The Belgian practice and attitudes towards introducing genomics in clinical oncology

The Belgian practice and attitudes towards introducing genomics in clinical oncology

Authors: Marc Van den Bulcke, Wannes Van hoof, Els Van Valckenborgh, Aline Hébrant, Gordana Rajcevic and Kristof Van Assche

Affiliations:

Marc Van den Bulcke, Wannes Van hoof, Els Van Valckenborgh, Aline Hébrant and Gordana Rajcevic: Cancer Centre, Sciensano, J. Wytsmanstraat 14, B-1050 Brussels, Belgium

Kristof Van Assche: Research Group Personal Rights and Property Rights, Faculty of Law, University of Antwerp, Venusstraat 23, B- 2000 Antwerp, Belgium

Corresponding author:

Marc Van den Bulcke

Acknowledgements:

The Cancer Centre is financed through a convention with the RIZIV-INAMI, Belgium.

Abstract

For most people, being in good health represents the most important factor to wellbeing. While environmental elements such as physical, chemical, biological, social and psychosocial factors in the environment are key for a person's wellbeing, also the genome of the individual and its interaction with the environment play an important role. In this paper, we will focus on attitudes towards genomics in the field of personalised medicine in oncology. We will document opinions encountered by patients and citizens on sharing health-related information for various purposes (e.g., research, cost-effectiveness, patient support) aiming to maximise the benefits for cancer patients. We will discuss ethical and legal considerations to be taken into account at the Belgian level to provide a secure, transparent framework for the use of genomics in the healthcare system.

Keywords: Patient-matching, Personalized medicine, ELSI, Cancer, genomics

INTRODUCTION

Health is of major importance to the wellbeing of an individual during his or her entire life. Thanks to recent advances in knowledge and technical progress, healthy-life prediction may start even before a person is born and important health-related information may continue to be generated after a person's death. To that aim, a healthy-life approach should optimally be seen within a life-course perspective with as the ultimate goal staying healthy (see figure 1). This holds in particular for cancer as a non-communicable disease for which the major risk factors have long been identified, as exemplified in the "European Code Against Cancer" and especially considering that 30 to 40% of cancers can be prevented.[1]

When looking at the life course of an individual, pre-life and early-life health risk parameters can be scored for a number of diseases and severe genetic deficiencies. Parents play a key role in this regard, either as contributors of the genome or as promotors of a certain lifestyle.[2] Prevention against major risk factors, such as tobacco, alcohol, and lack of physical exercise, is by far the most effective means to stay healthy. Prevention is inexpensive and it is highly recommended as such in the European Code against Cancer.[3] Screening and early detection offer a secondary level of prevention and are very well established for cancer, as demonstrated by the breast cancer screening as recommended by the European Commission.[4] Unfortunately, people do get sick. When that happens, a fast diagnosis of the correct disease is essential to determine the best treatment. Optimal care may also dependent on the individual, for instance when it allows that person to take up normal activities after a severe illness.

In all these aspects the genome, the environment, and their mutual interaction play an important role. Although environmental factors are by far the most important determinant, recent advances in genome analysis technology and Artificial Intelligence computational capacities are increasingly bringing to light the role and significance of genomics for health and wellbeing. Bringing to the forefront the role that genomics plays in people's life course represents a major paradigm shift in our society, which does not only impact health but may affect almost all aspects of life, including family relationships, work, social life, culture, and leisure.

To assess its impact, we feel that such broader life-course context needs framing on 5 axes: quality, ethics, solidarity, equity, and cost. We need to understand what this new paradigm really means, what genomics can be useful for, and how we will implement this paradigm in society. We need to guarantee that the benefits are accessible to all citizens and contribute to alleviating poverty and reducing inequalities, while at the same time respecting the individual's autonomous decision on whether or not to take part. This new approach should meet the highest technical standards of quality, safety, and confidentiality but should also ensure the highest quality of life, which may differ from one individual to the next. Since the uses of genomics may be expensive, we need to develop the genomics paradigm in such a way that they are accessible and affordable to all.

Although medicine and healthcare are very important in protecting health, societal influences and environment are also of considerable importance. In their relation to genomics, we consider public health and personalised medicine as a single approach towards ensuring healthy lives to all. This view is supported by the Council of the EU, which emphasised that: "Through better understanding and integrating information on the role of the genome in fighting diseases and in adaptation to environmental factors, novel approaches in the control or cure of diseases are envisaged." The latter is generally designated as 'personalised' or 'precision' medicine (dealing with 'cure'), the former, when studied at the population level, as 'Public Health Genomics' (focusing on 'control').[5]

In this paper, we will focus on attitudes towards genomics in the field of personalised medicine, with a view to: 1) assessing differences between patients and citizens; 2) sharing of health-related information for various purposes (e.g., research, cost-effectiveness, patient support); and 3) evaluating what is needed to maximise the benefits for cancer patients.

PERSONALISED MEDICINE: NGS ROADBOOK

Integration of genomics in the healthcare system is a complex process that requires careful planning involving many stakeholders. Bringing 'omics' medicine to patients is a major challenge for healthcare systems. In many countries, some form of omics testing is now being provided. Here we will highlight the approach taken in Belgium.

