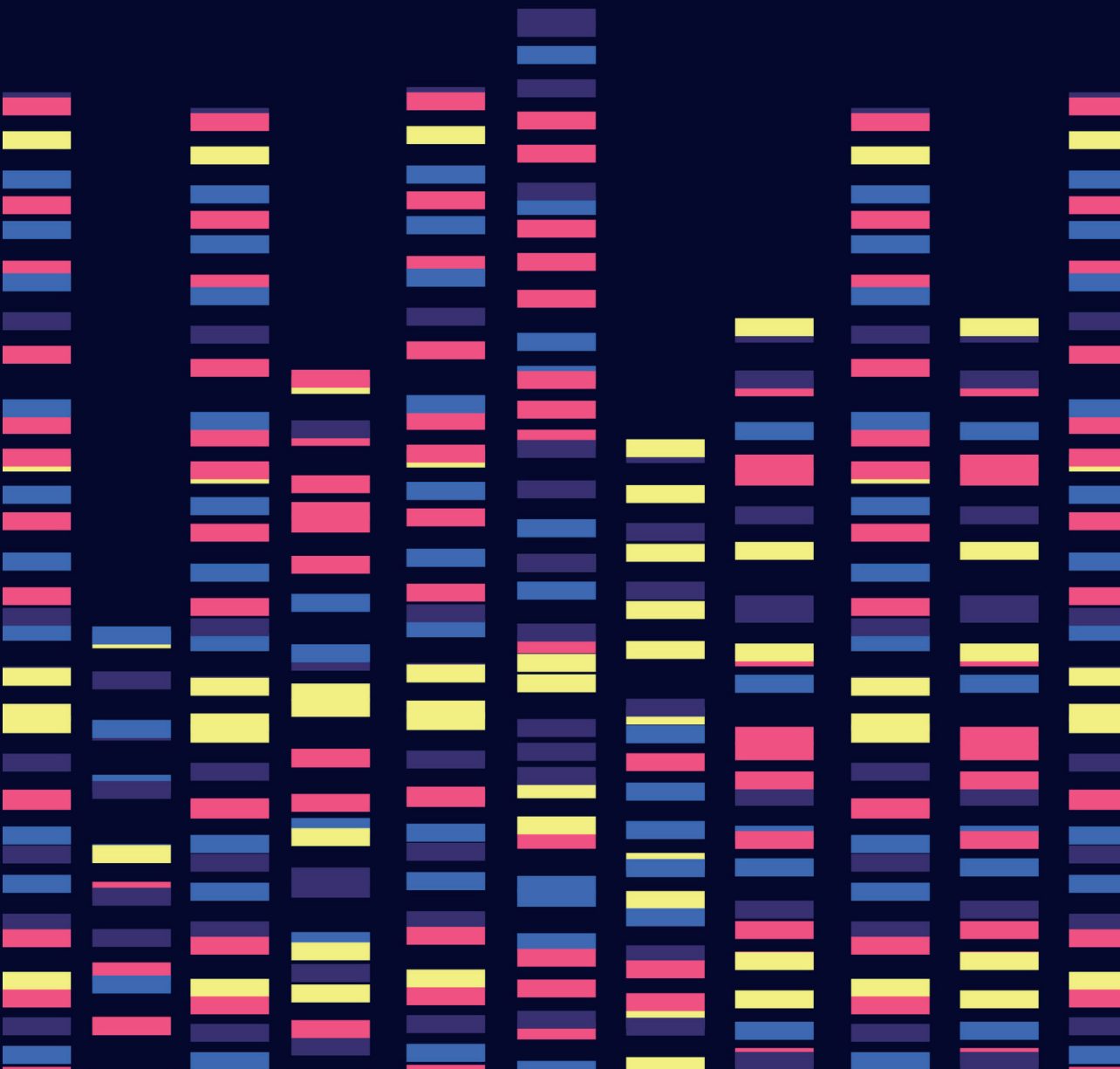
A SYSTEMS MODEL TO SUPPORT THE IMPLEMENTATION OF WHOLE GENOME SEQUENCING FOR LUNG CANCER PATIENTS IN A CONSTRAINED HEALTHCARE SYSTEM

Michiel van de Ven



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Michiel van de Ven

born on the 7th of March, 1991
in Rosmalen, The Netherlands

This dissertation has been approved by:

Supervisors
prof. dr. M.J. IJzerman
prof. dr. ir. H. Koffijberg

Co-supervisor
dr. V.P.R. Retèl

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Supervisors:	prof.dr. M.J. IJzerman University of Twente prof.dr.ir. H. Koffijberg University of Twente
Co-supervisor:	dr. V.P.R. Retèl University of Twente
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Chapter 1

General introduction

1.1 Personalized medicine in lung cancer

In recent years, cancer treatments have been developed that are more effective for specific genetic subgroups of patients. Instead of prescribing chemotherapy treatment to almost all patients, it is now understood that tumors can be characterized and treated based on their genomic profiles. Consequently, a personalized approach that stratifies patients into genetic subgroups based on the presence of biomarkers and prescribing treatments that match their genetic subgroup has become routine practice for many cancer types. This personalized medicine approach has been shown to lead to overall increased survival for genetic subgroups compared to a one-size-fits-all approach [1,2], and also helps to prevent prescribing potentially ineffective treatments.

This progress particularly has relevance for lung cancer. Worldwide, lung cancer is the cancer type with the second-highest incidence with an estimated 2.2 million new cases and 1.8 million deaths in 2020 [3]. The number of lung cancer deaths is expected to increase to 3 million in 2035 due to an aging population and increased tobacco consumption in some countries [4]. The largest subgroup of lung cancer is non-small cell lung cancer (NSCLC), which accounts for about 69% of all lung cancer cases in the Netherlands [5]. At the time of diagnosis of NSCLC, the tumor often is already advanced and may have spread to the lymph nodes and other parts of the body in most patients partly due to a late onset of symptoms and a late presentation at the hospital. As a result, 50% of all NSCLC patients are diagnosed with stage IV cancer [6]. The survival of patients with stage IV NSCLC is generally poor, as only 4% of patients are still alive after five years [7].

To address the poor survival of NSCLC patients, the role of biomarkers for treatment selection in NSCLC has rapidly advanced over the last decade [8]. In the most recent leading clinical practice guidelines [9], it is recommended to test at least the EGFR, ALK, KRAS, ROS1, BRAF, NTRK, MET, RET, and PD-L1 biomarkers in all patients with stage IV NSCLC. These biomarkers are used to target optimal treatment and indicate whether chemotherapy, targeted therapy, immunotherapy, or combination therapy will be the most effective. There are several different test techniques and platforms available to characterize these biomarkers, either single-gene tests or multi-gene tests. For single-gene tests, techniques such as immunohistochemistry and fluorescence in situ hybridization are frequently used. Multi-gene tests, primarily use Next Generation Sequencing (NGS) techniques that can test many genes simultaneously. In the current standard of care (SOC) for NSCLC, multiple diagnostic tests are required for a clinical diagnosis [10]. These tests can be either conducted in parallel or sequence. The number of available biomarkers and diversity

of the available diagnostic test techniques in different hospitals, together with the challenges of efficiently planning the tests lead to a complex and non-uniform diagnostic pathway for patients with advanced NSCLC.

Advances in genomics have increased the demand for more comprehensive testing. Whole Genome Sequencing (WGS) is a type of NGS that sequences all the coding and non-coding regions of the genome. Hence, WGS can be used to test all DNA-based biomarkers in one single test, compared to the current SOC where multiple tests are performed sequentially. As such, WGS is the most comprehensive type of NGS and offers a substantial amount of (additional) diagnostic information. Consequently, the clinical utility of WGS is potentially higher compared to current single and multi-gene tests if novel treatments are available that make use of the additional diagnostic information that WGS generates. Moreover, WGS can replace most, if not all, current molecular diagnostic tests, thereby simplifying and increasing the efficiency of the diagnostic pathway. In addition to the value that WGS may provide to current patients, the genomic information derived from WGS could potentially be even more valuable for future patients. For instance, new biomarkers may be discovered based on the genomic information from previous patients, which can drive the development of new cancer treatments targeting those biomarkers.

While benefits of WGS emerge, the implementation of WGS into healthcare is slowly moving forward particularly through national initiatives [11]. These initiatives include studies focusing on several disease areas such as oncology, rare diseases, and diabetes and are mainly aimed at building the required infrastructure and expertise, such as harmonizing data collection, setting up data-sharing platforms, and increasing genomic literacy among the healthcare workforce. The use of WGS for oncology is primarily in the clinical research setting. Currently, there are only five initiatives ongoing that implement WGS as a routine cancer diagnostic while also incorporating a health economic analysis [12]. These initiatives are the French plan for genomic medicine 2016-2025 [13], Australian Genomics [14], WGS Implementation in the standard Diagnostics for Every cancer patient (WIDE) project in the Netherlands, the 100,000 genomes project in the United Kingdom [15], and the European Beyond 1 Million Genomes project (https://b1mg-project.eu).

1.2 A disruptive technology

A disruptive technology, like WGS, is an innovation that, when implemented, substantially changes the way people or organizations work. WGS is considered disruptive because it can replace many of the current molecular diagnostics which requires consideration of the optimal position of WGS in the diagnostic pathway from a clinical and health economic perspective. WGS is also disruptive as it imposes

several challenges regarding (1) the organization and interpretation sequencing and its outcomes, (2) the total cost of the service, and (3) the handling of secondary findings. In this section, we will elaborate on this further.

First, WGS imposes logistical changes on the healthcare system. For example, there currently is one central facility in the Netherlands, operated by the Hartwig Medical Foundation, that performs the sequencing for all hospitals that participated in the Centre for Personalized Cancer Treatment study [16]. This is different from current offerings of molecular diagnostics in the Netherlands, which are either conducted within labs in the hospitals or through one of the many regional labs.

Furthermore, the complexity of the genomic information generated by WGS requires a clinical interpretation by a Molecular Tumor Board (MTB) to match the most relevant biomarkers identified with treatments. An MTB is a multidisciplinary group of experts representing expertise in pathology, clinical biology, genetics, and bioinformatics [17]. At the moment, molecular diagnostics of single-gene tests or small gene panels for targeted drugs do not require interpretation by an MTB. However, the expertise of an MTB is critical when using WGS.

Second, the cost of 2925 euro per patient makes WGS relatively expensive compared to SOC which costs up to 350 euro per test [23]. In the Netherlands, patients do not pay out of pocket to receive molecular diagnostics. However, hospitals are reimbursed by health insurers through the Diagnosis Treatment Combination (DTC) system. A DTC is a bundle of care at a fixed rebate that covers all similar activities from diagnosis until completing the treatment. For instance, one DTC covers all molecular diagnostics conducted for one patient. Until 2019, the maximum rebate was approximately 1060 euro for the complex molecular diagnostics DTC and approximately 466 euro for simple molecular diagnostics [24]. Because multiple SOC tests are often needed along the care pathway [10], the maximum rebate for complex molecular diagnostics does not always cover the total costs of the molecular diagnostics actually used [25]. So the use of the more expensive WGS would almost certainly be more costly than the maximum rebate for complex molecular diagnostics. Third, there are ethical, legal, and societal issues that should be addressed before implementing WGS [18,19]. Combined with conducting research using WGS data to discover novel biomarkers, the potential for secondary findings underlines the need to store the massive amounts of genomic data in a responsible, safe, and accessible way [21,22].

Since 2020, the maximum rebate for DTCs related to molecular diagnostics is no longer set by the Dutch Healthcare Authority [26]. Instead, they are now determined through negotiations between individual hospitals and health insurers. In addition to the distinction between complex and simple molecular diagnostics, a distinction based on the number of genes tested (few, several, many) has been added to the DTCs. Full reimbursement of hospitals for the cost of WGS would facilitate the implementation of WGS into SOC for cancer patients. However, as the cost of WGS is substantially higher than current SOC tests and cannot be reimbursed by existing DTCs, an evaluation is needed to assess whether the added value of WGS is worth the added costs.

1.3 Evaluating system-level constraints

To evaluate the incremental costs and health effects of a new health technology, health economic evaluations are conducted. They support decisions on which health technologies may be reimbursed through basic health insurance. In that way, health economic evaluations facilitate efficient spending of the available healthcare budget. There are multiple different types of health economic evaluations, such as cost-effectiveness analysis, cost-utility analysis, cost-benefit analysis, and cost-minimization analysis [27]. Additionally, budget impact analyses can be conducted to assess the potential total impact of a new health technology on the healthcare budget.

1.3.1 The need for a different class of models

Typical health economic evaluations investigate the long-term effects of using a health technology in a certain disease indication. Hence, they make use of evidence reflecting the long-term, stable impact of the new health technology. In other words, the impact of the imperfect and slow substitution of the current SOC by the new health technology is not taken into account [28]. This perspective is far from ideal when assessing a disruptive health technology such as WGS, as it is more likely that the implementation is gradual. There will be transition phases where the incumbent technology and the new technology co-exist and compete. In a transition phase, short-run inefficiencies may arise as healthcare professionals may need to be re-trained, equipment may be replaced, and logistics may need to be adapted. Thus, the chosen evaluation method must be able to accommodate variations in diffusion and actual use of the new health technology.

Besides the potential occurrence of short-run inefficiencies, the complexity of the healthcare delivery system makes it difficult to assert that a steady state is ever reached. The healthcare delivery system can be described as a complex adaptive system [29], which contains many moving and interacting parts, feedback loops,

and may also adapt to new circumstances. This leads to unpredictable behavior and the effects of changes in complex systems can be nonlinear: a minor or insignificant change in one area of the healthcare system can have large consequences in other areas of the healthcare system. Complex adaptive systems are also able to self-organize or display emergent behavior [30]. Emergence refers to the capability of a system to create order from interactions between system elements. For instance, intense cooperation between hospitals may lead to formal networks and potentially even hospital mergers, causing a change in market concentration. Most importantly, viewing the healthcare delivery system as a complex adaptive system promotes seeing the system as adaptive, and that implementing WGS may lead to unintended consequences.

In addition, most health economic evaluations only assume a constrained healthcare budget. However, other constraints, such as constraints in healthcare system design, implementation costs, system interdependencies, uncertainty in the estimates of costs and benefits, and governance [31], can potentially affect the delivery of health [32]. Yet, this type of constraint typically is very hard to incorporate in currently used health economic models, such as (cohort) state-transition models. Thus, a different class of models is needed to evaluate what the intended and unintended consequences are of implementing WGS in oncology in a constrained health system.

1.3.2 Systems models

A systems model uses the principles of systems science which entails taking a holistic or "big picture" view of complex systems [33]. A systems model is not limited to modeling disease progression, but a wide range of interrelated factors that potentially play a role in the implementation of WGS can be considered, such as clinical, technical, social, and economic factors. Due to interactions within the healthcare delivery system, these are likely correlated in some way. Investigating these factors individually would ignore potential interdependencies in the system. In contrast, a systems perspective acknowledges that interactions may occur, potentially at multiple levels in the system, and aims to quantify them.

Systems models can be implemented as simulation models using Dynamic Simulation Modeling (DSM). DSM is a set of modeling approaches consisting of Systems Dynamics (SD), Discrete-Event Simulation (DES), and Agent-Based Modeling (ABM) [34,35]. SD is an aggregate modeling approach and uses stocks and flows to quantify the relationships within the system. SD is often used for evaluating the potential effects of interventions at the policy level, and within health, its primary field of application is public health [36]. In contrast to SD, both DES and ABM are modeling approaches on the individual level, making it possible to track individual

patients. DES is a process-oriented modeling approach in which passive entities flow through a process that can be characterized as a series of events. Key concepts for DES are delays, resource constraints, and queues. DES has been applied to a wide range of issues in healthcare, such as for modeling screening interventions, health behavior and disease progression [37]. ABM comprises active, potentially interacting, agents that can display individual behavior. A key advantage of ABM is that it can reflect multiple levels of hierarchy of a system. The primary field of application of ABM is in modeling the transmission of infectious diseases and public health [38]. Hybrid models using a combination of SD, DES, and/or ABM can also be created to exploit the comparative advantage of each modeling approach [39].

In a systems model, a simplified version of the real-world healthcare delivery system can be represented. Developing systems models improves understanding of the real-world system and allows for experimentation with policy interventions using so-called "what-if" scenarios. However, the literature on systems models implemented with DSM that prospectively analyze the implementation of a new health technology remains sparse. One study used a hybrid SD-ABM model to assess the cost-effectiveness of mobile stroke units. Their model had interacting modules for economics, disease progression, population dynamics, and healthcare provision [40].

Concretely, there are several reasons for developing a systems model using DSM for the nationwide implementation of WGS. A major reason is that it is not necessary to assume an immediate perfect and complete implementation of WGS in a systems model, as it is possible to assume gradual implementation patterns. Moreover, patient and provider heterogeneity can be reflected and individual patients and their outcomes can be tracked across the continuum of care. Furthermore, a systems model implemented with DSM can have a multi-level structure (e.g., patients within hospitals within a country) and can reflect the complex and fluid care pathways [41] that have become ubiquitous in the context of precision medicine. However, the potential benefits of systems models can only be realized to the extent that data are available, either in the form of individual patient-level data, aggregate data, expert opinion, or assumptions. These potential benefits make systems models implemented as a DSM promising to use for informing a responsible nationwide implementation of WGS.

1.4 Aim and outline of the thesis

This thesis aims to identify the value of WGS from a systems perspective and under which conditions the value of WGS can be realized. The thesis focuses on NSCLC as the role of biomarkers for treatment selection is well established [8] and the NSCLC

patient population is very heterogeneous. Thus, the clinical utility of WGS becomes clearer. The studies presented in this thesis were part of the Technology Assessment of Next Generation Sequencing in Personalized Oncology (TANGO) study in which the comparative advantage of WGS compared to SOC molecular diagnostics is assessed. The research in this thesis was conducted as part of work package 5 of the TANGO study.

Chapter 2 is an expert review of early technology assessment of the use of WGS in personalized oncology, listing the ongoing national initiatives that aim to implement WGS into routine clinical practice. This chapter also introduces the TANGO study.

Chapter 3 is a population-based study on the variation in time-to-treatment for patients with stage III or IV across all hospitals in the Netherlands using patient-level data. Amongst others, the study explored associations between the time-to-treatment and patient and hospital characteristics. The time-to-treatment was compared with recommended maxima applicable in the Netherlands. The results from this chapter are subsequently used to validate the simulated time-to-treatment in the model constructed in chapter 6.

Detailed information on the use of biomarker testing for patients with NSCLC was lacking from existing literature. Therefore, chapter 4 investigated the costs, turnaround times, and utilization of biomarker testing for patients with advanced NSCLC based on data from a large tertiary referral site and from the hospitals the patients were referred from. This resulted in a unique real-world cohort of which the entire biomarker-testing history was known. The model constructed in chapter 6 uses the results from this chapter to define the diagnostic pathways.

Undoing or making a significant change in the direction of the implementation strategy of WGS can be very costly if even possible at all. Therefore, it is important to anticipate potential future developments that may affect the implementation of WGS. Chapter 5 aimed to do just that, by reviewing existing literature, drafting scenarios describing potential future developments, and eliciting probabilities for these scenarios from a diverse group of experts. Chapter 5 informed the implementation scenarios that were simulated in chapter 7.

Chapter 6 describes the systems model that was developed to inform organizational decisions regarding the use of WGS and how these decisions affect the value of WGS. This model was the main method of analysis for this thesis and was partly populated with results from the other chapters. The chapter presents the model development and implementation.

There is still uncertainty regarding for which subgroups of patients WGS will be used, which hospitals will offer WGS to their patients, and the position of WGS in the diagnostic pathway for the near future. To address that uncertainty, chapter 7 aimed to analyze multiple implementation scenarios. The emphasis of this study was on the time-to-treatment, costs, and aggregate demand for WGS. Chapter 7 presents the main results of the thesis.

Finally, chapter 8 concludes this thesis with a discussion of its findings, presents remaining challenges and directions for further research and summarizes its main conclusions.

References

[1] L. Gandhi, D. Rodríguez-Abreu, S. Gadgeel, E. Esteban, E. Felip, F. De Angelis, M. Domine, P. Clingan, M.J. Hochmair, S.F. Powell, S.Y.-S. Cheng, H.G. Bischoff, N. Peled, F. Grossi, R.R. Jennens, M. Reck, R. Hui, E.B. Garon, M. Boyer, B. Rubio-Viqueira, S. Novello, T. Kurata, J.E. Gray, J. Vida, Z. Wei, J. Yang, H. Raftopoulos, M.C. Pietanza, M.C. Garassino, Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer, N. Engl. J. Med. 378 (2018) 2078–2092. https://doi.org/10.1056/nejmoa1801005.

[2] T.S. Mok, Y.-L. Wu, M.-J. Ahn, M.C. Garassino, H.R. Kim, S.S. Ramalingam, F.A. Shepherd, Y. He, H. Akamatsu, W.S.M.E. Theelen, C.K. Lee, M. Sebastian, A. Templeton, H. Mann, M. Marotti, S. Ghiorghiu, V.A. Papadimitrakopoulou, Osimertinib or Platinum–Pemetrexed in EGFR T790M–Positive Lung Cancer , N. Engl. J. Med. 376 (2017) 629–640. https://doi.org/10.1056/nejmoa1612674.

[3] H. Sung, J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, F. Bray, Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries, CA. Cancer J. Clin. 71 (2021) 209–249. https://doi.org/10.3322/caac.21660.

[4] J. Didkowska, U. Wojciechowska, M. Mańczuk, J. Lobaszewski, Lung cancer epidemiology: Contemporary and future challenges worldwide, Ann. Transl. Med. 4 (2016) 1–11. https://doi.org/10.21037/atm.2016.03.11.

[5] Netherlands Cancer Registry, Incidence, Lung/bronchus | Non small-cell lung carcinoma | Small-cell lung carcinoma | Other/unspecified lung cancer, (2021). https://iknl.nl/nkr-cijfers?fs%7Cepidemiologie_id=506&fs%7Ctumor_id=200%2C202%2C203%2C205&fs%7Cregio_id=530&fs%7Cperiode_id=541&fs%7Cgeslacht_id=622&fs%7Cleeftijdsgroep_id=655&fs%7Cjaren_na_diagnose_id=665&fs%7Ceenheid_id=681&cs%7Ctype=line&cs%7CxAxis=tum (accessed July 13, 2021).

[6] E.J. Driessen, M.J. Aarts, G.P. Bootsma, J.G. van Loon, M.L. Janssen-Heijnen, Trends in treatment and relative survival among Non-Small Cell Lung Cancer patients in the Netherlands (1990–2014): Disparities between younger and older patients, Lung Cancer. 108 (2017) 198–204. https://doi.org/10.1016/j.lungcan.2017.04.005.

[7] Netherlands Cancer Registry, Survival, Non small-cell lung carcinoma, Stage at time of diagnosis, TNM, (2021). https://iknl.nl/nkr-cijfers?fs%7Cepidemiologie_id=507&fs%7Ctumor_id=202&fs%7Coverlevingssoort_id=511&fs%7Cklassificatie_stadium_id=616&fs%7Cstadium_id=659&fs%7Cjaren_na_diagnose_id=665%2C666%2C667%2C668%2C669%2C670%2C671%2C672%2C673%2C674%2C675&cs%7Ctype= (accessed July 14, 2021).

[8] B. Melosky, P. Wheatley-Price, R.A. Juergens, A. Sacher, N.B. Leighl, M.-S. Tsao, P. Cheema, S. Snow, G. Liu, P.B. Card, Q. Chu, The rapidly evolving landscape of novel targeted therapies in advanced non-small cell lung cancer, Lung Cancer. (2021). https://doi.org/10.1016/j.lungcan.2021.06.002.

[9] National Comprehensive Cancer Network, Non-Small Cell Lung Cancer (Version 5.2021), (2021). https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.

[10] E.N. Imyanitov, A.G. Iyevleva, E.N. Levchenko, Molecular testing and targeted therapy for non-small cell lung cancer: Current status and perspectives, Crit. Rev. Oncol. Hematol. 157 (2021) 103194. https://doi.org/10.1016/j.critrevonc.2020.103194.

[11] Z. Stark, L. Dolman, T.A. Manolio, B. Ozenberger, S.L. Hill, M.J. Caulfied, Y. Levy, D. Glazer, J. Wilson, M. Lawler, T. Boughtwood, J. Braithwaite, P. Goodhand, E. Birney, K.N. North, Integrating Genomics into Healthcare: A Global Responsibility, Am. J. Hum. Genet. 104 (2019) 13–20. https://doi.org/10.1016/j.ajhg.2018.11.014.

[12] M. Simons, M. van de Ven, V. Coupé, M. Joore, M. IJzerman, E. Koffijberg, G. Frederix, C. Uyl - De Groot, E. Cuppen, W. van Harten, V. Retèl, Early technology assessment of using whole genome sequencing in personalised oncology, Expert Rev. Pharmacoecon. Outcomes Res. 0 (2021) 14737167.2021.1917386. https://doi.org/10.1080/14737167.2021.1917386.

[13] F. Lethimonnier, Y. Levy, Genomic medicine France 2025, Ann. Oncol. 29 (2018) 783–784. https://doi.org/10.1093/annonc/mdy027.

[14] B.L. Burns, G.A. Bilkey, E.P. Coles, F.L. Bowman, J.P. Beilby, N.S. Pachter, G. Baynam, H.J.S. Dawkins, T.S. Weeramanthri, K.J. Nowak, Healthcare system priorities for successful integration of genomics: An Australian focus, Front. Public Heal. 7 (2019) 1–14. https://doi.org/10.3389/fpubh.2019.00041.

[15] C. Turnbull, R.H. Scott, E. Thomas, L. Jones, N. Murugaesu, F.B. Pretty, D. Halai, E. Baple, C. Craig, A. Hamblin, S. Henderson, C. Patch, A. O'Neill, A. Devereaux, K. Smith, A.R. Martin, A. Sosinsky, E.M. McDonagh, R. Sultana, M. Mueller, D. Smedley, A. Toms, L. Dinh, T. Fowler, M. Bale, T. Hubbard, A. Rendon, S. Hill, M.J. Caulfield, The 100 000 Genomes Project: Bringing whole genome sequencing to the NHS, BMJ. 361 (2018) 1–7. https://doi.org/10.1136/bmj.k1687.

[16] Center for Personalized Cancer Treatment, CPCT-02, (n.d.). https://www.cpct.nl/cpct-02/ (accessed February 24, 2020).

[17] D.L. van der Velden, C.M.L. van Herpen, H.W.M. van Laarhoven, E.F. Smit, H.J.M. Groen, S.M. Willems, P.M. Nederlof, M.H.G. Langenberg, E. Cuppen, S. Sleijfer, N. Steeghs, E.E. Voest, Molecular Tumor Boards: Current practice and future needs, Ann. Oncol. 28 (2017) 3070–3075. https://doi.org/10.1093/annonc/mdx528.

[18] S. Vos, J.J.M. van Delden, P.J. van Diest, A.L. Bredenoord, Moral Duties of Genomics Researchers: Why Personalized Medicine Requires a Collective Approach, Trends Genet. 33 (2017) 118–128. https://doi.org/10.1016/j.tig.2016.11.006.

[19] A.L. McGuire, T. Caulfield, M.K. Cho, Research ethics and the challenge of whole-genome sequencing, Nat. Rev. Genet. 9 (2008) 152–156. https://doi.org/10.1038/nrg2302.[20]J.S. Berg, M.J. Khoury, J.P. Evans, Deploying whole genome sequencing in clinical practice and public health: Meeting the challenge one bin at a time, Genet. Med. 13 (2011) 499–504. https://doi.org/10.1097/GIM.0b013e318220aaba.

[21] S.M. Wolf, B.N. Crock, B. Van Ness, F. Lawrenz, J.P. Kahn, L.M. Beskow, M.K. Cho, M.F. Christman, R.C. Green, R. Hall, J. Illes, M. Keane, B.M. Knoppers, B.A. Koenig, I.S. Kohane, B. Leroy, K.J. Maschke, W. McGeveran, P. Ossorio, L.S. Parker, G.M. Petersen, H.S. Richardson, J.A. Scott, S.F. Terry, B.S. Wilfond, W.A. Wolf, Managing incidental findings and research results in genomic research involving biobanks and archived data sets, Genet. Med. 14 (2012) 361–384. https://doi.org/10.1038/gim.2012.23.

[22] S. Narayanasamy, V. Markina, A. Thorogood, A. Blazkova, M. Shabani, B.M. Knoppers, B. Prainsack, R. Koesters, Genomic Sequencing Capacity, Data Retention, and Personal Access to Raw Data in Europe, Front. Genet. 11 (2020) 1–15. https://doi.org/10.3389/fgene.2020.00303.

[23 C.T.B. Pasmans, B.B.J. Tops, E.M.P. Steeghs, V.M.H. Coupé, K. Grünberg, E.K. de Jong, E.M.D. Schuuring, S.M. Willems, M.J. l. Ligtenberg, V.P. Retèl, H. van Snellenberg, E. de Bruijn, E. Cuppen, G.W.J. Frederix, Micro-costing diagnostics in oncology: from single-gene testing to whole- genome sequencing, Expert Rev. Pharmacoeconomics Outcomes Res. 21 (2021) 413–414. https://doi.org/10.1080/14737167.2021.1917385.

[24] Nederlandse Zorgautoriteit [Dutch Healthcare Authority], Tarieventabel dbc-zorgproducten en overige-zorgproducten per 1 januari 2019 [Tariffs dbc-careproducts and other careproducts per January 1 2019], n.d. https://puc.overheid.nl/nza/doc/PUC_236092_22/1/.

[25] M. van de Ven, H. Koffijberg, V. Retèl, K. Monkhorst, E. Smit, W. van Harten, M. IJzerman, Real-World Utilization of Biomarker Testing for Patients with Advanced Non–Small Cell Lung Cancer in a Tertiary Referral Center and Referring Hospitals, J. Mol. Diagnostics. 23 (2021) 484–494. https://doi.org/10.1016/j.jmoldx.2021.01.004.

[26] Nederlandse Zorgautoriteit [Dutch Healthcare Authority], Tarieventabel dbc-zorgproducten en overige-zorgproducten per 1 januari 2020 [Tariffs dbc-careproducts and other careproducts per January 1 2020], n.d. https://puc.overheid.nl/nza/doc/PUC_289994_22/.

[27] A.H. Briggs, K. Claxton, M.J. Sculpher, Decision modelling for health economic evaluation, Oxford University Press, 2006.

[28] G. Van De Wetering, W.H. Woertman, E.M. Adang, Time to incorporate time in cost-effectiveness analysis, Eur. J. Heal. Econ. 13 (2012) 223–226. https://doi.org/10.1007/s10198-011-0374-3.

[29] P.E. Plsek, T. Greenhalgh, The challenge of complexity in health care, Br. Med. J. 323 (2001) 625–628. https://doi.org/10.1136/bmj.323.7313.625.

[30] L. Paina, D.H. Peters, Understanding pathways for scaling up health services through the lens of complex adaptive systems, Health Policy Plan. 27 (2012) 365–373. https://doi.org/10.1093/heapol/czr054.

[31] K. Hauck, R. Thomas, P.C. Smith, Departures from Cost-Effectiveness Recommendations: The Impact of Health System Constraints on Priority Setting, Heal. Syst. Reform. 2 (2016) 61–70. https://doi.org/10.1080/23288604.2015.1124170.

[32] S. Verguet, I. Feldhaus, X. Jiang Kwete, A. Aqil, R. Atun, D. Bishai, M. Cecchini, A.A. Guerra Junior, M.K. Habtemariam, A. Jbaily, O. Karanfil, M.E. Kruk, S. Haneuse, O.F. Norheim, P.C. Smith, M.T. Tolla, S. Zewdu, J. Bump, Health system modelling research: Towards a whole-health-system perspective for identifying good value for money investments in health system strengthening, BMJ Glob. Heal. 4 (2019) 1–5. https://doi.org/10.1136/bmjgh-2018-001311.

[33] P.L. Mabry, D.H. Olster, G.D. Morgan, D.B. Abrams, Interdisciplinarity and Systems Science to Improve Population Health. A View from the NIH Office of Behavioral and Social Sciences Research, Am. J. Prev. Med. 35 (2008) S211–S224. https://doi.org/10.1016/j.amepre.2008.05.018.

[34] D.A. Marshall, L. Burgos-Liz, M.J. Ijzerman, N.D. Osgood, W. V. Padula, M.K. Higashi, P.K. Wong, K.S. Pasupathy, W. Crown, Applying dynamic simulation modeling methods in health care delivery research - The SIMULATE checklist: Report of the ISPOR simulation modeling emerging good practices task force, Value Heal. 18 (2015) 5–16. https://doi.org/10.1016/j.jval.2014.12.001.

[35] J.G. Burke, K.H. Lich, J.W. Neal, H.I. Meissner, M. Yonas, P.L. Mabry, Enhancing Dissemination and Implementation Research Using Systems Science Methods, Int. J. Behav. Med. 22 (2015) 283–291. https://doi.org/10.1007/s12529-014-9417-3.

[36] M.R. Davahli, W. Karwowski, R. Taiar, A system dynamics simulation applied to healthcare: A systematic review, Int. J. Environ. Res. Public Health. 17 (2020) 1–27. https://doi.org/10.3390/ijerph17165741.

[37] X. Zhang, Application of discrete event simulation in health care: a systematic review, BMC Health Serv. Res. 18 (2018) 687. https://doi.org/10.1186/s12913-018-3456-4.

[38] M. Tracy, M. Cerdá, K.M. Keyes, Agent-Based Modeling in Public Health: Current Applications and Future Directions, Annu. Rev. Public Health. 39 (2018) 77–94. https://doi.org/10.1146/annurev-publhealth-040617-014317.

[39] V.H. dos Santos, K. Kotiadis, M.P. Scaparra, A Review of Hybrid Simulation in Healthcare, in: 2020 Winter Simul. Conf., IEEE, 2020: pp. 1004–1015. https://doi.org/10.1109/WSC48552.2020.9383913.

[40] A. Djanatliev, P. Kolominsky-Rabas, B.M. Hofmann, A. Aisenbrey, R. German, Hybrid simulation approach for prospective assessment of Mobile Stroke Units, in: SIMULTECH 2012 - Proc. 2nd Int. Conf. Simul. Model. Methodol. Technol. Appl., 2012: pp. 357–366. https://doi.org/10.5220/0004029603570366.

[41] D.A. Marshall, L.R. Grazziotin, D.A. Regier, S. Wordsworth, J. Buchanan, K. Phillips, M. Ijzerman, Addressing Challenges of Economic Evaluation in Precision Medicine Using Dynamic Simulation Modeling, Value Heal. (2020) 1–8. https://doi.org/10.1016/j.jval.2020.01.016.

Chapter 2

Early Technology Assessment of using Whole Genome Sequencing in Personalized Oncology

Martijn Simons, Michiel van de Ven, Veerle Coupé, Manuela Joore, Maarten IJzerman, Hendrik Koffijberg, Geert Frederix, Carin Uyl-de Groot, Edwin Cuppen, Wim van Harten, Valesca Retèl, on behalf of the TANGO consortium

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Abstract

Introduction

Personalized medicine-based treatments in advanced cancer hold promise to offer substantial important health benefits to genetic subgroups, but require efficient biomarker-based patient stratification to match patients to the right treatment and may be expensive. Standard molecular diagnostics is currently very heterogeneous and tests are often performed sequentially. The alternative Whole Genome Sequencing (WGS), i.e. simultaneously tests for all relevant DNA-based biomarkers thereby allowing immediate selection of the most optimal therapy, is more costly than current techniques. In the current implementation stage, it is important to explore the added value and cost-effectiveness of using WGS on a patient level and to assess optimal introduction of WGS on the level of the healthcare system.

Areas covered

First, an overview of current worldwide initiatives concerning the use of WGS in clinical practice for cancer diagnostics is given. Second, a comprehensive, early Health Technology Assessment approach of evaluating WGS in the Netherlands is described, relating to the following aspects: diagnostic value, WGS-based treatment decisions, assessment of long-term health benefits and harms, early cost-effectiveness modelling, nation-wide organization, and Ethical, Legal and Societal Implications.

Expert opinion

This study provides evidence to guide further development and implementation of WGS in clinical practice and the healthcare system.

Keywords

Genome sequencing, implementation, oncology, Personalized Medicine, Technology Assessment

1. Introduction

Personalized medicine-based treatments in major diseases, such as advanced melanoma and non-small cell lung cancer (NSCLC), offer important health benefits to genetic subgroups [1]. These subgroups are based on genetic aberrations that are found in the genome of the tumor cell, which can be used for the selection of immunotherapies and targeted therapies [1]. Common examples are targets such as EGFR, ALK, ROS1 and BRAF, which can be found in NSCLC and the latter in melanoma [1,2]. However, especially in lung cancer, an increasing number of less common or hard to target genetic aberrations, e.g. RET, MET, HER2, NTRK, and KRAS, is being investigated that can also potentially be used for treatment selection [2,3]. To stratify cancer patients into these genetic subgroups, standard of care (SOC) molecular diagnostics have been introduced in clinical practice. SOC diagnostics can include a variety of tests, including but not limited to next generation sequencing (NGS) panels, Ribonucleic acid (RNA)-based NGS fusion analysis, Sanger sequencing, reverse transcription polymerase chain reaction (RT-PCR), fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC). Each of these tests cover only a single or limited part of relevant genomic changes in coding regions of the genome and are often performed sequentially. This is not ideal, as the tumor material required for multiple tests may not be available and it can be time consuming [4].

Because the number of common and uncommon actionable targets increases over time, it is recommended to use comprehensive NGS techniques over single-gene tests [2]. Whole Genome Sequencing (WGS) simultaneously tests for all relevant genetic aberrations in both coding and non-coding regions of the tumors' genome, thereby allowing immediate selection for optimal therapy [5,6]. This approach is likely to improve patient survival, avoid adverse effects, and to assist in controlling healthcare costs by potentially employing a more efficient diagnostic algorithm. While costs for WGS have decreased spectacularly over the past years, the test costs per patient were still higher than for SOC diagnostics [7-12]. Also, the turnaround time of WGS was initially longer than for SOC. Moreover, evidence on the clinical validity is still scarce, causing WGS to be mainly used in research and not yet fully in clinical practice. Additional challenges such as managing large amounts of WGS data and creating reports that can be used by clinicians for the treatment decision need to be addressed to enable widespread implementation of WGS.

Before widespread implementation, it should be considered whether the additional information obtained by WGS justifies the extra costs and under which conditions. Important questions in this respect are: Does WGS provide additional diagnostic information that would change current clinical decision making?; How large should

the average health benefits in terms of survival gain need to be to make WGS cost-effective?; What are the optimal implementation strategies for introducing WGS and what factors should be considered?; and should we use WGS for all advanced cancer patients, or for a subset?

To support decision making under uncertainty, Health Technology Assessment (HTA) can be used for this type of complex questions in an early stage of development and technology introduction, so-called early HTA. The challenges for HTA in personalized medicine have been described before [13-18] and cover different areas such as clinical utility (evidence generation, reliance on observational data), financial (reimbursement) and technical (turnaround times, diagnostic failures, centralization, test replacement) aspects, and the fast pace and sometimes unpredictable dynamics of innovation and implementation [14,19,20]. In particular for the introduction of WGS in clinical practice, Payne and colleagues described challenges and solutions as a starting point to perform robust HTAs concerning WGS [21]. Schwarze and colleagues found that there is very little health economic evidence base supporting widespread use of Whole Exome Sequencing (WES) and WGS. Most evidence is in rare diseases and congenital diseases, and very little has been reported yet in the oncology field [22].

As there are currently several large initiatives ongoing or in a starting phase concerning the introduction of WGS in clinical oncology practice, we explored the current state-of-the-art of HTA approaches in these programs and how existing challenges for HTA are met. Therefore, in this paper, we first provide an overview of current initiatives on the introduction of WGS in oncology and describe one initiative in detail which includes a comprehensive HTA. Second, we describe the outline of an ongoing comprehensive early HTA of the use of WGS for oncology in the Netherlands.

2. Current international initiatives on implementation of WGS

Stark and colleagues have published an overview of current genome initiatives worldwide [23]. In countries such as the UK, France, Australia, Saudi Arabia, and Turkey, "proof-of-principle" programs are running where workforce- and infrastructure development has been coupled with testing large numbers of patients with rare diseases and cancer, two applications of genomic sequencing expected to have immediate clinical benefits. Other countries such as the US, Denmark, Japan, and Qatar have invested in population-based WGS projects, whereas national

initiatives in Switzerland, the Netherlands, Brazil, and Finland are primarily focusing on the development of infrastructure, such as common standards and data-sharing policies and platforms.

2.1 WGS introduction initiatives incorporating HTA

We performed a scoping review on published literature regarding the use of a type of HTA or health economic evaluations concerning the implementation of WGS in oncology.

A systematic review of Schwarze and colleagues summarized in particular the current health economic (cost-effectiveness) evidence regarding WES and WGS in a clinical setting [22]. They found only one study that performed a full economic evaluation on the use of WGS in oncology regarding incidental findings [24]. In general, there is only limited evidence of the cost-effective use of multigene sequencing in clinical practice of oncology [14,25-29].

Currently, five ongoing programs introducing WGS in clinical practice have incorporated HTA or health economics in some form, and with focus (partly) on oncology. These programs are in the UK; Genomics England: the 100,000 genomes project [30], in France; the French plan for genomic medicine 2016-2025 [31-33]; in Australia: Australian Genomics [23]; the Netherlands [5]; and Europe wide: 1 Million genomes project (2020) [https://b1mg-project.eu/]. Besides the 100,000 genomes project in the UK, none of the programs have reported results regarding HTA studies. In the following paragraphs, we go in more detail of the 100,000 genomes project in the UK, and we will describe the program of the Netherlands, including some first results.

The 100,000 genomes project in the UK performed several qualitative studies about the use of WGS in rare diseases, including but not limited to cancer [34-37]. They investigated the opinions of different stakeholders and found that there is a positive attitude towards WGS. However, stakeholders had concerns about data safety, secondary findings, data sharing, and other practical aspects [34-37]. Additionally, a modelling study demonstrated issues that hindered the utility of actively seeking secondary findings using WGS in patients potentially at risk for breast cancer [38]. To our knowledge, there were no full economic evaluations published.

In the Netherlands, the Hartwig Medical Foundation (HMF) was founded by philanthropy in 2015 to facilitate comprehensive WGS-based cancer diagnostics nation-wide for cancer patients. Forty-three laboratories from medical centers are collaborating in the Center for Personalized Cancer Treatment (CPCT) in which

they send tumor tissue to HMF to perform WGS. The CPCT has set up a pipeline for the collection of fresh frozen tumor tissue and for storage in a central biobank. In parallel, all relevant clinical data are recorded in an electronic case record form and can be linked to the results of the tests performed on the tumor material [39]. Using this biobank, an in-depth retrospective pan-cancer WGS analysis on metastatic tumor and normal genome analysis was performed in 2,500 patients. Based on an analysis of a subset of these patients (n = 1,480), at least one 'clinically actionable' target could be identified for up to 62% of patients [5]. In 31% of this subset, a match was found for an actionable target and a registered and approved therapy.

Based on these important findings, the "Technology Assessment of Next Generation Sequencing in Personalized Oncology (TANGO)" study was funded by the Netherlands Organisation for Health Research and Development (ZonMw). The study aims to provide evidence on the optimal implementation of WGS in clinical practice in oncology. In the following paragraphs, we will describe the design and state-of-the-art of the TANGO study.

3. Design of the TANGO study

In the "Technology Assessment of Next Generation Sequencing in Personalized Oncology (TANGO)" study, we assess the (consequences of) potential implementation of WGS compared to SOC molecular diagnostics, by considering clinical, organizational, economical, ethical/legal and patient related issues for patients with advanced NSCLC and melanoma in the Netherlands. The purpose of the TANGO study is twofold: 1) to expand molecular profiling of tumors to improve immune- and targeted treatment selection in patients with advanced melanoma or NSCLC, and 2) to determine the cost-effectiveness and budget impact of WGS on different system levels to facilitate responsible introduction.

The TANGO study started in January 2017 and will end mid-2021. Approval was obtained for different parts of the study by the relevant medical ethical boards of various hospitals participating in the CPCT-02 study for gathering WGS data, additional clinical data and quality of life (QoL) data. Data management is secured via the Zenodo website [https://zenodo.org/communities/tango-wgs/?page=1&size=20]. When the study ends, (meta-)data, final syntaxes and contact details for, among others, the use of QoL data could be obtained via the website.

In the TANGO project, we distinguish 6 work packages: 1) to determine the diagnostic value of WGS, 2) to analyze treatment decisions based on WGS, 3) to project long-term health benefits and harms by means of micro-simulation using registry data, 4) to estimate the potential cost-effectiveness of WGS compared to SOC, 5) to inform the nation-wide organization of WGS, 6) to assess relevant Ethical, Legal and Societal Implications (ELSI) of WGS. In the following paragraphs, we describe the different work packages (WPs). Figure 1 provides a schematic representation of the TANGO study and Table 1 provides an overview of all key challenges that each work package addresses.

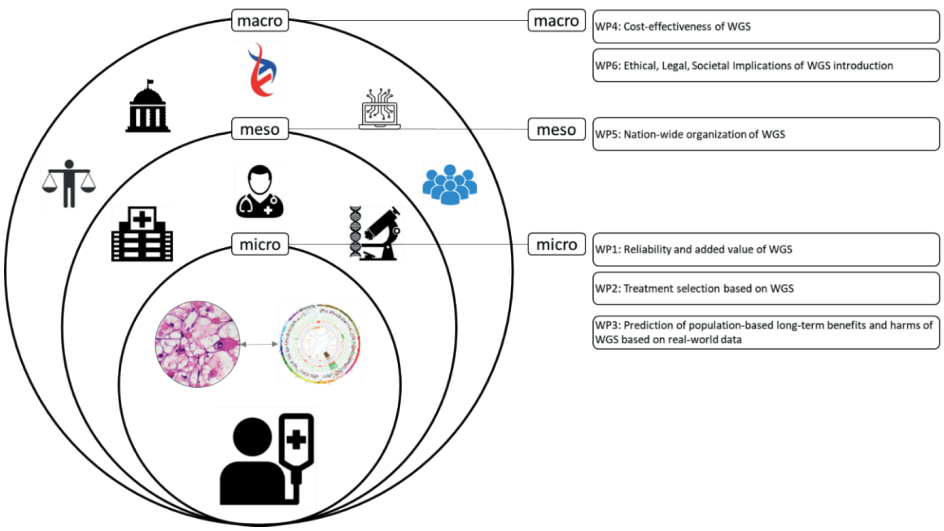

Figure 1. Design "Technology Assessment of Next Generation Sequencing in Personalized Oncology" (TANGO) study

Table 1. Summary of key challenges that each work package within the TANGO study addresses

Work package (WP)	Key challenges addressed
WP1	• Costs of SOC and WGS • Added value of WGS in terms of additional therapeutically relevant molecular aberrations • Logistical and data challenges
WP2	• Clinical benefit of WGS through improved immune- and targeted treatment selection • Biomarker discovery for immunotherapy non-response in advanced NSCLC and melanoma
WP3	• Long-term health benefits and harms of WGS • The effects of improved treatment selection by including a biomarker for immunotherapy non-response
WP4	• Cost-effectiveness of WGS compared to SOC • Wider public benefits of WGS • Uncertainty related to future implementation dynamics
WP5	• The effects of constraints in the organization of care of WGS • Real-world variation in the use of biomarker testing • Uncertainty related to future implementation dynamics
WP6	• Legal and moral duties related for a responsible introduction of WGS • The duty to 're-contact' patients • Practical guidance for moral duties in terms of re-contacting patients

3.1 WP1: Reliability and added value of WGS

A micro-costing study has been performed in which the total resources used for both WGS and SOC were calculated [8]. This paper showed and calculated the impressive decrease of costs for WGS (from € 6676 in 2015 to €2925 in 2020) for a paired tumor-normal WGS. To assess the potential of WGS, currently the number of additional therapeutically relevant molecular aberrations are being established that result from measuring a much larger part of the genome than required for SOC. This includes a retrospective cohort-based collection of data comparing the predictive results from WGS and SOC in advanced NSCLC and melanoma patients. Furthermore, logistical and data challenges are addressed related to implementation and interpretation of WGS in the routine clinical landscape by providing surveys to experts to explore their needs in molecular tumor boards.

