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Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

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

SUPPLEMENT

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HEALTH SERVICES RESEARCH

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SUPPLEMENT

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COLOPHON

Title:	The use of whole genome sequencing in clinical practice: challenges and organisational considerations for Belgium – Legal issues – Supplement
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SUPPLEMENT

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1. INTRODUCTION

This section explores a selection of legal and ethical issues related to WGS. As there is no specific legal framework that provides answers to the various legal issues related to WGS, concepts of the general legal frameworks related to liability, patients' rights, data protection are the starting point. Guidelines and recommendations of various international organisations in the field of genetics provide valuable input for the interpretation of these legal concepts. Yet, as it concerns ethically and culturally sensitive issues, these recommendations require nuanced discussions to ensure that they are adequate for the Belgian settings in which they will be conducted.

2. WHOLE GENOME SEQUENCING AND UNSOLICITED FINDINGS

2.1. Terminology

Whole genome sequencing has enormous potential to identify genetic causes of disease. Yet the nature of the technology means it can also identify additional information about the individual that is unrelated to the original rationale for sequencing. Although these are termed *incidental findings* by a number of organisations and professional bodies,[1-5] they have also been referred to as unsolicited, iatrogenic, serendipitous, additional or secondary findings.[2, 6-11] Not only has this inconsistent terminology caused considerable confusion, the term "incidental" has received criticism as it may lead patients to perceive these types of variants as trivial.[10] In addition, the term incidental implies that the finding is unexpected, whereas in whole genome sequencing, it can be anticipated that identification of these variants might occur.[6] Therefore, the term ***unsolicited findings***, which has been adopted by the European Society of Human Genetics (ESHG),[11] is more appropriate to describe variants in disease-causing genes that are unrelated to the original rationale for testing that are identified inadvertently. This is distinct from *secondary findings*, the term now used by the American College of Medical Genetics and Genomics (ACMG), to describe variants in disease-causing genes that are unrelated to the original rationale for testing but that are actively sought during the analysis.[12]

2.2. What are the obligations of the laboratory **to search** for findings that are unrelated to the clinical question?

In 2013, the ACMG issued a set of recommendations that suggested that a list of variants in 56 genes, which predispose individuals to 24 conditions, should always be reported by laboratories when sequencing was being undertaken.[2] This guideline recommended laboratories to **actively search for these 'secondary findings' that are unrelated to the primary (i.e. diagnostic) purpose to undergo this test.** This is recommended regardless of a) the condition for which sequencing was requested, and b) the age of the patient.[2] The rationale behind this recommendation was that the potential benefit from identifying that the patient was at risk of developing one of these 24 conditions (primarily adult onset hereditary cancers and cardiac conditions) prior to the onset of symptoms outweighed the potential harms. This was felt to be the case even in children, as the benefit would confer to their parents, one of whom would also be likely to carry the variant.

In contrast, a number of other guidelines and policy documents have presented alternative views about whether it is appropriate to actively search for secondary findings. The Canadian College of Medical Geneticists (CCMG) has explicitly stated that they "[…] do not endorse the intentional clinical analysis of disease genes unrelated to the primary indication, even if the results might be medically actionable".[1] This is because their working group does not feel that the clinical utility of the majority of these variants has been clearly established and that the potential for risk of disclosure is under explored. Similarly, the PHG Foundation has stated that, although this kind of *opportunistic screening* could have health benefits both for the individual and the population, at this point in time they **do not recommend interrogating genomic data "[…] for preventive purposes in the absence of a clinical indication**".[4] Similarly, in the paediatric context, while the American Society for Human Genetics (ASHG) has recognized the potential future benefit of searching for these secondary findings in the future, they too have expressed a need for more data and experience before this is implemented.[7]

However, their overall determination is that "[…] it be considered ethically acceptable, but not required, to search for secondary findings that are not relevant to the clinical or research indication for sequencing".[7] This contrasts with the recommendations by the CCMG and the PHG Foundation which more explicitly reject identification of secondary findings at this point in time.[1, 4]

Although other policies do not address the obligation to search for secondary findings explicitly, **there is general agreement that it is preferable not to identify, let alone actively search for, variants related to diseases unrelated to the clinical question.**[8, 9, 11] In line with this, a number of professional bodies have recommended that laboratories adopt a targeted approach to whole genome sequencing, using **selective filtering**, in order to limit the possibility of identifying unsolicited findings.[1, 4, 8, 9, 11] The European Society of Human Genetics has for example recommended 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)".[11] Similarly, in a document from EuroGentest and the European Society of Human Genetics, it was recommended that the "analysis pipeline of diagnostic laboratories should focus on the gene panel under investigation in order to avoid the chance of secondary findings, and be validated accordingly".[9]

It is important to note that from a very practical standpoint, the genetic centres can currently not offer a systematic search for incidental findings. Since the identification and evaluation of incidental findings would approximately require an extra 5 to 10% of time for the analysis of the NGS results, this would lead to 5 to 10% less clinical reports, unless the manpower would be extended. In addition, the interpretation of incidental findings requires broad skills. For example, the interpretation of variants with a role in cancer cannot easily be dealt with by laboratory geneticists with a primary expertise in cardio-, immune- or neurogenetics. Hence, the search for incidental findings can only be offered by centres that offer a large spectrum of genetic analyses.

2.3. What are the obligations of the laboratory **to return** clinically useful findings that are unrelated to the clinical question?

As mentioned, a number of professional bodies have recommended that laboratories adopt a targeted approach to whole genome sequencing, using selective filtering, in order to limit the possibility of identifying unsolicited findings.[1, 4, 8, 9, 11] However, there is acknowledgement that this is not always desirable in order to identify the genetic cause of the condition in the patient and that laboratories may want to adopt a broader analysis strategy.[1, 11, 13] In addition, even if the analysis is restricted, the possibility of identifying unsolicited findings, both medical and non-medical (such as non-paternity) in nature, cannot be eliminated entirely.[4, 8] A number of policies have called for more guidance and research in this area.[4, 14]

Guidelines and policy documents issued by professional bodies differ considerably with regard to their recommendations for the reporting of unsolicited findings. Although not always explicitly stated, the recommendations generally indicate that there **is no obligation for laboratories to report unsolicited findings**. However, most guidelines clearly point out that healthcare professionals might have responsibilities to disclose certain findings. For example, the European Society of Human Genetics states that health professionals **should disclose unsolicited findings to patients if they are "[…] indicative of serious health problems** (either in the person tested or his or her close relatives) that allow for treatment or prevention".[11] Likewise, the Danish Council of Ethics has stated "[…] doctors must actively inform patients and subjects about all findings of essential relevance to health".[13] Finally, the policy issued by the Public Health Genomics Foundation in 2014 suggested health professionals have an obligation to disclose information about unsolicited findings to patients if they are "[…] unavoidably discovered and have high predictive value".[4] These recommendations for health professionals to disclose unsolicited findings to patients imply that the laboratories have reported these findings to the clinicians.