To address a clear unmet need in the onco-diagnostics of lung cancer, in 2015 a health service feasibility study was performed on the possibility of, and the requirements for, introducing Next-Generation-Sequencing (NGS) in the healthcare system.[6] A Roadbook was developed by the Cancer Centre of Sciensano, the National Public Health Institute of Belgium with a budget of about €5.2M for 5 years.[7] The Roadbook consists of 10 actions that needed to be completed before NGS testing could be integrated structurally in the healthcare system (see figure 2). Subsequently, these actions were implemented over the course of almost five years, reflecting the complexity of launching such an initiative at the national level. After completing all preparatory actions, NGS testing is introduced as a pilot study in Belgian hospitals in July 2019.

The first action of the Roadbook was to establish a multidisciplinary committee of experts, called the 'Commission of Personalised Medicine' or 'ComPerMed'. The mission of the ComPerMed is to evaluate the clinical use of new somatic mutations and to provide advice to the reimbursement agency (i.e., the Platform Companion Diagnostics (CDx) that formulates advice on the practices and tests to be reimbursed and on the approval of the medicines).

Actions 2 and 3 involve the development of guidelines and criteria for NGS testing and were taken up by the ComPerMed. Independent technical guidelines as well as recommendations concerning the NGS reporting and variant interpretation were developed and are used as a reference by the national accreditation body Belac.[8,9] The criteria for NGS use comprise the evaluation of cancer indications that require NGS testing for patient care (i.e., diagnosis, prognosis, and therapy) and includes, for every particular type of cancer, the list of genes and gene regions to be analysed by NGS. Test levels linked to evidence gathered from clinical guidelines, clinical trials, standard of care, expert opinion, and approved drugs were defined and used as a tool in the selection of the genes. The conditions under which NGS should be performed are defined by way of workflows that position the NGS test in relation to the other molecular tests to be performed on a specific type of cancer.[10,11,12,13]

An adequate application of the results of NGS in the clinic requires the analysis and monitoring of the quality of the NGS tests that have been performed. Action 4 and 5 therefore include the establishment of evaluation procedures in a clinical setting, starting with benchmarking trials and resulting in a national external quality assessment (EQA) program.[14]

Action 6 facilitates the use of NGS data for different purposes (i.e., quality, outcome analysis, reimbursement reallocation, and clinical and public health research) by envisaging the implementation of a technical platform for the central collection and storage of NGS data in a uniform and secure manner. The development of this platform was assigned to Healthdata.be, a service established for the collection and management of health data in Belgium with a view to facilitating data exchange.[15]

Implementing a new technology such as NGS requires education and training and has to consider a variety of ethical, legal, and societal issues (ELSI). Accordingly, Action 7 stipulates the need for education and training in concert with the healthcare sector, with particular attention to technical, legal, and ethical aspects, also taking into account clinical applications and new evolutions. ELSI and the issue of informed consent are anticipated in Action 8 and are further discussed in this paper.

The last actions of the Roadbook involve considering a pilot study (Action 9) and the creation of hospital networks for NGS (Action 10).[16] Implementing NGS in the clinical routine diagnostics is a complex and new process, requiring a pilot phase with close monitoring and an assessment at the end of the transition period. It is also anticipated that the organisation of NGS testing, data analysis, and interpretation within a network infrastructure will facilitate the

process of implementation. In this way, the huge investments in infrastructure are expected to gradually decrease and pooling of expertise in NGS testing and analysis will be stimulated.

PATIENT BENEFIT

As indicated above, the DNA profiling of tumours using broad-spectrum NGS panels results in a fingerprint of the tumour material of a patient that represents a unique identifier of the particular tumour. Such information could be used in a so-called 'patient-matching' approach which consists of two major steps: 1) identifying the matching patients in order to access relevant clinical data to offer the best standard of care to one's own patient (see figure 3.A); and 2), where necessary, including a patient into an appropriate clinical trial, taking into account the tumour DNA profiling information (see figure 3.B).

As a first step, the treating physician can search in a central tumour DNA fingerprint database for profiles matching the tumour DNA profile of his or her patient. If a matching profile found in the database is also linked to minimal clinical information (such as treatment and outcome), the treating physician can use this information to support treatment decisions for his or her own patient. Collecting and sharing these data beyond their use for the patients' own treatment are in some cases only allowed if these patients have first given consent (see below). As a second step, if the existing standard of care does not offer appropriate options for treatment, this information could be used to suggest the patient to be included in a clinical trial with matching pathological criteria, preferentially conducted in Belgium or neighbouring countries (see figure 3.B).

In Belgium, the recently opened 'Precision' trial could represent an excellent opportunity to build such an initiative. The Belgian Molecular Profiling Program of Metastatic Cancer for Clinical Decision and Treatment Assignment (PRECISION) initiative is an academic program aimed at creating a national infrastructure for clinical and genomic data collection and sharing. This program, sponsored by the Belgian Society of Medical Oncology (BSMO) and financially supported by the "Foundation against Cancer" and "Kom op tegen Kanker" involves all Belgian academic and several non-academic hospitals and consists of two components: Precision 1 and Precision 2.