3.2 WP2: Treatment selection based on WGS

To demonstrate the value of immune- and targeted treatment selection and outcomes using WGS versus current diagnostics in patients diagnosed with advanced NSCLC and melanoma, clinical data from patients included in the CPCT-

02 study were retrieved. These data will be used to perform retrospective cohort-based genetic biomarker discovery for immunotherapy non-response in advanced NSCLC and melanoma patients. Endpoints will be progression free survival (PFS) at 6 months, response rates, and toxicities. Based on the findings, the most optimal WGS approach in advanced NSCLC and melanoma management can be determined. In the modeling work packages described later on, several potential approaches will be explored by means of scenario analysis.

Patients participating in the CPCT-02 study from 3 hospitals in the Netherlands were approached and asked to fill in a questionnaire concerning their health related quality of life (HRQoL), utilities, productivity and informal care. These aspects were measured by means of the European Organisation for Research and Treatment of Cancer questionnaire (EORTC-QLQ-C30), EuroQol 5D-5L, productivity and informal care questions selected from the modular questionnaire on productivity and disease for economic evaluation studies (PRODISC) [40-42]. The objective is to prospectively determine the patient reported outcomes and social consequences of patients with metastatic cancers treated with personalized treatment compared to those who were not.

3.3 WP3: Prediction of population-based long-term health benefits and harms of WGS

To project the long-term health benefits and harms, we will develop and validate two patient-level micro-simulation models of the treatment trajectory of patients with metastatic NSCLC and advanced melanoma in the Netherlands. We will use patient registry data to build the models. As patient registries usually lag behind in their registration and novel treatments are included in clinical guidelines and clinical practice at a rapid pace, the registry-based models need to be complemented with treatment effect estimates based on the latest literature. Furthermore, the outcomes of the biomarker discovery study for the identification of immunotherapy non-response will be included in the models to project potential long-term impact of improved selection for immunotherapy.

3.4 WP4: Cost-effectiveness of WGS compared to SOC

The cost-effectiveness and wider public benefits of WGS versus SOC for advanced NSCLC are being assessed, as a blueprint for tumor-overarching modeling. First, a systematic review was performed on the long-term treatment effects of targeted therapies and immunotherapies in patients with metastatic NSCLC [43].

Next, uncertainty resulting from unknown future implementation dynamics of WGS were explored in scenario analysis. Inspired by Royal Dutch Shell future scenario methodology, scenario analysis has been used before as a way to inform policy making in early stages of technology implementation with considerable degree of uncertainty [44]. In a step-wise process with many national and international experts and stakeholders, scenarios describing the possible future use of WGS as a molecular diagnostic in oncology were drafted and scored on likelihood to occur within the coming 5 years.

Subsequently, a cost-effectiveness (CE)-model regarding the use of WGS compared to SOC diagnostics in advanced NSCLC patients was constructed using the earlier work. Outcomes of the cost-effectiveness analysis were expected costs, effects (quality adjusted life year), and incremental cost-effectiveness ratio (ICER). Input was based on literature, including the systematic review [43] and extensive expert opinions. The aim of the CE-model was to estimate the ranges where WGS is potentially cost-effective compared to SOC. In ongoing analyses, the abovementioned scenarios will be quantified and incorporated in the CE-model. This model can be applied iteratively for policy making when new data become available. A final step will be to incorporate the scenarios into the CE-model, which will give a direction for future research by means of estimating the Expected Value of Perfect Partial Information.

3.5 WP5: Nationwide organization of WGS

To evaluate the interaction between providing WGS services and clinical management of NSCLC patients across a wide range of health services in the Netherlands, Dynamic Simulation Modeling (DSM) is used. It is increasingly recognized that to realize the potential value of WGS, the organization of care and constraints therein need to be considered. Amongst others, the biomarker testing strategy needs to be adapted, capacity constraints to conduct WGS and to provide a clinical interpretation must be addressed. However, it is debated whether current HTA methods are suitable for incorporating such considerations [15-18].

Therefore, a simulation model is being developed using DSM. DSM is a group of modeling methods consisting of Discrete-Event Simulation, Agent-Based Modeling and System Dynamics. These methods are well suited to capture the dynamics of the care delivery process, introduce real-world decision points, better handle discrete-time intervals and related interactions between events throughout the treatment episode [45,46]. Because of their versatility, these modeling methods can be used to evaluate the intended and unintended consequences of implementing WGS on system level, to estimate the resources required, and freed, at different levels, including the strategic and tactical level. The model was primarily populated with

patient-level data from existing real-world registries, complemented with expert opinion from the associations of e.g. medical (lung) oncologists, pathologists, and the WGS facility in the Netherlands. For instance, evidence about the process of care delivery, including delays in treatment [47] and biomarker test utilization [48] has been included. Based on these data, the developed simulation model can evaluate the interaction between providing WGS services and clinical management of NSCLC patients, with outcomes such as total duration of the diagnostic pathway, and cost per patient of biomarker testing.

3.6 WP6: Ethical, legal and societal implications (ELSI) of implementation of WGS

On the topic of the legal and moral duties related to a responsible introduction of WGS, the most important question we defined, is whether medical professionals carry a responsibility to 're-contact' their patients if they, while doing research with their patient data, discover new information about their patients which sheds new light on the initial treatment or provides new or additional options. First, the legal framework has been published, where we found that there are no explicit legal duties, but recommended that re-contact is a duty of effort [49]. Experts have been interviewed regarding this emerging duty, with the main finding that the variation in opinion demonstrated that further deliberations are desirable [50]. An overview of the literature regarding the moral duties showed that practical guidance is needed, and we provided 6 relevant factors that have to be taken into account (information features, costs and efforts, personal preferences, who is contacted, clinic or research setting, and time) [51]. The next step was organizing focus groups with patients and healthcare professionals to find consensus. While no roadblocks were identified, the final step is to combine the legal and ethical points of view and write recommendations for clinical practice.

4 . Conclusion

Currently, large international programs are ongoing and building up evidence to support the implementation of WGS in oncology clinical practice. HTA or health economics are in various degrees integrated in some of these programs, but challenges in methodology are apparent. We described a comprehensive approach of an implementation project of WGS in the Netherlands, where we involve geneticists, pathologists, clinicians, HTA experts and ethical and legal experts. With close collaboration and continuous integration of work packages, we strive for a comprehensive assessment framework as a first step towards responsible and optimal implementation of WGS in oncology practice in the Netherlands.

The current publications of the TANGO study have shown that challenges were identified in the present cost levels of WGS, jeopardizing cost-effectiveness and as a consequence coverage. Also, the current time-to-treatment and diagnostic pathways for SOC show long and complex pathways that may be simplified using comprehensive WGS-based diagnostics. The optimal way to organize or centralize services is yet to be determined and professionals should be prepared to inform patients and their relatives in earlier and later stages on secondary findings related to new treatment options or (familiar) disease risks.

In the near future, the ongoing work on the reliability of WGS compared to SOC, on a potential new biomarker to select non-responders of immunotherapy and the modeling work packages are being expected to present more evidence to support further (discussion on) implementation of WGS in clinical oncology practice.

5. Expert opinion

5.1. How could the advances or research being discussed impact real world outcomes (diagnosis, treatment guidelines, effectiveness, economics, drug utilization etc.)? Can changes be realistically implemented into clinical/research practice? What is preventing adoption in clinical practice?

There are several aspects identified that cause WGS to be not yet widely adopted in clinical practice. In view of the absence of exact diagnostic yield and actionable targets and related effectiveness and the presently high costs of establishing these services, the healthcare system is not fully equipped to handle the reimbursement question. Current HTA approaches do not seem to fit in the context of WGS for several reasons. In the TANGO study, we observe that the micro-costing study results were already outdated before it was published, because of the rapidly decrease of the price of WGS. Such analyses therefore should be constantly updated. In applying real-world data in cost-effectiveness modeling, we observed that real-world data is often lagging behind the current diagnostic and treatment standards. For full cost-effectiveness analyses there is a lack of up-to-date evidence regarding survival and quality-of-life. Furthermore, a cost-effectiveness analysis is often performed for one tumor type, which means that many CEAs should be performed as WGS could be potentially valuable for other tumor types as well. With the TANGO study, we aim to provide more evidence from various perspectives, in order to show the broader "added value" of WGS. To assess the impact for different tumor types, we most likely need a change in the healthcare system in the future, for example a learning healthcare system to have a feedback loop from research to clinic and back to build

an adequate knowledge base, with accompanying financial support. Large, nationwide data sets and linkages between pathology, WGS and clinical data are necessary to monitor and evaluate these type of diagnostic technologies in e.g. Personalized Medicine. To enable these linkages and to share data, digital pathology and data warehouses are necessary. It is inevitable that in these cases the investments have to be made before the benefits are fully known. The challenge is to obtain enough insights in the still uncertain benefits, to invest at the earliest possible time. Therefore, flexible and alternative financial arrangements are necessary.

5.2. *What are the key areas for improvement in the area being discussed and how can current problems and limitations be solved? Are there any technical, technological, or methodical limitations that prevent research from advancing as it could?*

In the TANGO study, the implementation of WGS was approached with three different types of models, due to the early stages and to incorporate the decision uncertainty. The "added value" of WGS cannot be easily summarized and assessed in a "conventional" HTA approach. First, for some tumor types new targets are found and offer added clinical benefit, while for other types this is not so straightforward. The added value is broader than health benefits alone, and also includes HRQoL, avoidance of adverse effects, costs, and wider public benefits and workability, macro-economic value for diagnostic labs and other social factors. Second, a "standard" control group is difficult to define, as WGS is mostly applied in very advanced tumors after several lines of therapy and it is currently unclear what the impact would be when WGS is performed early in the disease process [52]. New trial designs are promising for patients access, however there are also many unsolved issues, such as the small group analytics which could be necessary for this field but is likely to meet resistance in accepting the outcomes from traditional methodologists. Moreover, as WGS can be used in a tumor agnostic approach, this leads to a complex comparison. Regarding the technical considerations about platforms to perform this analyses, this is clearly a field that is in development. Sequencing platforms appear from different vendors, probably reducing the price per test through increased competition. The scale of testing and degree of centralization are still to be established with consequences for sample logistics and data warehousing and data management. Lastly, the expertise to interpret and take decisions based on the information, for instance through institutional or regional tumor boards, has to be built up and integrated in pathway decision making. Therefore, the optimal scale of introduction (i.e. degree of centralization) still has to be established.

5.3. What potential does further research hold? Is there a definitive end-point?

There are many additional values of WGS to mention, which are not easy to express in either life years, QoL or costs. Initially, clinical benefits are most likely to occur in the identification of actionable targets and in additional treatment options in metastatic disease. Subsequently, the scope of biomarker-based treatment decisions may expand to include earlier stages of disease. Another angle could be the macro-economic approach from a laboratory perspective; what does it mean to substitute certain standard tests with WGS?

In the Netherlands, there are currently two studies ongoing which may, in addition to the TANGO study, provide additional evidence on the value of WGS. In the first study, "WGS Implementation in the standard Diagnostics for Every cancer patient" (WIDE), tumor tissue of advanced cancer patients undergo both SOC and WGS. The aim of this study involving 1200 patients is to demonstrate feasibility of WGS-based diagnostics in routine practice, clinically validate WGS results compared to SOC, to identify potential added value for WGS, and to estimate the pan-tumor cost-effectiveness of WGS compared to SOC [53]. The second study, the Drug Rediscovery Protocol (DRUP) study is a basket and umbrella trial where treatments are tumor type-agnostic and based on defined mutational profiles associated with approved targeted (or immuno-) therapies [54]. Combining the results with all other ongoing studies as mentioned before, and (future) research in HTA is necessary to support the implementation and coverage of new diagnostic technologies enabling personalized medicine, such as WGS.

5.4. Does the future of study lie in this area? Are there other more promising areas in the field which could be progressed?

The TANGO study is unique in the sense that it investigates the introduction of WGS from various perspectives, not only clinical and cost-effectiveness. As personalized medicine based on comprehensive diagnostics is becoming increasingly integrated in clinical practice, we have to continue searching for more suitable HTA methods.

Apart from the topics raised above, it would be interesting to (broadly) assess whether liquid biopsies are a reliable source for tumor DNA for WGS. This would improve the accessibility of tumor DNA considerably, and if proven sufficiently representative of the original or relevant tumor sites, enables a wider scope of tumors to be covered by this technology.

5.5. How will the field evolve in the future? In your perspective, what will the standard procedure have gained or lost from the current norm in five or ten years?

Whole Genome Analysis, DNA and RNA sequencing is a dynamic field of diagnostics, many new developments in this area are evolving quickly. We believe that WGS could be reimbursed for some indications on the short term, if the added clinical value has been sufficiently proven and is accepted by relevant healthcare professionals.

While DNA sequencing technology has matured rapidly in the past decade and the basis of cancer resides in DNA errors, it is clear that other molecular measurements like transcriptomics, proteomics and metabolomics of both tumor and microenvironment are also highly relevant for understanding and predicting therapy response. However, today these technologies are less mature in terms of comprehensive and scalable measurement possibilities, lack the ability to use small amounts of biopsy material, or have limited clinical actionability. This is very likely to change in the next decade, which poses an additional challenge on cost management for covering all relevant molecular tumor characterizations.

Taking into account the diversity of cancer genomes and phenotypes, interpretation of the mutational data from cancer WGS will also require the analysis of much more WGS data and integration with multi-omics data, functional data, immuno-genomic data and clinic-pathological data in a larger sample set [6]. In addition, environmental and life style factors do also play a role, but pose an extra challenge as such data is not routinely collected in a clinical setting or systematically available for all patients from other sources.

When WGS is used systematically in a care system and integrated with extensive clinical and patient data, novel approaches for data mining and therapy response predications at individual patient level will be required to enable personalized treatments. Novel developments in machine learning and artificial intelligence approaches in combination with integrated molecular, pathological, and epidemiology data generation approaches are likely going to be instrumental to enable a learning care system that is continuously fed by new patient data and returns options for care improvements for future patients [55,56].

Besides WGS as a concrete example, the healthcare system faces comparable challenges. In view of increasing financial stress on the healthcare system, the way we perform research “from bench-to-bedside” must become more focused on the added clinical value in earlier stages. It needs to be more integrated in clinical practice to

guarantee innovations successfully reach patients as soon as possible. HTA will be an important tool in this process, assessed in a much earlier phase than it is currently to ascertain efficient allocation of research and healthcare budgets.

5.6. How do you see this area unfolding in the next 5 years?

The reimbursement status of WGS as a cancer diagnostic will have a significant effect on the wide-scale use of this technology. In the Netherlands, coverage largely depends on proving the cost effectiveness of WGS. This is a major challenge, as no study has yet been able to show that WGS is in fact cost-effective. However, a conditional coverage title was recently granted for patients with a carcinoma of unknown primary (CUP) and last resort patients, which improves the access to WGS for these groups of patients.

The ICER of WGS, a measure of the cost effectiveness of WGS compared with the SOC, will become more favorable if the cost of WGS and subsequent treatment decreases or if the health benefit for patients will increase through more effective treatments and improved patient selection. This may be achieved by discovering new biomarkers that can be detected with WGS to select patients for immunotherapies and targeted therapies, or by discovering biomarkers that help prevent prescribing ineffective treatments. We believe that biomarker discovery will be an ongoing challenge, as it turns out that it is more complex compared to conventional biomarkers.

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Declaration of interest

MJHGS, HK, MAJ, MvdV, VMHC, EPJC have nothing to disclose. MJIJ received unrestricted research funding and consulting fees from Illumina and RTI Health Solutions. VR and WvH received unrestricted research funding from Agendia BV and Intuitive Inc.

References

Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.

1. Marquart J, Chen EY, Prasad V. Estimation of the Percentage of US Patients With Cancer Who Benefit From Genome-Driven Oncology. *JAMA oncology*, 4(8), 1093-1098 (2018).
2. Lamberti G, Andrini E, Sisi M *et al.* Beyond EGFR, ALK and ROS1: Current evidence and future perspectives on newly targetable oncogenic drivers in lung adenocarcinoma. *Critical Reviews in Oncology/Hematology*, 156, 103119 (2020).
3. Mosele F, Remon J, Mateo J *et al.* Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group. *Annals of Oncology*, 31(11), 1491-1505 (2020).
4. Popper HH, Tímár J, Ryska A, Olszewski W. Minimal requirements for the molecular testing of lung cancer. *Transl Lung Cancer Res*, 3(5), 301-304 (2014).
5. Priestley P, Baber J, Lolkema MP *et al.* Pan-cancer whole-genome analyses of metastatic solid tumours. *Nature*, 575(7781), 210-216 (2019).

   * **This article reports genetic variants identified with WGS that can be used for targeted treatment selection and demonstrates the importance of comprehensive genomic tumor profilin for precision medcine in cancer.**
6. Nakagawa H, Fujita M. Whole genome sequencing analysis for cancer genomics and precision medicine. *Cancer Science*, 109(3), 513-522 (2018).
7. Katsila T, Patrinos GP. Whole genome sequencing in pharmacogenomics. *Front Pharmacol*, 6, 61 (2015).
8. Pasmans CT, Tops BB, Steegs EM *et al.* Micro-costing Diagnostics in Oncology: From Single-Gene Testing to Whole Genome Sequencing. *medRxiv*, 19009969 (2019).
9. Schwarze K, Buchanan J, Fermont JM *et al.* The complete costs of genome sequencing: a microcosting study in cancer and rare diseases from a single center in the United Kingdom. *Genetics in Medicine*, 22(1), 85-94 (2020).
10. van Nimwegen KJ, van Soest RA, Veltman JA *et al.* Is the $1000 Genome as Near as We Think? A Cost Analysis of Next-Generation Sequencing. *Clin Chem*, 62(11), 1458-1464 (2016).
11. Plöthner M, Frank M, von der Schulenburg JMG. Cost analysis of whole genome sequencing in German clinical practice. *The European Journal of Health Economics*, 18(5), 623-633 (2017).
12. Gordon LG, White NM, Elliott TM *et al.* Estimating the costs of genomic sequencing in cancer control. *BMC Health Services Research*, 20(1), 492 (2020).
13. Chenoweth MJ, Giacomini KM, Pirmohamed M *et al.* Global Pharmacogenomics Within Precision Medicine: Challenges and Opportunities. *Clin Pharmacol Ther*, 107(1), 57-61 (2020).
14. Weymann D, Pataky R, Regier DA. Economic Evaluations of Next-Generation Precision Oncology: A Critical Review. *JCO Precision Oncology*, (2), 1-23 (2018).
15. Degeling K, Koffijberg H, MJ IJ. A systematic review and checklist presenting the main challenges for health economic modeling in personalized medicine: towards implementing patient-level models. *Expert Rev Pharmacoecon Outcomes Res*, 17(1), 17-25 (2017).

16. Marshall DA, Grazziotin LR, Regier DA *et al.* Addressing Challenges of Economic Evaluation in Precision Medicine Using Dynamic Simulation Modeling. *Value Health*, 23(5), 566-573 (2020).

17. Phillips KA, Deverka PA, Marshall DA *et al.* Methodological Issues in Assessing the Economic Value of Next-Generation Sequencing Tests: Many Challenges and Not Enough Solutions. *Value Health*, 21(9), 1033-1042 (2018).

18. Faulkner E, Holtorf A-P, Walton S *et al.* Being Precise About Precision Medicine: What Should Value Frameworks Incorporate to Address Precision Medicine? A Report of the Personalized Precision Medicine Special Interest Group. *Value in Health*, 23(5), 529-539 (2020).

19. Barwell JG, O'Sullivan RBG, Mansbridge LK, Lowry JM, Dorkins HR. Challenges in implementing genomic medicine: the 100,000 Genomes Project. *Journal of Translational Genetics and Genomics*, 2, 13 (2018).

20. Love-Koh J, Peel A, Rejon-Parrilla JC *et al.* The Future of Precision Medicine: Potential Impacts for Health Technology Assessment. *PharmacoEconomics*, 36(12), 1439-1451 (2018).

21. Payne K, Eden M, Davison N, Bakker E. Toward health technology assessment of whole-genome sequencing diagnostic tests: challenges and solutions. *Personalized Medicine*, 14(3), 235-247 (2017).

22. Schwarze K, Buchanan J, Taylor JC, Wordsworth S. Are whole-exome and whole-genome sequencing approaches cost-effective? A systematic review of the literature. *Genet Med*, 20(10), 1122-1130 (2018).

*** This articles reviews and summarizes the current health economic evidence for whole exome (WES) and whole genome sequencing (WGS). They found that health economic evidence is limited and urge the need for studies that carefully evaluate the costs, effectiveness, and cost-effectiveness to support the translation of WES and WGS into clinical practice.**

23. Stark Z, Dolman L, Manolio TA *et al.* Integrating Genomics into Healthcare: A Global Responsibility. *The American Journal of Human Genetics*, 104(1), 13-20 (2019).

*** This article reviews the diversity of approaches and current progress made by national genomic-medicine initiatives in the UK, France, Australia, and US and provide a roadmap for sharing strategies, standards, and data internationally to accelerate implementation.**

24. Bennette CS, Gallego CJ, Burke W, Jarvik GP, Veenstra DL. The cost-effectiveness of returning incidental findings from next-generation genomic sequencing. *Genet Med*, 17(7), 587-595 (2015).

25. Tan AC, Lai GGY, Tan GS *et al.* Utility of incorporating next-generation sequencing (NGS) in an Asian non-small cell lung cancer (NSCLC) population: Incremental yield of actionable alterations and cost-effectiveness analysis. *Lung Cancer*, 139, 207-215 (2020).

26. Tan O, Shrestha R, Cunich M, Schofield DJ. Application of next-generation sequencing to improve cancer management: A review of the clinical effectiveness and cost-effectiveness. *Clinical Genetics*, 93(3), 533-544 (2018).

27. Veenstra DL, Mandelblatt J, Neumann P, Basu A, Peterson JF, Ramsey SD. Health Economics Tools and Precision Medicine: Opportunities and Challenges. *Forum Health Econ Policy*, 23(1) (2020).

28. Steuten L, Goulart B, Meropol NJ, Pritchard D, Ramsey SD. Cost Effectiveness of Multigene Panel Sequencing for Patients With Advanced Non–Small-Cell Lung Cancer. *JCO Clinical Cancer Informatics*, (3), 1-10 (2019).
29. Buchanan J, Wordsworth S. Evaluating the Outcomes Associated with Genomic Sequencing: A Roadmap for Future Research. *PharmacoEconomics - Open*, 3(2), 129-132 (2019).
30. Turnbull C, Scott RH, Thomas E *et al.* The 100 000 Genomes Project: bringing whole genome sequencing to the NHS. *Bmj*, 361, k1687 (2018).
31. Lethimonnier F, Levy Y. Genomic medicine France 2025. *Ann Oncol*, 29(4), 783-784 (2018).
32. Lévy Y. Genomic medicine 2025: France in the race for precision medicine. *The Lancet*, 388(10062), 2872 (2016).
33. Lejeune C, Amado IF. Valuing genetic and genomic testing in France: current challenges and latest evidence. *J Community Genet*, (2021).
34. Lewis C, Hammond J, Hill M *et al.* Young people's understanding, attitudes and involvement in decision-making about genome sequencing for rare diseases: A qualitative study with participants in the UK 100, 000 Genomes Project. *European Journal of Medical Genetics*, 63(11), 104043 (2020).
35. Lewis C, Sanderson S, Hill M *et al.* Parents' motivations, concerns and understanding of genome sequencing: a qualitative interview study. *European Journal of Human Genetics*, 28(7), 874-884 (2020).
36. Sanderson SC, Hill M, Patch C, Searle B, Lewis C, Chitty LS. Delivering genome sequencing in clinical practice: an interview study with healthcare professionals involved in the 100 000 Genomes Project. *BMJ Open*, 9(11), e029699 (2019).
37. Hassan L, Dalton A, Hammond C, Tully MP. A deliberative study of public attitudes towards sharing genomic data within NHS genomic medicine services in England. *Public Understanding of Science*, 29(7), 702-717 (2020).
38. Warren-Gash C, Kroese M, Burton H, Pharoah P. Implications of using whole genome sequencing to test unselected populations for high risk breast cancer genes: a modelling study. *Hereditary Cancer in Clinical Practice*, 14(1), 12 (2016).
39. Bins S, Cirkel GA, Gadellaa-Van Hooijdonk CG *et al.* Implementation of a Multicenter Biobanking Collaboration for Next-Generation Sequencing-Based Biomarker Discovery Based on Fresh Frozen Pretreatment Tumor Tissue Biopsies. *The Oncologist*, 22(1), 33-40 (2017).
40. Aaronson NK, Ahmedzai S, Bergman B *et al.* The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*, 85(5), 365-376 (1993).
41. Foundation ER. EQ-5D-5L User Guide. (Ed.^(Eds) (2019)
42. Koopmanschap MA. PRODISQ: a modular questionnaire on productivity and disease for economic evaluation studies. *Expert Review of Pharmacoeconomics & Outcomes Research*, 5(1), 23-28 (2005).
43. Simons M, Ramaekers B, Peeters A *et al.* Observed versus modelled lifetime overall survival of targeted therapies and immunotherapies for advanced non-small cell lung cancer patients - A systematic review. *Crit Rev Oncol Hematol*, 153, 103035 (2020).

* **This article is a systematic review that provides and overview of all published overall survival data of targeted therapies and immunotherapies in locally advanced and metastatic Non-small cell lung cancer. They digitized the survival data and provided the modelled output, which can be used to inform decision analytic models. Additionally, their findings also provide additonal proof for the limited capability of the programmed death-ligand 1 biomarker for identifying patients that benefit from immunotherapies.**

44. Retèl VP, Joore MA, Linn SC, Rutgers EJT, van Harten WH. Scenario drafting to anticipate future developments in technology assessment. *BMC Research Notes*, 5(1), 442 (2012).

45. Crown W, Buyukkaramikli N, Sir MY *et al.* Application of Constrained Optimization Methods in Health Services Research: Report 2 of the ISPOR Optimization Methods Emerging Good Practices Task Force. *Value Health*, 21(9), 1019-1028 (2018).

46. Marshall DA, Burgos-Liz L, MJ IJ *et al.* Applying dynamic simulation modeling methods in health care delivery research-the SIMULATE checklist: report of the ISPOR simulation modeling emerging good practices task force. *Value Health*, 18(1), 5-16 (2015).

47. van de Ven M, Retèl VP, Koffijberg H, van Harten WH, Ijzerman MJ. Variation in the time to treatment for stage III and IV non-small cell lung cancer patients for hospitals in the Netherlands. *Lung Cancer*, 134, 34-41 (2019).

* **This article provides an overview of variation in time to treatment for stage III and IV Non-small cell lung cancer patients for hospitals in the Netherlands, based on real word data, which can be used to inform decision analytic models.**

48. van de Ven M, Koffijberg H, Retèl V *et al.* Real-world utilization of biomarker testing for patients with advanced non-small-cell lung cancer in a tertiary referral center and referring hospitals. *J Mol Diagn*, (2021).

49. Ploem C, Mitchell C, van Harten W, Gevers S. A Duty to Recontact in the Context of Genetics: Futuristic or Realistic? *European Journal of Health Law*, 25(5), 537-553 (2018).

* **This article discusses the legal duty of health professionals and importance of recontacting patients when new information is discovered that links a disease to a specific mutaiton based on next generation sequencing data.**

50. Mitchell C, Ploem C, Retèl V, Gevers S, Hennekam R. Experts reflecting on the duty to recontact patients and research participants; why professionals should take the lead in developing guidelines. *Eur J Med Genet*, 63(2), 103642 (2020).

* **This article discusses the opinions of senior professionals with different backgrounds within the field of oncology from the UK and the Netherlands on possible and desirable obligations regarding the duty to recontact patients.**

51. Giesbertz NAA, van Harten WH, Bredenoord AL. A duty to recontact in genetics: context matters. *Nat Rev Genet*, 20(7), 371-372 (2019).

* **This article provides an outline of arguments in favour and against recontacting patients about new genetic information or developments that are relevant to their health. Additionaly, factors are discussed that influence a duty to recontact patients.**

52. Janiaud P, Serghiou S, Ioannidis JPA. New clinical trial designs in the era of precision medicine: An overview of definitions, strengths, weaknesses, and current use in oncology. *Cancer Treat Rev*, 73, 20-30 (2019).

53. Samsom KG, Bosch LJW, Schipper LJ *et al.* Study protocol: Whole genome sequencing Implementation in standard Diagnostics for Every cancer patient (WIDE). *BMC Medical Genomics*, 13(1), 169 (2020).

* **This protocol is of the Whole genome sequencing Implementation in standard Diagnostics for Every cancer patient (WIDE) study. The WIDE study aims to investigate the feasibility and validity of WGS-based diagnostics in clinical practice in the Netherlands.**

54. van der Velden DL, Hoes LR, van der Wijngaart H *et al.* The Drug Rediscovery protocol facilitates the expanded use of existing anticancer drugs. *Nature*, 574(7776), 127-131 (2019).

* **This article is about the Drug Rediscovery protocol which facilitates the defined use of approved drugs beyond their labels in rare subgroups of cancer, identifies early signals of activity in these subgroups, accelerates the clinical translation of new insights into the use of anticancer drugs outside of their approved label, and creates a publicly available repository of knowledge for future decision-making.**

55. Hamada T, Nowak JA, Milner DA, Song M, Ogino S. Integration of microbiology, molecular pathology, and epidemiology: a new paradigm to explore the pathogenesis of microbiome-driven neoplasms. *J Pathol*, 247(5), 615-628 (2019).

56. Ogino S, Nishihara R, VanderWeele TJ *et al.* Review Article: The Role of Molecular Pathological Epidemiology in the Study of Neoplastic and Non-neoplastic Diseases in the Era of Precision Medicine. *Epidemiology*, 27(4), 602-611 (2016).

Chapter 3

Variation in the time to treatment for stage III and IV Non-Small Cell Lung Cancer patients for hospitals in the Netherlands

Michiel van de Ven, Valesca Retèl, Hendrik Koffijberg, Wim van Harten, Maarten IJzerman

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Abstract

Objectives

Increased emphasis on molecular diagnostics can lead to increased variation in time to treatment (TTT) for patients with stage III and IV non-small cell lung cancer. This article presents the variation in TTT for advanced NSCLC patients observed in Dutch hospitals before the widespread use of immunotherapy. The aim of this article was to explore the variation in TTT between patients, as well as between hospitals.

Materials and Methods

Based on the Netherlands Cancer Registry, we used patient-level data (n = 4,096) from all 78 hospitals that diagnosed stage III or IV NSCLC in the Netherlands in 2016. To investigate how patient characteristics and hospital-level effects are associated with TTT (from diagnosis until start treatment), we interpreted regression model results for five common patient profiles to analyze the influence of age, gender, tumor stage, performance status, histology, and referral status as well as hospital-level characteristics on the TTT.

Results and Conclusion

TTT varies substantially between and within hospitals. The median TTT was 28 days with an inter-quartile range of 22 days. The hospital-level median TTT ranges from 17 to 68 days. TTT correlates significantly with tumor stage, performance status, and histology. The hospital-level effect, unrelated to hospital volume and type, affected TTT by several weeks at most. For most patients, TTT is within range as recommended in current guidelines. Variation in TTT seems higher for patients receiving either radiotherapy or targeted therapy, or for patients referred to another hospital and we hypothesize this is related to the complexity of the diagnostic pathway. With further advances in molecular diagnostics and precision oncology we expect variation in TTT to increase and this needs to be considered in designing optimal cancer care delivery.

Keywords

Time to treatment; non-small cell lung cancer; delay, diagnostic; treatment; cancer registry

1. Introduction

Non-small cell lung cancer (NSCLC) is a heterogeneous group of tumors that make up approximately 73% of lung cancers in the Netherlands [1]. 75% of patients with NSCLC are diagnosed with a tumor already at an advanced stage (stage IIIA, IIIB or IV) [2]. These patients typically have a poor prognosis. For example, median survival times are approximately 2 and 9 months, for untreated patients with stage IV NSCLC and systemically treated patients with stage IV NSCLC, respectively [3]. In order to improve their survival, increased emphasis is put on targeted therapy and immunotherapy in NSCLC [4,5]. Use of either treatment modalities requires detailed molecular testing for mutation analysis. Some of these molecular diagnostics can have a long turnaround time and thus potentially impose an increased time to treatment (TTT) [6]. While the association between TTT and mortality remains unclear in lung cancer [7], more evidence begins to indicate that a longer TTT is associated with poorer outcomes [8].

Previous research on TTT for lung cancer patients in the Netherlands has focused on a subset of patients [9], which makes a national, comprehensive analysis impossible. In addition, previous research on hospital variation in the Dutch setting in diagnostics or treatments for NSCLC patients has mostly looked at the utilization of care in the years 2001 until 2012 [10,11], or with only a relatively small sample of Dutch hospitals, probably reducing representativeness [12,13]. Previous studies conducted in other countries that analyzed the TTT for lung cancer patients nationally or regionally showed large variability. For example, a median TTT of 20 days and very large institutional variation was observed in Belgium [14]. A median TTT of 40 days and large regional variation was found in Canada [15], and 90% of first treatments started within 115 days. For 22 hospitals in Spain, the median TTT for lung cancer was 39 days [16].

TTT depends on several factors. The TTT consists of a diagnostic delay and a treatment delay [17]. Important components of the time to treatment is the turnaround time of diagnostic tests, hospital capacity for conducting diagnostic tests and initiating treatment. Moreover, referrals for treatment can also impact the time to treatment. It is possible that hospitals have designed their diagnostics pathway such that they will diagnose most of their patients within an acceptable interval. In addition, hospitals have different diagnostic pathways based on differences in case-mix. The diversity of available diagnostic techniques and platforms is substantial [18], and they have varying turnaround times [19]. We expect that the TTT varies

among hospitals and that, unless diagnostic procedures are planned carefully, further adoption of molecular diagnostics will increase the variation in the TTT. Increased variation in TTT can ultimately lead to increased variation in outcomes.

The individual and tailored diagnostic pathways partly explain variation in TTT as does the first-line treatment provided. There are several treatment options for patients with stage III and IV NSCLC. The Dutch Clinical Practice Guidelines (CPG) [20], which were last updated in 2015, indicate targeted therapy with tyrosine-kinase inhibitors for patients with metastatic disease with a tumor harboring an anaplastic lymphoma kinase (ALK) rearrangement or epidermal growth factor receptor (EGFR) mutation positive. Furthermore, a specific recommendation was issued in 2018 to use chemotherapy in combination with pembrolizumab [21] as a first-line treatment. Because this recommendation does not require testing for programmed death-ligand 1 (PD-L1) expression in the tumor and thus these patients potentially have a shorter diagnostic pathway and potentially a shorter TTT. Other, leading CPG [22–24] were updated after the study period of this research. According to those CPG, targeted therapy is also indicated for patients with a tumor that harbors a BRAF V600E mutation or ROS1 rearrangement. Patients who have a tumor harboring a high PD-L1 expression or patients who have a high tumor mutation burden (TMB) should receive immunotherapy in the first line.

This study examines hospital variation in TTT by using patient-level data from the population-based Netherlands Cancer Registry (NCR) from all stage III or IV NSCLC diagnosing hospitals in the Netherlands to analyze the TTT for each hospital. In addition, we investigated how patient characteristics are correlated with the TTT, as more complex cases may require a more elaborate diagnostic pathway, and how TTT was associated with hospital-specific aspects, such as hospital-side planning, capacity, and testing platforms.

2.Material and Methods

2.1 Data

We retrieved the data from the Netherlands Cancer Registry (NCR). The Netherlands Comprehensive Cancer Organisation (IKNL) manages the NCR and routinely registers all new cancer incidences in the Netherlands. The data include patient and tumor characteristics, diagnostics, and treatments prescribed in the first line. The NCR is notified of all newly diagnosed malignancies by the automated pathology archive (PALGA). Additional sources are the national registry of hospital discharge, hematology departments, and radiotherapy institutes. The data allow us to identify

at which hospital the patient was clinically diagnosed, at which hospital the patient received his or her first-line treatment, as well as the type of hospital (academic, teaching, general). All 8 academic hospitals, 27 teaching, and 43 general hospitals are included. Finally, patient-level data from 78 hospitals (100%) in the Netherlands that have diagnosed patients with stage III or stage IV NSCLC in 2016 were included. In total, the dataset contains 7,550 unique patients. Considering that this study is retrospective, it does not require approval from an accredited medical research ethics committee (MREC) or the Central Committee on Research involving Human Subjects (CCMO). However, the study has been reviewed and approved by the Privacy Review Board of the NCR.

2.2 Patient selection

Patients with stage IIIA, IIIB, or IV non-small cell lung cancer have been included in the analysis. We assigned patients to the hospital in which they were clinically diagnosed. Patients who did not receive a first-line treatment or patients who underwent active surveillance in the first line did not have a registered time of starting first-line treatment and thus were excluded from the analysis (n = 2,782; 37%). Patients who only received treatment that was aimed at only treating the metastases, for example with a metastasectomy, instead of the primary tumor, were also excluded (n = 592; 8%). Finally, patients with a registered time of starting first-line treatment but with an unknown performance status were excluded (n = 80; 1%). In total, we used 4,096 patients (54%) in the analysis, which is 99% of all stage III and IV NSCLC patients who have received a first-line treatment in the Netherlands in 2016.

2.3 Statistical analysis

Statistical analysis was conducted in Stata 14 [25] and consisted of descriptive statistics, data visualization, and regression analysis.

2.4 Variables

For the descriptive statistics and regression analysis, we used several patient-level and hospital-level variables. First, we discuss the patient-level variables. TTT is determined by calculating the time in days between the date of diagnosis and the start of the first-line treatment. The date of diagnosis is one of the following moments, with descending priority: the date of the first histological or cytological confirmation of a tumor, the date of first hospital admission related to the tumor, or the date of the first visit to outpatient clinic related to the tumor. Regarding the date of the first histological or cytological confirmation of a tumor, the following moments with descending priority are used: the date on which the sample was obtained, the date on which the sample was received, or the date on which the result was recorded. The NCR uses these criteria to determine the date of diagnosis.

The well-being of the patient is indicated by the Eastern Cooperative Oncology Group Performance Status (ECOG PS), which is bound between 0, indicating asymptomatic disease, and 5, indicating death. To improve statistical power, we have grouped the ECOG PS in 0-1, 2+, and unknown. For 5.6% of all patients, performance status was denoted on the Karnofsky scale (10-100) whereas scores for all others were reported on the WHO ECOG scale (0-5). The former was converted to the latter, using Buccheri et al. [26]. The performance status was registered prior to starting treatment.

Tumor staging is according to the seventh edition of the TNM classification. The histology of the tumor is grouped by type according to the WHO classification of lung tumors [27]. Histology groups were squamous cell carcinomas (ICD-O 8050-8078, 8083-8084), adenocarcinomas (ICD-O codes 8140, 8211, 8230-8231, 8250-8260, 8323, 8480-8490, 8550-8552, 8570-8574, 8576), large cell carcinomas (ICD-O codes 8010-8012, 8014-8031, 8035, 8310), unspecified malignant neoplasms (ICD-O codes 8000-8005), other specified carcinomas (remaining ICD-O codes between 8010-8576), and other (ICD-O codes 8972, 8980). The referral status of the patient was established by examining whether a patient was referred from hospital of clinical diagnosis to hospital of first-line treatment, as we expect that this will influence the TTT [28]. The first-line treatments were determined by, for each patient, cross-referencing the treatment indications and the time of treatment initiation. In cases where patients have received chemoradiotherapy, it means that a patient has received both chemotherapy that was not neoadjuvant or adjuvant to surgery, and radiotherapy within 12 weeks of each other. Due to the large variability in treatment combinations in the first-line, we decided to explore only the four most prescribed treatments.

Second, the hospital-level variables consist of hospital type and volume. Hospital type makes a distinction between academic, teaching, and general hospitals. Hospital volume is the number of patients that were diagnosed with stage III or IV NSCLC in that hospital in 2016.

2.5 Regression model

To investigate how patient characteristics and hospital-level effects are associated with TTT, we created a regression model. To increase the understanding of the results of the regression model, we predicted the TTT for five different patient profiles. These patient profiles are constructed such that statistically significant variables vary among the profiles, while also making sure that these profiles reflect a substantial percentage of patients. The prediction of TTT for the patient profiles also include the hospital-level effects.

The data have a hierarchical structure: patients are nested within hospitals, that is, patients who are treated at the same hospital are likely to be more similar than patients treated at a different hospital. When present, ignoring this non-independence of the data leads to biased results. Therefore, in order to estimate the effect of patient and hospital characteristics on TTT, we used a mixed model. A mixed model allows estimation of TTT caused by not only the patient-level variables, the so-called fixed effects, but also due to hospital-level variables, the so-called random effects. The magnitude of the random effects or hospital-level effect may differ between hospitals. The size of the hospital-level effect is identical for all patients treated at the same hospital. The random effects reflect the unobserved heterogeneity at the hospital level. Because the components of the heterogeneity between hospitals are unobserved, we cannot know for sure what it entails. However, if the goodness of fit of the model does not improve after including additional random effects, it is unlikely that the unobserved heterogeneity relates to the additional random effects. In other words, the hospital-level effects are reflective of the comparative performance of hospitals with respect to TTT, as the differences in case-mix caused this part of the variation in the TTT.

We have included patient-level variables that are often used to correct for differences in case-mix so that the unobserved heterogeneity among hospitals is not a reflection of differences in case-mix. We selected variables to include in the regression analysis by reviewing the literature on hospital variation in outcomes. We used the following patient-level or fixed-effects variables in the model: age, gender, ECOG PS, and tumor stage. These case-mix variables were similar to what was previously used [29], [30], but we lack other lung cancer-specific data, such as data on the presence of symptoms such as chest pain and hemoptysis. Additionally, we included the referral status of a patient. With respect to the random effects, we included a random intercept for each hospital to reflect unobserved heterogeneity between hospitals. The goodness of fit was assessed with the Akaike Information Criterion (AIC), residual diagnostics, and likelihood ratio tests.

We used a negative binomial mixed model (NBMM) with a log link function [31]. In this type of models, the dependent variable, in this case TTT, is expected to follow a negative binomial distribution. A negative binomial model is preferred over a linear model because we found that the residuals in a linear model to be not normally distributed, which violates an important assumption. Moreover, TTT contains only nonnegative integers, which makes it suitable for a negative binomial model [32].

3. Results

3.1 Patient population

Table 1 provides the patient characteristics for both treated and untreated patients with stage III or IV NSCLC. In addition, it includes the treatment history of patients with a known TTT.

Table 1. Characteristics of the patient population

Characteristics	Treated patients N (% or 95% CI)	Untreated patients N (% or 95% CI)	p-value
Patients	4,176 (55.1%)	3,374 (44.9%)	N.A.
Median TTT (in days)	28 (IQR: 22)	-	N.A.
Mean age (in years)	65.4 (65.1, 65.7)	72.4 (72.1, 72.8)	0.000
Gender			
Male	56.0% (54.4%, 57.5%)	61.7% (60.1%, 63.3%)	0.000
Female	44.0% (42.5%, 45.5%)	38.3% (36.7%, 40.0%)	0.000
ECOG PS			
0-1	62.4% (61.0%, 63.9%)	23.2% (21.8%, 24.6%)	0.000
2+	8.0% (7.1%, 8.8%)	23.3% (21.9%, 24.7%)	0.000
Unknown	27.7% (26.3%, 29.1%)	52.7% (51.0%, 54.4%)	0.000
Missing	1.9% (1.5%, 2.3%)	0.9% (0.6%, 1.2%)	0.000
Tumor stage			
IIIA	23.6% (22.3%, 24.9%)	9.9% (8.9%, 10.9%)	0.000
IIIB	15.5% (14.4%, 16.6%)	7.9% (7.0%, 8.9%)	0.000
IV	60.9% (59.4%, 62.4%)	82.1% (80.8%, 83.4%)	0.000
Histology			
Squamous cell carcinoma	24.0% (22.7%, 25.3%)	16.2% (15.0%, 17.5%)	0.000
Adenocarcinoma	58.0% (56.5%, 59.5%)	42.3% (40.6%, 43.9%)	0.000
Large cell carcinoma	3.9% (3.3%, 4.5%)	5.6% (4.8%, 6.4%)	0.000
Other specified carcinoma	12.2% (11.1%, 13.2%)	12.2% (11.1%, 13.3%)	0.920
Unspecified malignant	1.8% (1.4%, 2.3%)	23.6% (22.1%, 25.0%)	0.000
neoplasm	0.1% (0.0%, 0.1%)	0.1% (0.0%, 0.1%)	0.831
Other			

Referral			
No	70.0% (68.6%, 71.4%)	82.2% (80.9%, 83.5%)	0.000
Yes	30.0% (28.6%, 31.4%)	17.8% (16.5%, 19.1%)	0.000
Basis for diagnosis			
Clinical diagnostic examinations, explorative surgery, or obduction[a]	1.8% (1.4%, 2.2%)	22.7% (21.2%, 24.1%)	0.000
Biochemical or immunological laboratory tests	0.0% (0.0%, 0.0%)	0.0% (0.0%, 0.0%)	0.124
Hematological or cytological confirmation on primary tumor	31.7% (30.3%, 33.2%)	29.5% (28.0%, 31.0%)	0.036
Histological confirmation exclusively on metastasis	22.0% (20.8%, 23.3%)	22.6% (21.2%, 23.9%)	0.598
Histological confirmation on primary tumor or metastasis, or obduction[b]	44.4% (42.9%, 46.0%)	25.2% (23.8%, 26.7%)	0.000
First-line treatments			
Only chemotherapy	1,712 (41.8%)	-	N.A.
Only chemoradiotherapy	956 (23.3%)	-	N.A.
Only radiotherapy	464 (11.3%)	-	N.A.
Only targeted therapy	302 (7.4%)	-	N.A.
Only surgery	133 (3.3%)	-	N.A.
Only immunotherapy	11 (0.3%)	-	N.A.
Other	518 (12.6%)	-	N.A.

Note: P-values are based on t-tests. [a]Obduction without microscopically confirmation. [b]Obduction with histological confirmation.

3.2 Time to treatment

The population level median TTT was 28 days with a range of 0 to 395 days, while the hospital-level median TTT ranges from 17 to 68 days. Of all first-line treatments, 90% was initiated within 58 days of clinical diagnosis. Figure 1 displays the distribution of the TTT for each hospital. Note that hospital volume ranged from 3 to 144. The median, inter-quartile range (IQR), and mean patient volume was 68, 64, and 71, respectively. The figure shows that there is substantial variation in TTT between

hospitals, and there is large within-hospital variation as indicated by the lengths of the boxes and whiskers. No pattern can be deduced with respect to variation across hospital types.

Figure 1. Distribution of time to treatment across and within hospitals. The whiskers encompass the minimum and maximum TTT for each hospital, whereas the box depicts the 25th and 75th percentile, and the median. Values for time to treatment larger than 150 days are shown individually.

3.3 Relationship with treatment

Treatments correlate with TTT, as different treatments require different diagnostics to be conducted prior to starting first-line treatment. Table 2 shows summary statistics for the TTT for the four most frequently given first-line treatments, as well as the utilization of these treatments. To be clear, we only explore the relationship that TTT has with the four most prescribed treatments. On a population-level, most patients only receive chemotherapy in the first line, followed by chemoradiotherapy, radiotherapy, and targeted therapy.

Table 2. Summary statistics on time to treatment per first-line treatment

First-line therapy	Time to treatment					Utilization
	Median	Mean	Std. Dev.	Min.	Max.	
Only chemotherapy	29	34.7	23.0	0	286	41.8%
Only radiotherapy	32	38.3	31.9	0	288	11.3%
Only chemoradiotherapy	23	27.5	16.6	0	146	23.3%
Only targeted therapy	27	33.6	31.0	0	395	7.4%

The left-hand panel in figure 2 shows for each hospital the median TTT for the four most frequently given first-line treatments. Each horizontal line and bar represents the respective metrics for one hospital. Note that we used a logarithmic scale for the horizontal axis of the left-hand panel. The right-hand panel shows the percentage of patients for whom that was their first-line treatment. No distinction is made between hospital types in figure 2 because figure 1 indicates that there is no such pattern deducible in the variation of TTT. Figure 2 indicates that the between-hospital variation in TTT is smallest with chemotherapy, which is, in most hospitals, the treatment that most patients received in the first line. Between-hospital variation in TTT is larger for radiotherapy and targeted therapy. However, the right-side panel indicates their utilization is relatively low in most hospitals, which may indicate that the variation in TTT may be just a feature of a small sample.