In Canada, the CCMG has recommended that competent adult patients be offered the choice of whether or not they want to receive information regarding unsolicited findings prior to the test.[1] In contrast, the ACMG recommended that unsolicited findings **should not be reported** if they are not identified as part of their list of 59 genes (previously 56 genes) for which they recommend everyone receiving WGS for diagnostic purposes should be screened.[2, 12] Other policy documents leave the decision of whether to report unsolicited findings to the discretion of the individual laboratory.[3, 9]

Regardless of their overall recommendations for the reporting of unsolicited findings, a number of policies stress the importance of developing a clear protocol outlining their reporting policy.[2, 9, 11]

From a **legal point of view**, it can be argued that as the processing of unsolicited findings is legally to be considered as processing of personal data patients have the right to information and a right to access to the unsolicited findings (art. 12 European Directive 95/45/EC on the protection of personal data and art. 9 of the Belgian Data Protection Act). Patients should thus be made aware (by the data controller – see 0) of the fact that (possibly) unsolicited findings will become available and that they have a right to access. It is up to the patient to decide whether he/she wants to know the unsolicited findings or which selection of findings he/she wants to know. Laboratories should thus inform the patient, prior to testing, of the possibility that unsolicited findings are found and offer the patient options to know or not (a selection) of this information. At any time during the process the patient can decide to change the chosen options.

Another important question relates to the fact whether laboratory staff can be considered as healthcare professionals within the meaning of the Act of 10 May 2015 related to the exercising of health professions.[a] If so, patients have a right to health status information according to the Patient's Rights Act (art. 7), to be provided by the healthcare professional. If healthcare professionals omit to provide information on the patient's health status, they could be held liable for violating the patient's right to information, if the patient can prove that he/she would have made other decisions if he/she was appropriately informed. At the time of drafting the report, it is not clear whether laboratory staff can be considered as a paramedic in the sense of the Act of 10 May 2015, as the list of paramedics is still to be defined. Regardless the qualification of laboratory staff as healthcare professionals, the responsibilities of the involved professionals in WGS (including professionals in bio-informatics and lab geneticists), will be assessed based on the professional standards of care assigned to each professional community. If they omit to report clinically validated unsolicited findings – whereas the laboratory's policy is to report such data – they could be held liable. The liability questions underline the importance of a well-defined protocol outlining the reporting policy, as the obligations of the staff are related to it.

Importantly, several **policies** suggest that the obligations with regards to reporting in **children** differ compared to adults, recommending that if an unsolicited findings is identified in a child which is medically actionable in childhood, these should be reported and returned to parents so the children can receive appropriate care.[1, 8, 11, 15, 16] It has been suggested that parents should not be able to opt-out of this kind of information.[1] Also in Belgium, this can be supported by the idea of the Patient's Rights Act that indicates that physicians can overrule decisions of parents or legal guardians in case they are making decisions that go against the best interest of a minor.[b]

2.4. What are the rights of the patient "**not to know**" findings that are clinically important, but that are unrelated to the clinical question?

The 'right not to know' is addressed in both the 1997 Universal Declaration on the Human Genome and Human Rights of UNESCO and in the Council of Europe Convention on Human Rights and Biomedicine (Oviedo Convention[c]).[17, 18] Also the Belgian Patient Rights Legislation (article 7) foresees a right not to know. Applied to the context of whole genome sequencing for diagnostic purposes, these documents support the patient's right not to receive unsolicited findings if they do not wish to know this information.

Various documents have clearly endorsed that the patient's right not to know must be respected and stressed that, where ever possible, their wishes should be clarified prior to testing.[13] In this line, the Danish Council of Ethics indicated that, as patients have a right to access their medical records, these kinds of unsolicited findings should not be logged in the electronic records of the patient and, ideally, not be generated in the first place.[13] Likewise, the CCMG is supportive of the right not to know in that they suggest that competent adult patients be given the option regarding whether they wish to receive unsolicited findings prior to testing.[1] Although the ACMG initially suggested that screening for secondary findings should be mandatory for all patients receiving genomic sequencing, they have since recognised the patient's right to opt-out from receiving these findings.[12]

Nevertheless, the European Society of Human Genetics has recognised that the **right not to know as described in the Oviedo Convention is not absolute** (the right to provision of information supersedes this) in the following statement "Patients' claims to a right not to know do not automatically over-ride professional responsibilities when the patient's own health or that of his or her close relatives are at stake".[11] The Danish Council

[a] Act of 10 May 2015 related to the exercising of health professions, B.S./M.B. 18 June 2015.

[b] Art. 15 § 2 Patients Rights' Act of 22 August 2002, B.S./M.B. 26 September 2002.

[c] Not legally binding in Belgium.

of Ethics has also suggested that the duty to inform may, in some cases, **override the right not to know, even if the patient has previously declined receiving this information.**[13] However, they clarify that "Such a duty to furnish information presupposes that the **information is of concrete and self-evident life-saving importance, and that the examinee has not expressly said no to receiving information about that specific finding**".[13]

The Belgian Patient's rights act also recognises the treating physician's right to overrule the patient's right not to know if there is a serious danger for the patient's or a third party's health. To do so, the treating physician needs to discuss this option with another healthcare professional and with the patient's confidant (art. 7 § 3).

In addition, the idea that **one's personal information is also familial information** is more widely acknowledged. The art. 29 Data Protection Working party states in this regard: "To the extent that genetic data has a family dimension, it can be argued that it is "shared" information, with family members having a right to information that may have implications for their own health and future life. The precise legal consequences of this argument are not clear yet. At least two scenarios can be imagined. One is that other family members could also be considered as "data subjects" with all the rights that follow from this. Another option is that other family members would have a right of information of a different character, based on the fact that their personal interests may be directly affected. However, in both scenarios further options and conditions would have to be considered to accommodate the various conflicts that are likely to arise between the different claims of family members, either to have access to information or to keep it confidential."[d] The Danish policy states: "[…] it is not merely oneself but partly also one's closest family that is being tested".[13] In the medical context, for example the Australian Medical Association (AMA) Code of Ethics requires patient confidentiality to be protected yet makes some exception "where there is a serious risk to the patient or another person".[19] In relation to unsolicited findings, one could argue that identification of a BRCA variant predisposing a patient, and therefore a family member to hereditary breast and ovarian cancer, might constitute such a risk. The Danish Council of Ethics have also proposed that in situations such as this "[…] regard for the relatives weighs more heavily than regard for the duty of confidentiality, and that information can therefore be disclosed without consent".[13] According to Belgian legislation[e] and doctrine[f] related to the duty of confidentiality the same reasoning could be followed. It is up to the physician to judge on a case by case basis whether the (potential) damage for the relative outweighs the respect of the duty of confidentiality. Physicians confronted to this situation first need to try to convince the patient to consent to the informing of the family member. If the patient refuses to consent, the physician can communicate the risks to family members without the consent of the patient.