Precision 1 is a data sharing study. Patients with metastatic solid tumours that are candidates for NGS testing are enrolled in centres all over Belgium. After signature of an informed consent form, the genomic data are transferred to a central database. Clinical data including the tumour type, survival status, anti-cancer treatment, and outcomes are recorded in the clinic-genomic database that will empower future research initiatives. The Precision infrastructure has further allowed the design of novel projects that will provide comprehensive genomic profiling to patients with metastatic solid tumours. These large gene panels allow testing copy number variations and fusions in addition to single nucleotide variants. The "GeNeo" study aims to enrol 1000 patients and the Illumina TSO500 about 500 patients. Both studies share the objective of investigating the added value of comprehensive genomic profiling as compared to small panel testing. The results of these studies will be discussed virtually by a national molecular tumour board and recommendations will be provided to the treating oncologist, including information on genotype-driven clinical trials available all over Belgium.

Precision 2 is a platform that builds basket phase 2 studies in settings where clinical trials are lacking. Two clinical trials are currently enrolling patients: 1) afatinib in tumours harbouring mutations in EGFR, ERBB2 and ERBB3; and 2) olaparib in tumours harbouring somatic and germline mutations in homologous recombination deficiency genes. Other trials are currently under discussion.

These efforts from the Precision initiative aim at positioning Belgium as a preferred partner-country for precision medicine clinical trials by overcoming the obstacles of a population limited in size.

ELSI

The aims of precision genomics require strong support from our population. Indeed, successful application of the genome for preventive and medical purposes requires the development of a large representative dataset, which contains health and environmental information of the individuals over a life-course period. The realisation of such a project will depend on a strong commitment from the participants.

We foresee that ELSI will receive increasing attention in the European Commission's future Horizon Europe program. Within this program we will look to continue the development of platforms and strategies for a large-scale engagement of the population in this new genomics paradigm. The mutual learning approach, developed in the joint Action *Innovative Partnership Action Against Cancer* (iPAAC), is expected to facilitate the broader engagement of citizens and patients in this topic in other EU Member States.[17]

Ethical and societal issues

From an ethical point of view, attitudes towards genomics matter. Genomic data are personal and sensitive data. A positive or negative attitude towards genomics will determine the societal support for the implementation of genomic technologies and individual willingness to participate in genomic screening, research, and care. Therefore, it is important to understand how genomics is perceived in society and which norms and values are held by citizens regarding the governance of genomic data.

Recently, several countries have launched initiatives to engage patients and citizens on this subject. In France, the public was consulted on the review of the French Law on Bioethics. This initiative included: 1) the organisation of 271 events where the Law on Bioethics was discussed with stakeholders and citizens; 2) input from experts and professional organisations; and 3) a citizen forum with a specific interest in genomics.[18] Genomics England reported on their public engagement efforts regarding genomics that citizens call for a new social contract in healthcare.[19] Within the European Commission's Horizon 2020 program, a 'stakeholder involved ethics' project (SIENNA) was launched with genomics as one of the core subjects.[20]

In Belgium, we organised a focus group study with cancer patients to explore their attitudes and informational needs regarding NGS testing.[21] These patients expressed great expectations from genetics, in particular related to the diagnosis and, if possible, treatment of congenital, immutable, and hereditary mutations. We learned that it is important not only to inform the patients correctly, but also to take into account how information is understood. These patients argued for a personalised informed consent, noting that, especially when dealing with new information, they do not always think and act like rational agents. They expressed a preference for comprehensible oral communication over written forms and they felt that a written consent is only necessary for tests and treatments that are not considered as standard practice. These patients indicated a strong willingness to share data for the benefit of fellow patients, but they also expressed fears about possible abuse, especially through secondary use of their data for other goals than patient wellbeing (e.g., commercialisation, discrimination, violations of privacy).

To inform policy makers about the way citizens believe genomic information should be governed in society, we organised a citizen forum in collaboration with the King Baudouin

Foundation. Questions and topics to be addressed were discussed at an expert workshop. During three weekends, citizens discussed issues related to the use of genomic information in healthcare, based on objective information material and in interaction with a range of experts. On the final day of the citizen forum, they presented 32 concrete policy recommendations to the Belgian Minister of Public Health.[22] These recommendations were subsequently used as the basis for a stakeholder workshop, where policy makers and experts on genomics were invited to translate the citizens' preferences into practical policy outputs (23).

