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Federaal Kenniscentrum voor de Gezondheidszorg
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Belgian Health Care Knowledge Centre

THE USE OF WHOLE GENOME SEQUENCING IN CLINICAL PRACTICE: CHALLENGES AND ORGANISATIONAL CONSIDERATIONS FOR BELGIUM

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HEALTH SERVICES RESEARCH

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THE USE OF WHOLE GENOME SEQUENCING IN CLINICAL PRACTICE: CHALLENGES AND ORGANISATIONAL CONSIDERATIONS FOR BELGIUM

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ACMG	American College of Medical Genetics and Genomics
AMA	Australian Medical Association
ASHG	American Society for Human Genetics
BAM	Binary Alignment Map
BelCoCyt	BeSHG Workgroup on Constitutional Molecular Cytogenetics
BelMolGen	BeSHG Workgroup on Molecular Genetics
BeMGI	Belgian Genomic Medicine Initiative
BeSHG	Belgian Society for Human Genetics
CCMG	Canadian College of Medical Geneticists
CHG	Centre for human genetics
CLG	Clinical Laboratory Geneticist
CLIA	Clinical Laboratory Improvement regulations
CMA	Chromosomal microarray
CMG	College in Medical Genetics
CNIL	Comité National Informatique et Liberté
CNV	Copy number variations
ComPerMed	Commission Personalized Medicine
CRM – CTG	Commission de Remboursement des Médicaments – Commissie Tegemoetkoming Geneesmiddelen
DTC	Direct-to-consumer
EBMG	European Board of Medical Genetics
EMQN	European Molecular Genetics Quality Network
EQA	External quality assessments
ESHG	European Society of Human Genetics

EWGDA	Experts Working Group on Data Access
FTP	File Transfer Protocol
GDPR	General Data Protection Regulation
INAMI – RIZIV	Institut national d'assurance maladie-invalidité – Rijksinstituut voor Ziekte- en Invaliditeitsverzekering (National Institute for Health and Disability Insurance)
IPG	Institut de Pathologie et de Génétique
ISP – WIV	Institut Scientifique de Santé Publique – Wetenschappelijk Instituut Volksgezondheid (Scientific Institute of Public Health)
IVD	In vitro diagnostic medical devices
KCE	Belgian Health Care Knowledge Centre
MAF	Minor allele frequency. Minor allele frequency refers to the frequency at which the second most common allele occurs in a given population. Provides information to differentiate between common and rare variants in the population.
MD	Medical doctor
MLT	Medical Laboratory Technician
NDD	Neurodevelopmental disorders
NGS	Next generation sequencing
NICU	Neonatal intensive care unit
NIH	National Institutes of Health
NIPT	Non-invasive prenatal test
PDPD	European Directive on the protection of personal data
PGD	Pre-implantation genetic diagnosis
PM	Personalized medicine
QA	Quality assessment
SAM	Sequence Alignment Map
SNV	Single nucleotide variant

SV	Structural variations
TAT	Turn-around-time
TMC	Technical Medical Council
VCF	Variant Call Format
VUS	Variants of unknown significance
WES	Whole exome sequencing
WGS	Whole genome sequencing

SCIENTIFIC REPORT

1 BACKGROUND AND SCOPE

Over the past decades, an increasing number of diseases have been discovered to be caused by changes in the genes, and their number keeps increasing. Genetic testing, involving sequencing of genome DNA, has thus become an essential part of medical science.[1]

1.1 Genetic diseases

A gene is a DNA segment that is responsible for one (or more) characteristic(s) of an individual, and generally directs the formation of a protein. The human genome contains about 20 000 genes. Changes in gene DNA are called variants (or mutations), and can be harmless or responsible for causing disease. Diseases with a genetic cause may be classified as monogenic or polygenic disorders (Table 1). Monogenic diseases are classically rare inherited disorders, caused by variant(s) in a single gene, and the family history is suggestive of a hereditary component.[2] Polygenic disorders, which are multifactorial diseases resulting from the interaction between variants in several genes as well as other factors (environment, lifestyle etc.), are generally more frequent; they include a number of cardiovascular diseases, cancers, dementia and type 2 diabetes.[2]

Variants can affect one nucleotide, a DNA segment (a number of nucleotides), the chromosome (e.g. trisomy) or the number of copies of fragments. A germline variant refers to variant in germ cells, which can be passed on to the next generation, as in Mendelian diseases or as predisposition to some cancers (e.g. BRCA genes). A somatic variant is a DNA change in somatic cells, which can therefore not be passed to offspring, and is of particular interest in malignancies. Many variants, even larger ones such as structural variations, may occur without obvious pathological consequences.[3]

1.2 Progresses in DNA sequencing

Variants are detected by sequencing DNA. The first method to sequence DNA was introduced in 1975 by Sanger.[4] However, this technique has limitations in speed, ability to detect less frequent variants, capacity and cost of analysis. Next generation sequencing (NGS) was introduced in the years 2000, and in the past decade has tremendously progressed in terms of

speed and number of bases that are sequenced in one time, along with a sharp reduction in cost.[a] The NGS techniques currently used perform sequencing by synthesis, in which DNA fragments undergo massively parallel sequencing, sequencing thousands of genes for a single individual.

Today, genetic variants are mostly detected by using targeted genotyping (i.e. sequencing a pre-specified panel of genes, depending on the clinical picture) or by sequencing larger parts of the DNA by NGS technology. The latter involves sequencing the whole genome (WGS) or the whole exome (WES), which is the 1-3% of the genome that codes for proteins (Table 1).[5]

Traditional clinical genetics has long focused on identifying monogenic (rare) genetic diseases. The diagnosis is often based on targeted sequencing, at least in a first step.[2] If this step is negative or for more complex diseases, WES or WGS are considered. Variants are then identified by comparing sequencing results to reference genomes, using various software programs. However, the detection of variants is not sufficient to make a diagnosis. The clinical implication of these variants must then be determined in relation with the clinical picture (phenotype) and based on other clinical and family information, as well as on international databases of variants.

WGS has become increasingly attractive in recent years, due to its broader coverage of DNA, its recognized clinical value, the increasing availability of WGS machines and the dropping costs.[6] Initially used in clinical research, WGS is increasingly used in clinical medicine. In rare genetic diseases, it tends to progressively (but not completely) replace existing genetic tests and panels. In addition, WGS will also extend the diagnostic pallet, particularly for diseases in which non-coding variants will play a role. Its use may expand to more common diseases with a genetic component, such as epilepsy and diabetes. It may also be used for carrier testing.

In recent years, a number of projects have been launched in neighbouring countries, such as the 100 000 Genomes Project in the UK, which aims at sequencing 100 000 genomes from around 70 000 people. In her political note for health policy on 27th October 2016, the Health Minister M. De Block has asked to study the feasibility of using WGS for routine diagnosis,[b] in particular the infrastructure model, the social consequences and the training needs to ensure the availability of sufficient trained personnel. WGS will also be available in 2017 in some Belgian genetic centres.

1.3 Research questions and methodology

The objective of this study is to advise Belgian decision makers on the use of human WGS in clinical practice, in particular on its organisational aspects. Its scope is limited **to the very short term (2018-2020)** and focuses on the health insurance perspective. It does not address the research aspects of WGS nor its use in population screening. It does not aim to define the clinical indications for WGS, does not cover the use of WGS outside the health care system, such as over-the-counter use, and does not estimate the costs of WGS or other genetic tests. Finally, this study does not address the complex ethical challenges due to its short timeframe; besides, the Belgian Advisory Committee on Bioethics is specialised in the evaluation of ethical aspects. On the request of the Minister of Public Health, a societal debate will be launched in 2018 by the King Baudouin Foundation and the ISP-WIV on the use of genome-wide information in health care to identify and discuss the ethical, legal and societal issues.

To respond to the needs in decision making, this rapid and pragmatic study is based on lessons learned and expert opinion. As WGS is not routinely used in clinical care in Belgium (or in most other countries), this study is based on the experience accumulated in WES in many settings, and in WGS in some selected countries. Lessons learned were collected from the international literature, including the grey literature, experiences abroad (the Netherlands and the UK), and the Belgian experience with similar technology, such as WES and large gene panels. Information on the Belgian experience was collected by face-to-face interviews with each centre for human genetics (CHG), professionals of clinical biology, representatives of genetic working groups, the INAMI – RIZIV, the ISP – WIV, as well as by consulting legal texts, nomenclature, budgets and expenses, and material from the CHG. Further details on the experts interviewed are provided in Appendix 1.

[a] The KCE 2015 report on NGS addressed gene panels for targeted therapy in oncology, and did not relate to WGS but to a specific use of NGS techniques.

[b] Note de politique générale Politique de santé / Algemene beleidsnota Gezondheidsbeleid.

Table 1 – Glossary of terms used in genetic sequencing

Term	Definition	Additional information
Genome	An organism's complete genetic material, including both exome (2%) and the non-coding sequences or introns (98%)	20 000 coding genes 3000 million base pairs
Exome	Part of the genome DNA that code for proteins. It is assumed approximately 85% of the mutations that cause diseases are in the exome.	20 000 coding genes 30 million base pairs Represents 1-3% of the whole genome
Mendeliome	All genes known to be involved in Mendelian diseases, which are monogenic diseases whose inheritance within families complies with Mendel's laws	3000-4000 coding genes Mendeliome sequencing involves a higher read depth than WES/WGS
Variant	Change in DNA nucleotide sequence	Can be "pathogenic", "benign," or "of unknown clinical significance"
Single nucleotide variant (SNV)	Alteration affecting single position in the string of nucleotides within DNA	May alter encoded protein
Structural variations (SV)	Genomic rearrangements larger than 50 base pairs accounting for around 1% of the variation among human genomes. Change the larger structure.	Deletions, insertions, inversions, translocations, trisomy and copy number variations
Copy number variations (CNV)	Change in copy number (repeats in the genome varies between individuals)	Duplication or deletion affecting a high number of base pairs
Variants of unknown significance (VUS)	When a specific genetic variant is found and there is no data to support its role in a particular disease phenotype	Majority of variants
Monogenic diseases	Disorders caused by variant(s) in a single gene, associated with a high likelihood of developing the disorder	Usually rare diseases with a Mendelian inheritance pattern
Polygenic disorders	Multifactorial diseases resulting from the interaction between several genes as well as non-genomic factors	Non-genomic factors may be environment and lifestyle
NGS	Next generation sequencing, performing sequencing by synthesis, using massively parallel sequencing	WES and WGS are based on NGS method
CGH array	Comparative genomic hybridization array, method allowing to quickly scan an entire genome for imbalance in the DNA compositions (gains and losses), comparing the patient DNA with the reference DNA	Genome-wide screening for copy number variations
Read	Nucleotide sequences obtained from each fragment of DNA in sequencing	Represented as a series of letters (A, C, G, T), corresponding to the bases of the DNA sequence
Read depth	Number of times (average) each nucleotide is sequenced and thus represented within all the reads. This has an impact upon the confidence with which an observed variant can be identified.	Also called depth of coverage or coverage. In rare diseases, depth is usually around 30 times. Coverage may mean the breadth of coverage of a target genome (% target bases sequenced a given number of times)
Read length	The number of bases that are sequenced at one time	Differs between technologies

2 BACKGROUND ON WHOLE GENOME SEQUENCING

2.1 Advantages of Whole Genome Sequencing

Today, gene panels are generally favoured to WES/WGS for the diagnosis of Mendelian disorders and a number of heterogeneous genetic disorders such as neurodevelopmental disorders or epilepsia, because of low sequencing costs, short turnaround time (i.e. time to obtain a result) and low rate of incidental findings. However as said above, WGS may become more efficient than targeted sequencing (see 2.2).[7]

WGS offers important advantages compared to previous NGS technologies, and WES in particular.[6, 8, 9] Firstly, it offers longer read lengths, enabling direct detection of even whole chromosome, and it starts with small amounts of material. Secondly, current WGS techniques not using PCR amplification provide a more uniform sequencing coverage quality than WES, being thus more reliable.[4, 6, 9] Thirdly, WGS is more powerful than WES for detecting variants within WES regions, including single nucleotide variants (SNV) as well as small insertions and deletions.[6, 8] It is also superior to WES to detect structural variations (SV), such as copy number variations (CNV, Table 1). Fourthly, higher throughput and faster turnaround time could be reached as a uniform platform is used for different applications. Eventually, WGS is the only method that can characterise all types of genetic variant in all parts of the genome.[8, 10]

These last advantages improve the ability to establish a diagnosis. This increased diagnostic yield of WGS compared to other techniques have been illustrated in a number of studies. For example in the Netherlands among 50 patients with severe intellectual disability that did not received a diagnosis (after micro-array and WES), WGS identified de novo SV and CNV in 21 patients, reaching a diagnostic yield of 42% in this cohort.[10] In England among 217 individuals with broad spectrum of disorders in whom prior screening had not identified pathogenic variants, WGS identified disease causing variants in 21% of cases, rising to 34% (23/68) for Mendelian disorders.[8]

In addition, the rapidly dropping sequencing costs of WGS will soon become lower than those of other genetic analyses (see below).

WGS also brings a shift in paradigm: today, clinicians and geneticists determine the clinical diagnosis to restrict the sequencing to the number of genes potentially involved; with WGS, all genetic information will be available at once.

2.2 Disadvantages of Whole Genome Sequencing

However, there are many challenges to the use of WGS.

Both WGS and WES sequencing generates a vast amount of data that need to be transformed into a limited list of variants that may be related to the clinical picture of the given patient.[3, 4, 11] The handling, analysis and medical interpretation of these data represent a major challenge. The majority of variants identified by WGS are not known to be associated with a particular disease and are called “variant of uncertain significance” (VUS, Table 1).[3, 4, 11] Furthermore, the WGS technique results in some parts of the genome being more sequenced and some less, and this must be compensated by sequencing each nucleotide several times, for instance around 30 times for inherited rare diseases (see 2.3).[12] This high depth increases the amount of data to analyse.

WES/WGS analysis may also identify variants that are unrelated to the clinical condition for which the patient was prescribed the test but may have clinical relevance.[11] Due to its very wide coverage, WGS is more likely to produce these findings as a higher coverage results in a higher probability to identify rare variants. Two types of additional findings are considered:

- Variants may be deliberately searched for and are then termed *secondary findings*. For instance the American College of Medical Genetics and Genomics (ACMGG) recommends since 2013 that the laboratory actively search for variants in a list of genes.[13] These variants were selected by expert consensus as representing conditions which are “clinically actionable”, i.e. for which confirmatory diagnostic approaches are usually available.[2]

- Variants may also be accidentally discovered and usually called *incidental findings*.[13-18] The term "incidental" implies that the finding is unexpected, although identification of other variants should always be expected in WGS.[19] Therefore, the term *unsolicited findings* has been adopted by the European Society of Human Genetics (ESHG).[20]

The use of WGS for screening indications, such as NIPT and neonatal screening, brings also many ethical and legal challenges, which deserve an ethical debate at societal level. However as said above, the use of WGS for screening purpose and ethical questions are outside the scope of this study.

2.3 Potential use of Whole Genome Sequencing in clinical practice

The place and possible indications for WGS in clinical practice are not clearly established at international level and are in constant evolution. However, it is likely that the use of WGS will gradually increase. The following indications in clinical care are described in the literature (including those outside the scope of this study), and may be considered in the short and long term perspectives:[5, 11, 21]

1. Diagnosis of rare or complex inherited diseases (potentially in trio analysis).
2. Identification of the genetic component(s) in a number of *heterogeneous* genetic disorders, such as intellectual disability, myopathy, epilepsia, or some cancers. In genetic heterogeneity, multiple mutations in a specific gene may account for pathology or mutations in distinct genes may cause the same phenotype, in which the WGS analysis of multiple genes simultaneously is more practical.
3. Prenatal screening by testing fetal DNA in the maternal blood (non-invasive prenatal test or NIPT); it could replace the current NIPT and identify other variants.
4. Carrier screening, e.g. pre-conceptional testing, allowing to simultaneously test parents for a large number of variants with minimal incremental cost for each gene.
5. Neonatal screening to replace current tandem mass spectrometry used in neonatal blood screening (using filters for a handful of variants).
6. Precision or targeted therapy, including pharmacogenetic testing, to assess treatment prognosis, adjust drug dosage and select the best treatment for an individual patient with a specific diagnosis, e.g. for the treatment of cancers (for somatic variants, e.g. companion diagnostic) or in common diseases with significant genetic component (e.g. thrombosis).
7. Pre-implantation genetic diagnosis (PGD) to identify disorders in a cell embryo, as a basis for embryo selection following in vitro fertilization prior to implantation in the maternal uterus.
8. Cancer screening to identify which persons are at risk of developing specific forms of cancer (oncogenetics).

WGS may also play an important role in personalized medicine (PM). PM may be defined as a model for classifying, understanding, treating and preventing disease, based on data and information on individual biological and environmental differences. It stretches from prevention to screening and therapy.[5]

The depth of sequencing used differs with the indications:

- "Deep" sequencing, in which sequencing performed multiple times is indicated to detect rare mutations in rare diseases (around 30 times). Higher depth of sequencing (>100 times) may be required to detect somatic mutations in tumour cells, due to contamination by normal cell and because the tumours themselves likely contain multiple sub-clones of cancer cells.
- "Shallow" sequencing or low coverage, in which sequencing is performed 1-3 times, is mostly indicated for NIPT, chromosomal aberrations (e.g. translocations), and copy number variant (CNV) aberrations in tumour.

In the longer term, WGS is expected to replace most genetic tests but not all. In particular, genetic mosaics require very high sequencing depths to detect low-frequency variants, and WGS may remain too expensive for this application.[9]

Some scientists predict that in the future, sequencing will be performed once in a lifetime, namely, shortly after birth. This would replace current neonatal blood screening and potentially replacing other genetic tests that could be conducted later in life, including for PM and precision therapy.[21] As said above, this use of WGS for population screening is not addressed in this study.

2.4 Economic aspects of Whole Genome Sequencing

2.4.1 Costs of Whole Genome Sequencing

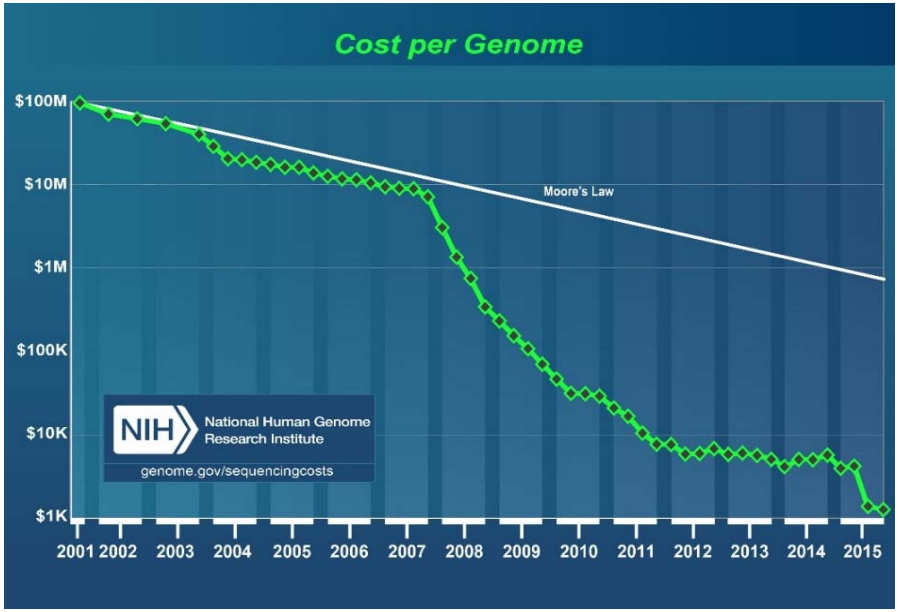
In 2014, the market leader Illumina announced that its HiSeq X Ten system (a set of 10 HiSeq X instruments) can sequence a human genome at the cost of $1000 when used at full capacity at 30x coverage.[c] Similar estimates have been made by the US National Human Genome Research Institute, which reports a constant decrease in the cost of sequencing a human genome since 2001, to reach $1245 in October 2015 (Figure 1).[22]

However not all costs necessary to complete a comprehensive WGS process are included in these estimates, and such a low cost per genome can only be achieved if a high volume throughput is guaranteed. The full cost of WGS (to be considered when performing a full economic evaluation, e.g. cost-effectiveness analysis) includes the following cost categories:[23]

- The sequencing, from DNA fragment to the raw sequencing data. These costs are not limited to the initial investment in WGS equipment, but also include implementing and validating the infrastructure for the production and the storage of sequenced data.
- The analysis, interpretation, confirmation and communication of WGS results: this includes the identification of potential variants, the comparison with international databases, the multidisciplinary consultations, the confirmatory tests, patient counselling etc. This is a labour intensive and thus highly costly task.
- The after-sequencing costs. The costs associated with all medical actions taken on the basis of the results. For example, the health consequences of ambiguous results that can include clinical follow-up, additional tests and also unnecessary interventions.

The cost of the quality insurance system should further be added to this list.

Figure 1 – Cost per genome computed by the US National Human Genome Research Institute[22]



[c] https://www.illumina.com/systems/sequencing-platforms/hiseq-x.html (Accessed November 2017).

A literature search (see methodological details and studies description in Appendix 2) identified four studies (2014-2017) detailing the costs of WGS and in which the total cost per genome was estimated at €3858[24] to $5519[25, 26] with the HiSeq2500, $2851[25, 26] with the HiSeq X, €1669[27] with the HiSeq X Five and €1411[24] with the HiSeq X Ten. This is in line with the rough estimates provided by the Belgian genetic centres (which excluded counselling costs as these are separately reimbursed in Belgium).

The 4 studies valued the direct medical and labour costs associated with WGS, as well as the confirmatory tests for primary findings. Some of them further incorporated the cost of counselling,[24, 28] data storage,[27, 25, 26-28] or management of secondary/incidental findings[25, 26-28] (Table 2). Compared with the others, the two studies incorporating counselling costs did not report the highest total cost per genome.[24, 28] After-sequencing costs were not considered in any of the studies. Even if the cost categories covered by the studies differed, it seems clear that WGS currently exceeds the prediction of a "$1000 per genome". In all studies the major cost drivers were related to the material, the equipment and the labour costs.

The cost per genome varied with the platform type. This suggests that, owing to its higher throughput, adopting the latest technology is a prerequisite for keeping average costs low. However, this assumes high rates of utilisation (e.g. 70%-80%)[24, 27] of the latest technology with a significantly higher capacity. To reach such low costs, the use of WGS should first be generalized.

Indeed, if in practice the demand for sequencing is not high enough this may lead to overcapacity of the machine and higher costs per genome. An estimation of the probable future needs of WGS analyses is thus essential before a new sequencing platform is implemented.

The studies' results further highlighted that increasing the coverage rate (sequencing depth) substantially increased the cost per WGS test.[24, 27]

The cost of the quality system that needs to be set up and kept was not described in any of the studies. This may however represent an increasing share in the total cost of WGS, especially considering the decreasing costs of the machines and consumables over time while quality insurance costs are recurrent and will likely remain constant.

Though the cost per genome keeps decreasing,[22] considering all costs relevant to perform WGS is essential.

