to adapt the management of the patient. The expected effects of this adapted management are important in terms of morbidity and/or mortality.

Tests that do not meet the stated criteria are unlikely to add value. However, meeting these minimum requirements is not sufficient to guarantee the economic value of screening (Ameisein *et al.*, 2008).

Economists have conducted evaluations of the costs and outcomes of genetic testing, applying established methods in this particular area (Assasi *et al.*, 2012; D'Andrea *et al.*, (2015)). Several difficulties quickly became apparent (Becker *et al.*, 2011; Grosse *et al.*, 2008; Rogoswki *et al.*, 2010). By reviewing the steps that constitute an evaluation, it is possible to clarify some of them.

Economic studies on genetic testing are mainly used to evaluate the benefits of a genetic test compared to other testing modalities (for diagnosis or screening) or to compare different genetic testing techniques. They use different evaluation methods, cost-effectiveness methods (the most numerous, where effectiveness is generally the number of cases detected according to several strategies), cost minimisation methods (when two testing strategies supposed to have the same effectiveness are compared), and few rare cost-utility methods (where the consequences of a screening are evaluated in terms of QALYs).

In terms of effectiveness, the result is quite systematically an intermediate result and not a health result, the number of positive screenings for example is measured and compared, and not the impact of the test on the management or the long-term improvement of the patient's health status. The rapid evolution of genetic testing costs makes the results fragile and does not allow them to be generalised over time. Literature reviews and meta-analyses converge on the very fragmentary nature of the economic data used. The choice of comparator is not easy either, as the speed of innovation means that strategies evolve very quickly and the alternatives studied can be quickly outdated. Finally, the results appear to be extremely scattered, depending very strongly on the type of disease, but also varying for the same group of diseases (depending on the possible alternatives, the costs covered and the study population). The robustness and generalisation of the conclusions in terms of the cost-effectiveness of the tests therefore remain problematical. However, some meta-analyses conclude that genetic testing is cost-effective in certain diseases. In this respect, we can cite the work of Rogowski (2006), which identifies 21 complete economic evaluations and attests to an acceptable cost-effectiveness ratio of genetic testing for, for example, breast and ovarian cancer (BRCA1/2 genes), familial adenomatous polyposis (APC gene) and Lynch syndrome (MMR genes).

3. Health economics evaluation for WES/WGS

A keyword search of the literature shows that the evaluation of NGS efficiency has seen an exponential increase in scientific publications over the last 10 years. There are several reasons for this: the upheaval that this methodology entails, its impact in terms of costs and possible results, and the speed with which this technology could spread. However, these evaluations face difficulties that are quite similar to those of genetic testing in general, with additional difficulties that are more specific to this technology.

As with genetic testing, but even more so, genomic testing is rapidly falling in cost, rapidly evolving in implementation and spreading in care.

NGS is the fastest growing type of precision medicine technology. These technologies have been used, largely for research purposes, since 2008. In 2006, a human genome cost about $20-25 million using the Sanger method. With the advent of NGS, there has been a significant and continuing decline in the cost of consumables, hence the expectation of a "$1000 genome." However, this expectation primarily reflects the consumables component and does not consider the overall costs of the sequencing process. Clinical interpretation, in particular, can be time-consuming and costly. This dichotomy has led to descriptions of the "$1,000 genome and $100,000 analysis." To ensure that NGS technologies are not simply an expensive addition to patient care, the demand for accurate figures on the "full" costs of the entire sequencing process is growing.

Sequencing technologies have developed rapidly, and in some countries have entered care quite quickly, with rapid changes in capacity and indications for use. For an economic evaluation, this context weakens the stability of the conclusions reached in terms of costs or efficiency. The literature reviews thus show a wide dispersion of costs. For example, Schwarze *et al.* (2018) in their systematic review for whole exome and genome sequencing found that cost estimates for a single test ranged from $555 (five hundred and fifty-five dollars) to $5,169 (five thousand one hundred and sixty-nine dollars) for exome and from $1,906 (one thousand nine hundred and six dollars) to $24,810 (twenty-four thousand eight hundred and ten dollars) for genome. In another review on the economic evaluation of sequencing performed for paediatric patients in the clinical setting (Alam and Schofield, 2018), the cost of sequencing was 11% to 64% lower than standard care.

This great diversity of costs in the literature reviews, which makes meta-analyses difficult, is not only due to the decreasing evolution of costs but also to more methodological obstacles. Taking the findings of several literature reviews (Annemans *et al.*, 2013; Berger and Olson, 2013; Buchanan *et al.* 2013;

Counti *et al.*, 2010; Frank *et al.*, 2013; Phillips *et al.*, 2013,2018; Regier *et al.* 2018; Weymann *et al.* 2019), these methodological difficulties can be clarified.

Few cost analyses published transparently present the data, and many publications didn't indicate which items are included in the cost estimates. Many studies did not calculate the real cost of exome or genome sequencing but used the prices charged by commercial operators. Few studies considered the number of samples that really need to be sequenced to obtain a diagnostic result; at least two for cancer cases and three for rare diseases. Furthermore, there are no possible conclusions on the results because the studies selected used different evaluation methods, making it difficult to compare them.

This variability in results is also reflected in the measures of effectiveness. In the study by Alam and Schofield the additional diagnostic rate of sequencing ranged from +16% to +79%.

This great diversity of results can of course be attributed to the diversity of the pathologies concerned by these assessments, to the diversity of the populations included in the study.

Some studies will focus on the evaluation of genetic tests in general, others on precision medicine, others on personalised medicine, others on genomic medicine in general, others more specifically on panels, ES or GS on a specific pathology or group of pathologies. All of this defines the types of results and the types of costs that are considered, and therefore reduces or even cancels out the comparability of these studies.

It would then be a question of not seeking an evaluation of the general efficiency of genomic tests but of their efficiency in a well-defined context.

The low robustness of evaluations also stems from a methodological weakness with regard to the usual criteria for the quality of an evaluation: the choice of methodology is not justified (e.g. justifying by identical effectiveness the possibility of simple cost minimisation), all the studies do not have a comparator (which is in principle essential), the data collection and cost calculation process is not explicit, and or the absence of statistical or sensitivity analysis, even though calculation hypotheses are made.

However, literature reviews and meta-analyses sometimes suggest ways of improving the quality of evaluations (Buchanan *et al.,* 2013; Christensen *et al., 2018*; Weymann *et al.,* 2019) and the most recent publications already show some improvement in the methodological quality of evaluations.

The analyses must integrate into their methodology the issue of the rapid evolution of these technologies (integrating costs and possible long-term effects, the evolution of relevant comparators). Costing makes it necessary to collect a wide range of costs, on a more frequent basis, with easily

updated data. Schwarze *et al.* (2020) use detailed microcosting to compare sequencing tests in cancer and rare diseases. Their methodology makes it possible to anticipate the impact on total costs of the different components of this cost, particularly in relation to the evolution of storage methods and the increase in the number of sequencing tests performed. The results and the outcomes should also be designed to be readjusted as the technology evolves. All this implies a very large amount of data to be collected and being able to update the source data of the evaluation. For example, Wordsworth *et al.* (2018) show the contribution of *big data* to the cost-effectiveness analysis of sequencing technologies. The scope of the results should also be broadened to include specific outcomes for certain individuals or groups of individuals. Technologies for personalised medicine cannot ignore more individualised preferences or impacts (for example Goranitis *et al.*, 2020; Jeong, 2018; Peyron *et al.*, 2018; Regier *et al.*, 2015, 2019). Cost-utility or cost-benefit analyses are therefore relevant methods.

In the end, the methodological challenges cannot be overcome by limiting ourselves to very standard approaches to evaluation. It is necessary to supplement these methods with approaches and results that may be less generalisable but are more in line with the singularity of individuals and pathologies, with the diversity of impacts and the possible horizons of these impacts. The scope of the costs and results is therefore a more important choice here than for other techniques to be evaluated.