The main conclusion of the citizen forum was that all citizens recognised the huge potential benefit of genomics for society in general and for healthcare in particular. For this common good, they showed great willingness to share data and participate in genomic medicine. However, from their point of view, making available one's genomic information requires a great deal of trust. The only way to foster this trust is to ensure that a strict legal framework is in place. This framework should protect them from genetic discrimination (i.e., identification of genetic variations should not be used to foster inequality) and violations of their rights to privacy, autonomy, and an open future.[23]

Legal and privacy aspects

All analyses performed within the healthcare system are aimed at improving patient health. The approach for diagnosing health problems is to get increased evidence-based data, especially when complex, expensive testing is considered. Evidence-based medicine is very fruitful in many domains of healthcare (see https://www.cochranelibrary.com). Similarly, also in broad-spectrum genomics testing evidence-based approaches are preferred and a number of clinical trial schemes specifically for genomic testing have been developed.[24]

A major concern with such testing is the so-called proportionality principle, which implies that one should not expose patients to testing that is not expected to directly result in better diagnosis, prognosis or treatment. In this regard, it should be acknowledged that for a large number of targets included in typical genomic test schemes not much evidence for clinical utility is currently available.

A critical element in making genomics medicine a success is therefore the implementation of the 'learning by doing' principle, ensuring that routine diagnostics in care is embedded in a larger evidence-generating framework. Such an approach will allow us to efficiently generate evidence and knowledge on innovation in real time, instead of having to resort to demanding, expensive, and time-consuming phase II and III clinical trials.

In order to protect the autonomy and privacy of persons who receive NGS testing, a variety of legal provisions have been put in place. Under the Law on the Rights of the Patient, their free and informed consent will be necessary when a sample is removed that will be used for NGS testing. For their consent to be valid, patients should first receive information on the nature, purpose and possible consequences of that intervention. They should later also be informed about the relevant findings of the test. (Art. 7 & Art. 8)[25]

Since NGS testing involves a processing of the patient's genetic information and possible associated health data, the General Data Protection Regulation (GDPR) is also applicable.[26] The GDPR, designed to safeguard the privacy rights of EU citizens over their personal data, is directly applicable in Belgium. However, some of its aspects (e.g., the regulation of research on personal data; imposing additional restrictions for the processing of genetic data or health data) were left to national authorities to decide. In Belgium, these elements are governed by the Law on the Protection of Natural Persons with Regard to the Processing of Personal Data (Data

Protection Law).[27] Under the GDPR, genetic data and health data are considered sensitive data, a special category of personal data that merits specific protection in view of the fact that the processing of these data could create significant risks to the privacy and other fundamental rights of the individual. In order to process these data, the free, informed, and explicit consent of the person concerned is required. (Art. 9(2), a)[26]

However, important exceptions to this rule exist. For instance, consent is not required when genetic data or health data are processed within the context of regular medical diagnosis or healthcare. (Art. 9(2), h)[26]. Because NGS testing is recently being considered as a basic diagnostic procedure, consent for the processing of these data with a view to improving the diagnosis or treatment of the patient is no longer required. However, as outlined above, an obligation to obtain consent for NGS testing when the sample is removed still exists under the Law on the Rights of the Patient.

A second exception concerns the processing of genetic data or health data within the context of the management of social security systems. (Art. 9(2), h) [26] As a result, the central registration and storage of NGS data through the Healthdata platform, for the purpose of the reimbursement of the tests, do not require the consent of the persons who receive these tests. This exception is only allowed if it is explicitly provided for by law. In Belgium, this requirement is fulfilled in that the registration and storage of NGS data for reimbursement by the National Institute for Health and Disability Insurance (*RIZIV*) has been made possible by Royal Decree.[28] In addition, the GDPR stipulates that stringent safeguards should be put in place. In this regard, it should be noted that a number of safeguards already need to be established for every type of processing of personal data, including data that are not sensitive. It should, for instance, be ensured that: 1) data are processed for a specified purpose only; 2) data processing is limited to what is necessary for that purpose; 3) data should not be stored longer than necessary; 4) security measures are taken to guarantee that data are protected against unauthorised or unlawful access; and 5) a record of processing activities is being kept. (Art. 5 & Art. 30)[26]

For sensitive personal data, such as genetic data and health data, extra safeguards need to be introduced. These data should, for instance, only be processed by, or under the responsibility of, a person who has an obligation of professional secrecy. (Art. 9(3))[26] Moreover, Member States may set additional conditions for the processing of genetic data or health data. In this way, the Belgian Data Protection Law also requires that a list of the categories of persons who will have access to the data is maintained and made available to the national Data Protection Authority (*Gegevensbeschermingsauthoriteit*). It should furthermore be ensured that the persons who will have access to the data are bound by law or contract to respect the confidentiality of the data. (Art. 9)[28]. As regards the purpose of reimbursing the NGS tests, these safeguards are ensured through a covenant signed by the participating hospital labs and the National Institute for Health and Disability Insurance, and through incorporating quality, safety, and confidentiality measures in the management of the NGS registry by the Cancer Centre of Sciensano.