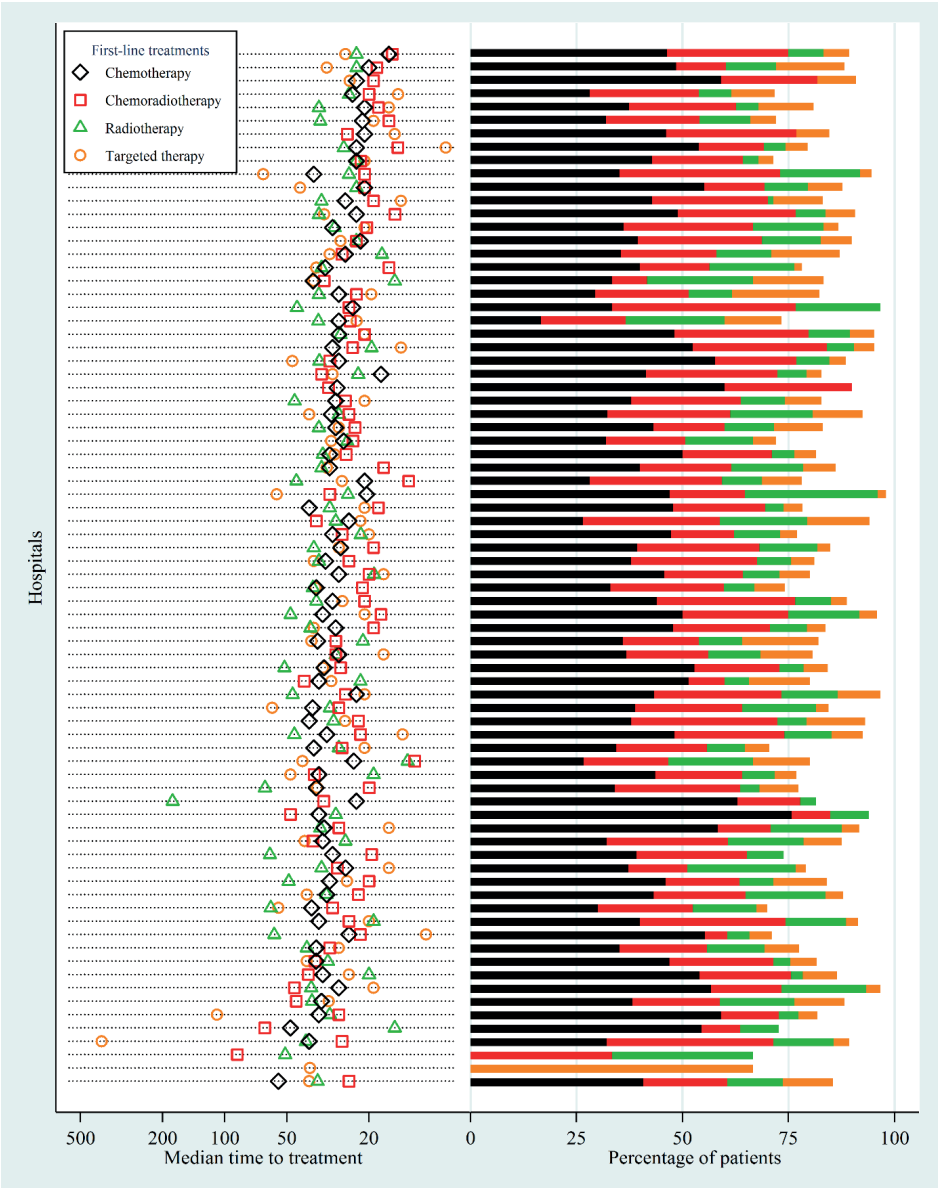

Figure 2. Hospital median time to treatment and the percentage of patients per first-line treatment. Only the four most prescribed treatments are shown.Relationship with patient characteristics and a hospital-level effect

Using the regression model, we have determined the association between TTT and patient characteristics, as well as predict the hospital-level effect on TTT for each hospital. These hospital-level effects are displayed in figure 3, where each dot represents the predicted hospital-level effect for one hospital. Including hospital type and hospital volume as additional random effects did not improve the goodness of fit, so the hospital-level effects is also not related to hospital type or the number of patients with stage III or IV NSCLC in each hospital. In figure 3, a negative value means that the hospital-level effect has led to a lower average TTT for that hospital, while a positive value means that the hospital-level effect has led to a higher average TTT for that hospital.

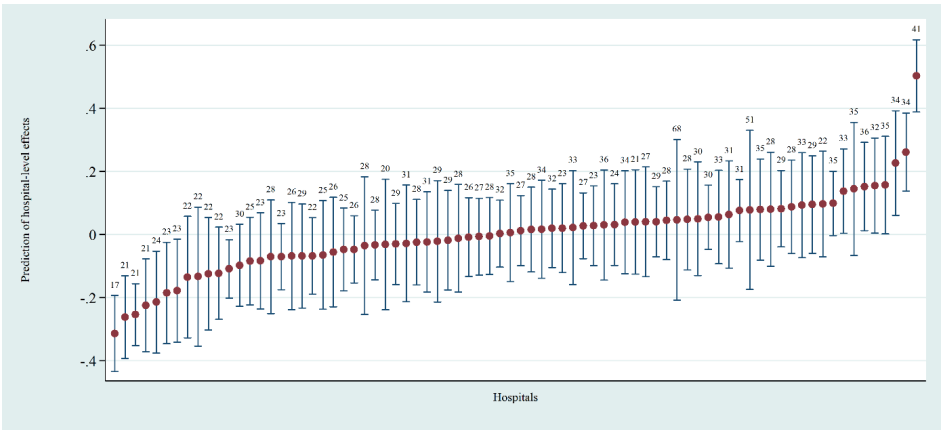

Figure 3. Hospital-level effects or i.e. Empirical Bayes predictions of the random effects. The 95% confidence intervals of the predicted hospital-level effects are indicated by the error bars. The number above the error bars is the hospital-level median time to treatment

Table 3 presents the relation between TTT and patient characteristics for five patient profiles defined using the regression model. The regression model indicated that the ECOG PS, tumor stage, histology, and referral status are associated with TTT, so these characteristics are varied among the patient profiles. Approximately 77% of the patients had one of the profiles listed in table 3. In addition, the regression model also allows us to estimate the hospital-level effect on TTT. As figure 3 indicates, that effect differs among hospitals, so table 3 does not only report the estimated TTT for a hospital with an average hospital-level effect, it also shows the estimated TTT for the hospitals with the largest positive and largest negative hospital-level effect, denoted by low and high in table 3 respectively. The largest change in TTT is related to the referral status of the patient. Patients who are referred to a different hospital for treatment are predicted to have an increase in TTT of at least a week.

Table 3. Predictions of time to treatment for patient profiles

	Patient profiles				
Characteristics	**(1)**	**(2)**	**(3)**	**(4)**	**(5)**
N (%)	1,353 (33.0%)	603 (14.7%)	99 (2.4%)	829 (20.2%)	261 (6.4%)
ECOG PS	0-1 or unknown	0-1 or unknown	2+	0-1 or unknown	0-1 or unknown
Tumor stage	IIIA or IV	IIIA or IV	IIIA or IV	IIIA or IV	IIIB
Histology	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma	SCC[a], LCC[b], other specified carcinomas, or other histology	SCC[a], LCC[b], other specified carcinomas, or other histology
Referral	No	Yes	No	No	No
TTT (Average)[c]	30.5	41.0	25.2	28.4	25.2
TTT (Low)[c]	22.5	30.3	18.6	21.0	18.6
TTT (High)[c]	50.8	68.3	41.9	47.3	41.9

Note: [a]Squamous cell carcinoma. [b]Large cell carcinoma. [c]Predictions of TTT in days for hospitals with an average, largest negative (low), and largest positive (high) hospital-level effect. The TTT is predicted for five different patient profiles in which statistically significant variables vary among the profiles, while also representing a substantial percentage of patients. The prediction of TTT for the patient profiles also include the hospital-level effects. The hospital-level effect is identical across patient profiles.

4. Discussion

In this study, we quantified the variation in TTT for advanced NSCLC patients in the Netherlands. We found a median TTT of 28 days, and considerable variation in TTT between and within hospitals. The median TTT found in this article is in the range of what previous studies reported that have analyzed the TTT for lung cancer patients nationally or regionally. However, a study from 2013 on a Canadian region reported that 90% of first treatments started within 115 days [15], which is almost twice the 58 days in the current article. By calculating the estimated TTT for five patient profiles, we showed how patient characteristics correlate with the TTT. We have also shown how a hospital-level effect affects the predicted TTT for these patient profiles. The TTT for the patient profiles ranged from approximately 19 days to 68 days.

There is no legally binding maximum TTT for cancer patients in the Netherlands. However, several institutions have created guidelines. The Dutch Cancer Society (KWF) deems a maximum TTT of 30 days acceptable [33], while SONCOS recommends a maximum of 6 weeks, but in case of referrals, an extra 3 weeks is granted [34]. Finally, the so-called "Treeknormen" [35], which were created by healthcare providers and health insurers, find a maximum TTT of 7 weeks to be acceptable. The hospital-

level median TTT, which incorporates all values for TTT of patients treated at each hospital, ranges from 17 to 68 days. We can conclude that the median TTT reported in this study is less than the maximum acceptable TTT. It means that at least 50% of the patients receive a first-line treatment within an acceptable time interval. However, for a small number of patients the maximum acceptable TTT is exceeded as only 50% of treatments is initiated within 28 days, and 90% of treatments have initiated within 58 days, while the guidelines recommend a maximum of 30 days [33], 7 weeks [35], and 9 weeks [34]. This conclusion is in line with previous research [36]. Additionally, the median TTT in 53 hospitals (68%) was below 30 days, which means it is below the strictest guideline. The median TTT in only one hospital exceeded the SONCOS guidelines of 9 weeks, which is the least strict. This supports the claim that hospitals have designed their diagnostic pathways in a way that they will diagnose most of their patients within an acceptable interval. In countries where there is a legally binding maximum TTT such as England, patients should receive first-line treatment within 31 days after diagnosis [37]. If we apply these maxima to our results, only approximately 57% of all patients would have received treatment in a timely manner.

Table 2 shows that the TTT varies for the different treatments and that the largest variation in TTT was found in patients who have received either radiotherapy or targeted therapy. For patients with stage IV disease, radiotherapy has often a palliative intent and is often only started once the patient experiences symptoms. Moreover, radiotherapy requires an appointment with the radiology department. This can be an explanation for the variation in TTT for radiotherapy. The variation in TTT for targeted therapy could be caused by the time required by molecular diagnostics, and the various test strategies hospitals employ, given the lack of a molecular diagnostic best practice [18]. The result that TTT tends to be longer for patients with adenocarcinomas (table 3), for whom molecular diagnostics are indicated, compared to patients with other histologies, supports this claim. Although the median TTT in most hospitals is below the recommended maxima, hospitals should be aware that, without careful planning, conducting diagnostics with long turnaround times could extend the TTTs beyond the recommended maxima. Finally, the role of immunotherapy has increased substantially since the study period. However, as the remaining parts of the treatment landscape, such as treatment with TKIs or chemotherapy, have remained similar, our study represents the key aspects of the current care pathway.

Table 3 shows that the predicted TTT is much longer if the patient is referred to a different hospital for treatment. Patient profile 1 and 2 indicate that the increase in predicted TTT resulting from the patient's referral status ranges from one week to several weeks, depending on which hospital the patient would visit. Considering

that 30% of the treated patients were referred, there is potential for significant improvement in the TTT if the planning of appointments of referred patients and cooperation between hospitals would become more efficient.

Figure 2 shows that at both extremes, the hospital-level effect on TTT is substantial. However, the hospital-level effect is modest or insignificant for most hospitals. In other words, a few hospitals perform either substantially better or substantially worse than expected considering their case-mix with respect to TTT, while most hospitals perform as expected considering their case-mix. The hospital-level effect is independent of hospital type and hospital volume. Both hospital type and hospital volume do not influence the TTT, which is not typically found in studies on the relationship between quality and volume [12], [38–40]. An explanation for our findings could be that TTT is not necessarily a metric in which experience and thus volume are involved, but it is rather a consequence of the design and efficiency of the diagnostic care pathway.

We chose to include also patients that had other additional primary tumors. Excluding these patients (n = 705) did not influence the overall TTT. On the population level, it resulted in the same median TTT, as well as the same minimum and maximum TTT. Moreover, the hospital-level median TTT remained in a similar range compared to when these patients are included. The validity of extreme values for TTT, i.e. values of zero and larger than 200 days, was confirmed by the NCR. In cases where TTT of zero days was registered, either a tumor was confirmed in the operating room or chemotherapy started on the same day as the diagnosis was registered. TTT larger than 200 days was mostly caused by extensive diagnostic pathways or observed in patients who were first treated for tuberculosis. Table 1 indicates that untreated patients typically have a worse performance score, a higher age, and a more advanced tumor stage, and that their diagnosis is more often non-microscopically confirmed. The combination of these factors makes a strong case that untreated patients are correctly classified in our study. Previous research shows that that the number of patients with stage IV NSCLC that did not receive anticancer treatment ranges from approximately 25% to 50% [41–43]. In our data, this percentage was within that range, at approximately 37%. Thus, it is likely that an appropriate subset of patients was selected in our study.

One of the major strengths of this article is the national coverage of first-line NSCLC care that allows us to draw conclusions based on the entire population and to make comparisons between hospitals. The data used in this study allow for some degree of hospital benchmarking, but increased transparency for example through linking hospitals to regions would facilitate benchmarking even better. This study

also has limitations. For instance, having direct evidence on what happened during the TTT, e.g. the types of diagnostics and the dates at which they were conducted, would put us in a better position to explain the variation in the TTT. For example, in cases where patients have started with chemotherapy whilst still waiting on the results from molecular diagnostics, knowing the types of diagnostics conducted would allow us to explain better their TTT. In addition, having extra information on, for example, comorbidities and other prognostic factors might have improved our case-mix adjustment. While socio-economic status is associated with variation in outcomes [44], this does not seem to be the case with time to treatment [45]. However, the presence of a hospital-level effect indicates that the differences in case-mix did not solely cause the variation in TTT. In addition, we assigned patients to the hospital in which they were clinically diagnosed. Our underlying assumption is that in the hospital of diagnosis certain decisions are made that could affect the TTT, for example, what diagnostics should be conducted and possibly deciding on the type of first-line treatment. In fact, we do not know how early in the care pathway a patient was referred to a different hospital, so the influence of the hospital of diagnosis on the TTT will vary case-by-case. A different source of potential bias is the heterogeneity in which moment was used to determine the date of diagnosis. While our data do not provide direct evidence on this matter, table 1 indicates that the diagnosis of approximately 98% of the patients who have received treatment was microscopically confirmed. The date of first histological or cytological confirmation of the tumor has the highest priority when determining the date of diagnosis, it is likely that the date of first histological or cytological confirmation was used as the date of diagnosis for most patients. Hence, we believe that the heterogeneity in the date of diagnosis is relatively limited.

Currently, the TTT for similar patients that are treated at different hospitals is considerably different. This variation is undesirable and should be eliminated by trying to optimize diagnostic procedures in hospitals. Consequently, determining an optimal TTT for lung cancer is thus an interesting topic for future research. Additionally, finding the causes of variation between hospitals in TTT as well as possible approaches to reduce this type of variation would be of significant value. Even so, TTT warrants its own study, as timeliness of care is an important aspect of the accessibility and quality of healthcare.

5. Conclusion

This article described the TTT for stage III and stage IV NSCLC patients, by using patient-level data from the NCR from all NSCLC diagnosing hospitals in the Netherlands in 2016. We found a median TTT of 28 days and considerable variation in TTT between and within hospitals, however, for most patients, TTT is within the acceptable norms. Variation in TTT seems higher for patients receiving either radiotherapy or targeted therapy. We hypothesize this is related to the complexity of the diagnostic pathway. Also patient referral to another hospital seems to increase TTT. With further advances in molecular diagnostics and precision oncology, we expect variation in TTT to increase and needs to be considered in designing optimal cancer care delivery. By estimating the TTT for five patient profiles, we showed how ECOG PS, tumor stage, histology, and referral status correlate with the TTT. We have shown the extent to which TTT may vary for these patients through estimating the best (lowest) and worst (highest) TTT across all hospitals.

Conflict of interest statement
The authors declare no conflict of interest.

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References

[1] Netherlands Cancer Registry, Incidence | Lung/bronchus / NSCLC / SCLC / Lung carcinoid / Other/unspecified / Pleuropulmonal blastoma, (n.d.). https://www.cijfersoverkanker.nl/selecties/Dataset_1/img5b87ea6e2a0ff (accessed August 30, 2018).

[2] E.J. Driessen, M.J. Aarts, G.P. Bootsma, J.G. van Loon, M.L. Janssen-Heijnen, Trends in treatment and relative survival among Non-Small Cell Lung Cancer patients in the Netherlands (1990–2014): Disparities between younger and older patients, Lung Cancer. 108 (2017) 198–204. doi:10.1016/j.lungcan.2017.04.005.

[3] B.J.M. Peters, C.M. Cramer-vd Welle, A.A.J. Smit, F.M.N.H. Schramel, E.M.W. van de Garde, Trends in prescribing systemic treatment and overall survival for non-small cell lung cancer stage IIIB/IV in the Netherlands: 2008–2012, Cancer Epidemiol. 51 (2017) 1–6. doi:10.1016/j.canep.2017.08.001.

[4] K.W. Lau, C. Seng, T.K.H. Lim, D.S.W. Tan, Expanded molecular interrogation for potential actionable targets in non-squamous non-small cell lung cancer., Ann. Transl. Med. 5 (2017) 372. doi:10.21037/atm.2017.08.42.

[5] K.R. Voong, J. Feliciano, D. Becker, B. Levy, Beyond PD-L1 testing-emerging biomarkers for immunotherapy in non-small cell lung cancer, Ann. Transl. Med. 5 (2017) 376–376. doi:10.21037/atm.2017.06.48.

[6] C. Lim, M.S. Tsao, L.W. Le, F.A. Shepherd, R. Feld, R.L. Burkes, G. Liu, S. Kamel-Reid, D. Hwang, J. Tanguay, G. Da Cunha Santos, N.B. Leighl, Biomarker testing and time to treatment decision in patients with advanced nonsmall-cell lung cancer, Ann. Oncol. 26 (2015) 1415–1421. doi:10.1093/annonc/mdv208.

[7] J.K. Olsson, E.M. Schultz, M.K. Gould, Timeliness of care in patients with lung cancer: A systematic review, Thorax. 64 (2009) 749–756. doi:10.1136/thx.2008.109330.

[8] R.D. Neal, P. Tharmanathan, B. France, N.U. Din, S. Cotton, J. Fallon-Ferguson, W. Hamilton, A. Hendry, M. Hendry, R. Lewis, U. Macleod, E.D. Mitchell, M. Pickett, T. Rai, K. Shaw, N. Stuart, M.L. Tørring, C. Wilkinson, B. Williams, N. Williams, J. Emery, Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review, Br. J. Cancer. 112 (2015) S92–S107. doi:10.1038/bjc.2015.48.

[9] C. Helsper, N. van Erp, P. Peeters, N. de Wit, Time to diagnosis and treatment for cancer patients in the Netherlands: Room for improvement?, Eur. J. Cancer. 87 (2017) 113–121. doi:10.1016/j.ejca.2017.10.003.

[10] M. Heins, I. Spronk, J. De Jong, V. Ho, M. Brink, J. Korevaar, Variatie tussen ziekenhuizen in de behandeling van vijf soorten kanker -Een verkennend onderzoek naar aanknopingspunten voor verbetering van zorg [Variation among hospitals in the treatment of five cancer types - An explorative research on leads for the improvement in care], 2015.

[11] M.W.J.M. Wouters, S. Siesling, M.L. Jansen-Landheer, M.A.G. Elferink, J. Belderbos, J.W. Coebergh, F.M.N.H. Schramel, Variation in treatment and outcome in patients with non-small cell lung cancer by region, hospital type and volume in the Netherlands, Eur. J. Surg. Oncol. 36 (2010) S83–S92. doi:10.1016/j.ejso.2010.06.020.

[12] N. van der Linden, M.L. Bongers, V.M.H. Coupé, E.F. Smit, H.J.M. Groen, A. Welling, F.M.N.H. Schramel, C.A. Uyl-de Groot, Treatment Patterns and Differences in Survival of Non-Small Cell Lung Cancer Patients Between Academic and Non-Academic Hospitals in the Netherlands, Clin. Lung Cancer. 18 (2017) e341–e347. doi:10.1016/j.cllc.2015.11.011.

[13] R. Sluga, B.E.E.M. van den Borne, P. Roepman, B.J.M. Peters, E.A. Kastelijn, F.M.N.H. Schramel, Utilization of Molecular Testing and Survival Outcomes of Treatment with First- or Second-line Tyrosine Kinase Inhibitors in Advanced Non-small Cell Lung Cancer in a Dutch Population, Anticancer Res. 38 (2018) 393–400. doi:10.21873/anticanres.12235.

[14] F. Vrijens, C. De Gendt, L. Verleye, J. Robays, V. Schillemans, C. Camberlin, S. Stordeur, C. Dubois, E. Van Eycken, I. Wauters, J.P. Van Meerbeeck, Quality of care and variability in lung cancer management across Belgian hospitals: a population-based study using routinely available data, Int. J. Qual. Heal. Care. 30 (2018) 306–312. doi:10.1093/intqhc/mzy027.

[15] X. Li, A. Scarfe, K. King, D. Fenton, C. Butts, M. Winget, Timeliness of cancer care from diagnosis to treatment: a comparison between patients with breast, colon, rectal or lung cancer, Int. J. Qual. Heal. Care. 25 (2013) 197–204. doi:10.1093/intqhc/mzt003.

[16] G. Pérez, M. Porta, C. Borrell, M. Casamitjana, X. Bonfill, I. Bolibar, E. Fernández, Interval from diagnosis to treatment onset for six major cancers in Catalonia, Spain, Cancer Detect. Prev. 32 (2008) 267–275. doi:10.1016/j.cdp.2008.05.006.

[17] F. Olesen, R.P. Hansen, P. Vedsted, Delay in diagnosis: The experience in Denmark, Br. J. Cancer. 101 (2009) S5–S8. doi:10.1038/sj.bjc.6605383.

[18] M. Dietel, L. Bubendorf, A.-M.C. Dingemans, C. Dooms, G. Elmberger, R.C. García, K.M. Kerr, E. Lim, F. López-Ríos, E. Thunnissen, P.E. Van Schil, M. von Laffert, Diagnostic procedures for non-small-cell lung cancer (NSCLC): recommendations of the European Expert Group, Thorax. 71 (2016) 177–184. doi:10.1136/thoraxjnl-2014-206677.

[19] S. Cardarella, T.M. Ortiz, V.A. Joshi, M. Butaney, D.M. Jackman, D.J. Kwiatkowski, B.Y. Yeap, P.A. Jänne, N.I. Lindeman, B.E. Johnson, The introduction of systematic genomic testing for patients with non-small-cell lung cancer, J. Thorac. Oncol. 7 (2012) 1767–1774. doi:10.1097/JTO.0b013e3182745bcb.

[20] Oncoline, Niet kleincellig longcarcinoom: Landelijke richtlijn versie 2.3 [Non-small cell lung carcinoma: National guideline version 2.3], 2015.

[21] Commissie BOM, Pembrolizumab met chemotherapie als eerstelijns behandeling voor gemetastaseerd niet-kleincellig longcarcinoom [Pembrolizumab with chemotherapy as a first-line treatment for metastatic non-small cell lung cancer], Med. Oncol. (2018) 63–66. https://medischeoncologie.nl/download/55509.pdf.

[22] NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Non-Small Cell Lung Cancer (Version 3.2019), 2019. https://www.nccn.org/professionals/physician_gls/pdf/nscl_blocks.pdf.

[23] N. Hanna, D. Johnson, S. Temin, S. Baker, J. Brahmer, P.M. Ellis, G. Giaccone, P.J. Hesketh, I. Jaiyesimi, N.B. Leighl, G.J. Riely, J.H. Schiller, B.J. Schneider, T.J. Smith, J. Tashbar, W.A. Biermann, G. Masters, Systemic Therapy for Stage IV Non–Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update, J. Clin. Oncol. (2017) JCO.2017.74.606. doi:10.1200/JCO.2017.74.6065.

[24] D. Planchard, S. Popat, K. Kerr, S. Novello, E.F. Smit, C. Faivre-Finn, T.S. Mok, M. Reck, P.E. Van Schil, M.D. Hellmann, S. Peters, Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 29 (2018) iv192–iv237. doi:10.1093/annonc/mdy275.

[25] StataCorp, Stata Statistical Software: Release 14, (2015).

[26] G. Buccheri, D. Ferrigno, M. Tamburini, Karnofsky and ECOG performance status scoring in lung cancer: A prospective, longitudinal study of 536 patients from a single institution, Eur. J. Cancer Part A. 32 (1996) 1135–1141. doi:10.1016/0959-8049(95)00664-8.

[27] F. Bray, M. Colombet, L. Mery, M. Piñeros, A. Znaor, R. Zanetti, F. J, eds., Cancer Incidence in Five Continents, Vol. XI (electronic version), Lyon, 2017. http://ci5.iarc.fr.

[28] M. Iachina, E. Jakobsen, A.K. Fallesen, A. Green, Transfer between hospitals as a predictor of delay in diagnosis and treatment of patients with Non-Small Cell Lung Cancer - A register based cohort-study, BMC Health Serv. Res. 17 (2017) 1–8. doi:10.1186/s12913-017-2230-3.

[29] E.M. Von Meyenfeldt, G.M.H. Marres, E. Van Thiel, R.A.M. Damhuis, Variation in length of hospital stay after lung cancer surgery in the Netherlands, Eur. J. Cardio-Thoracic Surg. 54 (2018) 560–564. doi:10.1093/ejcts/ezy074.

[30] N. Beck, F. Hoeijmakers, E.M. van der Willik, D.J. Heineman, J. Braun, R.A.E.M. Tollenaar, W.H. Schreurs, M.W.J.M. Wouters, National Comparison of Hospital Performances in Lung Cancer Surgery: The Role of Case Mix Adjustment, Ann. Thorac. Surg. 106 (2018) 412–420. doi:10.1016/j.athoracsur.2018.02.074.

[31] A. Gelman, J. Hill, Data analysis using regression and multilevel/hierarchical models, Cambridge. (2007) 651. doi:10.2277/0521867061.

[32] W. Gardner, E.P. Mulvey, E.C. Shaw, Regression analysis of counts and rates: poission, overdispersed, Quant. Methods Psychol. 118 (1995) 392–404.

[33] Dutch Cancer Society, Wachttijden [Waiting times], Zorg Het Ziekenh. (2017). https://www.kanker.nl/algemene-onderwerpen/zorg-in-het-ziekenhuis/zorg/wachttijden (accessed October 23, 2018).

[34] SONCOS, Multidisciplinaire normering oncologische zorg in Nederland [Multidisciplinary standardization oncologic care in the Netherlands], 2018.

[35] Ministerie van VWS, C.10. Maximaal aanvaardbare wachttijden (Treeknormen) [C.10. Maximum acceptable waiting times (Treeknormen)], Actuele Cijfers | Minist. van Volksgezond. Welz. En Sport. (2014). http://www.zorgcijfers.nl/actuele-cijfers/c10-maximaal-aanvaardbare-wachttijden-treeknormen/58 (accessed October 23, 2018).

[36] M.M. Jacobsen, S.C. Silverstein, M. Quinn, L.B. Waterston, C.A. Thomas, J.C. Benneyan, P.K.J. Han, Timeliness of access to lung cancer diagnosis and treatment: A scoping literature review, Lung Cancer. 112 (2017) 156–164. doi:10.1016/j.lungcan.2017.08.011.

[37] Department of Health, The Handbook to The NHS Constitution, 2019. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/770675/The_Handbook_to_the_NHS_Constitution_-_2019.pdf.

[38] M.A.G. Elferink, P. Krijnen, M.W.J.M. Wouters, V.E.P.P. Lemmens, M.L.E.A. Jansen-Landheer, C.J.H. Van De Velde, J.A. Langendijk, C.A.M. Marijnen, S. Siesling, R.A.E.M. Tollenaar, Variation in treatment and outcome of patients with rectal cancer by region, hospital type and volume in the Netherlands, Eur. J. Surg. Oncol. 36 (2010) S74–S82. doi:10.1016/j.ejso.2010.06.028.

[39] F. Vernooij, A.P.M. Heintz, J.W. Coebergh, L.F.A.G. Massuger, P.O. Witteveen, Y. van der Graaf, Specialized and high-volume care leads to better outcomes of ovarian cancer treatment in the Netherlands, Gynecol. Oncol. 112 (2009) 455–461. doi:10.1016/j.ygyno.2008.11.011.

[40] R.R.G. Knops, E.C. van Dalen, R.L. Mulder, E. Leclercq, S.L. Knijnenburg, G.J.L. Kaspers, R. Pieters, H.N. Caron, L.C.M. Kremer, The volume effect in paediatric oncology: A systematic review, Ann. Oncol. 24 (2013) 1749–1753. doi:10.1093/annonc/mds656.

[41] S.Y. Brule, K. Al-Baimani, H. Jonker, T. Zhang, G. Nicholas, G. Goss, S.A. Laurie, P. Wheatley-Price, Palliative systemic therapy for advanced non-small cell lung cancer: Investigating disparities between patients who are treated versus those who are not, Lung Cancer. 97 (2016) 15–21. doi:10.1016/j.lungcan.2016.04.007.

[42] A.C. Small, C.K. Tsao, E.L. Moshier, B.A. Gartrell, J.P. Wisnivesky, J.H. Godbold, C.B. Smith, G. Sonpavde, W.K. Oh, M.D. Galsky, Prevalence and characteristics of patients with metastatic cancer who receive no anticancer therapy, Cancer. 118 (2012) 5947–5954. doi:10.1002/cncr.27658.

[43] B.J.M. Peters, C.M.C. Welle, A.A.J. Smit, F.M.N.H. Schramel, E.M.W. Van De Garde, Trends in prescribing systemic treatment and overall survival for non-small cell lung cancer stage IIIB/IV in the Netherlands: 2008 – 2012, 51 (2017) 1–6. doi:10.1016/j.canep.2017.08.001.

[44] A. Sidorchuk, E.E. Agardh, O. Aremu, J. Hallqvist, P. Allebeck, T. Moradi, Socioeconomic differences in lung cancer incidence: A systematic review and meta-analysis, Cancer Causes Control. 20 (2009) 459–471. doi:10.1007/s10552-009-9300-8.

[45] L.F. Forrest, S. Sowden, G. Rubin, M. White, J. Adams, Socio-economic inequalities in stage at diagnosis, and in time intervals on the lung cancer pathway from first symptom to treatment: Systematic review and meta-analysis, Thorax. 72 (2017) 430–436. doi:10.1136/thoraxjnl-2016-209013.Socio-economic.

Appendix

Supplementary table 1. Utilization of diagnostics and treatments across tumour stages

	Tumor stage		
Tumor staging	**IIIA**	**IIIB**	**IV**
Exploratory surgery	16 (2.0%)	1 (0.3%)	19 (2.4%)
Endobronchial ultrasound	483 (59.1%)	233 (66.2%)	472 (59.3%)
Endoscopic ultrasound	140 (17.1%)	85 (24.1%)	262 (32.9%)
Mediastinoscopy	178 (21.8%)	33 (9.4%)	43 (5.4%)
Total:	817 (100%)	352 (100%)	796 (100%)
DNA test results			
None found or testing not required	202 (57.4%)	169 (56.2%)	817 (41.5%)
Only KRAS positive	100 (28.4%)	88 (29.2%)	664 (33.7%)
Only EGFR positive	9 (2.6%)	9 (3.0%)	245 (12.5%)
Only ALK positive	<5 (<1.4%)	5 (1.7%)	52 (2.6%)
Only ROS1 positive	<5 (<1.4%)	<5 (1.7%)	10 (0.5%)
Only BRAF positive	15 (4.3%)	11 (3.7%)	61 (3.1%)
Only RET positive	0 (0.0%)	<5 (1.7%)	<5 (0.3%)
Only HER2/neu positive	<5 (<1.4%)	<5 (1.7%)	14 (0.7%)
Other not specified	11 (3.1%)	9 (3.0%)	57 (2.9%)
Multiple found	6 (1.7%)	5 (1.7%)	37 (1.9%)
Result unknown	5 (1.4%)	<5 (<1.7%)	9 (0.5%)
Total:	352 (100%)	301 (100%)	1,968 (100%)
Most utilized first-line treatments			
Chemotherapy	64 (6.7%)	135 (21.5%)	1,513 (60.4%)
Chemoradiotherapy	457 (47.5%)	318 (50.7%)	181 (7.2%)
Radiotherapy	147 (15.3%)	73 (11.6%)	244 (9.7%)
Targeted therapy	2 (0.2%)	8 (1.3%)	292 (11.7%)
Total:	670 (69.6%)	534 (85.8%)	2230 (89.0%)

Supplementary table 2. Cross table of patient and hospital characteristics with time to treatment

Characteristics	Time to treatment ≤ median (28 days)	Time to treatment > median (28 days)	p-value
Patients	2,165 (60.4%)	1,931 (39.6%)	N.A.
Time to treatment (in days)	18.5 (18.2, 18.8)	49.2 (48.0, 50.3)	0.000
Mean age (in years)	65.6 (65.2, 66.0)	65.3 (64.9, 65.8)	0.400
Gender			
Male	56.3% (54.2%, 58.3%)	55.9% (53.7%, 58.1%)	0.806
Female	43.7% (41.3%, 45.6%)	44.1% (41.9%, 46.3%)	0.806
ECOG PS			
0-1	61.4% (59.4%, 63.5%)	66.1% (64.0%, 68.2%)	0.002
2+	9.2% (8.0%, 10.4%)	6.9% (5.8%, 8.0%)	0.007
Unknown	29.4% (27.5%, 31.3%)	27.0% (25.0%, 29.0%)	0.090
Tumor stage			
IIIA	24.6% (22.8%, 26.4%)	22.3% (20.5%, 24.2%)	0.090
IIIB	18.8% (17.1%, 20.4%)	11.4% (10.0%, 12.9%)	0.000
IV	56.7% (54.6%, 58.8%)	66.2% (64.1%, 68.3%)	0.000
Histology			
Squamous cell carcinoma	25.6% (23.8%, 27.5%)	22.3% (20.4%, 24.1%)	0.012
Adenocarcinoma	56.4% (54.3%, 58.5%)	60.0% (57.8%, 62.1%)	0.023
Large cell carcinoma	3.7% (2.9%, 4.5%)	4.0% (3.1%, 4.9%)	0.683
Other specified carcinoma	13.0% (11.6%, 14.4%)	11.2% (9.8%, 12.6%)	0.089
Unspecified malignant neoplasm	1.2% (0.8%, 1.7%)	2.5% (1.7%, 3.2%)	0.003
Other	0.0% (0.0%, 0.0%)	0.1% (0.0%, 0.02%)	0.134
Referrals	20.8% (19.1%, 22.5%)	41.0% (38.8%, 43.2%)	0.000
Hospital types:			
Academic	4 (9.1%)	4 (11.8%)	0.704
General	23 (52.3%)	20 (58.8%)	0.570
Teaching	17 (38.6%)	10 (29.4%)	0.402
Mean hospital volume	57.8 (47.8, 67.8)	45.6 (35.7, 55.4)	0.086

Note: 95% confidence intervals listed in parentheses unless stated otherwise. P-values are based on t-tests.

Supplementary table 3. Regression model estimates

Regression coefficients (fixed effects)	Coef.	Standard error	95% Confidence interval
Intercept	3.354**	0.076	(3.203, 3.502)
Age	0.000	0.001	(-0.002, 0.002)
Gender (male = 1)	-0.004	0.019	(-0.042, 0.034)
ECOG PS			
0-1 (ref. category)	-	-	-
2+	-0.193**	0.036	(-0.263, -0.123)
Unknown	-0.043	0.024	(-0.089, 0.003)
Tumor stage			
IIIA (ref. category)	-	-	-
IIIB	-0.122**	0.031	(-0.183, -0.061)
IV	0.041	0.024	(-0.006, 0.088)
Histology			
Squamous cell carcinoma (ref. category)	-	-	-
Adenocarcinoma	0.070**	0.025	(0.022, 0.119)
Large cell carcinoma	0.063	0.053	(-0.041, 0.167)
Other specified carcinoma	0.015	0.034	(-0.052, 0.081)
Unspecified malignant neoplasm	0.411**	0.072	(0.269, 0.553)
Other	0.458	0.416	(-0.357, 1.274)
Referral			
No (ref. category)	-	-	-
Yes	0.296**	0.021	(0.255, 0.338)
Variance components (random effects)			
Variance of intercept	0.021	0.005	(0.013, 0.032)
Model summary			
Alpha (dispersion)		0.322**	
Observations		4,096	
Clusters		78	

Note: Coefficients are on the logarithmic scale. P-values based on Wald tests; *p<0.05; **p<0.01. Likelihood ratio tests showed that adding an additional level to the model, e.g. hospital type, or adding a hospital-level random coefficient for hospital volume did not improve model fit. Anscombe residuals displayed approximate normality, while the Pearson residuals did not indicate influential outliers.

Chapter 4

Real-world utilization of biomarker testing for patients with advanced non-small cell lung cancer in a tertiary referral center and referring hospitals

Michiel van de Ven, Hendrik Koffijberg, Valesca Retèl, Kim Monkhorst, Egbert Smit, Wim van Harten, Maarten IJzerman

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Abstract

The continued introduction of biomarkers and innovative testing methods makes the already complex diagnostic landscape for patients with stage IV non-small cell lung cancer (NSCLC) even more complex. This study primarily aimed to analyze variation in biomarker testing in the real-world for patients referred to a comprehensive cancer center (CCC) in the Netherlands. The secondary aim was to compare the cost per patient for biomarker testing observed in the present study with the current cost of WGS. The cohort includes 102 stage IV NSCLC patients who received biomarker testing in 2017 or 2018 at CCC. We identified the complete biomarker testing history of the cohort using linked data from CCC and the nationwide network and registry of histopathology and cytopathology in the Netherlands. Unique biomarker test combinations, costs, turnaround times, and test utilization were examined. The results indicate substantial variation in test utilization and sequences. The mean cost per patient for biomarker testing was 2259.92 US dollar (Std. Dev.: 1217.10) or 1881.23 euro (Std. Dev.: 1013.15). Targeted gene panels were most frequently conducted, followed by PD-L1 with immunohistochemistry. Typically, most common biomarkers were tested within the first tests, and emerging biomarkers are tested further down the test sequence. At its current cost level, replacing current biomarker testing with WGS would have led to cost savings for only two patients (2%).

Keywords

Non-small cell lung cancer, molecular diagnostics, biomarker testing, real-world evidence

1. Introduction

The use of biomarker testing [1,2] to predict treatment response and disease progression has made the diagnostic pathway of patients with advanced non-small cell lung cancer (NSCLC) increasingly complex [3]. Moreover, this pathway is expected to become even more complex in the near future with the introduction of new biomarkers and innovative testing methods, such as Whole Genome Sequencing (WGS) and evaluating circulating tumor DNA using liquid biopsies [4]. For response prediction and for selecting the optimal treatment [5], biomarker testing needs to be completed before treatment initiation. Hence, the turnaround time of biomarker testing directly influences when a patient can start treatment [6]. In practice, multiple biomarker tests, such as targeted gene panels and immunohistochemistry (IHC), are often conducted, which can result in unnecessary delays if there is a cascade of tests along the pathway that is not carefully planned. If these delays are substantial, priority could be given to initiating treatment with a suboptimal therapy even before receiving the results of biomarker testing [7]. While there is no consensus on the relationship between delays and survival is unclear due to confounding by indication [8], a large study found an association between time to treatment and mortality across all tumor stages in NSCLC [9].

Testing the biomarkers with the highest prevalence first maximizes the likelihood of finding an actionable target as early as possible and minimizes the number of tests conducted. Current Clinical Practice Guidelines (CPG) recommend routine testing for several biomarkers, among which are *EGFR*, *ALK*, *BRAF V600E*, and *ROS1*, to predict response to targeted therapy, and PD-L1 to predict response to immunotherapy [10,11]. The prevalence of biomarkers varies across genes and patient subgroups. In European subgroups, a high PD-L1 expression level is present in 22% of NSCLC patients [12], while 14% of European patients harbor an *EGFR* mutation [13]. Across all NSCLC patient subgroups, 2-7% of patients harbor an *ALK* translocation, 3-5% of patients harbor a *BRAF V600E* mutation, and *ROS1* rearrangements can be detected in 1-2% of patients.

There is a wide variety of techniques and platforms available to test for these biomarkers. Single-gene tests such as Sanger sequencing, IHC, and a range of in situ hybridization (ISH) tests are, in most cases, less expensive tests [14] and have a shorter turnaround time compared to multi-gene methods such as Next Generation Sequencing (NGS). However, NGS, and particularly WGS, can increase efficiency by substituting all other tests used for biomarker testing. However, WGS is more expensive compared to other biomarker tests [15–18], which is one of the reasons

that it is not yet widely used in clinical practice. However, most patients will receive multiple biomarker tests, and it is currently unclear whether WGS is also more expensive compared to the total cost per patient of biomarker testing.

Nonetheless, relatively little detailed information is available about the use of biomarker testing in the real-world setting and so the total cost of the diagnostic pathway. It would add essential information as previous budget impact studies of biomarker testing in lung cancer report aggregated measures such as healthcare utilization [19–21]. Additionally, other relevant information, such as how tests are sequenced [22], test techniques used [6,23], or the actual costs of these tests sequences, is not yet known in detail.

This study, therefore, aims to provide a complete overview of biomarker testing, potentially spanning multiple treatment lines, for a cohort with stage IV NSCLC in the Netherlands. The entire cohort was referred to a comprehensive cancer center, but also biomarker testing prior to referral is included in the current study. More specifically, we will provide an estimate of the utilization, the sequence, turnaround time, and total cost of biomarker testing.

2. Materials and methods

2.1 Methods

We have used exploratory data analysis and process mining techniques for our analysis into the biomarker testing pathway. Process mining is a set of techniques that exploit the information contained in event logs. Event logs describe activities in terms of when they were executed and who was involved with the activity. It allows us to discover the actual ordering of care processes and to evaluate its characteristics such as turnaround times and costs. More specifically, for each patient, biomarker tests were ordered based on the times they were recorded. We used R 3.5.2 (https://www.r-project.org, accessed on June 5, 2020) [24] for the analysis and R package bupaR 0.4.2 [25] for process mining.

2.2 Data sources

Patients were identified through a large tertiary referral site, a comprehensive cancer center (CCC), and then linked to pathology data from the referring hospital to ensure analysis of the complete diagnostic pathway, resulting in one event log that contains highly granular information on the type and timing of the activity that was conducted for each patient. PALGA (the nationwide network and registry of histopathology and

cytopathology in the Netherlands) was used to extract the biomarker testing history at other hospitals for our patient cohort. Thus, this cohort is unique because of the access to diagnostics used in the referring hospital and CCC.

2.3 Data cleaning and enriching

We have removed duplicate activities, i.e., tests with either a duplicate start or completion time, assuming these are reporting errors. Activities that were not executed due to reasons such as insufficient tumor material available were also excluded (n = 51; 5.5%). This lead to exclusion of 9 patients (8.1%). We have enriched our event log with cost data on tests used for biomarker testing from a micro-costing study in which 24 Dutch pathology labs participated [15]. For tests for which no cost data are available, we have used reimbursement tariffs from 2017 retrieved from the Dutch Healthcare Authority (NZa) [26]. These were retrieved from https://puc.overheid.nl/nza/doc/PUC_13010_22/ (accessed on May 22, 2020).

2.4 Patient selection

The cohort consists of patients with stage IV NSCLC who received immunohistochemistry or molecular diagnostics at CCC. We included only patients who received biomarker testing at CCC between January 1, 2017, and December 31, 2018. Patients who received biomarker testing at CCC before or beyond this period were excluded. The data from CCC spanned until August 2019, so we can be reasonably confident that we captured all relevant activities within the patient episode. This limited time interval was applied to minimize heterogeneity between patients in tests received caused by the implementation of new testing techniques over time while retaining a patient cohort with an acceptable size. In total, we included 102 patients.

2.5 Biomarker testing in the comprehensive cancer center

CCC is a non-teaching and non-academic specialized comprehensive cancer center. CCC frequently organizes and participates in clinical trials. Biomarker testing is indicated for all patients with stage IV NSCLC. The oncologist requests biomarker testing and, in most cases, does request a specific biomarker test. However, the oncologist does specify whether it is biomarker testing an initial diagnosis or resistance analysis. The pathologist decides together with the pulmonologist or oncologist which genes will be tested, while the molecular pathology department has determined which technique or test will be used for each biomarker. Biomarker tests can be conducted sequentially according to the biomarker testing strategy for NSCLC in CCC in place during the study period. In other words, identifying an actionable target means that no further testing is undertaken since actionable targets rarely overlap [27]. CCC conducted all testing in-house.

In this case, CCC is a tertiary referral hospital, which means that almost all patients treated at CCC have previously received diagnostics and potentially also treatment elsewhere. Reasons for referral to CCC can be enrolment into a clinical trial, case complexity, and exhausting treatment options at the referring hospital. Even though most patients that were referred to CCC already have received diagnostics and treatment previously, it is possible that not all relevant biomarkers for an initial diagnosis were tested at the referring hospital. Additionally, testing at CCC is sometimes conducted to establish the eligibility of patients to enroll in clinical trials. Therefore, biomarker testing at CCC may be more elaborate and thus more expensive, compared to testing at non-specialized and non-academic hospitals. Physicians in CCC trust the results from tests conducted elsewhere in most cases, minimizing the need to re-test the same biomarkers. Given the sequential nature of the test strategy, the test sequence conducted at CCC is dependent on the tests conducted at other hospitals.

2.6 Validation with clinicians

We iteratively validated our findings with a lung pathologist (author KM) and pulmonologist (author ES) employed at CCC. First, during the initial stages of the analysis, discussions improved our understanding of the large degree of variation in tests utilized and in test sequences. Second, once the analysis was completed, the results of the study were presented to the clinicians. It became clear that the pathology department is responsible for the order of the individual tests, and whether they are conducted in parallel or sequentially. Once all individual tests included in one order are completed, the results are sent to the requesting oncologist or pulmonologist. Therefore, how individual tests are sequenced is typically not known to the oncologist or pulmonologist. After discussing the results of the current study, both clinicians were confident that the results reflect what they experience in daily clinical practice.

3. Results

3.1 Patient population and healthcare utilization

Table 1 describes our final patient cohort. The cost per patient reported in table 1 includes costs for all biomarker tests conducted. Additionally, patients who received biomarker testing also at other centers had a mean total cost per patient of 2550.91 US dollar (Std. Dev.: 1221.51) or 2124.87 euro (Std. Dev.: 1017.50). For these patients, on average, the cost is estimated to be 1778.44 US dollar (Std. Dev.: 1197.39) or 1481.42 euro (Std. Dev.: 997.41) for biomarker tests conducted at CCC.

Table 1. Characteristics of the patient population

Characteristics	N (%)
Number of patients	102
Median age (in years)	58.8 (IQR: 12.6)
Gender	
Female	51 (50.0%)
Male	51 (50.0%)
Stage	
4	37 (36.3%)
4A	23 (22.5%)
4B	42 (41.2%)
Histology[a]	
Adenocarcinoma	75 (73.5%)
Squamous cell	12 (11.8%)
Other specified carcinomas	9 (8.8%)
Unspecified carcinomas (NOS)	6 (5.9%)
Median number of tests	7 (IQR: 4)
Mean cost per patient for biomarker testing[b]	2258.42 US dollar (Std. Dev.: 1216.29) or 1881.23 euro (Std. Dev.: 1013.15)
Patients received biomarker testing also at (an) other center(s)	49 (48.0%)

[a]Classification of histology is based on ICD-0 codes [28]. [b] Calculated by dividing the sum of all biomarker test costs by the number of patients in the cohort.

Biomarker tests that were conducted at CCC and the referring centers are summarized in tables 2 and 3, respectively. Some patients received the same test more than once, indicated by the difference between the absolute frequency and the number of unique patients tested in table 2. In the cases where IHC showed a low PD-L1 expression level, a re-test with a different antibody was conducted for 14 patients. CCC used antibody clones 22C3 and SP142 to test PD-L1 expression level with IHC. It is unknown which antibody clones were used elsewhere. Out of 102 patients, 94 patients (92.2%) were tested with a gene assay using either NGS

or Sequenom MassARRAY, and 82 patients (80.4%) were tested with IHC for PD-L1 expression level. Although turnaround times for IHC tests are not available in table 2, these tests typically have a relatively short turnaround time of up to several days.