Beside a breakdown of their total cost estimates, Tsiplova et al. provide a comprehensive list of cost data to be used for future economic evaluations of WGS, that can be easily adapted to other countries' needs (see Appendix 2.5).[25, 26]

Table 2 – Main characteristics of the studies valuing the costs of WGS

	Tsiplova et al. [25, 26]	Plothner et al.[24]	Christoja et al.[28]	van Nimwegen et al.[27]
Country, year	Canada, 2016	Germany, 2017	USA, 2014	Netherlands, 2016
Cost categories considered				
Direct medical costs	Yes	Yes	Yes	Yes
Labour	Yes	Yes	Yes	Yes
Overhead (water, energy, rent…)	Yes	No	No	No
Confirmation test for primary finding	Yes	Yes	Yes	Not reported
Confirmation test for secondary/incidental findings	Yes	No	Yes	Not reported
Development bio-informatics pipeline and protocols	No	No	No	Free software
Quality system	No	No	No	No
Genetic counselling	No	Yes	Yes	No
IT and storage	Yes	No	Yes	Yes
Characteristics of the sequencing machine				
Machine type	HiSeq 2500 HiSeq X	HiSeq 2500 HiSeq X Ten	Not reported	HiSeq X Five
Utilisation rate	Not reported	80%	Not reported	70%
Machine lifetime (years)	5	3	Not reported	5
Sequencing depth (times)	30-40	30	30	30

2.4.2 Pharmaco-economic evaluations of WGS

There is little published evidence on the cost-effectiveness of WGS (see details on the literature search in Appendix 2). At this time there is not enough evidence to indicate whether WGS is cost-effective compared to other standard genetic tests.

In a full economic evaluation, WGS was compared to chromosomal microarray (CMA) for the diagnosis of autism disorders in Canadian children.[25, 26] Compared to CMA, WGS was found to improve the diagnostic yield at an increased cost valued at CAN$26 020 (HiSeq X platform) and CAN$58 959 (HiSeq 2500 platform) per additional positive diagnosis. Their sensitivity analysis highlighted that future reductions in material and equipment costs, and better understanding of new variants and VUS will lead to improved efficiency.

In September 2016, the Dutch Rare Disease Consortium reported the results of a preliminary partial economic evaluation comparing the costs of WGS diagnostic test versus standard tests in patients with rare genetic disorders: neurodevelopmental disorders (NDD) and critically ill neonates admitted to the neonatal intensive care unit (NICU).[29] Estimates of the annual costs spent on obtaining a diagnosis with the standard care pathway were €15 836 per NDD patient and €40 500 per NICU patient. Compared to the standard care pathway, WGS was found to substantially reduce the annual medical costs through reductions in hospital stays and assuming WGS would substitute all standard genetic tests. They conclude that WGS might be cost-saving for the diagnostic of rare diseases. This study is a preliminary assessment that requires refinement with more precise and updated estimates of costs and epidemiological data.

Not only the technology is very recent and robust clinical evidence is lacking but there are also methodological challenges associated with conducting economic evaluations of WGS:[30-32]

- The diagnostic yield of WGS is unknown, which prevents to establish its effectiveness.
- The diagnostic pathways with traditional techniques are heterogeneous and difficult to model.
- The impact of a diagnosis on the patient's (and his/her family) treatment and outcome is highly variable and difficult to quantify. Complex models are required that simulate the impact of sequencing on both the patient and his/her multiple relatives.
- The yield of incidental findings is difficult to predict, let alone to model.
- The true cost of WGS-based diagnostic tests are unknown, changing rapidly, and any economic evaluation will be quickly outdated.
- As the technology is evolving rapidly, findings would not be generalizable from an earlier version to an updated version of a machine.

It has been argued that, as the costs of WGS are steadily falling and as the diagnostic yields are anticipated to improve with increased knowledge, WGS may be cost-effective compared to traditional techniques for individual conditions/genes. However, WGS may result in a higher number of false-positives (with respect to the primary indication) that generate additional confirmatory tests and costs, thus negatively affecting the cost-effectiveness.[33, 34] Incidental findings will also negatively impact the cost-effectiveness of WGS, if they are of unproven benefit and costly due to unwarranted testing.[35] The expectation is that, as the technology matures and as our ability to correctly predict the malignant or benign aspects of the variants improves, the need for confirmatory testing will diminish.[34]

3 PLACE OF WGS IN CLINICAL PRACTICE

3.1 In countries implementing WGS (or WES) in clinical care

3.1.1 The Dutch experience

3.1.1.1 Organisation

The Netherlands has a similar organisation for medical genetics compared to Belgium. It has today eight centres for medical genetics, each located in one university hospital. The prescription of genetic tests is so far restricted to the geneticists of the CHG. They function with a closed budget for genetic testing, at about €140 million per year (2014 data, see also 5.8), which increases by 1% annually.

The largest CHG is the result of an integration of the Nijmegen and Maastricht genetic teams (Radboudumc) and performs around 50% of the national WES analyses. They have commercialized their diagnostic offer for service of patients abroad. Most Belgian CHG refer samples to them for specific analyses.

3.1.1.2 WES experience

WES is performed in the Netherlands since 2011, following negotiations with national authorities. The arguments to get WES funded were that the change from the analysis of individual genes to WES would be budget neutral, with improved quality, increased amount of information for diagnosis, and no additional cost in terms of side effects. The Radboudumc centre, which was behind this proposal, was then among the first in the world to implement exome sequencing for routine diagnostic use. An initial budget of €2 million has been made available for investment (from innovation funds) and the reimbursement fees allowed to cover the running costs. WES became budget neutral after a few years because of the initial investment, the fixed fee of some other tests decreased, making some budget available, and WES could progressively substitute part of the existing tests. It should be noted that the fees for genetic tests are substantially (around twice) higher per gene in the Netherlands compared to Belgium (a number of insurers refund €1500 per patient) and this reportedly helped to be budget neutral in a shorter time frame.

WES is mostly used by panel for specific syndromes (“pakketanalyse”), and the list of syndromes is evolving (from 5 in 2015 to 21 in 2016), in close interactions with other medical specialties.[d] The request form for WES “panels” has a checklist of clinical information to help geneticists to determine if WES is indicated. The turn-around-time (TAT) is four months for gene panel and three months for full WES. Gene panels are preferred to WES for low number of genes (<50) and high volume, due to the costs of the specific gene panel method. For >50 genes to be analysed and low volumes, WES is preferred. The Radboudumc experience is that there are hidden costs in doing many different tests, due to the need for expertise for each test. There is a gain in simplifying the analysis procedure to a single one, which is the case with WES and WGS. For instance, they plan to substitute the array CGH by shallow WGS; CGH is expensive at Radboudumc, around €800 per test, and in deficit. WGS is expected to become soon cheaper than WES due to its higher simplicity, and this was the experience of Canada and the UK.

WES is now available at all Dutch CHG, but some outsource the sequencing part. In 2016 in the Netherlands, around 14 000 WES were done, and around 50% of this activity was through the Radboudumc centre. This centre outsources WES sequencing to BGI Europe in Copenhagen. This is done by a service level agreement.

BGI sends sequencing data in BAM format (see 5.3.4) to a secure File Transfer Protocol (FTP) server located in Radboudumc campus. These files contain the mapped reads but also the unmapped reads, which allows to convert them into FastQ files if needed. Radboudumc team checks files for completeness, and when completed, informs BGI to proceed and remove

[d] The use of WES here also includes WES analyses that are used as “gene panels” by applying filters to mask other genes/variants than those assessed.

the data from their servers. Any left-over DNA is sent back to Radboudumc, which destroys them. BGI receives no patient information.

Radboudumc controls the quality of services. Facilities are checked according to ISO guidelines. All data received from BGI are checked for important quality parameters. For instance, BGI is obligated to provide a median 75x read depth. Radboudumc checks median and mean coverage; if median depth is lower, BGI has to resequence the sample.

Incidental findings concerned only 1% of patients, as the analysis focused on specific genes. They do not actively search the exome for genes unrelated to the patient's disorder. In a first step, the genes involved are analysed; when results are positive, they stop the analysis; if they are negative, they continue analysing and may find incidental findings.[e] This analysis includes the list of ~50 "actionable" genes recommended by the ACMGG, but they do not actively search for them one by one, as recommended in the US guidance, but may find them by accident. They do not include pharmaco-genetic variants in this search. These limited number of incidental and/or secondary findings were easily handled by explaining the result during post-test counselling.

A database of all variants is shared between CHG. There are 10 bio-informaticians, who mostly use in-house software. Most of bio-informaticians were initially IT but some were laboratory personal; it took around two years to get them work as bio-IT. The centre recently bought a super-computer to cope with the needs.

3.1.1.3 WGS plans for health care

WGS is not routinely undertaken in clinical care in the Netherlands, but is limited to the research setting. However, it will soon be introduced through a (research) pilot project funded by ZonMw and called "One-test-fits-all to diagnose rare genetic disorders". This project will help to guide the practical application of WGS into health care for the diagnosis of rare diseases. The approach of a project to introduce WGS has the advantages to cover part of the additional and investment costs, to set up a single national database, to limit the introduction of this new techniques in a few centres involved, and to foster expert discussion and consensus on how to manage this new technique. The aim of this project is to assess the ability of the diagnostic test to ameliorate diagnostic yield, cost-effectiveness, patients' perspectives, and the ethical and psychological impact on patients and their families. It will also analyse the budget impact on the Dutch health care system, develop best practice guideline for WGS analysis, interpretation and reporting, and to facilitate a national (and international) platform for sharing WGS data. Its budget is around €1.5 million over a 36-month period, complemented by co-financing by the centres.

In practice, this project may buy time for the health insurance to decide on WGS budget and organisational issues, and allows its implementation in a limited scale and on a controlled approach. It is expected that WGS will be undertaken for the same indications as for WES, and the aim is to be budget neutral by substituting indications from WES to WGS.

3.1.2 The English experience

WGS activities have been launched in England as a project, the 100 000 Genomes Project. The project was launched by the government in 2012 and is run by a state-owned company called Genomics England.[7] The principal objective is to sequence 100 000 genomes from patients with cancer, rare disorders, and infectious diseases, and to link sequence data to diagnosis, treatment, and outcomes. One main aim is thus to build up a unique database for treatment and research.

To identify and enrol participants, the project has set up "Genomic Medicine Centres" (GMCs) within the National Health Services (NHS). Each GMC includes several NHS services and hospitals, recruits and consents patients, and provides DNA samples and clinical information for analysis. Roughly 25 000 cancer patients should each contribute two genomes (their own and tumour genome), about 17 000 people with rare diseases and two relatives

[e] If the exome gene panel analysis does not reveal the genetic cause of the disorder, an exome wide analysis is performed, and informed consent is requested (due to risk of incidental findings).

for each (trio analysis), and the project is also sequencing genomes from a smaller number of patients with severe infections.[36]

DNA sequencing is outsourced to Illumina, which was selected after a competitive evaluation of performance, capability, quality, and timeliness to generate WGS among several providers. The initial deal was that Genomics England will pay £78 million for Illumina to carry out the genetic sequencing, and the company will invest £162 million in the country over the next 4 years. Genomics England oversees quality assurance with a standard operating procedure for QA processes. In 2016, Genomics England announced a partnership with Illumina to develop bio-informatics tools, i.e. interpretation and reporting tools to deliver reports on all WGS. Illumina received access to the database with WGS sequence and anonymized medical data for the development of these tools.[f]

Most analysis and interpretation is centralized at the 100 000 Genomes Project. The genomic centre receives all medical file from the clinicians or obtain clinical data by linkage to other databases for the medical interpretation. The pipelines are managed by the project, and outputs are sent to clinicians in the form of a clear textual report, as well as a list of variants (VCF file).

3.2 Potential use of WGS in Belgium

In Belgium, WES started to be used in recent years mostly for research, and to some extent for clinical practice. Its most common use is to substitute large gene panels, using filters, or to investigate some undiagnosed cases of rare disease.

WGS has only been used for research purpose or for a few selected cases, mostly by CHG. Sequencing was usually sub-contracted abroad, e.g. in the Netherlands.

3.2.1 Possible indications for WGS in Belgium

According to CHG interviews, a number of indications that are currently investigated by gene panels could currently benefit from WGS, as the costs could become similar to those of some current tests, and the sequencing quality and diagnostic yield could be superior; in most of those indications however, filters would be used to select the relevant genes and avoid the very high burden of looking at variants in all genes.

The list of indications for which WGS could be used in the medium and long terms is more difficult to determine. There was no consensus among experts and this depends on funding and WGS cost evolution. However, we present below an attempt to classify the general trends in a time perspective, based on the opinion of Belgian experts.

In the short term (<3 years, 2018-2020)

WGS could substitute WES, mendeliome, large gene panels and array CGH for the following conditions (although there was no consensus for the indications indicated with a *):

- Rare monogenic diseases, with deep sequencing
- Heterogeneous genetic disorders (e.g. cardio-vascular, neurodevelopmental, epilepsia), with deep sequencing
- Prenatal and post-natal diagnosis (replacing array CGH), with shallow sequencing
- Neonatal testing for rapid diagnosis of unexplained phenotypes
- Non-Invasive Prenatal Test (NIPT), with shallow sequencing*

[f] https://www.genomicsengland.co.uk/bioinformatics-partnership-with-illumina/

In the medium term (4-10 years 2021-2027)

WGS could substitute the following techniques, as costs drop:

- Small targeted gene panels for other diseases, when declining WGS costs would be lower than costs of small gene panels
- Common multigenic / multifactorial diseases, depending on the evolution and state-of-art in the field (e.g. inflammatory bowel disease, inflammatory diseases)
- Somatic variants, with deep sequencing, for targeted therapy in cancers, by very deep sequencing of tumour cells (500 to 1000x).*
- Neonatal screening

In the long term (>10 years)

As the technology will continue to evolve and costs will further drop, WGS could substitute the following techniques:

- Non-Invasive Prenatal Test (NIPT), with shallow sequencing*
- NGS gene panels for targeted therapy in cancers (very deep sequencing of tumour cells).* However the time frame for such use of WGS is difficult to establish, and would depend on the policy for companion diagnostics.

In the longer term, WGS is expected to replace most genetic tests but a limited number of targeted genetic tests will remain more efficient and reliable than WGS, even in the long term, such as cystic fibrosis. Kits are available to detect these variants at reasonable costs, and good turn-around-times can be offered. Some older technologies do perform better than WGS or are needed for specific situations, such as somatic mosaicism and methylation defects. It may be that novel techniques are developed that allow to replace these approaches as well. In any case, the applications of WGS are similar in Belgium as in other countries (see the UK and the Netherlands).

Today, genetic tests are increasingly used in multigenic multifactorial diseases, such as neurological or cardio-vascular diseases, and contribute substantially to the increase in genetic tests performed by the CHG. The introduction of WGS, that will provide information on all potential variants, may further increase that trend.

4 ORGANISATION OF GENETIC TESTING IN BELGIUM

4.1 Centres for human genetics

Belgium has eight Centres for Human Genetics (CHG), one in each of the seven university hospitals and the eighth one is located in the IPG (Institut de Pathologie et de Génétique), an independent institute with a ASBL statute.

These eight CHG are:

- Centrum Menselijke Erfelijkheid – UZ Leuven, KUL
- Centrum Medische Genetica – UZ Gent, Ghent University
- Centre de Génétique Humaine – CHU Sart-Tilman, Ulg
- Centrum voor Medische Genetica – UZ Brussel, VUB
- Centrum voor Medische Genetica UZ Antwerpen, UA
- Centre de Génétique Humaine – Erasme, ULB
- Centre de Génétique Humaine – Cliniques Universitaires Saint-Luc, UCL
- Institut de Pathologie et de Génétique, Charleroi

The CGH were created under the legal base of the Royal Decree of 14 December 1987 for the diagnosis of constitutional genetic disorders,[37] that were followed by Royal Decrees of 1988 and 1989. These decrees aimed to stimulate the development of CHG and restrict the reimbursement of genetic consultations and analyses to recognized centres.

The 1987 Decree includes the following requirements for CHG:

- A CHG is a centre where diagnoses are made on “heredity or not of malformations and abnormalities, whether physical or psychological, the nature of those and the carrier status for hereditary characters”.
- Each CHG should offer genetic consultations to reach a diagnosis, ensure that patients receive the necessary information to make informed choices, and offer genetic testing that include all types of tests and all technologies. Genetic testing is provided by the centre but can be done in cooperation with other centres or abroad.
- The CHG should undertake research activities.
- Each CHG must be headed by a physician specialised in genetics (see below 4.5.1).
- The CGH inside the hospital must function as separated clinical services, having its own infrastructure and equipment.

Following the state reform, the CHG have been regionalised in 1995.[g] However, the CHG must still follow the conditions of the Royal Decrees from 1987-1989. Most of the CHG belonging to a university are located in the hospital structure.[38] They have a separate status but there is a strong involvement of the university hospital in the management of the CHG.[38]

Although CHG are traditionally focused on rare genetic disorders (including rare cancers), their scope has progressively included other types of diseases with a genetic component, such as cancers and neurological disorders.

4.2 Genetic testing and analysis

All CHG are performing genetic tests included in a limitative list of tests (see 4.4). However, each CHG is specialised in a number of specific disorders and organise targeted testing by gene panel for these disorders. Samples from the other CHG are referred for analysis for these cases to the specialised CHG. ULB and VUB CHG have a joint genomics platform called BRIGHTcore (http://www.brightcore.be); ULB has specialised in small gene panel testing while VUB UZ Brussel has specialised in large gene panels, and they have jointly developed and validated their mendeliome analysis. All other centres also apply either exome or mendeliome analysis, besides usual genetic tests.

In some university hospitals such as UZ Leuven or UZ Gent, a molecular (or diagnostic) platform has been set up, pooling resources from clinical biology, genetic centres and pathological anatomy. WGS sequencing is - or is planned to be - integrated in some of these platforms.

The majority of the tests performed by the centres are reimbursed by the INAMI – RIZIV using a stratified nomenclature (article 33, see 4.4).[h] The INAMI – RIZIV article 33 also establishes that the laboratory must have the accreditation ISO 15189 for a minimum of 80 % of provided services (“prestations effectuées”). For the analyses for which there is no accreditation system, the laboratory must prove the monitoring by an internal quality control system.[39]

For large gene panels and WES, sequence datasets are large and the analysis requires the help of biostatistics (see 4.5.3).[40] For WES or mendeliome, most CHG report to use algorithms and pipelines that were developed in-house. A list of variants is then analysed together with the clinical geneticists, together with a multi-disciplinary team for more complex variants (such as VUS). The diagnosis is then made by using additional information on the patient and his family, as well as international databases.

[g] 3 MEI 1995 - Besluit van de Vlaamse regering betreffende de Centra voor menselijke erfelijkheid.

[h] In accordance with the law, these tests are carried out in laboratories linked with a recognised CHG and are restricted to the physicians authorized to perform them by the Minister for Public Health.

4.3 Genetic counselling

Genetic counselling is defined in a convention article 22 INAMI – RIZIV (see under 4.4), as a set of clinical activities that include to assess the risk of occurrence of a disorder in a person (or his descendants), to inform her/him on the disease (diagnosis, prognosis and management) and to propose psychological support.[41] These activities are undertaken by a "multi-disciplinary team" (see 4.4). This convention, which aimed at improving the insufficient financing of genetic counselling, has been concluded with the eight CHG in 2012. It stipulates that genetic counselling can be performed outside the CHG premises, under the supervision of the CHG; there is also a corporation agreement with other hospitals or health care institutions, but only CHG can invoice this counselling. The convention distinguishes standard and complex genetic counselling, which have different scope, criteria and reimbursement (see 4.4).

Each CHG has its own informed consent form, but there is a plan within the College to harmonise it.

4.4 Financing and reimbursement

Further details about the financing of the CHG genetic activities are provided in Appendix 3. As said above, we only cover in this report the financing of genetic activities that are not related to research.

4.4.1 Article 33 of the nomenclature and convention article 22

Part of the financing of the CHG comes from the INAMI – RIZIV reimbursements for the genetic tests performed according to article 33 of the nomenclature,[39] which was created in 1988 to cover the diagnosis of hereditary disorders and revised in 2012 with the introduction of a fixed budget to monitor expenses.[42] The revised article 33 was enforced on 1/1/2013. It contains 32 codes. The INAMI – RIZIV rules stipulate that the tests must be performed in a CHG to be reimbursed by the INAMI – RIZIV.[h]

Six codes (starting 1/1/2013) concern "complex molecular analyses" to search for hereditary disorders or to detect mutations in the context of cancer or familial cancer syndrome (Table 3).

To be reimbursed by INAMI – RIZIV, the complex molecular analyses must be prescribed for an indication listed in a limitative list established by the Belgian College in Medical Genetics (CMG) (Diagnostic Rule 10).[i] The list is updated annually by the CMG; and there are no formal requirements to base this update on evidence. Each year the list revised by the CMG is transmitted to and examined by the Working Group Clinical Biology of the INAMI – RIZIV Technical Medical Council which, upon approval, submits it to the Insurance Committee for approval.[43] Quality criteria are also established to allow reimbursement of tests (see 4.2).

Table 3 – Nomenclature codes and reimbursement fees for complex molecular analyses (article 33)

Label	Complexity	Nomenclature code	INAMI – RIZIV reimbursement
Complex molecular analysis to search for a constitutional disease	Level 3	565493-565504	€1407.87
	Level 2	565471-565482	€570.45
	Level 1	565456-565460	€365.00
Complex molecular analysis for the detection of mutations in the context of cancer or familial cancer syndrome	Level 3	565552-565563	€1407.87
	Level 2	565530-565541	€570.45
	Level 1	565515-565526	€365.00

Reimbursement fee at 1/1/2017.

The evolution of the number of complex molecular analyses performed per level of complexity (Table 4) shows that for all 6 codes, the number of analyses increased between 2013 and 2015. This increase is even more pronounced for the analyses with the highest level of complexity (level 3).

[i] The limitative list of indications and the convention for genetic counselling and tests conducted abroad can be found on https://www.college-genetics.be/fr/legislation.html.

Table 4 – Number of complex molecular analyses per level of complexity

N (%)	Search for a constitutional disease *			Detection of mutations in the context of cancer **		
Complexity	**1**	**2**	**3**	**1**	**2**	**3**
2013	7889(62)	3809(30)	1100(9)	634(15)	675(15)	3046(70)
2014	9545(62)	4027(26)	1766(12)	972(16)	929(15)	4109(68)
2015	10456(55)	4701(25)	3797(20)	1469(19)	1237(16)	5145(66)
2016* **	7790(55)	3220(23)	3139(22)	1142(19)	908(15)	3974(66)

** Nomenclature codes: 565456-565460, 565471-565482, 565493-565504;*
*** Nomenclature codes: 565515-565526, 565530-565541, 565552-565563;*
**** Year not complete. NB: The sum of the % per year is not 100 due to rounding.*

Genetic activities of the CHG are also financed via a convention with the INAMI – RIZIV, according to article 22, 18° of the law 14/7/1994,[44] that covers genetic counselling and DNA tests conducted abroad.[i, 45] This convention, enforced at the same time as the 2013 reform of article 33 of the nomenclature, covers all pathologies (i.e. cancer, rare diseases etc.) for which genetic counselling or a DNA test conducted abroad is necessary, in order to avoid discrimination between patients.[42]

The convention specifies that to obtain a reimbursement each CHG must have a multidisciplinary team (consisting of geneticists, a psychologist, a nurse or social worker and a secretary) specialized in genetic counselling. Only the CHG can charge genetic counselling to the INAMI – RIZIV. The convention distinguishes standard and complex genetic counselling (see 4.3), for which different reimbursement fees are defined: €229.42 for standard and €625.10 for complex counselling (Reimbursement fees at 1/1/2017 for the codes 589750-589761 and 589772-589783). The budget allocated to genetic counselling is a closed envelope.

Genetic tests conducted abroad are reimbursed by the INAMI – RIZIV when Belgian laboratories are not carrying out the tests. The convention lists the reimbursement rules of the tests, among them the annual elaboration by the CHG of a list of authorised tests, the clinical interest of the test, the quality criteria to be met by the foreign laboratory etc. The INAMI – RIZIV reimburses both the laboratory tests and the shipping costs. The budget allocated to the "tests conducted abroad" is a closed envelope.

Since the reform of article 33 and the start of the new convention on 1/1/2013, the budget for the genetic activities of the CHG under article 33 and for the counselling and the tests conducted abroad is fixed annually by the INAMI – RIZIV General Council. For 2013, this budget was fixed at €42.65 million, with €37.79 million for article 33, €4.28 million for genetic counselling and €566 000 for genetic tests performed abroad (Table 5). Implementation of these budgets started on 1/1/2013. No transfer is allowed between the 3 parts of the budget. The budget allocated represents < €4 per inhabitant per year.