Family members may also wish to assert a right not to know about the results of a test taken by a family member to determine the presence or absence of a serious genetic disorder. The Comité National Informatique et Liberté (CNIL) came to the conclusion that it was not appropriate to systematically inform the family of patients who carry a gene of an incurable disease and to generate in this way permanent anxiety without a possible direct benefit

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d Art 29 Data Protection Working Party, Working Document on Genetic Data, p. 9; http://ec.europa.eu/justice/policies/privacy/docs/wpdocs/2004/wp91_en.pdf

e Article 458 Penal Code.

f See doctrine related to the "noodtoestand": A. DE NAUW, "La consécration jurisprudentielle de l'état de nécessité", (noot onder Cass. 13 mei 1987), RCJB 1989, 593-630; P.E. TROUSSE, Les Novelles. Droit pénal, Brussel, Larcier, 1956, 418-424; C.J. VANHOUDT en W. CALEWAERT, Belgisch strafrecht, Gent, Story-Scientia, 1976, 434- 439; L. DUPONT en R. VERSTRAETEN, Handboek Belgisch Strafrecht, Leuven, Acco, 1989-90, 227- 233. The "noodtoestand" is defined as an exception situation justifying the violation of penal law (in casu art. 458 Penal Code = professional secrecy) because it is the only way to protect higher values and legal interests (in casu: the possible prevention of breast cancer in a family member).

for the members of the family, as no useful treatment would be available to them in the near future.[g]

In contrast to the general consensus to respect the competent adult's right not to know genetic information about themselves, a number of guidelines suggest that **there are situations where a parent should not have the right to refuse to receive unsolicited findings about their children.**[1, 7] The CCMG diagnostic policy is quite clear in its recommendations that variants are identified which indicate the child is at risk of a condition which is **both highly penetrant and medically actionable**, then this should be disclosed to the parents, regardless of whether they have given consent to receive this information.[1] Also the ASHG indicates that parents should generally be offered the choice to know (or not know) unsolicited findings and have the right to decline receiving secondary findings identified in their children, they stipulate that "[…] when there is strong evidence that a secondary finding has urgent and serious implications for a child's health or welfare, and effective action can be taken to mitigate that threat, ASHG recommends that the clinician communicate those findings to parents or guardians regardless of the general preferences stated by the parents regarding secondary findings".[7] As stated higher in the text, also according to the Belgian Patient's Rights Act, physicians can overrule decisions of parents or legal guardians in case they are making decisions that go against the best interest of a minor.[h]

3. DATA STORAGE AND SHARING

3.1. Different types of data

In terms of storage of raw data, it is important to clarify first, what **types of data** resulting from WGS could be stored by the laboratories. It has been noted that WGS generates large numbers of image files that are processed in real time to produce base call files (base calling is the process of assigning bases to chromatogram peaks). According to Evans et al., "Both image and base call files are kept only transiently to conserve data storage space.

Data analysis then produces three file types in sequential order:

(i) FASTQ, which contains raw sequences with corresponding quality scores;
(ii) BAM (binary alignment/map), generated by mapping of raw sequences to the human genome reference and
(iii) VCF (variant call format) file, which contains a list of sequence variants, sorted by genomic position, at which the individual differs from the reference genome.

Many laboratories produce an annotated VCF with numerous details (such as variant type, function, frequency in the population) to aid in the classification and interpretation of each variant. This information, in part, is used to generate the final report for clinicians and patients".[20]

[g] Art 29 Data Protection Working Party, Working Document on Genetic Data, p. 9; http://ec.europa.eu/justice/policies/privacy/docs/wpdocs/2004/wp91_en.pdf

[h] Art. 15 § 2 Patients Rights' Act of 22 August 2002, B.S./M.B. 26 September 2002.

3.2. What are the storage obligations for raw data and variant information?

In Europe, there is no legislation specifying which genetic data should be kept and for how long. Yet, general rules can be found in the EU regulatory framework on data protection which is currently primarily based on European Directive 95/45/EC on the protection of personal data ("PDPD").[21] All EU member states currently have a data protection regime in place based on the PDPD with a view of its implementation into national law. In Belgium the Directive has been transposed into the data protection Act of 8 December 1992.[i] Furthermore the general obligations (consent; access rights; etc.) related to data protection are (partly) implemented in several other legislative acts related to specific contexts (e.g. clinical trials (Article 39 of the Act of 7 May 2017[j]) / biobanks (Article 22 of the Act of 19 December 2008[k])). According to the PDPD, several data protection requirements must be met before personal data can be processed. As of 25 May 2018 the EU regulatory framework on data protection will be governed by the General Data Protection Regulation ("GDPR").[l] The GDPR will have direct effect in the EU member states.

Pursuant to article 2(b) PDPD personal data (Raw data, list of variants, information on the patient's condition and behaviour, provided they contain information that *identifies* the patient or that can be reasonably used to identify the patient) is "processed" if it is the subject of any (set of) operations whether or not by automatic means (e.g. collection, recording, organization, storage, adaptation, alteration, retrieval, consultation, use, disclosure by transmission, dissemination or otherwise making available, alignment or combination, blocking, erasure or destruction). As such the rules of the PDPD apply to the storage of raw data and lists of variants identifying the patient.

As a general rule personal data can only be collected for a specified, explicit and legitimate purpose and cannot be processed any further in a way that is incompatible with those purposes. No more data should be collected or kept if it is not necessary for these purposes.[m] In that scope, it is of an utmost importance for laboratories to clarify the purpose of the processing and the necessity to store data for this purpose. A clear protocol on the policy related to data storage is therefore primordial. **It is likely that the quality of sequencing will continuously improve in the future and that resequencing will thus not only be economically (cost of resequencing<cost of storage) but also clinically more beneficial. Moreover, resequencing does not imply that clinical data (of the first sequencing) will be lost. Consequently, there are strong arguments to plead for storage of variant information but not the raw data.**

The European Society of Human Genetics also pointed to the potential informational risks that could result from long-term storage of raw genomic data within patient medical records and the risks of access by third parties (such as insurance companies and employers).[11] A **report by Public Health Genomics Foundation in the UK** goes in the same direction and summarizes the main points: "*If the practical issues can be overcome and the ethical issues managed, storing individual genomic assay information has the obvious advantage that the data would be instantly available if needed in the future (e.g. for pharmacogenetic analysis, or additional diagnoses) and that different analyses or tests could be offered to an individual based on their age, further clinical circumstances and/or personal preferences. It could be argued that not storing individual genomic data and re-analysing it in this way would present an enormous missed*

i Act of 8 December 1992 on the protection of privacy in relation to the processing of personal data, B.S./M.B. 18 March 1993; Act of 7 May 2017 on clinical trials with pharmaceuticals for human use, B.S./M.B. 22 May 2017.

j Act of 7 May 2017 on clinical trials with pharmaceuticals for human use, B.S./M.B. 22 May 2017.

k Act of 19 December 2008 on the reception and use of human tissue for medical or scientific purposes, B.S./M.B. 30 December 2008.

l Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC, *O.J.L.* 4-5-2016, L119/1.

m Art. 6(b)(c) and (e) PDPD.

opportunity to improve both individual and population health. ***However, storing entire or minimal genome sequences for individual patients would require the use of electronic health records (at least in part), which has major practical and ethical implications. In addition, future technological developments may result in a substantial improvement in the quality of sequencing and genome assembly, and thus make re-sequencing an individual (as required) a better option***."