3.2 Unique biomarker test combinations

Including testing both at CCC and referring centers, ninety-nine unique biomarker test combinations are found for 102 patients. Thus, almost none of the patients have received exactly the same tests in the same order. Figure 1 shows for our entire cohort all unique biomarker test combinations, ordered chronologically. Figure 1 does not show which biomarker tests were conducted sequentially or in parallel. The degree of uniformity across patients is higher at the beginning of the test sequences, compared to the tests conducted at a later stage in the test sequences. Moreover, the number of conducted tests also shows a substantial degree of variation across patients. Most patients are tested first for biomarkers that are recommended by leading CPG [10,11], while emerging biomarkers such as *MET*, *NRAS*, and *RET* are typically tested at a later stage. These biomarkers were tested for to determine eligibility for clinical trials. Overall, 69 out of 102 patients eventually were tested with targeted gene panel, and for 19 of these patients, it was the first test received. In some cases, the same gene is tested twice back to back. For example, the second test is an ISH test to confirm the positive IHC test. Furthermore, when *ALK*, PD-L1, *ROS1*, and in most cases also *NTRK* are tested one after another, they are tested with IHC and are part of the same workflow.

By zooming in on the first three weeks of the test sequence, we can observe from figure 2 that tests are completed at different times for each patient. Moreover, for most patients, more than one test is completed, even within this relatively short interval.

Table 2. Descriptives of biomarker tests conducted at CCC

Biomarkers	Test technique or platform	Absolute frequency	No. of unique patients tested (%)	Median turnaround time in days (IQR)	Costs (in euro)	Costs (euro converted to US dollar)
MET exon 14 deletion	RT-PCR	85	78 (77.2)	8.1 (4.1)	275.24	330.43
EGFR, HER2	Multiplex fragment analysis	77	73 (72.3)	8.3 (5.0)	436.26[a]	523.73
PD-L1	IHC	70	70 (69.3)	NA	93.74	112.53
Assay	TSACP MiSeq[b]	44	41 (40.6)	11.8 (3.8)	258.96	310.88
	Path v2D[c]	23	17 (16.8)	86.9 (100)	993.67[d]	1192.90
	Archer FusionPlex MiSeq[e]	2	2 (2.0)	9.1 (9.1)	993.67[d]	1192.90
	Total	69	54 (53.5)	12.8 (9.2)	417.57	501.23
ALK	IHC	54	54 (53.5)	NA	101.88	122.31
	FISH	5	3 (3.0)	7.7 (4.8)	134.48	161.44
	Total	59	55 (54.5)	7.7 (4.8)	102.16	122.64
ROS1	IHC	50	50 (49.5)	NA	101.88	122.31
	FISH	8	6 (5.9)	9.9 (3.1)	134.48	161.44
	Total	58	51 (50.5)	9.9 (3.1)	102.69	123.28
Hotspot panel	Sequenom MassARRAY	51	46 (45.5)	7.8 (3.2)	436.26[a]	523.73
MET	FISH	33	29 (28.7)	9.1 (4.8)	134.48	161.44
	DISH	8	8 (7.9)	NA	436.26[a]	523.73
	IHC	1	1 (1.0)	NA	97.81	117.42
	Total	42	34 (33.7)	9.1 (4.8)	151.18	181.49
NTRK	IHC	41	41 (40.6)	NA	97.81	117.42
RET	FISH	38	34 (33.7)	10.9 (7.4)	134.48	161.44
HER2	IHC	12	12 (11.9)	NA	97.81	117.42
	DISH	7	7 (6.9)	NA	436.26[a]	523.73
	Sanger	3	2 (2.0)	10.3 (6.4)	71.19	85.46
	FISH	1	1 (1.0)	10.9	134.48	161.44
	Total	23	14 (13.9)	10.6 (3.6)	178.51	214.30
FGR1	FISH	5	5 (5.0)	17.8 (4.6)	134.48	161.44
EGFR	FISH	3	2 (2.0)	9.2 (5.9)	134.48	161.44
	Sanger	2	1 (1.0)	NA	71.19	85.46
	Total	5	3 (3.0)	9.2 (5.9)	115.01	138.07
EGFR T790M	HRM sequencing	4	4 (4.0)	5.9 (2.0)	97.62	117.19
NRAS	Sanger sequencing	1	1 (1.0)	55 (0.0)	60.58	72.73
	HRM sequencing	1	1 (1.0	7.8 (0.0)	74.56	89.51
	Total	2	2 (2.0)	31.4 (23.6)	67.57	81.12
NRAS exon 4	Sanger sequencing	2	2 (2.0)	9.2 (2.4)	60.58	72.73
TP53	Sanger sequencing	2	2 (2.0)	9.2 (0.0)	65.40	78.51
KRAS	HRM sequencing	1	1 (1.0)	8.2 (0.0)	97.62	117.19
	Sanger sequencing	1	1 (1.0)	6.8 (0.0)	67.33	80.83
	Total	2	2 (2.0)	7.5 (0.7)	82.47	99.01

The table includes only biomarkers that were tested more than once. All assays consist of at least the following genes: *ALK*, *EGFR*, *BRAF*, *KRAS*, and *MET*. All genes included in the assays and hotspot panel are listed in supplementary table 1.

[a] Maximum reimbursed amount for simple molecular diagnostics in 2017 [26]. [b] 48-gene DNA assay. [c] 29-gene DNA assay.

[d] Maximum reimbursed amount for complex molecular diagnostics in 2017 [26]. [e] 14-gene RNA assay.

Table 3. Descriptives of biomarker tests conducted at referring centers

Biomarkers	Test technique or platform	Absolute frequency	No. of unique patients tested (%)	Costs (in euro)	Costs (euro converted to US dollar)
Assay	Ion Ampliseq[a]	44	34 (69.4)	296.45	355.89
	TSACP MiSeq[b]	4	4 (8.2)	258.96	310.88
	Total	48	36 (73.5)	258.96	310.88
ALK	IHC	22	21 (42.9)	101.88	122.31
	FISH	7	6 (12.2)	134.48	161.44
	Technique Unknown	4	3 (6.1)	436.26[c]	523.73
	Total	33	25 (51.0)	114.53	137.49
PD-L1	IHC	29	25 (51.0)	93.74	112.53
ROS1	IHC	11	11 (22.4)	101.88	122.31
	FISH	6	6 (12.2)	134.48	161.44
	Technique Unknown	2	2 (4.1)	436.26[c]	523.73
	Total	58	51 (50.5)	102.69	123.28
KRAS	Technique Unknown	7	6 (12.2)	436.26[c]	523.73
	Sanger sequencing	1	1 (2.0)	67.33	80.83
	Biocartis Idylla	1	1 (2.0)	257.74	309.42
	Total	9	8 (16.3)	425.53	510.85
EGFR	Technique Unknown	8	8 (16.3)	436.26[c]	523.73
	Sanger sequencing	1	1 (2.0)	71.19	85.46
	Total	9	8 (16.3)	425.53	510.85
RET	FISH	5	5 (10.2)	134.48	161.44
	IHC	1	1 (2.0)	97.81	117.42
	Total	6	6 (12.2)	133.07	159.75
MET	FISH	3	3 (6.1)	134.48	161.44
HER2	IHC	1	1 (2.0)	97.81	117.42
	Sanger	1	1 (2.0)	71.19	85.46
	Technique Unknown	1	1 (2.0)	436.26[c]	523.73
	Total	3	3 (6.1)	201.75	242.20

The table includes only biomarkers that were tested more than once. All assays consist of at least the following genes: *ALK*, *EGFR*, *BRAF*, *KRAS*, and *MET*. All genes included in the assays and hotspot panel are listed in supplementary table 1. [a]50-gene DNA assay. [b]48-gene DNA assay. [c]Maximum reimbursed amount for simple molecular diagnostics in 2017 [26].

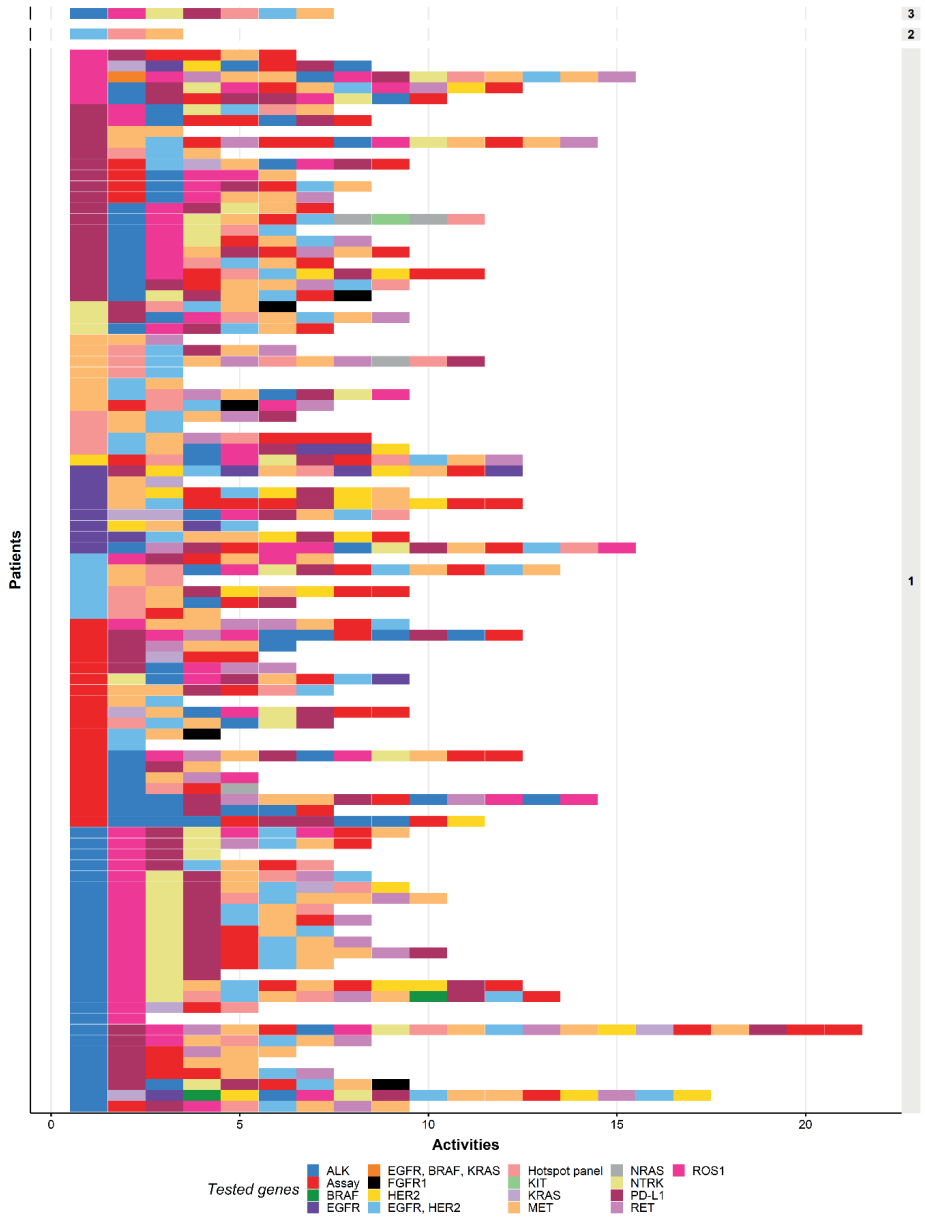

Figure 1. Unique biomarker test combinations for all individual patients included in the patient cohort. The tests are ordered chronologically. Each row represents the biomarker test combination for one patient. Numbers shown on the right indicate the number of patients who received the same biomarker test combination.

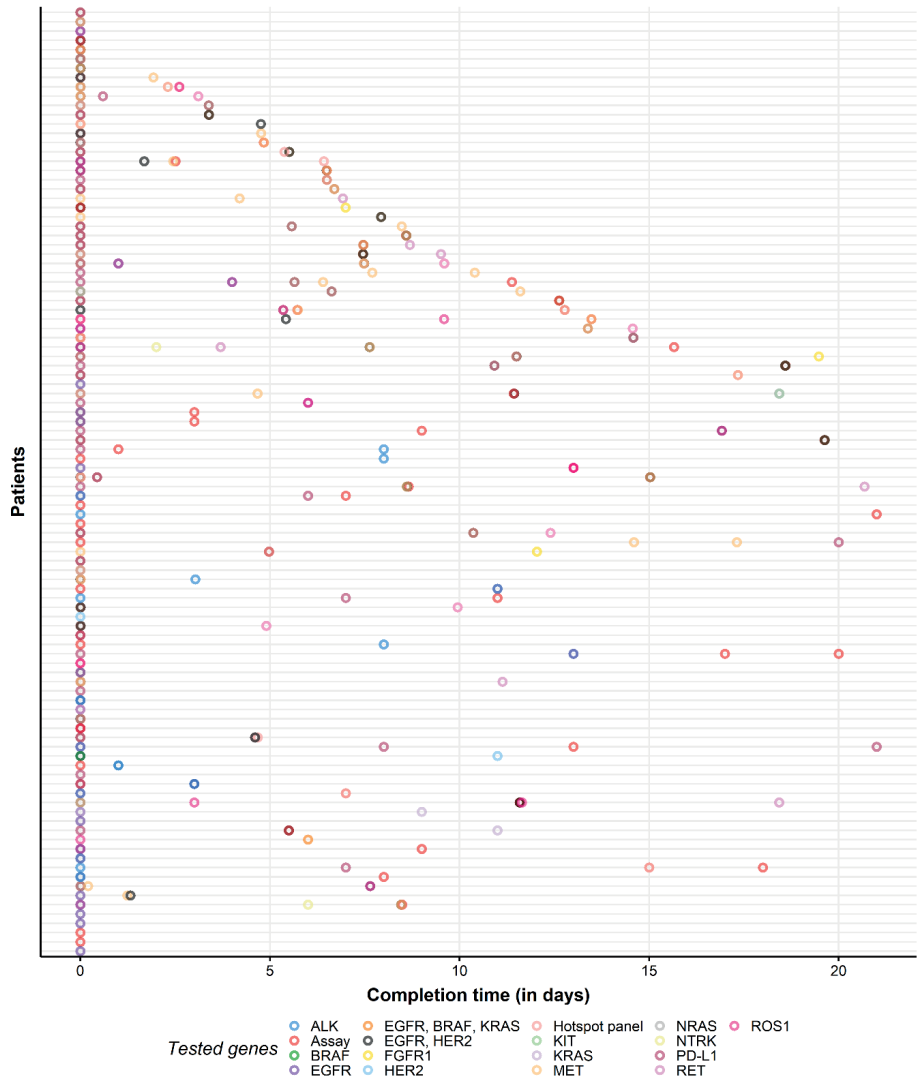

Figure 2. Distribution of biomarker tests over time zoomed in on the first three weeks after completion of the first biomarker test. Each row represents one patient. Each dot represents one biomarker test. Patients are ordered by the total duration of their care pathway and may continue beyond the three weeks shown here.

3.3 Distribution of cost per patient

Figure 3 presents the distribution of the total cost per patient for the biomarking tests conducted at both CCC and other centers. The figure shows a typical right-skewed distribution, meaning that are several patients with costs much higher than the mean. Patients with a relatively low cost received a relatively low number of tests. Since WGS can potentially replace all other biomarker tests conducted, we can derive the number of patients that would have incurred fewer costs if they would have received WGS as their only test. The cost of WGS may be different in other countries and may continue to decrease over the years. Therefore, figure 2 includes multiple hypothetical cost levels for WGS.

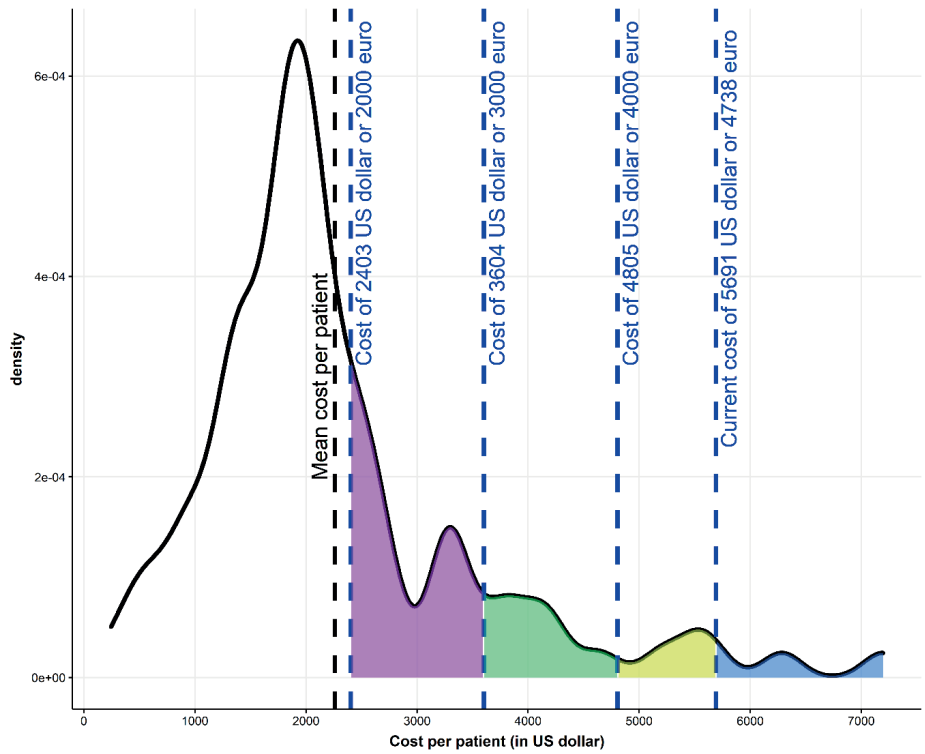

Figure 3. Distribution of the total cost per patient for biomarker testing. The black dashed lines indicate the mean cost per patient. Blue dashed lines indicate the current price of WGS, a hypothetical cost of 2000, 3000, and 4000 euro per patient, respectively. Shaded areas represent the number of patients for whom WGS may have been equally expensive or less expensive at each respective price level. Purple-shaded area: 17 (16.7%). Green-shaded area: 7 patients (6.9%). Yellow-shaded area: 3 patients (2.9%). Blue-shaded area: 2 patients (2.0%).

4. Discussion

In this study, we have provided more insight into the biomarker tests used for patients with stage IV NSCLC, based on their complete biomarker testing history, either conducted at CCC or other centers. We have described our patient cohort using clinical characteristics and other patient characteristics. We have examined at what cost level WGS would be equally expensive or less expensive compared to the cost per patient observed in our cohort. The cohort had a lower median age compared to the total population of stage IV NSCLC patients [29], potentially caused by the fact that younger patients are in more cases eligible for treatment and thus require biomarker testing. The cohort was overrepresented in adenocarcinoma, as compared to the total population of stage IV NSCLC patients, the cohort contained relatively more patients with adenocarcinoma. This could be caused by the fact that these patients typically have a higher probability of harboring biomarkers [30].

Our results illustrate the sequential nature of these test sequences and differences in testing capabilities across referring and referral centers. They show 99 unique biomarker test combinations for 102 patients, including both tests conducted at CCC and at referring centers. We found a mean cost per patient for biomarker testing of 2258.42 US dollar (Std. Dev.: 1216.29) or 1881.23 euro (Std. Dev.: 1013.15), of which, on average, 1778.44 US dollar or 1481.42 euro (75%) is incurred at CCC. Costs incurred at CCC show a marked increase from 1369.77 US dollar or 1141 euro reported in 2015, also based on data from CCC [22]. The median number of biomarker tests per patient for our cohort was substantially higher compared to the number of tests per patient assumed in [22], which may be one of the causes of the increase in costs per patient. This increase in costs has no direct financial consequences to patients, as these costs are reimbursed through basic health insurance in the Netherlands. However, it does increase the budget impact of biomarker testing. Figure 3 shows a long-tailed distribution, which highlights that a relatively small number of patients incurs substantial higher total costs for biomarker testing.

Figure 1 and 2 indicate that the most common biomarkers are tested within the first few tests for most patients, and emerging biomarkers are typically tested further down the test sequence. An exception is testing for an *NTRK* fusion, which is an emerging biomarker with a relatively low prevalence [31]*NTRK* in CCC is often conducted in the same workflow as testing *ALK*, PD-L1, and *ROS1*, and is therefore tested at a relatively early stage in the test sequence. Given the sequential nature of the strategy used for biomarker testing, whether additional tests are conducted is partly dependent on the results of previous tests. Further testing is also dependent

on the availability of tumor material. An additional source of variation among test sequences is the highly dynamic landscape of biomarker testing, illustrated by the test protocol in CCC that changes monthly or bimonthly.

Testing the most prevalent biomarkers first maximizes the likelihood of finding an actionable target as early as possible and minimizes the number of tests conducted. Testing the most prevalent biomarkers first is especially relevant in a setting where obtaining enough biopsy material is challenging. While some patient subgroups have a higher likelihood of harboring biomarkers [14], it is difficult to predict which patients will require a high number of tests to find a positive result. Even so, 69 out of 102 patients eventually were tested with targeted gene panel, and for 19 of these patients, it was the first test received. Additionally, 15 patients were tested more than once with the same gene assay. This is not unexpected as the same panel used for initial testing is also used for resistance testing in CCC. Evidence from a decision-analytic model suggests that using NGS as the initial test can lead to cost-savings compared to a sequential approach [32]. However, we are not in favor of conducting only NGS, as some biomarkers are currently not testable with NGS, such as PD-L1 expression, and because NGS requires a large amount of tumor material, which leads to a higher failure rate compared to IHC [33]. In general, careful management of tumor material and test techniques that are able to test many genes concurrently while using a limited amount of tumor material would be advisable.

We also analyzed the number of patients for whom biomarker testing would have been equally expensive or less expensive if their entire test sequence were replaced with WGS. Depending on the assumed cost level of WGS, this number ranges from 2 patients (2.0%) at the current cost level of approximately 5691 US dollar or 4700 euro per patient to 29 patients (28.4%) at a hypothetical cost of 2403 US dollar or 2000 euro per patient. However, studies in other countries have reported different price levels [16–18], and others have predicted future decreases in costs [15]. Therefore, it is likely that this number will change soon. The costs of other tests are also dynamic, so the costs of testing need to be compared regularly. Moreover, it is likely that testing for progression or treatment resistance would still be required after WGS, which would lead to higher costs. We decided to exclude the costs of tests for treatment resistance and progression in the cost comparison in figure 3, as it is unknown what the costs of those tests would be. Nonetheless, the downstream value that more comprehensive molecular diagnostics provide by improving the treatment decision is potentially much higher than a reduction in the costs of testing [34].

One of the strengths of this article is the reported amount of detail on the conducted tests. To our knowledge, we are the first to provide a comprehensive report that includes tested genes, utilized techniques, costs, and turnaround times on the entire sequence of tests patients with stage IV NSCLC receive. Another strength is that the data used in this study is not confined to one center. Obtaining data from multiple centers is especially significant, given that the test sequence is also dependent on the tests previously conducted at other centers. Thus, the test sequence should be evaluated in its entirety. Moreover, our application of process mining techniques to report test sequences for biomarker testing is novel and, to our knowledge, the first attempt. While process mining has been previously applied to discover care pathways [35], only a few studies have analyzed care pathways in lung cancer [36–38], all of which propose a novel method to conduct process mining without providing an empirical application. Even though not all process mining methods are useful in this context, it does offer a valuable approach for describing care pathways.

This study also has some limitations. First, the generalizability of the results may be limited, given that CCC is a comprehensive cancer center that may use a more elaborate test strategy to establish the eligibility of patients to enroll in clinical trials, compared to non-academic and non-specialized hospitals. Additionally, the cost of testing is specific to each setting, so the same tests in other centers may be more or less costly [39]. The cost estimates we have primarily used should give an accurate representation of the national average, as they were based on cost data from 24 laboratories in the Netherlands [14]. Nonetheless, generalizing biomarker test costs to centers in other countries remains challenging. Second, the size of the patient cohort is relatively small. However, after validating our results, we are confident that our results reflect the heterogeneity observed in clinical practice. Third, for some test techniques, no costs are known. By using reimbursed tariffs, we have attempted to minimize the impact of this limitation. Fourth, we were not able to calculate turnaround times for tests conducted with IHC or for tests conducted at referring centers, as only completion times for these tests were reported.

With the introduction of new biomarkers and testing techniques, test strategies will likely become even more complex. Perhaps the value of WGS should be seen in the light of reducing the complexity of the diagnostic pathway, as it is unlikely that WGS will be able to compete on costs. The value of reducing the complexity of the diagnostic pathway is an aspect of the value that WGS may provide but has not yet been explored in detail. It could be an exciting avenue for future research.

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References

[1] R. Chalela, V. Curull, C. Enríquez, L. Pijuan, B. Bellosillo, J. Gea, Lung adenocarcinoma: From molecular basis to genome-guided therapy and immunotherapy, J. Thorac. Dis. 9 (2017) 2142–2158.

[2] N.I. Lindeman, P.T. Cagle, D.L. Aisner, M.E. Arcila, M.B. Beasley, E.H. Bernicker, C. Colasacco, S. Dacic, F.R. Hirsch, K. Kerr, D.J. Kwiatkowski, M. Ladanyi, J.A. Nowak, L. Sholl, R. Temple-Smolkin, B. Solomon, L.H. Souter, E. Thunnissen, M.S. Tsao, C.B. Ventura, M.W. Wynes, Y. Yatabe, Updated molecular testing guideline for the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors guideline from the college of American pathologists, the international association for the study of lung cancer, and the a, Arch. Pathol. Lab. Med. 142 (2018) 321–346.

[3] J.K. Sabari, F. Santini, I. Bergagnini, W.V. Lai, K.C. Arbour, A. Drilon, Changing the Therapeutic Landscape in Non-small Cell Lung Cancers: the Evolution of Comprehensive Molecular Profiling Improves Access to Therapy, Curr. Oncol. Rep. 19 (2017).

[4] E. Heitzer, I.S. Haque, C.E.S. Roberts, M.R. Speicher, Current and future perspectives of liquid biopsies in genomics-driven oncology, Nat. Rev. Genet. 20 (2019) 71–88.

[5] M. Reck, K.F. Rabe, Precision diagnosis and treatment for advanced non–small-cell lung cancer, N. Engl. J. Med. 377 (2017) 849–861.

[6] C. Lim, M.S. Tsao, L.W. Le, F.A. Shepherd, R. Feld, R.L. Burkes, G. Liu, S. Kamel-Reid, D. Hwang, J. Tanguay, G. Da Cunha Santos, N.B. Leighl, Biomarker testing and time to treatment decision in patients with advanced nonsmall-cell lung cancer, Ann. Oncol. 26 (2015) 1415–1421.

[7] J.P. Gregg, T. Li, K.Y. Yoneda, Molecular testing strategies in non-small cell lung cancer: Optimizing the diagnostic journey, Transl. Lung Cancer Res. 8 (2019) 286–301.

[8] M.L. Tørring, M. Frydenberg, R.P. Hansen, F. Olesen, P. Vedsted, Evidence of increasing mortality with longer diagnostic intervals for five common cancers: A cohort study in primary care, Eur. J. Cancer. 49 (2013) 2187–2198.

[9] C.H. Tsai, P.T. Kung, W.Y. Kuo, W.C. Tsai, Effect of time interval from diagnosis to treatment for non-small cell lung cancer on survival: A national cohort study in Taiwan, BMJ Open. 10 (2020) e034351.

[10] D. Planchard, S. Popat, K. Kerr, S. Novello, E.F. Smit, C. Faivre-Finn, T.S. Mok, M. Reck, P.E. Van Schil, M.D. Hellmann, S. Peters, Corrigendum: Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 30 (2019) 863–870.

[11] D.S. Ettinger, D.E. Wood, C. Aggarwal, D.L. Aisner, W. Akerley, J.R. Bauman, A. Bharat, D.S. Bruno, J.Y. Chang, L.R. Chirieac, T.A. D'Amico, T.J. Dilling, M. Dobelbower, S. Gettinger, R. Govindan, M.A. Gubens, M. Hennon, L. Horn, R.P. Lackner, M. Lanuti, T.A. Leal, J. Lin, B.W. Loo, R.G. Martins, G.A. Otterson, S.P. Patel, K.L. Reckamp, G.J. Riely, S.E. Schild, T.A. Shapiro, J. Stevenson, S.J. Swanson, K.W. Tauer, S.C. Yang, K. Gregory, M. Hughes, Non-small cell lung cancer, version 1.2020: Featured updates to the NCCN guidelines, JNCCN J. Natl. Compr. Cancer Netw. 17 (2019) 1464–1472.

[12] M. Dietel, N. Savelov, R. Salanova, P. Micke, G. Bigras, T. Hida, J. Antunez, B. Guldhammer Skov, G. Hutarew, L.F. Sua, H. Akita, O.S.H. Chan, B. Piperdi, T. Burke, S. Khambata-Ford, A.C. Deitz, Real-world prevalence of programmed death ligand 1 expression in locally advanced or metastatic non–small-cell lung cancer: The global, multicenter EXPRESS study, Lung Cancer. 134 (2019) 174–179.

[13] Y.L. Zhang, J.Q. Yuan, K.F. Wang, X.H. Fu, X.R. Han, D. Threapleton, Z.Y. Yang, C. Mao, J.L. Tang, The prevalence of EGFR mutation in patients with non-small cell lung cancer: A systematic review and meta-analysis, Oncotarget. 7 (2016) 78985–78993.

[14] C.T. Pasmans, B.B. Tops, E.M. Steegs, V. Coupe, K. Grunberg, E. de Jong, E.M. Schuuring, S. Willems, M. Ligtenberg, V. Retel, H. van Snellenberg, E. de Bruijn, E. Cuppen, G.W. Frederix, Micro-costing Diagnostics in Oncology: From Single-Gene Testing to Whole Genome Sequencing, MedRxiv. 19009969 (2019). https://doi.org/10.1101/19009969.

[15] K. Schwarze, J. Buchanan, J.M. Fermont, H. Dreau, M.W. Tilley, J.M. Taylor, P. Antoniou, S.J.L. Knight, C. Camps, M.M. Pentony, E.M. Kvikstad, S. Harris, N. Popitsch, A.T. Pagnamenta, A. Schuh, J.C. Taylor, S. Wordsworth, The complete costs of genome sequencing: a microcosting study in cancer and rare diseases from a single center in the United Kingdom, Genet. Med. 22 (2020) 85–94.

[16] M. Plöthner, M. Frank, J.M.G. von der Schulenburg, Cost analysis of whole genome sequencing in German clinical practice, Eur. J. Heal. Econ. 18 (2017) 623–633.

[17] D. Weymann, J. Laskin, R. Roscoe, K.A. Schrader, S. Chia, S. Yip, W.Y. Cheung, K.A. Gelmon, A. Karsan, D.J. Renouf, M. Marra, D.A. Regier, The cost and cost trajectory of whole-genome analysis guiding treatment of patients with advanced cancers, Mol. Genet. Genomic Med. 5 (2017) 251–260.

[18] K. Schwarze, J. Buchanan, J.C. Taylor, S. Wordsworth, Are whole-exome and whole-genome sequencing approaches cost-effective? A systematic review of the literature, Genet. Med. 20 (2018) 1122–1130.

[19] S. Brinkhof, H.J.M. Groen, S.S. Siesling, M.J. IJzerman, Resource utilization in lung cancer diagnostic procedures: Current use and budget consequences, PLoS One. 12 (2017) 1–7.

[20] A. Chawla, M. Peeples, N. Li, R. Anhorn, J. Ryan, J. Signorovitch, Real-world utilization of molecular diagnostic testing and matched drug therapies in the treatment of metastatic cancers, J. Med. Econ. 21 (2018) 543–552.

[21] R. Sluga, B.E.E.M. Van Den Borne, P. Roepman, B.J.M. Peters, E.A. Kastelijn, F.M.N.H. Schramel, Utilization of molecular testing and survival outcomes of treatment with first- or second-line tyrosine kinase inhibitors in advanced non-small cell lung cancer in a Dutch population, Anticancer Res. 38 (2018) 393–400.

[22] R.A. Van Amerongen, V.P. Retèl, V.M.H. Coupé, P.M. Nederlof, M.J. Vogel, W.H. Van Harten, Next-generation sequencing in NSCLC and melanoma patients: A cost and budget impact analysis, Ecancermedicalscience. 10 (2016) 1–16.

[23] M.E. Gutierrez, K. Choi, R.B. Lanman, E.J. Licitra, S.M. Skrzypczak, R. Pe Benito, T. Wu, S. Arunajadai, S. Kaur, H. Harper, A.L. Pecora, E. V. Schultz, S.L. Goldberg, Genomic Profiling of Advanced Non–Small Cell Lung Cancer in Community Settings: Gaps and Opportunities, Clin. Lung Cancer. 18 (2017) 651–659.

[24] R Core Team, R: A language and environment for statistical computing, (2020).

[25] G. Janssenswillen, B. Depaire, M. Swennen, M. Jans, K. Vanhoof, bupaR: Enabling reproducible business process analysis, Knowledge-Based Syst. 163 (2019) 927–930. https://doi.org/10.1016/j.knosys.2018.10.018.

[26] Nederlandse Zorgautoriteit [Dutch Healthcare Authority], Tarieventabel dbc-zorgproducten en overige-zorgproducten per 1 januari 2017 [Tariffs dbc-careproducts and other careproducts per January 1 2017], 2016.

[27] A.F. Farago, C.G. Azzoli, Beyond ALK and ROS1: RET, NTRK, EGFR and BRAF gene rearrangements in non-small cell lung cancer, Transl. Lung Cancer Res. 6 (2017) 550–559.

[28] A. Fritz, C. Percy, A. Jack, K. Shanmugaratnam, L. Sobin, D.M. Parkin, S. Whelan, International Classification of Diseases for Oncology, Third, World Health Organization, Geneva, 2000. https://doi.org/10.32388/5xg1qe.

[29] M. van de Ven, V.P. Retèl, H. Koffijberg, W.H. van Harten, M.J. IJzerman, Variation in the time to treatment for stage III and IV non-small cell lung cancer patients for hospitals in the Netherlands, Lung Cancer. 134 (2019) 34–41.

[30] F.R. Hirsch, G. V. Scagliotti, J.L. Mulshine, R. Kwon, W.J. Curran, Y.L. Wu, L. Paz-Ares, Lung cancer: current therapies and new targeted treatments, Lancet. 389 (2017) 299–311.

[31] Z. Gatalica, J. Xiu, J. Swensen, S. Vranic, Molecular characterization of cancers with NTRK gene fusions, Mod. Pathol. 32 (2019) 147–153.

[32] N.A. Pennell, A. Mutebi, Z.-Y. Zhou, M.L. Ricculli, W. Tang, H. Wang, A. Guerin, T. Arnhart, A. Dalal, M. Sasane, K.Y. Wu, K.W. Culver, G.A. Otterson, Economic Impact of Next-Generation Sequencing Versus Single-Gene Testing to Detect Genomic Alterations in Metastatic Non–Small-Cell Lung Cancer Using a Decision Analytic Model, JCO Precis. Oncol. 3 (2019) 1–9.

[33] M.S. Tsao, Y. Yatabe, Old Soldiers Never Die: Is There Still a Role for Immunohistochemistry in the Era of Next-Generation Sequencing Panel Testing?, J. Thorac. Oncol. 14 (2019) 2035–2038.

[34] L.M. Sabatini, C. Mathews, D. Ptak, S. Doshi, K. Tynan, M.R. Hegde, T.L. Burke, A.D. Bossler, Genomic Sequencing Procedure Microcosting Analysis and Health Economic Cost-Impact Analysis: A Report of the Association for Molecular Pathology, J. Mol. Diagnostics. 18 (2016) 319–328.

[35] A.P. Kurniati, O. Johnson, D. Hogg, G. Hall, D. Hogg, O. Johnson, D. Hogg, G. Hall, Process Mining in Oncology: a Literature Review, in: Proc. 6th Int. Conf. Inf. Commun. Manag. ICICM 2016, 2016: pp. 291–297.

[36] Z. Huang, X. Lu, H. Duan, W. Fan, Summarizing clinical pathways from event logs, J. Biomed. Inform. 46 (2013) 111–127.

[37] F. Ju, H.K. Lee, R.U. Osarogiagbon, X. Yu, N. Faris, J. Li, Computer modeling of lung cancer diagnosis-to-treatment process, Transl. Lung Cancer Res. 4 (2015) 404–414.

[38] Z. Huang, W. Dong, L. Ji, C. Gan, X. Lu, H. Duan, Discovery of clinical pathway patterns from event logs using probabilistic topic models, J. Biomed. Inform. 47 (2014) 39–57.

[39] P. Marino, R. Touzani, L. Perrier, E. Rouleau, D.S. Kossi, Z. Zhaomin, N. Charrier, N. Goardon, C. Preudhomme, I. Durand-Zaleski, I. Borget, S. Baffert, E. Barillot, S. Bezieau, L. Coppin, C. Descapentries, S. Forget, T. Frebourd, P. Guardiola, C. Houdayer, P. Hupe, L. Lacroix, J. Leclerc, A. Lespagnol, S. Longuemare, J. Mosser, M.F. Odou, F. Revillion, N. Sevenet, I. Soubeyran, D. Vaur, Cost of cancer diagnosis using next-generation sequencing targeted gene panels in routine practice: A nationwide French study, Eur. J. Hum. Genet. 26 (2018) 314–323.

4

Chapter 5

Whole genome sequencing in oncology: Using scenario drafting to explore future developments

Michiel van de Ven, Martijn J.H.G. Simons, Hendrik Koffijberg, Manuela A. Joore, Maarten J. IJzerman, Valesca P. Retèl, Wim H. van Harten

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Abstract

Background

In oncology, Whole Genome Sequencing (WGS) is not yet widely implemented due to uncertainties such as the required infrastructure and expertise, costs and reimbursements, and unknown pan-cancer clinical utility. Therefore, this study aimed to investigate possible future developments facilitating or impeding the use of WGS as a molecular diagnostic in oncology through scenario drafting.

Methods

A four-step process was adopted for scenario drafting. First, the literature was searched for barriers and facilitators related to the implementation of WGS. Second, they were prioritized by international experts, and third, combined into coherent scenarios. Fourth, the scenarios were implemented in an online survey and their likelihood of taking place within five years was elicited from another group of experts. Based on the minimum, maximum, and most likely (mode) parameters, individual Program Evaluation and Review Technique (PERT) probability density functions were determined. Subsequently, individual opinions were aggregated by performing unweighted linear pooling, from which summary statistics were extracted and reported.

Results

Sixty-two unique barriers and facilitators were extracted from 70 articles. Price, clinical utility, and turnaround time of WGS were ranked as the most important aspects. Nine scenarios were developed and scored on likelihood by eighteen experts. The scenario about introducing WGS as a clinical diagnostic with a lower price, shorter turnaround time, and improved degree of actionability, scored the highest likelihood (median: 68.3%). Scenarios with low likelihoods and strong consensus were about better treatment responses to more actionable targets (26.1%), and the effect of centralizing WGS (24.1%).

Conclusions

Based on current expert opinions, the implementation of WGS as a clinical diagnostic in oncology is heavily dependent on the price, clinical utility (both in terms of identifying actionable targets as in adding sufficient value in subsequent treatment), and turnaround time. These aspects and the optimal way of service provision are the main drivers for the implementation of WGS and should be focused on in further research. More knowledge regarding these factors is needed to inform strategic decision making regarding the implementation of WGS, which warrants support from all relevant stakeholders.

Keywords
Whole genome sequencing; implementation; scenario drafting; uncertainty; oncology

1. Background

Next Generation Sequencing (NGS) is used in oncology to select the optimal treatment and prevent overtreatment. Compared to single sequencing techniques, NGS is a set of techniques that sequences many genes at once. Targeted gene panels (TGP) sequence an assay of a certain number of genes. In contrast, Whole Exome Sequencing (WES) sequences all protein-coding regions of the genome and Whole Genome Sequencing (WGS) sequences, both all coding and non-coding regions of the genome. Therefore, WGS is one of the most comprehensive forms of NGS, potentially allowing more biomarkers to be identified. Although the prices of all NGS techniques have been decreasing, WGS is currently more costly [1,2]. Even though WGS yields more genetic information compared to TGP and WES, the number of available therapies that can be prescribed based on this information remains limited [3]. However, the genetic information obtained by WGS facilitates research towards a better understanding of cancer and the discovery of new biomarkers [4], thus providing value for future patients. Consensus on the most optimal way to implement WGS in clinical practice is still lacking.

The potential of genomics to transform healthcare in several disease areas has been widely recognized, illustrated by coordinated efforts [5] towards implementation in countries worldwide [6,7]. These are mainly focused on the organisation of care to provide WGS efficiently. So far, WGS is mostly restricted to central facilities and/or the academic setting. This means that the logistics are different from other forms of NGS, which are more frequently conducted within hospital labs. To interpret the genetic information from WGS correctly, additional expertise in bioinformatics and molecular biology is required. Thus, workforce education is another important component in implementing WGS [8–10]. Moreover, determining which subgroups of patients sufficiently benefit from WGS is needed as costs are still prohibiting sequencing at large scale.

Access to WGS for patients varies across countries. For instance, the 100,000 genomes project [11], primarily focused on cancer and rare diseases, has met its target in 2019 [12] and has been extended to sequence 300,000 genomes. In the Netherlands, WGS is only accessible for cancer patients through enrolment in the "Center for Personalized Cancer Treatment (CPCT-02)" or "WGS Implementation in the standard Diagnostics for Every cancer patient (WIDE)" studies. In general, WGS

is primarily being used in the clinical research setting, while implementation into clinical practice is currently limited. The Technology Assessment of Next Generation Sequencing in Personalized Oncology (TANGO) study investigates the value of WGS for clinical diagnostics compared to other NGS techniques in the Netherlands [13]. The current study was conducted from this perspective, by drafting scenarios as part of the Health Technology Assessment.

Scenario drafting makes possible future pathways more explicit [14], thus leading to a better understanding of important uncertainties [15] and improved ability to anticipate future changes. Scenarios are drafted through an iterative process, starting with a literature search, followed by several expert discussions on potential future developments [16]. Scenarios are coherent stories that describe deviations from the current situation. They are not meant as predictive, but they are a useful tool to explore possible futures [17]. Scenario drafting is often used in environmental and management sciences [16], while its application and that of similar approaches in healthcare is limited [18–20]. Scenarios can be quantified by using expert elicitation to parametrize unknown variables. Subsequently, these scenarios can be used to inform model-based analyses [18], thereby quantifying the consequences of the scenarios.

The key objective of this study is to draft scenarios that reflect several different possible future pathways for the implementation of WGS into clinical practice in oncology. Subsequently, the likelihood that each of these scenarios will occur within a time horizon of five years will be estimated using expert elicitation.

2. Methods

A four-step process was adopted for scenario drafting: “literature search”, “prioritizing barriers and facilitators”, “creating coherent scenarios”, and “eliciting the likelihood of the scenarios.” Within these steps, validation and plausibility checks with international experts were included. An overview is displayed in figure 1. Barriers and facilitators are factors that can either have an impeding or facilitating role in the implementation of WGS.

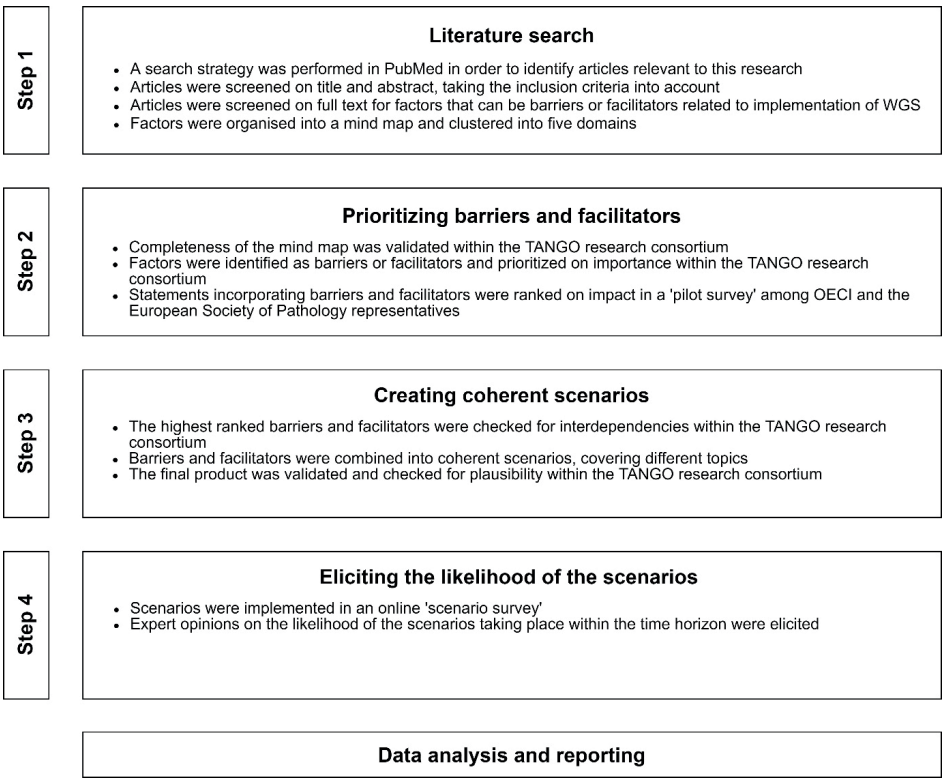

Figure 1. Flowchart of the used methodology for creating and eliciting the probability of the scenariosWGS, whole genome sequencing; TANGO, Technology assessment of next generation sequencing for personalized oncology; OECI, Organisation of European Cancer Institutes.

2.1 Step 1: Literature search

PubMed was searched for literature, using MeSH-terms and free text words. The full detailed search strategy is listed in the supplementary materials; Appendix I. Studies were included that described barriers and facilitators related to the implementation of complex and disruptive technologies in general and of WGS as a clinical diagnostic in particular. The articles found by the search strategy were screened on title and abstract by two authors (MV, MS), taking the inclusion criteria into account. Subsequently, the remaining articles were screened on full text for factors that may be barriers or facilitators in the implementation of WGS. The identified factors were summarized under common headers and organized into a mind map. The factors were clustered into five domains*: 'clinical utility and evidence generation', technical', 'reimbursement', 'social',* and *'market access'* [19]. In a research consortium session, we verified that no important factors were missing. The TANGO consortium

comprised of experts within the field of oncology, pathology, genetics, informatics, health economics, health technology assessment, legislation, ethics, and of patient representatives.

2.2 Step 2: Prioritizing barriers and facilitators

We identified the factors as barriers or facilitators and prioritized them in an interactive session with our research consortium. Additionally, statements that incorporate barriers and facilitators were ranked on their potential impact on the implementation of WGS in a questionnaire, further called 'pilot survey', among 14 representatives from the Organisation of European Cancer Institutes (OECI) and the European Society of Pathology. These representatives included pathologists, oncologists, pulmonologists, clinical scientists based in Croatia, Denmark, Italy, the Netherlands, Portugal, Moldova, Russia, Switzerland, Turkey, and the United Kingdom. Seven statements were ranked from most to least important by each representative. The statement that was ranked as most important would receive seven points, and the statement that was ranked as least important, one point. The final ranking was made by tallying the awarded points across representatives.

2.3 Step 3: Creating coherent scenarios

Barriers and facilitators that were ranked highest in the pilot survey were used to develop coherent scenarios. The principles of Cross Impact Analysis [21] were used to create coherent scenarios that include multiple interdependent developments or consequences. Possible interdependencies between barriers and facilitators were considered by consulting the experts within our research consortium. The reasoning behind creating scenarios with multiple interdependent barriers and facilitators is that the future developments and their consequences are most likely related. Therefore, it would lead to bias if interdependent factors would be viewed in isolation. Subsequently, barriers and facilitators were combined in scenarios so that they cover several topics related to the implementation and cost-effectiveness of WGS. Each scenario had a similar structure: one possible future development followed by two or three consequences of that development.

2.3.1 Validation

The final product of the scenarios was validated and checked for plausibility by discussing its content with the experts within the TANGO research consortium. Additionally, the scenarios were checked on ambiguity in language.

2.4 Step 4: Eliciting the likelihood of the scenarios

The scenarios were implemented in an online survey, using QualtricsXM [22], further called the 'scenario survey.' The target population was international experts with expertise of genomics or related fields, as well as patients that may be affected by the use of WGS.