Table 5 shows that since 2015 the expenses for the genetic activities of the CHG exceed the budget. Indeed, expenses related to article 33 have sharply increased in 2015 and 2016. The deficit was aggravated following the decision in 2015 to cut by €2 million the budget allocated to genetic counselling, on the grounds that the convention had not been fully used in the two preceding years. In 2016, the budget for article 33 was increased by about €8 million to cope with the increasing demand for genetic tests.

Article 33: a closed or fixed budget?

The definitions around the nature of this budget differ. A 2011 note from the « Commission Nationale Médico-Mutualiste » about the revision of article 33 refers to a closed budget (« gesloten budget ») for the genetic activities of the CHG (the medical acts in article 33 and the convention).[47] A 2015 note from the same Commission refers to an overall budget "fixed" by the RIZIV/INAMI General Council;[48] and for which correction measures may be taken in case of budget overrun (as such not a closed budget stricto sensu).

Table 5 – CHG budget and INAMI – RIZIV expenses for the genetic activities covered by article 33 and the convention article 22

	2010	2011	2012	2013	2014	2015	2016
Budget							
Nomenclature article 33				€37 795 000	No info received	€37 964 000	€45 407 000
Genetic counselling				€4 288 000	No info received	€2 244 000	€ 2 027 000
Tests conducted abroad				€566 000	€580 000	€580 000	€580 000
Total				€42 649 000	No info received	€40 788 000	€48 014 000
INAMI – RIZIV expenses							
Nomenclature article 33	€40 068 034	€38 790 081	€41 666 225	€35 814 350	€37 348 178	€43 770 045	€49 639 101
Genetic counselling	-	-	-	€278 133	€1 154 331	€1 599 618	€1 793 887
Tests conducted abroad	-	-	-	€240 000	€401 260	€599 405*	€580 000
Total	€40 068 034	€38 790 081	€41 666 225	€36 332 482	€38 903 509	€46 206 061	€52 012 988

*NB: additional financing source of the CHGs is INAMI – RIZIV reimbursement for genetic tests of article 33bis (see below). * Accounting for the transfer of budget overrun to the genetic counselling. Source: CNMM/NCGZ reports (2011/71, 2015/92);[46, 47] and communication C. Mathy and J. Peetermans (INAMI – RIZIV), 2016 data received on 25/10/2017.*

4.4.2 Article 33bis and article 33ter of the nomenclature

Article 33bis of the nomenclature was created in 2007 to cover the genetic tests for acquired diseases, mostly cancers.[48] It contains 26 codes. The reimbursement of tests covered by article 33bis is not restricted to the CHGs and is also open to the laboratories of clinical biology or anatomo-pathology. There was a continuous and marked rise in the expense of article 33bis, from €3.8 million in 2008 up to €14.8 million in 2016 (INAMI – RIZIV, Doc N). Since July 2017, a new nomenclature code for the non-invasive prenatal tests (NIPT) was added to article 33bis, and this will likely increase the article 33bis budget.

Since 2016, INAMI – RIZIV is elaborating on new generic nomenclature codes (article 33ter) to cover the diagnostic tests associated to targeted therapies (e.g. “companion diagnostic tests”).

4.4.3 Regions and Communities

Additional budgets were/are provided by the Belgian federated entities.

- Between 2006 and 2012, the French Community (“Fédération Wallonie Bruxelles”) gave an annual ~€775 000 scientific research grant to the 4 French-speaking CHG.[j] In 2013 and 2014, the Walloon region allocated two grants for genetic research (GENHU and GENHU-2) with the aim to create a centralised biobank of ADN samples and to use it for research purpose. A total of €1.56 and €1.67 million were allocated to the French-speaking CHG.[k] The programme stopped in 2016; negotiations are under way to obtain new subsidies.
- Annual subsidies are allocated by the Flemish Community to the 4 Flemish-speaking CHG.[49] Subsidies must be spent on personnel and operating costs (mostly) and on infrastructure and equipment. Budgets of €2.24 (2014) and €2.26 (2015) million were allocated.

j Source: http://www.budget-finances.cfwb.be/ - Accueil > Budget > Direction du Budget > Budgets en ligne (Mai 2017). Budgets are published as decrees in the ‘Moniteur Belge’.

k Département des Programmes de Recherche de la Direction Générale Opérationnelle de l’Economie, de l’Emploi et de la Recherche (DGO6). (Mai 2017). https://recherche-technologie.wallonie.be/projets/index.html and https://recherche-technologie.wallonie.be/projets/index.html?IDD=26183.

4.5 Genetic professions

The professional profiles that are involved in genetic health care are: medical geneticist (physician - médecin spécialiste en génétique clinique / arts-specialist in de klinische genetica), clinical laboratory geneticist, medical laboratory technician, bio-informatician, genetic counsellor, psychologists and social workers. Genetic counsellors may also be medical geneticists.

The specialty of medical geneticist has only been recently recognized in Belgium (May 2017).[50, 51] There is no official recognition for the other professions, but two of them are included in the list of medical specialties targeted by the reform of the Royal Decree 78: medical laboratory technician (not limited to genetics) and genetic counsellor. The documents on the reform of the Royal Decree 78 also include a "technician in rare diseases", but it is unclear whether this refers to the Clinical Laboratory Geneticist in the EU terminology (see below).

There are however recognitions or defined standards at European level, in particular the European Board of Medical Genetics (EBMG) has established standards of good practice for the following four professional branches: medical geneticist, clinical laboratory geneticist, genetic nurse and genetic counsellor,[l] with the European Society of Human Genetics (ESHG).

There is also no officially recognized training in genetics in Belgium. The Belgian Society for Human Genetics (BeSHG) organises an inter-university postgraduate course in human genetics in the eight CHG ("Permanent Education Course in Human Genetics"). This curriculum includes limited material on WGS.

We describe below the professions that are specific to genetics. In addition, psychologists, nurses and social workers are also involved in the genetic diagnostic process, to help in counselling and in coping with the social consequences.

4.5.1 Medical or Clinical Geneticist

The main role of a physician specialised in clinical genetics in Belgium (called clinical geneticist at EU level) includes the clinical evaluation of the patients, the screening and approval of prescriptions, the selection of the appropriate genetic analyses, the medical interpretation, the reporting of test results, in a multi-disciplinary team when required, and the genetic counselling of patients.

This medical specialty (médecin spécialiste en génétique clinique / arts-specialist in de klinische genetica) has been recognized in the Royal Decree of 23 May 2017.[50] The criteria to be clinical geneticist foresee to have a medical specialty (internal medicine, neurology, paediatrics or gynecology-obstetrics) or a 2-year practice in these specialties, followed by a 4-year training in human genetics in a CHG. In the absence of national recognition up to May 2017, the BeSHG has organized a recognition in accordance with the standards for good practice established by the EBMG. This allows a European recognition of Belgian clinical geneticists.[51] In October 2016, the INAMI – RIZIV had a list of 54 clinical geneticists who were "qualified to perform the genetic tests".[52] It is however unclear which proportion of them are working in the CHG.

4.5.2 Clinical Laboratory Geneticist

The Clinical Laboratory Geneticist (CLG) is responsible for the practical organisation of the genetic laboratories, and has an important role in the interpretation of genetic variants and in the formulation of the laboratory reports for the patients. Their task is to supervise the diagnostic laboratory activities, including quality control, produce laboratory reports and foster the interdisciplinary discussion of the patient's results, together with the medical geneticist and other medical specialists for the medical interpretation. They represent the non-medical staff in the genetic centres.

This profession is defined at EU level by the EBMG/ESHG:[53] they are recognized as European registered Clinical Laboratory Geneticists (ErCLG). Unlike in the Netherlands, the non-medical scientists working in genetic

[l] https://www.eshg.org/ebmg.0.html

laboratories do not have a specific recognition in Belgium. They may be recognized as generic *collaborateurs de laboratoire médical / medisch laboratorium medewerker*, whether they have a bachelor, master or PhD degree. However they can be certified by the BeSHG and obtain a "BeSHG Medical Genetic Laboratory Supervisor Certificate", for a 5-year period that can be repeatedly extended. As this certificate is in line with the standards and requirements of the EBMG, it allows a European recognition.[54]

This profession is accessible to both physicians and non-physicians, and the main requirements include a scientific PhD degree and a 4-year training in either molecular genetics or cytogenetics. It is unclear whether this profession is included in the proposal for the Royal Decree 78. In October 2016, 63 recognized "medical genetic laboratory supervisors" were listed by the BeSHG.[55]

4.5.3 Medical Laboratory Technician

Medical Laboratory Technician (MLT) is an analyst/technician with a Bachelor degree working in different laboratory fields, such as clinical biology, anatomo-pathology, genetic laboratory and fertility laboratory. This profession is thus not exclusive to genetics, and is mentioned in the proposal for the reform of the Royal Decree 78 (as Medisch laboratorium technoloog).

4.5.4 Bio-informatician in genetics

Bio-informaticians have a key role in handling the high amount of sequencing data. Bio-informatics (defined under 5.3.1) represents a young but growing field in high-throughput sequencing, in particular in WGS. There is no specific profile for genetic bio-informaticians but their role is to ensure the analysis and the interpretation of raw sequencing data. In this early phase, this requires in many instances to construct (in-house) algorithms and analysis "pipelines".

There is also no official recognition for genetic bio-informaticians in Belgium or in Europe. There is no registry or list of bio-informaticians working in genetics in Belgium, but an average of 2 bio-informaticians (range 1-3) were reported to perform work related to genetic clinical care in each of the eight CHG. A number of bio-informaticians also work in research or in some other laboratories, such as in microbiology (performing WGS of pathogens).

Although there is no official training track for genetic bio-informatics, bio-informatics is a growing domain in a number of Belgian university scientific training programmes.[m] Most bio-informaticians currently working in CHG have a master or a PhD in a life science field (e.g. biology, bioengeneering) and additional training and/or experience in bio-informatics, or are trained as informaticians with additional training and/or experience in biology and genetics. Some "wet lab" technicians have also been reoriented, whenever possible, in data analysis.

There is thus not one single profile for bio-informatician. Some of them are more oriented towards constructing pipelines and designing analysis strategies while others apply existing tools (algorithms and softwares) to sequenced data.

4.5.5 Genetic counsellors

Again, there is no official recognition for genetic counsellor in Belgium but this profession is mentioned in the plan of reform of the Royal Decree 78 ("genetische consultant"). There is also no official training in genetic counselling in Belgium, and most counsellors are trained on the field or abroad. To address that need, the Gent University has launched a training course on genetic counselling in 2016 (10 trainees). In 2016, the Health Minister has requested a working group to advice on the opportunity to involve non-medical genetic counsellors, including genetic nurses, the pre-requisites and the required skills for them. A document has been issued and is publicly available (see main proposals in 5.7.4).[41]

At European level, the Genetic Counsellor Branch of the EBMG holds a registration of recognized genetic nurses and counsellors in Europe.[56]

[m] Interuniversity Institute of Bioinformatics in Brussels.

Table 6 – Estimated number of genetic specialized staff in CHG

Profession	Total number (date)	Estimated average of persons by CHG (not full time equivalent)
Clinical geneticist (MD)	54 in Belgium (2016)†	7
Clinical laboratory geneticist	63 in Belgium (2016)‡	8
Genetic counsellor (non-MD)	NA	Around 4 (range 1-6)*
Bio-informatician working in genetics	NA	2 (range 1-3)*

** Based on interviews but incomplete picture; † According to INAMI – RIZIV 2016 list of medical geneticists "qualified to perform the genetic tests".[52]; ‡ According to 2016 list of the BeSHG.[55]*

4.6 Professional organisations and interactions with other groups

The High Council of Human Genetics has been set up in 1973 to advise the Health Minister in human genetics. It was replaced in 2012 by the College in Medical Genetics (CMG) under the Federal Public Service of Public Health and its main task is to "establish and maintain the excellence in terms of genetic clinical care and research in Belgium".[41] The College includes 1-2 representative(s) of each CHG. Its duties are to formulate guidance in terms of diagnosis and treatment of genetic disorders, and organise regular evaluations in all genetic domains.[57] Through a number of working groups, it aims to get the different professions in clinical human genetics recognised, improve the reimbursement system, including the update of article 33, serve as a platform where the CHG can harmonise their organisation, collaborate with other medical specialties and represent the CHG or the Belgian human genetics in various working groups and national plans.

A number of working groups have been set up by the College, the BeSHG or other initiatives (e.g. the Cancer Centre). These working groups formulate guidelines, establish common tools, progress on harmonisation and prepare the necessary changes in practice and financing. Those who would be the most involved in WGS are the BelMolGen (BeSHG Workgroup on Molecular Genetics), BelCoCyt (BeSHG Workgroup on Constitutional Molecular Cytogenetics) and the ComPerMed (Commission Personalized Medicine) led by the Cancer Centrum. These platforms allow interactions and cooperation across CHG for the discussion and development of solutions for new technologies. In addition, each CHG has developed a specific expertise in specific fields, as illustrated by the development of specific gene panels.

5 MAIN CHALLENGES AND LESSONS LEARNED IN WGS IMPLEMENTION

The main challenge in the use of WGS in clinical care is not the sequencing technology itself. The challenges of the use of WGS in clinical practice described in the literature comprise organisation models for sequencing, costs, issues related to the management of the huge volume of information generated, including the storage of data and informatics burden, the analysis and interpretation of variants, and the management of incidental findings.[8] In addition, the particular organisation of medical genetic services in Belgium is enticing other challenges.

This section assumes that WGS will mostly address germline variants in the short term, based on expert opinion (see 3.2.1). This implies that the challenges specific to somatic variants are not covered in this report which focuses on the short term use of WGS.

5.1 Infrastructure models for sequencing

5.1.1 Centralised or decentralised sequencing?

Given the challenges of WGS, one possible option would be to limit the sequencing activity of WGS to one or a few reference centres.[40] However, as the cost of WGS decreases and the speed of sequencing and analysis increases, it is likely that WGS will be anyway decentralised, at least to some extent. Potential advantages of centralised sequencing in one or a few reference centres are described in the literature:[40] higher quality due to concentration of technical expertise, experience and high requirements for accreditation, ability to use performing variant calling programmes, higher volume resulting in lower costs, and easier constitution of a unique database. Furthermore, high capacity could allow a reduction of the turn-around-time.

A complex issue for the infrastructure choice of WGS in Belgium is the need for investment and how it can be done. Despite the decrease in sequencing costs, the purchase of a high-throughput sequencing machine able to perform WGS is still very expensive. The HiSeq X Ten system costs around 10 million US dollars.[n] In 2015-16, a consortium led by the KULeuven CHG negotiated for a centralised purchase of (five) machines HiSeq X Five for Belgium and the investment cost was around five millions euros. In the Belgian health system, genetic centres do not have access to investment funds: investment costs are not covered by the 1987 Royal Decree, nor (usually) by the regions and CHG do not have access to the hospital financing system (see 5.8). In the current system, a sufficient investment is difficult to achieve without the collaboration with research teams (academic or private), which implies that the sequencing facility has to be shared. Although such collaboration may seem efficient, this is more difficult to address in a hospital management perspective. A HiSeq X (Five or Ten) model also implies that all sequencing has to be centralized in one single place. In Belgium, this option may be favourable for smaller centres that have difficult access to funds to invest in sequencing machines, but more complex to handle for larger centres, due to a lower visibility and the competition between hospitals in terms of service offered, timeliness and infrastructure. Some level of centralisation has been experienced by the CHG of ULB and VUB with the creation of BRIGHTcore. The experience is reportedly very valuable, especially for research, but is more difficult for clinical care because of competition between hospitals.

However in January 2017, Illumina marketed a smaller sequencing instrument, the NovaSeq, which presents more flexibility, a lower volume needed to reach efficiency, and at a lower investment cost (around $900 000).[o] Due to the lower cost, some of the CHG purchased or are considering to purchase this machine with the collaboration of local partners (often the University).

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n http://nextgenseek.com/2014/01/what-is-the-price-of-nextseq-500-and-hiseq-x-ten/, http://massgenomics.org/2015/01/illuminas-new-hiseq-x-instruments.html

o https://www.illumina.com/company/news-center/press-releases/press-release-details.html?newsid=2236383

Decentralised sequencing would offer equal access to WGS for all centres, and an easier collaboration between laboratory, bio-informatics and clinical experts (integrated system). A lesson learned in Belgium and abroad is also that any investment in sequencing machine entices the risk that the equipment may rapidly be outdated, as it is generally less efficient than the new generation coming on the market. Indeed, the rapid evolution in technology is resulting in cheaper, higher quality and better performing sequencing machines being proposed over time (e.g. the recent NovaSeq series from Illumina).

5.1.2 Sequencing outsourced?

One alternative to invest in sequencing machines would be to outsource sequencing. This option has been selected by (at least) two large projects, the Radboudumc genetic center in the Netherlands (for WES) and the 100 000 Genomes Project in the UK.[7]

The Dutch Radboudumc center has a positive experience in outsourcing 7000 WES per year to BGI Europe in Copenhagen. Their lessons learned are lower costs, due to higher volume compared to a sequencing volume limited to their centre and to the competition between providers, savings on investment, maintenance and training, shorter turn-around-time and higher flexibility in planning as it does not need to wait for sufficient volume. In addition, the Radboudumc staff could save time and rather focus on the analysis and interpretation of variants, and on reporting of the results, which is more time consuming. The Radboudumc experience highlights the need to trust the provider and the importance of good negotiations. However, advantages depend on the negotiating power and the efficiency of the current laboratory setting. In that experience, only sequencing was outsourced, and the bio-informatic analyses, medical interpretation and all other activities were kept in the centre.

The 100 000 Genome Project in the UK is outsourcing DNA sequencing to the company Illumina since 2014 (after formal evaluation of several providers), and in 2016 outsourced as well the development of bio-informatics tools to the same company, for interpretation and reporting. To do so, the company received access to the database with WGS sequence and anonymized medical data. No lessons learned on that project was found but Belgian experts pointed to the frustration of English clinical geneticists that miss insight into the diagnosis process.

5.1.3 Should WGS be restricted to genetic centres?

In most documented experiences so far, in particular in the UK and the Netherlands, the management of WGS is limited to human genetic centres. The main arguments in favour of limiting WGS to human genetic centres are that those facilities concentrate a high amount of genetic expertise with specialised and trained staff, a higher volume of tests, an easy access to national and international databases on variants and phenotypes as well as results from other family members, and quality assurance schemes for genetic testing. Additionally in a number of settings (including Belgium), these centres have a monopoly in approving the genetic tests prescribed. This may facilitate that WGS would be restricted to indications with sufficient clinical utility (see 5.2). Disadvantages are that only clinical geneticists may decide on WGS, other medical specialties have a less direct access to the technique, and geneticists may lack an in-depth knowledge in other medical specialties that will request WGS (e.g. cardio-vascular or encocrinology). However, WGS is already offered by private companies, including direct-to-consumer services, as many other genetic tests (not addressed in this report).

5.2 Decisions on medical indications for WGS

In the diagnostic field for clinical care, indications for specific tests are usually based on criteria such as diagnostic validity, clinical validity and clinical utility. A key aspect here is the clinical utility, which refers to whether a test would provide information that can be used to develop a clinical intervention, leading to improved health outcomes.[20]

In genetics, the concept of medical actionability is more used but has a wide range of definitions and its understanding differs among groups.[40, 58] A narrow definition of medical actionability is whether an early intervention is likely to reduce or prevent serious morbidity or early mortality. But the concept may also extend to whether the diagnosis may alter the treatment or surveillance of a patient, or remove such management in a genotype-negative family member.[18, 58, 59] But many geneticists, including in Belgium,

also consider that using WGS to help in the diagnosis, or to have a better diagnosis, can be considered actionable if the diagnosis may change the management plan for a patient, even in the absence of specific therapeutic choices.[40] Information on these criteria are needed to select WGS indications and prescription rules. However, evidence is lacking to evaluate the clinical utility of WGS technique as we deal most often with rare diseases, and the use of WGS in clinical practice is fairly new.

Currently in Belgium, the indications for genetic tests in clinical practice are defined in the article 33 and 33bis (see 4.4.1 and 4.4.2). The "limited list of indications" of the article 33 is discussed and updated yearly. So far, WGS is mostly prescribed in research (i.e. outside RIZIV/INAMI reimbursement) e.g. when all other tests (genetic and others) are negative; this represents a very small number of requests and sequencing is usually outsourced abroad.

According to an ESHG expert review, WGS testing for common disorders would often not satisfy the criteria of clinical utility.[20] Ideally, independent information about the pros and cons of WGS should be available to the public and the patient, based on expert judgements from professionals explaining the issues at stake.

Clinical guidelines or algorithms can help determine which indications could help in deciding on WGS indications, but do not exist yet. Similar guidelines are being published for NGS testing in oncology but these do not involve WGS.[60] Several authors of published studies have highlighted the difficulty in elaborating WGS guidelines aimed at clinicians: the lack of evidence (and the difficulty to generate such evidence), the disagreement among guideline groups on the required level of evidence, the constant adaptation of guidelines needed as new evidence arises, and the differences in the concept of clinical actionability.[5]

Besides the prescription of WGS in the health care setting, anyone can also purchase WGS directly from companies. In those cases, criteria such as clinical utility of a test would no longer prevail, which is problematic.[20]

5.3 Data analysis and interpretation of WGS results

Although sequencing using WGS is likely to become less costly than gene panels, the interpretation of test results is much more complex, due to the vast amount of sequencing data that need to be transformed into a limited list of variants that may have a clinical significance in the given patient.[3, 4, 11]

5.3.1 Genetic bioinformatics

Bioinformatics is defined as the branch of biology that is concerned with the acquisition, storage, display and analysis of the information found in sequence data, using computers and bioinformatics softwares.[61]

Machines performing WGS provide raw data, consisting of millions of fragments of reads. Genetic variants are inferred by comparing these data with international databases (reference genomes). Five steps are described in the analysis: assessment of the quality of raw data, pre-processing, alignment to a reference genome (reads are "mapped" to the reference genome), post-processing, and variant analysis.[62] Subsequently, the known and unknown variants are interpreted.[1]

As WGS datasets are very large, the analysis represents a huge bio-informatics hurdle and must be automated by bio-informatics tools.[40] However, the variants identified may depend on the analysis algorithm that is applied.[3] The process of data analysis requires skilled and trained bio-informatics personnel, efficient bio-informatics pipelines[p] and high computing capacity to treat, filter and analyse data on variants. Commercial softwares or analysis pipelines are increasingly being developed to analyse sequence data "from sequence mapper to bedside".[3] However these are still expensive, often opaque (black boxes), and may use imperfect algorithms.[11]

In Belgium, all interviewees agreed that the current capacity in bio-informatics is not sufficient to cope with WGS analysis. The specific issue of bio-informaticians is developed below in a specific section under 5.7.3. Each CHG developed in-house bio-informatics pipelines according to their needs,

[p] An analysis pipeline consists of different analysis tools, algorithms, and computational steps.

usually complemented by some commercial package. There is neither sharing nor harmonization of analysis pipelines yet, except between ULB and VUB bio-informatics teams. Powerful computers that are needed to process the huge amount of sequence data are usually not available at the CHG. Although one super-computer is accessible per region, its use must be negotiated.