This brief summary of economic evaluations of genomics and sequencing highlights the challenges of this economic approach. The difficulties are numerous and are due to the characteristics of these treatments and technologies. The advances already made in the most recent work show that economists have been able to find strategies to respond effectively to the expectations of professionals and decision-makers. Evaluating the contribution and efficiency of these new health technologies is a key to their relevant dissemination.

In conclusion, it also seems important to stress that medico-economic evaluation in the strictest sense is only a small part of what can be put in place to evaluate health technologies. Other complementary approaches are possible and quite relevant in the context of sequencing. The Health Technology Assessment or HTA makes it possible to supplement the assessment of costs and efficiency with an analysis of "social acceptability": the decision whether or not to adopt sequencing must also take account of ethical, legal and also psychological factors in the population (Nurchis *et al.*, 2022). The expectations and preferences of the public and patients are therefore a condition for the socially efficient dissemination of these methods.

II - Synthesis of studies assessing cost effectiveness and clinical utility of WES/WGS presented in the ECOgenomics conference (Dijon may 2021)

As part of the project Sole-RD, the "European Conference on the Diffusion of Genomic Medicine: Health Economics & Policy" has been organised by the Health Economics Team of the Economics Laboratory of Dijon (University of Burgundy) from 26th to 28th May 2021 (please see the annex for the program).

This symposium has brought together researchers in the human sciences, mainly in health economics, but also researchers from other disciplines. The presentations provided an insight into the methodological advances, problems and challenges of the most recent work on the evaluation of genomic medicine and WGS.

The following synthesis of the presentations and discussions completes the previous summary of the literature about economic evaluation of genomic testing (most of the presentations at the conference concerned work not yet published at the time of the conference, we just present their subject, objectives and methods[1]).

The presentations are grouped by theme of interest for economic evaluation: the choice of the viewpoint, of the methodological framework, the way of assessing costs and results. Three others - complementary for these methodological issues but important - themes for the evaluation are also presented: the challenges in terms of data, the evaluation of value and preferences for genomics and, more broadly, elements on the dissemination of genomics in health systems.

These presentations show recent advances in the evaluation of genomic tests, but also that this evaluation always faces particular challenges. Sometimes these challenges involve going beyond standard evaluation methods or objectives, and are important fields of research for health economics and the human and social sciences.

[1] We indicate for each topic the title of the oral presentation, the name of the speaker and the conference session of this presentation.

1. Methodological issues for cost and effectiveness of WES/WGS.

1.1. Choosing a point of view

As in any evaluation, the choice of a point of view is decisive in defining the nature of the results and the scope of the costs. In the field of genomics, there are many stakeholders and their expectations and expected results are not necessarily convergent.

No fewer than 14 stakeholders are identified by Mitropoulo *et al.* (2020) : 1. Academic and research organisations, 2. Private and public genetic laboratories, 3. Physicians, 4. Payers, 5. Genetics and genomics professional associations, 6. Pharmaceutical and biotechnology corporate entities, 7. National Medicines Organisation, 8. Ministry of Health, 9. National Bioethics Council, 10. Various religious organisations and the church, 11. Public and private providers in the field of genomics and personalised medicine, 12. Pharmacy practices, 13. Consumers and citizens, 14. Press and the media.

The dissemination of genomic medicine in our healthcare systems will depend in particular on the preferences and expectations of these stakeholders. They may act as levers for or barriers to the spread of genomic medicine. The literature on views, expectations and preferences as to genomic medicine is growing. The aim is, of course, to reveal the preferences of each of these stakeholders but also to highlight commonalities and differences in order to identify issues that could influence the diffusion of genomic medicine in different contexts. A good analysis of these points of view is a necessary preliminary step to ensure that the methodology and indicators chosen for the economic evaluation are consistent with the point of view chosen *a priori* for this evaluation.

Samantha Pollard[2] focused on the views of patients and Canadian society through a qualitative study on cancer. Chloé Mayeur[3] presented the results of a large-scale survey of Belgian citizens. And, finally Wendy Ungar[4] explained how Ontario is trying to develop an approach to produce HTA evidence in order to rapidly implement these technologies in the health system while trying to consider the objectives of the different stakeholders. Each presentation showed that despite the popularity of these

[2] Stakeholders perspectives for precision oncology: balancing patient and public support with evidentiary uncertainty – Samantha POLLARD (speaker) in Session F "Perspectives on Genomic Medicine: Between Public Policy and Citizens", 28 May 2021, 6.30 p.m. (GMT+2).
[3] DNA debate: engaging citizens on genomics – Chloé MAYEUR (speaker) in Session F "Perspectives on Genomic Medicine: Between Public Policy and Citizens", 28 May 2021, 6.30 p.m. (GMT+2).
[4] Health technology assessment and funding of genomic medicine technologies in Ontario, Canada – Wendy UNGAR (speaker), in Session F "Perspectives on Genomic Medicine: Between Public Policy and Citizens", 28 May 2021, 6.30 p.m. (GMT+2).

technologies, it can be difficult to reconcile different perspectives, objectives and timeframes to ensure ethical and equitable access for patients and the general population.

The importance of the views and stakeholders considered can be addressed more specifically for certain diseases, such as cancer. The spread of genomics in paediatric oncology practice has consequences for the relationships and expectations of stakeholders such as public authorities, professionals, children and their parents. With three different perspectives three presentations showed the transformations underway or desirable. Catherine Bourgain[5] looked at two types of regulation of the use of and access to genetic testing, regulation by the state and regulation by professionals. She analysed how professionals react and resist to what could limit their professional autonomy. Solenne Carof and Lucile Hervouet[6] developed the challenges of genetic screening for paediatric cancers from three points of view: professionals, parents and children. Emmanuelle Rial-Sebbag [7]was also interested in oncopaediatrics and the three parties involved, *i.e.*, children, their families and their doctors, but she approaches their relationship within the current French legal framework and analyses its relevance.

1.2. Choosing a methodology for the evaluation

The medico-economic evaluation of next-generation sequencing technologies faces methodological challenges whether one is interested in measuring the effectiveness, or more broadly the benefits of these technologies, or their cost. However, this evaluation is essential to justify and guide the dissemination of these technologies and to help public decision making. Evaluations are multiplying with various methodologies and results that allow us to begin to make progress on how to evaluate these technologies and to establish reference values. The choice of the evaluation model as well as the choice of the methodology for measuring costs and results appear important in terms of the

[5] Negotiating the regulation of routine genome sequencing in a care setting – Catherine BOURGAIN (speaker) in Session D2 "Implementing new generation sequencing in care for paediatric cancers: impacts for patients, healthcare providers and public policies." - Proposed by Sandrine DE MONGOLFIER and Sylvain BESLE, 28 May 2021, 10.00 a.m. (GMT+2).

[6] Routinisation of sequencing techniques: What impact on patient care pathways in oncopaedatrics? – Solenne CAROF and Lucile HERVOUET (speakers) in Session D2 "Implementing new generation sequencing in care for paediatric cancers: impacts for patients, healthcare providers and public policies." - Proposed by Sandrine DE MONGOLFIER and Sylvain BESLE, 28 May 2021, 10.00 a.m. (GMT+2).

[7] Legally assuring minors patients' rights in oncopaediatrics: between rights and practices – Emmanuelle RIAL SEBBAG (speaker) in Session D2 "Implementing new generation sequencing in care for paediatric cancers: impacts for patients, healthcare providers and public policies." - Proposed by Sandrine DE MONGOLFIER and Sylvain BESLE, 28 May 2021, 10.00 a.m. (GMT+2).

robustness and relevance of the results. Analysing and comparing methodological choices helps to define the appropriate methods.

Camille Level[8] analysed the heterogeneity of recently published studies and the difficulty of comparing their results to produce a quality meta-analysis. Based on two prospective studies currently being conducted in France on the care of patients with intellectual disabilities, Catherine Lejeune[9] highlighted the contribution of multidisciplinary evaluations and qualitative studies.