In **Belgium**, patient rights legislation provides to patients the right of a cautiously updated and secured medical file (art. 9§1). This was already foreseen in the Hospital Law (Ziekenhuiswet art. 20 and art. 25). The main purpose of a medical file is the improvement of the continuity and the quality of the care for the patient. However, the patient rights legislation doesn't specify exactly what type of information should be kept in a medical file. A Royal Decree specified a few miminum requirements that should be fulfilled by hospitals with regard to medical files.[n] Art. 2 §1.3° specifies that the results of clinical and biological investigations should be kept ("de uitslagen van de klinische, radiologische, biologische, functionele en histo-pathologische onderzoeken"). Based on this article and on the arguments supporting that resequencing is a clinically and economically better option, **one could conclude that it might be sufficient as a minimum requirement to keep a report summarizing the main results of the genetic investigation (such as variant information i.e. VCF file) and not the raw data.** The above mentioned Royal Decree stipulates in article 1§3 that the medical file should be kept for 30 years.

In the United States, the **American College of Medical Genetics and Genomics** clinical laboratory standards for next-generation sequencing assert: "***Laboratories should make explicit in their policies which file types and what length of time each type will be retained, and the data retention policy must be in accordance with local, state, and federal requirements.*** *The Clinical Laboratory Improvement regulations (CLIA)[o] (section 493.1105) require storage of analytic systems records and test reports for at least 2 years. For more specific suggestions for NGS technologies,* we *recommend that the laboratory* ***consider a minimum of 2-year storage of a file type that would allow regeneration of the primary results as well as reanalysis with improved analytic pipelines*** *(e.g., bam or fastq files with all reads retained). In addition, laboratories should consider* ***retention of the VCF****, along with the final clinical test report interpreting the subset of clinically relevant variants, for as long as possible, given the likelihood of a future request for reinterpretation of variant significance*".[22] In practice, some laboratories provide the patients with options to decide if they want a complete report based on their WGS to be sent to their electronic medical reports (e.g., See: Laboratory of Personalized Medicine at Columbia University Consent form http://pathology.columbia.edu/diagnostic/PGM/pdf/CWESInformedConsent_12-10-2014.pdf).

[n] KB van 3 mei 1999 houdende bepaling van de algemene minimumvoorwaarden waaraan het medische dossier bedoeld in artikel 15 van de wet op ziekenhuizen, gecoördineerd op 7 augustus 1987, moet voldoen.

[o] In general terms, the CLIA regulations establish quality standards for laboratory testing performed on specimens from humans, such as blood, body fluid and tissue, for the purpose of diagnosis, prevention, or treatment of disease, or assessment of health. https://wwwn.cdc.gov/CLIA/Regulatory/default.aspx.

3.3. Legal implications for storage/sequencing by third party? (i.e. not health care service)

Storage and sequencing are acts that can be qualified as data processing as defined in the PDPD. To protect the personal data during processing, the PDPD imposes several **requirements**. The fulfilment of these requirements is mainly the responsibility of the **data controller**. Therefore it is primordial to define who can be considered as a data controller. Pursuant to article 2(d) PDPD the controller is defined as:

> "*the natural or legal person, public authority, agency or any other body which alone or jointly with others determines the purposes and means of the processing of personal data; (…)*"

According to the art. 29 data protection working party, when determining whether a party is "controller" or mere "processor", the focus should be on determining the purposes, rather than determining the means.[p] The capacity to determine the purposes and means of the personal data processing must always be evaluated on a case by case basis, taking into account elements such as the level of factual influence and control by a party, contractual relations and the visibility towards the data subject. It must be kept in mind that there can be more than one controller.[q]

As a general rule it can be assumed that the **hospital who gathers the patient data (possibly through the physician/lab),** must be considered the **controller**. This follows from the fact that the hospital decides – with the consent of the patient - which patient data is processed for which purpose, and how the data are possibly used. Furthermore, the hospital is in direct contact with the data subject (*i.e.* the patient). Even if the same could be said about each individual health care professional involved, preference should nevertheless be given to qualifying as controller the institution as such rather than a specific person within the institution.[r]

In case of a **third party (e.g. a private company)** to whom the sequencing or the storage has been subcontracted (= outsourcing by the hospital or physician), the patient data will be processed outside the hospital for analysis. The question then arises whether this outsourced manufacturer acts as a second controller or only as a "*processor*" who merely processes the personal data on the hospital's behalf in the meaning of article 2(e) PDPD. There are enough arguments to say that the **private company to whom the storage/sequencing is outsourced** generally will qualify as a mere **processor**. The private company would not process the patient data were it not for his engagement to the hospital.[s] In doing so the private company follows the instructions of the hospital's healthcare professional/lab in performing the sequencing. Even if private companies have their own reporting ways, this does not necessarily prevent a qualification as a mere processor. Another argument supporting the qualification as a processor is that the private company does not directly come into contact with the patient. Even if the outsourced private company has quite some input on the means of the data processing, it is nevertheless advisable to attach more weight to determining the purposes of the data processing on which the manufacturer does not have any control.[t] It is up to the parties involved to determine who will be considered as a processor or controller depending on the interpretation of who has the capacity to determine the purposes and means of the personal data processing.

According to the PDPD, the controller can legitimately process personal health data either on the basis of the patient's informed consent or on one of several other legitimate bases as specifically defined in the PDPD. One of the legitimate bases defined in the PDPD for which the controller does not

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p Opinion 1/2010 of the article 29 Data Protection Working Party on the concepts of "controller" and "processor", http://ec.europa.eu/justice/policies/privacy/docs/wpdocs/2010/wp169_en.pdf p.13-14.

q Opinion 1/2010 of the article 29 Data Protection Working Party on the concepts of "controller" and "processor", p.32-33.

r Opinion 1/2010 of the article 29 Data Protection Working Party on the concepts of "controller" and "processor", p.32.

s Compare: V. HORDERN, "Data Protection Compliance in the Age of Digital Health", *EJHL* 2016, (248) 254.

t Opinion 1/2010 of the article 29 Data Protection Working Party on the concepts of "controller" and "processor", p. 13.