5.3.2 Medical interpretation and reporting

Analysis of WES and WGS data generates a long list of variants, and the difficulty in interpreting these variants has created a bottleneck in the clinical application of the technology.[11] The challenge is to distinguish disease-related variants from the neutral ones, and to interpret the causality versus the correlation of findings, since the presence of a particular variant does not necessarily inform on its pathogenicity in the context of a genetic disorder.[1, 3] This process is even more difficult for variants outside the exome, because little is known on their pathogenicity.[3] The list of variants must be interpreted in the specific clinical context, in relation with the patient clinical picture and family information. This is easier in case of well-defined monogenic Mendelian disease, but becomes challenging in multifactorial polygenic diseases where disease results from the interaction between several genes as well as other factors.[2] Medical interpretation thus requires interdisciplinary collaboration, and should involve the medical specialists, the medical laboratory and clinical geneticist. In the Belgian setting, the medical interpretation of some complex cases could require inter-disciplinary meetings of various specialists lasting up to half a day. Medical interpretation of variants also requires large (ideally international) databases that link variants to patient phenotypes (characteristics, including clinical picture). These databases should be easily accessible to the whole scientific community.[11, 20]

There is a general consensus that only results that are medically actionable should be reported to the patient. The information of complex results to the patient should be conducted during counselling sessions (see 5.5) and will cost more time if more variants are involved.

5.3.3 Variant of uncertain significance

A major challenge in data analysis, medical interpretation of variants and counselling is the management of the “variants of uncertain significance” (VUS, Table 1). These represent the majority of variants identified by WGS.[3, 4, 11] The assessment of VUS pathogenicity is a long, complex and expensive process that represents a heavy burden for geneticists and genetic counsellors.[11] Some variants may have low penetration, or are only found in one or two families in the world, which makes the assessment of their pathogenicity challenging. Not only the clinical or medical data are required, but also the ethnicity, genealogical information and possible sequence data on relatives. The collaboration of different specialists, including bio-informaticians, biologists and clinicians is needed.[1, 11] In a number of cases, functional studies (e.g. cellular or animal models) are needed to interpret VUS, to confirm or infirm their pathological meaning, but there is no reimbursement for these in Belgium and they are expensive. These studies may be critical to the assignment of causality.[8] However, international collaboration would better address this problem, with specialised international networks concentrating expertise and sharing data. This will be done for instance by the EU reference networks (ERN) initiated in 2017 under the umbrella of the Commission Expert Group on Rare Diseases and funded by the EC.

In some situations, reclassification of a particular variant may occur based on new scientific evidence. The question is whether the geneticist should be considered as responsible to re-analyse old data systematically and report novel findings.

Reporting VUS may cause (sometimes unnecessary) anxiety among patients, especially in the case of variants contributing to rare diseases. Some centres decide not to report (or rather not to look at) VUS. There is a need to develop consensus on whether and, if so, how to report VUS to patients and their families.[11]

Further details are described in the sections on incidental findings (5.4) and counselling (5.5).

5.3.4 Data storage, protection and sharing

There are different formats for WGS sequencing results, differing in content and size (Table 7). Raw data provided by the sequencing machines are usually stored as large FASTA or FASTQ files (100-300 Gb). These data are aligned against a reference genome and compressed into BAM files (around 100-150 Gb).[63] These data are then processed, using "variant calling" programmes, into information on each variant (VCF, around 125 Mb).[64] NGS companies would usually send BAM files, which can be reverted to raw data. The size of files also depends on the depth of coverage and read length.

As comparison, the average size of a BAM file may be approximately 2-6 Gb for a gene panel and 10-16 Gb for a WES analyse (using NGS).[63, 65]

Table 7 – Data files used for storage of WGS data[3, 64]

Type of file	Description	Size
FASTA/Q	FASTA: text-based format containing multiple DNA sequences, each with some text. FASTQ: as FASTA but also stores a corresponding quality scores for each base.	FASTA: 100-300 Gb per sample (for deep sequencing) FASTQ: 70Gb with Illumina X Ten[3]
SAM (Sequence Alignment Map)	Format for storing large sequence alignments against a template, with quality score.	~500 Gb per sample
BAM (Compressed binary format)	Binary format of SAM for storing sequence data, thus compressed format for SAM. It aligns reads and is technology independent.	~100 Gb per sample
VCF (Variant Call Format)	Text file format containing a list of sequence variants, sorted by genomic position, at which the individual differs from the reference genome.	125 Mb

There is no clear consensus or guidelines in Belgium - nor at international level - on which type of WGS data should be stored, how, where and for how long. Each centre has its own system, usually storing FASTA/Q, BAM and VCF files for varying lengths of time. However, a review of the legal framework and guidelines in this project allowed to answer to some of the questions, as shown below (see also Legal Supplement).

The main question is whether raw data should be stored. An advantage of storing it is the possibility to access the genome information later, when new knowledge could allow other actions or interpretations, and to possibly share it. However, the challenge is how to manage huge storage capacities and to finance it. As these growing costs are not covered, the centres (or hospitals) might try to reduce these costs, which would affect the service levels and could put the protection of the data at stake.[38] Some CHG started to keep raw data for long time duration as they assume it is part of the medical file, but this will soon not be longer feasible. Given the rapidly decreasing costs and increasing quality in DNA sequencing, it is likely that it will be soon more cost-effective to sequence the patient DNA again when needs arise, compared to storing raw data.[40]

The legal analysis did not find Belgian or European rules stating which type of genetic data should be kept and for how long (see Legal Supplement). However, general rules can be found in the EU regulatory framework on data protection, based on the European Directive on the protection of personal data ("PDPD"). The PDPD states that no more data should be collected or kept than is not necessary for the explicit purpose. This suggests that the storage of variant information (VCF file) may be sufficient to keep as a minimum requirement, and not the raw data, since re-sequencing does not imply that clinically relevant data are lost.

If long storage of raw data would be opted for, then the question is how and where to store it. In the current situation, most CHG have to negotiate with the hospital, the university or other research platforms, to ensure sufficient storage capacity, or they store raw data on the clouds. Several stakeholders fear that the level of data security is not sufficient. There is no harmonisation of process and quality of storage in Belgium but a working group within the College of Genetics is working on the centralisation of data, including security.

One option is to outsource data storage. The PDPD is providing a legitimate basis for situations in which a third party (e.g. a private company) would store patient's data. However, the requesting centre should provide certain information to the patient regarding storage of his/her data. If at any point the patient data is to be transferred to a country outside the EU, then this country must ensure an adequate level of data protection.

An important and consensual issue is the need to share a national database of variants, initially between CHG, containing phenotypic information as well, and allowing to compare sequencing data of family members of patients. The challenges involved are the ease and security of access, an effective system to search database, and data protection (including ISO norms). Various data sharing policies and guidelines are being issued by international and national institutions (see Legal Supplement). Protecting the right to privacy of the individuals is essential.

5.4 Management of incidental and secondary findings

One of the predominant issues brought in papers discussing WES and WGS is the management of incidental and secondary findings.[3, 11] As explained under 2.2, *secondary findings* refer to variants that are not related to the clinical question but that are deliberately searched for and *incidental* or *unsolicited findings* to those "accidentally" discovered during the course of sequencing.[18] These are expected to be much more frequent with WGS than with WES and targeted panels. They may represent a potential additional burden for health providers and a source of anxiety for patients and their family.[11] Incidental findings may be partly prevented by using filters (or masks) to focus on the part of the genome that is targeted and mask all other genes (or sequencing data from other genes).

The decision on whether or not to communicate unsolicited and secondary findings to the patient should be determined by the physician and the patient before ordering the test, during an extensive informed consent process of the counselling session. However, a number of factors must be taken into account: the "penetrance"[q] and pathogenicity of many variants are unclear, the results may have implications for the patient relatives as well (who were not consulted and did not consent), the majority of patients prefer to know everything but they may receive more information than can be understood, and this depends on their level of health literacy.[1, 3, 66] Research also showed that the level of understanding that is needed to decline to learn a result is deeper than the one required to accept it.[66] Given these difficulties, it appears that robust informed consent is required for (non-targeted) WGS, which is time consuming and an increasingly heavy task.

The proportion of unsolicited and secondary findings depends on the sequencing strategy.[2] Many studies are from the US, where the American College of Medical Genetics and Genomics (ACMG) has defined "medically actionable" variants in 56 genes associated with 24 medically actionable conditions.[59, 67] The ACMG recommends that laboratories actively search for variants in these 56 genes. In the clinical context of Europe, most genetic centres use filters to select relevant variants after sequencing ("in silico" filtering); this also allows to explore new variants in a later phase.[20] In European guidelines, there is a general agreement that it is preferable not to identify, let alone actively search for, variants related to diseases unrelated to the clinical question (see Legal Supplement).[21, 68, 69] Laboratories are usually recommended to adopt a targeted approach to WGS, using selective filtering, in order to limit the possibility of identifying unsolicited findings. For instance the European Society of Human Genetics recommends in its guideline: "When in the clinical setting either targeted sequencing or analysis of genome data is possible, it is preferable to use a targeted approach first in order to avoid unsolicited findings or findings that cannot be interpreted. Filtering should limit the analysis to specific (sets of) genes. Known genetic variants with limited or no clinical utility should be filtered out (if possible neither analyzed nor reported".[20] Indeed in Belgium and the Netherlands, WES/WGS is so far using filters, except for specific cases.

[q] Penetrance: probability that carrying this variant is associated with a high likelihood of developing the disorder.

However even if the analysis is restricted, the possibility of identifying unsolicited findings is not eliminated. Practical experience with this approach (for WES and/or WGS) suggests that unsolicited findings concern around <1% of patients. They generally are not reported to represent major problems but a concern mentioned by some CHG is the difficulty encountered by laboratory technicians, who identified unsolicited findings, to decide not to report them. They also question their responsibility in this process. The legal framework is unknown by health providers. Guidelines and policy documents issued by professional bodies differ considerably with regard to their recommendations, but they generally indicate that there is no obligation for laboratories to report unsolicited findings. However, most guidelines state that geneticists should disclose unsolicited findings to patients if they have high predictive value and are indicative of serious health problems that allow for treatment or prevention.

5.5 Genetic counselling

The new issues related to VUS and unsolicited / secondary findings highlight the increasing complexity and burden of genetic counselling when WGS is used, and thus the increasing needs in counselling professionals. The issue of the (non-physician) genetic counsellors is developed in the Human resources section (5.7.4). According to the convention 22, most of the counselling burden relies on clinical geneticists, who are already absorbed with other activities.[r]

The KCE 2007 report also revealed the insufficient reimbursement for genetic counselling. This has been addressed by the convention 22 on genetic counselling, with standard and complex genetic counselling (4.4) that improved the reimbursement for counselling activities. However, this convention is underused for the reasons explained below under 4.4.1.

As WGS will be increasingly used in common multifactorial diseases, other medical specialties (than genetics) should be involved in the counselling of patients, as they know the patient and his specific pathology. However, the current convention for genetic counselling does not include the intervention of these other medical specialties.

5.6 WGS quality

Only few papers address the issue of quality and reliability of WGS. The literature review did not identify formal assessment of quality of human WGS in the health care setting, except for the assessment of specific pipelines for processing WGS data or for the detection of specific variants. Most quality problems described in the literature concern somatic variants that are not covered here.

In general, WGS is considered to have a higher analytic validity (i.e. ability to accurately measure a genetic characteristic of interest) compared to WES (see 2.1).[4, 9, 70] Validity will also depend on the read depth that is selected: in a study comparing both techniques, WES had a 95% sensitivity in SNP detection at a mean depth of 40 reads, whereas WGS only requires a mean of 14 reads.[70] The downside is then that higher depth produces more data to analyse.

The quality of WGS analysis thus depends on the quality of sequencing but also the quality of data analysis. There is still a risk of false positive and false negative results as errors and gaps (missing bases) are still present in the reference data to which new sequence data are aligned.[3, 40] A 2012 study reported that differences in the generation and analysis of genome sequences resulted in a 4-14% range in the number of variants called in the same sample. There may also be errors in the variant calling pipelines.[3, 40] However, rapid advances in that field imply that these sources of error will likely disappear. Positive and negative predictive values will vary with the disease and variant involved, but depends also on the disease prevalence, which may be very low in Mendelian diseases.[71]

[r] « Le conseil génétique comprend au minimum 2 consultations du médecin spécialisé en génétique clinique avec le patient ou la personne concernée par le problème génétique. »

In Belgium, the ISP – WIV is responsible for the accreditation of laboratories for clinical biology and anatomo-pathology, but nothing is stated for medical genetics. The article 33 requests that all CHG laboratories have the accreditation ISO 15189 for a minimum of 80 % of provided services. They all participate to external quality assessments (EQA) for NGS organised at EU level by the European Molecular Genetics Quality Network (EMQN), but not to EQA for WGS so far.[39] Laboratory accreditation is controlled by BELAC. In the Plan for rare diseases, one action is related to the quality of genetic testing, but does not involve WGS.

5.7 Human resources

The introduction of WGS will increase the needs in professionals trained and experienced in genetics, certainly in a first phase. One obstacle is the current lack of official recognition of most professionals in medical genetics in Belgium. This implies a lack of clear status, but also a lower ability to negotiate salary scale and career plan. As said above, the European Board of Medical Genetics (EBMG) has established standards for good practice for the following four professional branches: medical geneticist, clinical laboratory geneticist, genetic nurse and genetic counsellors (4.5).

Now that WGS will be increasingly used for the routine diagnosis and management of common diseases and the estimation of disease risk, many - if not most - health care professionals will need to understand how to interpret test results and risk information and to be able to explain the implications to patients. A recommendation of the EC Committee of Ministers (European Council) to member states was that primary care providers should have the necessary skills to assess the family history, recognise genetic risks, discuss with patients and relatives the implications of genetic disorders and to appropriately refer them to genetic services.

5.7.1 Clinical geneticist

The use of WGS will put an extra burden on clinical geneticists. The KCE 2007 report already stated that clinical geneticists are the critical resource of the centres. With WGS, clinical geneticists will have to invest more time in the discussion of indications for WGS, the medical interpretation of variants, the inter-disciplinary work and the genetic counselling.[38]

A challenge is to attract physicians into this profession. Medical human genetics was not recognized as a medical specialty up to May 2017.[38, 50] According to the 2007 KCE report, medical human geneticists tend to have longer consultations, significant work in between consultations, medical interpretation, multidisciplinary work and family versus patient, compared to other medical specificities.[38]

A part of the counselling work of clinical geneticists could be shared with other (non-physician) counsellors, for instance for the pre-test or simple counselling.[38, 41] A recent Belgium report highlighted that, although recruitment of genetic non-physician counsellors may partly respond to increased counselling needs, there will anyway be a need for more clinical geneticists than the currently low estimated number of 3 per million inhabitants.[41]

5.7.2 Clinical laboratory geneticist

The use of WGS will also require more time investment from clinical laboratory geneticist (CLG), at least in the initial phase, as they will have to develop and supervise sequencing activities (or its outsourcing), contribute to the selection of variants, organise quality control for this technology and foster an increasing amount of inter-disciplinary work. Considering the increased amount of data to analyse and interpret, they will face a higher burden in defining analysis strategies and interpreting variant. However at longer term, when the WGS will replace other techniques, this extra burden should lessen as experience (a.o. in the Netherlands) showed that it easier to master a single technique.

A profession of “technician in rare diseases” was mentioned in the proposal for the reform of the Royal Decree 78 (“menselijke erfelijkheidstechnoloog”) but it is unclear whether this refers to CLG, and it seems that the recognition of this profession is not anymore on the agenda.[72]

5.7.3 Bio-informaticians in genetics

All those interviewed and most articles express that the most urgent need today is to have trained staff in genetic (clinical) bio-informatics. Without a strong bio-informatics capacity in genetics, WGS cannot be used. However, this profession does not exist yet in Belgium, nor in EU, and is not included in the proposal for reform of the Royal Decree 78.

In Belgium, this professional category is still scarce and difficult to find, but numbers are slowly growing as training curriculum are now offered by the universities. There are different profiles among current bio-informaticians, from data analyst to high profile PhD to design analysis strategies. There is usually no defined status in the hospital staff for bio-informaticians (often categorized as informaticians), their role is not easily understood and hospital salary scales are not always favourable for the highly trained ones. There is a thus need to attract and train professionals in that profession.

On the other side, there will be a decreasing need in laboratory technicians working in “wet lab”. In some CHG, these technicians are currently being recycled into data analysis but this transformation is not always possible. The substitution of old “wet lab” genetic tests into sequencing requires a reorganisation of career for these technicians.

5.7.4 Genetic counsellors

We describe above that the use of WGS will further increase the needs in counselling professionals (5.5). This was also discussed in the inter-professional working group requested by the Health Minister in 2016 to advice on the role of non-medical genetic counsellors, including genetic nurses, in the Belgian health care system.[41] The report highlighted that in recent years, requests for genetic counselling increased due to different factors such as the rapid evolution in technology, including high throughput WGS for monogenic diseases but also for wider indications such as neurogenetics.[41] As a major part of genetic counselling currently relies on clinical geneticists, the report pointed to the need for new profiles of genetic counsellor. The working group proposed a unique training curriculum, that should be accessible to nurses, midwifes, paramedics and other non-MD professions. It would be a master level (Master in Genetic Counselling), after a bachelor or a master in a (bio)medical field, of a duration of three or two years, respectively, and include a minimum of 50% of field practice.

Genetic counsellor is not a recognized profession in Belgium but the profile was included in the proposal for the reform of the Royal Decree 78 (“genetische consultant”). The need for the recognition and a specific training for genetic counsellor was already highlighted in the 2007 KCE report and in the working group report,[s, 38] which stated that this situation is no longer tenable.

In several European countries, non-medical genetic counsellors are working as part of the clinical team. Many of these have a background in nursing or other health profession or have completed a Master level degree in genetic counselling.[56, 73] This profile is officially recognized in some other EU countries, such as France and the United Kingdom.

[s] « Le rôle de ‘conseiller en génétique’ devrait se voir accorder une place essentielle dans le conseil génétique. Une formation appropriée devrait être mise sur pied pour ces nouveaux professionnels (niveau Master). »

5.8 Cost and financing

The description of the current funding system for genetic tests above (4.4) highlights the following challenges:

- The current financing system of the CHG is complex as not fully integrated. Different sources of financing coexist, such as articles 33 and 33bis of the nomenclature, and the convention for genetic counselling and tests conducted abroad.
- The CHG are functioning with an overall budget fixed annually by the INAMI – RIZIV General Council. Though monitoring the expenditure is legitimate, budget flexibility seems essential in a field that is in constant progression regarding technology and clinical indications. A further increase in the demand for genetic tests from other medical specialties is expected, especially for common diseases. Whether the CHG could face the upcoming increasing demand for WGS with the current budget needs to be explored. For information in the Netherlands, the total budget (2014) for the genetic centres is €143.4 million which represents about €10 per inhabitant per year. Although the medical acts covered by the two countries may not be similar, in Belgium the 2014 CHG budget represents ~€4 per inhabitant per year. Given the current context of budget restrictions, obtaining additional funding represents a serious challenge. Nevertheless in 2016, the CHG budget was increased by about 20% compared to 2015. In 2017, the CHG introduced a request to the Minister of Public Health to increase their budget.
- The budget allocated to genetic counselling is underused (Table 5). Geneticists report that the reimbursement criteria are too stringent and prevent to use the convention for all conducted counselling sessions. For simple genetic counselling the convention requires the intervention of at least 2 professionals, i.e. a geneticist and a psychologist or a social worker / nurse. For complex genetic counselling, the intervention of all 3 professionals is simultaneously required. This does not seem to be applicable for all cases in practice.
- The current financing rules do not allow for the reimbursement of trio-testing, e.g. patient and 2 biologic relatives. Currently there is no other option than to charge 3 single tests, which is not optimal for the budget (and not allowed). For instance in the Netherlands, trio-testing is reimbursed twice the cost of a single test.
- The introduction of a broad - and still expensive - technique such as WGS is not planned. In the short-term, the “largest” code (level 3) for complex molecular analysis (€1407, see 4.4.1) would not allow an appropriate reimbursement of WGS at its current cost (estimated between €1411 and $5519, see 2.4.1), unless a combination of level 2 and level 3 codes is possible. WGS costs are however steadily decreasing.
- The annual revision of the limitative list of indications of article 33 allows to easily adapt to the rapid evolution of the sector (e.g. new indications or cost variations reflected in the reimbursement levels, Table 3). However this flexibility comes with an increased complexity along with scientific progress, as the list has grown to nearly 800 indications since its inception. There was also a shift over time in the number of indications to level 3 mainly, the most complex level (Communication Chantal Mathy, INAMI – RIZIV). Adding indications to the limitative list requires approbation from the Working Group Clinical Biology. There are however diverging views between the different actors involved.[t]

[t] Le Médecin Spécialiste, Mars 2016: "L’avenir des biologistes cliniques réside uniquement dans la biologie moléculaire. L’idée de 8 centres de génétique humaine, qui date de 40 ans, ne peut continuer à exister que si ces centres se limitent strictement aux anomalies génétiques et ne se mêlent de vouloir étendre leurs activités aux maladies biomoléculaires acquises telles que l’oncohématologie." (http://www.gbs-vbs.org/fileadmin/user_upload/Unions/BC/03.16_fr.pdf)
Le Médecin Spécialiste, Avril 2014: "Obtenir l'accès à (une partie de) la nomenclature génétique est indispensable pour préserver l'avenir des laboratoires cliniques. Mais nous savons depuis longtemps que les généticiens ne renonceront pas si facilement à leur position de monopole bien protégée"… "D'ici peu, les tests génétiques (techniquement très semblables aux tests moléculaires réalisés en laboratoire) pourront aussi dans un avenir

- Though implementing WGS requires high investment costs, e.g. to purchase expensive sequencing machines, no dedicated budgets are allocated to cover these initial costs. For instance, the CHG have no direct access to the Budget of Financial Means (the main funding source for the general operating costs of the Belgian hospitals). Obtaining hospital funds seems thus contingent on the overall budgetary policy of the hospital to which the CHG are related. It was further reported that the funds cannot be used freely.

The lack of precise estimates of the full costs and the potential demand for WGS is another challenge to its implementation. WGS could possibly reach the same cost as small gene panels or array CGH in the future when sequencing and computing cost will decline, if high volumes are ensured, depending on indications. However, the expected WGS volume is hard to predict. In the short-term, high volume needed for low average costs per test may be difficult to reach. Over time however, it can be expected that the mere availability of sequencing machines will create a demand high enough to reach the required volumes. Also in terms of sequencing, performing WGS may become less costly than testing for a number of genes, especially when little is known about the genetic background of the disease. However, because WGS adds layers of complexity to the interpretation of test results, it is likely to add cost in data analysis and management.[3, 4, 11]

5.9 The organisation of medical genetics in Belgium

The legal basis for the organisation of medical genetic services dates from 30 years (Royal Decree 1987). Since 1987, decree updates, regionalisation of the CHG, new Royal Decrees for genetic tests and conventions with the INAMI – RIZIV have tried to respond to the changing needs, the technical progresses in genetics and the institutional evolution such as health reforms. This means that the current system is based on a patchwork of legal and financial chunks that is not efficient and lacks coherence - as illustrated by the requirement of geneticists for reimbursement of article 33 while this specialty was not recognized in Belgium.

While this field is in constant progression, the budget for CHG has not increased between 2013 and 2015 (4.4). The budget increased substantially in 2016, but the expenses still exceed the budget. Genetics was a discipline belonging to the Clinical Biology up to 1988. The request to introduce changes in the reimbursement of genetic tests (e.g. new nomenclature code) has first to be discussed in the Working group Clinical biology. Geneticists are currently not present in that group. There are also diverging views between these two disciplines.[t]

In addition, the CHG have a hybrid situation in the Belgian health care system, as they have an independent legal basis (Royal Decree 1987) but are integrated into a university hospital (except for the IPG). As noted in the KCE 2007 report, the CHG are requested by hospital management to give more attention to the productivity and production aspects and less to the research contents and links.[38] And as explained above under 5.8, CHG have no direct access to funding for investment.

This situation resulted in a complex situation of medical genetics in the Belgian health care system and an organisation of the CHGs with varying relationship to universities and hospitals. The current framework will not facilitate the implementation of a more complex technique such as WGS, although this technology can contribute to many other specialties of health care.