The search for a methodology should also make it possible to respond to one of the difficulties always present in the results of evaluations: their variability. There is indeed a lot of variability in measuring the cost and effectiveness of sequencing. Strategies and methods need to be sought to control this variability and produce relevant measures to inform access and reimbursement decisions. Four original contributions are presented for measuring costs or effectiveness. Wendy Ungar[10] used a bottom-up micro-costing approach to estimate the costs of care for two cohorts of paediatric patients who have undergone sequencing. She showed that there are significant differences in sequencing costs and analyses the determinants of these differences. Deirdre Weymann[11] looked to measure the effectiveness of genetic information by comparing time on treatment and time to next treatment initiation for cancer patients according to whether or not management has integrated this information. Using a difference-in-difference method that eliminates patient heterogeneity, she shows the effectiveness of genetic information. Jason Wassy[12] showed that the use of polygenic risk scores has clinical utility, shortening the time to diagnosis of one of the six common diseases targeted in his study. Liliana Sousa[13] demonstrated that preventive management of CDH1 mutation carriers is less costly and saves more lives than treating patients with a clinical expression of diffuse gastric cancer.

---

[8] Systematic review or meta-analysis: how to consider the high heterogeneity of studies to access the clinical utility of WGS/WES? – Camille LEVEL (speaker) in Session B1 "How to assess the cost effectiveness of WES/WGS?" 27 May 2021, 5.10 p.m. (GMT+2).

[9] Genomic testing in the field of developmental disorders: the added value of human and social sciences studies – Catherine LEJEUNE (speaker) in Session B1 "How to assess the cost effectiveness of WES/WGS?" 27 May 2021, 5.10 p.m. (GMT+2).

[10] Accurate and comprehensive micro-costing of genome sequencing in paediatric populations – Wendy UNGAR (speaker) in Session E1 "Comparative evaluation of two strategies" 28 May 2021, 5.05 p.m. (GMT+2).

[11] Time-varying effects of genomics-informed treatment in patients with advanced cancers: a difference-in-difference analysis – Deirdre WEYMANN (speaker) in Session E1 "Comparative evaluation of two strategies" 28 May 2021, 5.05 p.m. (GMT+2).

[12] The GenoVA Study: design of a pragmatic randomised trial of polygenic risk scoring for common diseases in primary care – Jason VASSY (speaker) in Session E1 "Comparative evaluation of two strategies" 28 May 2021, 5.05 p.m. (GMT+2).

13 A cost-effective model for the pathway of care of CDH1-related hereditary diffuse gastric cancer syndrome – Liliana SOUSA (speaker) in Session E1 "Comparative evaluation of two strategies" 28 May 2021, 5.05 p.m. (GMT+2).

1.3. Evaluate costs

The increasing inclusion of genomic medicine in clinical practice will increasingly rely on medico-economic analysis to guide resource allocation and the challenges of cost estimation are crucial to integrating genomic medicine into clinical practice and funding it. Wendy Ungar[14] set out the challenges confronting health economists looking to evaluate genomic medicine: the possibility of estimating costs and comparing different healthcare strategies are two major issues. In the domain of rare diseases, for instance, John Buckell[15] looked to highlight the costs that could be avoided through healthcare provision that includes genomic medicine and that could shorten the diagnostic odyssey and the medical costs it entails. Patrick Fahr[16] nonetheless showed that it is very difficult for economists to evaluate these avoided costs and the medical costs entailed by the different episodes of healthcare provision despite the wealth of databases completed by clinical practitioners. It is not enough just to have these data; the real challenge for health economists now lies in being able to use them.

Michael Abbot[17] showed that it is not easy to compare costs between WGS/WES and standard care. He presented the results obtained in Scotland on the costs of WGS and WES for patients with rare diseases, but highlights the great variability in the costs of the standard care diagnostic pathway, which are highly dependent on the patient diagnostic odyssey.

In addition, determining the cost effectiveness of genomic medicine has been limited by available data. Many studies have focused on the cost of genomic sequencing with cost effectiveness often assessed on the basis of the cost per additional diagnosis. However, due to the relatively recent capacity to provide a molecular diagnosis for many conditions, and lack of direct access to clinical cohorts, many studies have been unable to take account of the impact of health outcomes using standard measures such as QALYs. This is a particular limitation when studies are required to support access to public funding as there is no recognised threshold for funding of a diagnosis alone. Further, genetic

14 Considerations for cost-effectiveness analysis of genome sequencing – Wendy UNGAR (speaker) in Session E2 "Genome sequencing: new evidence on costs, and challenges for health technology assessment." - Proposed by James Buchanan, 28 May 2021, 5.05 p.m. (GMT+2).

15 Estimating the diagnostic pathway costs of patients with suspected rare genetic diseases – John BUCKELL (speaker) in Session E2 "Genome sequencing: new evidence on costs, and challenges for health technology assessment." - Proposed by James Buchanan, 28 May 2021, 5.05 p.m. (GMT+2).

16 Costing genome sequencing in large-scale, national initiatives: challenges and opportunities – Patrick FAHR (speaker) in Session E2 "Genome sequencing: new evidence on costs, and challenges for health technology assessment." - Proposed by James Buchanan, 28 May 2021, 5.05 p.m. (GMT+2).

17 Next Generation Sequencing for the next generation of patients: building the economic evidence base – Michael ABBOTT (speaker) in Session B1 "How to assess the cost effectiveness of WES/WGS?" 27 May 2021, 5.10 p.m. (GMT+2).

information is often of benefit to other family members including to inform reproductive planning where there is a risk of recurrence of the condition. Due to the highly disabling and life-long nature of many genetic conditions, the costs beyond the health system are also often large, suggesting the importance of taking a societal perspective. The issues on the choice of a point of view and the associated scope of costs can be found here.

Three presentations demonstrate how addressing these issues in several ground-breaking studies of the benefits and cost effectiveness of genomic medicine. Deborah Schofield[18] presented an estimate of the costs of intellectual disability for the community but also for the families who bear a heavy economic and psychological burden. Evelyn Lee and Rupendra Shrestha[19] proposed a model to evaluate the costs and effectiveness of preconception screening for genetic diseases. They used their modelling to compare the cost-effectiveness of such screening for spinal muscular atrophy with standard care. Owen Tan[20] developed a microsimulation model to evaluate the costs and benefits of using next-generation sequencing (NGS) in the management of childhood cancer.

1.4. Evaluate results and clinical utility

Professionals are key players in assessing the effectiveness and clinical utility of genomic tests. The diffusion of WGS in clinical practice will depend on the usefulness that professionals perceive and the reorganisation of their activity that this new technology will require. The notion of clinical utility is a multidimensional concept that can be apprehended differently depending on the evaluator considered. Robin Hayeems[21] first presented the work of a group of experts who proposed a framework that can be adapted to different WGS applications and that is operational for evaluating this clinical utility through four dimensions and specific indicators. She then presented the construction

[18] Capturing the widespread ripple effects of familial intellectual disability and potential benefits of genomics – Deborah SCHOFIELD (speaker) in session D1 "Cost effectiveness of genomic medicine: Beyond the cost of diagnosis." - Proposed by Deborah SCHOFIELD, 28 May 2021, 10.00 a.m. (GMT+2).

[19] An economic-modelling framework to assess the impact of population-wide preconception carrier screening for genetic disease with specific reference to spinal muscular atrophy – Evelyn LEE and Rupendra SHRESTHA (speakers) in session D1 "Cost effectiveness of genomic medicine: Beyond the cost of diagnosis." - Proposed by Deborah SCHOFIELD, 28 May 2021, 10.00 a.m. (GMT+2).

[20] Modelling the economic impact of next generation sequencing on childhood cancer management: a microsimulation approach – Owen TAN (speaker) in session D1 "Cost effectiveness of genomic medicine: Beyond the cost of diagnosis." - Proposed by Deborah SCHOFIELD, 28 May 2021, 10.00 a.m. (GMT+2).