The current situation in practice, i.e. the status quo, was presented in the scenario survey as the framework from which the scenarios deviate. Experts were asked for their opinion on the likelihood of the development and consequences taking place within the time horizon. Furthermore, the likelihood that the entire scenario, meaning both the development and its consequences, would occur within the time horizon was elicited. Three probabilities were elicited for scoring a likelihood: the mode or most likely probability that the development may occur; the lowest plausible bound where it would be extremely implausible that the real probability was below this number; and the highest plausible bound where it would be extremely implausible that the real probability was above this number. An example is displayed in figure 2. Each elicited likelihood could be scored between 0% (extremely unlikely) and 100% (extremely likely). Eliciting the mode as well as the lower and upper bounds provided a measure of uncertainty at the individual level and was based on the Sheffield elicitation framework [23]. While no calibration questions were used, experts could skip a scenario if it were beyond the scope of their expertise. The survey was anonymised, and experts were asked for informed consent beforehand. The scenario survey was distributed among the authors' professional networks using (social) media channels.

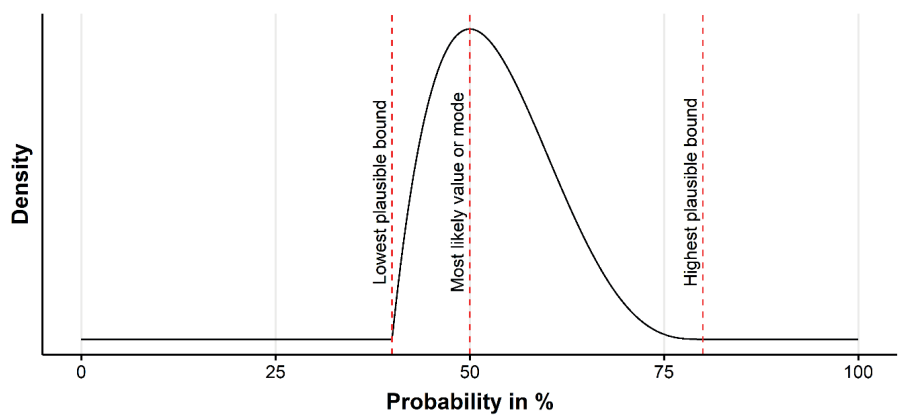

Figure 2. Example of the values elicited in the scenario survey related to the PERT distribution. In this example, the lowest plausible bound equals 40%, most likely value or mode equals 50%, and highest plausible bound equals 80%

2.5 Data analysis

Based on the elicited probabilities, individual Program Evaluation and Review Technique (PERT) probability density functions (PDF) were determined. In addition to a point estimate, this approach provides a measure of uncertainty at the individual level. The PERT distribution is a modified beta distribution [24] and is defined by three parameters: a minimum, maximum, and most likely value (mode). Subsequently, to aggregate individual opinions, we performed unweighted linear opinion pooling by taking 50,000 random samples from each individual PERT PDF. The combined random samples from all experts were visualized using kernel density estimation. The benefit of this nonparametric approach is that it can visualize the consensus, or lack thereof, among experts. The mean, median, and the highest density intervals (HDI) for the 80th percentile of these linear pools were extracted and reported. HDI is the narrowest possible interval that covers a given amount of density and therefore provides insight into how uncertain the group of experts is about the likelihood of a scenario. We have classified questions that have an 80% HDI bandwidth below or equal to 50, to have a relatively strong consensus. In comparison, an 80% HDI bandwidth larger than 50 indicates a relatively weak consensus among experts. The 80% HDI bandwidth is calculated by subtracting the 80% HDI lower bound from the 80% HDI upper bound. Data analyses were performed in R statistical software [25]. The R-code of the data analysis is provided in a supplementary file.

3. Results

3.1 Step 1: Literature search

The literature search includes articles up to June 2019. The search strategy resulted in 111 articles, of which 41 were excluded based on title and abstract. The remaining 70 articles were screened on full text. One hundred ninety-two factors were identified after screening the full texts and were summarized under 62 common headers, which are displayed in figure 3. These factors were clustered into the domains: clinical utility and evidence generation (n=24), technical (n=15), reimbursement (n=7), social (n=12), and market access (n=4). More details on the literature search are provided in the supplementary materials, appendix II.

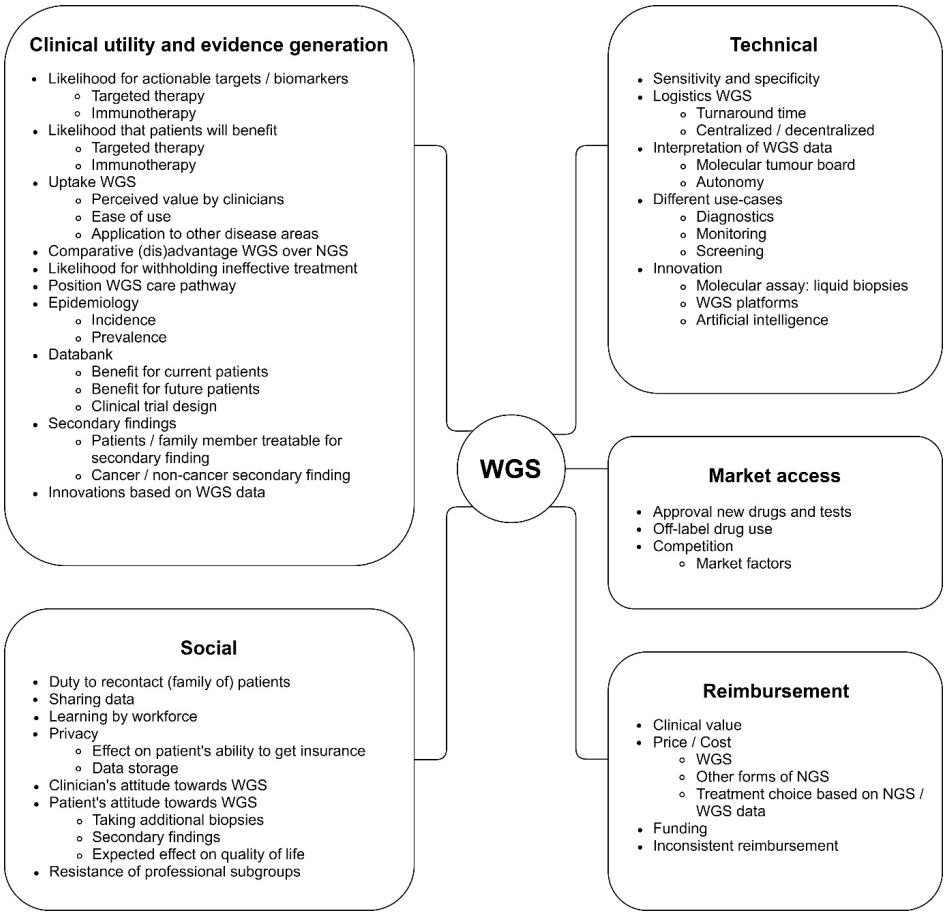

Figure 3. Factors identified with the literature search, stratified per domain. WGS, Whole Genome Sequencing; NGS, Next Generation Sequencing.

3.2 Step 2: Prioritizing barriers and facilitators

The barriers and facilitators that were prioritized from most to least important by experts in the pilot survey, are listed in table 1.

3.3 Step 3: Creating coherent scenarios

A full description of the status quo and scenarios are listed in the supplementary materials; Appendix III. Nine scenarios were created and are listed in table 2. These scenarios were labelled as: 'innovation in WGS devices' (scenario 1); 'the discovery of a new actionable biomarker for immunotherapy' (scenario 2); 'the effect of centralizing WGS' (scenario 3); 'introducing WGS as a clinical diagnostic in oncology' (scenario 4); 'a new competing NGS panel 'X'' (scenario 5); 'technical performance' (scenario 6);

'approval of new drugs for new actionable targets' (scenario 7); 'approval for off-label drug prescription' (scenario 8); and 'better treatment response to actionable targets found by WGS' (scenario 9).

Table 1. Ranking of barriers and facilitators, results from the pilot survey

Rank	Barriers	Facilitators
1	The clinical utility of WGS compared to TGPs will not be demonstrated sufficiently.	The clinical utility of WGS compared to TGPs has been demonstrated sufficiently.
2	The turnaround time of WGS will remain significantly longer compared with that of TGPs.	WGS will be included in basic health insurance.
3	The price of WGS will remain too high.	The price of WGS will drop significantly.
4	A technology that is superior in terms of cost and/or clinical utility compared to WGS will become available.	The interpretation of WGS results will become as easy as TGP results.
5	The interpretation of WGS results will not become easier.	The turnaround time of WGS will decrease and become equal to that of TGPs.
6	Fresh frozen biopsies will remain the only reliable source of DNA for WGS.	Other type of biopsies can be used for WGS, for example, liquid biopsies and FFPE biopsies.
7	WGS will not become part of basic health insurance.	No other technology that would compete with WGS will become available.

The ranked barriers and facilitators are ordered from most important to least important. WGS, Whole Genome Sequencing; TGP, Targeted Gene Panel; DNA, deoxyribonucleic acid; FFPE, Formalin-Fixed Paraffin-Embedded.

3.4 Step 4: Likelihood of the scenarios

Twenty-two international experts responded to the scenario survey of whom 19 completed the survey, 1 expert did not fill in any question, and 2 experts wished not to participate. The scenario survey was completed by experts within the field of oncology, genetics, informatics, pathology, health economics, health technology assessment, pulmonary disease and lung cancer, who resided in the Netherlands, Australia, Denmark, and Singapore. One expert completed the survey in a different way than was statistically intended and was removed from the quantitative analysis. More details are listed in supplementary materials, appendix IV.

The results of the scenario survey are listed in table 2. Figure 4 depicts the linear opinion pools of the overall likelihood of each scenario. Differences in opinion among experts are reflected in the observed multimodality in the linear opinion pools. There was a relatively weak consensus on most overall scenarios. Therefore, we also report on some of the sub-scenarios that had a relatively strong consensus.

Based on the median, the scenario concerning 'the introduction of WGS as a clinical diagnostic' (scenario 4) had the highest likelihood, but with a relatively weak consensus (median: 68.3%, [80% HDI: 15.5 – 99.0]). Within this scenario, there was a relatively strong consensus on the likelihoods that: 'WGS will detect more actionable targets than current standard diagnostics (74.7%, [55.3 – 100.0)'; 'the turnaround time will decrease to fourteen days (80.3%, [61.2 – 99.8])'; and 'the costs will decrease to €3,000 per patient (83.6%, [69.7 – 99.8])'.

The scenario concerning 'innovations in WGS devices' (scenario 1) had the second-highest likelihood, but also with a relatively weak consensus (52.1%, [0.1 – 85.5]). Within this scenario, there was only a relatively strong consensus on the likelihood of 'the development of a new WGS testing kit that is 50% cheaper in initial investment costs (69.2%, [51.5 – 100.0])'.

The scenario concerning 'the discovery of a new actionable biomarker for immunotherapy' (scenario 2) had the third-highest overall likelihood and had a relatively weak consensus (45.5%, [0.3 – 81.3]). Within this scenario, there was only a relatively strong consensus on the likelihood that 'WGS is the only technique that can identify new biomarkers (21.8%, [0.0 – 49.0])'.

The scenario concerning 'a new competing NGS panel 'X'' (scenario 5) had the fourth-highest overall likelihood and had a relatively weak consensus (39.8%, [0.0 – 78.1]). Within this scenario, there was only a relatively strong consensus on the likelihood that 'NGS panel 'X' detects actionable targets in 8% of the patients (77.4%, [46.2 – 95.2])'.

The scenario concerning 'the approval of new drugs for new actionable targets' (scenario 7) had the third-lowest likelihood, with relatively weak consensus (28.1%, [0.0 – 69.8]). Within this scenario, there was only a relatively strong consensus on the likelihood that '90% of the physicians prefer using WGS as a molecular diagnostic (71.4%, [53.6 – 95.2])'.

The scenario concerning 'better response to actionable targets found by WGS' (scenario 9) had the second-lowest likelihood, with a relatively strong consensus (26.1%, [0.0 – 42.3]). Within this scenario, there was also a relatively strong consensus about the likelihood of 'a better treatment response in patients with targets identified with WGS (9.3%, [0.0 – 39.7])'.

The scenario concerning 'the effect of centralizing WGS' (scenario 3) had the lowest likelihood, with a relatively strong consensus (24.1%, [0.0 – 45.1]).

Table 2. Scored likelihoods of the linear pooled estimates

Scenario questions (Q)	Brief description	Experts (n)	Mean	Median	80% HDI	80% HDI bandwidth
Scenario 1	**Innovation in WGS devices**					
Q1	WGS testing kit with 50% cheaper initial investment costs	18	65.5	69.2	51.5 – 100.0	48.5
Q2	Interpretation MTB only required for 5% of the patients	17	38.8	31.6	1.8 – 68.9	67.1
Q3	Average turnaround time reduced to 7 days	17	54.2	63.4	17.6 – 98.1	80.5
Q4	**Overall scenario taking place within the next five years**	**16**	**46.0**	**52.1**	**0.1 – 85.5**	**85.4**
Scenario 2	**The discovery of a new actionable biomarker for immunotherapy**					
Q1	WGS is the only technique that can identify new biomarkers	17	28.3	21.8	0.0 – 49.0	49.0
Q2	WGS detects new biomarker for immunotherapy in 20% of the patients	17	46.9	48.4	11.6 – 90.2	78.6
Q3	90% of the physicians offer WGS to patients	16	65.5	72.1	43.7 – 98.0	54.3
Q4	90% of patients prefer WGS to other molecular diagnostics	15	66.7	80.3	25.9 – 99.3	73.4
Q5	**Overall scenario taking place within the next five years**	**17**	**45.3**	**45.5**	**0.3 – 81.3**	**81.0**
Scenario 3	**The effects of centralizing WGS**					
Q1	Centralizing WGS leads to large reduction costs and turnaround time	16	52.5	51.4	19.3 – 88.8	69.5
Q2	Costs WGS decreased to €1,000.- per patient	16	54.9	54.9	30.7 – 85.6	54.9
Q3	Turnaround time WGS decreased to 5 days	16	37.9	29.9	0.0 – 69.5	69.5
Q4	All hospitals will adopt WGS	15	58.7	68.7	24.1 – 97.1	73.0
Q5	**Overall scenario taking place within the next five years**	**15**	**26.5**	**24.1**	**0.0 – 45.1**	**45.1**

Scenario 4	**Introducing WGS as a clinical diagnostic**					
Q1	WGS available as standard diagnostic test in clinical practice	17	64.5	76.1	31.6 – 99.9	68.3
Q2	WGS detects actionable target (targeted therapy) in 12% of the patients	17	68.8	74.7	55.3 – 100.0	44.7
Q3	Turnaround time WGS decreased to 14 days	17	76.1	80.3	61.2 – 99.8	38.6
Q4	Costs WGS decreased to €3,000.- per patient	16	81.1	83.6	69.7 – 99.8	30.1
Q5	WGS will be used instead of standard diagnostics	17	58.7	65.7	23.2 – 95.9	72.7
Q6	**Overall scenario taking place within next five years**	**17**	**55.3**	**68.3**	**15.5 – 99.0**	**83.5**
Scenario 5	**A new competing NGS panel 'X'**					
Q1	New liquid NGS panel 'X' enters the market	16	67.1	75.7	45.0 – 100.0	55.0
Q2	NGS panel 'X' detects actionable targets in 8% of the patients	15	66.6	77.4	46.2 – 95.2	49.0
Q3	Less invasive liquid biopsies can be used for NGS panel 'X'	15	56.1	59.9	16.7 – 88.0	71.3
Q4	Turnaround time NGS panel 'X' is on average two days	15	48.5	51.9	0.0 – 74.5	74.5
Q5	Costs NGS panel 'X' are €300.- per patient	15	51.6	51.6	18.4 – 93.4	75.0
Q6	NGS panel 'X' will be used instead of WGS	16	56.3	62.4	21.6 – 94.2	72.6
Q7	**Overall scenario taking place within the next five years**	**15**	**40.8**	**39.8**	**0.0 – 78.1**	**78.1**
Scenario 6	**Technical performance**					
Q1	Success rate tissue biopsies and sequencing process of WGS improve	15	59.0	64.7	22.9 – 86.1	63.2
Q2	Tissue biopsies successfully taken in 80% of the patients	15	55.1	58.5	20.2 – 96.9	76.7
Q3	Sequencing process of WGS successful in 95% of the patients	14	50.7	59.6	0.0 – 73.3	73.3
Q4	More than 80% of the patients sequenced successful	14	52.7	58.4	18.5 – 89.9	71.4
Q5	Costs WGS stay fixed at €4,500.- per patient	14	47.0	47.3	22.8 – 80.0	57.2
Q6	**Overall scenario taking place within the next five years**	**15**	**40.0**	**39.2**	**0.0 – 69.7**	**69.7**
Scenario 7	**Approval of new drugs for new actionable targets**					
Q1	Approval new targeted therapies for new targets discovered by WGS	14	55.0	54.6	26.1 – 97.8	71.7

Q2	New actionable targets can only be detected by WGS	15	34.6	27.9	0.0 – 56.2	56.2
Q3	WGS detects new biomarker for targeted therapy in 20% of the patients	15	41.5	44.4	0.0 – 62.8	62.8
Q4	90% of the physicians prefer using WGS as molecular diagnostic	14	66.8	71.4	53.6 – 95.2	41.6
Q5	90% of patients prefer to receive WGS as molecular diagnostics	14	68.6	78.6	28.4 – 98.7	70.3
Q6	**Overall scenario taking place within the next five years**	**14**	**35.5**	**28.1**	**0.0 – 69.8**	**69.8**
Scenario 8	**Approval for off-label drug prescription**					
Q1	Off-label drug use will be allowed based on research on WGS data	15	65.6	66.9	39.5 – 99.7	60.2
Q2	Off-label drug prescription only allowed for targets found by WGS	14	47.9	42.0	6.3 – 92.0	85.7
Q3	WGS detects actionable target for off-label targeted therapy in 5% of the patients	14	60.4	73.1	17.8 – 89.8	72.0
Q4	95% of the physicians prefer using WGS as molecular diagnostic	15	72.1	83.6	43.9 – 98.8	54.9
Q5	All patients prefer to receive WGS as molecular diagnostics	14	69.5	85.2	36.6 – 99.5	62.9
Q6	**Overall scenario taking place within the next five years**	**14**	**47.3**	**43.9**	**25.2 – 92.3**	**67.1**
Scenario 9	**Better response to actionable targets found by WGS**					
Q1	Better treatment response in patients with targets identified with WGS	14	18.5	9.3	0.0 – 39.7	39.7
Q2	Treatment response targeted therapy increased to 10%	16	35.7	24.0	0.0 – 73.7	73.7
Q3	WGS detects biomarkers that are better predictors for treatment response	14	42.5	48.6	0.0 – 64.7	64.7
Q4	All physicians prefer using WGS as molecular diagnostic	16	54.6	60.3	13.1 – 96.4	83.3
Q5	All patients prefer to receive WGS as molecular diagnostics	16	55.5	60.5	15.9 – 96.9	81.0
Q6	**Overall scenario taking place within the next five years**	**15**	**25.7**	**26.1**	**0.0 – 42.3**	**42.3**

80% HDI, 80% Highest Density Interval; WGS, Whole Genome Sequencing; MTB, Molecular Tumour Board; NGS, Next Generation Sequencing.

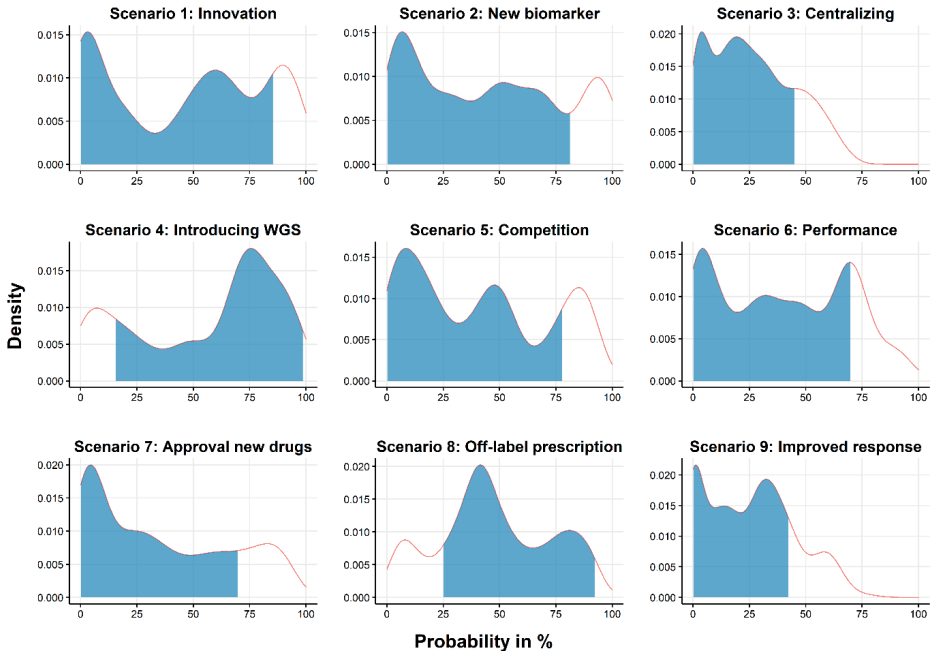

Figure 4. Linear pools of individual PERT distributions for the overall likelihood of each scenario. The blue-shaded area under the curve represents the 80% highest density interval. The scenarios concerned: 'innovation in WGS devices' (scenario 1); 'the discovery of a new actionable biomarker for immunotherapy' (scenario 2); 'the effect of centralizing WGS' (scenario 3); 'introducing WGS as a clinical diagnostic in oncology' (scenario 4); 'a new competing NGS panel 'X'' (scenario 5); 'technical performance' (scenario 6); 'approval of new drugs for new actionable targets' (scenario 7); 'approval for off-label drug prescription' (scenario 8); and 'better treatment response to actionable targets found by WGS' (scenario 9).

4. Discussion

This study aimed to investigate possible future developments facilitating or impeding the use of WGS by means of scenario drafting. Based on our literature review, we identified 62 unique barriers and facilitators for the implementation of WGS. Price, clinical utility, and turnaround time were considered as most essential for the implementation of WGS. We created nine coherent scenarios covering different pathways for the implementation of WGS into clinical practice in oncology, by combining various aspects and parameters. The scenario in which WGS would be introduced as a clinical diagnostic (scenario 4) had the highest likelihood of taking place within the next five years with a relatively weak consensus (68.3%, [15.5 – 99.0]). The scenarios about a better treatment response to actionable targets that were

found with WGS (scenario 9) and the centralization of organizing WGS (scenario 3) had the lowest likelihoods, with a relatively strong consensus (26.1%, [0.0 – 42.3] and 24.1%, [0.0 – 45.1], respectively).

The factors that were found in the literature search span several different domains. It implies that, even if one barrier is overcome, other barriers may still prevent widespread use of WGS. For example, if the clinical utility of WGS is clearly established, barriers in the social domain may hinder the use of WGS. Therefore, a strategy to responsibly introduce WGS would be most effective if multiple or all these domains are considered.

Ranking the barriers and facilitators in order of importance could assist with selecting those that should receive the most attention. Most important seems to address the unknown clinical utility of WGS compared to other NGS techniques. The unknown or unclear benefit to patients has been identified earlier, as a common problem in the implementation of healthcare technologies [26]. Additionally, being able to demonstrate the added value of a technology is often the basis for reimbursement, thereby increasing the rate of diffusion [27]. However, the scenario concerning a better treatment response to actionable targets identified by WGS (scenario 9) was with a relatively strong consensus, deemed unlikely by experts to take place within the foreseeable future. Other scenarios describing the potential clinical value of WGS were also deemed unlikely but with widely varying opinions. This concerned for instance the chance of discovering a new biomarker for immunotherapy that can be found by WGS (scenario 2), or the discovery of new actionable targets based on WGS data for which new targeted treatments will become available (scenario 7). This means that with current knowledge it is not very likely that WGS will receive reimbursement for use in the clinical practice, limiting the use of WGS to clinical research for the foreseeable future.

Furthermore, the results related to the scenario in which WGS was introduced as a clinical diagnostic (scenario 4) show that most experts find it relatively likely, with a relatively strong consensus that within five years costs of WGS will have decreased to 3,000 euros per patient. This coincides with a previous study analysing the potential developments in the costs of WGS [2]. Additionally, experts deem it rather likely that the turnaround time will have decreased to 14 days. Even so, there is little consensus among experts whether those reductions would mean that WGS would be used instead of current standard diagnostics. Apparently, either the reductions in costs and turnaround time are not substantial enough to warrant the use of WGS, or other factors play a more dominant role in the decision to use WGS instead of current standard diagnostics. Although these other factors were not included in

the scenario, table 1 provides evidence that the clinical utility plays a significant role in the implementation of WGS. In scenario 4, the clinical utility of WGS remains unchanged relative to the base-case, which may be the reason that the consensus among experts is not stronger.

A strength of this study is that we included a diverse group of international experts in multiple steps of scenario drafting. While our approach does not guarantee that important barriers and facilitators were not missed, involving a diverse group of experts minimizes the likelihood that important barriers and facilitators were missed, while it also provides a diverse range of opinions. This is especially important in a field as complex and fast-moving as molecular oncology. An additional strength is that our approach of scoring likelihoods allowed us to estimate uncertainty at both the individual and group levels. Unlike in a stepwise, Delphi-like approach where the goal is to reach consensus in a group discussion, we were able to quantify the degree of consensus among the participating experts.

A limitation of this study is that the degree of consensus or uncertainty among experts for the overall likelihood is relatively large for most scenarios. This can have multiple causes. First, it may have been challenging to quantify and score the scenarios as we noticed that experts find difficulty in giving a quantitative estimate when evidence is lacking. Second, future developments of technologies like WGS may just be too inherently difficult to predict. Third, the sample size could have been too small. However, it is not very likely that increasing the sample size would have in fact reduced uncertainty. Fourth, the cognitive burden imposed by the scenarios may have been too high. This is a common issue with scenarios that are based on the principles of Cross Impact Analysis [28]. An attempt was made to limit the cognitive burden of the scenarios by limiting the number of included barriers or facilitators. Simplifying the scenarios can be challenging, given that the scenarios need to remain internally valid.

The scores of the scenarios give a clear view on what experts think is likely and what they agree and disagree on regarding the implementation of WGS. This information can be used to give direction to policy and future research about WGS to reduce this lack of knowledge and thus uncertainty. This is important since WGS is deemed likely to be implemented as clinical diagnostic in oncology within the upcoming years.

Future research should be focussed on investigating what clinical benefits WGS potentially has to offer and when it will have been demonstrated sufficiently. Even though the respondents in our study found it relatively unlikely that response will be better to actionable targets found by WGS, the clinical utility can be increased

by, among others, approving more treatment for off-label use and the discovery of novel biomarkers that can be identified with WGS. However, this is a very fast-moving field, so statements on expected time frames in the scenarios have to be interpreted in the correct context. Establishing a clear clinical benefit can also have consequences for other barriers and facilitators, such as the reimbursement status of WGS. Research on making WGS as a technique cheaper and faster to perform, will also contribute to its implementation in clinical practice. Additionally, WGS may provide value through other types of utility beyond clinical utility, such as personal utility. Establishing how personal utility can contribute towards the implementation of WGS might also be an exciting avenue for future research.

5. Conclusion

Based on current expert opinions, the implementation of WGS as a clinical diagnostic in oncology depends heavily on the price, clinical utility (both in terms of identifying actionable targets as in adding sufficient value in subsequent treatment), and turnaround time. These aspects and the optimal way of service provision are the main drivers for the implementation of WGS and should be focused on in further research. More knowledge regarding these factors is needed to inform strategic decision making regarding the implementation of WGS, which warrants support from all relevant stakeholders.

List of abbreviations

WGS:	Whole Genome Sequencing
NGS:	Next Generation Sequencing
TGP:	Targeted Gene Panel
WES:	Whole Exome Sequencing
CPCT:	Center for Personalized Cancer Treatment
WIDE:	WGS Implementation in the standard Diagnostics for Every cancer patient
TANGO:	Technology Assessment of Next Generation Sequencing in Personalized Oncology
OECI:	Organisation of European Cancer Institutes
PERT:	Program Evaluation and Review Technique
PDF:	Probability Density Function
HDI:	Highest Density Interval
FFPE:	Fixed Paraffin-Embedded

Declarations

Ethics approval and consent to participate

The need for ethics approval is waived, as the participants in the study are not subject to procedures and are not required to follow rules of behaviour [29]. All participants signed written consent forms before participating in the study.

Consent for publication

All participants gave permission for their comments to be published in anonymized form.

Availability of data and materials

The datasets generated and analysed during the current studyhttps://doi.org/10.5281/zenodo.4650466

Competing interests

Dr. van Harten and Dr. Retèl have both received non-restricted research grants from Agendia B.V. and Novartis. All other authors have no conflicts of interest to disclose.

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Authors contributions

MV, MS, HK, MJ, MIJ, VP and WH participated in designing the study. MV and MS drafted the first version of the article. MV and MS performed the data analysis. MV, MS, HK, MJ, MIJ, VP and WH participated in the data interpretation. MV, MS, HK, MJ, MIJ, VP and WH read, revised, and approved the final manuscript. Authors MV and MS are joint first authors. Authors VP and WH are joint last authors.

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References

[1] J. Gong, K. Pan, M. Fakih, S. Pal, R. Salgia, Value-based genomics, Oncotarget. 9 (2018) 15792–15815. https://doi.org/10.18632/oncotarget.24353.

[2] K. Schwarze, J. Buchanan, J.M. Fermont, H. Dreau, M.W. Tilley, J.M. Taylor, P. Antoniou, S.J.L. Knight, C. Camps, M.M. Pentony, E.M. Kvikstad, S. Harris, N. Popitsch, A.T. Pagnamenta, A. Schuh, J.C. Taylor, S. Wordsworth, The complete costs of genome sequencing: a microcosting study in cancer and rare diseases from a single center in the United Kingdom, Genet. Med. 22 (2020) 85–94.

[3] C. Massard, S. Michiels, C. Ferté, M.C. Le Deley, L. Lacroix, A. Hollebecque, L. Verlingue, E. Ileana, S. Rosellini, S. Ammari, M. Ngo-Camus, R. Bahleda, A. Gazzah, A. Varga, S. Postel-Vinay, Y. Loriot, C. Even, I. Breuskin, N. Auger, B. Job, T. De Baere, F. Deschamps, P. Vielh, J.Y. Scoazec, V. Lazar, C. Richon, V. Ribrag, E. Deutsch, E. Angevin, G. Vassal, A. Eggermont, F. André, J.C. Soria, High-throughput genomics and clinical outcome in hard-to-treat advanced cancers: Results of the MOSCATO 01 trial, Cancer Discov. 7 (2017) 586–595. https://doi.org/10.1158/2159-8290.CD-16-1396.

[4] P. Priestley, J. Baber, M.P. Lolkema, N. Steeghs, E. de Bruijn, C. Shale, K. Duyvesteyn, S. Haidari, A. van Hoeck, W. Onstenk, P. Roepman, M. Voda, H.J. Bloemendal, V.C.G. Tjan-Heijnen, C.M.L. van Herpen, M. Labots, P.O. Witteveen, E.F. Smit, S. Sleijfer, E.E. Voest, E. Cuppen, Pan-cancer whole-genome analyses of metastatic solid tumours, Nature. 575 (2019) 210–216. https://doi.org/10.1038/s41586-019-1689-y.

[5] A.B. Hamilton, S. Oishi, E.M. Yano, C.E. Gammage, N.J. Marshall, M.T. Scheuner, Factors influencing organizational adoption and implementation of clinical genetic services, Genet. Med. 16 (2014) 238–245. https://doi.org/10.1038/gim.2013.101.

[6] Z. Stark, L. Dolman, T.A. Manolio, B. Ozenberger, S.L. Hill, M.J. Caulfied, Y. Levy, D. Glazer, J. Wilson, M. Lawler, T. Boughtwood, J. Braithwaite, P. Goodhand, E. Birney, K.N. North, Integrating Genomics into Healthcare: A Global Responsibility, Am. J. Hum. Genet. 104 (2019) 13–20. https://doi.org/10.1016/j.ajhg.2018.11.014.

[7] T.A. Manolio, M. Abramowicz, F. Al-Mulla, W. Anderson, R. Balling, A.C. Berger, S. Bleyl, A. Chakravarti, W. Chantratita, R.L. Chisholm, V.H.W. Dissanayake, M. Dunn, V.J. Dzau, B.G. Han, T. Hubbard, A. Kolbe, B. Korf, M. Kubo, P. Lasko, E. Leego, S. Mahasirimongkol, P.P. Majumdar, G. Matthijs, H.L. McLeod, A. Metspalu, P. Meulien, S. Miyano, Y. Naparstek, P.P. O'Rourke, G.P. Patrinos, H.L. Rehm, M. V. Relling, G. Rennert, L.L. Rodriguez, D.M. Roden, A.R. Shuldiner, S. Sinha, P. Tan, M. Ulfendahl, R. Ward, M.S. Williams, J.E.L. Wong, E.D. Green, G.S. Ginsburg, Global implementation of genomic medicine: We are not alone, Sci. Transl. Med. 7 (2015) 1–9. https://doi.org/10.1126/scitranslmed.aab0194.

[8] S.D. Mooney, Progress towards the integration of pharmacogenomics in practice, Hum. Genet. 134 (2015) 459–465. https://doi.org/10.1007/s00439-014-1484-7.

[9] K. Kampourakis, E. Vayena, C. Mitropoulou, R.H. Schaik, D.N. Cooper, J. Borg, G.P. Patrinos, Key challenges for next-generation pharmacogenomics, EMBO Rep. 15 (2014) 472–476. https://doi.org/10.1002/embr.201438641.

[10] P. Robbe, N. Popitsch, S.J.L. Knight, P. Antoniou, J. Becq, M. He, A. Kanapin, A. Samsonova, D. V. Vavoulis, M.T. Ross, Z. Kingsbury, M. Cabes, S.D.C. Ramos, S. Page, H. Dreau, K. Ridout, L.J. Jones, A. Tuff-Lacey, S. Henderson, J. Mason, F.M. Buffa, C. Verrill, D. Maldonado-Perez, I. Roxanis, E. Collantes, L. Browning, S. Dhar, S. Damato, S. Davies, M. Caulfield, D.R. Bentley, J.C. Taylor, C. Turnbull, A. Schuh, Clinical whole-genome sequencing from routine formalin-fixed, paraffin-embedded specimens: pilot study for the 100,000 Genomes Project, Genet. Med. 20 (2018) 1196–1205. https://doi.org/10.1038/gim.2017.241.

[11] C. Turnbull, Introducing whole-genome sequencing into routine cancer care: The Genomics England 100 000 Genomes Project, Ann. Oncol. 29 (2018) 784–787. https://doi.org/10.1093/annonc/mdy054.

[12] M. Caulfield, Translating genomics for clinical benefit, Postgrad. Med. J. 95 (2019) 686.3-686. https://doi.org/10.1136/postgradmedj-2019-fpm.6.

[13] Technology assessment of next generation sequencing in personalized oncology (TANGO) consortium, TANGO Project, (2020). https://zenodo.org/communities/tango-wgs/?%0Apage=1&size=20%0A (accessed August 19, 2020).

[14] P. Bishop, A. Hines, T. Collins, The current state of scenario development: An overview of techniques, Foresight. 9 (2007) 5–25. https://doi.org/10.1108/14636680710727516.

[15] G.D. Peterson, G.S. Cumming, S.R. Carpenter, Scenario planning: A tool for conservation in an uncertain world, Conserv. Biol. 17 (2003) 358–366. https://doi.org/10.1046/j.1523-1739.2003.01491.x.

[16] P. Cornelius, A. Van de Putte, M. Romani, Three decades of scenario planning in Shell, Calif. Manage. Rev. 48 (2005). https://doi.org/10.2307/41166329.

[17] R.J. Swart, P. Raskin, J. Robinson, The problem of the future: Sustainability science and scenario analysis, Glob. Environ. Chang. 14 (2004) 137–146. https://doi.org/10.1016/j.gloenvcha.2003.10.002.

[18] V.P. Retèl, M.A. Joore, S.C. Linn, E.J. Rutgers, W.H. Van Harten, Scenario drafting to anticipate future developments in technology assessment, BMC Res. Notes. 5 (2012) 442. https://doi.org/10.1186/1756-0500-5-442.

[19] S.E.P. Joosten, V.P. Retèl, V.M.H. Coupé, M.M. van den Heuvel, W.H. van Harten, Scenario drafting for early technology assessment of next generation sequencing in clinical oncology, BMC Cancer. 16 (2016) 66. https://doi.org/10.1186/s12885-016-2100-0.

[20] R.G. Salloum, E.A. Shenkman, J.J. Louviere, D.A. Chambers, Application of discrete choice experiments to enhance stakeholder engagement as a strategy for advancing implementation: A systematic review, Implement. Sci. 12 (2017) 1–12. https://doi.org/10.1186/s13012-017-0675-8.

[21] R. Bradfield, G. Wright, G. Burt, G. Cairns, K. Van Der Heijden, The origins and evolution of scenario techniques in long range business planning, Futures. 37 (2005) 795–812. https://doi.org/10.1016/j.futures.2005.01.003.

[22] Qualtrics, (2002). https://www.qualtrics.com (accessed June 9, 2020).

[23] J.E. Oakley, A. O'Hagan, SHELF: the Sheffield Elicitation Framework, (2019). http://tonyohagan.co.uk/shelf.

[24] D. Johnson, The triangular distribution as a proxy for the beta distribution in risk analysis, J. R. Stat. Soc. Ser. D Stat. 46 (1997) 387–398. https://doi.org/10.1111/1467-9884.00091.

[25] R Core Team, R: A language and environment for statistical computing, (2020).

[26] T. Greenhalgh, J. Wherton, C. Papoutsi, J. Lynch, G. Hughes, C. A'Court, S. Hinder, N. Fahy, R. Procter, S. Shaw, Beyond adoption: A new framework for theorizing and evaluating nonadoption, abandonment, and challenges to the scale-up, spread, and sustainability of health and care technologies, J. Med. Internet Res. 19 (2017). https://doi.org/10.2196/jmir.8775.

[27] J.A. Steffen, C. Lenz, Technological evolution of diagnostic testing in oncology, Per. Med. 10 (2013) 275–283. https://doi.org/10.2217/pme.13.19.

[28] W. Weimer-Jehle, Cross-impact balances: A system-theoretical approach to cross-impact analysis, Technol. Forecast. Soc. Change. 73 (2006) 334–361. https://doi.org/10.1016/j.techfore.2005.06.005.

[29] Central Committee on Research Involving Human Subjects, Your research: Is it subject to the WMO or not?, Leg. Framew. Med. Sci. Res. (2020). https://english.ccmo.nl/investigators/legal-framework-for-medical-scientific-research/your-research-is-it-subject-to-the-wmo-or-not (accessed December 21, 2020).

[30] M. van de Ven, M.J.H.G. Simons, H. Koffijberg, M.A. Joore, M.J. IJzerman, V.P. Retèl, W.H. Van Harten, Expert elicitation data on future perspectives regarding whole genome sequencing in clinical oncology', (2021). https://doi.org/10.5281/zenodo.4650466.

[31] Zenodo, Technology Assessment of Next Generation Sequencing in Personalized Oncology - TANGO Project, (2021). https://zenodo.org/communities/tango-wgs (accessed March 31, 2021).

Appendix I. Literature search terms

Literature was searched using the search strategy that is listed in table A1. The following search terms were used: 'advanced cancer', 'metastatic cancer', 'Non-small cell lung cancer', 'disruptive technology', 'innovation', 'scenario drafting', 'future scenario', 'implementation', 'whole genome sequencing', 'next generation sequencing', 'molecular diagnostic', 'clinical diagnostic', 'personalised medicine'. These search terms were incorporated in the search strategy, using MeSH-terms, synonyms, and truncations in combination with Boolean operators ('AND' and 'OR').

Table A1 search strategy

Search	Query	Hits
	Patient	
#1	(Neoplasm Metastasis[MESH]) OR (advanced cancer[tiab]) OR (metastatic cancer[tiab])	217,931
#2	(Carcinoma, Non-Small-Cell Lung[MESH]) OR (non-small cell lung cancer[tiab])	71,427
#3	**#1 OR #2**	**283,465**
	Intervention	
#4	(Disruptive Technology[MESH]) OR (Disruptive Technology[tiab])	235
#5	(Diffusion of Innovation[MESH]) OR (innovation[tiab])	49,947
#6	(Forecasting[MESH]) OR (scenario drafting[tiab]) OR (scenario creation[tiab]) OR (future scenario*[tiab])	85,753
#7	(Implementation[tiab])	243,124
#8	**#4 OR #5 OR #6 OR #7**	**370,393**
	Control	
#9	(whole genome sequencing[MESH]) OR (whole genome sequencing[tiab]) OR (next generation sequencing[tiab])	50,998
#10	(Pathology, Molecular[MESH]) OR (molecular diagnostic[tiab]) OR (Diagnostic Test Approval[MESH]) OR (clinical diagnostic[tiab]) OR (Genetic Testing[MESH]) OR (genetic test*[tiab]) OR (molecular test*[tiab])	80,018
#11	(Precision Medicine[MESH]) OR (personalised medicine[tiab])	18,428
#12	**#9 OR #10 OR #11**	**143,684**
	Patient & Intervention & Control	
#13	**#3 AND #8 AND #12**	**111**

Appendix II. Flowchart of the literature search including the extracted factors that were used for scenario drafting

The literature search includes articles up to June 2019. The flowchart of the literature search is displayed in figure A1. From the 66 resulting articles, 192 factors were extracted by reading the full text. Many of these factors were synonyms from one another or different descriptions of the same thing. Therefore, we were able to summarize these factors under 62 common headers and clustered them into the domains: clinical utility and evidence generation (n=24), technical (n=15), reimbursement (n=7), social (n=12), and market access (n=4). The original 192 factors are listed in table A2.

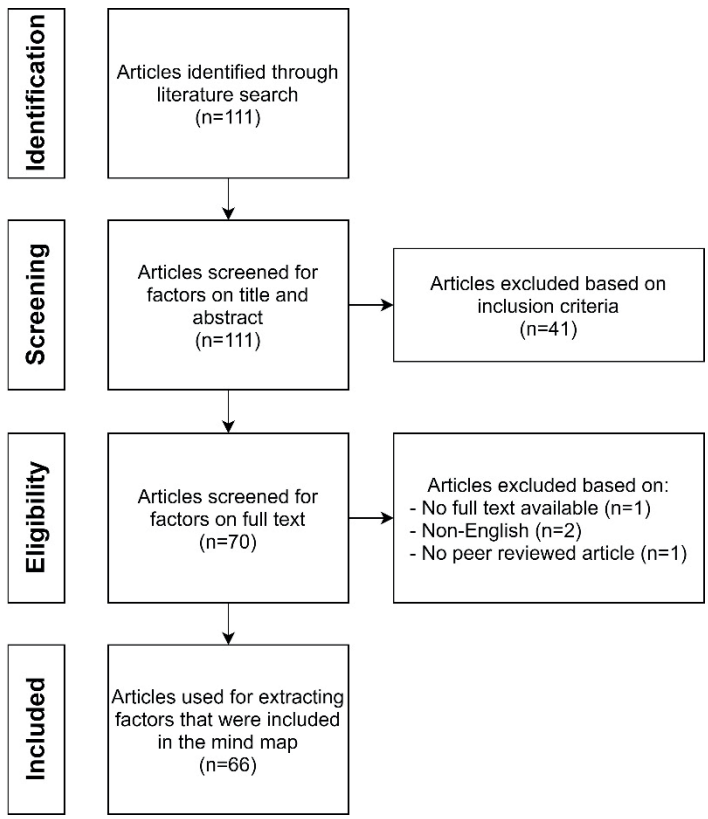


Figure A1. Flowchart of the literature search

Table A2. Factors extracted from literature clustered into the domains

Domain (*)	Factors extracted from literature
Clinical utility and evidence generation (n=76)	Actionable genetic variants; Biomarkers; Genomic alterations in lung, Adenocarcinoma; Identification of driver mutations; Immunotherapies; Molecular pathway; Tailoring treatment; Targeted therapies; Targeted therapy in cancer; Chromosomal aberration; Tumour mutational burden, micro satellite instability, mismatch repair; Patient heterogeneity; Challenges of treatment of NSCLC; Challenges of effective diagnosis and predictive analysis; Clinical benefits; Efficacy; Patient selection; Pharmacogenetics; Pharmacogenomic potential in advanced cancer patients; Selecting patients who benefit most; Tumour heterogeneity; Unclear survival benefits; Detection rate; Translational research; Implementation of molecular diagnostics; Reliability of subtyping in NSCLC; Validation; Validity; Quality assurance; Quality indicators; Cancer dynamics; Differences in biomarker tests; Differences in quality of care; Differences in tests; Analytical and clinical validity; Adjustment of treatment decision support; Optimal treatment approach; Optimal treatment strategies; optimized testing strategies; Treatment resistance; The possibility of clinical sequencing in the management of cancer; Need for developing biomarkers to optimise drug development and clinical use; DNA and transcriptome data integration; Big data; Biobanking; Bioinformatic analysis; Biomarker discovery biomarker driven clinical trials; Clinical trial implementation and feasibility; Trial recruitment; Clinical trial design; Clinical trial enrolment based on genomic testing; Complex data; Complex molecular landscape; Comprehensive genomic profiling; Data interpretation; Development of new therapies through biomarker-driven clinical trials; Development of novel drugs and the implementation of precision medicine; Larger clinical trials; Larger trials; New actionable targets; New biomarkers; New drugs; New molecular targets and biomarkers; New targeted therapies; Novel targets and therapeutics; Novel therapies; Novel trial design; Patient access to trials; Patient participation in clinical trials; Sequencing data; Standardized patient databases; Trial designs; Delays; Unsolicited findings.
Technical (n=59)	Sensitivity; Sensitivity / specificity; Success rate; Biopsy often infeasible; Appropriate tissue samples; Failure rate; False positives; Improved test performance; Test discordance; Re-biopsy; Sample quality; Test prioritization; Centralization; Delays; Efficiency; Efficient regulatory procedures; Inhouse testing or outsourcing; Logistical and operational issues; Logistics; Organisation of care; Turnaround time; Clinical interpretation; Necessity of specialized personnel, instrumentation, software, quality management; Need for optimized clinical workflows; Required expertise; Cancer screening; Early diagnosis; Monitoring; Monitoring cancer progression; Place in care pathway; Population wide implementation of testing; Position in care pathway; Position molecular testing in care pathway; Standardization of testing; Surveillance; Artificial intelligence; Breakthroughs in technology; Limited tissue material; Limited tumour samples; Liquid biopsy; Machine learning; Choosing between gene-panel and comprehensive approaches; Circulating tumour cells; Cytology samples; DNA input requirement; DNA yield; Quality assurance; Fresh frozen biopsies; Invasiveness biopsy; IT support; Optimization of tissue acquisition; Sample collection; Single gene tests; Targeted gene panels; Tissue optimization; Tissue preservation protocols; Tissue requirements; Using circulating cell-free DNA to monitor personalized cancer therapy; Technological / scientific advancements.

Reimbursement (n=22)	Clinical utility; Affordability of testing and treatments; Affordable testing; Cost; Cost-effectiveness; Economic impacts; Decreased costs; Future directions NGS; NGS; No biopsy costs / adverse events; Reproducibility and costs of microarray platforms; Test affordability; Treatment selection; WES; Disconnect between the funding of drugs and the related biomarker test; Financing; Funding; Funding from industry; Funding of tests and treatments; National strategy; Inconsistent reimbursement for molecular diagnostics; Reimbursement.
Social (n=20)	ELSI; Data sharing; Data storage; Workload of involved specialist; Education; Lack of knowledge; Specialist knowledge; Privacy concerns; Patient expectations; Attitude of pathologists to and level of involvement; Unsolicited findings; Clinical trial ethics; Population health impacts; Informed consent and patient education; Invasiveness biopsy; Patient and physician goals; Patient-reported outcomes; Quality of life; Resistance testing; Adoption.
Market access (n=15)	Approved treatments; Affordable testing and therapies; Access to drugs; Access to innovative drugs; Challenge of implementing targeted therapies; Lack of novel therapies; Access to testing; Novel NGS technique; The difficulties in developing novel molecularly targeted agents; Suboptimal drug development; Off-label drug use; Off-label treatment; Reduction in off-label targeted therapy costs; Market factors; Regulatory environment.