However, there is a lot of exchanges, interactions and collaboration between the CHG, which are favourable to harmonisation of practices, exchange of data and collective decisions. The College and its working groups, and the ComPerMed, may allow to progress on many different fronts.

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proche être effectués dans les laboratoires cliniques. Cela doit devenir possible par la création d'une nouvelle nomenclature ou par l'ouverture d'une partie de la nomenclature génétique existante aux médecins biologistes cliniques."

6 ORGANISATIONAL PROPOSALS TO ADRESS THESE CHALLENGES

6.1 Organisation of WGS in the short term

The previous section highlights a number of challenges that should be addressed to permit an effective introduction of WGS in clinical practice in Belgium. Some of these challenges depend on political decisions, such as the recognition of genetic professions and financing. Other challenges require to develop new tools (e.g. harmonized pipelines), new systems (e.g. unique database) and to identify the best organisational and financing systems.

In the two other European countries implementing or planning to implement WGS in clinical care and described in this report, the UK and the Netherlands, WGS has been initiated under the form of a project (see 3.1). Such project seems the most appropriate approach to introduce WGS in Belgium. The main advantages are that it could address the specific activities needed to launch a complex technology, i.e. the elaboration of guidelines and algorithms to determine indications for WGS, the harmonisation of analysis pipelines, the determination on the type of data to store and how, the creation of a unique database of variants, the assessment of WGS costs and the most appropriate reimbursement models and the collection of data for evaluation. It can also allow to test different models of organisation for sequencing, such as shared or centralised units and/or outsourcing. It could enhance exchanges between experts, including with other medical specialties and bio-informatics.

Although WGS will be available in a few CHG before such pilot project can start, the technique will likely be mostly used to substitute a number of current tests (such as array CGH and large gene panels) and to diagnose unresolved cases of rare diseases, at least in the first phase. This prior use of WGS should not be an obstacle to set up a project and will favour the gain in WGS experience.

In theory, such project could be possible under an article 56 convention with the INAMI – RIZIV but the burning point would be the availability of an INAMI – RIZIV budget (see 6.8). A similar approach is considered for the NGS detection of somatic variants in oncology; the experience of this project and the roadmap developed for the sequential introduction of the NGS technology in routine health care could be used as a source of inspiration.[64] Such project could also largely benefit from the dynamic and expertise of the College working groups, the BelMolGen and the ComPerMed.

6.2 Infrastructure for WGS

6.2.1 Options for sequencing infrastructure

There are several options for the organisation of sequencing activity of WGS in Belgium. The main questions are: should it be centralised in one or a few centres or should it be outsourced.

Centralisation or not?

Most stakeholders consider that, at least in the long term, sequencing should be decentralized. This is made possible by the recent availability of smaller sequencing machines, with lower investment and running costs. The KCE 2007 report indicated that for the genetic tests available at that time, no major advantages would be realised by concentrating activities in only a few centres. The potential option to centralise sequencing in e.g. one to three facilities in Belgium, could allow to share investment costs, optimise volumes and concentrate expertise, for instance in a first phase until sequencing machines can be purchased in more centres. However, the question remains theoretical as in 2018 some CHG will already perform WGS. If sequencing would be centralised in only one unit, it would be advised to install it in a public and neutral structure, e.g. the public health institute (ISP – WIV), to avoid competition (and tensions) between centres and hospitals. Only sequencing should be centralised.

Whether sequencing would be centralised or decentralised would also depend on the investment options available, the willingness of centres to acquire the machine and time, as costs are decreasing and instrument performance is improving. Each option has advantages and disadvantages

that must be considered (Table 9). These different factors may have different weights for different decision-makers, and there is no clear preferred option.

Sequencing outsourced or not?

In both centralised and decentralised models, the decision must be taken on whether to outsource sequencing to an external provider, as done in the UK and the Netherlands (3.1). Arguments in favour of outsourcing are lower running costs per WGS (due to high volume and competition between providers), savings on investment, maintenance and training, probably a shorter turn-around-time to obtain the results and staff could invest more time in the analysis and interpretation of variants and counselling. Arguments against it are the risk for the data protection and privacy of results, the inability for Belgian teams to gain expertise in WGS sequencing, the lower insight into quality control and the complexity of setting up contracts for outsourced services that are in line with the legal regulations.

The European Directive on the protection of personal data ("PDPD") states the protection requirements that must be met before personal data can be processed. The centre must decide which patient data is processed for which purpose, and how the data are eventually used, and the private company must follow the instructions in performing the sequencing. In 2018, the EU regulation on General Data Protection Regulation (GDPR) requests that in case of outsourcing, the requesting service has to ensure that a written contract governs its relationship with the third party. This must cover the duration of the processing, obligations for safety measures, and deletion of the data held by the processor after the end of its services.

Negotiation power on prices with external providers would also be more challenging for Belgium (compared to the Dutch and English experience) due to more limited amount of tests. It is anyway essential to keep data analysis and medical interpretation (and all other aspects) in the Belgian centres, as in the Dutch model, for the reasons explained below.

The best options may vary over time, and according to cost and availability of the technology. As the different options have different implications, policy makers should state their priorities when selecting the future model: whether to favour cost and speed (i.e. centralised model, outsourced or not) or to favour gain of expertise by Belgian teams (decentralised model).

If outsourced or centralised, raw data should be communicated to the requesting centre (6.4), allowing for analysis and medical interpretation at local level, together with other information on the patient. Data that should be communicated to the requesting physician should also be established: partly processed data (e.g. SAM/BAM) or information on variants (VCF file), see also 6.4.

6.2.2 Should WGS be restricted to CHG?

The question is whether this complex technique should be under the supervision of the CHG, at least in the short term during which a majority of indications would be related to genetic disorders, as it is organised in e.g. the UK and the Netherlands. Other options would be that WGS could be undertaken in any clinical biology or anatomo-pathology laboratory, without previous approval of prescriptions by a clinical geneticist. Pro and contra of restricting WGS to CHG are described above under 5.1.3 and summarized in Table 8.

Advantages of restricting it to the CHG include a better control of WGS prescriptions for actionable indications, a concentration of a sufficient amount of genetic expertise, specialised and trained staff in all genetic specialties, direct access to counselling and a higher volume of tests.

The organisation of medical genetics in Belgium provides also some advantages to keep WGS in the CHG: these are legally bound to maintain high quality laboratory standards for genetic tests (under article 33) and CHG permit easy interactions between medical geneticists, clinical laboratory geneticists, bio-informaticians and genetic counsellors for the counselling of patients, the medical interpretation of variants and the communication of results. The current system of genetic test prescriptions under the article 33, which requires the approval of each test prescription by the CHG geneticists, could allow to control the clinical utility and volume of WGS prescriptions, and hence the expenses. As described in the KCE 2007 report, the geneticist serves as the gatekeeper to avoid overconsumption of tests, by screening the test demands based on their clinical utility.[38] In addition, CHG could have access to a single database of variants, to help determine the association between variants and clinical picture (phenotype),

and in which variants of other members of the families could be entered, as well as to international databases.

Table 8 – Pro and contra of restricting whole genome sequencing to the CHG

Pro	Contra
Complex technique concentrated in a few "reference" centres with higher volume, higher expertise and experience, working exclusively on that field	Risk of bottleneck if high volume of requests to authorize and realise
Availability of staff and infrastructure already specialized in the different medical genetic fields: • Medical geneticists for clinical assessment, medical interpretation of variants and counselling of complex cases • Clinical laboratory geneticists already trained in sequencing and quality norms • Genetic bio-informaticians with expertise into analysis pipelines	When prescribed by another medical specialty: • Lack of knowledge of the geneticist/CHG in the medical specialties (or indications) requesting WGS • Access restricted for the other specialties (if need approval of geneticist)
Genetic counselling available locally; CHG counsellors have experience in the communication of complex information to a wide public	Monopoly of CHG in WGS, which may not be sustainable in the long term when WGS becomes indicated for a wide range of conditions
The CHG has access to database on variants and results from other family members, including international databases	Difficult to apply for WGS indications outside article 33, such as article 33bis and 33ter indications (open to clinical biology and anatomo-pathologists)
Exchanges with foreign experts and international working groups to improve variant interpretation	WGS will soon be available in larger diagnostic or molecular platforms in some university hospitals
Ability to control that prescriptions are for "actionable" indications	
Quality control ensured by law if article 33	

Note that the weight of the different pro and contra arguments is not equal.

Main disadvantages of this option are the risk that geneticists lack knowledge into other medical specialties that may request WGS (such as in cardio-vascular and neurological indications), a risk of bottleneck of WGS requests and a (usually undesired) situation of monopoly which would limit the access of other medical specialties to WGS. This model would also be difficult to apply for future WGS indications that are today open to the clinical biology and anatomo-pathology laboratories, such as those of the article 33bis and 33ter e.g. NIPT or targeted therapy in oncology. In addition in the near future, some university hospitals may incorporate WGS into large diagnostic platforms that are shared between clinical biology, medical genetics and anatomo-pathology teams.

Among interviewed experts, most clinical geneticists proposed to keep WGS, at least in a first phase, under the supervision of the CHG, as the early WGS indications concern mostly (rare) genetic disorders. However, a number of clinical biologists also recommend to avoid a situation of monopoly. Whatever model is selected, decisions on and implementation of WGS should be steered by multi-disciplinary teams, which include the clinical specialties that would be the most involved.

6.2.3 Centralisation and harmonisation

Besides sequencing (see above), other aspects of WGS could be centralised or at least harmonised at national level. The advantages and disadvantages of centralising each aspect are described in Table 9.

The WGS aspects that could be centralized and/or harmonized could include:

- Harmonisation and/or sharing of protocols and analysis pipelines: it is essential that in a given sample the same raw data produces the same results in each centre, and this could be done by sharing protocoles, algorithms and even analysis piplelines. The use of filters or masks per clinical picture should also be harmonized. This is important not only for efficacy reason but also for equity among patients. Some of these activities have been initiated by the "Belgian medical genomic initiative" (BeMGI)

- Computing tools: there is a need for highly powerful computers for WGS data analysis. Some CHG already use a powerful computer that is available in their region. One option could be a common purchase of a high capacity computer for some centres. This could also relieve the tension with the hospital due to competing requests for computing capacity, which is easily saturated with WGS.
- Data storage: data storage is also using a large capacity in drives if raw data are stored. Centralised data storage would also help in harmonizing policies: which type of data should be kept, for how long, which format, with which protection level.
- A common database of variants: see further details below 6.4.
- Informed consent form and policy for incidental findings: see below 6.7.

Medical analysis of variants and genetic counselling would always be conducted at local level (in CHG or in hospitals, by CHG staff for counselling). Indeed medical interpretation requires access to clinical file and other information.

Table 9 – Pro and contra of centralisation / harmonisation of WGS activities

Activity	Pro	Contra
Centralised sequencing (e.g. 1 to 3 centres)	WGS could be available more rapidly for every patient, and equity of access to WGS Concentration of technical expertise and experience Higher volume, thus lower costs Share investment costs Easier constitution of a unique national database of variants Laboratory staff could invest more in other activities (e.g. analysis and counselling)	Difficulty to select a single or 2-3 centres, with risk for language and political tensions Risk of bottleneck in this(ese) center(s) Data storage and communication of results should be organised and controlled for cybersecurity Difficulty to determine optimal sequencing capacity and to set priority in processing requests from different centres No large acquisition of expertise in Belgium (for other centres)
Harmonisation and/or sharing of protocols and analysis pipelines	Harmonisation of results: same variant information from same patient would provide same report, regardless of the centre Savings in bio-informatician time and costs Improved quality and completeness, compared to the in-house tools of one centre Easier to validate	Lower flexibility of analysis for complex cases
Centralisation of computing tools (e.g. computer capacity, expensive software)	Savings in investment costs Improved computing capacity Decrease tension with hospital (when relevant)	Requires procedures and high security to send and receive data Need organisation to meet the computing needs of each centre Legal aspects of data protection must be addressed
Centralisation of data storage	Harmonisation in type of data, format, duration and protection of storage Lower costs and improved capacity Decrease tension with hospital	Requires procedures and security to send and receive data Need to ensure data protection requirements
A common database of variants - phenotypes	Facilitate access to variant information in the Belgian population, improving management of other family members Improve variant analysis and interpretation Increase knowledge	Need to ensure data protection requirements Need to address intellectual property issues

Note that the weight of the different pro and contra arguments is not equal.

6.3 Bio-informatics and medical interpretation

In Belgium, the limited number of bio-informaticians working in genetics (around 2 per CHG) is unlikely to be sufficient to fully address the needs in data analysis if WGS starts to be more widely used. Most interviewed geneticists consider that the number of bio-informaticians should be doubled to meet the future needs (see also 5.7.3). This would require to develop strategies to attract and train/recycle persons in that profession.

The need to harmonize analysis pipelines and protocols has been described above under 6.2.3. These pipelines should also be validated and regularly updated, to ensure quality for variant interpretation. The work of the College and the ComPerMed working groups will be crucial for that. Access to sufficient computer capacity should be fostered for all centres.

The report issued by the laboratory should be clear in stating that the interpretation and classification of variants is based on the knowledge at the time the analysis takes place. This is especially important with regard to VUS. According to the recommendations issued by EuroGentest and ESHG, the laboratory is not expected to re-analyse old data systematically and report novel findings.

Medical interpretation of variants in complex cases and exchanges on newly discovered variants should use the resources of an expert consortium.

Functional studies that are needed to interpret some VUS are expensive and complex. They should benefit from international collaboration of genetic laboratories, based on a common platform, with sharing of data and concentration of expertise. This could be under the form of an EU reference network (ERNs) under the umbrella of EUCERD (European Union Committee of Experts on Rare Diseases), now replaced by the European Commission Expert Group on Rare Diseases.

6.4 Data storage

Based on the EU legislation that no more data should be collected or kept if not necessary for the purpose (see 5.3.4), laboratories should clarify the purpose of sequencing, the necessity to store data for this purpose and establish a clear protocol on the policy related to data storage. Guidelines should describe which data should be stored, under which format, for how long, under which conditions of security (including ISO norms) and how to (re)access and search data. A working group within the College of genetics is already progressing on these issues and should be encouraged.

As explained under 5.3.4, storing raw data for long periods of time does not seem legally mandatory (as no clinical information is lost by resequencing) and is probably not an efficient option, given current costs. It will become soon more cost-effective to sequence the patient DNA again when needs arise. At least the VCF file must be stored, as part of the medical file. A Royal Decree (3 May 1999) specified that the results of clinical and biological investigations should be kept as part of medical files, and these must be kept for 30 years. The costs of storage should be included in the evaluation of costs for WGS.

Data storage can be outsourced, based on information provided by the centre. If the patient data would be stored outside the EU, then this country must ensure an adequate level of data protection.

6.5 A common database of variants

A common database, containing variant and phenotypic information, should be constituted and shared, at least at national level. This database will facilitate access to variant information in the Belgian population, increase knowledge on the relationship variant-phenotype, improve the variant interpretation and allow to find back variant information on family members of patients. In a first phase, at least a database of variants from rare diseases should be initiated, and could complement the Register for Rare Diseases. However, the register contains only “positive” cases of rare diseases, while information should be collected from positive (diagnosed) and negative cases.

Such database will require a high level of data protection, easy access and an effective system to search database. This would be possible by using Healthdata. However, this platform is set up for research, not to store diagnosis data, and would need to be organized, e.g. with a 2nd layer of data and various options for access. HealtData progresses for the NGS companion diagnostic project in oncology can benefit to WGS.

EU legal instruments state that the further processing of data for scientific research should be compatible with the initial purpose and should not permit the identification of the data subject. However in the perspective of clinical diagnosis, this is possible without explicit consent

In a longer term, this database could also be shared at international level. Access to international database is also the only way to better categorise VUS by increased sharing of human genome sequence data.

The organisation of this database and harmonization of data collection would require dedicated resources and staff, which could be covered by the pilot project.

6.6 WGS indications and prescription

The indications for WGS will certainly evolve with decreasing costs (i.e. with WGS progressively replacing a number of gene panels for existing indications). In the longer term, WGS is expected to replace most genetic tests (but not all) and the evolution in indications should be decided by an expert steering group. This could be constituted by members of the College, representatives from other medical specialties and other involved institutes (INAMI – RIZIV, Centre du Cancer and ISP – WIV). Guidelines should be established to define for which indications and criteria a WGS could be performed, to prevent over-prescription.

In a first phase, the authorization of prescription of WGS would be restricted to geneticists of the CHG, if the financing option selected (see 6.8) for WGS would be a nomenclature code within article 33: prescription under article 33 is not limited to clinical geneticists, but clinical geneticists may refuse requests.

A good option would be to charge multidisciplinary teams to evaluate and authorize WGS requests. Indeed medical specialists may be better placed to prescribe WGS, but the overall modalities should be discussed with the clinical and laboratory geneticists.

6.7 Incidental findings and genetic counselling

Although incidental findings do not seem to represent a substantial challenge, due to the use of WGS filters so far, the development of a common protocol outlining the reporting policy and common tools is advised. In particular, it would be useful to develop an appropriate informed consent policy and a harmonized form for WGS. Patients should have opt-in/opt-out options with regards to whether to receive unsolicited findings, and should be made aware during the consent process of which findings will and will not be disclosed. The form should thus cover the issues of reporting unsolicited findings.

The current resources in counselling are insufficient to meet the expected increased needs for appropriate pre and post-test counselling. An option would be to increase the capacity in non-physician genetic counsellors, to help address the needs in simple counselling, but this would require that this profession is recognized and that training is organised (see 5.7.4.). These counsellors should however benefit from continuous education and supervision from the CHG (as organised in the current convention).

6.8 Financing options

As said above under 6.1., the implementation of WGS in Belgium could be initiated as a pilot project. This would require a dedicated budget to determine the indications for WGS, work on the harmonisation of analysis pipelines, informed consent and filters, define data storage policies, create a unique database of variants, assess the costs of this innovative technology and explore different organisational models for sequencing.

One option would be an article 56 convention with the INAMI – RIZIV (article 56, §2, 1° of the Law 14/7/1994).[44] The aim of this convention is to fund (among others) innovative techniques for a limited period of time (generally 2-3 years, renewable) to allow for further data collection; and to evaluate the technology at the end of the convention. The criteria against which the technology is assessed must be agreed on in the convention; for WGS this could be an estimate of the costs and health outcomes at regular intervals.

The independent entities responsible for the evaluation must also be specified, e.g. an accompanying committee or an external actor such as KCE or ISP – WIV.

The establishment of a convention according to article 56, §2, 1° of the law 14/7/1994 first requires the publication of a Royal Decree setting out the conditions under which the Insurance Committee may conclude such a convention with specific centres. The elaboration of the draft Royal Decree entails a preparatory phase of scientific evaluation and budget determination. Evaluation by the INAMI – RIZIV Technical Medical Council (TMC) is based on the following criteria: the scientific data on the "innovative" nature of the technology, the disease(s) concerned, the clinical impact, public health impact, impact on health care insurance and impact on society. After consultation of the Commission for Budget Control, the INAMI – RIZIV General Council decides upon the possibility of granting a new budget and upon the budget compatibility of the convention. The project goes then through the Insurance Committee, which sets the conditions for its intervention and transfers the draft decree to the office of the Minister of Social Affairs and Public Health. The Minister takes advice from the Finance Inspector, the Minister who has the budget in his attributions and the State Council. If deemed receivable, the King signs the draft and it is published as a Royal Decree in the Belgian Monitor.

On average this process lasts about 12 months, even longer if no budget is available. This deadline may be shortened if the impact of the new convention is neutral for the budget (the consultation of the Commission for Budget Control is then no longer required).

After the publication of the Royal Decree, the interested parties may submit a request to settle a convention for WGS financing according to article 56, §2, 1°; with respect to the conditions stated in the decree. Although not mandatory by law, the draft convention is also in practice evaluated by the Working Group Clinical Biology of the TMC.

As article 56 conventions help the INAMI – RIZIV at addressing uncertainties and make decisions, their budgets are directly charged to the administrative costs of the INAMI – RIZIV, and not to the overall health care budget. This may increase the chances to obtain a budget for WGS. Part of it could be earmarked for initial investment costs; and it could cover specific activities such as the creation of a national database, the harmonisation of analysis pipelines, informed consent and filters etc. for which structural funding is currently lacking. The allocated budget should allow some flexibility to account for the rapid evolutions in this field.

A convention is constructed from scratch and all constituting terms are negotiated, such as who is entitled to perform the technology. If restriction of WGS to the CHG is opted for, as is currently the case for the genetic tests in article 33, this will have to be explicitly stated to be guaranteed within such convention.

At the end of an article 56 convention, various options are open for the reimbursement of WGS:

- Through the existing nomenclature, using the codes for the diagnostic of constitutional diseases in article 33 (see 4.4.1); allowing e.g. a reimbursement of €1408 for the tests with the highest level of complexity (level 3), potentially combined with the reimbursement of another test as long as the cumulative rules of article 33 are observed. The limitative list of indications would need to be updated to include all indications relevant to WGS. An advantage of working with a list of indications - reflecting the complexity of a test - is that all technical evolutions are open. With this option, reimbursement of WGS tests would have to fit within the annual budget for article 33. However, the demand for WGS is expected to be high in the coming years, with other medical specialties being aware of its clinical value. The budget could be adapted according to the cost estimates obtained from the pilot project.
- Through a new code in article 33 of the nomenclature. This would follow a long process of discussions and approvals by many authorities, among them the Working Group Clinical Biology, the TMC, the National Committee for Physicians-Insurers (“Medico-mut”) for budget negotiation, the Insurance Committee, etc. The decisions are published as Royal Decrees. A requirement to adding a new code for WGS is the preparation of a dossier describing, among others, estimates of the volume of WGS tests to be performed and the required budget; for which results of the article 56 pilot project could be used. Another

prerequisite is to obtain a budget for the new codes. The whole process takes 18 months at least, even longer if no budget is available.

- Through an article 22, 6bis° convention of the law 14/7/1994.[44] This convention is also related to innovative technologies and aims to fund complex, multidisciplinary and/or expensive services in routine care. As for article 56 conventions, the elaboration of an article 22 convention requires a long process of negotiations and approvals, starting with discussions in the Working Group Clinical Biology and ending with a publication as a Royal Decree. An article 22 convention is also built from scratch with all terms negotiated, including who is entitled to perform the technology.

Table 10 presents the pro and contra of each option.

Table 10 – Pro and contra of the financing options for WGS

	Existing article 33	New code in article 33	Article 56 convention	Article 22 convention
Procedure	+ Simple and rapid	- Complex and very long	- Complex and long - New negotiation at convention end	- Complex and long
Who	De facto restricted to CHG*	De facto restricted to CHG*	Result of a negotiation process	Result of a negotiation process
Activities	- Reduction in other tests required	+ Transparency about WGS tests and indications	+ Transparency about WGS tests and indications	+ Transparency about WGS tests and indications
Financing	+ Long-term	+ Long-term	- Short-term	+ Long-term
Budget INAMI – RIZIV	+ Monitoring of the overall budget	+ Monitoring of the overall budget + Monitoring expenses / test - Difficult to find additional budget - Fixed reimbursement not adaptable to decreasing sequencing costs	+ Budget control if closed + Monitoring expenses / test - Difficult to find additional budget	+ Budget control if closed + Monitoring expenses / test - Difficult to find additional budget
Budget provider	- Expenditure higher than budget, due to requests for larger indications	- Conditional on obtaining additional budget	- Conditional on obtaining additional budget + Opportunity to obtain additional budget - Multiple budgets	- Conditional on obtaining additional budget + Opportunity to obtain additional budget - Multiple budgets
Other	+ Annually revised limitative list : adaptation to a rapidly evolving sector - Fee not estimated for WGS	+ Fee estimated for WGS	+ Possibility to set an annually revised system to adapt to evolutions + Opportunity for quality and reporting requirements - Risk for high expenditure if open to all labs	+ Possibility to set an annually revised system to adapt to evolutions + Opportunity for quality and reporting requirements - Risk for high expenditure if open to all labs

** As long as article 33 is not revised. CHG: centre for human genetics. Note that the weight of the different pro and contra arguments is not equal.*

In the long-term, the impact on the budget could be neutral, as WGS would replace other genetic tests, as sequencing costs decrease and as the scientific knowledge progresses to, e.g. improve pipelines and reduce analysis costs. However the demand for WGS will likely keep growing with new indications. In any case, the cost impact of WGS should be explored in the pilot phase to serve as a basis to determine a fair reimbursement fee for WGS and for trio WGS. Reimbursement should not be settled too early and should be flexible enough to adapt to the (downward) cost evolutions of the field.