[21] Clinical utility of genomic sequencing: a measurement toolkit – Robin HAYEEMS (speaker) in Session C2 "What place and articulation for professionals?" 27 May 2021, 6.30 p.m. (GMT+2).
The development of the clinician-reported genetic testing utility index (C-GUIDE): a novel strategy for measuring the clinical utility of genetic testing – Robin HAYEEMS (speaker) in Session C2 "What place and articulation for professionals?" 27 May 2021, 6.30 p.m. (GMT+2).

of the Clinician-reported Genetic testing Utility InDEx which should lead to a standardised and robust tool to evaluate the clinical utility of genetic tests. Based on a survey of clinical geneticists and genetic counsellors. Léa Gaudillat[22] showed that these professionals anticipate changes in their practice in connection with the dissemination of the WGS, in particular in order to respond to the increased need for support in prescribing and reporting results.

2. Data challenge

In genomics and its evaluation, data have specific characteristics: they are heterogeneous in nature, in very large numbers (in this sense they correspond to big data), and face challenges of dissemination and sharing. Knowing how to exploit them while respecting their confidentiality and the wishes of patients appears to be an important objective for effective and ethical uses.

The individualisation that characterises precision medicine implies extreme heterogeneity in the clinical, genetic and environmental characteristics of patients, their treatments and their pathways. Health technology assessment must be able to control this heterogeneity in order to produce results that are general enough to contribute to collective health policy decisions. Methods and strategies must be developed to exploit the available data in this way. James Buchanan[23] shows how big data can be used to integrate rare situations into more homogeneous groups of patients, while reducing heterogeneity. Big data also make it possible to jointly exploit data from different domains (pathways, health outcomes, socio-demographic data) and to broaden the dimensions taken into account in the evaluation. Deirdre Weymann[24] proposed to use quasi-experimental methods and machine learning to identify comparators for precision medicine in the event of missing data. In a single-arm study, control patients are matched to treated cases and the impacts of genomic sequencing on overall survival compared to usual care can then be estimated. Dean Regier[25] presented the contribution of

[22] The evolution of the profession of clinical geneticist and genetic counsellors with the arrival of new technologies in genetics – Lea GAUDILLAT (speaker) in Session C2 "What place and articulation for professionals?" 27 May 2021, 6.30 p.m. (GMT+2).

[23] Can big data from precision medicine observational cohorts reduce evidentiary uncertainty? A Perspective from the UK 100,000 Genomes Project – James BUCHANAN (speaker) in Session B3 "Addressing evidentiary uncertainty in precision medicine health technology assessment." - Proposed by Dean REGIER (CA), 27 May 2021, 5.10 p.m. (GMT+2).

[24] Quasi-experimental Methods for Evaluating Precision Medicine: Case Studies in Personalised OncoGenomics – Deirdre WEYMANN (speaker) in Session B3 "Addressing evidentiary uncertainty in precision medicine health technology assessment." - Proposed by Dean REGIER (CA), 27 May 2021, 5.10 p.m. (GMT+2).

[25] Life-cycle health technology assessment to enable sustainable precision medicine diffusion – Dean REGIER (speaker) in Session B3 "Addressing evidentiary uncertainty in precision medicine health technology assessment." - Proposed by Dean REGIER (CA), 27 May 2021, 5.10 p.m. (GMT+2).

life-cycle based evaluation. He builds on the construction of a database for cancer management in Canada and a framework for life-cycle assessment of precision medicine applications.

In addition, the data made available to clinicians and researchers is a key element. It implies a donation upstream and then takes on a collective informational and economic value. Patients' consent must be a constraint when they give their data, agree to share them but also for the use that will be made of them in terms of medical results as well as for research. Wannes Van Hoof[26] reported on the conclusions of expert workshops and citizens' forums that indicate both a willingness to share genetic data and the importance of a protective legal framework to govern this sharing. Laurence Faivre[27] looked at the results available to patients after analysis of their data, and particularly at the secondary data made possible with next generation sequencing, and how patients may or may not wish to access them. Sarah Carvallo[28] analysed how genetic data take on a bio-economic value and how the donation of genetic data integrates (or not) all dimensions of this value. Marie Darrason[29] developed the idea that the more data that are available, the more possible outcomes can mean more uncertain and more complex information.

3. Assessing value and preferences in genomics

Economic evaluation needs a measure of the outcomes produced by a test or genetic information. Behind this measure, there are conceptions of the usefulness and value of the results made possible by this approach. It is therefore necessary to go beyond mere methodological and operational considerations to broader reflections on the value of genomic medicine and the usefulness it can have for patients in particular. These more theoretical reflections also lead to questions about the way in which this value and usefulness can be known and even measured. This field of research is an important one for the human sciences and economics.

[26] My DNA, everybody's business? A citizen forum on the use of genomic information in society – Wannes VAN HOOF (speaker) in Session C3 - "Use and value of genetic information" 27 May 2021, 6.30 p.m. (GMT+2)
[27] Additional data obtained from exome/genome sequencing: two national studies to discuss the risk-benefit balance for implementation in France – Laurence FAIVRE (speaker) in Session C3 "Use and value of genetic information" 27 May 2021, 6.30 p.m. (GMT+2).
[28] Donation, free and informed consent, genetic data – Sarah CARVALLO in session C3 "Use and value of genetic information" 27 May 2021, 6.30 p.m. (GMT+2).
[29] Next Generation Sequencing techniques and the "information illusion" – Marie DARRASON (speaker) in Session C3 "Use and value of genetic information" 27 May 2021, 6.30 p.m. (GMT+2).

Mandy Ryan[30] showed that the notion of value is central in economics and had always been the subject of debate. In the context of genomic medicine, health economists are repositioning this debate by questioning in particular the value of this new technology, of the care it implies both upstream and downstream of genetic testing, of the information it produces and of the consequences it is likely to have for patients and their relatives.

Thus, economists are increasingly seeking to estimate the preferences of the various stakeholders (patients, health professionals, regulators, citizens) – in particular by means of discrete choice experiments – with the aim of highlighting the dimensions that influence the usefulness of high-throughput sequencing technologies.

If we stick to medico-economic evaluation as we know it today, the value of genomic medicine is certainly underestimated. It is known that preferences for genetic information extend beyond the primary indication for which the test is performed, but also beyond the medical elements that might concern other pathologies highlighted in the secondary data. Dean Regier's[31] showed how these different elements are valued by the Canadian public. Genetic information from genomic medicine can have an impact on the lives of patients but also on those of their relatives. That said, it is not easy to incorporate these different elements to evaluate the benefits of genomic medicine. Wendy Ungar[32] presented an attempt based on measuring QALYs for different members of the patient's family. Robin Hayeems[33] presented another way to highlight the different values associated by patients with genetic information through the P-Guide: the Patient-reported Genetic testing Utility InDEx (P-GUIDE), a patient-reported measurement tool for genomic medicine to highlight the preferences related to psychosocial, behavioural, ethical and familial impacts of genomic sequencing.

In the debates on the value and usefulness of genomic medicine, the issue of secondary data dissemination is a focus of research attention. The possibility of obtaining such data is directly linked

[30] Plenary 2 "What's important in the delivery of healthcare… and what does this mean for valuing Next Generation Sequencing?" presented by Mandy Ryan, 27 May 2021, 4.00 p.m. (GMT+2).
[31] Demand for precision medicine: a discrete choice experiment and external validation study – Dean REGIER (speaker) in Session C1 "Methodological considerations for measuring preferences for genome sequencing." - Proposed by Wendy Ungar, 27 May 2021, 6.30 p.m. (GMT+2).
[32] Family matters: measuring the preferences of family members for genome sequencing – Wendy UNGAR (speaker) in Session C1 "Methodological considerations for measuring preferences for genome sequencing." - Proposed by Wendy Ungar, 27 May 2021, 6.30 p.m. (GMT+2).
[33] Defining and measuring the value of genetic testing from patients' perspectives: developing the patient-reported genetic testing utility InDEx (P-GUIDE) – Robin HAYEEMS (speaker) in Session C1 "Methodological considerations for measuring preferences for genome sequencing." - Proposed by Wendy Ungar, 27 May 2021, 6.30 p.m. (GMT+2).

to the technical modalities of genomic testing. Should secondary data be actively sought or not? Who should make this choice? What secondary data? For what purpose?