When research on these data is considered, the GDPR imposes a number of obligations on the persons and institutions responsible for the control and processing of these data.[29] Interestingly, when data obtained through NGS testing would later be used for research, these obligations do not necessarily involve securing the consent of the patient. Under the GDPR, EU Member States are allowed to introduce a so-called research exemption to the principle of free, informed, and explicit consent when data are re-used for scientific research. (Art. 9(2), j & Art. 89)[26] In Belgium, such an exemption has indeed been introduced by the Data Protection Law. As prescribed in the GDPR, this Law makes the research exemption subject to the implementation of a number of additional safeguards, complementing the ones that always apply to the processing of genetic data or health data. For instance, when, in the absence of consent, data

are re-used for research, they should be anonymised or, if that is impossible, pseudonymised and encrypted. Exceptionally, personally identifiable data may be used if it is impossible to achieve the research objective by processing pseudonymised data. (Art. 197) [30] As a rule, the patient whose data will now be used for research needs to be informed about this before the research starts. Information should be provided inter alia about the exact research purposes, the categories of the data that will be used, the recipients of the data, whether the data will be transferred to a recipient outside of the EU, and the right to object. The GDPR indicates that information does not need to be provided if this proves impossible or would involve a disproportionate effort. (Art. 14(5), b)[26] Similarly, the GDPR allows a derogation from the right to object, in so far as removing that person's particular data from the research data set would render impossible or would seriously impair the research purpose. (Art. 89(2))[26].

It should be noted that an explicit, written informed consent for re-using human body material, including DNA, is still required by the Belgian Law Regarding the Procurement and Use of Human Body Material for Human Medical Applications or Scientific Research.[31] However, in case it proves impossible to ask for consent to the re-use of the data for research, that Law still allows that research to go ahead without consent, subject to the approval from a research ethics committee as stipulated in the Law Regarding the Procurement and Use of Human Body Material for Human Medical Applications or Scientific Research (Art. 20(1)).[32] One way to avoid these complexities is to ask patients for their explicit and written consent to the future research use of their NGS data already when the sample is removed for diagnosis.

When research would be performed on NGS data previously obtained for diagnosis but, in the context of that research, additional information would need to be obtained from the patient or interventions on that person would be envisaged, that research would be considered as an experiment, falling within the scope of the Belgian Law Regarding Experiments on the Human Person.[33] As a result, the patient will from that moment onwards be considered as a research participant, whose free, informed, and written consent will be required, and a positive advice from an ethics committee will need to be obtained (Art. 6 & Art. 11) [34]

Data obtained through NGS testing and associated health data may be transferred to countries outside of the EU, but only if that country guarantees an adequate level of data protection. The European Commission has the power to award the status of GDPR adequate country when, after a thorough assessment and subject to period reviews, it has decided that the country concerned ensures an adequate level of protection. So far, the European Commission has recognised 13 countries, including Canada, Israel, Japan, New Zealand, Switzerland, and the US (limited to the Privacy Shield framework), as providing adequate protection.[34] In the absence of such an adequacy decision, personal data may still be transferred outside of the EU if appropriate safeguards, including enforceable rights and effective legal remedies for the individual whose data are transferred, are provided in another way. These safeguards can be laid down in contractual clauses or other legally binding and enforceable instruments which first need to be submitted to, and under certain circumstances approved by, the national Data Protection Authority.

CONCLUSIONS

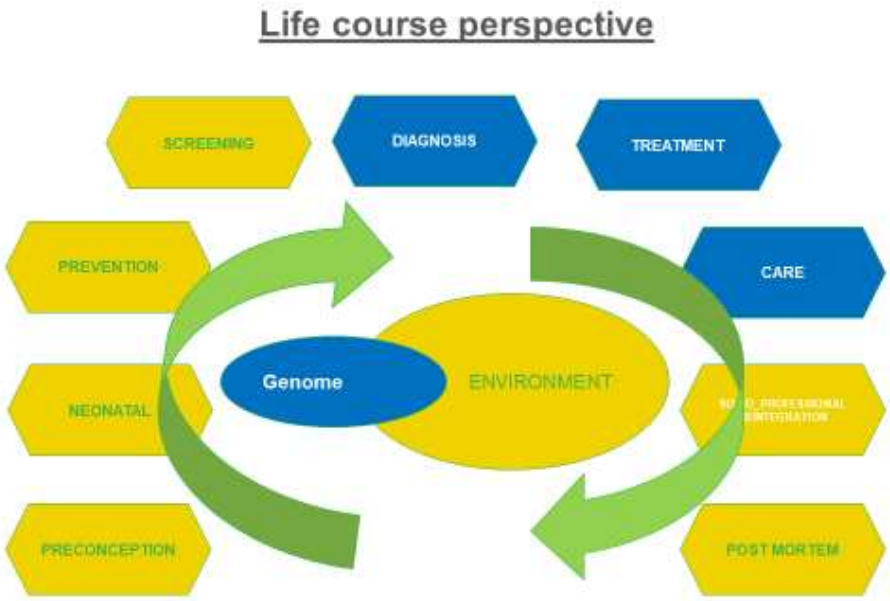
Creating a patient-matching platform for oncology would be a major step forward in providing innovative treatments to cancer patients in the best possible way. Such an initiative is, however, a novel approach in cancer patient care and requires thorough preparation at the technical, logistic, legal and organizational level. Although no unsurmountable hurdles were identified, the success of such a platform will largely depend on the support by the patients, the health professionals, the hospitals, and the healthcare authorities. The NGS Roadbook has already paved part of the way (with its focus on, for instance, harmonisation of testing, central