need the patient's consent is the processing of health related data "required for the purposes of preventive medicine, medical diagnosis, the provision of care or treatment or the management of healthcare services, and where those data are processed by a health professional subject under national law or rules established by national competent bodies to the obligation of professional secrecy or by another person also subject to an equivalent obligation of secrecy".[u] Although his provision could act as a legitimate basis for the storage and sequencing of the patient's health data, this does not alter the fact that the patient needs to consent to the medical intervention (the sequencing itself) which obviously also includes the processing. Furthermore, the art. 29 Data protection working party stated in a working document on genetic data that: "***the data subject should be duly informed about the necessity of carrying out such tests and give its explicit consent for that purpose and for the processing of its genetic data (Art 8. 2 (a)). Informed consent is particularly crucial in the field of genetic testing as the information that individuals will receive about themselves could have serious implications. Free consent should mean that an individual is not coerced into undergoing genetic testing and without it being his express will to do so."***[v]

The controller has the duty to **provide certain information** to the patient with regard to the data processing, such as the identity of the controller (or his representative), the purposes of the processing, the (categories of) data recipients (e.g. a third party processor) and the existence of the patient's rights of access and of rectification to/of his personal data,...[w]

It is not explicitly forbidden to transfer raw data to a third party processor, as long as the general principles and obligations defined in the PDPD are respected. This implies a.o. that no more data than those necessary for the initial purposes of data processing can be transferred to the third party.

In case of **outsourcing** of sequencing by the hospital or physician to a third party data processor, the processing of the health related personal data by the data processor must always be governed by a **written contract** with the hospital-controller.[x] This contract must *at least* stipulate that:

- the processor shall act only **on instructions from the controller**. As a general rule neither the processor (including the person's acting under his authority) nor the persons acting under the autority of the controller can process personal data except on instructions from the controller.[y]
- the processor will implement appropriate **technical and organizational measures** to protect data against accidental or unlawful destruction or accidental loss, alteration unautorized disclosure or access, in particular for transmission over a network. The hospital can only choose a data processor who provides sufficient guarantees in respect of the technical securtiy measures and organizational measures and must ensure compliance with those measures.[z] Evidently, the controller must implement the appropriate technical and organizational measures for his own data processing as well.[aa]

Member states must furthermore provide for **liability of the controller** to compensate any damage resulting from an unlawful processing operation or from an act incompatible with the national provisions adopted pursuant the PDPD. The controller may however be (wholly or partly) exempt from this liability if he proves that he is not responsible for the event giving rise to the damage.[bb] Moreover, member states must lay down **penalties** in case of infringement of the provisions adopted pursuant to the PDPD.[cc]

u Art. 8, para. 3 PDPD.
v Article 29 Data Protection Working Party, Working Document on Genetic Data, p. 7
w Art. 10 and art. 11 PDPD.
x Art. 17, para. 3 and 4 PDPD.
y Art. 16 PDPD.
z Art. 17, para. 2 PDPD.
aa Art. 17, para. 1 PDPD.
bb Art. 23 PDPD.
cc Art. 24 PDPD.

The controller must also **notify the national public supervisory authority** according to the provisions of national law before carrying out any (wholly or partly) automatic (set of) processing operations intended to serve a single purpose or several related purposes.[dd]

The PDPD requirements apply within the EU. If at any point the patient data is to be **transferred to a country outside the EU** (*e.g. sequencing* facilities outside the EU), then this third country must first ensure an adequate level of data protection.[ee] There are different ways to guarantee an adequate data protection under the PDPD, *e.g.* through binding corporate rules,[ff] through model contractual clauses recognized by the European Commission,[gg] under the framework of the EU-US Privacy Shield or following a binding decision of the European Commission that recognizes the third country as a country that provides an adequate level of data protection.[hh] The PDPD also allows the transfer without the assurance of adequate data protection under certain legally defined conditions, such as the patient's unambiguous consent to such transfer or the fact that the transfer is necessary for either the performance of a contract between the patient and the controller or the protection of the patient's vital interests.[ii]

When the new GDPR comes into force the current processing requirements for (health related) personal data will be strengthened and several **new requirements will be added**. In general this will lead to a better protection of the data subject (*i.e.* the patient), but also to a more expensive and administrative burdensome data protection regime for the hospital-controllers and even the outsourced third party-processors. The most important changes with regard to data processing of genetic data will be outlined below. In contrast with the PDPD, the GDPR provides a definition of genetic data. Genetic data means personal data relating to the inherited or acquired genetic characteristics of a natural person which give unique information about the physiology or the health of that natural person and which result, in particular, from an analysis of a biological sample from the natural person in question (art. 4, 13°). As under the PDPD, the processing of health data – and thus the transfer to a third party for sequencing or storage- is in principle possible without consent of the patient when those data are processed by or under the responsibility of a professional subject to the obligation of professional secrecy and the processing is necessary for medical diagnosis (art. 9 (2, h)) However, Member States may maintain or introduce further conditions, including limitations, with regard to the processing of genetic data. **(art. 9 (4)). Furthermore, as mentioned above, the art. 29 Data Protection Working Party explicitly states that consent is needed for the test and the processing of genetic data. Although this guidance relates to the interpretation of the PDPD, there is no reason to assume that this would not apply for the GDPR.**

Under the GDPR the hospital-controller's duty to provide certain information to the patient is more elaborate as it entails new types of information to be provided,[jj] such as contact data of the controller's data protection officer,[kk] the legal basis of the processing (*e.g.* processing is necessary for medical diagnosis), the intention to transfer data to a third country or international organization, the (criteria to determine) ***the period for which the data is stored,*** the data subject's rights (including his or her right of portability of his or her data allowing him or her to transmit the data to another controller (*e.g.* another hospital), his or her right to lodge a complaint with a supervisory authority, his or her right to withdraw consent (without however affecting the lawfulness of the consent based processing before the withdrawal),

dd Art. 18 PDPD.

ee Art. 25 PDPD.

ff These are considered "*adequate safeguards*" within the meaning of art. 26, para. 2 PDPD.

gg Art. 26, para. 4 PDPD.

hh Art. 25, para. 6 PDPD. The European Commission already recognized several countries providing adequate data protection. See: http://ec.europa.eu/justice/data-protection/international-transfers/adequacy/index_en.htm.

ii Art. 26 PDPD.

jj Art. 13 and 14 GDPR.

kk A data protection officer is basically a person who is responsible for advising on the implementation of the GDPR requirements and for supervising the implementation thereof (*cf.* art. 39 GDPR).

information on whether the data is required or not to enter in to a contract (*e.g.* a treatment contract), as well as the existence of profiling.[ll]

In case of **outsourcing**, the hospital-controller still has to make sure that its relation with the third party-data processor is governed by a **written contract**. Under the GDPR, this contract must set out quite some additional aspects when compared to the PDPD,[mm] including the **subject-matter and duration of the processing, an obligation of confidentiality for the processor's personnel, a more specific obligation to take the necessary safety measures,**[nn] **conditions for engaging another processor,**[oo] **assistance to the controller for complying with the required technical and organizational safety measures** and deletion of the data held by the processor after the end of its services. The GDPR provides that the following measures may be appropriate:

- encryption;
- pseudonymisation;
- measures which ensure the confidentiality, integrity and resilience of processing systems and services;
- methods which enable the timely access, restoration or availability to personal data in the event of an incident; and
- regular tests and evaluation to ensure that the measures implemented meet their desired objective of maintaining security of data processing.