In this context, the question arises both of patients' informed consent and of the legitimacy of restricting the scope of information that can be sought and disclosed to patients. The scientific community is divided on this point: some geneticists think that one should only pass on to patients the result for the initial purpose for which the test was prescribed while others argue secondary data are useful and justify an active search for them and their disclosure to those patients who so consent. The American College of Medical Genetics and Genomics publishes to this end a pre-established list of 59 medically actionable genes (Green *et al.*, 2013; Kalia *et al.*, 2017). In France, the *Société Française de Médecine Prédictive et Personnalisée* recommends disclosure to patients concerning 36 genes related to cancerology (Pujol *et al.*, 2018). Recently a working group of the *Agence de la Biomédecine* has come out against such systematic analysis of secondary data on a pre-established list of genes unrelated to the initial indication (Isidor *et al.*, 2019).

In her lecture, Emmanuelle Rial-Sebbag[34] enquired into these two debates by tracing more specifically the history of ethical thinking since the rise of genetics after the Second World War. She emphasised the strains that may be found between individual and collective interests; questions that also reflect research by health economists particularly when they look both to reveal the preferences of the various stakeholders (patients, health professionals, citizens) and to highlight the points of agreement and disagreement.

Based on a qualitative study conducted in Vancouver, Samantha Pollard[35] showed that parents of children with rare diseases value genetic information beyond the diagnosis alone, from the perspective of access to treatment, changes in their child's care or their lifestyle. The results have a medical value, but not only that. In the literature, we find this idea that the usefulness of genomic medicine is not only linked to the primary indication of the test or to the medical value of the results: this is the so-called "personal utility". It can also extend beyond this to non-health outputs. Martin Eden[36] and

[34] Plenary 3 "Introducing NGS in healthcare: challenges for patients' rights and for Public Health?" presented by Emmanuelle Rial-Sebbag, 28 May 2021, 4.00 p.m. (GMT+2).
[35] "Anything to make things a bit better for my child": parental preferences for genomic testing in rare childhood diseases – Samantha POLLARD (speaker) in Session B2 - "Preferences, expectations, representations of patients, professionals and general population" 27 May 2021, 5.10 p.m. (GMT+2).
[36] Quantifying how individuals trade health for non-health value deriving from genomic-based diagnostic information – Martin EDEN (speaker) in Session B2 "Preferences, expectations, representations of patients, professionals and general population" 27 May 2021, 5.10 p.m. (GMT+2).

Aurore Pélissier[37] each presented the results of two population-based SHDs, respectively in the UK and in France, which support this view. Deborah Marshall[38] presented an approach that allows patient preferences to be considered in the economic evaluation of genomic medicine.

4. Dissemination of genomics in health systems

The objective of the economic evaluation of genomic medicine is to be able to argue for its dissemination in health systems and, more precisely, to be able to choose the modalities of this dissemination, for which pathologies, with which technologies. Economists are therefore interested in a more global way in the way each health system, care system as well as financing system, can favour and accompany this diffusion.

Genomic medicine is spreading and gradually transforming our health systems. Genomic medicine enlarges the potential uses of genetic testing in medicine (McCarthy *et al.*, 2013[39]) at a drastically decreasing cost (McKinsey Global Institute, 2013). Thus, the implementation of genomic medicine in clinical practice is accelerating. US$ 4 billion worth of initiatives supported by 15 countries[40] have been identified by Stark *et al.* (2019)[41] for the period 2013–19. That number is growing: in July 2021, the Global Genomic Medicine Initiative[42] listed 68 initiatives in 36 locations. The experiences are nevertheless very varied. According to Stark *et al.* (2019) three types of national approach to support the development and dissemination of genomic medicine can be distinguished. The approaches differed in their coverage objective, funding modalities and infrastructure development. Kathryn

[37] "It is written in our genes! What we would like to know?" Understanding the demand for genetic testing using a discrete choice experiment to assess the French population's preferences – Aurore PELISSIER (speaker) in Session B2 "Preferences, expectations, representations of patients, professionals and general population" 27 May 2021, 5.10 p.m. (GMT+2).

[38] Simulation modelling methods for economic evaluation in precision medicine that consider patient preferences – Deborah MARSHALL (speaker) in Session B2 "Preferences, expectations, representations of patients, professionals and general population" 27 May 2021, 5.10 p.m. (GMT+2).

[39] McCarthy JJ, McLeod HL, Ginsburg GS. (2013). Genomic medicine: a decade of successes, challenges, and opportunities. *Sci Transl Med*, 5(189).

[40] Australia, Brazil, Canada, China, Denmark, Estonia, France, Japan, Netherlands, Qatar, Saudi Arabia, Switzerland, Turkey, UK, USA.

[41] Stark et al. (2019). Integrating Genomics into Healthcare: A Global Responsibility. *The American Journal of Human Genetics*, 104(3), 13-20.

[42] Please, click here to access the website.

Phillips, Sarah Wordsworth and James Buchanan [43] thus offered an illustration of this for three countries: Canada, the UK and the USA.

Personalised medicine is an attractive and relevant field of research for microeconomic theory. Personalised medicine modifies the information potentially available to patients, professionals and insurers, whether public or private. Without eliminating uncertainty in decisions (medical or insurance), it stratifies more finely the probabilities of pathologies as well as those of the effectiveness of treatments. A certain number of models used in health economics can then be re-examined, firstly those of health insurance supply and demand behaviour, but also those of prevention behaviour or doctors' activity. In all these theoretical models, the evolution of the level of information associated with personalised medicine will modify the equilibria and the optimal behaviour. Philippe De Donder[44] modelled the impact of genetic information on the prevention behaviour of policyholders and the nature of insurance contracts at equilibrium. Samuel Kembou Nzale[45] used an experimental economics approach to determine which remuneration methods would encourage physicians to integrate the benefits of personalised medicine into their practice. This theoretical work, which complements the economic evaluation of the current functioning of genomic medicine, makes it possible to envisage the levers and consequences of its future dissemination, in the organisation of care and its financing,

[43] Session A "Implementation of Exome and Genome Sequencing: Who Has Access, Who Pays, and What are Solutions? for Implementation Challenges?" - Session organised by Deborah Marshall, with the participation of Kathryn Phillips, Sarah Wordsworth and James Buchanan, 28 May 2021, 5.00 p.m. (GMT+2).

[44] Welfare impacts of genetic testing in health insurance markets: Will cross-subsidies survive? – David BARDAY, Philippe DE DONDER (speaker) in Session E3 "Theoretical microeconomics in genomic medicine." 28 May 2021, 5.05 p.m. (GMT+2).

[45] Physicians' incentives to adopt personalised medicine: experimental evidence – Samuel KEMBOU NZALE (speaker) IN Session E3 "Theoretical microeconomics in genomic medicine." 28 May 2021, 5.05 p.m. (GMT+2).

Bibliography

Alam K, Schofield D. (2018). Economic evaluation of genomic sequencing in the paediatric population: a critical review. *Eur J Hum Genet*, 26(9), 1241-7.

Ameisen JC, Cambien F, Dervaux B, et al. (2008). Inserm (dir.). Tests génétiques : questions scientifiques, médicales et sociétales. Rapport. Paris : Les éditions Inserm, XXXV - 351p. - (Expertise collective).

Anderson C. (2018). Cost Conscious: MedSeq Project Provides Snapshot to Suggest Genomic Sequencing does not Increase Downstream Healthcare Costs. *Clinical OMICs*, 5, 12-4.

Annemans L, Redekop K, Payne K. (2013). Current Methodological Issues in the Economic Assessment of Personalized Medicine. Value in Heath 16; S20-S26.

Assasi N, Schwartz L, Tarride JE, *et al.* (2012). Economic evaluations conducted for assessment of genetic testing technologies: a systematic review. *Genet Test Mol Biomarkers*, 16(11):1322-35.

Balloux F, Brønstad Brynildsrud O, van Dorp L, *et al.* (2018). From Theory to Practice: Translating Whole-Genome Sequencing (WGS) into the Clinic. *Trends in Microbiology*, 26(12), 1035-48.