The broad cost categories to be considered to assess the cost impact of WGS are listed below. A detailed list can be found in Tsiplova et al.[25, 26] Note that counselling is not included in the list of costs, as it is separately reimbursed in Belgium.

- Specimen preparation and DNA extraction
- Sequencing machine, service contract, small equipment
- Supplies (reagents etc.)
- Library preparation
- Sequencing
- Storage of data
- Software purchase and/or in-house development of bioinformatics tools (pipelines)
- Data analysis (alignment, recalibration, variant calling etc.)
- (Potential) confirmatory tests
- Clinical interpretation (including multidisciplinary consultations and consultation of international databases)
- Report writing
- Quality insurance system costs

6.9 Plan for human resources

The EC made recommendations in 2010 to train health professionals to understand how to interpret test results and risk information and to be able to explain the implications to patients, as genomic tests and information are incorporated into the routine diagnosis and management of common diseases and the estimation of disease risk.[u] It recommends that generalists and specialists should have the necessary skills to assess the family history, recognise genetic risks, discuss with patients and relatives the implications of genetic disorders and to appropriately refer them to genetic services.

The most important need for professionals in medical genetics is to have their profession recognized. A good news in this field is that the specialisation of medical geneticist (4.5.1) is recognized since May 2017.

According to a presentation from the Cabinet of Health, the proposal for reform of the Royal Decree 78 included the revision of two other genetic professions among the list of medical specialties targeted: “genetic consultant” (genetic counsellor) and “technician in rare diseases”.[v] However, these professions are no longer included in the current process of this reform (personal communication, K. van de Woude). Until a clear status is provided to these professionals, it will be very difficult to attract the required numbers. A dialogue with the genetic sector, in particular with the BeSHG, is important, and the work in this field could take advantage of the standards of good practice defined at European level for the clinical laboratory geneticist and the genetic counsellor (EBMG and ESHG).

[u] Recommendation CM/Rec(2010)11 of the Committee of Ministers to member states on the impact of genetics on the organisation of health care services and training of health professionals. https://search.coe.int/cm/Pages/result_details.aspx?ObjectID=09000016805ce4c9

[v] http://www.ar78.be/ Conférence de lancement. Réforme de l’AR n° 78, 28 septembre 2016.

As explained above (5.3.1), the number of bio-informaticians working in genetics should be increased (probably doubled) to meet the future needs of WGS, and strategies to attract and train/recycle persons in that profession must be developed. In a first phase, as the number of bio-IT is still low, the needs could be addressed by training scientists from the biological genetic field (including from wet lab) into informatics, and training informaticians into genetics. The increasing offer in bio-informatics training would probably meet the needs in the medium term. The profession of bio-informaticians should also be distinguished from the other informaticians.

WGS will also need more medical geneticists, and it is crucial to attract physicians into that specialty. The recent recognition of this medical specialty by the Minister of Health (Reform of the Royal Decree 78) will undoubtedly help in this direction.

A part of simple counselling could be delegated to non-physician genetic counsellors, under the supervision of the medical geneticists, who could then invest more time into complex counselling and multi-disciplinary work. It is hoped that the work on the profile and training of these genetic counsellors concretise. According to the working group appointed by the Minister of Health, this profession should be included into the health care professions recognized by the law, as done in some neighbouring countries, to ensure a uniform curriculum and a better framework for the conduct of the profession. Second, a specific training for genetic counsellor should be organised, as proposed and described under 5.7.3.

It is also important that non-physician geneticists, although essential for WGS, receive an official status in the Belgian health care system.

The existing interuniversity certificate in human genetics should cover all aspects of WGS and be followed by all professionals in human genetics.

6.10 Organisation of genetics in Belgium

As described under 5.9, the legal set up for medical genetics dates from 1987, but the functioning of the genetic centres is based on different decrees to cover emerging needs. It is considered to present gaps and to lack efficiency. The lack of access to investment funds also complicates development in this rapidly growing field.

There is a need for a more coherent and homogenous framework for the medical genetics in Belgium, which would require a new (and uniform) legal basis adapted to the current situation, including the 6th state reform that would cover the different activities of the CHG.

APPENDIX 1. EXPERTS CONSULTED FOR THIS STUDY

Institution	Experts interviewed
Centrum Menselijke Erfelijkheid, KU Leuven	Eric Legius, Gert Matthijs, Joris Vermeesch
Center for Medical Genetics, Ghent University	Elfride De Baere, Paul Coucke, Bruce Poppe
Centre de Génétique, Université de Liège, Ulg	Vincent Bours
Centrum voor Medische Genetica (CMG), UZ Brussel	Sonia Van Dooren, Maryse Bonduelle, Ben Caljon, Didier Croes
Centrum Medische Genetica Antwerpen, UA	Geert Mortier
Centre de Génétique Humaine, ULB	Marc Abramowicz, Julie Désir, Isabelle Migeotte, Françoise Wilkin, Catherine Rydlewski, Laurence Desmyter and Julie Soblet
Centre de Génétique Humaine (CGH), Cliniques Universitaires Saint-Luc, UCL	Yves Sznajer
Institut de Pathologie et de Génétique (IPG), Gosselies	Isabelle Maystadt, Pascale Hilbert
Biologie Clinique, Cliniques Universitaires Saint-Luc, UCL	Marie-Françoise Vincent
Klinische Biologie, UZ Leuven	Marc van Ranst
Klinische Biologie, Eenheid Hematologie, UZ Brussel	Kristin Jochmans, Christian Demanet
ISP – WIV	Marc Van den Bulcke, Aline Hebrant, Aline Antoniou, Philippe van de Walle
Radboudumc	Han Brunner
INAMI – RIZIV	Chantal Mathy, Geneviève Haucotte, Anouk Waeytens, Koen De Smet, Michel Breda, Jean Legrand, Johan Peetermans
Kabinet De Block	Koen Vandewoude

APPENDIX 2. COSTS OF WHOLE GENOME SEQUENCING

Appendix 2.1. Methods

Two questions are addressed:

- What is the cost-effectiveness of WGS versus traditional techniques for the diagnostic of rare diseases?
- What are the implementation costs of WGS?

A pragmatic approach was used to identify relevant studies and reports; most of them being identified during the course of the project and during the experts meetings. Studies were further obtained via google searches and via the bibliographies of relevant studies. For publications ahead of print, two succinct search strategies were developed in (Pre)Medline(OVID): 1) (whole genome sequencing.mp. OR wgs.mp.) AND "Costs and Cost Analysis"/; 2) Genome, Human/ AND cost.mp.

All searches were performed up to June 2017; only publications from the last 4 years were considered.

Of the 3 identified published reviews of the health economic literature on genome sequencing (with literature searches up to November 2014), none of them found a cost-effectiveness analysis of WGS.[31, 33, 34]

Appendix 2.2. Ongoing studies

Two ongoing projects on the cost-effectiveness (full economic evaluation) of WGS were identified (as of June 2017).

- The Dutch Rare Disease Consortium (led by the Radboud university medical centre) is conducting a prospective study with the aim to evaluate the effectiveness and cost-effectiveness of WGS versus standard sequential diagnostic in patients with a rare genetic disorder (neurodevelopmental disorders and critically ill neonates admitted to the neonatal intensive care unit). The study started on December 2016 and is planned for a duration of 3 years (up to December 2019).[29]

- The MedSeq Project is a randomized clinical trial of WGS in cardiology and primary care conducted in the United States. It aims to assess the medical consequences and healthcare costs associated with the use of WGS. The economic evaluation of WGS is performed alongside the primary clinical trial. The project received approval in 2012, preliminary results were presented in 2016.[74, 75]

Appendix 2.3. Brief description of the cost studies

A brief description of the 4 published studies detailing the cost of WGS is provided here.

- A US study (2014) estimated the costs of WGS at $17 620 per test, including sequencing, pre- and post-counselling, bioinformatics processing, confirmatory testing and data storing. Reagent, equipment and labour accounted for the highest cost categories. Very few methodological details were provided.[28]
- Tsiplova et al. (2016) performed a microcosting analysis of WGS for the diagnosis of autism spectrum disorders in Canadian children. Overhead costs were included (energy, water, rent and administration expenses). Confirmation testing on all positives and equivocal findings to rule out false positives was performed with Sanger sequencing. The costs of pre- and post-test counselling, and the costs of variant discovery research & development and validation were excluded. The cost per sample (30-40-times depth) was $2851 (95% CI: 2750, 2956) for the HiSeq X platform and $5519 (95% CI: 5244, 5785) for the HiSeq 2500 platform. Overall, reagent supplies, followed by equipment and labour, constituted the largest proportion of the total cost for both tests. Though a 5 year machine lifetime was assumed, the life cycle may be shorter due to rapid evolution of the technology, which would result in higher costs.[25, 26]
- The cost of WGS on the HiSeq X Five platform for germline mutations were computed in the Netherlands (2016). Only direct medical costs were included (no overhead and genetic counselling costs). It was estimated that free software would be used for read mapping, variant calling and annotation. Using a 5-year machine lifetime, a 30-time sequencing depth and a 70% utilisation rate, the costs per sample was €1669, with the major cost drivers being the consumable (€1085). Reducing the consumable costs by 50% decreases the per sample cost by more than 30%. Increasing the sequencing depth considerably influenced the per-sample costs of WGS: up to €5430 for a 100-time coverage instead of a 30-time.[27]
- In a German cost study (2017) two sequencing platforms were analysed: HiSeq 2500 and HiSeq X Ten (Illumina, inc). Only direct medical and labour costs were included (no overhead costs, no confirmation of secondary findings and no IT and storage costs). With an 80% utilisation rate, a 30-times depth and a 3-year machine lifetime, the cost per WGS test was estimated at €1411 with the HiSeq X Ten and €3858 with the HiSeq 2500. For both platforms, the highest expenses were related to the material (supplies and reagent), the acquisition/maintenance of the sequencing platform and the personnel time. The cost per genome increased with improved coverage rate, e.g. the cost per test almost doubled with a 60 instead of a 30-times depth (€2015 with the HiSeq X Ten and €6880 with the HiSeq 2500).[24]

Only one early US study (2014) valued the after sequencing costs (follow-up testing) at $2000 to $10 000. The methodological quality of this study was weak as this was based on expert opinion.[28]

Beside a breakdown of their total cost estimates, Tsiplova et al. provide a comprehensive list of cost data to be used for future economic evaluations of WGS, which can be easily adapted to other countries' needs.[25, 26]

Appendix 2.4. Breakdown of the costs of WGS implementation

Table 11 – Costs per WGS test reported in Chrystoja et al. 2014, USA[28]

Clinical procedure	Service performed	Approximate cost (2013 US dollar)
Prior informed consent (pre-test counselling)	Clinician/counsellor's time to discuss ramifications of incidental findings (6–8 h)	3000
Sequence	Reagents and labor (for 30–40 fold coverage with Illumina's technology)	6500
Bioinformatic analysis pipeline	Reads alignment, variant calling, Identify variants, disruptive variants, inactivating genes	120
Interpretative consultation	Explaining results to patients (5 h)	2000
Confirmatory testing (post-test counselling)*	Confirm that variants considered clinically relevant are present in the genome, and are not a sequencing-related error, using a gold standard method (Sanger sequencing). Approximately 5 or more mutations ($200/mutation)	1000
Confirming disease presence**	Patients may harbour disease-associated variants but may not have the disease. Additional follow-up testing (endoscopic, imaging, laparoscopic, etc.)	2000–10 000
Genome data storage	Lifelong storage or resequencing in the future with more accurate methods	5000

** Costs expected to drop in future as technological accuracy improves. ** Costs not determined for overdiagnosis, patient anxiety and distress.*

Table 12 – Costs per WGS test reported in Van Nimwegen et al. 2016, The Netherlands[27]

WGS cost per sample (in 2015 €)		HiSeqX5
Capital costs	Cost for the platform	175.33
Maintenance costs	Maintenance of the platform	72.04
Operational costs		
- Blood withdrawal		10.64
- DNA extraction		31.53
- Sample preparation consumables		27.61
- Sequencing consumables		1057.81
- Laboratory technician personnel§		70.08
- Data processing*	1000 CPU hours	100.00
- Data storage*	600 GB per year during 5 years	30.00
- Data interpretation and report	90 min of a clinical geneticist time§	93.97
Total operational costs		1421.64
Total costs		**1669.02**

*§ Personnel costs computed based on annual gross salaries: €32 268 for a laboratory technician, €69 408 for a clinical geneticist. * Costs for data processing and data storage are estimated on €0.10 per CPU hours and €0.01 per GB, based on the commercial pricing of Amazon for cloud computing and data storage. It is assumed that data is stored for 5 years.*

Table 13 – Costs per WGS test reported in Tsiplova et al. 2016, Canada[25, 26]

WGS cost per sample (in 2015 CAN$)*		HiSeq 2500	HiSeq X
Labour **	Specimen and library preparation, sequencing, bioinformatics, maintenance, clinical interpretation, reporting	518.4	250.5
Large equipment	Sequencing equipment and service contract	385.6	583.8
Small equipment	Tube, plate, thermomixer, pipette…	8.9	8.9
Supplies	Sample handling, preparation kits, consumables, reagents	4066.3	1380.1
Follow-up	Validation with Sanger technology or qPCR	178.6	178.8
Bioinformatics	File storage and computation use §	123.2	207.5
Overhead	Administrative and infrastructure (water, energy, rent)	238.3	241.7
Total		**5519.3**	**2851.2**

** Assumes a 5-year machine lifetime and a 30-times coverage/depth. ** Labour costs were computed for nurses, lab technicians, lab technologists, bioinformatics analyst and high performance computing staff; salaries were not reported. § Costs for data processing and data storage are estimated at $0.011 (HiSeq 2500) and $0.612 (HiSeq X) per CPU hours and $0.40 per GB.*

Table 14 – Costs per WGS test reported in Plöthner et al. 2016, Germany[24]

WGS cost per sample (in €)			HiSeq 2500	HiSeq Xten
Pre-sequencing process				
Obtaining blood sample			5.65	5.65
Clinical geneticist time*	Pre-test counselling	52.5 minutes (45-60 minutes)	40.43	40.43
Total pre-sequencing process			*46.08*	*46.08*
Sequencing process				
Technical staff time*	Mechanical and biochemical processing of genetic material; setting up and cleaning the sequencing devices	338 – 378 minutes	136.08	121.84
Allocated acquisition costs	Sequencing platform acquisition	80% utilisation, 30-times coverage/ depth, 3-year machine lifetime	485.29§	199.89§
Allocated maintenance costs	Technical service and maintenance		122.11	41.38
Sequencing materials			2848.08	781.58
Total sequencing process			*3591.56*	*1144.69*
Post-sequencing process				
Clinical geneticist time*	Post-test counselling	52.5 minutes (45-60 minutes)	40.43	40.43
Bioinformatician time*	Analysis, interpretation and validation (Sanger technology) of acquired data.	6 hours	180.00	180.00
Total post-sequencing process			*220.43*	*220.43*
Total (in €)			**€3858.06**	**€1411.20**

** Personnel costs computed based on annual gross salaries: €40 809 for chemical-technical assistant, €55 903 for bioinformatician, €87 544 for clinical geneticist. § Despite the lower acquisition costs of the HiSeq 2500, its higher cost per genome is due to the time and quantity of genomes per run. The "time per run" and the "number of sequenced genome per run" significantly influence overall costs.*

Appendix 2.5. Generic costing model for WGS

Table 15 – Generic costing model for WGS from Tsiplova et al. 2016, Canada[25, 26]

Cost Items (in 2015 CAN$)	Volume of use per sample		Unit price	
	HiSeq 2500	HiSeq x	HiSeq 2500	HiSeq x
LABOUR [§]				
Specimen preparation (units: minutes)				
- Pediatric venipuncture	7.6	7.6	Confidential	Confidential
- Packaging with testing documentation	1.0	1.0	Confidential	Confidential
- Service recipient primary registration	1.8	1.8	Confidential	Confidential
- Printing and sorting of specimen labels	0.4	0.4	Confidential	Confidential
- Creation of recipient folder	5.0	5.0	Confidential	Confidential
- Packaging with testing documentation	1.0	1.0	Confidential	Confidential
- Service recipient limited registration	1.8	1.8	Confidential	Confidential
Library preparation (units: minutes)				
- DNA quantification	1.7	0.4	Confidential	Confidential
- Pre-prep reagents	1.7	0.4	Confidential	Confidential
- Shearing	1.7	0.4	Confidential	Confidential
- Purification	3.3	0.8	Confidential	Confidential
- End repair	3.3	0.8	Confidential	Confidential
- A-tailing	3.3	0.8	Confidential	Confidential
- Adapter ligation	3.8	0.9	Confidential	Confidential
Sequencing (units: minutes)				
- HiSeq wash	5.0	1.9	Confidential	Confidential
- Sequencing prep	5.0	1.9	Confidential	Confidential
- HiSeq post-run wash	7.5	2.8	Confidential	Confidential
- Run quality control	2.5	0.9	Confidential	Confidential
- cBot	5.0	1.9	Confidential	Confidential
Bioinformatics (Units: minutes)				
- Variant calling	373.3	-	Confidential	-
- Annotation	93.3	-	Confidential	-
- Data processing	-	84.0	-	Confidential
Bioinformatics maintenance (units: minutes)				
- Alignment	0.57	0.022*	Confidential	Confidential
- Remove Duplicates	0.10		Confidential	
- Recalibration	0.58		Confidential	
- Post-recalibration merge	0.29		Confidential	
- SNV/indel variant calling	0.88	0.005*	Confidential	Confidential
- CNV/SV calling	-	0.004*	Confidential	Confidential

Cost Items (in 2015 CAN$)	Volume of use per sample		Unit price	
	HiSeq 2500	HiSeq x	HiSeq 2500	HiSeq x
- Annotation (ANNOVAR)	0.021	0.021	Confidential	Confidential
Clinical interpretation (units: minutes)				
- Classification of primary variants	75	75	Confidential	Confidential
- Classification of secondary variants	1.2	1.2	Confidential	Confidential
Report writing (units: minutes)				
- Addressing primary variants	45	45	Confidential	Confidential
- Addressing secondary variants	1.2	1.2	Confidential	Confidential
LARGE EQUIPMENT				
- Illumina HiSeq machine	1/all tests	1/all tests	750 000	1 150 000
- 1-year service contract	1/all tests	1/all tests	75 000	119 025
- Agilent BioAnalyzer/Tape station	1/all tests	1/all tests	38 500	38 500
SMALL EQUIPMENT				
- Tube microcentrifuge	1/all tests	1/all tests	2276	2276
- Plate microcentrifuge	1/all tests	1/all tests	5059	5059
- Thermomixer	1/all tests	1/all tests	5059	5059
- Vortex	1/all tests	1/all tests	455	455
- Pipette sets	2/all tests	2/all tests	1619	1619
- Magnet particle concentrator for tubes	1/all tests	1/all tests	708	708
- Thermocyclers	2/all tests	2/all tests	3035	3035
SUPPLIES				
- Shipping & Handling	1	1	52.5	52.5
- Illumina Nano DNA library prep	1	1	30.0	30.0
- Other library prep consumables	1	1	50.0	50.0
- Sequencing reagents	1	1	4055	1290
FOLLOW-UP TESTING (proportion of patients)				
- Sanger sequencing	0.5	0.5	38.5	38.5
- qPCR follow-up	0.1	0.1	684.8	684.8
BIONFORMATICS				
Bioinformatics file storage (units: GB per year)				
- (trimmed) fastq	75.0	90	0.40	0.40
- Temporary BAM files	12.5	-	0.40	-
- Final rem-dup, recalibrated, locally re-aligned BAM file	150.0	60	0.40	0.40
Bioinformatics computation use (units: CPU time per hour)				
- Alignment	750.0	160*	0.011	0.612
- Remove Duplicates	17.5		0.011	
- Recalibration	752.5		0.011	
- Post-recalibration merge	4.4		0.011	

Cost Items (in 2015 CAN$)	Volume of use per sample		Unit price	
	HiSeq 2500	HiSeq x	HiSeq 2500	HiSeq x
- SNV/indel variant calling	1200	35	0.011	0.612
- CNV/SV calling	-	30	-	0.612
- Statistics	-	25	-	0.612
- Annotation (ANNOVAR)	60.0	60	0.011	0.011

*[§] Labor costs were computed for nurses, lab technicians, lab technologists, bioinformatics analyst and high performance computing staff; salaries were not reported. * HiSeq Analysis Software.*

APPENDIX 3. FINANCEMENT ACTUEL DES ACTIVITÉS GÉNÉTIQUES EN BELGIQUE

Appendix 3.1. Nomenclature des prestations de santé

La **nomenclature** est la liste codée des prestations de santé remboursées (en tout ou en partie) par l'assurance soin de santé. La liste est une annexe à l'arrêté royal du 14/9/1984 établissant la nomenclature des prestations de santé en matière d'assurance obligatoire soins de santé et indemnités. Les mises à jour de la liste sont publiées au Moniteur belge comme des modifications à cette annexe.

Pour chaque prestation remboursée, la nomenclature donne l'information suivante :

- La qualification requise du prestataire pour pouvoir porter en compte la prestation à l'assurance soins de santé.
- Un numéro de 6 chiffres identifiant la prestation (ou code de nomenclature). Dans la plupart des cas, il y a deux numéros par prestation : un pour les patients ambulatoires et un pour des patients hospitalisés.
- Un libellé: une définition de la prestation même, complétée ou non par les conditions quantitatives ou qualitatives pour le remboursement.
    - Une valeur relative qui détermine le montant du remboursement. Elle consiste en une lettre-clé et un coefficient :
    - La lettre-clé a une valeur déterminée selon la prestation/le groupe de prestations. Par exemple N pour des consultations et des visites, M pour la kinésithérapie, W pour l'art infirmier, B pour la biologie clinique;
    - Le nombre-coefficient indique, par prestation, la valeur relative de cette prestation individuelle;
    - En multipliant ces deux valeurs, on obtient le montant des honoraires ou le prix de la prestation.

Appendix 3.1.1. Article 33

Début : A.R. 22/7/1988 (en vigueur 1/8/1988) ; modification : A.R. 10/11/2012 (en vigueur 1/1/2013).

L'article 33 de la nomenclature couvre le diagnostic génétique des maladies héréditaires (rares) ; il ne couvre pas les maladies acquises au cours de la vie.[39]

Historique – Nomenclature article 33

En 2009, le Conseil Supérieur d'anthropogénétique a proposé une réforme de la nomenclature de génétique humaine dans le cadre du Groupe de travail Biologie clinique du Conseil Technique Médical. Une nouvelle formulation de cette nomenclature s'imposait notamment :

- pour renforcer la transparence en matière de génétique,
- pour se conformer aux exigences actuelles de qualité,
- pour mieux contrôler les dépenses du secteur, et
- pour préciser les indications cliniques et les tests utilisés.

Le Comité de l'assurance de l'INAMI a approuvé la nouvelle nomenclature (ainsi qu'une convention conclue avec les 8 centres de génétique humaine) en mars 2012. L'arrêté royal du 10/11/2012 y afférent est entré en vigueur le 1/1/2013.