In case there **are two or more joint controllers**, they should determine their respective responsibilities for compliance with the obligations under the GDPR in an arrangement between them, although the data subject may exercise his or her rights against each of the controllers irrespective of this arrangement.[pp]

The hospital-controller will also have perform to perform a **data protection impact assessment** with regard to the processing of health related data and biometric data of patients prior to this processing.[qq]

Under the GDPR the **liability** for compensation of any damage resulting from an infringement of the GDPR is further elaborated. The focus not only lies on the liability of the controller but also on the (less extensive) **liability of the processor**. The data subject can however address both the controller and the processor for compensation of the entire damage if they are both liable with regard to the same processing.[rr] Moreover, the GDPR provides that the national supervisory authorities can impose significant **administrative fines** in case of infringement of the GDPR. Some of these fines can constitute a percentage of the undertaking's worldwide annual turnover.[ss] It is still left up to the EU member states to determine the **penalties** applicable to the infringement of the GDPR.[tt]

Unlike the PDPD, the GDPR no longer requires the controller to notify the supervisory authority for carrying out automatic operations. Instead, the hospital-controller must **maintain a record of processing activities** which contains information such as the controller's contact data, the purposes of the processing and the categories of data, data subjects and recipients. The outsourced manufacturer-processor must maintain a similar record of all categories of processing activities.[uu]

The requirements for **transfer of personal data to third countries or even international organisations** is also further elaborated under the GDPR. Such transfer is only allowed under specifically defined conditions such as

ll Pursuant to art. 22, para. 1 GDPR, the patient has to right not to be subject to a decision based solely on profiling.
mm Art. 28, para. 3 GDPR.
nn *Cf.* art. 32 GDPR.
oo *Cf.* art. 28, para. 2 GDPR.
pp Art. 26 GDPR.
qq Art. 35, para. 3(b) GDPR.
rr Art. 82 GDPR.
ss Art. 83 GDPR.
tt Art. 84 GDPR.
uu Art. 30 GDPR.

an adequacy decision of the European Commission, appropriate safeguards or explicit informed consent of the data subject.[vv]

3.4. Data sharing: data exchange between genetic centres (at least variants, possibly raw data)

In order to make the promises of genomic medicine a reality, the optimal use of genomic data generated within research and clinical settings is key. Access to a large volume of genomic data plays an important role in identifying areas of the human genome, which contain recurrent variants influencing health risks.

To date, various data sharing policies and guidelines are being issued by international and national institutions, such as the Genomic Data Sharing Policy by the National Institutes of Health (NIH) (2014) and the Governance of data access report by Experts Working Group on Data Access (EWGDA) in the U.K. In addition, recent initiatives seek to develop frameworks for responsible genomic data sharing both in clinical and research settings. The Global alliance for genomics and health issued a framework for responsible sharing of genomic and health related data. The framework argues that the right to data sharing is grounded on the Article 27 of the 1948 Universal Declaration of Human Rights. Article 27 guarantees the rights of every individual in the world "to share in scientific advancement and its benefits" (including to freely engage in responsible scientific inquiry), and at the same time "to the protection of the moral and material interests resulting from any scientific…production of which [a person] is the author."[ww]

In addition to data sharing in the research setting, laboratory and clinical genomic data sharing are recognized as crucial to improving health. **Recommendations issued by EuroGentest and ESHG**, for instance, also state "To be able to manage disease variants, the laboratory has to set up a local variant database for the different diseases for which testing is offered on a clinical basis".[9] **A recent position statement issued by the American College of Medical Genetics and Genomics in January 2017, goes a step further and states**: "Responsible sharing of genomic variant and phenotype data will provide the robust information necessary to improve clinical care and empower device and drug manufacturers that are developing tests and treatments for patients".[23]

In contrast to genomic research data sharing, the sharing of de-identified clinical genetic data has been less common to date, due to concerns related to informed consent, the commercial interests of certain healthcare providers, and the lack of mechanism for such data sharing. In order to facilitate access to and communication about the relationships asserted between human variation and observed health status, public databases such as Clinvar are recently established. Submission of variant data and the interpretation of results by clinicians and laboratories through databases such as Clinvar are encouraged in order to identify consensus or conflict in the submitted interpretation and calculate the clinical significance of the aggregated records.

Sharing research and clinical genomic data should of course be undertaken with caution. Genomic data contains sensitive health and non-health related personal information about individuals and their family members. The availability of linkable reference databases (such as data in health care, administrative, criminal and disaster-response databases) intensifies the concerns regarding cross-referencing data in different databases, potential re-identification, and privacy breaches. Therefore, protecting the right to privacy of the individuals is key. The privacy rights are recognized at the international and European level in various binding and non-binding legal documents. With respect to privacy in the context of genetic data, Article 7 of the UNESCO Universal Declaration on the Human Genome and Human Rights from 1997 states that 'genetic data associated with an identifiable person and stored or processed for the purposes of research or any other

[vv] Art. 44 to 49 GDPR.

[ww] Many other international conventions and national laws, regulations, codes and policies also guide responsible data sharing behaviour. For the full list of such documents please: https://genomicsandhealth.org/files/public/Framework%20for%20Responsible%20Sharing%20of%20Genomic%20and%20Health-Related%20Data%20-%20Version%2010%20September%202014.pdf

purpose must be held confidential in the conditions set by law.' The 2003 International Declaration on Human Genetic Data also underlines that 'states should endeavour to protect the privacy of individuals and the confidentiality of human genetic data linked to an identifiable person, family, or where appropriate, group.

At the European level, the privacy of individuals and the protection of personal data are addressed under Article 8 of the Charter of Fundamental Rights of the European Union as it reads 'Everyone has the right to the protection of personal data concerning him or her (...).' The Convention also articulates the respect for private life in relation to health information in Article 10. As mentioned above, in Europe, there are legal instruments that coordinate privacy and data protection in the context of personal data processing, including genetic data. Of particular interest to data sharing is the elucidation for the first time of the term "pseudonymization" in the new GDPR. The Regulation asserts that pseudonimized data (key-coded data) are considered identifiable and will fall within the scope of the personal data. Therefore, processing key-coded genomic data should be pursuant to the conditions set at the Article 6.

In addition, GDPR allows further processing of data (i.e. the processing of personal data for purposes other than those for which the personal data were initially collected), only where the processing is compatible with the purposes for which the personal data were initially collected. Recital 50 adds, "further processing for archiving purposes in the public interest, scientific or historical research purposes or statistical purposes should be considered to be compatible lawful processing operations". Arguably, the sharing of data for the purpose of scientific research could be allowed under the provisions of further processing of GDPR, when all other necessary requirements related to lawful processing of data are met.