Beale S, Sanderson D, Sanniti A, *et al.* (2015). A scoping study to explore the cost-effectiveness of next-generation sequencing compared with traditional genetic testing for the diagnosis of learning disabilities in children. *Health Technol Assess,* 19, 1-90.

Becker F, van El CG, Ibarreta D, *et al.* (2011). Genetic testing and common disorders in a public health framework: how to assess relevance and possibilities. *Eur J Hum Genet*, 19(S1): S6-44.

Berger A, Olson S. (2013). The economics of genomic medicine: workshop summary. The National Academy Press: Washington D.C., 129p.

Birney E. (2019). The Convergence of Research and Clinical Genomics. *Am J Hum Genet*, 104(5), 781–3.

Buchanan J, Wordsworth S, Schuh A. (2013). Issues surrounding the health economic evaluation of genomic technologies. *Pharmacogenomics*, 14(15), 1833-47.

Buchanan S, Wordsworth A. (2016). Schuh, Patients' preferences for genomic diagnostic testing in chronic lymphocytic leukaemia: a discrete choice experiment. *Patient*, 9, 525-36.

Christensen KD, Phillips KA, Green RC, Dukhovny D. (2018). Cost Analyses of Genomic Sequencing: Lessons Learned from the MedSeq Project. *Value Health*, 21(9), 1054-61.

Clark MM, Stark Z, Farnaes L, *et al.* (2018). Meta-analysis of the diagnostic and clinical utility of genome and exome sequencing and chromosomal microarray in children with suspected genetic diseases. *NPJ Genom Med, 3*(16).

Counti R, Veenstra DL, Armstrong K, *et al.* (2010). Personalized Medicine and Genomics: Challenges and Opportunities in Assessing Effectiveness, Cost-Effectiveness, and Future Research Priorities. *Medical Decision Making*, 30(3): 328-40.

D'Andrea E, Marzuillo C, Pelone F, *et al.* (2015). Genetic testing and economic evaluations: a systematic review of the literature. *Epidemiol Prev*, 39(4 Suppl 1), 45-50. PMID: 26499415.

Drummond MF, Sculpher MJ, Claxton K, *et al.* (2015). *Methods for the Economic Evaluation of Health Care Programmes*. (4th ed.) Oxford University Press.

Flowers C.R., Veenstra D. (2004). The role of cost-effectiveness analysis in the era of pharmacogenomics. PharmacoEconomics, 22(8), 481–493.

Foster JJ, Mulvihill RR. (2009). Sharp Evaluating the utility of personal genomic information. *Genet Med*, 11, 570-4.

Frank M, Prenzler A, Eils R, Graf von der Schulenburg JM. (2013). Genome sequencing: a systematic review of health economic evidence. Health Econ Rev. Dec 12;3(1):29.

Gallego CJ, Bennette CS, Heagerty P, *et al.* (2014). Comparative effectiveness of next generation genomic sequencing for disease diagnosis: Design of a randomized controlled trial in patients with colorectal cancer/polyposis syndromes. *Contemporary Clinical Trials*, 39, 1-8.

Gaudin F, Velazquez X, Djeyaramane G. (2014). L'évaluation médico-économique des médicaments et dispositifs médicaux. Vol 13.

Ginsburg GS, Phillips KA. (2018). Precision Medicine: From Science to Value. *Health Aff.,* 37(5), 694-701.

Goranitis I, Best S, Christodoulou J, *et al*. (2020). The personal utility and uptake of genomic sequencing in pediatric and adult conditions: eliciting societal preferences with three discrete choice experiments. *Genet Med*, 22(8), 1311-9.

Green RC, Berg JS, Grody WW, *et al.* (2013). ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet Med*, 15(7), 565-74.

Griffith G., Edwards R., Gray, J. (2004). Cancer genetics services: a systematic review of the economic evidence and issues*. Br J Cancer*, 90, 1697-703.

Grosse SD, Kalman L, Khoury MJ. (2010). Evaluation of the validity and utility of genetic testing for rare diseases. *Adv Exp Med Biol*, 686, 115-31.

Grosse SD, Khoury MJ. (2006). What is the clinical utility of genetic testing? *Genet Med,* 8, 448-50.

Grosse SD, McBride CM, Evans JP, Khoury MJ. (2009). Personal utility and genomic information: Look before you leap. *Genet Med*, 11, 575-6.

Grosse SD, Wordsworth S, Payne K. (2008). Economic methods for valuing the outcomes of genetic testing: beyond cost-effectiveness analysis. *Genet Med*, 10(9), 648-54.

Haute Autorité de Santé. Choices in Methods for Economic Evaluation [Internet]. 2011. Available from: link here.

Haute Autorité de Santé. Methods for Health Economic Evaluation [Internet]. 2015. Available from: link here.

Henneman L, Vermeulen A, van El CG, *et al.* (2013). Public attitudes towards genetic testing revisited: comparing opinions between 2002 and 2010. *Eur J Hum Genet*, 21(8), 793-9.

Higashi MK, Veenstra DL. (2003). Managed care in the genomics era: assessing the cost effectiveness of genetic tests. *Am J Manag Care*, 9(7), 493-500.

Isidor B, Nizon M, Vincent M. (2018). *Données secondaires : un enjeu scientifique et éthique*. In: E. Hirsch (éd.), Traité de bioéthique : IV - Les nouveaux territoires de la bioéthique, pp. 261-70. Toulouse: ERES.

Jeong G. (2018). Public preferences regarding adoption of personal genomic testing based on best–worst scaling. *Health Policy and Technology*, 7, 358-64.

Kalia SS, Adelman K, Bale SJ, *et al.* (2017). Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. *Genet Med*, 19(2), 249-55.

Levenseller BL, Soucier, DG, Miller, VA, *et al.* (2014). Stakeholders' opinions on the implementation of pediatric whole exome sequencing: implications for informed consent. *J Genet Counsel*, 23(4), 552-6.

Lewis MA, Stine A, Paquin RS, *et al.* (2018). Parental preferences toward genomic sequencing for non-medically actionable conditions in children: a discrete-choice experiment. *Genet Med*, 20, 181-9.

Marshall DA, Gonzalez JM, Johnson FR, *et al.* (2016). What are people willing to pay for whole-genome sequencing information, and who decides what they receive? *Genet Med*, 18(12), 1295-302.

Marshall DA, Gonzalez JM, MacDonald KV, Johnson FR. (2017). Estimating preferences for complex health technologies: lessons learned and implications for personalized medicine. *Value Health*, 20, 32-9.

Marshall DA, MacDonald KV, Heidenreich S, *et al.* (2019). The value of diagnostic testing for parents of children with rare genetic diseases. *Genet Med*, 21, 2798-806.

McCarthy JJ, McLeod HL, Ginsburg GS. (2013). Genomic medicine: a decade of successes, challenges, and opportunities. *Sci Transl Med*, 5(189).

McKinsey Global Institute (2013). Disruptive technologies: Advances that will transform life, business, and the global economy. McKinsey & Company, 176p.

Mitropoulo C, Politopoulou K, Vizikis A, Patrinos GP. (2020). *Assessing the stakeholder landscape and stance point on genomic and personalized medicine*. In: Applied Genomics and Public Health. Ed. Patrinos G.P. Elsevier, Academic Press. 404p.

Nestler-Parr S, Korchagina D, Toumi M, *et al.* (2018). Challenges in Research and Health Technology Assessment of Rare Disease Technologies: Report of the ISPOR Rare Disease Special Interest Group. *Value Health*, 21(5), 493-500.

Nurchis MC, Riccardi MT, Damiani G. (2022). Health technology assessment of whole genome sequencing in the diagnosis of genetic disorders: a scoping review of the literature. *Int J Technol Assess Health Care*, 26; 38(1): e71.

Park ST, Kim J. (2016). Trends in Next-Generation Sequencing and a New Era for Whole Genome Sequencing. *Int Neurourol J*., 20(Suppl 2), S76-83.

Personalized Medicine Coalition. The Personalized Medicine Report Opportunity Challenges and the Future [Internet]. 2020. Available from: link here.