registration, reimbursement schemes, and ELSI) but several topics remain to be addressed and need concrete decisions and actions. We identify for example: 1) a precise patient needs analysis as to clearly define what we want to do for whom (scope and patient involvement); 2) a fine-mapping based on the current state of Belgian cancer care wherein such a platform could be integrated at the national and the international level (crystallisation); 3) a market/landscape analysis on what options/tools are currently already available (business case) and on what links to other local or international initiatives need to be established (interoperability); 4) a comprehensive legal, ethical, and privacy assessment so as to create a solid and transparent legal basis for this initiative (compliance); and 5) a cost model so as to guarantee the operation and maintenance of the platform in time (sustainability). Considering that this non-limited list of topics covers a very broad range of domains (i.e., technical, medical, logistic, legal, societal, and political), we believe that the development of a cancer patient matching platform should be accompanied by a prior feasibility analysis (type *Health Services Evaluation*) which could then be transformed into a Roadbook, describing in more detail all of the actions required for the establishment of an integrated novel cancer care facility.

.

FIGURES

Figure 1: Life-course perspective



450 **Figure 2: NGS roadbook**

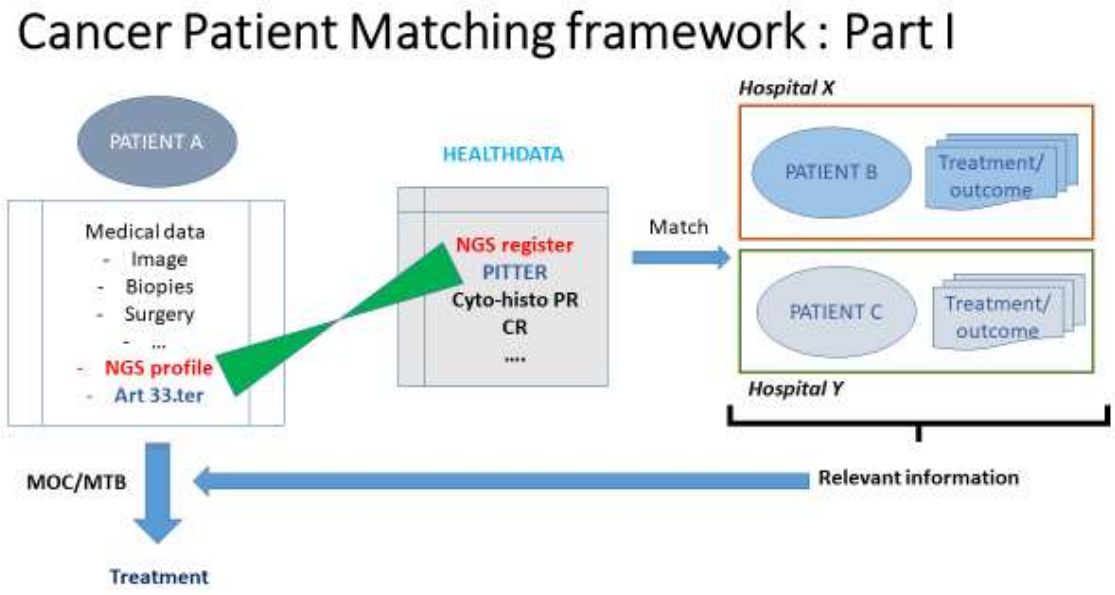
451

Roadbook for the implementation of next-generation sequencing in clinical practice in oncology and hemato-oncology	
ACTION 1	Establish a commission: Commission Personalized Medicine (ComPerMed)
ACTION 2	Develop guidelines for NGS use in (hemato)-oncology
ACTION 3	Develop criteria for NGS use in (hemato)-oncology
ACTION 4&5	Develop and organize a benchmarking trial and EQA for NGS use in (hemato)-oncology
ACTION 6	Implement NGS registration, storage and data management
ACTION 7	Provide NGS education and training
ACTION 8	Address informed consent, legal and ethical implications of NGS use in (hemato)-oncology molecular diagnostics
ACTION 9	Establish pilot study 'NGS use in routine diagnostics'
ACTION 10	Build on hospital networks for NGS use in (hemato)-oncology