In addition, the GDPR recognizes genomic data as special category/sensitive data (Article 9), which are principally banned from being processed. However, under certain circumstances, such as when the explicit consent is obtained, or for the purpose of scientific research, it is allowed to process such data, if the requirements set under Article 89 are met. This provision requires that the further processing for scientific research should not permit the identification of the data subject if the research can be performed this way. Otherwise, the processing for scientific research requires technical and organizational measures to ensure respect for the principle of data minimisation. Those measures may include pseudonymisation provided that the research can be fulfilled in that manner.

Tools for the effective data mining and sharing are available, like e.g. NGS Logistics[xx] and have been implemented in several genetic centres (through the Belgian Genomic Medicine Initiative (BeMGI)).

[xx] NGS-Logistics: federated analysis of NGS sequence variants across multiple locations. Ardeshirdavani A, Souche E, Dehaspe L, Van Houdt J, Vermeesch JR, Moreau Y. Genome Med. 2014 Sep 17;6(9):71. doi: 10.1186/s13073-014-0071-9. eCollection 2014. PMID: 25328540.

4. RESPONSIBILITIES AND LIABILITY

WGS raises important questions concerning the responsibility and (possible) liability of the core staff members in WGS. Notably, the responsibilities of the involved professionals in WGS (including professionals in bio-informatics and lab geneticists), will be assessed based on the professional standards of care assigned to each professional community. As clinical tests are never 100% reliable, **it is possible that false positive or false negative results are communicated to the patient. As the reporting of false positive or false negative results is inherent to clinical test and not related to the skills of the involved professionals, professionals cannot be held liable. Nevertheless, patients should be duly informed about the possibility of receiving false positive or false negative test results.**

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 variants of unknown significance. It should be noted that in some situations reclassification of particular variants might occur based on new scientific evidence available. This could be from benign or likely benign, to pathogenic or likely pathogenic, in which case the variant becomes the answer for the patient. The reclassification could also be from pathogenic or likely pathogenic to benign or likely benign, in which case the variant is no longer considered to be the cause of the patient's disease.[24]

According to the recommendations issued by EuroGentest and ESHG, the **laboratory is not expected to re-analyze old data systematically and report novel findings, not even when the core disease gene panel changes.**[9] The Canadian College of Medical Geneticists (CCMG) holds a similar view on this issue, and asserts that **request for re-analysis of the sequence data could be initiated by a referring physician based on an established policy.**[1] In this light, it is important that patients are informed that they might be recontacted in the future. Re-analysis on the initiative of the laboratory of the clinician should be possible in the interests of the patient, but it would be impossible to impose clinicians or laboratories a duty to re-analyze sequence data on a routine basis. However, patients could regularly inquire if new scientific insights have developed with regard to their condition. Patient organizations could also play a role, by informing their members when new scientific evidence are available.

In terms of liability issues, an ongoing lawsuit in the U.S., namely Williams v. Quest Diagnostics, Inc., et al. would be of interest to this discussion, in particular in terms of the arguments provided for clarifying the responsibilities of the involved parties.[25] "In this case plaintiff Amy Williams sued Athena Diagnostics and its corporate parent, Quest Diagnostics, alleging that Athena negligently misclassified a genetic variant it identified in testing the DNA of her late son. Ms. Williams claims that the misclassification caused the boy's doctors to prescribe a potentially dangerous course of treatment that ultimately led to his death. Williams also contends that Athena's failure to notify anyone of the reclassification of Christian's DNA variant (after issuing the updated report) was a daily, recurring failure to comply with CLIA regulations, and thus represents a continuous and ongoing injury".[yy] The outcome of the case is still unknown, however, it

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yy The details of the case could be accessed here: Conley, John; Genomics Law Report: https://www.genomicslawreport.com/index.php/2017/01/26/williams-v-athena-motion-to-dismiss-hearing-sc-supreme-court-may-be-asked-to-decide-whether-a-diagnostic-laboratory-qualifies-as-a-healthcare-provider/

"The complaint alleges that Athena was negligent and breached the applicable standard of care by (1) failing to provide a genetic confirmation that Christian had Dravet syndrome and (2) failing to adhere to its own DNA variant classification criteria. The alleged negligent misclassification of Christian's DNA variant originates from the fact that in 2007, Christian's DNA variant had been reported, studied, and known in a patient with Dravet syndrome. Specifically, a genotype-phenotype association between his variant and Dravet syndrome had been established in two clinical publications, Berkovic et al., 2006, and Harkin et al., 2007. Per Athena's DNA variant classification criteria as defined in the June 2007 report, the requirement for deeming a variant to be a "known disease-associated

already raised important discussions about the scope of responsibility of the laboratories in interpreting the data, the legal standards that applies to variant interpretation by the laboratories, and obligations regarding communication of re-classification of variants to the patients.

5. WHOLE GENOME SEQUENCING AND DIRECT-TO-CONSUMER GENETIC TESTING

Over the past few years, several companies have been marketing and offering direct-to-consumer (DTC) genetic testing services through the Internet, often without the involvement of health-care professionals and outside of any effective regulation of such services.

Genetic testing (and consequently direct-to-consumer genetic testing) is covered by a patchwork of regulations, including laws related to anti-discrimination, consumer protection, data protection, research or patient rights. Indeed, various legislations have prohibited the misuse of genetic information by insurers and employers. Consumer protections laws have been elaborated to protect consumers from misleading actions and omissions, as well as from aggressive commercial practices coming from traders (e.g. Directive 2005/29 EC on unfair commercial practices). Data protection regulations affect the way genetic data is being processed. Laws exist that regulate research on biological samples and genetic data.

When it comes to the provision of genetic tests in Europe, some national legislations have been influenced by the Council of Europe Convention on Human Rights and Biomedicine (Oviedo Convention) as well as the Additional Protocol on Genetic Testing for Health Purposes**.** The Oviedo Convention, which aims at protecting human dignity and identity and sets

mutation" was whether it was reported in the literature to be associated with the disease. Thus, the plaintiff alleges, the existence of Berkovic et al., 2006 and Harkin et al., 2007 made Athena's classification of Christian's variant as VUS (i.e., "has not been correlated with clinical presentation and/or pathology in the current literature") demonstrably false. According to the June 2007 report, "the results of this analysis cannot be definitively interpreted due to the absence of published studies correlating these variant(s) with clinical presentation and/or pathology." Christian's June 2007 report was signed off by Sat Dev Batish, chief director of genetics at Athena, and also an author of the Harkin et al., 2007 publication. According to the complaint, Christian's DNA variant was cited as an SCN1A DNA mutation that "disrupts the functioning of an assembled ion channel so as to produce an epilepsy phenotype" in a patent for SCN1A testing. This patent originated from the laboratory that produced the Berkovic et al., 2006 and Harkin et al., 2007 publications—the same laboratory that also licensed use of the patent for SCN1A testing to Athena in 2004. Thus, the information used to gain patent rights of SCN1A testing included a citation of Christian's variant causing an epilepsy phenotype. Finally, the June 2007 report lists a manuscript that was published in 2005 as "pending," suggesting that Athena's integration of the biomedical literature into their DNA variant database was at least two years behind."

out fundamental principles applicable to daily medical practice,[17] restricts (as it will be elaborated below) the use of predictive, carrier and predisposition genetic tests to health purposes or scientific research linked to health purposes and it mandates genetic counseling for these tests. The Additional Protocol on Genetic Testing for Health Purposes touches upon issues of clinical utility, the obligation of individualized medical supervision, genetic counseling and informed consent in the context of genetic testing. However, the Convention doesn't apply to all European countries, and the Additional Protocol has yet to come into force, since, in order for this to happen, at least five Member States should express their consent to be bound by it. Belgium didn't sign or ratify the Convention or its Additional Protocol.