Peyron C, Pélissier A, Béjean S. (2018). Preference heterogeneity with respect to whole genome sequencing. A discrete choice experiment among parents of children with rare genetic diseases. *Soc Sci Med*, 214, 125-32

Phillips KA. (2018). Assessing the Value of Next-Generation Sequencing Technologies: An Introduction. *Value Health*, 21(9), 1031-2.

Phillips KA, Deverka PA, Marshall DA, *et al.* (2018). Methodological Issues in Assessing the Economic Value of Next-Generation Sequencing Tests: Many Challenges and Not Enough Solutions. *Value Health*, 21(9), 1033-42.

Phillips KA, Deverka PA, Marshall DA, Wordsworth S, Regier DA, Christensen KD, Buchanan J. (2018). Methodological Issues in Assessing the Economic Value of Next-Generation Sequencing Tests: Many Challenges and Not Enough Solutions. *Value Health*, 21(9), 1033-42.

Phillips KA, Douglas MP, Trosman JR, Marshall DA. (2017). "What Goes Around Comes Around": Lessons Learned from Economic Evaluations of Personalized Medicine Applied to Digital Medicine. *Value Health*, 20, 47-53.

Phillips KA, Sakowski JA, Liang S-Y, Ponce NA. (2013). Economic Perspectives on Personalized Health Care and Prevention. *Forum for Health Economics and Policy*, 16(2), S23-52.

Phillips KA, Sakowski JA, Trosman JR, *et al.* (2014). The economic value of personalized medicine tests: what we know and what we need to know. *Genet Med*, 16(3), 251-7.

Plöthner M, Klora M, Rudolph D, Graf von der Schulenburg JM. (2017). Health-Related Genetic Direct-to-Consumer Tests in the German Setting: The Available Offer and the Potential Implications for a Solidarily Financed Health-Care System. *Public Health Genomics*, 20(4):203-17.

Pokhrel S., Owen L., Lester-George A., Coyle K., Coyle D., West R., Trapero-Bertran M., Meads C. (2014). Tobacco Control Return on Investment Tool. London: National Institute for Health and Care Excellence

Pujol P, Vande Perre P, Faivre L, *et al.* (2018). Guidelines for reporting secondary findings of genome sequencing in cancer genes: the SFMPP recommendations. *Eur J Hum Genet*, 26(12): 1732-42.

Regier DA, Peacock SJ, Pataky R, *et al.* (2015). Societal preferences for the return of incidental findings from clinical genomic sequencing: a discrete-choice experiment. *CMAJ*, 187, E190–E7.

Regier DA, Veenstra DL, Basu A, Carlson JJ. (2019). Demand for Precision Medicine: A Discrete-Choice Experiment and External Validation Study. *Pharmacoeonomics*, 38(1), 57-68.

Regier DA, Weymann D, Buchanan J, *et al.* (2018). Valuation of Health and Nonhealth Outcomes from Next-Generation Sequencing: Approaches, Challenges, and Solutions. *Value Health*, 21(9), 1043-7.

Reuter JA, Spacek D, Snyder MP. (2015). High-Throughput Sequencing Technologies. *Mol Cell*, 58(4), 586-97.

Rogowski WH. (2006). Genetic screening by DNA technology: a systematic review of health economic evidence. Int J Technol Assess Health Care. 22(3):327–37.

Rogoswki WH, Grosse DS, John J, *et al.* (2010). Points to consider in assessing and appraising predictive genetic tests. *J Community Genet*, 1(4), 185-94.

Rogowski WH, Grosse SD, Khoury MJ. (2009). Challenges of translating genetic tests into clinical and public health practice. *Nat Rev Genet*, 10, 489-95.

Schwarze K, Buchanan J, Fermont JM*, et al.* (2020). The complete costs of genome sequencing: a microcosting study in cancer and rare diseases from a single center in the United Kingdom. *Genet Med*, 22(1), 85-94.

Schwarze K, Buchanan J, Taylor JC, Wordsworth S. (2018). Are whole-exome and whole-genome sequencing approaches cost-effective? A systematic review of the literature. *Genet Med*, 20(10), 1122-30.

Stark Z, Dolman L, Manolio TA, *et al.* (2019). Integrating Genomics into Healthcare: A Global Responsibility. *The American Journal of Human Genetics*, 104(3), 13-20.

Steinbock LJ, Radenovic A. (2015). The emergence of nanopores in next-generation sequencing. *Nanotechnology*, 26(7):074003.

Taylor JC, Martin HC, Lise S, *et al.* (2015). Factors influencing success of clinical genome sequencing across a broad spectrum of disorders. *Nat Genet*, 47(7), 717-26.

Trosman JR, Weldon CB, Gradishar WJ, *et al.* (2018). From the Past to the Present: Insurer Coverage Frameworks for Next-Generation Tumor Sequencing. *Value Health*, 21(9), 1062-8.

Vallejo-Torres L, García-Lorenzo B, Castilla I, *et al.* (2016). On the Estimation of the Cost-Effectiveness Threshold: Why, What, How? *Value Health*, 19(5), 558-66.

Weymann D, Dragojlovic N, Pollard S, Regier DA. (2019). Allocating healthcare resources to genomic testing in Canada: latest evidence and current challenges. *J Community Genet*, 13(5), 467-76.

Weymann D, Pataky R, Regier DA. (2018). Economic Evaluations of Next-Generation Precision Oncology: A Critical Review. *JCO Precision Oncology*, 2, 1-23.

Weymann D, Veenstra DL, Jarvik GP, Regier DA. (2018). Patient preferences for massively parallel sequencing genetic testing of colorectal cancer risk: a discrete choice experiment. *Eur J Hum Genet*, 26, 1257-65.

Wordsworth S, Doble B, Payne K, *et al.* (2018). Using "Big Data" in the Cost-Effectiveness Analysis of Next-Generation Sequencing Technologies: Challenges and Potential Solutions. *Value Health*, 21(9), 1048-53.

Young T, Morton A, Soorapanth S. (2018). Systems, design and value-for-money in the NHS: mission impossible? *Future Health J*, 5(3), 156-9.

Yu JH, Harrell TH, Jamal SM, *et al.* (2014). Attitudes of genetics professionals toward the return of incidental results from exome and whole-genome sequencing. *Am J Hum Genet*, 95(1), 77-84.

Annex - Program of the conference

Please click on Join here to go directly to the session of your choice. Don't forget to log in with the guest IDs that were sent to you for the conference.
If you have any technical problems during the conference, please send an email to dominique.salvi@chu-dijon.fr
Enjoy the conference !

PROGRAM

Wednesday 26th May 2021

-9 (Vancouver)	-6 Quebec, NY, ...)	-1 (London, Lisbon)	Paris (ref.)	+8 (Melbourne, Sydney)	
06:30 a.m.	09:30 a.m.	02:30 p.m.	***03:30 p.m.***	11:30 p.m.	*Welcome and Introductions* Join here
Plenary 1 (1h)					
07:00 a.m.	10:00 a.m.	03:00 p.m.	*04:00 p.m.*	00:00 p.m.	**"Solve-RD - on the impact of diagnostic rare disease research on the diffusion of genomic medicine"** **Holm GRAESSNER** *(Centre for Rare Diseases, University Hospital Tübingen, Germany)* Join here
Session A (1h)					
08:00 a.m.	11:00 a.m.	04:00 p.m.	*05:00 p.m.*	(Day +1) 01:00 a.m.	*A - Implementation of exome and genome sequencing: who has access, who pays, and what are solutions for implementation challenges?* Proposed by Deborah Marshall **Deborah MARSHALL, Kathryn A. PHILLIPS, Sarah WORDSWORTH, James BUCHANAN, Dean REGIER** Join here