*, Number of factors that were originally extracted from literature before they were summarized under common headers.
NSCLC, Non-small cell lung cancer; DNA, deoxyribonucleic acid; IT, information technology; NGS, next-generation sequencing; WES, whole exome sequencing; ELSI, ethical, legal and social implications.

Appendix III. Scenarios

ExplanationYou will be first shown a status quo; the current situation from which the scenarios deviate. Following the status quo, you will be presented with nine scenarios. **The time horizon of each scenario is five years.**

How are the scenarios structured?

Each scenario starts with a possible future development, followed by potential consequences of that future development.

Which questions will you ask about scenarios?

We will ask you a series of questions about each scenario. The first question is always about the likelihood that that specific future development may occur. The following questions are related to the likelihood that the consequences of the future development may occur. Finally, we ask you to assess the likelihood that the overall scenario may occur.

Which inputs do I need to provide?

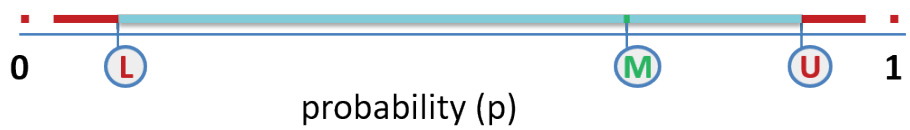
We ask you to provide us with your personal judgements of three values:

1. The most likely probability (M) or modus that something may occur;

2. The lowest plausible bound (L); it should be extremely unlikely that the real probability is below this number;

3. The highest plausible bound (U); it should be extremely unlikely that the real probability is above this number.

Each of these values should be between 0 and 100.



Status quo

The status quo represents the current situation and provides you with more context. Keep in mind that the scenarios are deviations from the status quo. The status quo is primarily based on available literature. In cases where no literature is available, estimates are used.

Organization

- WGS is **organized centrally**: one central facility conducts WGS for all hospitals
- **50% of the hospitals** that treat patients with advanced NSCLC offer WGS to their patients

Clinical

- Only NSCLC patients in stage IIIB and IV are eligibile for WGS
- Types of **standard diagnostic** tests: FISH, IHC, real-time PCR, Sanger sequencing, and NGS *[1]*
- Probability that an actionable target is found with **standard diagnostics** for on-label:
  1. Targeted therapy: 8% *[2]*
  2. Immunotherapy: 20% *[3]*

- Probability that an actionable target is found with **WGS** for:
  1. Targeted therapy: 8%
  2. Immunotherapy: 0%

- Probability that patients diagnosed with **standard diagnostics** have a treatment response to:
  1. Chemotherapy: 30%*[4]*
  2. Targeted therapy: 5% *[2]*
  3. Immunotherapy: 7% *[3]*

- Off-label drug prescription of targeted therapy is not allowed outside of clinical trials.

Costs

- Average costs of **standard diagnostics** per patients: €400,-
- Average costs of **WGS** per patient: €4500,-

Technical

- Turnaround time **standard diagnostics**: 1 week
- Turnaround time **WGS**: 4 weeks- WGS results for all patients need to be interpreted by a **molecular tumor board**
- Probability that a tissue biopsy contains sufficient tumour cells to initiate diagnostic tests (especially for NGS, WGS): 60%
- Probability that **standard diagnostic** tests are successfully, resulting in useable information on which treatment selection can be made: 80%
- Probability that **WGS** is successfully, resulting in useable information on which treatment selection can be made: 80%

Social

- 80% of the physicians offer WGS to their patients
- 80% of the patients prefer WGS to other testing techniques

Scenario 1: Technological innovation in WGS has led to the development of a new WGS testing kit that is 50% cheaper in initial investment costs. Because of improvements in decision support in the new WGS device, interpretation by a molecular tumor board is only required for 5% of patients. This has decreased the average turnaround time of WGS to seven days. It enables all hospitals that treat advanced NSCLC to conduct WGS themselves and offer WGS to their patients.

What is the probability that a WGS testing kit that is 50% cheaper in initial investment costs will be developed within five years?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that, because of improvement in decision support, interpretation by a molecular tumor board is only required for 5% of the patients?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that, because interpretation by an MTB is only required for 5% of the patients, the average turnaround time of WGS will be reduced to seven days?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that this given overall scenario will take place in the next five years?

Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

Scenario 2: A new actionable biomarker has been identified that predicts response to immunotherapy. It is prevalent in 20% of patients with advanced lung cancer. Only WGS can detect this biomarker. The clinical utility of WGS has increased. Approximately 90%% of physicians are convinced of the value of WGS and thus offer WGS to all their patients with advanced NSCLC. Approximately 90% of patients with advanced NSCLC are also convinced of the value of WGS and thus prefer WGS to other molecular diagnostics.

What is the probability that WGS is the only testing technique that can identify a new biomarker for the next five years?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that a new biomarker identifies approximately 20% of the patients with advanced NSCLC as responsive to immunotherapy?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that, because of the increased clinical utility of WGS, a large majority of physicians will offer WGS to all their patients?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that, because of the increased clinical utility of WGS, a large majority of patients with advanced NSCLC prefer WGS to other molecular diagnostics?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that this given overall scenario will take place in the next five years?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

Scenario 3: WGS is organized completely centralized; one central facility that conducts all WGS for all hospitals. Due to economies of scale, this has led to large reductions in costs and turnaround time. The cost of WGS decreased to 1000 euro

per patient. The average turnaround time decreased to five days. Because of the lower costs and a shorter turnaround time of WGS, all hospitals that treat patients with advanced lung cancer have adopted WGS.

What is the probability that centralizing the organisation of WGS leads to large reductions in the costs and turnaround time of WGS?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that the cost of WGS will decrease to 1000 euro per patient with cancer in this given scenario?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that the average turnaround time of WGS will decrease to five days in this given scenario?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that, because of lower cost and shorter turnaround time of WGS, all hospitals that treat patients with advanced NSCLC will adopt WGS?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that this given overall scenario will take place in the next five years?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

Scenario 4: WGS will become available as a diagnostic tool for NSCLC in clinical practice. The probability that WGS detects an actionable target for which targeted therapies are available is 12%. The average turnaround time is slightly reduced to 14 days. The costs of WGS are decreased to 3000 euro per patient.

What is the probability that WGS becomes available as a standard diagnostic tool for advanced NSCLC in clinical practice?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that WGS will detect an actionable target for which targeted therapies are available in 12% of the cases?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that the turnaround time of WGS is on average 14 days?
Most likely probability (in%) :lower plausible limit (in%): upper plausible limit (in%):

What is the probability that the costs of WGS are reduced to 3000 euro per patient?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that WGS will be used as diagnostic tool instead of standard diagnostics, given this scenario?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that this given overall scenario will take place in the next five years?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

Scenario 5: A new liquid NGS panel 'X' will enter the market which provides only information about actionable targets that are needed for treatment selection. The probability that NGS panel 'X' detects an actionable target for which treatment is available is equal to that of standard diagnostics. For this new NGS panel 'X', less invasive and easy to obtain liquid biopsies can be used. The average turnaround time for this NGS panel 'X' is two days. The costs of NGS panel 'X' are 300 euro per patient.

What is the probability that a new liquid NGS panel 'X' will enter the market?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that NGS panel 'X' will detect an actionable target in 8% of the cases?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that less invasive and easy to obtain liquid biopsies can be used by NGS panel 'X'?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that the turnaround time of NGS panel 'X' is on average two days?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that the costs of NGS panel 'X' are 300 euro per patient?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that the new liquid NGS panel will be used instead of WGS in this given scenario?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that this given overall scenario will take place in the next five years?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

Scenario 6: New technical innovations have resulted in better performance in cancer diagnostics. Tissue samples are still needed for WGS but due to new technologies there is a 80% probability that they contain enough tumour cells to initiate WGS. Another technical improvement is that there is a 95% probability that the sequencing process of WGS succeeds, resulting in useable information on which treatment selection can be made. Because of these low failure rates, more than 80% of the patients eligible for WGS can be sequenced and thus potentially receive better treatment. However, these new technologies come at a price and therefore, costs for sequencing one patients remain 4500 euro.

What is the probability that new technical innovations improve the success rate of taking tissue biopsies and the sequencing process of WGS?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that tissue biopsies have a 80% probability to be successfully taken in this given scenario?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that WGS has a 95% probability to be successfully sequenced in this given scenario?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that more than 80% of the patients can be sequenced and thus potentially receive better treatment in this given scenario?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that these new technologies are expensive and keep the costs of WGS per patient fixed at 4500 euros in this given scenario?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that this given overall scenario will take place in the next five years?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

Scenario 7: Research on WGS data results in the discovery of new molecular targets. As a result, new targeted therapies will be approved for these new targets. These new targets can only be detected with WGS, and therefore, the clinical utility has risen. The probability that an actionable target is found by WGS on which targeted therapies are indicated is increased to 20%. Because of this increase in actionable targets, 90% of the physicians prefer using WGS as molecular diagnostics. Because of this increase in actionable targets, 90% of patients prefer to receive WGS as molecular diagnostics.

What is the probability that research on WGS data results in the discovery of new molecular targets and as a result, new targeted therapies will be approved for these new targets?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that these new actionable targets can only be detected by WGS and therefore the clinical utility rises?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that WGS will detect an actionable target in 20% of the cases for which targeted therapies are available, given this scenario?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that physicians' preference for WGS as molecular diagnostics increases to 90%, given this scenario?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that patients' preference for WGS as molecular diagnostics increases to 90%, given this scenario?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that this given overall scenario will take place in the next five years?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

Scenario 8: Research on WGS data provides evidence about the effectiveness of targeted therapies indicated for other tumour types for mutations that are found in patients with advanced NSCLC. For this reason, off-label drug prescription in this patient population is allowed only for actionable targets detected with WGS. As a result, the clinical utility of WGS has risen. The probability that WGS detects an actionable target for off-label targeted therapies is 5%. Due to the possibility of receiving off-label targeted therapy when no on-label drugs are available, 95% of physicians prefer to use WGS as molecular diagnostics. Due to the possibility of receiving off-label targeted therapy when no on-label drugs are available, all patients prefer to receive WGS as molecular diagnostics.

What is the probability that research on WGS data provides evidence for effective off-label drug use and as a result off-label drug use will be allowed?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that off-label drug prescription is allowed only on actionable targets that are found with WGS?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that WGS detects an actionable target for off-label targeted therapies in 5% of the cases, given this scenario?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that physicians' preference for WGS as molecular diagnostics increases to 95%, given this scenario?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that all patients prefer to receive WGS as molecular diagnostics, given this scenario?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that this given overall scenario will take place in the next five years?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

Scenario 9: Patients with a particular actionable target for targeted therapy identified with WGS have a higher probability to respond to treatment than patients with the same target identified with standard diagnostics. The probability for having a treatment response to targeted therapy is increased to 10% for a patient with an actionable target detected with WGS. Since WGS detects biomarkers that are better predictors for treatment response, its clinical utility has risen. For this reason, all physicians prefer to use WGS as molecular diagnostics. For this reason, all patients prefer to receive WGS as molecular diagnostics.

What is the probability that patients with a particular actionable target identified with WGS have a better treatment response than patients with the same target identified with standard diagnostics?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that the probability for having a treatment response to targeted therapy is increased to 10% for a patient with an actionable target detected with WGS?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that the clinical utility of WGS has risen since it detects biomarkers that are better predictors for treatment response?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that all physicians prefer to use WGS as molecular diagnostics, given this scenario?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that all patients prefer to receive WGS as molecular diagnostics, given this scenario?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

What is the probability that this given overall scenario will take place in the next five years?
Most likely probability (in%): lower plausible limit (in%): upper plausible limit (in%):

References

[1] *Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology. 2018;29(Supplement_4):iv192-iv237*

[2] *Marquart J, Chen EY, Prasad V. Estimation of the Percentage of US Patients With Cancer Who Benefit From Genome-Driven Oncology. JAMA oncology. 2018;4(8):1093-8.*

[3] *Haslam A, Prasad V. Estimation of the Percentage of US Patients With Cancer Who Are Eligible for and Respond to Checkpoint Inhibitor Immunotherapy Drugs. JAMA network open. 2019;2(5):e192535.*

[4] *Ardizzoni A, Boni L, Tiseo M, Fossella FV, Schiller JH, Paesmans M, et al. Cisplatin- versus carboplatin-based chemotherapy in first-line treatment of advanced non-small-cell lung cancer: an individual patient data meta-analysis. Journal of the National Cancer Institute. 2007;99(11):847-57.*

Appendix IV. Characteristics of the experts that responded to the scenario survey

Table A3. Characteristics of the experts that responded to the scenario survey

Expert #	Field(s) of expertise	Nationality
1	Genetics	the Netherlands
2	Genetics / informatics	the Netherlands
3	Genetics / informatics / oncology	the Netherlands
4	Genetics / oncology / pathology	the Netherlands
5	Genetics / Pathology	the Netherlands
6	Health economics / health technology assessment	the Netherlands
7	Lung cancer / Pulmonary disease	the Netherlands
8	Oncology	the Netherlands
9	Oncology	the Netherlands
10	Oncology	the Netherlands
11	Pathology	the Netherlands
12	-	the Netherlands
13	-	the Netherlands
14	-	the Netherlands
15	-	the Netherlands
16	-	the Netherlands
17	Genetics / Oncology	Singapore
18	-	Australia
19	-	Denmark

'-', not specified.

Appendix V. Linear pools of individual distributions

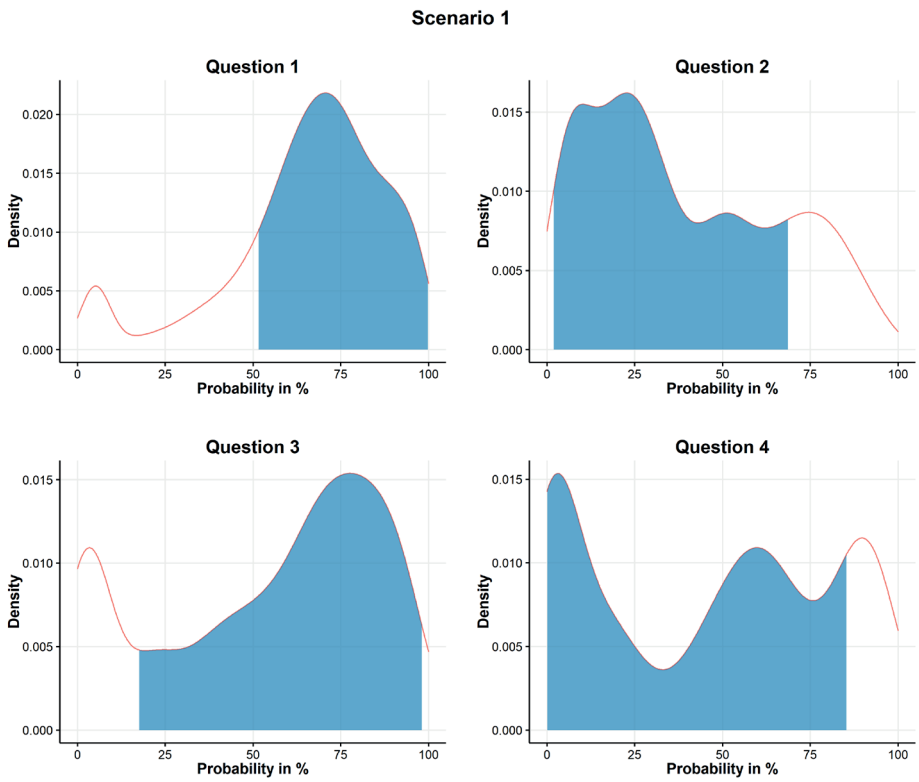


Figure A2. Linear pools of individual PERT distributions of scenario 1.

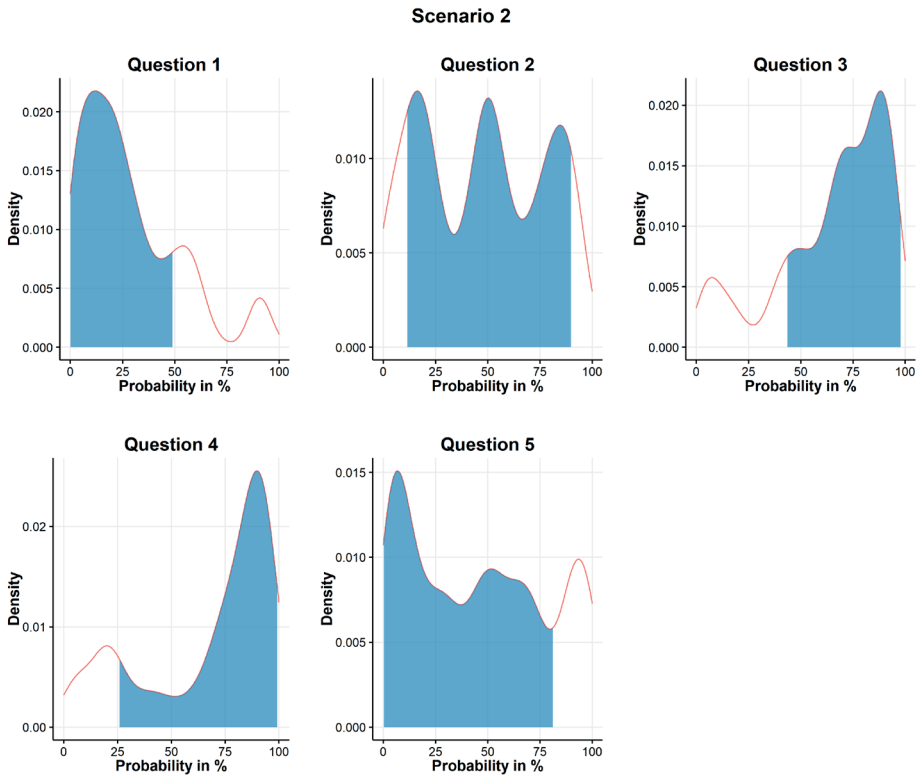


Figure A3. Linear pools of individual PERT distributions of scenario 2.

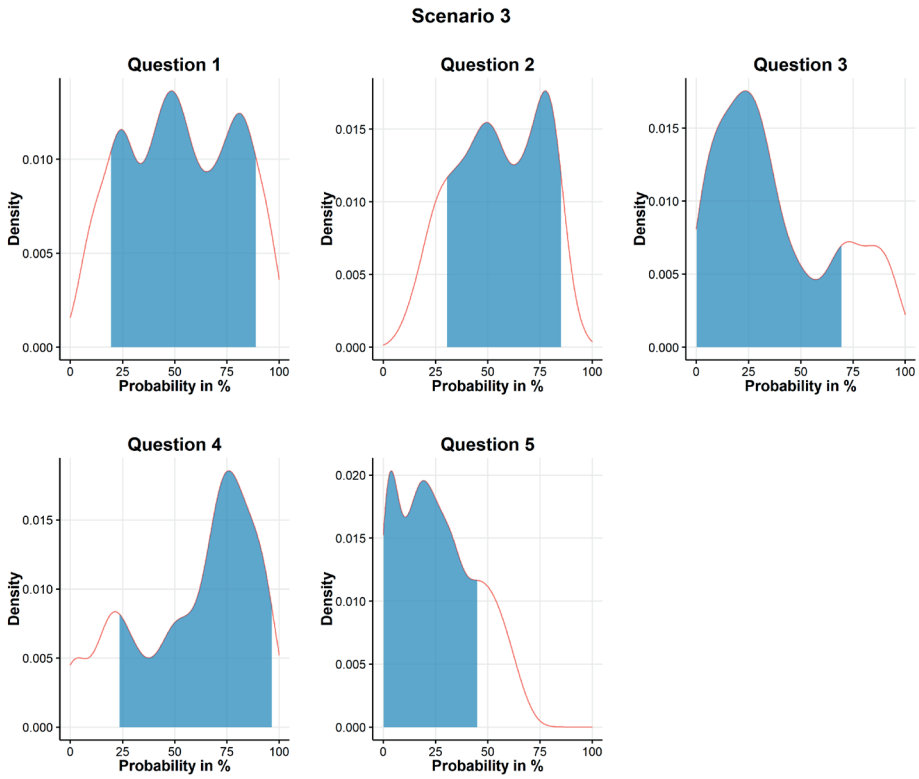


Figure A4. Linear pools of individual PERT distributions of scenario 3.

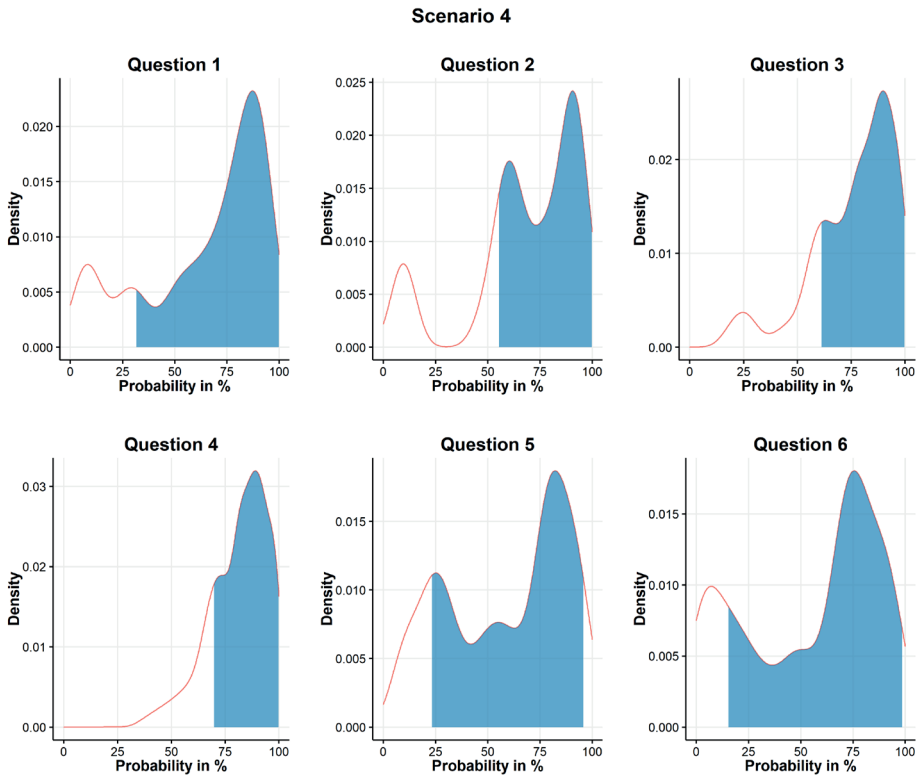


Figure A5. Linear pools of individual PERT distributions of scenario 4.

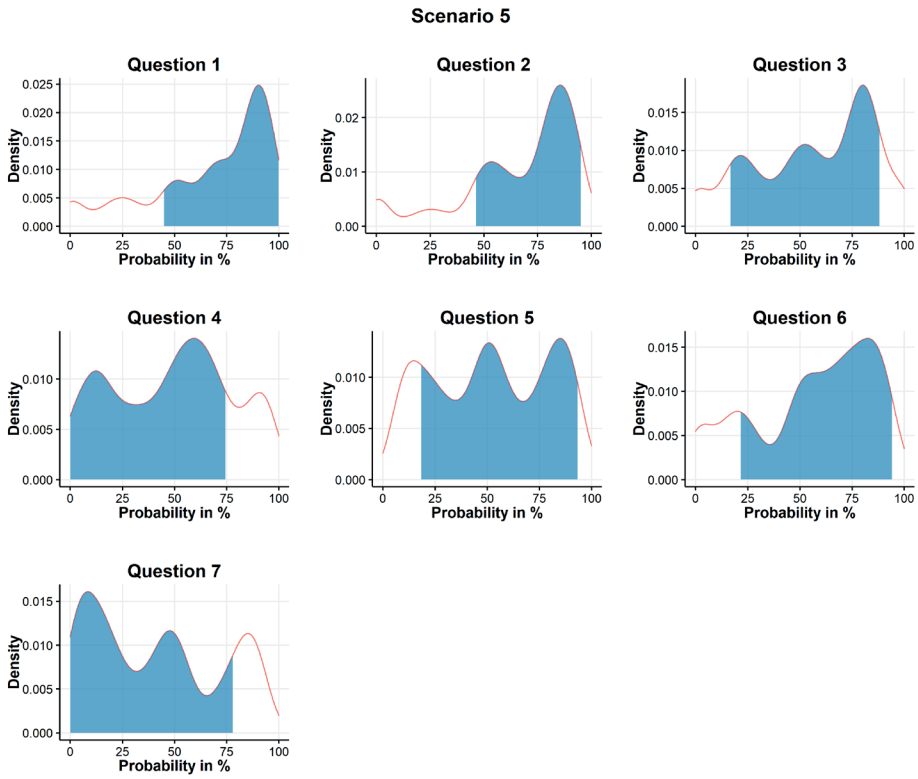


Figure A6. Linear pools of individual PERT distributions of scenario 5.

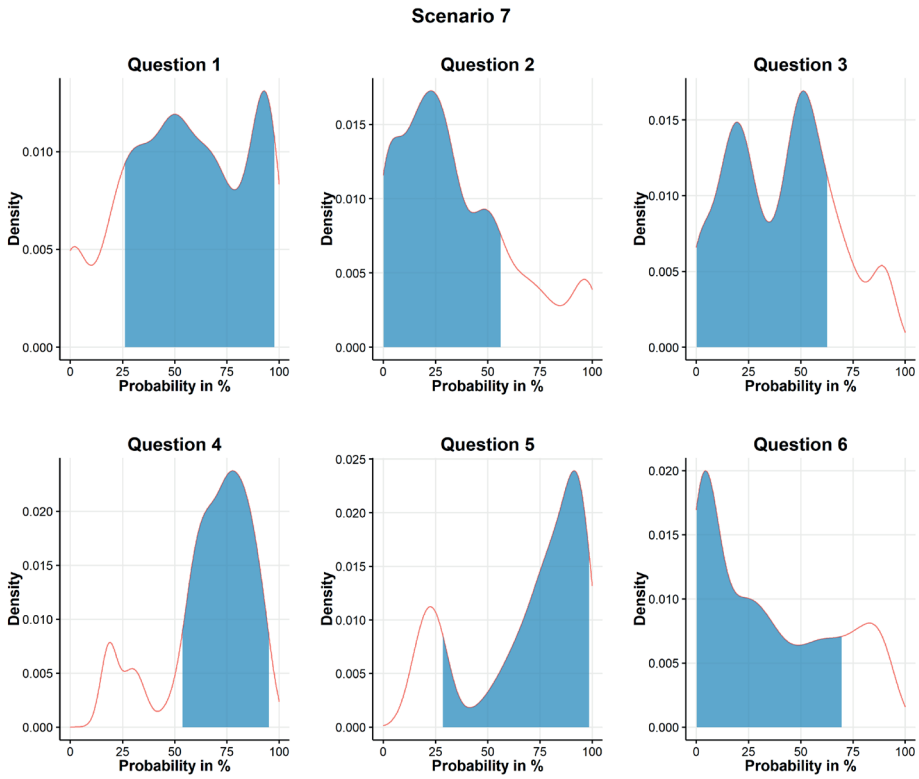


Figure A8. Linear pools of individual PERT distributions of scenario 7.

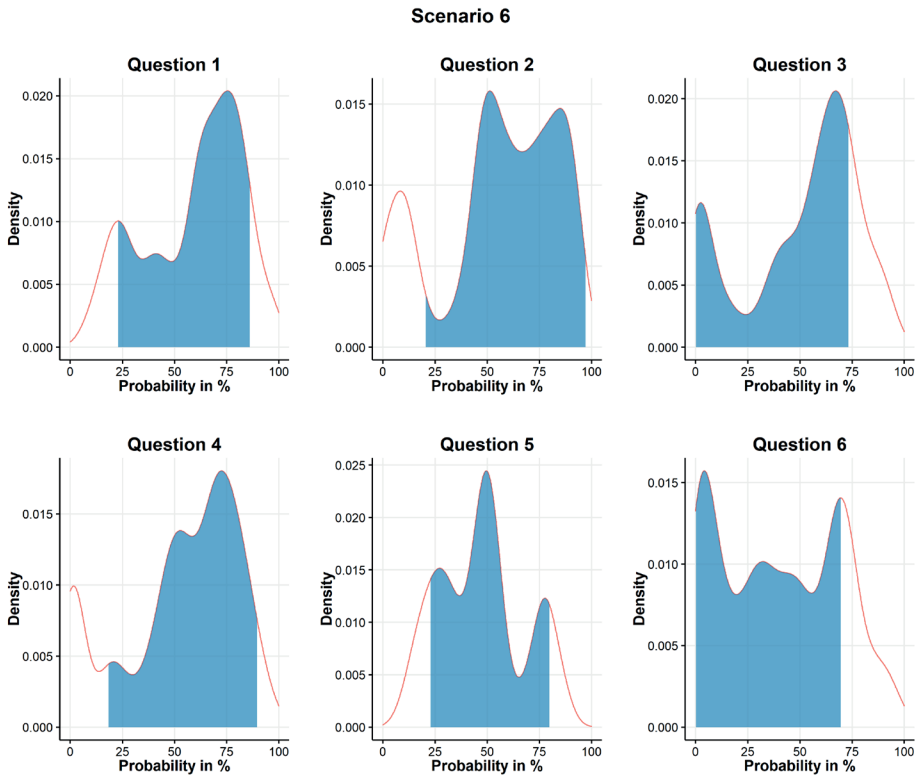


Figure A7. Linear pools of individual PERT distributions of scenario 6.

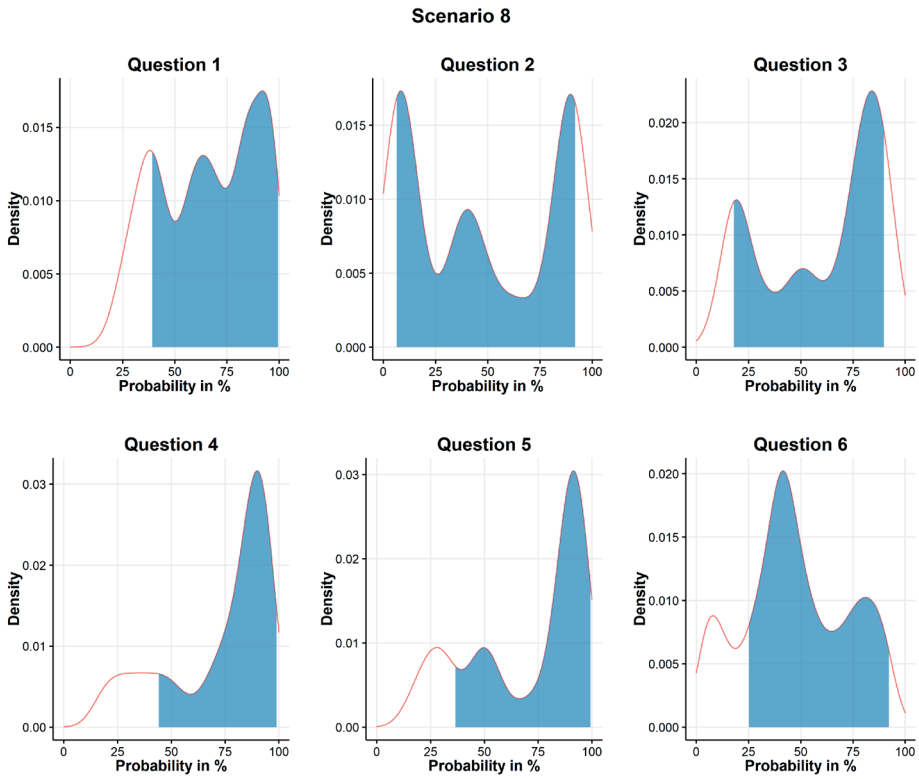


Figure A9. Linear pools of individual PERT distributions of scenario 8

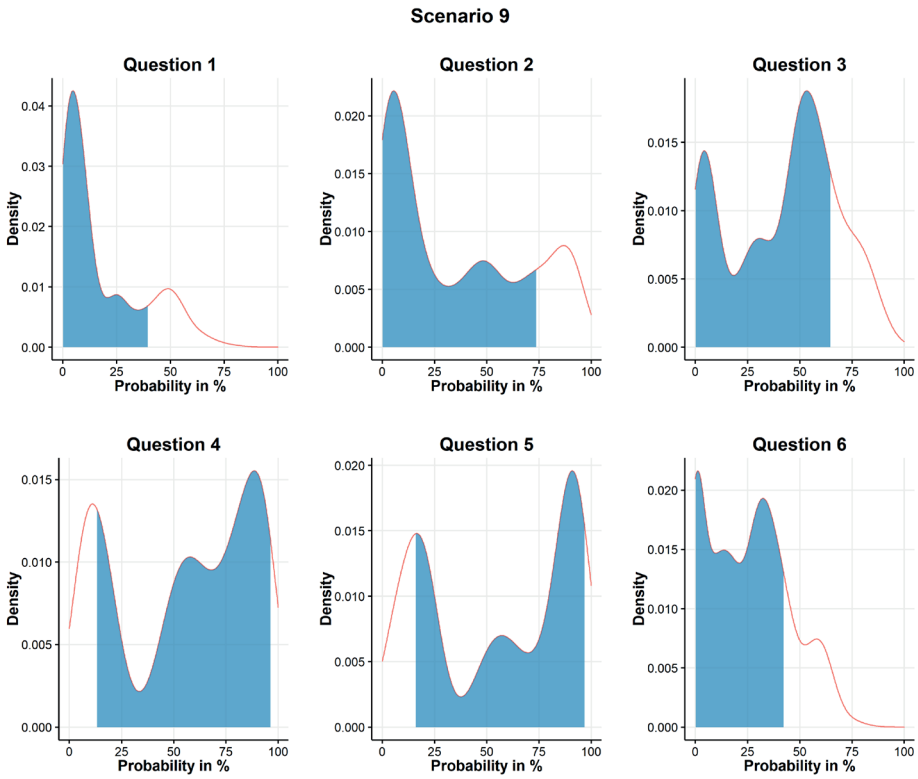


Figure A10. Linear pools of individual PERT distributions of scenario 9.

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	N.A.
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	3-5
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	5
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	N.A.
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	5-6
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	5
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Appendix I, page 1-2
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	5-6
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	6

Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	6
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	N.A.
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	6
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	9, appendix II: page 3
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	Data reported elsewhere
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	N.A.
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	9
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	9
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	12
Limitations	20	Discuss the limitations of the scoping review process.	14
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	15
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	16

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is

more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.

5

Chapter 6

Developing a dynamic simulation model to support the nationwide implementation of Whole Genome Sequencing in lung cancer

Michiel van de Ven, Maarten IJzerman, Valesca Retèl, Wim van Harten, Hendrik Koffijberg

This chapter has been accepted by BMC Medical Research Methodology as: Developing a dynamic simulation model to support the nationwide implementation of Whole Genome Sequencing in lung cancer. van de Ven, M., IJzerman, M.J., Retèl, V.P., van Harten, W., Koffijberg, H.

Abstract

Background

This paper shows how dynamic simulation modeling can be applied in the context of the nationwide implementation of Whole Genome Sequencing (WGS) for non-small cell lung cancer (NSCLC) to inform organizational decisions regarding the use of complex and disruptive health technologies and how these decisions affect their potential value.

Methods

Using the case of the nationwide implementation of WGS into clinical practice in lung cancer in the Dutch healthcare system, we developed a simulation model to show that including service delivery features across the diagnostic pathway can provide essential insight into the affordability and accessibility of care at the systems level. The model was implemented as a hybrid Agent-Based Model and Discrete-Event Simulation model in AnyLogic and included 78 hospital agents, 7 molecular tumor board agents, 1 WGS facility agent, and 5313 patient agents each year in simulation time.

Results

The model included patient and provider heterogeneity, including referral patterns, capacity constraints, and diagnostic workflows. Patient preference and adoption by healthcare professionals was also modelled. The model was used to analyze a scenario in which only academic hospitals have implemented WGS. To prevent delays in the diagnostic pathway, capacity to sequence at least 1600 biopsies yearly should be present. There is a two-fold increase in mean diagnostic pathway duration between no patients referred or all patients referred for further diagnostics.

Conclusions

The systems model can complement conventional health economic evaluations to investigate how the organization of the workflow can influence the actual use and impact of WGS. Insufficient capacity to provide WGS and referral patterns can substantially impact the duration of the diagnostic pathway and thus should be considered in the implementation of WGS.

Keywords

Implementation; Whole Genome Sequencing; Dynamic Simulation Modeling; Diagnostics; Oncology.

1. Introduction

Whole Genome Sequencing (WGS) is a genomic test that sequences the whole genome with one single test compared to targeted gene panels (TGP) that sequence a subset of genes. While WGS has the benefit of more comprehensive diagnostic information, it is currently more expensive at 2925 euro per patient, whereas the cost of current SoC tests range from 70 to 400 euro (1). Furthermore, even though it has steadily declined over time, the turnaround time of 10 working days for WGS (2), not including clinical interpretation, remains longer than the turnaround time of TGPs. The implementation of WGS into routine clinical practice in oncology is ongoing in several countries worldwide (3,4). However, the health economic evidence on the optimal use of WGS as a cancer diagnostic is sparse, as only five initiatives are performing a health technology assessment of WGS with the focus on oncology (2).

In addition to demonstrating the clinical and economic value of WGS (5), the actual utilization as part of the diagnostic and treatment episode can impact its affordability and accessibility. For instance, WGS can potentially substitute all DNA-based biomarkers and the optimal position of WGS in the biomarker test strategy therefore needs to be determined. Moreover, the impact on the selection, availability, and start of treatments needs to be addressed. This requires consideration of the required capacity to conduct WGS, curate, and interpret the WGS data. These challenges are not unique to WGS but can also apply to other complex and disruptive health technologies, such as proton therapy (6). Additionally, short-term inefficiencies may arise during implementation. These inefficiencies can be caused by overcapacity of the existing technology during the transition phase or due to gradual implementation of the innovative technology (7).

Cost-effectiveness, cost-benefit, or budget impact analyses typically ignore these additional challenges. These analyses focus on the long-term consequences of specific healthcare interventions and do not typically consider organizational constraints. They implicitly assume that demonstrating the benefits of a new technology will ensure an optimal implementation in clinical practice, perhaps led by the fact that HTA agencies do not generally require evidence on how organizational constraints can affect outcomes. However, this may be an unrealistic assumption when considering complex and disruptive health technologies.

Healthcare delivery systems can be characterized as complex adaptive systems (8). They contain feedback loops and interaction between different system elements, such as patient-provider interactions. Complex adaptive systems can adapt to changes over time and display nonlinear and delayed behavior. For example, WGS

reimbursement increases its budget impact initially through increased use. However, economies of scale could decrease the cost per patient and thus reduce its budget impact in the long term. Additionally, reducing the turnaround time of WGS can lead to an increased adoption rate of physicians and, possibly, to improved benefits for patients. By applying the "big picture" (holistic) principle of systems science (9), we can learn more about the health care delivery system as a whole, compared to evaluating its components in isolation.

Traditional health economic evaluation methods such as decision trees and Markov models, are usually not flexible enough to reflect the nonlinear and interdependent properties of the healthcare system. Hence, other methods are required when both organizational aspects as well as care process and technology aspects need to be reflected. Suitable alternative methods should be able to measure the short and long-term consequences to the system and be flexible enough to reflect complex care pathways (10), often seen in precision medicine.

Dynamic simulation modeling (DSM) has been proposed as a potential approach to reflect the complexity observed in the healthcare system (11). It consists of three modeling paradigms: System Dynamics (SD), Discrete-Event Simulation (DES), and Agent-Based Modeling (ABM) (10). SD models relationships between the system elements at an aggregate level using stocks and flows and often contain feedback loops. DES is a process-oriented individual-level modeling approach where entities flow through a process that typically contains delays, resource constraints, and queues. ABM is also an individual-level modeling approach, but its agents are active and may display behavior, unlike in DES. While ABM, DES, and SD are not new, the literature on their application in the context of systems science within health technology assessment is sparse (12). One article in the healthcare setting combines SD and ABM to assess the value of mobile stroke units (13) while considering the disease and population dynamics, and the organization of care and its economics.

This paper aims to demonstrate how DSM can be applied to the nationwide implementation of WGS for non-small cell lung cancer (NSCLC) by conceptualizing and constructing a dynamic simulation model. Technical model details are described in Additional file 1. Moreover, we will illustrate how adjustments in the organization of the diagnostic workflow can provide essential insights into the affordability and accessibility of WGS in the care for cancer patients.

2. Case study: Whole Genome Sequencing as a clinical diagnostic in lung cancer

2.1Background

For many tumor types, choosing the optimal treatment for patients with advanced or metastatic disease depends on the outcomes of biomarker testing. Biomarker testing helps selecting the optimal treatment and avoid overtreatment with ineffective treatments. The role of biomarkers for treatment selection is especially substantial in lung cancer (14). Therefore, lung cancer is one of the first tumor types for which WGS will potentially be implemented.

However, it is not clear whether the potential value of WGS outweighs the incremental costs that WGS incurs. Its clinical utility is currently limited to those genes for which a targeted treatment is available. Critics assume that current standard of care (SoC) testing that entails the use of TGP and other tests that test one or a few genes, provide enough information for a clinical diagnosis in most cases. However, proponents hypothesize that WGS adds value in cases where SoC would not have identified a biomarker. Recently, a study concluded that the actionable genome shows limited evolution while under therapeutic pressure, meaning that conducting WGS once is sufficient for most patients (15).

The clinical utility of WGS must be weighed against the incremental costs. WGS requires a significant upfront investment due to the required lab facilities and infrastructure for data storage amongst others. Additionally, WGS has a higher cost per patient. Changes in the organization of care, such as adapting diagnostic workflows to accommodate WGS and putting the required infrastructure in place, will help to realize the potential value of WGS. The need to transform health services underlines the importance of assessing the full, system-wide requirements posed by WGS to support its implementation in routine clinical practice.

2.2 Problem conceptualization

2.2.1 Current workflows for biomarker testing in the Netherlands

Figure 1 depicts a schematic representation of the healthcare system considered to implement WGS. The system elements shown in figure 1 interact with other system elements. For example, patients visit hospitals to be diagnosed and treated, while hospitals use WGS services and molecular tumor boards (MTB) to provide that care. Currently, WGS for cancer patients is primarily used in the clinical research setting as the clinical and/or economic value of WGS has not been clearly demonstrated. One central facility in the Netherlands conducts WGS for cancer patients in hospitals

participating in the Centre for Personalized Cancer Treatment study (16). However, this centralized organization may shift to a regional organization of WGS in the near future if hospitals invest in building up their own WGS capacity. Interpretation of the complex genetic information that WGS provides is preferably performed by a group of multidisciplinary experts in an MTB (17). Currently, the development of MTBs is still in an early phase. Nonetheless, Dutch academic hospitals each organize an MTB who meet regularly.

Biomarker testing for treatment selection is used by all hospitals (n = 78) that treat lung cancer patients. Patients can receive treatment with chemotherapy and targeted therapy in most hospitals (18). Conversely, immunotherapy prescription is concentrated in a subset of hospitals that meet specific quality requirements (19). Most hospitals that meet these requirements are academic or teaching hospitals or general hospitals with a high patient volume. Enrollment into clinical trials is also initiated via these hospitals. In most cases, patients are referred to one of these hospitals for treatment, or the patient's tumor material is sent to a hospital with a more elaborate testing capability.

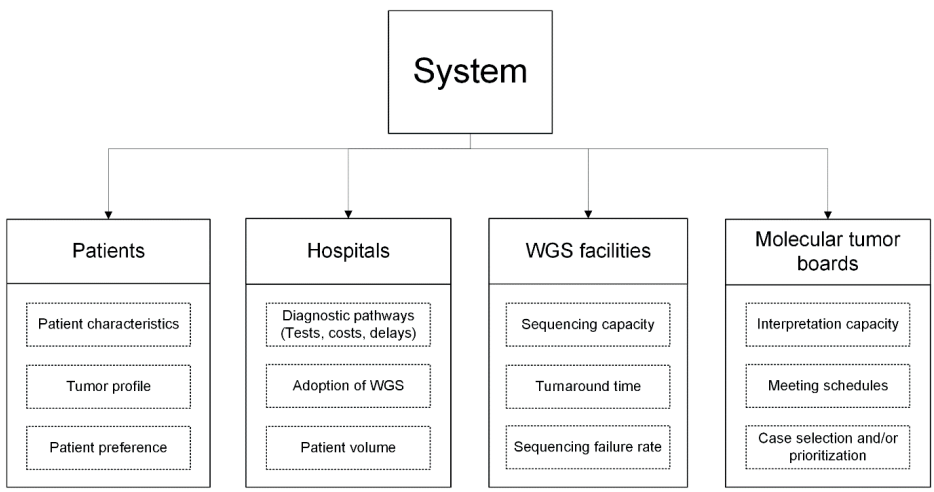


Figure 1. A schematic representation of the healthcare system in which WGS is potentially implemented, comprising the following system elements: patients, hospitals, WGS facilities, and Molecular Tumor Boards. The boxes with dotted lines below each stakeholder represent stakeholder characteristics that may influence the system's behavior and system outcomes.

2.2.2 The potential value of WGS from a systems perspective

Diagnostic workflows

A major challenge related to the diagnostic workflows is adapting the current workflows to accommodate WGS. Currently WGS is only used in the clinical research setting in oncology. Therefore, an important step is to determine the patient subgroups that will receive WGS, as the current price level of WGS (1) makes it prohibitive to provide WGS to all patients with lung cancer. This is linked to determining which tests will be substituted by WGS and how tests will be planned. Careful planning is essential, as there is a risk that the time-to-treatment will increase beyond the recommended maxima (18).

Additionally, it has been widely recognized that MTBs should interpret the genetic information that WGS provides (20). For an adequate interpretation, an MTB should at least consist of clinicians, pathologists, clinical biologists, geneticists, and bioinformaticians (17). However, there is still a large variety in the composition of MTBs in the Netherlands (21), and MTBs need to be able to cope with a potential increase in the number of patients who receive WGS. This can be achieved, for instance, by automating workflows and setting up clinical decision support systems (22).

The process of conducting WGS differs substantially from the current SoC biomarker tests. When conducting WGS, the patient's tumor material is sent to a WGS facility. Once sequencing is completed, a report containing the results is sent to the MTB. The MTB discusses the results from WGS and reports an evidence-based treatment recommendation back to the hospital. Ultimately, the treating physicians can, together with the patient, use this recommendation to make a treatment decision. Hence, using WGS involves more and different steps than SoC, which is usually conducted in-house and typically does not use the services of an MTB.

Impact of policy decisions

At present, WGS is offered from one location in the Netherlands. While the evidence is still lacking on the effects of centralization (23), focusing all sequencing in one facility can potentially lead to improved efficiency and economies of scale as the throughput increases (24,25). However, it is possible or perhaps even desirable that, over time, a regional organization emerges, such that several hospitals can conduct WGS independently. The required capacity to conduct WGS should be carefully predicted, as a decentralized organization potentially leads to overcapacity, similar to what happened with proton therapy in the Netherlands (26). Overcapacity may be utilized to conduct WGS for new patient indications, for whom a clinical benefit is perhaps not demonstrated yet. However, this will lead to an increase in the overall budget impact of WGS.

Additionally, the reimbursement status of WGS plays a role in how affordable and accessible WGS is. Currently, WGS is not reimbursed through health insurance in the Netherlands. Especially at the current price level of WGS, lack of reimbursement presents a substantial barrier to wide-scale use (27). If the reimbursement status of WGS does not change, only a few hospitals will likely implement WGS into their clinical practice, and then only for narrowly defined patient subgroups. Hence, the reimbursement decision will influence the required sequencing capacity and the likelihood of decentralization.

Technical considerations

Technical considerations that separate WGS from other biomarker tests are primarily related to the tissue used for WGS. While WGS is increasingly able to handle formalin-fixed, paraffin-embedded tissue (28), WGS using fresh frozen tissue remains more accurate. Fresh frozen biopsies are not routinely taken, which means that an additional biopsy needs to be taken for WGS. Moreover, biopsies for WGS need to comprise at least 20% of tumor cells for successful sequencing, meaning that approximately 28% of biopsies is not suitable for WGS (29). These biopsy requirements pose substantial hurdles for successfully conducting WGS, as tumor material is often limited and difficult to access.

2.3 Model implementation

The conceptual model has been implemented as a hybrid dynamic simulation model using both DES and ABM. The SIMULATE checklist (30) was used to describe the systems model and can be found in supplementary file 2. We have opted for a hybrid model as it allows us to benefit from the comparative advantage of each modeling paradigm. Furthermore, both DES and ABM are individual-level modeling paradigms. Individual-level models can make optimal use of available patient-level data to make future events or trajectories dependent on each individual's history and characteristics, which is very informative in the context of precision medicine. For instance, when modeling care pathways, a treatment decision can be based on the outcome of a diagnostic test and patient characteristics.