Genetic tests with a medical purpose are considered to be in vitro diagnostic medical devices (IVD) and, as such, their safety and performance when entering the European market are regulated by Directive 98/79 EC on in vitro diagnostic medical devices (IVD Directive). The IVD Directive will be replaced by the newly adopted Regulation on in vitro diagnostic medical devices, which will apply after a 5-year transition period. This new Regulation introduces several changes that are expected to affect regulation of genetic tests entering the European market and cover some of the gaps of the current regulatory framework. Such changes focus mostly on the scope of the tests covered by the Regulation, their risk classification, the clinical evidence required before such tests enter the market, their advertising, informed consent and genetic counselling.[26] These changes will also apply to direct-to-consumer genetic tests.

With regard to the scope, the Regulation explicitly recognizes IVD devices providing information on 'predisposition to a medical condition or a disease' (Article 2(2)) as being subject to the Regulation.[27] Importantly, the Regulation also stipulates that all IVD medical devices offered through the Internet to a person established in the EU must adhere to its standards.[27] It becomes, therefore, apparent that companies established outside the Europe should comply with the Regulation when offering their products to consumers residing within the EU.

Furthermore, the Regulation introduces a risk-based classification system determining the level of scrutiny a device has to undergo before being allowed to enter the European market. According to this system, devices may be divided into four risk categories, varying from Class A (low risk devices), to Class D (high risk devices). Genetic tests fall under Class C (moderate to high risk devices). As such, and they have to go through a pre-market assessment performed by a notified body before being offered to consumers. This premarket assessment should be based on 'scientific validity, analytical and clinical performance data providing sufficient clinical evidence' (Article 56).[27] The notion of clinical performance, in this context, incorporates evidence of clinical validity, making it more challenging for tests with low clinical validity to enter the European market.

In this Regulation, for the first time, the advertising of IVD medical devices is explicitly addressed. The regulation includes an article, according to which, labelling, instructions for use and advertising of such devices must not be misleading regarding the device's purpose, safety or performance.[27] This could be of particular importance in the case of DTC GT, the business model of which is heavily relying on advertising, Nevertheless, there is no prohibition at the European level on the advertising of genetic tests, as has been done for example at the national level in Spain where a Royal Decree (1662/2000) prohibits any kind of publicity of medical devices for genetic diagnosis.

Finally, the Regulation introduces an article on genetic information, genetic counselling and informed consent. According to this article, individuals undergoing genetic tests in the context of healthcare and 'for the medical purposes of diagnostics, improvement of treatment, predictive or prenatal testing' should be 'provided with relevant information on the nature, the significance and the implications of the genetic test'. In addition, when it comes to genetic predisposition testing for untreatable conditions and diseases, Member States shall make sure that patients have access to genetic counselling. As this article refers to the obligations of Member States, its impact will most likely be limited to the clinical context and will not affect the provision of DTC GT.

In sum, it is clear that the new IVD Regulation applies to DTC GT for WGS as long as they are offered to consumers established in the EU, regardless of the where the company offering them is based. Furthermore, DTC GT for WGS will have to go through a premarket assessment and fulfil requirements for clinical evidence. The advertising of such tests should meet the requirements of the Regulation and not be misleading, which may deter companies from making exaggerated and unsubstantiated tests.

As was written in publication No. 8714 of the Superior Health Council on direct-to-consumer genetic testing services, **"in Belgium, no specific legislation forbids or regulates the provision of DTC genetic tests. A** Royal Decree of 14 December 1987 (Published in the Belgian Official Journal of 25 December 1987) lays down the rules for the provision of genetic testing in the Centres for medical Genetics in Belgium. Additionally, the Royal Decree of June 7th 2007, modifying the Royal Decree of September 7th 1984, sets requirements for laboratories performing reimbursed molecular biological tests for the determination of acquired pathologies in human genetic material. The only legal basis applying to DTC genetic tests could be found in article 2 of the Law on the practice of health care professions (Royal decree n°78 (B.S. 14.11.1967)) which stipulates that a physician should be involved in the practice of medicine. Hence, if a DTC genetic test falls under the practice of medicine, as a consequence, a physician should be involved and the Law on patient rights would apply. In this respect, it is important to determine whether a DTC genetic test could be considered the 'practice of medicine'. As we know, most DTC companies write in their 'terms of services' that they are not practicing medicine, and that their tests should not be considered medical information, but only serve "informational purposes." Whether or not this statement would stand further legal or judicial scrutiny has yet to be proven.

In Flanders, the Flemish regulatory framework on screening has been laid down in the Flemish Parliament Act of 21 November 2003 concerning the preventative health policy. Within the framework of disease prevention and based on the Decision of the Flemish Government of 12 December 2008 on population screening in the framework of the prevention of illness, Flanders organizes population-based screening programmes, which are generalized and structured forms of detection, or screenings for specific diseases or risks in people who are, in principle, free of health complaints. This method allows for advancing the time of diagnosis and thus either obtaining a better treatment results, or preventing complications. The Flemish Government aims to protect the population against unessential or unproven screening and to ensure the quality of population based screenings. Although DTC genetic testing might fall under this regulatory framework, the Flemish authorities (until now) have not stipulated that DTC genetic tests fall under the application of this legislation. That being said, in the case where healthcare professionals or pharmacists would be involved in the provision of DTC tests, then this practice would fall under this legislation."

As a conclusion, we can repeat here some of the conclusions that were already provided in publication No. 8714 of the Superior Health Council on direct-to-consumer genetic testing services. Firstly, more information should be available to health care professionals and the general public on limitations and concerns of some genetic tests that are being advertised and sold through the internet. Secondly, Belgium lacks at this moment a specific legislative framework that regulates the provision of genetic testing services, in contrary to other E.U. member states. Therefore, the current regulations don't cover in a satisfactory way the provision of genetic tests outside the context of Centres for Human Genetics. Thirdly, although the new Regulation on in vitro diagnostic medical devices provides a new regulatory framework for genetic testing, various issues of this regulation could be strengthened at a national level, such as issues related to medical supervision, genetic counselling, prohibition on advertising of genetic tests, or the accreditation of labs.

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