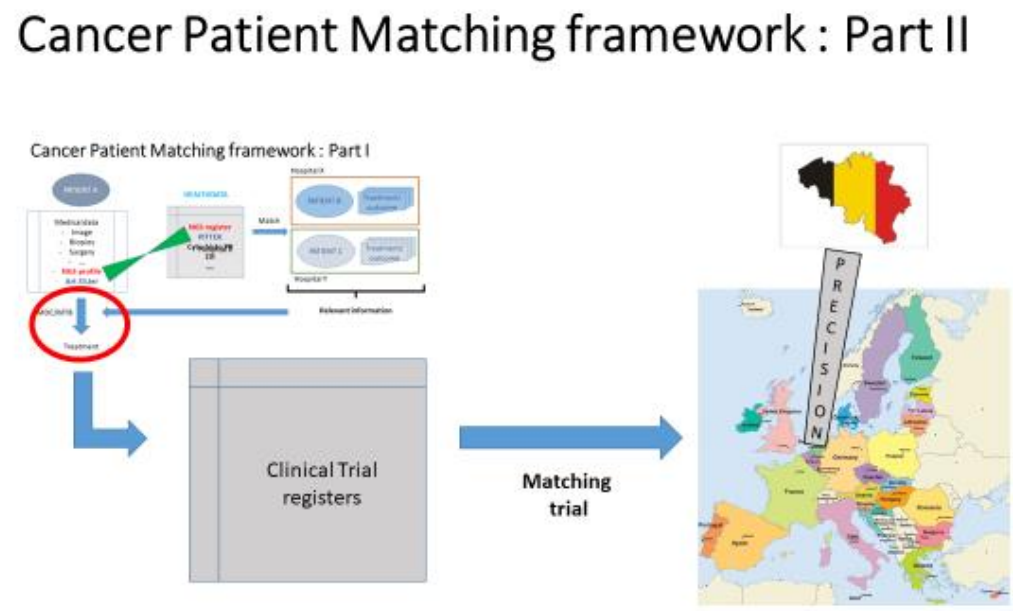
452
453
454
455
456

457 **Figure 3: Cancer Patient Matching Framework**

458



459



460
461
462

Legends to figures

Figure 1: **Life-course perspective on health.** Two key elements define health during the life of an individual: his/her genome and the environment, which interact with each other. The human lifecycle mapped on health interventions/domains runs from pre-conceptual over prevention, disease and survivorship to death steps wherein both central elements play a role. In blue, the domains that today have received major attention from the genomic point of view, in yellow the domains where environment is prevailing.

Figure 2: **List of actions taken up in the Belgian NGS roadbook** (NGS: Next Generation Sequencing; EQA: external quality assurance).

Figure 3: **Cancer Patient Matching Framework:** Schematic view of the two large layers to be developed within a patient matching framework: ***Part I***: a patient matching tool that allows clinicians to match their patient with other Belgian cancer patients based on similar disease profiles (such as tumor type, tumor DNA profile, and immunochemistry data), and ***Part II***: a tool that allows to search for clinical trials, such as the 'Precision' trial, based on the clinical data available in the patient matching tool (CR = cancer register; cyto-histo PR: cyto-histopathology register; PITTER: predictive tests for a therapeutic response).

REFERENCES

[1] World Health Organization, Cancer Prevention. Available from: https://www.who.int/cancer/prevention/en/.

[2] World Health Organization, Global Strategy on Diet, Physical Activity and Health, The Role of Parents. Available from: https://www.who.int/dietphysicalactivity/childhood_parents/en.

[3] World Health Organization, International Agency for Research on Cancer, European Code Against Cancer. Available from: https://cancer-code-europe.iarc.fr.

[4] European Commission. European Guidelines on Breast Cancer Screening and Diagnosis. Available from: https://healthcare-quality.jrc.ec.europa.eu/european-breast-cancer-guidelines.

[5] Council of the European Union, Council Conclusions on Personalised Medicine for Patients, OJ. C 421/03, 17 December 2015. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52015XG1217(01)&from=EN.

[6] Van den Bulcke M, San Miguel L, Salgado R, et al. Next generation sequencing gene panels for targeted therapy in oncology and haemato-oncology. Health Technology Assessment (HTA) Brussels: Belgian Health Care Knowledge Centre (KCE). 2015. KCE Reports 240, D/2015/10.273/26.

[7] Van Valckenborgh E, Hébrant A, Antoniou A, et al. Roadbook for the implementation of next-generation sequencing in clinical practice in oncology and hemato-oncology in Belgium. Arch Public Health. 2018;76:49

[8] Belgische Accreditatie-instelling. Bijzondere bepalingen voor de accreditatie van medische laboratoria die Next Generation Sequencing analysen voor hematologische en solide tumoren uitvoeren, BELAC 2-405-NGS Rev 2-2019 1/34 (Dutch; French version also available).

[9] Froyen G, Le Mercier M, Lierman E, et al. Standardization of Somatic Variant Classifications in Solid and Haematological Tumours by a Two-Level Approach of Biological and Clinical Classes: An Initiative of the Belgian ComPerMed Expert Panel. Cancers. 2019;11(12):2030.

[10] Hébrant A, Mourin A, Froyen G, et al. Molecular test algorithms for digestive tumours. Belg J Mol Oncol. 2019;13(1):4-10.

[11] Hébrant A, Punie K, Duhoux F, et al. Molecular test algorithms for breast tumours. Belg J Mol Oncol. 2019;13(2):40-45.

[12] Van Valckenborgh E., Bakkus M., Boone E., et al. Diagnostic testing in myeloid malignancies by next-generation sequencing: recommendations from the Commission Personalised Medicine. Belg J Hematol. 2019;10(6):241-9.