The model has been developed in AnyLogic 8.3.3 (The AnyLogic Company). AnyLogic is one of several software packages in which multiple DSM model types can be combined in a single, hybrid model, thus providing high flexibility to model developers.

2.4 Model structure

Figure 2 provides a high-level representation of the model structure. Defining a model boundary is a necessary but subjective decision. The focus of this study is on the required changes in the organization of care. Therefore, system elements that have the largest potential influence on how care is organized or system elements most affected by changes in the organization of care are included in the model.

A hypothetical stage IV NSCLC patient who requires biomarker testing for the initial diagnosis is generated. Upon entering the nearest hospital's workflow, it is determined whether that specific hospital has implemented WGS and whether the patient matches the indication. If the patient receives SoC, all care processes are conducted within that hospital. If the patient should receive WGS, it is assessed whether the pathologist has adopted WGS and whether the patient prefers WGS over SoC. Subsequently, the patient's biopsy is sent to the WGS facility (n = 1), and once sequencing is completed, a report is sent to the MTB (n = 7). Finally, once either SoC or WGS has been concluded, a guideline-based treatment recommendation is given. Thus, the model's starting point is the diagnosis of stage IV NSCLC, and the endpoint is either death during the diagnostic pathway or the conclusion of the diagnostic pathway.

All hospitals that provide biomarker testing for lung cancer patients are reflected in the model. Hospitals are stratified according to type: general (n = 43), teaching (n = 21), and academic hospitals (n = 8). They differ in the testing strategy they employ. General hospitals have a relatively simple testing strategy; they test ALK rearrangement status using IHC and test the EGFR and KRAS oncogenes' mutation status with Sanger Sequencing. Teaching and academic hospitals test PD-L1 expression and ALK with immunohistochemistry (IHC) and use the same TGP to test for EGFR, ROS1, BRAF, and KRAS. It is assumed that these tests are conducted in parallel.

If SoC testing in a general hospital did not identify a biomarker, that patient is referred to a teaching hospital. If the biomarker testing strategy in a teaching hospital also did not identify a biomarker, that patient is referred to an academic hospital. Academic hospitals have implemented WGS for referred patients and patients for whom SoC testing in that academic hospital did not identify a biomarker. If biomarker testing in the academic hospital also did not identify a biomarker, that patient is not referred further. Hence, WGS is implemented as a last-resort diagnostic test. A technical model description, describing of the different agent types and parametrization is available in Additional file 1.

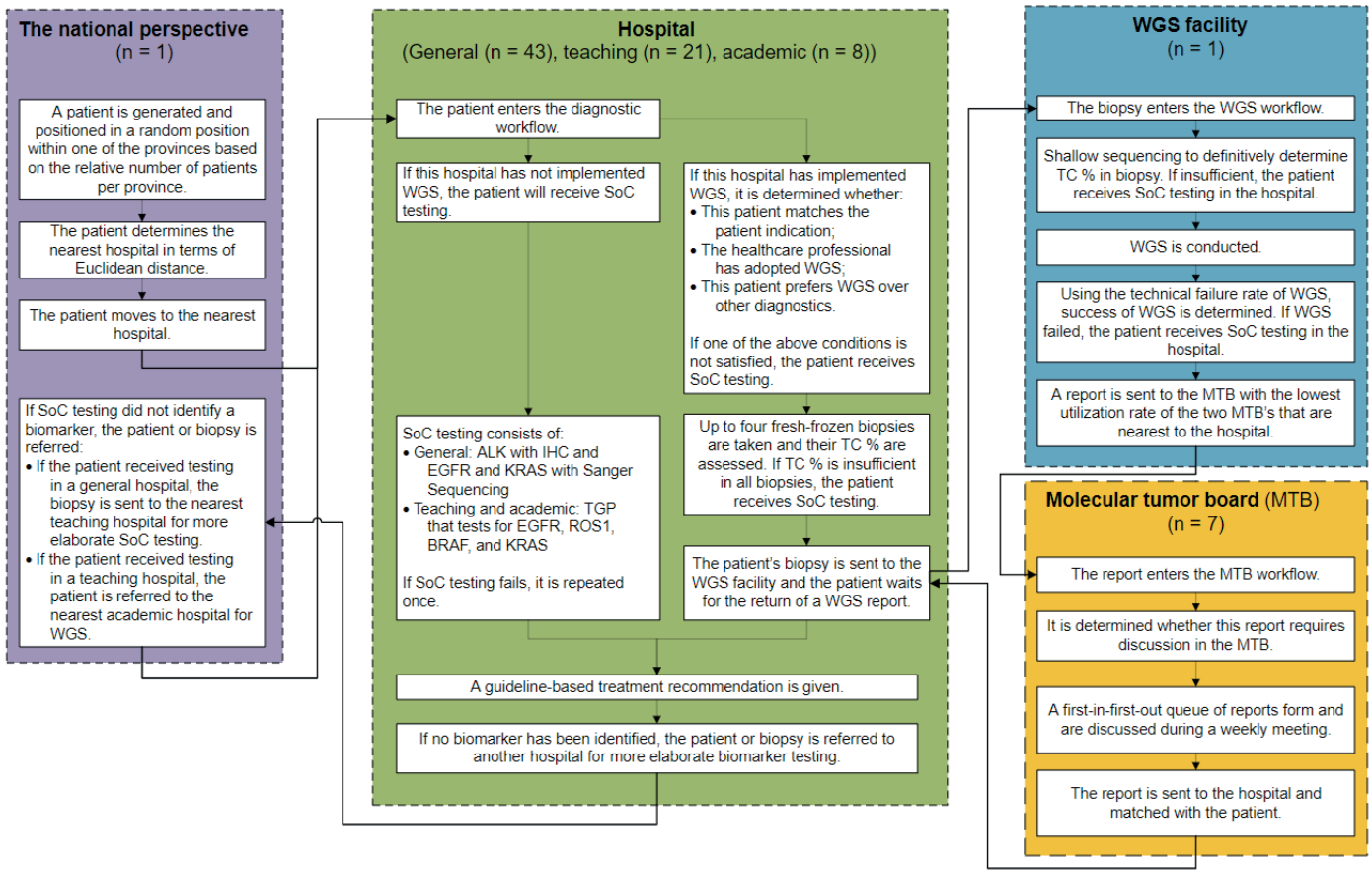


Figure 2. The model structure representing the general flow of patients through the simulation. The model has a multileveled structure: patients, hospitals, the WGS facility, and MTBs are located within the national perspective, which represents the Netherlands. TC %: tumor cell percentage.

2.5 Model transparency and validation

We aimed to create model transparency by providing a clear description of the model and its software implementation. Furthermore, the model has been uploaded to AnyLogic Cloud (31). Systems models are typically relatively complex and, therefore, difficult to extensively validate. In this case, validating the outcomes of a scenario in which WGS is not used against real-world data was not possible as those data were not available. Achieving face validity is often seen as an important first step (32). Face validity was achieved through several discussions with stakeholders during and after model development to discuss modeling choices, assumptions, and outcomes. During model development, interactive discussions were held with the Technology Assessment of Next Generation Sequencing in Personalized Oncology (TANGO) consortium (33), which investigates the added value of WGS for clinical diagnostics in the Netherlands. This group consisted of experts on oncology, pathology, genetics, bioinformatics, ethics, and health economics. Once model development was concluded, an interactive discussion with patient representatives, stakeholders from the current genomic services provider, and the TANGO consortium was organized to evaluate whether the model's face validity was sufficient.

2.6 Model-based analysis

Sensitivity analyses were conducted for model verification and to illustrate several relationships within the model. The following parameters were varied: the cost of WGS, the percentage of patients who need to be referred to another hospital that are in fact referred, and the capacity to conduct WGS. For each parameter setting, the model was run 500 times to quantify the stochastic uncertainty in the outcomes (34). To achieve stable outcomes, each simulation ran for 2000 days. With an annual expected patient population of 5313 (18), each run approximately simulated 29000 patients.

2.7 Results

2.7.1 The cost of WGS

Figure 3 shows the impact of changes in the cost of WGS on the mean cost per patient. Figure 3 includes all patients; patients who received only SoC and patients who received both SoC and WGS. The changes in the cost of WGS have no impact on the mean cost of patients who did not receive WGS and only received SoC. Additionally, not every patient received WGS, and therefore, the mean cost per patient does not increase on a one-to-one basis with the cost level of WGS.

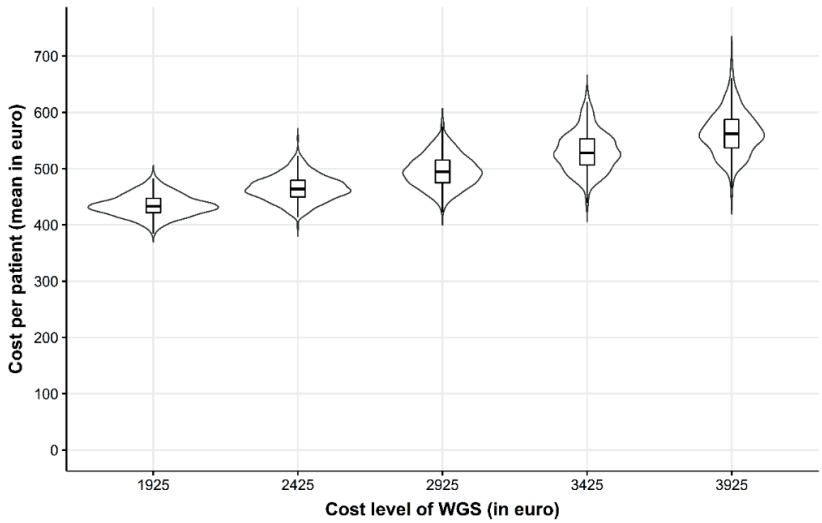


Figure 3. The impact of the cost of WGS on the mean cost per patient across all patients. The length of each violin symbolizes the uncertainty in the estimate of the mean cost per patient. The boxplots show the median and interquartile ranges. The horizontal axis represents the current cost level of WGS (2925 euro) (1) and hypothetical cost levels with 500 euro increments.

2.7.2 Referral patterns for biomarker testing

All hospitals are placed in networks with other hospitals to facilitate referrals of patients among hospitals. To benefit from more extensive biomarker testing, general hospitals refer patients to the nearest teaching hospital, and teaching hospitals refer patients to the nearest academic hospital. Patients who received WGS will not be referred, as there is no additional biomarker test available. Figure 4 shows these hospital networks, as well as the size of the referral flows and patient volume per hospital. For example, general hospital 5 (GH[5]) has a patient volume of below 1500 patients and referred between 367 and 671 patients to teaching hospital 2 (TH[2]). TH[2] has a patient volume of between 1501 and 3000 patients. While TH[2] also received referred patients from general hospitals 4 and 7 but refers only to academic hospital 0 (AH[0]), with a referral volume exceeding 642 patients. AH[0] has a patient volume of between 4501 and 6000 patients. AH[0] does not refer patients, but did receive referred patients from teaching hospital 0, 1, 2, and 4. Note that figure 4 is a visualization based on data from one simulation run. In each simulation run, the distribution of hospital across networks can vary, but how patients are referred is constant across runs. From figure 4, we can observe that hospitals vary in patient volume, patient referrals (both sending and receiving), and the degree of relative importance of hospitals in the network.

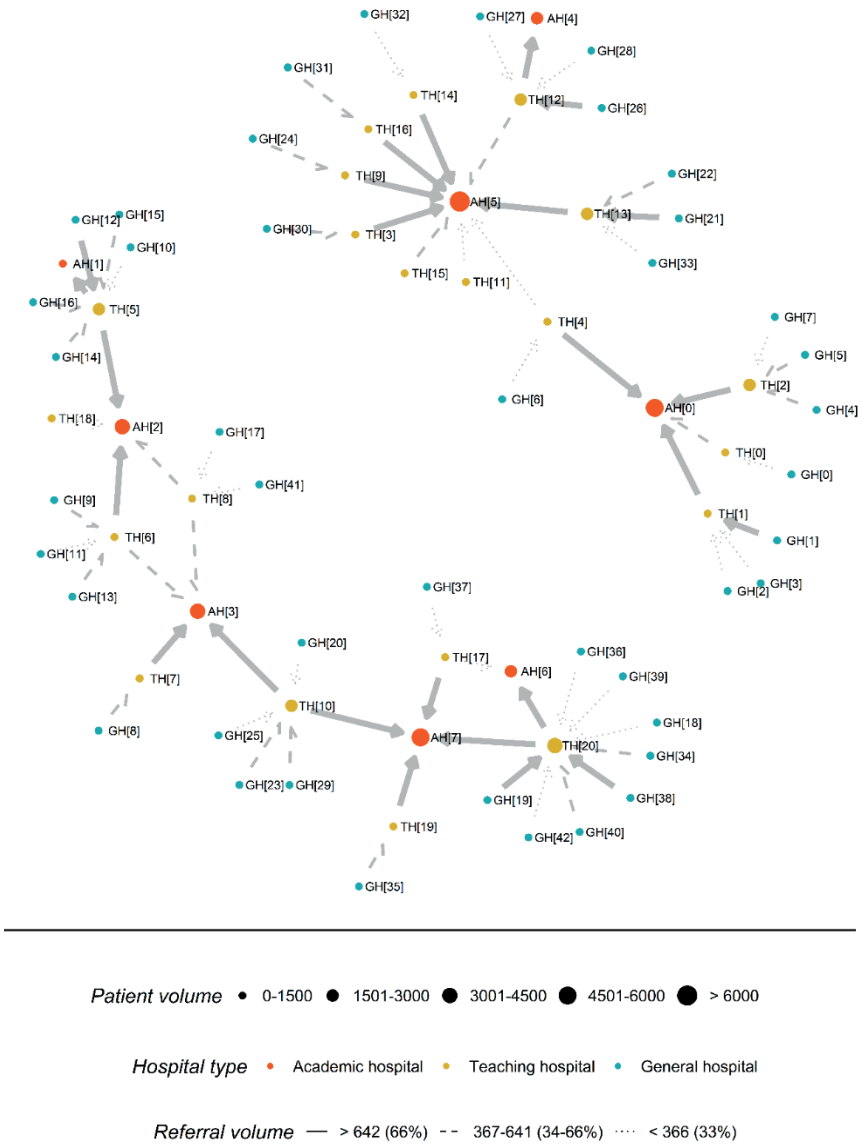


Figure 4. Hospital networks in one simulation run. The nodes represent hospitals. Node size represents total patient volume in the simulation run. Node color represents the hospital type. Edge line type and edge width represents the referral volume expressed in number of patients between two hospitals. Space between hospitals does not represent geographic distance.

Patients are referred to other hospitals if no actionable target has been found and more elaborate biomarker testing is available elsewhere. Figure 5 shows that a higher percentage of referrals lead to, on average, a longer diagnostic pathway. The diagnostic pathway's mean duration increases when more patients are referred due to a model mechanism that extends the diagnostic pathway for several days when a patient is referred, reflecting that referrals cause a delay (18). Moreover, the uncertainty in the mean diagnostic pathway duration increases once more patients are referred.

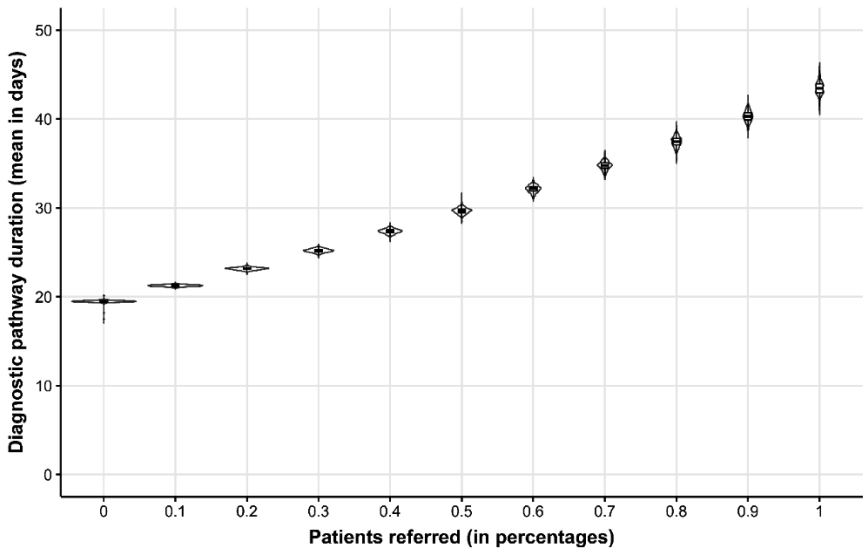


Figure 5. The impact of the percentage of patients who should be referred to a different hospital on the diagnostic pathway duration expressed in days. The assumption underlying referrals is that all patients for whom no biomarker was identified in their current hospital are patients who should be referred if there is more elaborate biomarker testing available elsewhere. The length of each violin symbolizes the uncertainty in the estimate of the mean diagnostic pathway duration. The boxplots show the median and interquartile ranges.

2.7.3 Capacity constraints for WGS

Figure 6 illustrates how constraining the capacity to conduct WGS and the MTB capacity to give a clinical interpretation of the WGS report impacts the percentage of patients who died before receiving a treatment recommendation. Figure 6 is stratified by MTB meeting frequency; weekly or every two weeks. Once the sequencing capacity is below 1600 biopsies annually, which is enough capacity to prevent long queues in this scenario, the diagnostic pathway's mean duration increases. At a capacity of 1450 biopsies annually, the effects are noticeable but

not as extreme compared with a capacity of 1300 biopsies annually. This extreme undercapacity leads to a significantly increased mean duration of the diagnostic pathway and increased uncertainty surrounding that mean estimate. The MTB meeting frequency is also a form of capacity constraint, as it affects the waiting time for the clinical interpretation of WGS results. If MTBs meet once every 14 days, the duration of the diagnostic pathway increases slightly, approximately equal to seven days.

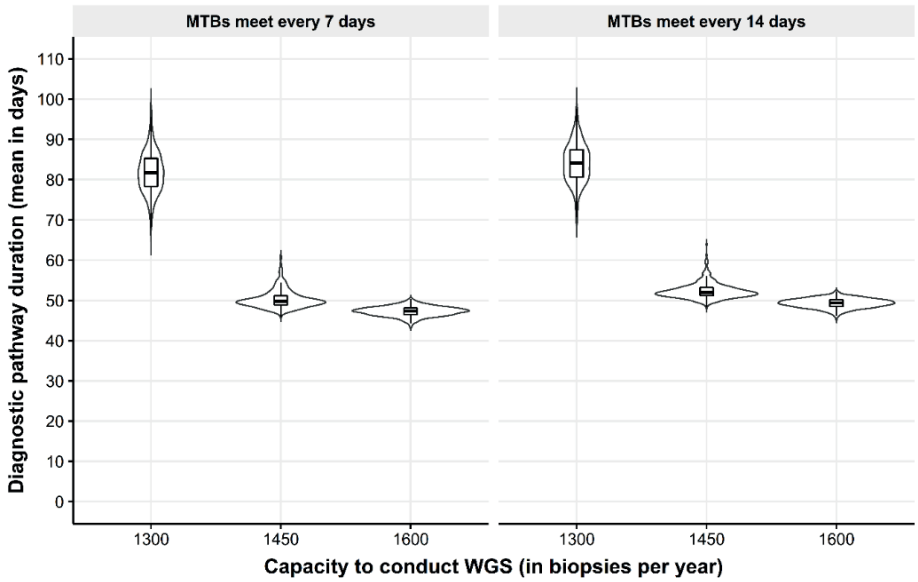


Figure 6. The impact of capacity constraints to provide WGS on the diagnostic pathway duration expressed in days for patients who received WGS. The length of each violin symbolizes the uncertainty in the estimate of the mean the diagnostic pathway duration expressed in days. The boxplots show the median and interquartile ranges.

3. Discussion

In this study, we have demonstrated how DSM can be utilized to develop a systems model that can be used to evaluate the impact of the nationwide implementation of WGS for NSCLC. The study first described the intended use of WGS in oncology and the challenges related to the organization it faces. Subsequently, this real-world

problem has been translated into a proof-of-concept dynamic simulation model reflecting the heterogeneity in patients and providers, behavioral aspects, and geographic variation. Visualization of hospital networks and the sensitivity analyses have illustrated that aspects related to the organization of care, such as capacity constraints and referral patterns, can substantially impact outcomes of interest such as the duration of the diagnostic pathway and the cost per patient.

The main benefit of a DSM with a system-level perspective is the ability to reflect care processes, geographic variation, and behavioral aspects, such as patient preferences and the adoption by individual physicians, which are typically neglected in traditional (Markov type) simulation models (35).

Moreover, dynamic simulation models can reflect the organization of care across multiple heterogeneous providers. Therefore, a dynamic simulation model can investigate multiple different domains that may influence a health technology's actual use and outcomes in a particular context. Oncology and genomics are fast-moving fields. In an effort to make the model more futureproof, the model is set up in a way that potential future developments can be reflected in the model in a relatively straightforwardly and would not impose changes to the model structure.

For instance, in the systems model, it is not necessary to assume that the implementation of WGS is immediate and perfect. It is more plausible that the implementation of WGS will be gradual and that the organization of WGS will affect the benefits of WGS and vice versa, which can be appropriately reflected in a systems model. Figures 3, 5, and 6 show that a traditional model assuming perfect and complete implementation of WGS and assuming unlimited capacity would produce different outcomes regarding the diagnostic pathway's duration and mean cost per patient.

The systems model in this paper combines mechanisms from ABM and DES. A hybrid model benefits from the comparative advantage of each modeling paradigm, allowing the efficient simulation of processes, events, and resources, as well as behavior and interactions. This combination would be much harder to achieve and requires more assumptions when using either DES or ABM by itself. A practical benefit of creating a hybrid model is that it offers flexibility to the model developer, which is valuable if unforeseen model components need to be included. Note that no transformation of inputs and outputs is necessary as both ABM and DES are individual-level modeling paradigms, making it straightforward to combine them.

Given the increasing complexity of the healthcare system, systems models that focus on the organization of care may become more desirable in the future. Though, a systems model requires different and additional data to reflect the system's interdependencies, such as referral patterns, and provider heterogeneity, such as the SoC testing strategy in hospitals. Moreover, conceptualizing the problem and defining model boundaries with stakeholders requires a larger time investment than traditional health economic models. Therefore, it would be worthwhile to determine beforehand whether a systems model would provide additional insights compared to a traditional cost-effectiveness or budget impact analysis. Whether there are benefits depends on the characteristics of the health technology in question, the anticipated required changes to the organization of care for optimal implementation, the diversity of involved stakeholders, and the disruptive nature of the health intervention.

A fundamental challenge for all modelers is defining the model structure required to represent the real-world problem adequately. As our model aims to inform organizational decisions regarding the use of WGS, we naturally focused on the flow of patients and information between the involved actors. To achieve face validity, we have used multiple interactive discussions with stakeholders, before and during model development, to ensure our model was fit for purpose and credible. To minimize model complexity (36), we added model components incrementally when warranted by the stakeholder discussions. Nonetheless, it is possible that involving different stakeholders might have led to slightly different modeling decisions.

Another challenge is the degree of detail that is reflected in the model. That decision was partly driven by data availability. Assumptions were made if the data were lacking for model components that were deemed critical. For instance, we assumed that SoC testing was identical in hospitals of the same type. Therefore, it may not be a perfect representation of the actual test strategy in all hospitals. However, we have aimed to match the degree of detail reflected in the model with the type of research question this model will answer. The model we developed will be used for tactical and strategic purposes. Therefore, details that probably do not impact the outcomes significantly can be omitted. Omitting unnecessary details leads to a less complex model, which reduces the model's computational burden and makes it easier to validate the model with stakeholders.

Many aspects of a systems model will, by design, be country specific. Hence, generalizability may be limited, depending on the extent to which the organization of care differs across countries. Nevertheless, the basic concepts of developing and implementing a systems model are independent of a country-specific context and can be applied generally.

There are many exciting avenues for future research. Given that the healthcare system comprises intelligent agents that can adapt to new circumstances [30], it would be challenging and exciting to explore the healthcare system's adaptive and dynamic behavior and incorporate it into the systems model using different implementation scenarios to WGS. Additionally, developing creative ways to validate the model structure, such by comparing the consequences of natural experiments in the healthcare system with model outcomes, would be valuable.

4. Conclusions

In this study, we have demonstrated how DSM can be applied to the nationwide implementation of WGS for NSCLC. Sensitivity analyses have illustrated that aspects related to the organization, such as capacity constraints and referral patterns, can substantially impact outcomes. The systems model can complement conventional health economic evaluations to investigate how aspects in organizational and behavioral domains influence the actual use and impact of WGS.

Declarations

Ethics approval and consent to participate

The need for ethics approval is waived, as the study does not concern medical scientific research and does not include human subjects (37).

Consent for publication

Not applicable.

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Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

Dr. van Harten and Dr. Retèl have both received non-restricted research grants from Agendia B.V. and Novartis. All other authors have no conflicts of interest to disclose.

Authors contributions

All authors participated in designing the study. MV drafted the first version of the article. MV performed the data analysis. Authors MV, VR, HK, WH, MIJ participated in the data interpretation, and read, revised, and approved the final manuscript.

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References

1. Pasmans CTB, Tops BBJ, Steeghs EMP, Coupé VMH, Grünberg K, de Jong EK, et al. Micro-costing diagnostics in oncology: from single-gene testing to whole- genome sequencing. Expert Rev Pharmacoeconomics Outcomes Res [Internet]. 2021 May 6;21(3):413–4. Available from: https://doi.org/10.1080/14737167.2021.1917385
2. Roepman P, de Bruijn E, van Lieshout S, Schoenmaker L, Boelens MC, Dubbink HJ, et al. Clinical Validation of Whole Genome Sequencing for Cancer Diagnostics. J Mol Diagnostics [Internet]. 2021 Jul;23(7):816–33. Available from: https://doi.org/10.1016/j.jmoldx.2021.04.011
3. Manolio TA, Abramowicz M, Al-Mulla F, Anderson W, Balling R, Berger AC, et al. Global implementation of genomic medicine: We are not alone. Sci Transl Med. 2015;7(290):1–9.
4. Stark Z, Dolman L, Manolio TA, Ozenberger B, Hill SL, Caulfied MJ, et al. Integrating Genomics into Healthcare: A Global Responsibility. Am J Hum Genet [Internet]. 2019;104(1):13–20. Available from: https://doi.org/10.1016/j.ajhg.2018.11.014
5. Phillips KA, Deverka PA, Marshall DA, Wordsworth S, Regier DA, Christensen KD, et al. Methodological Issues in Assessing the Economic Value of Next-Generation Sequencing Tests: Many Challenges and Not Enough Solutions. Value Heal [Internet]. 2018;21(9):1–10. Available from: http://dx.doi.org/10.1016/j.jval.2018.06.017
6. Bortfeld TR, Loeffler JS. Three ways to make proton therapy affordable. Nature. 2017;549(7673):451–3.
7. Van De Wetering G, Woertman WH, Verbeek AL, Broeders MJ, Adang EMM. Quantifying short run cost-effectiveness during a gradual implementation process. Eur J Heal Econ. 2013;14(6):911–8.
8. Plsek PE, Greenhalgh T. The challenge of complexity in health care. Br Med J [Internet]. 2001;323(7313):625–8. Available from: http://www.bmj.com/cgi/doi/10.1136/bmj.323.7313.625
9. Mabry PL, Olster DH, Morgan GD, Abrams DB. Interdisciplinarity and Systems Science to Improve Population Health. A View from the NIH Office of Behavioral and Social Sciences Research. Am J Prev Med. 2008;35(2 SUPPL.):S211–24.
10. Marshall DA, Grazziotin LR, Regier DA, Wordsworth S, Buchanan J, Phillips K, et al. Addressing Challenges of Economic Evaluation in Precision Medicine Using Dynamic Simulation Modeling. Value Heal [Internet]. 2020;1–8. Available from: https://doi.org/10.1016/j.jval.2020.01.016
11. Marshall DA, Burgos-Liz L, Eng I, IJzerman MJ, Crown W, Padula W V., et al. Selecting a dynamic simulation modeling method for health care delivery research - Part 2: Report of the ISPOR dynamic simulation modeling emerging good practices task force. Value Heal [Internet]. 2015;18(2):147–60. Available from: http://dx.doi.org/10.1016/j.jval.2015.01.006
12. Richardson M, Ramsay LC, Bielecki JM, Berta W, Sander B. Systems thinking in health technology assessment: a scoping review. Int J Technol Assess Health Care. 2021;37(1):e71.
13. Kolominsky-Rabas PL, Djanatliev A, Wahlster P, Gantner-Bär M, Hofmann B, German R, et al. Technology foresight for medical device development through hybrid simulation: The ProHTA Project. Technol Forecast Soc Change [Internet]. 2015;97:105–14. Available from: http://dx.doi.org/10.1016/j.techfore.2013.12.005

14. Sabari JK, Santini F, Bergagnini I, Lai WV, Arbour KC, Drilon A. Changing the Therapeutic Landscape in Non-small Cell Lung Cancers: the Evolution of Comprehensive Molecular Profiling Improves Access to Therapy. Curr Oncol Rep. 2017;19(4).

15. van de Haar J, Hoes LR, Roepman P, Lolkema MP, Verheul HMW, Gelderblom H, et al. Limited evolution of the actionable metastatic cancer genome under therapeutic pressure. Nat Med [Internet]. 2021 Aug 9; Available from: http://dx.doi.org/10.1038/s41591-021-01448-w

16. Center for Personalized Cancer Treatment. CPCT-02 [Internet]. [cited 2020 Feb 24]. Available from: https://www.cpct.nl/cpct-02/

17. van der Velden DL, van Herpen CML, van Laarhoven HWM, Smit EF, Groen HJM, Willems SM, et al. Molecular Tumor Boards: Current practice and future needs. Ann Oncol [Internet]. 2017;28(12):3070–5. Available from: http://academic.oup.com/annonc/article/doi/10.1093/annonc/mdx528/4259145

18. van de Ven M, Retèl VP, Koffijberg H, van Harten WH, IJzerman MJ. Variation in the time to treatment for stage III and IV non-small cell lung cancer patients for hospitals in the Netherlands. Lung Cancer. 2019;134(May):34–41.

19. SONCOS. Multidisciplinaire normering oncologische zorg in Nederland [Multidisciplinary standardization of oncological care in the Netherlands] [Internet]. Normeringsrapport [Standardization report]. 2020. Available from: https://www.soncos.org/wp-content/uploads/2020/03/SONCOS-normeringsrapport-versie-8-1.pdf

20. Van De Haar J, Hoes L, Voest E. Advancing molecular tumour boards: Highly needed to maximise the impact of precision medicine. ESMO Open. 2019;4(2):5–6.

21. Willemsen AECAB, Krausz S, Ligtenberg MJL, Grünberg K, Groen HJM, Voest EE, et al. Molecular tumour boards and molecular diagnostics for patients with cancer in the Netherlands: experiences, challenges, and aspirations. Br J Cancer [Internet]. 2019;121(1):34–6. Available from: http://dx.doi.org/10.1038/s41416-019-0489-3

22. Hinderer M, Boerries M, Haller F, Wagner S, Sollfrank S, Acker T, et al. Supporting molecular tumor boards in molecular-guided decision-making -The current status of five German university hospitals. Stud Health Technol Inform. 2017;236:48–54.

23. Bhattarai N, McMeekin P, Price C, Vale L. Economic evaluations on centralisation of specialised healthcare services: A systematic review of methods. BMJ Open. 2016;6(5):1–12.

24. van Nimwegen KJM, van Soest RA, Veltman JA, Nelen MR, van der Wilt GJ, Vissers LELM, et al. Is the $1000 Genome as Near as We Think? A Cost Analysis of Next-Generation Sequencing. Clin Chem [Internet]. 2016 Nov 1;62(11):1458–64. Available from: https://academic.oup.com/clinchem/article/62/11/1458/5612015

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

26. Mot E, Aalbers R, Stuut K, Douven R. De introductie van dure technologie in de zorg: analysekader en case studies [The introduction of expensive technology in healthcare: analysis framework and case studies] [Internet]. 2017. Available from: https://www.cpb.nl/sites/default/files/omnidownload/CPB-Achtergronddocument-18mei2017-De-introductie-van-dure-technologie-in-de-zorg-alalysekader-en-casestudies.pdf

27. Steffen JA, Lenz C. Technological evolution of diagnostic testing in oncology. Per Med. 2013;10(3):275–83.

28. Robbe P, Popitsch N, Knight SJL, Antoniou P, Becq J, He M, et al. Clinical whole-genome sequencing from routine formalin-fixed, paraffin-embedded specimens: pilot study for the 100,000 Genomes Project. Genet Med [Internet]. 2018 Oct 1 [cited 2020 Aug 20];20(10):1196–205. Available from: https://www.nature.com/articles/gim2017241

29. Monkhorst K, Samsom K, Schipper L, Roepman P, Bosch L, Bruijn E de, et al. Validation of whole genome sequencing in routine clinical practice. ESMO Annu Meet [Internet]. 2020 [cited 2020 Sep 29];31:1189O. Available from: https://doi.org/10.1016/j.annonc.2020.08.083

30. Marshall DA, Burgos-Liz L, Ijzerman MJ, Osgood ND, Padula W V., Higashi MK, et al. Applying dynamic simulation modeling methods in health care delivery research - The SIMULATE checklist: Report of the ISPOR simulation modeling emerging good practices task force. Value Heal [Internet]. 2015;18(1):5–16. Available from: http://dx.doi.org/10.1016/j.jval.2014.12.001

31. Ven M van de, IJzerman M, Retèl V, Harten W van, Koffijberg H. The nationwide implementation of Whole Genome Sequencing in oncoloy in the Netherlands [Internet]. AnyLogic Cloud. 2021 [cited 2021 Aug 16]. Available from: https://cloud.anylogic.com/model/6f5c67f2-1423-422a-be35-63f0f664cc77?mode=SETTINGS

32. Vemer P, Corro Ramos I, van Voorn GAK, Al MJ, Feenstra TL. AdViSHE: A Validation-Assessment Tool of Health-Economic Models for Decision Makers and Model Users. Pharmacoeconomics. 2016;34(4):349–61.

33. Technology assessment of next generation sequencing in personalized oncology (TANGO) consortium. TANGO Project [Internet]. 2020 [cited 2020 Aug 19]. Available from: https://zenodo.org/communities/tango-wgs/?%0Apage=1&size=20%0A

34. Briggs AH, Weinstein MC, Fenwick EAL, Karnon J, Sculpher MJ, Paltiel AD. Model parameter estimation and uncertainty analysis: A report of the ISPOR-SMDM modeling good research practices task force working group-6. Med Decis Mak [Internet]. 2012 [cited 2020 Nov 27];32(5):722–32. Available from: http://www.ohsu.edu/epc/mdm/modeling.cfm.

35. Kunc M, Harper P, Katsikopoulos K. A review of implementation of behavioural aspects in the application of OR in healthcare. J Oper Res Soc [Internet]. 2020;71(7):1055–72. Available from: https://doi.org/10.1080/01605682.2018.1489355

36. Axelrod R. Advancing the art of simulation in the social sciences. Complexity [Internet]. 1997;3(2):16–22. Available from: http://doi.wiley.com/10.1002/%28SICI%291099-0526%28199711/12%293%3A2%3C16%3A%3AAID-CPLX4%3E3.0.CO%3B2-K

37. Central Committee on Research Involving Human Subjects. Your research: Is it subject to the WMO or not? [Internet]. Legal framework for medical scientific research. 2020 [cited 2020 Dec 21]. Available from: https://english.ccmo.nl/investigators/legal-framework-for-medical-scientific-research/your-research-is-it-subject-to-the-wmo-or-not

Appendix 1: Model description

The purpose of this model is to show how dynamic simulation modeling can be applied in the context of the nationwide implementation of WGS for NSCLC to inform organizational decisions regarding the use of complex disruptive health technologies and how these decisions affect their potential value. This document is intended to provide more detailed information on the model implementation in AnyLogic. The model has been uploaded to AnyLogic Cloud and is publicly accessible (1).

The model is initially populated with six different agent types: patient, general hospital, teaching hospital, academic hospital, WGS facility, MTB. These agents are all placed within a top-level agent (Main) that represents the Netherlands. A distinction is made between three hospital types to reflect differences in diagnostic testing capabilities. During model runtime, agents of a seventh type, WGS biopsy, are generated within in academic hospital-agents.

Agent types

Table 3 lists the model input parameters including a reference for each parameter.

Main

The top-level agent in a hierarchical model represents the highest level of abstraction and serves as the stage for the other agents. In this model, the top-level agent represents the Netherlands, shown in figure 1.

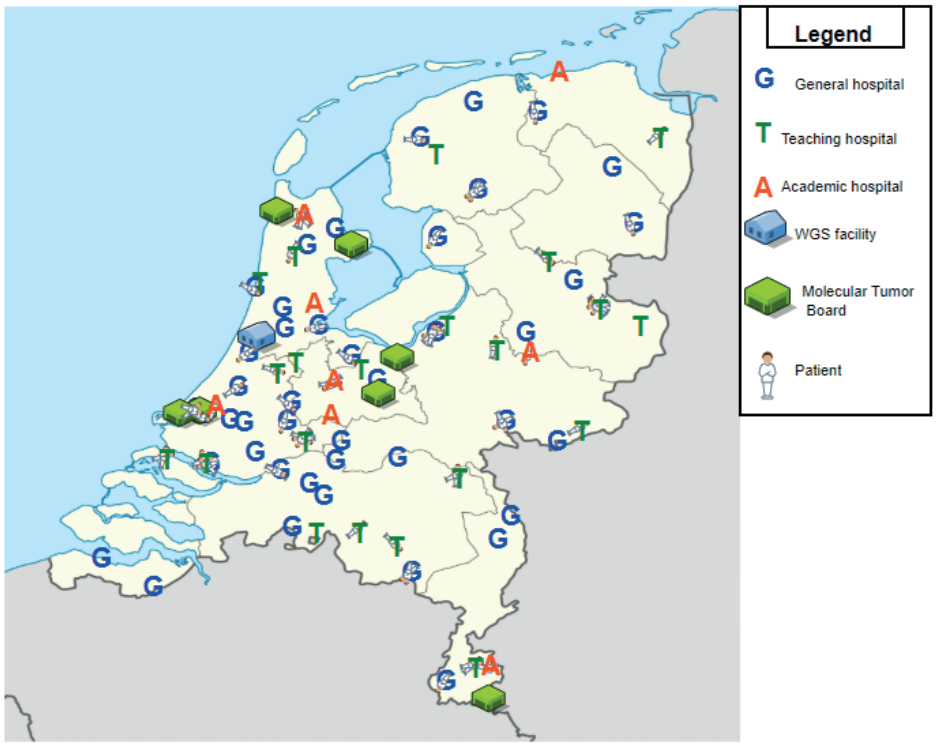

Figure 1. Top-level agent or highest abstraction level in the model representing the Netherlands. Map of the Netherlands was retrieved from Wikimedia Commons: https://commons.wikimedia.org/wiki/File:Netherlands_location_map.svg

Since AnyLogic does not provide a method to reflect geographic variation in agent populations, we have implemented our own approach to reflect geographic variation in terms of patient population size. This is implemented as follows. The relative number of patients per province (2) is calculated. This relative number is then used to slice a range from 0 to 1 into 12 segments, one for each province. The size of each segment is based on the relative number of patients per province, which is displayed in table 1. Subsequently, a random number from a uniform distribution between 0 and 1 is drawn. It is then checked in which segment this random number falls. The province to which this segment corresponds is selected to place the newly generated Patient-agent.

Table 1. Input data for agent placement

Province	Patient-agents
Groningen	0.0349
Friesland	0.0371
Drenthe	0.0291
Overijssel	0.0700
Flevoland	0.0183
Gelderland	0.1220
Utrecht	0.0610
Noord-Holland	0.1514
Zuid-Holland	0.2090
Zeeland	0.0250
Noord-Brabant	0.1585
Limburg	0.0838

Once a province is determined, the patient is placed at a random location in the specified province. Thus, this approach only considers differences between provinces, and not within provinces. In contrast, a specific number of general hospitals, teaching hospital, academic hospital, WGS facility, and MTB agents is placed within each province. In total, 43 general hospitals, 21 teaching hospitals, and 8 academic hospitals (including a comprehensive cancer center) are placed in Main which represents the national perspective and contains all other agents.

Treatment algorithm

Figure 2 shows the algorithm that is used in all hospitals to provide a guideline-based treatment recommendation once the diagnostic workflow has been concluded, and is based on the NCCN clinical practice guidelines (3). It uses the outcomes of the biomarker tests for each patient. In cases where the patient-agent is eligible for both immunotherapy and targeted therapy, the latter takes precedence over the former.

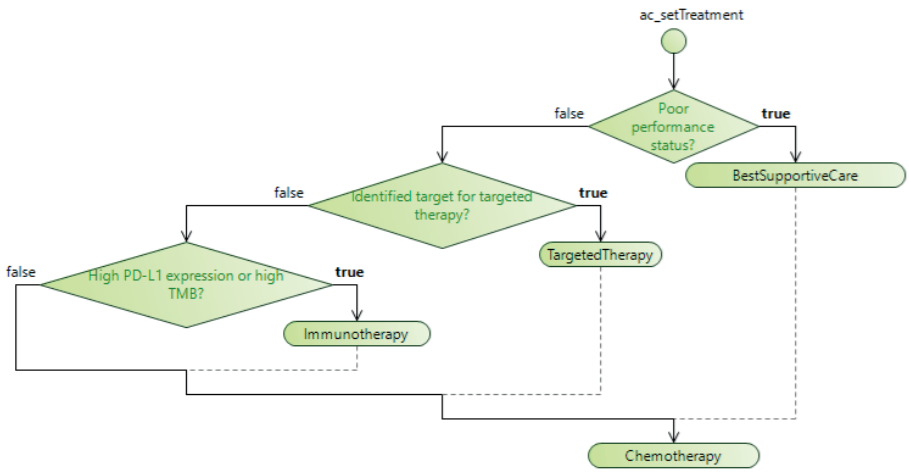

Figure 2. The treatment algorithm used to give treatment recommendations.

Patient

This agent type reflects patients who have been diagnosed with stage IV NSCLC, but who have not yet received biomarker testing or treatment. The patient population is open, meaning that each time period new patients are being generated. The number and interarrival time of patients is determined using a Poisson distribution ($\lambda = 5313$). When a patient-agent is generated, the patient-agent selects the nearest hospital, irrespective of hospital type, and moves to that hospital to receive biomarker testing. Patient-agents will only be removed from the model once their diagnostic pathway has been concluded or because they have died.

General, teaching, and academic hospitals

All three types of hospital-agents contain a DES workflow that reflects the diagnostic pathway for patients with stage IV NSCLC at a high level, which is depicted in figure 3 and 4. Either a patient receives standard of care (SoC) biomarker testing or WGS. In the model, only academic hospitals have implemented WGS.

When a patient-agent enters the workflow in one of the hospitals, it is checked whether this specific hospital has implemented WGS. If that is the case, it is checked whether the patient matches the indication for WGS. If the patient does not match the indication for WGS, the patient will receive standard of care biomarker testing. If the patient matches the indication for WGS, it is further checked whether the patient prefers WGS over SoC ($P = 0.90$) and whether the physician has adopted WGS ($P = 0.90$). Both conditions need to be true for the patient to receive WGS.

Subsequently, a new agent is generated, representing a biopsy to be used for WGS. To be suitable for WGS the biopsy must contain at least 20% tumor cells. In reality, this is visually inspected by a pathologist. In the model, this is evaluated within the hospital care flow. The probability that a given biopsy contains at least 20% tumor cells is determined using a beta distribution (p = 570, q = 297, min = 0, max = 1). If the biopsy indeed contains at least 20% tumor cells, the biopsy is sent to most nearby WGS facility-agent, where it enters a workflow that represents the process of conducting WGS.

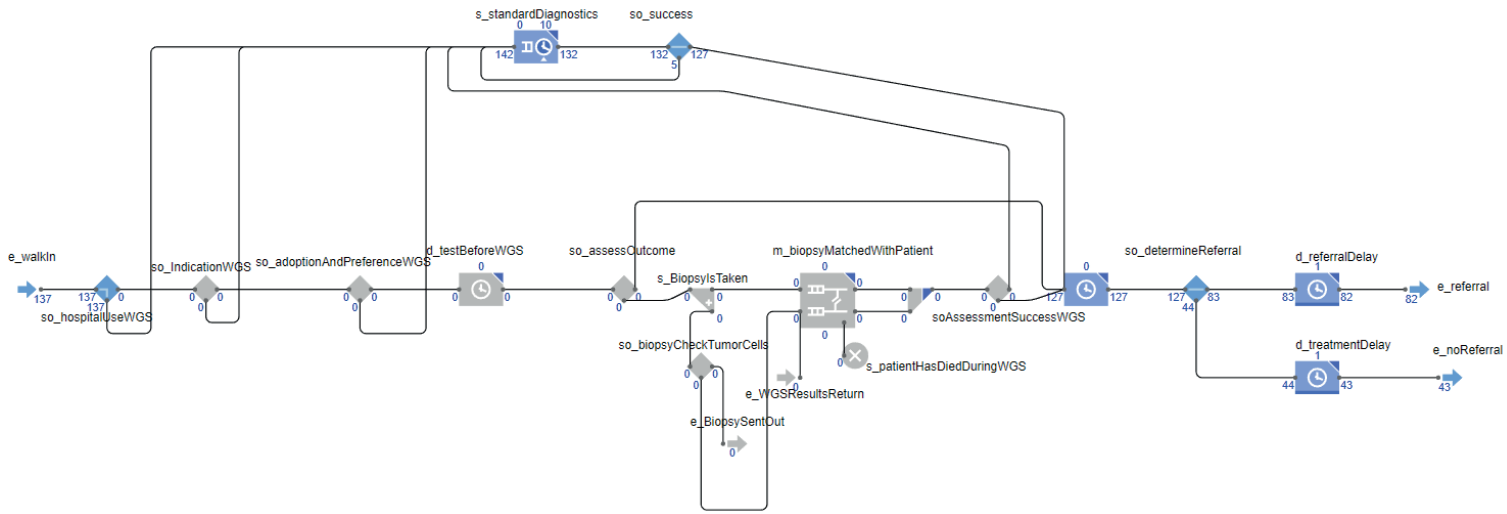

Figure 3. Care workflow in general and teaching hospitals. The top pathway is for SoC biomarker testing, while the bottom pathway is for WGS, which is not in use (greyed out) in general and teaching hospitals. The numbers below each block represent that number of patients that are currently in that block or that have passed that block.

The patient-agent remains located in the hospital and waits while WGS is being conducted. Once the biopsy returns from the WGS facility, it is checked whether WGS was conducted successfully. This is dependent on whether the biopsy passed quality control check in the WGS facility and the technical success rate of WGS, but this is further discussed in section 1.1.4. If it was unsuccessful, the patient-agent will receive SoC. If WGS was successful and the MTB has interpreted the resulting genetic information, the biopsy-agent is sent back to the hospital-agent where it links up with its original patient-agent.

If the patient receives SoC biomarker testing, all processes take place within the hospital. Both SoC and WGS incur a delay. Once either SoC or WGS has been completed, a guideline-based treatment decision is made based on the test outcomes and the performance status of the patient.

Biomarker testing strategies

There is a difference in the SoC biomarker testing strategy among hospital types. General hospitals have the simplest test strategy, as they test genes PD-L1 and ALK with immunohistochemistry (IHC), and EGFR and KRAS using Sanger Sequencing. It is assumed that these tests are conducted in parallel. Teaching hospitals test for ALK and PD-L1 using IHC in parallel with a targeted gene panel that tests for KRAS, BRAF, EGFR, and ROS1. Academic hospitals use the same SoC test strategy as teaching hospitals for non-referred patients. Additionally, they conduct WGS for referred patients and for non-referred patients for whom the combination of the targeted gene panel and IHC test did not result in the identification of a biomarker. For simplicity, we have assumed that the biomarker test strategies are identical for all hospitals of each hospital type.

If a patient is KRAS mutation-positive, that patient cannot be EGFR mutation-positive. All other mutations are not considered mutually exclusive in the model. The model reflects that biomarker testing will occasionally fail. When WGS fails, the patient shall receive WGS. If SoC testing fails, SoC testing will be repeated once.