Source : INAMI – RIZIV, Plan cancer, État des lieux, Janvier 2014.[42]

Le §1 de l'article 33 contient 32 prestations réparties en 5 catégories : 1. Analyses cytogénétiques, 2. Analyses prénatales, 3. Culture, 4. Analyses moléculaires (13 prestations, Table 16) et 5. Dosage. Ce paragraphe contient en outre 2 règles de cumul (aucune ne s'applique aux analyses moléculaires) et 20 règles diagnostiques qui définissent les conditions d'utilisation des codes de prestations.

Les §2 à 11 définissent les conditions auxquelles les prestataires doivent satisfaire afin que les prestations puissent être facturées à l'INAMI. Les prestations ne sont remboursées que si elles sont effectuées dans un laboratoire appartenant à un des 8 centres de génétique humaine agréés, et par un médecin autorisé à les pratiquer par le Ministre de la Santé Publique (§2).[w] En outre, les centres doivent respecter certains critères de qualité (§6 : accréditation ISO 15189 pour minimum 80 % des prestations effectuées, §8 : rapport annuel du coordinateur de qualité), et de transparence (§7 : rapport d'activité annuel, §9 : registre de prestations par indication, §10 : manuel de mise au point diagnostique). Un rapport d'analyse doit être rédigé et adressé au médecin prescripteur (§4 et §5).

Les six analyses moléculaires complexes (en gris dans la table infra), ainsi que 4 autres prestations d'analyse moléculaire de l'article 33 ne sont remboursées par l'INAMI que lorsqu'elles sont prescrites pour une indication reprise sur une liste limitative établie par le Collège de Génétique belge (Règle diagnostique 10). Cette liste est remise à jour annuellement par le Collège. La liste mise à jour est transmise et examinée par le Groupe de travail Biologie clinique du Conseil Technique Médical qui, après avoir donné son aval, la présente pour approbation au Comité de l'assurance au plus tard le 31 janvier de chaque année. Cette règle a pour but d'obtenir plus de précision et de transparence dans les activités couvertes par l'article 33 et leurs dépenses.[43]

Deux autres règles diagnostiques régissent la fréquence d'utilisation des codes d'analyse moléculaire complexe : 1) les 3 codes pour la recherche d'affections constitutionnelles ne sont remboursés par l'INAMI qu'une fois par phase d'investigation diagnostique par type de tissu, avec un maximum de trois tissus différents (règle 6), 2) les 6 codes d'analyse moléculaire complexe ne peuvent être répétés que sur base de nouveaux éléments cliniques ou de nouvelles possibilités diagnostiques, à condition que les motivations soient mentionnées sur la prescription et qu'elles soient prescrites par le médecin spécialiste traitant en concertation avec le médecin généticien (règle 18).

[w] La liste des médecins autorisés à pratiquer les tests génétiques de l'article 33 est publiée sur le site web de l'INAMI : http://www.inami.fgov.be/fr/professionnels/etablissements-services/laboratoires/ > Plus d'informations > Centres de génétique humaine agréés (Mai 2017).

Table 16 – Analyses moléculaires couvertes par l'article 33 de la nomenclature

Honoraire	Code	Libellé FR	Libellé NL
€79.26	565316-565320*	Analyse moléculaire pour la recherche des mutations fréquentes du gène HFE, incluant l'extraction de l'ADN	Moleculair onderzoek voor het opsporen van frequente mutaties in het HFE gen, inclusief DNA isolatie
	565331-565342*	Analyse moléculaire simple pour la recherche d'affections constitutionnelles, incluant l'extraction de l'ADN, maximum trois mutations par gène analysé	Enkelvoudig moleculair onderzoek voor het opsporen van constitutionele aandoeningen, inclusief DNA isolatie, drie of minder mutaties per onderzocht gen
€158.52	565353-565364*	Analyse moléculaire pour la recherche d'anomalies fréquentes dans le gène CFTR, incluant l'extraction de l'ADN	Moleculair onderzoek voor het opsporen van frequente afwijkingen in het CFTR gen, inclusief DNA isolatie
	565375-565386	Analyse moléculaire pour la recherche d'anomalies dans le gène FMR-1, incluant l'extraction de l'ADN	Moleculair onderzoek voor het opsporen van afwijkingen in het FMR-1 gen, inclusief DNA isolatie
	565390-565401*	Analyse moléculaire pour la recherche d'affections constitutionnelles ou établissement d'un profil génétique individuel à des fins de conseil génétique et/ou à des fins diagnostiques, incluant l'extraction de l'ADN	Moleculair onderzoek voor het opsporen van constitutionele aandoeningen of voor het bepalen van een individueel genetisch profiel met het oog op genetisch advies en/of voor diagnostische doeleinden, inclusief DNA isolatie
	565412-565423	Examen génétique prédictif d'une mutation familiale dans le cadre d'une affection neurodégénérative ou autre apparentée, incluant l'extraction de l'ADN	Predictief genetisch onderzoek naar een familiale mutatie in het kader van neurodegeneratieve en verwante aandoeningen, inclusief DNA isolatie
	565434-565445	Examen génétique prédictif d'une mutation familiale dans le cadre de cancer ou d'un syndrome cancéreux familial, incluant l'extraction de l'ADN	Predictief genetisch onderzoek naar een familiale mutatie in het kader van kanker of familiaal kankersyndroom, inclusief DNA isolatie
€365.00	565456-565460*	Analyse moléculaire complexe pour la recherche d'une affection constitutionnelle (niveau 1)	Complex moleculair genetisch onderzoek voor het opsporen van een constitutionele aandoening (niveau 1)
	565515-565526*	Analyse moléculaire complexe pour la recherche de mutations dans le cadre de cancer ou de syndrome cancéreux familial (niveau 1)	Complex moleculair genetisch onderzoek voor het opsporen van mutaties in het kader van kanker of familiaal kankersyndroom (niveau 1)
€570.45	565471-565482*	Analyse moléculaire complexe pour la recherche d'une affection constitutionnelle (niveau 2)	Complex moleculair genetisch onderzoek voor het opsporen van een constitutionele aandoening (niveau 2)
	565530-565541*	Analyse moléculaire complexe pour la recherche de mutations dans le cadre de cancer ou de syndrome cancéreux familial (niveau 2)	Complex moleculair genetisch onderzoek voor het opsporen van mutaties in het kader van kanker of familiaal kankersyndroom (niveau 2)
€1407.87	565493-565504*	Analyse moléculaire complexe pour la recherche d'une affection constitutionnelle (niveau 3)	Complex moleculair genetisch onderzoek voor het opsporen van een constitutionele aandoening (niveau 3)
	565552-565563*	Analyse moléculaire complexe pour la recherche de mutations dans le cadre de cancer ou de syndrome cancéreux familial (niveau 3)	Complex moleculair genetisch onderzoek voor het opsporen van mutaties in het kader van kanker of familiaal kankersyndroom (niveau 3)

*Honoraires au 1/1/2017. * Règle diagnostique 10 : prestation remboursable par l'INAMI que si prescrite pour une indication reprise dans la liste limitative du Collège de Génétique belge. NB : Les autres règles diagnostiques ne sont pas reproduites dans ce tableau.*

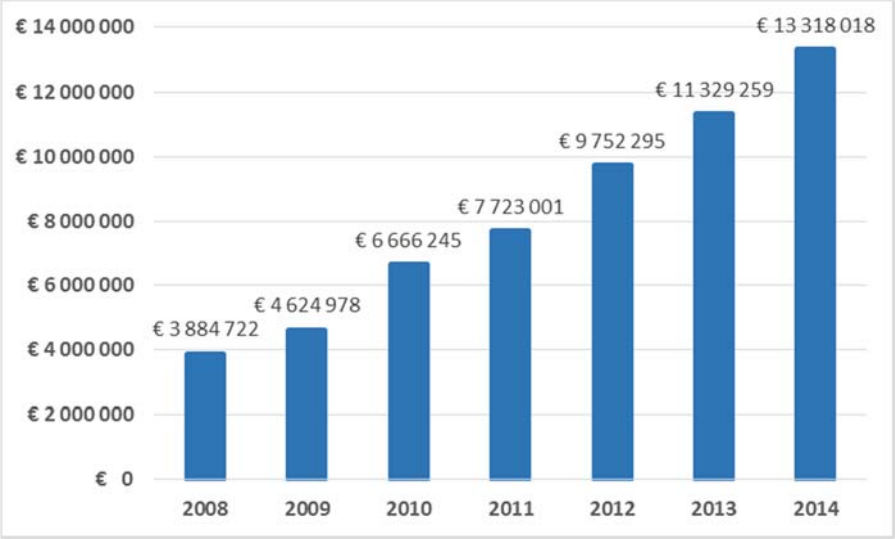
Appendix 3.1.2. Article 33bis

Début : A.R. 7/6/2007 (en vigueur 1/8/2007) ; modifications : A.R. 31/8/2009 (en vigueur 1/11/2009), A.R. 4/5/2010 (en vigueur 1/8/2010), A.R. 18/3/2011 (en vigueur 1/5/2011), A.R. 11/9/2016 (en vigueur 1/11/2016).

L'article 33bis de la nomenclature a été créé pour les « tests de biologie moléculaire sur du matériel génétique humain pour des affections acquises » (art. 33bis, §1).[48]

Le §1 de l'article 33bis décrit 26 prestations réparties en 2 catégories : une pour les affections oncologiques et une pour les affections hématologiques. L'article contient 3 règles de cumul ainsi que 20 règles diagnostiques. Le remboursement des prestations de l'article 33bis n'est pas limitées aux laboratoires des 8 centres agréés de génétique humaine ; il est aussi ouvert aux laboratoires de biologie clinique ou d'anatomopathologie (§2).

Figure 2 – Dépenses de l'INAMI pour les prestations de l'article 33bis



Source : INAMI, Doc N, dépenses comptables.

Ces laboratoires sont tenus de respecter certains critères de qualité (§5, 3° : accréditation ISO 15189 ; §5, 4° et 5° : contrôles de qualité) et de transparence (§5, 2bis° : registre de prestations pour la catégorie B) ; un rapport d'analyse doit être rédigé et adressé au médecin traitant (§4).

Le budget de l'article 33bis est inclus dans le budget global de la Biologie Clinique fixé chaque année par le Conseil Général de l'INAMI. L'évolution des dépenses comptables de l'INAMI pour les prestations de l'article 33bis a été obtenue par l'analyse des données Doc N de l'INAMI (Figure 2).

Appendix 3.1.3. Article 33ter

Un nouvel article 33ter de la nomenclature est en cours d'élaboration. La création de cet article provient de la volonté d'adapter les procédures actuelles de remboursement des soins de santé afin de permettre le remboursement simultané de nouveaux traitements thérapeutiques et de leurs tests diagnostiques « compagnons ». En Belgique, en effet, les demandes de remboursement de nouveaux médicaments et de nouveaux tests suivent deux procédures distinctes, la première étant initiée auprès de la Commission de Remboursement des Médicaments (CRM/CTG) et la deuxième auprès du Conseil Technique Médical de l'INAMI. Les durées de traitement de ces demandes sont de 6 mois (avec d'éventuelles suspensions) pour les médicaments, contre un minimum de 18 mois pour les tests ; ce qui empêche le remboursement rapide et simultané d'un médicament et de son test « compagnon ».

La Plateforme « Companion Diagnostic » de l'INAMI, un groupe de travail constitué de membres de la Commission de Remboursement des Médicaments (CRM/CTG) et du Conseil Technique Médical, a été créée le 19/1/2016 afin de proposer des solutions à ce problème.

A cet effet, l'article 33ter sera constitué de nouveaux codes de nomenclature génériques pour le remboursement de tests liés à un traitement personnalisé. Ces traitements personnalisés seront regroupés sous un nouveau chapitre (Chapitre VIII) de la liste des spécialités pharmaceutiques remboursables qui reprendra en annexe la liste des tests « compagnons » de ces traitements. Les médicaments du Chapitre VIII ne seront remboursés que si leurs tests compagnons sont effectués selon les conditions de l'article 33ter. En outre, lorsque la décision est prise de rembourser un traitement

personnalisé, son test diagnostic compagnon est automatiquement ajouté à la liste en annexe.

Source : Présentation d'Anouck Waeytens, INAMI – RIZIV. "Platform CRM – TMC: a linked procedure for companion reimbursement". Cancer Centre - Symposium NGS. 25 Octobre 2016.

Appendix 3.2. Convention article 22 avec les centres

Base légale – Convention article 22, 18°

Le principe de la convention conclue entre le Comité de l'assurance et les 8 centres de génétique humaine est décrit à *l'article 22, 18° de la loi coordonnée du 14/7/1994* :[44] « Le Comité de l'assurance conclut des conventions avec les centres de génétique humaine, […], pour des prestations concernant des pathologies héréditaires, et qui sont exclues d'un remboursement par la nomenclature des prestations de santé visée à l'article 35, § 1er. »

La convention article 22, 18° conclue avec les centres de génétique couvre à la fois le « conseil génétique » et les « tests ADN effectués à l'étranger ».[45]

Appendix 3.2.1. Le conseil génétique

Historique – Convention « conseil génétique »

En novembre 2011, un projet de convention pour la revalorisation du conseil génétique et son encadrement a été finalisé, en concertation avec les centres de génétique humaine. Cette proposition a été approuvée par le Comité de l'assurance de l'INAMI en mars 2012 et est entrée en vigueur le 1er janvier 2013.

La convention ne porte pas uniquement sur des pathologies cancéreuses, mais couvre toutes les pathologies pour lesquelles un conseil génétique est nécessaire, afin de ne pas introduire de discrimination entre les malades bénéficiaires de l'assurance soins de santé obligatoire.

Source : INAMI – RIZIV, Plan cancer, État des lieux, Janvier 2014.[42]

Depuis le 1/1/2013, les 8 centres de génétique bénéficient d'un remboursement pour leurs consultations de conseil génétique. Deux codes de nomenclature sont prévus : l'un pour un conseil génétique standard et l'autre pour un conseil génétique complexe (Table 17). Ces prestations comprennent au minimum deux consultations au cours desquelles les antécédents personnels et familiaux sont examinés. Le conseil génétique complexe peut aussi consister en une demande d'informations médicales sur les membres de la famille et une exploration diagnostique complexe (littérature, deuxième avis…). Le conseil génétique standard et le conseil génétique complexe exigent tous deux la rédaction d'un rapport médical (art. 3 et 4).

Afin de bénéficier de cette convention, le centre de génétique doit disposer d'une équipe multidisciplinaire spécialisée en conseil génétique, composée au minimum de 2 médecins spécialistes (en médecine interne ou en pédiatrie) avec une formation en génétique humaine de minimum 5 années, d'un psychologue, d'un infirmer ou d'un travailleur social ainsi que d'un secrétaire (art. 10 à 14). Les centres de génétique sont les seuls habilités à facturer ce conseil génétique, qu'ils peuvent aussi effectuer en dehors de leurs murs (art. 6). À cette fin, en 2013, un budget fermé d'un peu plus de 4 millions d'euros a été prélevé du budget de l'article 33 et a été affecté au conseil génétique par la Commission Nationale médico-mutualiste (voir plus bas).

Table 17 – Remboursement INAMI du conseil génétique

Code de pseudo-nomenclature	Libellé FR	Libellé NL	Honoraire
589750-589761	Forfait pour conseil génétique standard	Forfait voor de standaard genetic counseling	€229.42
589772-589783	Forfait pour conseil génétique complexe	Forfait voor de complexe genetic counseling	€625.10
589794-589805	Forfait de rattrapage (négatif)	Inhaalforfait (negatief)	Pas de tarif fixe

Honoraire au 1/1/2017. Source : Nomensoft + Circulaire OA 2016/390 du 23 décembre 2016.

Appendix 3.2.2. Les tests ADN exécutés à l'étranger

Historique – Convention « tests ADN effectués à l'étranger »

Cette mesure a été intégrée au projet de convention dans le contexte de la revalorisation du conseil génétique avec les centres de génétiques. Le Comité de l'assurance de l'INAMI a approuvé cette proposition en mars 2012. Elle est entrée en vigueur le 1er janvier 2013.

La convention ne porte pas uniquement sur des pathologies cancéreuses, mais couvre toutes les pathologies pour lesquelles un test ADN effectué à l'étranger est nécessaire, afin de ne pas introduire de discrimination entre les malades bénéficiaires de l'assurance soins de santé obligatoire.

Source : INAMI – RIZIV, Plan cancer, État des lieux, Janvier 2014.[42]

Depuis le 1/1/2013, la convention conclue entre le Comité de l'assurance et les 8 centres de génétique humaine autorise le remboursement d'examens génétiques réalisés à l'étranger, si aucun laboratoire belge spécialisé n'effectue le test. Auparavant, les patients ne pouvaient bénéficier d'un remboursement pour leurs analyses sur des échantillons ADN effectuées à l'étranger que s'ils se rendaient en personne à l'étranger et que le test était remboursé dans le pays de destination.

Un budget fermé de €566 000 a été fixé en 2012 (voir plus bas). Les examens sont directement facturés à l'INAMI par les centres de génétique qui les envoient à l'étranger. Le remboursement couvre les coûts du test et les frais d'envoi.

Les conditions de remboursement des tests sont (art. 7 et 8):

- Les tests doivent être repris sur une liste établie annuellement par les centres de génétique et approuvée par le Conseil d'accord.
- Les tests doivent être effectués par un laboratoire agréé pouvant effectuer des tests sur du matériel génétique humain, présentant toutes la garanties de qualité, et repris sur une liste de laboratoires de référence étrangers. Cette liste est établie annuellement par les centres de génétique conventionnés et validée par le Conseil d'accord.
- Les tests doivent présenter un intérêt clinique démontré pour le diagnostic et le suivi des patients, ils doivent être prescrits par des médecins spécialistes de la pathologie concernée, la prescription doit être validée par un médecin spécialisé en génétique humaine.
- Si un laboratoire d'un centre de génétique installé sur le territoire belge développe l'expertise nécessaire pour effectuer un test repris sur la liste, avec toutes les garanties de qualité, l'exécution de ce test à l'étranger n'est alors plus couverte par la convention.

Source : Convention et http://www.riziv.fgov.be/fr/professionnels/etablissements-services/laboratoires/ (Mai 2017).

Appendix 3.3. Financement de l'article 33 de la nomenclature, du conseil génétique et des tests ADN effectués à l'étranger

Appendix 3.3.1. Budget global

Le 6/9/2010, la Commission Nationale Médico-mutualiste (la « Médico-mut ») a opté pour un budget global afin de couvrir les prestations de l'article 33 et de la convention article 22 des centres de génétique humaine.[x] Ce budget est fixé annuellement par le Conseil Général de l'INAMI.

Le budget a été fixé à €42,65 millions et couvre les prestations de l'article 33 de la nomenclature à hauteur de €37,79 millions ; le « conseil génétique » à hauteur de €4,28 millions ; et les « tests génétiques exécutés à l'étranger » à hauteur de €566 000 (Table 18). L'application de ces

[x] Les définitions autour du statut de ce budget varient. Une note de 2011 de la Commission Nationale Médico-Mutualiste traitant de la révision de l'article 33 mentionne la notion de budget fermé (« gesloten budget ») pour les activités de génétique (dont les prestations de l'article 33). Une autre note de la même Commission, datant de 2015, mentionne la notion de budget fixé par le Conseil Général (et donc pas une enveloppe fermée stricto sensu).

budgets annuels a débuté le 1/1/2013, au moment de l'entrée en vigueur de la nouvelle version de l'article 33 et de la convention. Aucun transfert ne peut être normalement opéré entre les trois parties du budget.

Appendix 3.3.2. Dépassement du budget

Les dépenses liées à l'article 33 sont suivies régulièrement par l'INAMI de manière à pouvoir prendre des mesures correctrices en cas de dépassement de l'objectif budgétaire. Ceci ne se fait toutefois pas automatiquement.

Par contraste, la convention « conseil génétique » et « tests réalisés à l'étranger » prévoit, dans ses modalités de facturation et de paiement, ce qui doit être appliqué automatiquement en cas de dépassement du budget:

- Art. 25, §4 pour le conseil génétique : « En cas de dépassement du budget total prévu, la récupération du budget sera effectuée au moyen d'un forfait de rattrapage (négatif) temporaire sur les prestations effectuées l'année suivante, jusqu'à récupération du montant. Le montant de ce forfait de rattrapage sera calculé sur base du montant à récupérer et de l'activité totale (nombre total de forfaits standards et complexes) après clôture annuelle des comptes ».
- Art. 26, §§2, 5 et 6 pour les tests ADN exécutés à l'étranger : Chaque centre de génétique reçoit une avance de €30 000 au début de chaque année. « Sur base des factures envoyées à l'INAMI, le remboursement du solde sera versé à chaque centre dans la limite du budget disponible. En cas de dépassement du budget, le solde sera réparti entre chaque centre proportionnellement à leurs dépenses ».

Les budgets et dépenses enregistrés par l'INAMI pour la période 2010-2016 sont présentés à la Table 18.

Table 18 – Budget et dépenses de l'INAMI pour les analyses de l'article 33 et la convention article 22 des CGH

	2010	2011	2012	2013	2014	2015	2016
Budget							
- Prestations de l'article 33				€37 795 000	*	€37 964 000	€45 407 000
- Convention « conseil génétique »				€4 288 000	*	€2 244 000	€ 2 027 000
- Convention « tests génétiques à l'étranger »				€566 000	€580 000	€580 000	€580 000
Budget total				€42 649 000	*	€40 788 000	€48 014 000
Dépenses de l'INAMI							
- Prestations de l'article 33	€40 068 034	€38 790 081	€41 666 225	€35 814 350	€37 348 178	€43 770 045	€49 639 101
- Convention « conseil génétique »				€278 133	€1 154 331	€1 599 618	€1 793 887
- Convention « tests génétiques à l'étranger »				€240 000	€401 260	€599 405	€580 000
Dépenses totales	€40 068 034	€38 790 081	€41 666 225	€36 332 482	€38 903 509	€46 206 061	€52 012 988

*NB : Les CGH bénéficient aussi du remboursement par l'INAMI des prestations de l'article 33bis de la nomenclature. * Info non reçue.*
Source : rapports de la CNMM/NCGZ (2015/92, 2011/71)[46, 47] et communication Chantal Mathy et Johan Peetermans (INAMI), données 2016 reçues le 25/10/2017.

De manière générale on observe que les dépenses sont supérieures au budget depuis 2015. On observe aussi une forte augmentation de dépenses depuis 2015.

Dans les deux premières années de sa mise en application, le budget alloué au conseil génétique a été sous-utilisé. Les dépenses enregistrées étaient d'au plus €1,15 millions en 2014 pour une enveloppe totale d'un peu plus de €4,28 millions. Les raisons de cette sous-utilisation du budget semblent liées, entre autres, aux modalités exigées par la convention « conseil génétique » pour prétendre au remboursement. Par consultation de conseil génétique, la convention couvre en effet le travail du médecin spécialisé en génétique (minimum 2 consultations) mais aussi celui du personnel paramédical (psychologue et infirmier/travailleur social) et d'un secrétariat. Pour un conseil génétique simple, l'intervention d'un psychologue ou d'un travailleur social/infirmier est requise. Pour un conseil génétique complexe la convention requiert l'intervention de tous ces prestataires. En 2015, en vertu de cette sous-utilisation, le budget alloué au conseil génétique a été revu à la baisse et est passé de €4,28 à €2,24 millions.

En 2015, les dépenses des centres de génétique pour les tests effectués à l'étranger se sont élevées à €836 397, tandis que le budget partiel alloué était de €580 000. À la demande du Collège de Génétique, le Conseil d'accord a accepté de réaliser un déplacement unique (que pour 2015) du budget « conseil génétique » vers le budget « tests effectués à l'étranger » pour le montant du surplus, soit €256 397. Les montants présentés dans le tableau ci-dessus tiennent compte de ce transfert.