Thursday 27th May 2021

-9 (Vancouver)	-6 Quebec, NY, ...)	-1 (London, Lisbon)	Paris (ref.)	+8 (Melbourne, Sydney)			
Plenary 2 (1h)							
07:00 a.m.	10:00 a.m.	03:00 p.m.	*04:00 p.m.*	00:00 p.m.	***"What's important to you in the delivery of health care... and what does this mean for valuing Next Generation Sequencing?"*** **Mandy RYAN** *(Health Economics Research Unit, University of Aberdeen, United Kingdom)* Join here		
Short break (10min)							
Sessions B (1h15)							
08:10 a.m.	11:10 a.m.	04:10 p.m.	*05:10 p.m.*	01:10 a.m.	*B1 - How to assess the cost effectiveness of WES/WGS?* *Systematic review or meta-analysis : how to consider the high heterogeneity of studies to access the clinical utility of WGS/WES ?* - **Camille LEVEL** *Genomic testing in the field of developmental disorders: the added value of human and social sciences studies* - **Catherine LEJEUNE** *Next Generation Sequencing for the next generation of patients: building the economic evidence base* - **Michael ABBOTT** Join here	*B2 - Preferences, expectations, representations of patients, professionals and general population* *"Anything to make things a bit better for my child": parental preferences for genomic testing in rare childhood diseases* - **Samantha POLLARD** *Quantifying how individuals trade health for non-health value deriving from genomic-based diagnostic information* - **Martin EDEN** *Simulation modeling methods for economic evaluation in precision medicine that consider patient preferences* - **Deborah MARSHALL** *"It is written in our genes! What we would like to know?" Understanding the demand for genetic testing using a discrete choice experiment to assess the French populations' preferences* - **Aurore PELISSIER** Join here	*B3 - Addressing evidentiary uncertainty in precision medicine health technology assessment* Proposed by Dean REGIER (CA) *Can Big Data from Precision Medicine Observational Cohorts Reduce Evidentiary Uncertainty? A Perspective from the UK 100.000 Genomes Project* - **James BUCHANAN** *Quasi-experimental Methods for Evaluating Precision Medicine: Case Studies in Personalized OncoGenomics* - **Deirdre WEYMANN** *Life-cycle Health Technology Assessment to Enable Sustainable Precision Medicine Diffusion* - **Dean REGIER** Join here
Short break (5min)							
Sessions C (1h15)							
09:30 a.m.	12:30 p.m.	05:30 p.m.	*06:30 p.m.*	02:30 a.m.	*C1 - Methodological considerations for measuring preferences for genome sequencing* Proposed by Wendy UNGAR (CA) *Family matters: measuring the preferences of family members for genome sequencing* - **Wendy UNGAR** *Demand for precision medicine: a discrete choice experiment and external validation study* - **Dean REGIER** *Defining and mesuring the value of genetic testing from patients' perspectives: developing the patient-reported genetic testing utility InDEx (P-GUIDE)* - **Robin HAYEEMS** Join here	*C2 - What place and articulation for professionals ?* *Clinical utility of genomic sequencing: a measurement toolkit* - **Robin HAYEEMS** *The development of the clinician-reported genetic testing utility index (C-GUIDE): a novel strategy for measuring the clinical utility of genetic testing* - **Robin HAYEEMS** *The evolution of the profession of clinical geneticist and genetic counsellors with the arrival of new technologies in genetics* - **Lea GAUDILLAT** Join here	*C3 - Use and value of genetic information* *My DNA, everybody's business? A citizen forum on the use of genomic information in society* - **Wannes VAN HOOF** *Additional data obtained from exome/genome sequencing : two national studies to discuss the risk-benefit balance for implementation in France* - **Laurence FAIVRE** *Donation, free and informed consent, genetic data* - **Sarah CARVALLO** *Next Generation Sequencing techniques and the "information illusion"* - **Marie DARRASON** Join here

Friday 28th May 2021

-9 (Vancouver)	-6 Quebec, NY, ...)	-1 (London, Lisbon)	Paris (ref.)	+8 (Melbourne, Sydney)			
Sessions D (1h15)							
01:00 a.m.	04:00 a.m.	09:00 a.m.	*10:00 a.m.*	18:00 p.m.	*D1 - Cost effectiveness of genomic medicine: Beyond the cost of diagnosis* Proposed by Deborah SCHOFIELD (AUST) *Capturing the widespread ripple effects of familial intellectual disability and potential benefits of genomics* – **Deborah SCHOFIELD** *An economic-modelling framework to assess the impact of population-wide preconception carrier screening for genetic disease with specific reference to spinal muscular atrophy* – **Evelyn LEE and Rupendra SHRESTHA** *Modelling the economic impact of next generation sequencing on childhood cancer management – a microsimulation approach* – **Owen TAN** Join here	*D2 - Implementing new generation sequencing in care for pediatric cancers: impacts for patients, healthcare providers and public policies* Proposed by Sandrine DE MONGOLFIER and Sylvain BESLE *Negotiating the regulation of routine genome sequencing in care setting* - **Catherine BOURGAIN** *Routinization of sequencing techniques: what impact on patient care pathways in oncopediatrics?* – **Solenne CAROF and Lucile HERVOUET** *Legally assure minors patients'right in oncopediatric: between rights and practices* – **Emmanuelle RIAL SEBBAG** Join here	
Long break							
Plenary 3 (1h)							
07:00 a.m.	10:00 a.m.	03:00 p.m.	*04:00 p.m.*	24:00 p.m.	*"Introducing Next Generation Sequencing in healthcare: challenges for patients' rights and for public health"* **Emmanuelle RIAL-SEBBAG** *(Laboratoire d'épidémiologie et de santé publique, Université de Toulouse, France)* Join here		
Short break (5min)							
Sessions E (1h15)							
08:05 a.m.	11:05 a.m.	04:05 p.m.	*05:05 p.m.*	(Day +1) 01:05 a.m.	*E1 - Comparative evaluation of two strategies* *Accurate and comprehensive microcosting of genome sequencing in pediatric populations* - **Wendy UNGAR** *Time-varying effects of genomics-informed treatment in patients with advanced cancers: a difference-in-difference analysis* - **Deirdre WEYMANN** *The GenoVA Study: design of a pragmatic randomized trial of polygenic risk scoring for common diseases in primary care* - **Jason VASSY** *A cost-effective model for the pathway of care of CDH1-related hereditary diffuse gastric cancer syndrome* - **Liliana SOUSA** Join here	*E2 - Genome sequencing: new evidence on costs, and challenges for health technology assessment* Proposed by James BUCHANAN (UK) *Estimating the diagnostic pathway costs of patients with suspected rare genetic diseases* - **John BUCKELL** *Costing genome sequencing in large-scale, national initiatives: challenges and opportunities* - **Patrick FAHR** *Considerations for cost-effectiveness analysis of genome sequencing* - **Wendy UNGAR** Join here	*E3 - Theoretical microeconomics in genomic medicine* *Welfare impacts of genetic testing in health insurance markets will cross-subsidies survive ?* - **Philippe DE DONDER** *Implementation of personalized medicine in a context of moral hazard and uncertainty about treatment efficacy* - **Stéphane ALCENAT** *Physicians' incentives to adopt personalized medicine: experimental evidence* - **Samuel KEMBOU NZALE** Join here
Short break (10min)							
Sessions F (1h15)							
09:30 a.m.	12:30 p.m.	05:30 p.m.	*06:30 p.m.*	02:30 a.m.	*F - Perspectives on Genomic Medicine: Between Public Policy and Citizens* *Stakeholders perspectives for precision oncology: balancing patient and public support with evidentiary uncertainty* - **Samantha POLLARD** *DNA debate: engaging citizens on genomics* - **Chloé MAYEUR** *Health technology assesment and funding of genomic medicine technologies in Ontario, Canada* - **Wendy UNGAR** Join here		
10:45 a.m.	01:45 p.m.	06:45 p.m.	***07:45 p.m.***	03:45 a.m.	***Close of the conference***		

The Solve-RD project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement N° 779257

The conference also benefits from the financial support of:

- the Burgundy Franche-Comté region, within the framework of the regional call for projects 2020 dedicated to "International Scientific Colloquium"

RÉGION
BOURGOGNE
FRANCHE
COMTE

- the University of Burgundy, as part of the call for project named "BQR 2020"

UNIVERSITÉ DE BOURGOGNE