[13] Dendooven A, Hébrant A, Van den Bruel A. Algorithms for molecular testing in solid tumours. Belg J Med Oncol. 2019;13(7):286-95.

[14] Sciensano. Kwaliteit van laboratoria, Rapporten. Available from: https://www.wiv-isp.be/QML/activities/NGS/_nl/rapports_annee.htm (Dutch; French version also available).

[15] Sciensano. Documentation for Registry NGS. Available from: https://support.healthdata.be/articles/en_US/Support_Article/Documentation-for-Registry-NGS.

[16] Rijksinstituut voor ziekte- en invaliditeitsverzekering. Oncologie: Terugbetaling van de moleculair biologische testen met "next generation sequencing" (NGS). Available from: https://www.riziv.fgov.be/nl/professionals/verzorgingsinstellingen/laboratoria/Paginas/oncologie-terugbetaling-moleculair-biologische-ngs.aspx (Dutch; French version also available).

[17] Innovative Partnership for Action Against Cancer. Available from: https://www.ipaac.eu/.

[18] Comité consultatif national d'éthique, 2018. États généraux de la bioéthique, rapport de synthese. EDP Sciences. Available from: https://www.ccne-ethique.fr/sites/default/files/publications/eg_ethique_rapportbd.pdf.

[19] Ipsos MORI. A public dialogue on genomic medicine: time for a new social contract?, April 2019. Available from: https://www.genomicsengland.co.uk/?wpdmdl=17028.

[20] Rodrigues R, Broadhead S, Trilateral Research, et al. SIENNA project. The consortium's methodological handbook, version 0,5, October 2019. Available at https://www.sienna-project.eu/digitalAssets/801/c_801912-l_1-k_d1.1siennahandbook.pdf.

[21] Van Hoof W, Moens K. Kankerpatiënten spreken over NGS. Een focusgroep studie over ervaringen en informatienoden. Sciensano, D/2019/14.440/44.

[22] KBF, Sciensano. Mijn DNA, een zaak van iedereen? Burgers geven advies over het gebruik van genoominformatie in de gezondheidszorg, March 2019. Available from: https://www.kbs-frb.be/nl/Activities/Publications/2019/20190225PP2 (Dutch; French version also available).

[23] KBF, Sciensano. Genoomkennis verandert de gezondheidszorg – Burgeradvies zet beleid en stakeholders aan tot veranderagenda, July 2019. Available from: https://www.kbs-frb.be/nl/Activities/Publications/2019/20190717PP (Dutch; French version also available).

[24] Hingorani A, Kuan V, Finan C, et al. Improving the odds of drug development success through human genomics: modelling study. Sci Rep. 2019;9:18911.

[25] Law of 22 August 2002 on the Rights of the Patient. Belgian Official Gazette. 26 September 2002, 43719. Available from: https://www.ejustice.just.fgov.be/mopdf/2002/09/26_2.pdf#Page22 (Dutch and French).

[26] Regulation (EU) 2016/679 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, OJ L, 119, 4 May 2016, 1-88. Available from: https://eur-lex.europa.eu/eli/reg/2016/679/oj.

[27] Law of 30 July 2018 on the Protection of Natural Persons with Regard to the Processing of Personal Data. Belgian Official Gazette. 5 September 2018, 68607. Available from: https://www.ejustice.just.fgov.be/mopdf/2018/09/05_1.pdf (Dutch and French).
[28] Royal Decree of 17 May 2019 Amending the Appendix to the Royal Decree of 14 September 1984, Regarding the Provisions of Genetic Tests. Belgian Official Gazette. 5 June 2019, 55072. Available from: http://www.ejustice.just.fgov.be/mopdf/2019/06/05_1.pdf (Dutch and French).
[29] Broeckx, N. GDPR-verantwoordelijkheid in de medische sector: een toepassing op medisch-wetenschappelijk onderzoek. T. Gez./Rev. dr. santé. 2019; 2: 102-19.

[30] Vijverman, A. Gezondheidsgegevens verwerken voor wetenschappelijk onderzoek: toestemming vereist of niet? T. Gez./Rev. dr. santé. 2019;2:98-101.
[31] Law of 19 December 2008 Regarding the Procurement and Use of Human Body Material for Human Medical Applications or Scientific Research. Belgian Official Gazette. 30 December 2008, 68774. Available from: https://www.ejustice.just.fgov.be/mopdf/2008/12/30_1.pdf (Dutch and French).
[32] Sterckx S, Van Assche, K. The New Belgian Law on Biobanks: Some Ethical Reflections, Health Care Anal. 2011;19(3):247-58.
[33] Law of 7 May 2004 Regarding Experiments on the Human Person. Belgian Official Gazette. 18 May 2004, 39516. Available from: https://www.ejustice.just.fgov.be/mopdf/2004/05/18_2.pdf (Dutch and French).
[34] European Commission. Adequacy Decisions. Available from: https://ec.europa.eu/info/law/law-topic/data-protection/international-dimension-data-protection/adequacy-decisions_en.