Appendix 3.4. Autres sources de financement

Appendix 3.4.1. Fédération Wallonie-Bruxelles

Le site internet de la Direction générale du Budget et des Finances de la Fédération Wallonie-Bruxelles publie en ligne le budget général annuel de ses dépenses depuis 2006. Ces budgets sont publiés au Moniteur Belge sous forme de Décrets. Dans les budgets 2006 à 2012, il est rapporté que la Communauté française peut accorder des subventions facultatives pour les activités de recherche scientifique des 4 centres francophones de génétique humaine reconnus (Division Organique 45 - Programme 3). A partir du budget 2013, il n'est plus fait mention de cette possibilité.

Les budgets 2006 à 2011 rapportent les subventions suivantes pour les 4 centres de génétique francophones:

- 2006 : €743 000
- 2007 : €758 000
- 2008 : €781 000
- 2009, 2010 et 2011 : €794 000

Source : http://www.budget-finances.cfwb.be/ - Accueil > Budget > Direction du Budget > Budgets en ligne (Mai 2017).

Appendix 3.4.2. Région wallonne

Les 4 centres francophones de génétique ont obtenu un soutien financier de la région wallonne, via le Département des Programmes de Recherche de la Direction Générale Opérationnelle de l'Économie, de l'Emploi et de la Recherche (DGO6) du Service Public Wallon. Deux subventions (GENHU et GENHU-2) ont été allouées avec pour but de recherche : 1) d'unifier et fédérer les échantillons ADN des quatre centres francophones de génétique en une bio-banque virtuelle unique, et 2) de participer à la création d'une large banque d'ADN autorisant des études de population.

- 2013 : €1 564 000 (durée de la recherche 24 mois)
- 2014 : €1 669 759 (durée de la recherche : 24 mois)

En Juin 2016, le versement de ces subventions a été stoppé ; des négociations sont en cours actuellement afin de tenter de les rétablir.

Source : https://recherche-technologie.wallonie.be/projets/index.html?IDD=25066 et https://recherche-technologie.wallonie.be/projets/index.html?IDD=26183 (5/2017).

Appendix 3.4.3. Communauté flamande

Base légale – Financement de la génétique par la communauté flamande

L'arrêté du Gouvernement flamand (AGF) du 3/5/1995, relatif aux Centres de génétique humaine, décrit les modalités d'octroi de subventions aux 4 centres de génétique flamands.[49]

Début : A.G.F. 3/5/1995 (en vigueur 1/1/1995) ; modifications : A.G.F. 17/12/1997, A.G.F. 23/07/1998, A.G.F. 30/11/2001, A.G.F. 31/03/2006, A.G.F. 24/09/2010, A.G.F. 30/01/2015. (A.G.F. = Besluit van de Vlaamse regering)

Pour pouvoir bénéficier d'une subvention, les centres de génétique doivent 1) être agréés en application de *l'arrêté royal du 14/12/1987*[37] *fixant les normes auxquelles les Centres de génétique humaine doivent répondre* et 2) répondre aux conditions suivantes :

- étudier le caractère génétique d'affections et rechercher des alternatives afin de prévenir des maladies héréditaires ou des handicaps ;
- conseiller et soutenir les parents notamment par la communication des résultats des recherches aux parents concernés ainsi que donner de l'aide morale et psychologique aux parents lors du processus d'acceptation ;
- apporter leur collaboration à la Communauté flamande dans le domaine des recherches scientifiques.

Les centres doivent en outre participer à l'enregistrement uniforme des données de génétique (article 3) et fournir un rapport annuel (en ce compris un compte rendu financier) à l'agence "Zorg en Gezondheid" (article 4).

Les subventions peuvent être utilisées « pour le paiement des frais de personnel et de fonctionnement ainsi que pour le financement de l'infrastructure et de l'équipement du centre » (art. 6). La subvention se compose d'un forfait de base et d'une subvention supplémentaire en cas de crédit budgétaire. En 2014, un budget de €2 238 231 a été alloué aux 4 centres flamands ; en 2015, ce montant s'élevait à €2 259 000.

Source : A.G.F. 3/5/199549 et question parlementaire (Vlaams parlement) à Mr Jo Vandeurzen, 10/5/2015.

Appendix 3.4.4. Financement du Registre national de la Génétique humaine

Base légale – Financement du Registre national de la Génétique humaine

Divers arrêtés royaux, relatifs au Registre national de la Génétique humaine, précisent chaque année les montants alloués au « Centrum voor Menselijke Erfelijkheid de la KUL » ainsi que les modalités d'octroi de cette subvention.

Sources : A.R. 13/06/2007, A.R. 27/9/2006 (en vigueur 9/11/2006), A.R. 10/11/2005 (en vigueur 20/1/2006), A.R. 5/12/2004 (en vigueur 12/2/2005), A.R. 30/11/2003 (en vigueur 24/5/2004), A.R. 14/11/2002 (en vigueur 17/5/2003), A.R. 3/11/2001 (en vigueur 19/3/2002).

Chaque année entre 2002 et 2007, un arrêté royal du SPF Santé Publique a été publié octroyant un subside au « Centrum voor Menselijke Erfelijkheid de la KUL » pour l'établissement et la tenue à jour du Registre national de la Génétique humaine. Ces subsides couvrent les frais de fonctionnement (indemnités, salaires, traitements, charges sociales, petits frais de bureau et frais de prestation de service) ainsi que les frais d'investissement dans la mesure où ils sont justifiés dans le cadre de la recherche subsidiée. Les montants sont les suivants :

- 2007 : €102 000
- 2006 : €100 000
- 2005 : montant non disponible
- 2004 : €97 000
- 2003 : €97 000
- 2002 : €97 000
- 2001 : €96 678

APPENDIX 4. OPTIONS POUR L'INTRODUCTION DU WGS

Appendix 4.1. Disclaimer

Ce chapitre n'a pas la prétention de détailler in extenso l'ensemble des procédures à suivre pour obtenir un financement via l'une des procédures évoquées.

Appendix 4.2. Adaptation potentielle du budget

Le budget nécessaire à l'introduction du WGS devrait faire l'objet d'une évaluation détaillé de l'ensemble des coûts générés par cette technologie, comme cela a été fait par exemple dans les rapports du KCE sur le NGS[y] ou la radiothérapie.[z]

Il semble toutefois peu probable qu'à court terme l'introduction du WGS soit neutre pour le budget, étant donné son coût élevé et le fait que l'on s'attende à une demande croissante pour ces tests de la part de diverses spécialités médicales, outre la génétique.

Si un budget supplémentaire est souhaité, il faut garder à l'esprit qu'il est peu probable que la Commission nationale médico-mutualiste ou la Commission de contrôle budgétaire accèdent à une telle demande eu égard au contexte économique actuel requérant des efforts budgétaires de la part de chacun. Le budget global des soins de santé est en effet gelé et plus aucune augmentation de budget n'a récemment été accordée. Dans ce contexte, seul un transfert de budget d'un secteur des soins de santé à un autre est possible ; ou éventuellement une décision ministérielle comme ce fut le cas récemment pour le NIPT où un budget de €15 millions a été dégagé (*Source : Communiqué de presse du Cabinet, 29/5/2017)*.

Appendix 4.3. Les options de financement

Appendix 4.3.1. Via la nomenclature existante

Une option de financement pour le WGS est l'utilisation des codes actuels de l'article 33 de la nomenclature. Les analyses moléculaires complexes de niveau 3 sont financées à hauteur de €1408 (honoraire au 1/1/2017) ; celles de niveau 2 et 1 à hauteur de €570 et €365, respectivement (Table 19). Cette option requiert toutefois que les règles de cumul et les règles diagnostiques de l'article 33 de la nomenclature soient respectées.

Aucune règle de cumul de l'article 33 ne concerne ces codes. Par contre, en respect de la règle diagnostique 10, la liste limitative d'indications autorisées au remboursement devra être adaptée régulièrement pour s'étoffer en fonction des évolutions scientifiques ; étant donné l'impossibilité à l'heure actuelle d'établir une telle liste de façon exhaustive pour le WGS. Deux autres règles diagnostiques (règles 6 et 18) régissent la fréquence d'utilisation des codes précités et devront être respectées (cf. supra).

Table 19 – Nomenclature des analyses moléculaires complexes

Libellé	Niveau	Nomenclature	Honoraire
Analyse moléculaire complexe pour la recherche d'une affection constitutionnelle – Complex moleculair genetisch onderzoek voor het opsporen van een constitutionele aandoening.	3	565493-565504	€1407,87
	2	565471-565482	€570,45
	1	565456-565460	€365,00
Analyse moléculaire complexe pour la recherche de mutations dans le cadre de cancer ou de syndrome cancéreux familial – Complex moleculair genetisch onderzoek voor opsporen van mutaties in het kader van kanker of familiaal kankersyndroom.	3	565552-565563	€1407,87
	2	565530-565541	€570,45
	1	565515-565526	€365,00

Note : honoraire au 1/1/2017.

[y] Van den Bulcke M, San Miguel L, Salgado R, et al. Tests de Panels de gènes par Next Generation Sequencing pour un traitement ciblé en oncologie et en hémato-oncologie. Health Technology Assessment (HTA). Bruxelles : Centre Fédéral d'Expertise des Soins de Santé (KCE). 2015. KCE Reports 240.

[z] Hulstaert F, Mertens A-S, Obyn C, et al. Techniques innovantes en radiothérapie: une étude multicentrique d'évaluation du coût via la méthode ABC pilotée par le temps. Health Technology Assessment (HTA). Bruxelles: Centre Fédéral d'Expertise des Soins de Santé (KCE). 2013. KCE Reports 198.

Bien que cette option permette un accès rapide au financement du WGS et une certaine souplesse grâce à l'adaptation continue de la liste limitative, son principal inconvénient est que le remboursement des prestations additionnelles de WGS se ferait dans le cadre du budget actuel.

Appendix 4.3.2. Via un nouveau code de nomenclature

Une deuxième option de financement est la création d'un nouveau code de nomenclature. Cette option pourrait prendre la forme d'une modification de l'article 33 de la nomenclature, ce qui aurait pour conséquence de limiter le remboursement de cette nouvelle prestation aux centres agréés de génétique humaine (à moins d'une révision de cet article). Toutefois la création d'un nouveau code de nomenclature suit une procédure complexe et longue, qui requiert l'aval de nombreux intervenants.

Base légale – Modification de la nomenclature

La base légale pour une modification de la nomenclature est décrite à *l'article 35, §2, 1° de la loi coordonnée du 14/7/1994* :[44] « Le Roi peut apporter des modifications à la nomenclature des prestations de santé visée au §1 sur la base de la proposition formulée d'initiative par le Conseil technique compétent, soumise à la commission de conventions ou d'accords correspondante qui décide de sa transmission au Comité de l'assurance (et à la Commission de contrôle budgétaire) ».

Le rôle et la composition des Conseils techniques (dont le Conseil technique médical) sont décrits dans *les articles 27 et 28 de la loi coordonnée du 14/7/1994* ; le rôle principal des conseils étant de « faire les propositions et donner les avis prévus à l'article 35, §2 (...) ». Les Conseils Techniques sont conseillés par des Groupes de travail (dont le Groupe de travail Biologie clinique).

Le rôle du Comité de l'assurance est décrit dans *l'article 22, 4° de la loi coordonnée du 14/7/1994* : « Le Comité de l'assurance décide de la transmission au Ministre des propositions de modification de la nomenclature des prestations de santé (…). » « Le Comité de l'assurance prend sa décision après avis de la Commission de contrôle budgétaire rendu au plus tard dans le mois qui suit l'envoi simultané des changements de nomenclature concernés au Comité de l'assurance et à la Commission de contrôle budgétaire. A défaut d'un avis rendu dans le délai précité d'un mois, l'avis est considéré comme donné. Le Comité de l'assurance peut adapter les propositions susmentionnées de modifications de la nomenclature avant qu'elles ne soient envoyées au ministre, si tous les membres du Comité de l'assurance présents ayant voix délibérative marquent leur accord avec cette adaptation. »

La création d'un nouveau code dans l'article 33 de la nomenclature nécessite qu'une demande de modification soit introduite, dans ce cas-ci par le Collège de Génétique belge, auprès du Conseil Technique Médical de l'INAMI.

La demande doit être documentée et préciser entre autres une estimation du nombre de tests WGS qui seraient effectués ainsi que du budget requis. A l'heure actuelle, de telles estimations ne sont pas faciles à fournir étant donné que le coût du WGS évolue rapidement, et que les indications pour son utilisation ne cessent de s'étendre.

Le dossier préparatoire est alors remis au Groupe de travail Biologie clinique du Conseil Technique Médical de l'INAMI pour évaluation. Ce Groupe de travail est actuellement constitué d'experts en biologie clinique et de cliniciens, et il peut consulter les membres de la Commission de Biologie clinique de l'Institut Supérieur de Santé publique pour avis. Si le Groupe de travail estime le dossier recevable, il formule une proposition qu'il transmet au Conseil Technique Médical pour discussion. En cas d'avis positif lors de la réunion plénière du Conseil Technique Médical, la proposition est transmise à la Commission nationale médico-mutualiste (la « médico-mut ») où la possibilité de l'octroi d'un nouveau budget est négociée. L'obtention de ce budget supplémentaire dépend du budget global des soins de santé alloué par le gouvernement (or celui-ci n'a plus augmenté depuis des années), ainsi que des demandes de budget des autres secteurs qui concourent tous pour le même but. La proposition est ensuite transmise directement au Comité de l'assurance et à la Commission de contrôle budgétaire. La Commission de contrôle budgétaire donne son avis et le Comité de l'assurance décide de transmettre ou non la proposition au cabinet du Ministre des Affaires sociales et de la Santé publique. Ce dernier prend avis auprès de l'Inspecteur des finances, du Ministre qui a le budget dans ses attributions et du Conseil d'état. Si l'issue est favorable, le Roi signe la proposition d'insertion d'un nouvel article dans la nomenclature et celle-ci est publiée au Moniteur belge dans un arrêté royal modifiant l'annexe

de l'arrêté royal du 14 septembre 1984 établissant la nomenclature des prestations de santé en matière d'assurance obligatoire soins de santé et indemnités. Lorsque cet arrêté royal ne contient pas de disposition fixant son entrée en vigueur, il entre en vigueur le dixième jour qui suit sa publication au Moniteur belge (Figure 3).

Aucune limite de temps n'est définie pour cette procédure ; mais au vu des multiples approbations à obtenir, elle prend au minimum 18 mois, voire plus si aucun budget ne peut être dégagé.

Figure 3 – Étapes pour la création ou la modification d'un code de nomenclature

Appendix 4.3.3. Via une convention article 56, §2, 1°

Une troisième option est la conclusion par le Comité de l'assurance d'une convention sur base de l'article 56, §2, 1° de la loi coordonnée du 14/7/1994.[44]

Base légale – Convention article 56, §2, 1°

Le **principe** de cette convention est décrit à *l'article 56, §2, 1° de la loi coordonnée du 14/7/1994* :[44] « Dans les conditions à fixer par le Roi et par dérogation aux dispositions générales de la présente loi coordonnée et de ses arrêtés d'exécution, le Comité de l'assurance peut conclure des conventions qui sont limitées dans le temps et/ou dans leur champ d'application et qui ont pour but d'accorder une intervention pour des modèles spéciaux à caractère expérimental de prescription, de dispensation ou de paiement de soins de santé. » (…) « Les dépenses qui accompagnent les conventions en question sont imputées au budget prévu pour les frais d'administration de l'Institut et sont intégralement prises en charge par le secteur des soins de santé. »

Cette convention vise à financer, pour une durée déterminée (généralement 2-3 ans, renouvelable), des techniques médicales expérimentales afin d'en tester la pertinence. Elle s'apparente à un projet pilote qui permettrait d'encadrer l'introduction phasée du remboursement du WGS, tout en collectant des informations essentielles (budget, liste d'indications…) pour son évaluation, et pour la mise en place d'un financement structurel. Elle pourrait permettre en outre le financement des investissements initiaux. Toutefois la conclusion d'une nouvelle convention nécessite une négociation *de novo* de toutes les règles de la convention, notamment pour la qualification des prestataires autorisés. Ainsi, contrairement aux prestations de l'article 33 de la nomenclature, les prestations de cette nouvelle convention ne sont pas limitées aux centres de génétique humaine.

La conclusion d'une convention article 56, §2, 1° pour le financement du WGS nécessite au préalable la publication d'un arrêté royal fixant les conditions dans lesquelles le Comité de l'assurance peut conclure une telle convention avec les prestataires. L'élaboration du projet d'arrêté royal passe par une phase préparatoire d'évaluation scientifique et de détermination du budget. L'évaluation par le Conseil Technique Médical de l'INAMI se base sur les critères suivants : les données scientifiques sur le caractère « innovant » de la technologie, la ou les pathologies concernées, l'impact clinique, l'impact de santé publique, l'impact pour l'assurance soins de santé et l'impact pour la société. Le Conseil général de l'INAMI décide, après avis

de la Commission de contrôle budgétaire, de la possibilité d'octroi d'un nouveau budget et de la compatibilité budgétaire de la convention. Le projet est transmis au Comité de l'assurance qui fixe les conditions de son intervention et qui transmet le projet d'arrêté royal au cabinet du Ministre des Affaires sociales et de la Santé publique. Ce dernier prend avis auprès de l'Inspecteur des finances, du Ministre qui a le budget dans ses attributions et du Conseil d'état. Si l'issue est favorable, le Roi signe le projet et celui-ci est publié dans un arrêté royal au Moniteur Belge.

Source : présentation de G. Haucotte - European Challenges for laboratory medecine: Reimbursement of innovative technologies. Leading authorities responsable for Reimbursement in European countries: Belgium, 26/11/2010.

Bien que les différentes étapes de ce processus soient de durées variables, le délai global de conclusion d'une telle convention est de minimum 12 mois. Ce délai peut encore être rallongé si aucun budget ne peut être dégagé. A contrario, si l'impact de la nouvelle convention est neutre pour le budget (comme dans le cas de la convention article 56 pour le Next Generation Sequencing), le passage par la Commission de contrôle budgétaire n'est plus nécessaire et le délai peut être raccourci.

Après la publication de l'arrêté royal, les parties intéressées peuvent introduire une demande de conclusion d'une convention selon l'article 56, §2, 1° pour le financement du WGS moyennant le respect des conditions fixées par cet arrêté royal.

Bien que ce ne soit obligatoire que pour une modification de la nomenclature ou une convention article 22 (voir plus bas), le projet de convention est aussi en pratique évalué par le Groupe de travail Biologie clinique du Conseil Technique Médical de l'INAMI.

Les dépenses liées aux conventions article 56, §2, 1° ne sont pas imputées au budget global des soins de santé mais au budget des frais d'administration de l'INAMI, ce qui pourrait favoriser l'obtention d'un budget supplémentaire. Ces conventions expérimentales sont en effet envisagées comme des projets apportant une réponse aux questions que l'INAMI se pose et dont il a besoin pour fonctionner et prendre ses décisions. Le budget alloué à cette convention devrait être évalué de manière à permettre une certaine marge de manouvre.

Une convention article 56, §2, 1° finance tant la technique innovante que son évaluation à l'échéance de la convention. Ainsi, les modalités de l'évaluation du WGS devront être précisées dans la convention, comme par exemple une estimation des coûts et bénéfices à intervalles réguliers, ainsi que les instances chargées de l'évaluation (un Comité d'accompagnement ou un acteur externe tel le KCE ou l'ISP).

Une convention article 56, §2, 1° étant temporaire, elle nécessite un nouveau processus de négociation à son terme, après la phase d'évaluation. Ainsi, les possibilités de financement « post-évaluation » du WGS sont :

- Le renouvellement de la convention article 56, §2, 1° ; ou
- La conclusion d'une convention article 22, 6°bis (cf. infra) ; ou
- L'inclusion de la prestation dans la nomenclature des prestations courantes pour un financement structurel (cf. supra).

Appendix 4.3.4. Via une convention article 22, 6°bis

Une quatrième option est la constitution d'une convention sur base de l'article 22, 6°bis de la loi coordonnée du 14/7/1994.[44]

Base légale – Convention article 22, 6°bis

Le **principe** de cette convention est décrit à *l'article 22, 6°bis de la loi coordonnée du 14/7/1994* :[44] « Le Comité de l'assurance conclut, sur proposition des Commissions de conventions et des accords et après avis du Conseil technique compétent, rendu dans les deux mois, des conventions avec des établissements de soins ou autres prestataires de soins portant sur les prestations visées à l'article 34. Ces conventions fixent le remboursement et les conditions d'exécution d'ordre quantitatif et qualitatif en ce qui concerne l'application de techniques innovatrices et nouvelles existantes ou encore à introduire et en ce qui concerne des prestations complexes, multidisciplinaires et/ou coûteuses, sur avis du Conseil scientifique de l'INAMI, à condition qu'il ne soit pas porté atteinte aux normes d'agrément et de programmation. Les projets de conventions sont également communiqués au conseiller budgétaire et financier visé à l'article 17, deuxième alinéa, 6°. »

Cette convention revêt aussi un caractère innovant et a pour but le financement de prestations complexes, multidisciplinaires et/ou coûteuses en soins courants. Tout comme la convention article 56, §2, 1°, la convention article 22, 6°bis nécessite une négociation *de novo* de toutes les règles de la convention, notamment pour la qualification des prestataires autorisés. Ainsi, contrairement à l'article 33 de la nomenclature (et pour autant que celui-ci ne soit pas renégocié), les prestations couvertes par la convention ne sont pas limitées aux centres de génétique humaine. La convention article 22, 6°bis représente un financement à long-terme ; qui pourrait aussi couvrir les investissements initiaux (bien que ce ne soit pas courant).

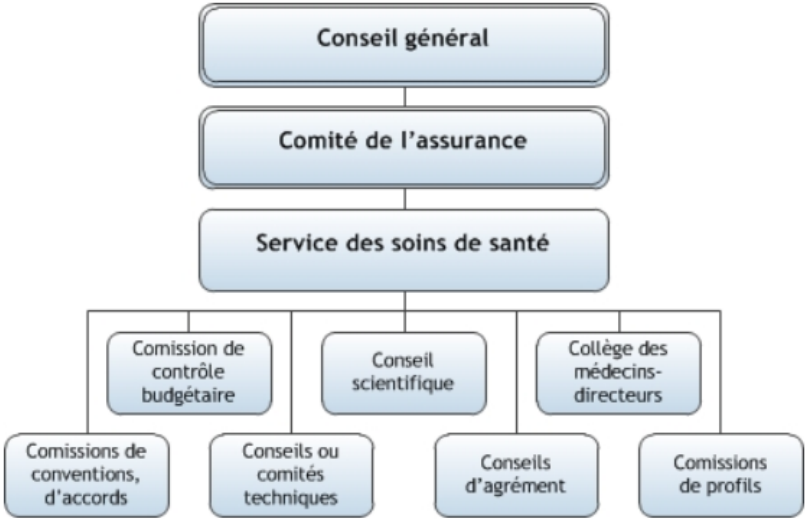
Les conventions article 22, 6°bis ont souvent été utilisées pour les projets de revalidation multidisciplinaire, notamment après qu'une demande du Collège des médecins directeurs ou de la Commission Nationale médico-mutualiste ait été introduite selon leurs observations et leurs souhaits d'amélioration.

Les dépenses liées aux conventions article 22, 6°bis sont imputées au budget global des soins de santé. Celui-ci étant fermé seul un transfert de budget d'un secteur à un autre permettrait de trouver un financement.

Appendix 4.4. Les organes du Service des soins de santé de l'INAMI

Le site web de l'INAMI fournit un descriptif du rôle des différents organes assurant la gestion de l'assurance soins de santé. La page web peut être obtenue en suivant ce chemin à partir du site web de l'INAMI (http://www.inami.fgov.be/): Accueil ▶ L'INAMI ▶ Nos organes ▶ Les organes du Service des soins de santé.

Figure 4 – Organes du service des soins de santé de l'INAMI



Source: http://www.inami.fgov.be/fr/inami/organes/Pages/soins-sante-organes.aspx#.WQs-d03oupo

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