Diagnostic turnaround times and delays

The turnaround times of diagnostics and the length of the treatment delay in the care workflow of hospitals are obtained from a survey that was distributed in 2019 among 17 oncologists employed in different hospitals and hospital types. Oncologists were asked to map the timeline of individual steps in the care pathway until treatment initiation. Table 2 lists the survey data for each oncologist. Discrete empirical distributions were created for each delay type (result molecular diagnostics, result PD-L1 test, and treatment delay) and for each hospital type. The values for the

empirical distributions for treatment delay were determined by subtracting either the delay for result molecular diagnostics or result PD-L1 test, whichever one is largest, from the time until treatment initiation. The resulting number is the time between conclusion of the diagnostic pathway and treatment initiation, thus, the treatment delay.

Given our assumption that all SoC tests are conducted in parallel, to determine the delay for SoC, a random value was drawn from the empirical distributions for result molecular diagnostics and result PD-L1 test for the matching hospital type. The largest value of the two was used as the delay for SoC.

Table 2. Survey data for diagnostic turnaround times and treatment initiation

Oncologist	Hospital type	Request molecular diagnostics or PD-L1 test (start interval)	Result PD-L1 test	Result molecular diagnostics	Treatment initiation
1	Academic	0	15	21	28
2	Academic	0	4	10	12
3	Academic	0	14	14	18
4	Academic	0	10	21	21
5	Academic	0	9	21	28
6	Academic	0	15	20	30
7	General	0	4	21	22
8	General	0	10	10	14
9	General	0	7	14	19
10	Teaching	0	5	10	14
11	Teaching	0	8	14	20
12	Teaching	0	12	14	21
13	Teaching	0	14	21	25
14	Teaching	0	15	23	32
15	Teaching	0	12	15	20
16	Teaching	0	6	12	20
17	Teaching	0	7	10	14

Hospital networks and referrals

At the start of each simulation, nearby hospitals form a network. More specifically, general hospitals connect to the nearest teaching and nearest academic hospital, and teaching hospitals connect to the nearest academic hospital. These hospital networks are used to facilitate referrals between hospitals. If biomarker testing in a general hospital has not identified a biomarker, that patient will be referred to the teaching hospital that is connected to the general hospital in the network. Similarly, if biomarker testing in a teaching hospital has not identified a biomarker, that patient will be referred to the academic hospital in the network. Academic hospitals do not refer patients elsewhere, as they have most elaborate testing capabilities.

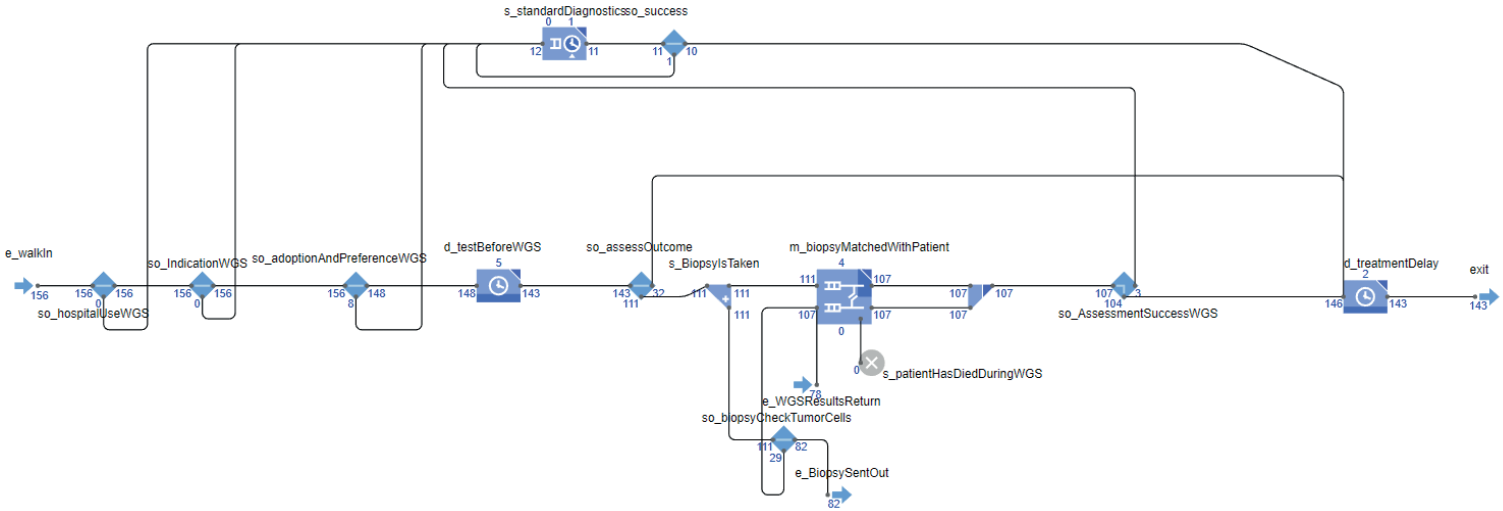

Figure 4. Care workflow in academic hospitals. Both the trajectory for SoC biomarker testing (top pathway), and the trajectory for WGS (bottom pathway) are active. The numbers below each block represent that number of patients that are currently in that block or that have passed that block.

WGS facility

This agent-type is responsible for conducting WGS. Even though the tumor cell percentage is visually inspected by a pathologist in the hospital, a definitive check, using shallow WGS, is performed in the WGS facility. The probability that a given biopsy passes this definitive check is determined using a beta distribution (p = 570, q = 28, min = 0, max = 1). If it is confirmed that the biopsy contains enough tumor cells, WGS will be conducted. Otherwise, the patient will receive SoC biomarker testing. The workflow presented in figure 5 reflects this workflow. When WGS is concluded, the biopsy-agent is sent to the MTB-agent that is closest to the hospital-agent the biopsy-agent was sent from.

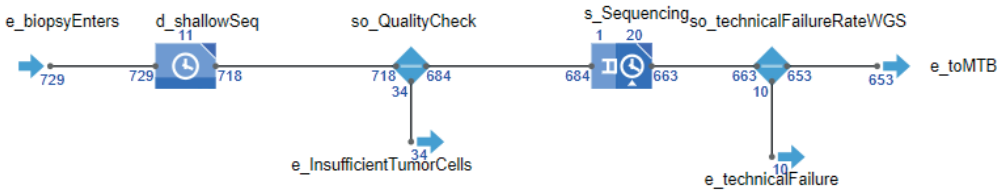

Figure 5. WGS facility workflow. The numbers below each block represent that number of biopsies that are currently in that block or that have passed that block.

From figure 5, we can observe that both the quality check and sequencing itself incur a delay. For the entire sequencing workflow delay, we draw for each biopsy-agent one value from a truncated normal distribution (min = 7, max = 21, mean = 14, sigma = 5). The delay incurred by the quality assessment accounts for 25% of this delay, and the sequencing itself accounts for the remaining 75%. These percentages are based on assumptions. This is implemented as such, given that only the total turnaround time of WGS is known and the turnaround time of individual components of this process is unknown. Even though the 25%/75% split is an assumption, the mean turnaround time of WGS is based on literature.

In the base-case analysis, we assumed that the capacity to conduct WGS is unlimited. While it is unlikely that the capacity is truly unlimited, it is plausible that the capacity is sufficiently large to have little or no impact on outcomes. The capacity to conduct WGS was varied in the sensitivity analyses to illustrate the potential effects of these constraints on outcomes.

MTB

MTB-agents contain a workflow the represents at a high level the workflow used for interpreting the genetic information from WGS. The fact that not the interpretation itself but rather the infrequent meeting schedule of the MTB causes a delay in the diagnostic pathway is reflected in the modeled workflow. Figure 6 illustrates the workflow within the MTB-agents. First, it is determined if the complexity of this case warrants discussion in the MTB. For simplicity, we have assumed that all patients that have received WGS need to be discussed in an MTB. Subsequently, a first-in-first-out (FIFO) queue of biopsy-agents that require interpretation is formed. However, interpretation requires experts, and they meet according to a given schedule. Thus, if a biopsy-agent narrowly missed a meeting, it waits in the queue until the next meeting is scheduled. When interpretation has concluded, the biopsy-agent is sent back to the original hospital where it is linked to the patient it was taken from.

To which MTB the report is sent to from the WGS facility, is determined based on the distance to the hospital. This is either the nearest MTB to the hospital, or the second nearest MTB if the nearest MTB has a utilization rate greater than the utilization rate of the second nearest MTB.

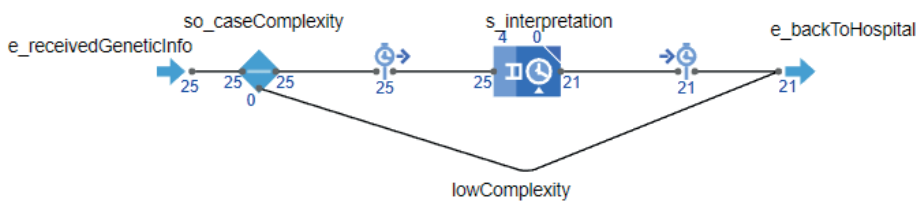

Figure 6. MTB workflow. The numbers below each block represent that number of patients that are currently in that block or that have passed that block.

WGS biopsy

An agent of this agent-type is only generated whenever a patient will receive WGS. Once WGS has concluded, the biopsy-agent and the patient it originates from are matched using a shared unique identifier and merged into one agent. Figure 7 shows the statechart that controls the movement of biopsy-agents between hospital-agents, WGS facility-agents, and MTB-agents. Transitions between states are fired using messages whenever the biopsy-agent has received a specific point in the workflow in the WGS facility-agent or the MTB-agent. For example, once WGS is concluded,

the workflow within the WGS facility sends a message ("Move to MTB") to the biopsy-agent, which fires a transition in the statechart, and the biopsy-agent then moves to the MTB.

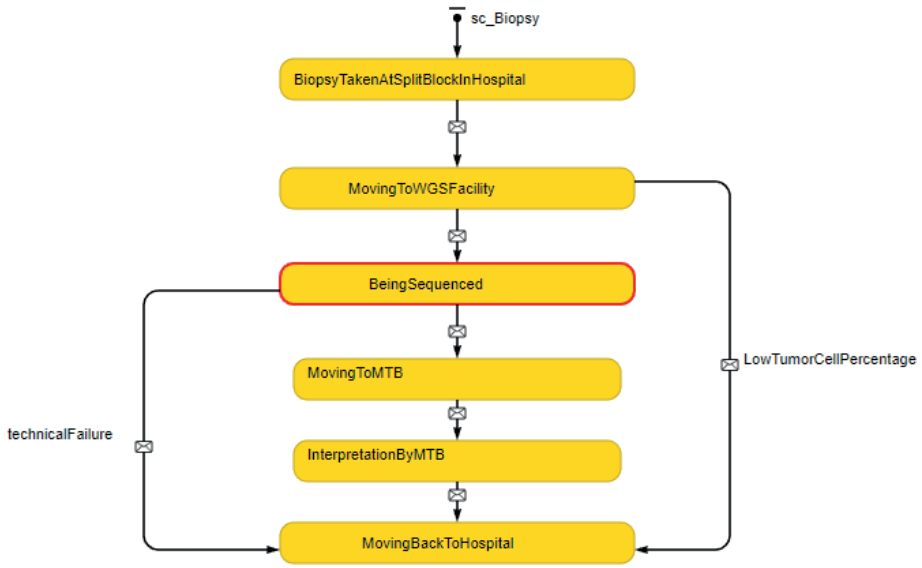

Figure 7. Biopsy-agent statechart

Model parameterization

Table 1 lists the model input parameters, which are based on literature, expert opinion, or assumptions. The model is intended as a proof-of-concept and an illustration of how dynamic simulation modeling and systems science can be utilized in HTA to inform organizational decisions regarding the use of complex disruptive health technologies. That goal can be achieved even if, for some parameters, data is lacking, and assumptions had to be made.

Table 3: Model input parameters

Parameter category	Parameter name	Description	Value	Reference
Global	Annual patient rate	Number and interarrival time of patients diagnosed with stage IV NSCLC each year	Poisson(λ = 5313) (integer)	(4). The type of distribution for the interarrival time is based on assumption.
	MTB count	MTB agent population size	8 (integer)	(5)
	WGS facility count	WGS agent population size	1 (integer)	Reflects the current situation in the Netherlands
	Patient indication WGS	Probability of 0 or 1 that a given patient matches the patient indication for whom WGS is indicated	$P(X \mid referred\ to\ academic\ hospital = 1) \mid P(X \mid SoC\ in\ academic\ hospital\ identified\ biomarker = 0) = 1$ $P(X \mid referred\ to\ academic\ hospital = 0) \mid P(X \mid SoC\ in\ academic\ hospital\ identified\ biomarker = 1) = 0$ (fraction)	Assumption
	WGS Adoption rate	The proportion of physicians who have adopted WGS	0.90 (fraction)	Assumption
	Patient preferences	Probability that the patient-agent prefers WGS over SoC	0.90 (fraction)	Assumption
	Proportion of patients who are discussed MTB	The proportion of patients who received WGS that are discussed in an MTB	1 (fraction)	Assumption

Patient characteristics	KRAS mutation prevalence	Probability that patient harbors an EGFR mutation	Non-squamous cell carcinoma: Beta(p = 784, q = 1268) Squamous cell carcinoma: Beta(p = 3, q = 26) (fraction)	Non-squamous: (6) Squamous: (7)
	EGFR mutation prevalence	Probability that patient harbors an EGFR mutation. EGFR mutations do not overlap with KRAS mutations.	Non-squamous cell carcinoma: Beta(p = 218, q = 1834) Squamous cell carcinoma: Beta(p = 1, q = 28) (fraction)	Non-squamous: (6) Squamous: (7)
	ALK rearrangement prevalence	Probability that patient harbors an ALK rearrangement	Beta(p = 238, q = 7538) (fraction)	(8)
	ROS1 rearrangement prevalence	Probability that patient harbors a ROS1 rearrangement	Beta(p = 7, q = 530) (fraction)	(9)
	BRAF mutation prevalence	Probability that patient harbors a BRAF mutation	Beta(p = 143, q = 7633) (fraction)	(8)
	MET mutation prevalence	Probability that patient harbors a MET mutation	0.04 (fraction)	(10)
	RET rearrangement prevalence	Probability that patient harbors a RET rearrangement	Beta(p = 22, q = 975) (fraction)	(11)
	HER2 mutation prevalence	Probability that patient harbors a HER2 mutation	Beta(p = 64, q = 7712) (fraction)	(8)
	NTRK rearrangement prevalence	Probability that patient harbors a NTRK rearrangement	Uniform distribution(0.02, 0.03) (fraction)	(10)
	High PD-L1 expression level prevalence	Probability that patient has a tumor proportion score (TPS) equal or greater than 50%	Beta(p = 181, q = 650) (fraction)	(8)
	Performance status	Patients' clinical condition on the Eastern Cooperative Oncology Group Performance Status (ECOG PS) scale	PS 0-1: 0.695 PS 2: 0.192 PS 3: 0.079 PS 4: 0.033 (fraction)	(12)
	Time to death	The time in days after which a patient-agent will die during the diagnostic pathway	Weibull(shape = 1.72, scale = 669.73, min = 0) (continuous)	Digitized KM-curve for patient subgroup chemotherapy with PD-L1 TPS score ≥ 50% (13)

MTB	Meeting schedule	The frequency that each MTB meet and discuss cases.	Weekly 3-hour meeting	(5), assumed to be identical across MTB-agents
	Time required for each case	The time in minutes required to discuss one patient in the MTB.	Normal distribution(mean = 4, variance = 1.5, min = 0, max = 10) (continuous)	Expert opinion
WGS facility	Sequencing capacity	The number of biopsies that can be sequenced concurrently at any given moment	Unlimited	Assumption
	WGS technical success rate	The proportion of biopsies were not successfully sequenced even though they contained enough tumor cells	Beta(p = 570, q = 28) (fraction)	(14)
	Turnaround time WGS	Represents turnaround time of WGS in days	Truncated normal distribution (min = 7, max = 21, mean = 14, sigma = 3) (continuous)	Mean: (14) Type of distribution, min, max, sigma is based on assumption.
	Cost shallow WGS	The cost of conducting shallow WGS on one biopsy	25% * Cost WGS (continuous)	Expert opinion
	Shallow WGS quality assessment	The probability that a given biopsy fails the quality assessment by shallow WGS	Beta(p = 28, q = 570) (fraction)	(14)
Hospital (academic, teaching, general)	NGS technical success rate	Probability that an NGS panel is successfully conducted	Beta(p = 845.775, q = 49.225) (fraction)	(9)
	Cost WGS	The cost of conducting WGS for one patient with NSCLC	2925.25 euro (continuous)	(15)
	Cost NGS panel	The cost of conducting one targeted gene panel for one patient with NSCLC.	The mean of reported costs for three different NGS panels $cost = \frac{329.85 + 263.04 + 258.96}{3} = 283.95$ (continuous)	(15)
	Cost test ALK with IHC	The cost of conducting one IHC for an ALK rearrangement for one patient	101.88 euro (continuous)	(15)
	Cost test PD-L1 with IHC	The cost of conducting one IHC for the PD-L1 expression level for one patient	93.74 euro (continuous)	(15)
	Cost test EGFR Sanger Sequencing	The cost of conducting one Sanger Sequencing test for EGFR for one patient	71.19 euro (continuous)	(15)
	Cost test KRAS Sanger Sequencing	The cost of conducting one Sanger Sequencing test for KRAS for one patient	The mean of reported costs for two different platforms (continuous) $cost = \frac{71.19 + 63.47}{2} = 67.33$	(15)

Turnaround time PD-L1 test general hospitals	The time in days from ordering PD-L1 test until receiving results in a general hospital for one patient	Discrete empirical distribution(min = 4, max = 10) (discrete)	Survey data, see section 1.1.3.2 and table 2.
Turnaround time PD-L1 test teaching hospitals	The time in days from ordering PD-L1 test until receiving results in a teaching hospital for one patient	Discrete empirical distribution(min = 5, max = 15) (discrete)	Survey data, see section 1.1.3.2 and table 2.
Turnaround time PD-L1 test academic hospitals	The time in days from ordering PD-L1 test until receiving results in an academic hospital for one patient	Discrete empirical distribution(min = 4, max = 15) (discrete)	Survey data, see section 1.1.3.2 and table 2.
Turnaround time molecular diagnostics general hospitals	The time in days from ordering molecular diagnostics until receiving results in a general hospital for one patient	Discrete empirical distribution(min = 10, max = 21) (discrete)	Survey data, see section 1.1.3.2 and table 2.
Turnaround time molecular diagnostics teaching hospitals	The time in days from ordering molecular diagnostics until receiving results in a teaching hospital for one patient	Discrete empirical distribution(min = 10, max = 23) (discrete)	Survey data, see section 1.1.3.2 and table 2.
Turnaround time molecular diagnostics academic hospitals	The time in days from ordering molecular diagnostics until receiving results in an academic hospital for one patient	Discrete empirical distribution(min = 10, max = 21) (discrete)	Survey data, see section 1.1.3.2 and table 2.
Treatment delay general hospitals	The time in days after concluding diagnostics and between treatment initiation in a general hospital for one patient	Discrete empirical distribution(min = 1 , max = 5) (discrete)	Survey data, see section 1.1.3.2 and table 2.
Treatment delay teaching hospitals	The time in days after concluding diagnostics and between treatment initiation in a teaching hospital for one patient	Discrete empirical distribution(min = 4, max = 9) (discrete)	Survey data, see section 1.1.3.2 and table 2.
Treatment delay academic hospitals	The time in days after concluding diagnostics and between treatment initiation in an academic hospital for one patient	Discrete empirical distribution(min = 0, max = 10) (discrete)	Survey data, see section 1.1.3.2 and table 2.
Sufficient Tumor cells in WGS biopsy	Probability that any of the biopsies taken for WGS contain enough tumor cells	Beta(p = 570, q = 297) (fraction)	(14)
Referral error	Probability that a patient for whom no biomarker was identified in the current hospital is not referred to either a teaching or academic hospital for further testing	0 (fraction)	Assumption

Outcome stability

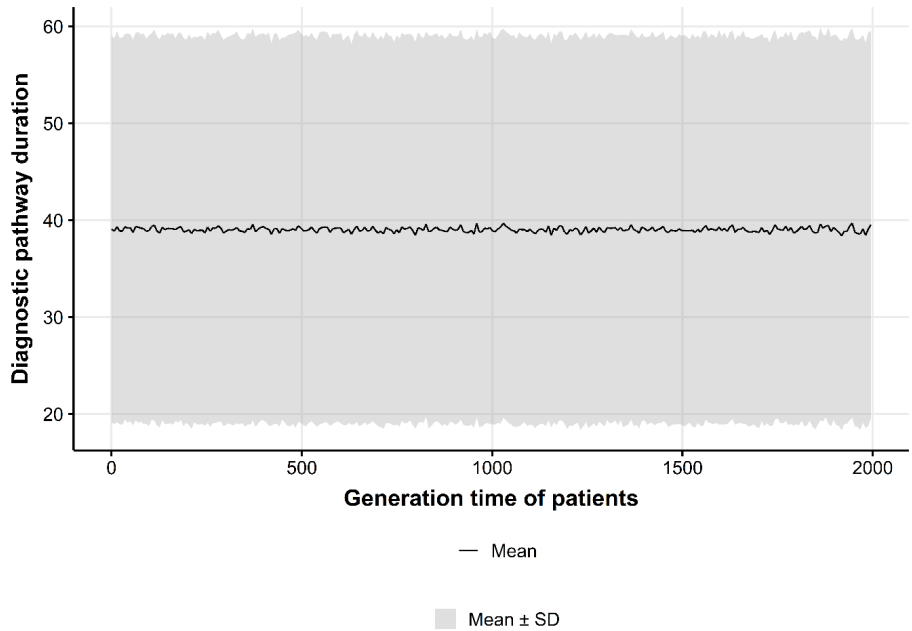

Figure 8. The duration of the diagnostic pathway for patients generated at different simulation times based on 500 simulation runs.

Appendix 1 references

1. Ven M van de, IJzerman M, Retèl V, Harten W van, Koffijberg H. The nationwide implementation of Whole Genome Sequencing in oncoloy in the Netherlands [Internet]. AnyLogic Cloud. 2021 [cited 2021 Jan 26]. Available from: https://cloud.anylogic.com/model/6f5c67f2-1423-422a-be35-63f0f664cc77?mode=SETTINGS
2. Nederlandse Kankerregistratie [Netherlands Cancer Registry]. Incidentie, Niet-kleincellig longcarcinoom, 2017, Aantal [Incidence, Non-small cell lung cancer, 2017, Amount] [Internet]. Available from: https://www.iknl.nl/nkr-cijfers?fs%7Cepidemiologie_id=6&fs%7Ctumor_id=260&fs%7Cregio_id=161%2C159%2C157%2C164%2C158%2C160%2C165%2C163%2C167%2C166%2C156%2C162&fs%7Cperiode_id=106&fs%7Cgeslacht_id=15&fs%7Cleeftijdsgroep_id=67&fs%7Cjaren_na_diagnose_id=16&fs
3. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer (version 6.2020) [Internet]. 2020. Available from: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
4. van de Ven M, Retèl VP, Koffijberg H, van Harten WH, IJzerman MJ. Variation in the time to treatment for stage III and IV non-small cell lung cancer patients for hospitals in the Netherlands. Lung Cancer. 2019;134(May):34–41.
5. PATH. Moleculaire tumor boards [Molecular tumor boards] [Internet]. [cited 2020 Jun 17]. Available from: https://www.netwerk-path.nl/index.php/tumor-boards
6. Kuijpers CCHJ, Hendriks LEL, Derks JL, Dingemans AMC, van Lindert ASR, van den Heuvel MM, et al. Association of molecular status and metastatic organs at diagnosis in patients with stage IV non-squamous non-small cell lung cancer. Lung Cancer. 2018 Jul 1;121:76–81.
7. Kerner GSMA, Schuuring E, Sietsma J, Hiltermann TJN, Pieterman RM, de Leede GPJ, et al. Common and Rare EGFR and KRAS Mutations in a Dutch Non-Small-Cell Lung Cancer Population and Their Clinical Outcome. Batra SK, editor. PLoS One [Internet]. 2013 Jul 29 [cited 2020 Sep 29];8(7):e70346. Available from: https://dx.plos.org/10.1371/journal.pone.0070346
8. Dietel M, Savelov N, Salanova R, Micke P, Bigras G, Hida T, et al. Real-world prevalence of programmed death ligand 1 expression in locally advanced or metastatic non–small-cell lung cancer: The global, multicenter EXPRESS study. Lung Cancer. 2019;134(February):174–9.
9. VanderLaan PA, Rangachari D, Majid A, Parikh MS, Gangadharan SP, Kent MS, et al. Tumor biomarker testing in non-small-cell lung cancer: A decade of change. Lung Cancer [Internet]. 2018;116(December 2017):90–5. Available from: https://doi.org/10.1016/j.lungcan.2018.01.002
10. Hirsch FR, Scagliotti G V., Mulshine JL, Kwon R, Curran WJ, Wu YL, et al. Lung cancer: current therapies and new targeted treatments. Lancet. 2017;389(10066):299–311.
11. Michels S, Scheel AH, Scheffler M, Schultheis AM, Gautschi O, Aebersold F, et al. Clinicopathological characteristics of RET rearranged lung cancer in European patients. J Thorac Oncol [Internet]. 2016 Jan 1 [cited 2020 Sep 29];11(1):122–7. Available from: http://dx.doi.org/10.1016/j.jtho.2015.09.016

12. Simmons CP, Koinis F, Fallon MT, Fearon KC, Bowden J, Solheim TS, et al. Prognosis in advanced lung cancer - A prospective study examining key clinicopathological factors. Lung Cancer [Internet]. 2015 [cited 2020 Jun 16];88(3):304–9. Available from: http://dx.doi.org/10.1016/j.lungcan.2015.03.020

13. Mok TSK, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet. 2019;393(10183):1819–30.

14. Monkhorst K, Samsom K, Schipper L, Roepman P, Bosch L, Bruijn E de, et al. Validation of whole genome sequencing in routine clinical practice. ESMO Annu Meet [Internet]. 2020 [cited 2020 Sep 29];31:1189O. Available from: https://doi.org/10.1016/j.annonc.2020.08.083

15. Pasmans CTB, Tops BBJ, Steeghs EMP, Coupé VMH, Grünberg K, de Jong EK, et al. Micro-costing diagnostics in oncology: from single-gene testing to whole- genome sequencing. Expert Rev Pharmacoeconomics Outcomes Res [Internet]. 2021 May 6;21(3):413–4. Available from: https://doi.org/10.1080/14737167.2021.1917385

Appendix 2. The SIMULATE checklist

An application of the SIMULATE checklist [1] accompanying the manuscript titled 'Developing a dynamic simulation model to support the nationwide implementation of Whole Genome Sequencing in lung cancer' by van de Ven et al. (2021).

System

The modelled system reflects a part of the healthcare system in the Netherlands. Specifically, the modelled system reflects the current diagnostic pathway for lung cancer patients. As the purpose of the model is to analyze the consequences of implementing Whole Genome Sequencing (WGS) at a national level, the modelled system includes multiple hospitals, as well as care providers involved with conducting WGS and providing clinical interpretations of the genetic information that WGS provides. In short, the stakeholders involved include patients, hospitals, the WGS facility, and Molecular Tumor Boards (MTB).

Interaction

The model includes nonlinear and spatial relationship among its stakeholders. When patients are generated, they will select and move to a hospital in which they will undergo initial diagnostics. This hospital selection is based on distance. Moreover, hospitals may refer patients to other hospitals; whichever hospital they refer to is dependent on hospital type (academic, teaching, general) and distance. Similarly, hospitals send WGS reports corresponding to patients who received WGS to either one of the two nearest MTBs. These flows of agents lead to nonlinear behavior within the system and makes it difficult to predict the outcomes.

Multilevel

The model takes a tactical and strategic perspective. While certain model components such as the modelled care processes are more of an operational nature, these are necessary to answer questions at the tactical and strategic level. Given that the model includes all hospitals that treat lung cancer patients in the Netherlands, it is able to provide valuable information both at the hospital level as well as at the national level. If so desired, the insights gained from the model can be interesting for individual hospital managers, but also policymakers at the national level.

Understanding

A closed-form analytical approach would not able to address the research questions. This is primarily due to the randomness that is included in the model; patient characteristics, outcomes of diagnostics, time-to-events, costs, etc., all contain

stochasticity. More traditional models such as Markov models or microsimulation models would not be able to reflect the multi-levelled nature of the system and research questions.

Loops

The model contains feedback loops in two areas of the model: (1) feedback loops between hospitals (due to patient and referral flows), (2) feedback loops in diagnostic pathways within hospitals (e.g., if a test fails, it can be repeated). These feedback loops increase the nonlinear behavior of the system and may lead to queues within the modelled care processes. Ultimately, these queues can lead to delays and potentially prevent patients from receiving the care that was indicated for them.

Agents

The model includes multiple agent populations: patients, hospitals, the WGS facility, MTBs, and WGS biopsies that are generated if a patient receives WGS. Beyond the hospital selection by patients, these agents are passive. In other words, the behavior of these agents is purely informed by relatively simple rules specified by the authors.

Time

Time is a key component of the model. Delays caused by the modelled care processes influence the time-to-treatment, which is one of the primary endpoints for this study. Moreover, the patient population is an open population, meaning that patients are continuously being generated and added to the model.

Emergence

While this study is not a full-fledged application of the model, the model has the potential to illuminate both the intended and unintended consequences of implementing WGS nationally in the healthcare system. For instance, by aiming to reflect a part of the real-world healthcare system, thereby including real-world constraints, it is able the consequences of these constraints and contrast them with the outcomes of unconstrained analyses, such as what is typically assumed in cost-effectiveness analyses.

Appendix 2 references

[1] D.A. Marshall, L. Burgos-Liz, M.J. Ijzerman, N.D. Osgood, W. V. Padula, M.K. Higashi, P.K. Wong, K.S. Pasupathy, W. Crown, Applying dynamic simulation modeling methods in health care delivery research - The SIMULATE checklist: Report of the ISPOR simulation modeling emerging good practices task force, Value Heal. 18 (2015) 5–16. https://doi.org/10.1016/j.jval.2014.12.001.

Chapter 7

Nationwide implementation of whole genome sequencing in lung cancer: a dynamic simulation model to analyze the impact of implementation scenarios on time-to-treatment, costs, and aggregate demand

Michiel van de Ven, Hendrik Koffijberg, Valesca P.J. Retèl, Wim H. van Harten, Maarten J. IJzerman

This chapter has submitted to *Genome Medicine* as: Nationwide Implementation of Whole Genome Sequencing in Lung Cancer: A Dynamic Simulation Model to Analyze the Impact of Implementation Scenarios on Time-to-Treatment, Costs, and Aggregate Demand. van de Ven, M., Koffijberg, H, Retèl, V.P., van Harten, W., IJzerman, M.J.

Abstract

Background

This study is the first-ever to analyze different national implementation scenarios to maximize the benefits of Whole Genome Sequencing (WGS) for lung cancer patients ensuring sustainable and accessible use.

Materials and methods

A base case and three scenarios with different patient groups, hospital types that offer WGS, and the position of WGS in the diagnostic work-up were simulated with a dynamic simulation model. The model included patient and healthcare provider heterogeneity, diagnostic workflows, and referral patterns of lung cancer patients. Model outcomes were the time-to-treatment, costs, and aggregate demand for WGS services.

Results

The time-to-treatment ranged between 20-46 days. The cost of diagnostics per patient ranged from 621 euro in the base case to 1930 euro in the scenario where all patients would receive upfront WGS. Compared to the base case, WGS upfront testing for all lung cancer patients led to a 33% reduction of the time-to-treatment, a 210% increase in the cost per patient and a six-fold increase in total diagnostic costs.

Conclusion

WGS upfront testing for all lung cancer patients reduces the time to treatment, is more expensive, and reduces diagnostic pathway complexity. This may change when price discounts are offered and more actionable targets are determined.

Keywords

Genome sequencing, scenario analysis, simulation modelling, implementation, delivery of healthcare

1. Introduction

Whole Genome Sequencing (WGS) is a comprehensive genomic test that analyzes the entire genome and therefore has a higher diagnostic yield compared to the commonly used targeted single gene tests or targeted gene panels. Several countries have taken initiatives for the implementation of WGS in clinical oncology [1], with an emphasis on rare cancers and cancers with unmet needs.

There are multiple areas in which WGS can provide additional value compared to the current standard of care (SOC) for treatment selection, in particular in assisting with diagnosing complex or rare tumor types such as carcinoma of unknown primary (CUP) and blood cancers [3]. Furthermore, WGS is currently used as a last-resort diagnostic for patients with refractory cancers to identify actionable mutations, which would otherwise be complex and inefficient to identify using SOC testing. Moreover, WGS can be considered a substitute in cancers where multiple SOC tests are required to test for all relevant biomarkers. WGS can increase the efficiency of the diagnostic pathway by streamlining workflows [4]. Ultimately, this may have benefits for the healthcare system and for patients. Implementation studies such as "WGS Implementation in the standard Diagnostics for Every cancer patient" (WIDE) study in the Netherlands, aim to investigate the feasibility to provide WGS-based diagnostics as part of routine diagnostics for metastatic cancer patients [5].

While the clinical evidence for using WGS is increasing, it is less clear how the benefits are to be demonstrated. First, it is not defined which patient subgroups would benefit most from upfront WGS and how that will change over time when (more) evidence of clinical utility becomes available. Second, the extent that current SOC testing will be replaced, i.e., the degree of substitution, by WGS is unclear. Tumor types such as lung cancer require multiple different biomarker tests conducted for a clinical diagnosis, such as immunohistochemistry, Next Generation Sequencing (NGS) panels, and fluorescence in situ hybridization [6]. While WGS can be a substitute for all DNA-based biomarker tests, the most efficient use of WGS as either an upfront test for all or for metastatic cancers only is unknown. Third, realizing the benefits of WGS implies that there should be equal access for patients and, hence, enough hospitals need to offer WGS and associated treatments. Performing a prospective clinical study would be challenging and only partly provide the answers to these questions, so a simulation model that can analyze different scenarios would be appropriate ahead of implementation.

In addition to the modeling that is used to inform reimbursement decisions, simulation models can potentially inform health policy by incorporating implementation characteristics relevant for actual use in the health service. This particularly is relevant as WGS is a disruptive technology and thus the full benefits of WGS can only be realized if care pathways are adapted to accommodate WGS. For example, data curation and clinical interpretation of WGS data should be performed in molecular tumor boards (MTB) [7,8], which are typically not needed for SOC testing.

Simulation models can be implemented using Dynamic Simulation Modeling (DSM), which is a set of modeling approaches. Amongst others, DSM can be used to model patient-level variation, care provider heterogeneity, dynamic diagnostic and treatment processes [9,10] and can reflect the multi-levelled nature of macro-level or nationwide implementation of WGS.

The primary objective of this study is to investigate how the cost per patient and time-to-treatment is affected by the nationwide implementation of WGS as a cancer diagnostic and how these outcomes differ among patient subgroups. Both current costs of WGS and discounted costs of consumables for WGS will be used. This discount is potentially attainable when conducting WGS at scale. The secondary objective is to estimate the aggregate demand for sequencing and analytic capacity with the respect to WGS, based on the assumed delivery of WGS services.

In the analysis, a base case reflecting the current situation and three scenarios will be analyzed: one with a 2-year time horizon and two with a 5-year time horizon. These scenarios differ on three dimensions: the patient indication, the hospital types that use WGS, and the position of WGS in the diagnostic strategy. The scenarios will be simulated with a previously developed dynamic simulation model [11] that reflects the organization of care for WGS in the Netherlands. Non-small cell lung cancer (NSCLC), the largest subtype of lung cancer, will be used a case study, as the role of molecular diagnostics is substantial in the prediction of treatment response in this cancer type [12].

2. Methods

2.1 Simulation model

The previously created dynamic simulation model [11] on the diagnostic pathway for NSCLC allows studies into the affordability and accessibility of the use of WGS. The model reflects the diagnostic pathway for lung cancer in the Netherlands and included patient and institute heterogeneity, diagnostic workflows, referral patterns,

and a spatial representation of the hospital landscape in the Netherlands. For a detailed technical description of the simulation model and input parameters, we refer to the supplementary document of van de Ven et al. [11]. The simulation model can be inspected and run on AnyLogic Cloud [13].

2.2 Outline of the simulation

Figure 1 provides a schematic representation of the model structure. The model was implemented as a hybrid dynamic simulation model, combining Discrete-Event Simulation (DES) and Agent-Based Modeling (ABM), and was developed in AnyLogic 8.3.3 (The AnyLogic Company). The model contained the following agents: academic (n = 8), teaching (n = 21), and general (n = 43) hospitals, a sequencing facility (n = 1), regional MTBs (n = 8). Additionally, patients with NSCLC were being generated over time according the to the incidence of NSCLC patients in the Netherlands [14].

Hypothetical patients with NSCLC who require biomarker testing for initial treatment selection are generated and enter the diagnostic workflow of the nearest hospital to receive biomarker testing, either a form of SOC testing or WGS. Depending on the scenario, WGS is preceded by one or multiple tests. If the patient receives WGS, the biopsy material is sent to the WGS facility, and if sequencing was successful, a report is sent to the MTB nearest to the hospital for a clinical interpretation. The biopsies of patients are referred to another hospital with more extensive testing capabilities if no actionable target has been identified so far and one or more biomarkers has not yet been tested. The selection for the referral hospital is dependent on distance and on the type of the referring hospital, so that a general hospital refers to nearest teaching hospital, and a teaching hospital refers to the nearest academic hospital. The endpoint in the model is when either SOC has been concluded or when the clinical interpretation of WGS results have been reported back to the hospital.

2.3 Base case and simulated implementation scenarios

In the base case, all patients receive SOC. Three implementation scenarios were defined in consultation with a medical oncologist and the managing director of the Hartwig Medical Foundation, the one central facility in the Netherlands that conducts WGS for cancer patients that are enrolled in clinical trials. The scenarios describe potential variants of how WGS might be used as a diagnostic test for lung cancer in the Dutch healthcare system in the future. This includes a scenario with a two-year time horizon (short term), and two scenarios with a five-year time horizon (long term). To provide a bandwidth of possible outcomes, these two longer-term scenarios describe a neutral and a progressive perspective regarding the implementation rate of WGS. Table 1 provides a summary description of the content of the base case and scenarios.

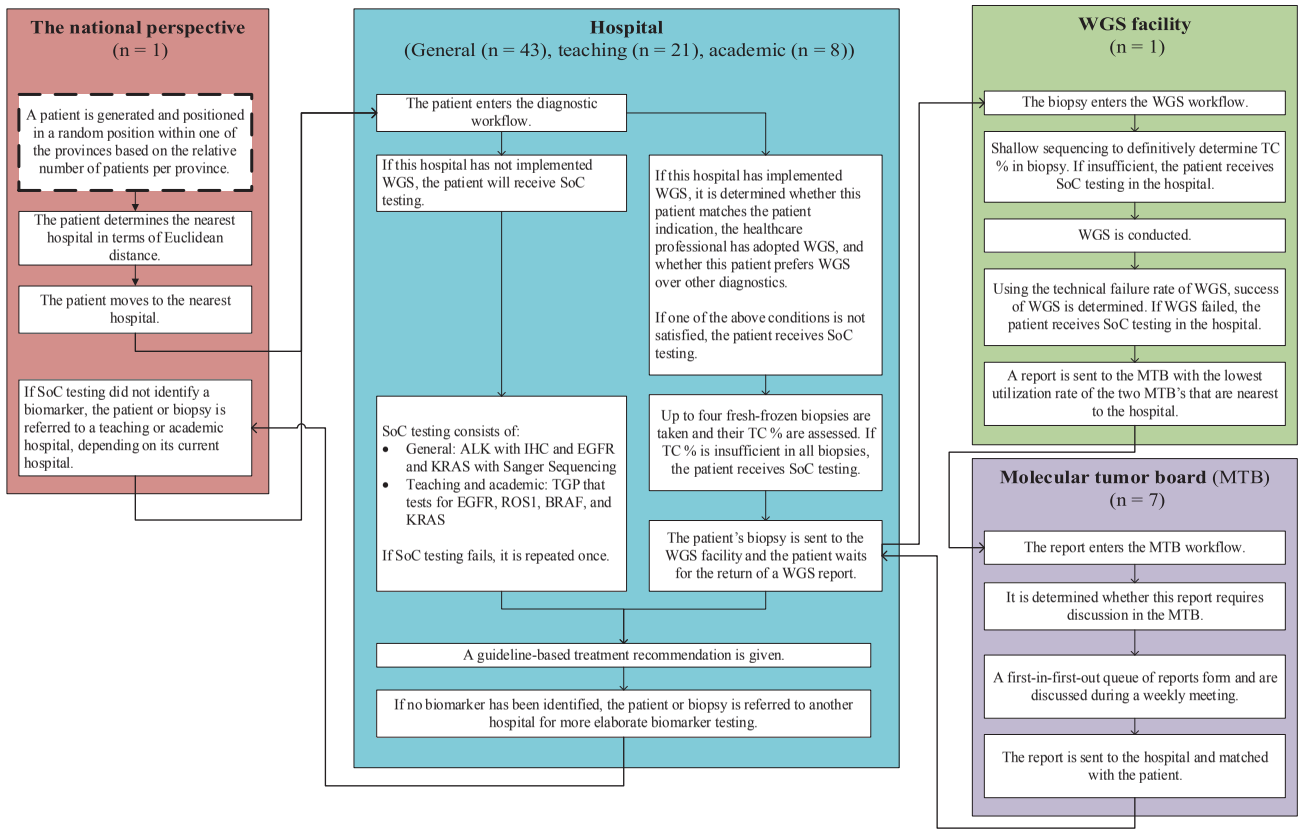

Figure 1. Schematic representation of the model structure, adapted from [11]. SoC, Standard of Care; WGS, Whole Genome Sequencing; IHC, immunohistochemistry; TGP, targeted gene panel; TC, tumor cell; MTB, molecular tumor board. The flow of the figure starts at the box with the dashed outline in the national perspective.

The implementation scenarios vary across three dimensions: the patients for whom WGS is used, the type of hospitals offering WGS, and the position of WGS in the biomarker test strategy. In scenarios that state that only academic hospital services use WGS, only patients that are receiving diagnostics in one of the academic hospitals can receive WGS, and patients who are receiving diagnostics in either a teaching or general hospital will only be able to receive SOC, after which they may be referred to an academic hospital if necessary.

Table 1. Characteristics of the implementation scenarios as well as the current situation (base case). IHC, immunohistochemistry; PD-L1, programmed death-ligand 1.

Dimension	Base case	Expected use of WGS		
		Short term (<2 years)	**Long term (Neutral) (5 years)**	**Long term (Progressive) (5 years)**
Patient indication	Only SoC is used for all patients	All stage IV NSCLC patients receive WGS (n = 5313 annually [15])	All stage III and IV NSCLC patients (n = 7550 annually [15])	All stage I-IV lung cancer patients receive WGS (n = 9974 annually [14])
Hospital services using WGS	WGS is used in none of the hospitals	Only academic hospitals and not teaching or general hospitals		Academic, teaching, and general hospitals
Position WGS in test strategy	Only SOC diagnostics are used	WGS after an IHC test for PD-L1	WGS after an NGS panel and IHC test for PD-L1	WGS upfront in all patients

The cost of consumables make up the majority of the total cost of WGS at 2187.20 euro of a total of 2925.25 euro per patient [16]. Suppliers may be able to give discounts when conducting WGS at scale. To illustrate the effects of these potential discounts, we also simulated the base case and the scenarios using a reduced cost of WGS, in which the cost of consumables was decreased by 50%. This reduction in the cost of consumables reduced the cost of WGS to 1831.65 euro per patient.

2.3.1 Outcomes

The outcomes of interest are the time-to-treatment, costs per patient for biomarker testing, total annual diagnostic cost, and the aggregate demand for WGS. The time-to-treatment is defined as the time in days from initiating the first biomarker test until the start of treatment. The aggregate demand for WGS is split into the number of biopsies that enter the WGS workflow and the number of WGS reports that require a clinical interpretation in MTBs. The average annual diagnostic cost is the sum of the costs for all patients across all hospitals, divided by the number of years in simulation time.

Outcomes are stratified by patient subgroups: patients for whom WGS was not initiated, patients for whom WGS was successfully completed, and patients for whom WGS was initiated but not successfully completed. Not being able to complete WGS successfully can be due to not meeting the tumor percentage requirements or due to technical failures. Not initiating WGS can be due to not matching the patient indication, receiving only SOC as WGS was not used in that specific hospital, patient preferences, or due to a healthcare professional that has not adopted WGS. If WGS was not initiated for patients, they received SOC diagnostics.

2.4 Analysis

For the base case and each scenario, the simulation model was run 1000 times to quantify the stochastic uncertainty in the outcomes [17]. Each simulation ran for 2500 days, but the generation of new patients halted on day 2000 to ensure that enough patients were simulated while also giving all patients opportunity to flow through the model. The simulated patient-level outcomes accumulated by patients generated between 500 and 2000 days were used in the analysis. The data analysis and visualization was conducted using R software version 4.0.3 [18].

3. Results

3.1 Time-to-treatment

Figure 2 shows the distribution of the time-to-treatment for patients in each scenario. Comparing scenario 'long term (progressive)' with the other scenarios, figure 2 shows that the mean time to treatment is shorter for patients in scenario 'long term (progressive)' compared with the other scenarios (base case: 30 days, short term: 43 days, long term (neutral): 46 days, long term (progressive): 20 days). This is because biopsies of patients are not referred to another hospital if WGS was initiated, as there is no superior test available in other hospitals. In scenario 'long term (progressive)' all patients are eligible for WGS, but WGS is not initiated for all patients, as we assumed that 90% of healthcare professionals has adopted WGS and 90% of patients prefer WGS over other diagnostics. Moreover, biopsies of patients for whom WGS was not initiated may still be referred if SOC testing identified no actionable biomarker.

To explain the peaks in the figure, looking at scenario 'short term', the first peak at 20 days for the subgroup of patients for whom WGS was not initiated, represents a group of patients for whom their biopsy was not referred to another hospital as an actionable biomarker was identified. The second peak at 40 days represents a group of patients for whom their biopsy was referred once either to a teaching or academic

hospital. The remainder of patients with a time-to-treatment beyond 50 days are patients for whom their biopsy was sent to two other hospitals, as SOC testing in the general and teaching hospital were unable to identify an actionable target, and thus, these biopsies were referred finally to an academic hospital. Additionally, if the initial attempt of SOC testing fails, SOC testing is repeated once, which increases the time-to-treatment.

3.2 Cost per patient

The mean cost per patient was 621 euros in the base case, 1444 euros in scenario 'short term', 1495 euros in scenario 'long term (neutral)', and 1930 euros in scenario 'long term (progressive)'. The mean cost per patient for patients for whom WGS was successfully conducted in scenario 'long term (progressive)' is substantially lower compared to the same subgroup in other scenarios (3595 euros in scenario 'short term', 3877 euros in scenario 'long term (neutral)', 2951 euro in scenario 'long term (progressive)'. In scenario 'long term (progressive)', this patient subgroup only receives WGS and no prior SOC diagnostics.

The multiple peaks that are displayed in Figure 3 are caused by the different diagnostic trajectories that patients traversed in the simulation model. As the definition of SOC testing varies between hospital types, so do the costs that SOC testing incurs. This means that it matters to which hospital type a patient first presents themselves. Moreover, as biopsies of patients may be referred, they incur costs in multiple hospitals. Additionally, patients may receive SOC or WGS, or both, leading to differences in costs between patients. Furthermore, SOC may have a technical failure, in case which SOC is repeated once, and thus, costs for SOC are counted twice. Likewise, not all biopsies have a high enough tumor cell percentage to be used for WGS, which means that only the costs for shallow sequencing are included, which is 25% of the total costs for WGS.

The total annual diagnostic cost, averaged over all simulation runs, is 4.2 million euros (SD: 54,000 euros) in the base-case, 9.7 million euros (SD: 96,000 euros) for scenario 'short term', 14.3 million euros (SD: 119,000 euros) for scenario 'long term (neutral)', and 24.5 million euros (SD: 148,000 euros) for scenario 'long term (progressive)'.

3.3 Discounted cost of consumables for WGS

If the cost of consumables is discounted by 50%, the cost of WGS would fall to 1831.65 euros. Figure S1 in supplementary file 1 shows that the mean cost per patient in scenario 'long term (progressive)' at 1258 euros is approximately equal to the mean cost per patient of scenario 'long term (neutral)' at 1236 euros, in which the use of and

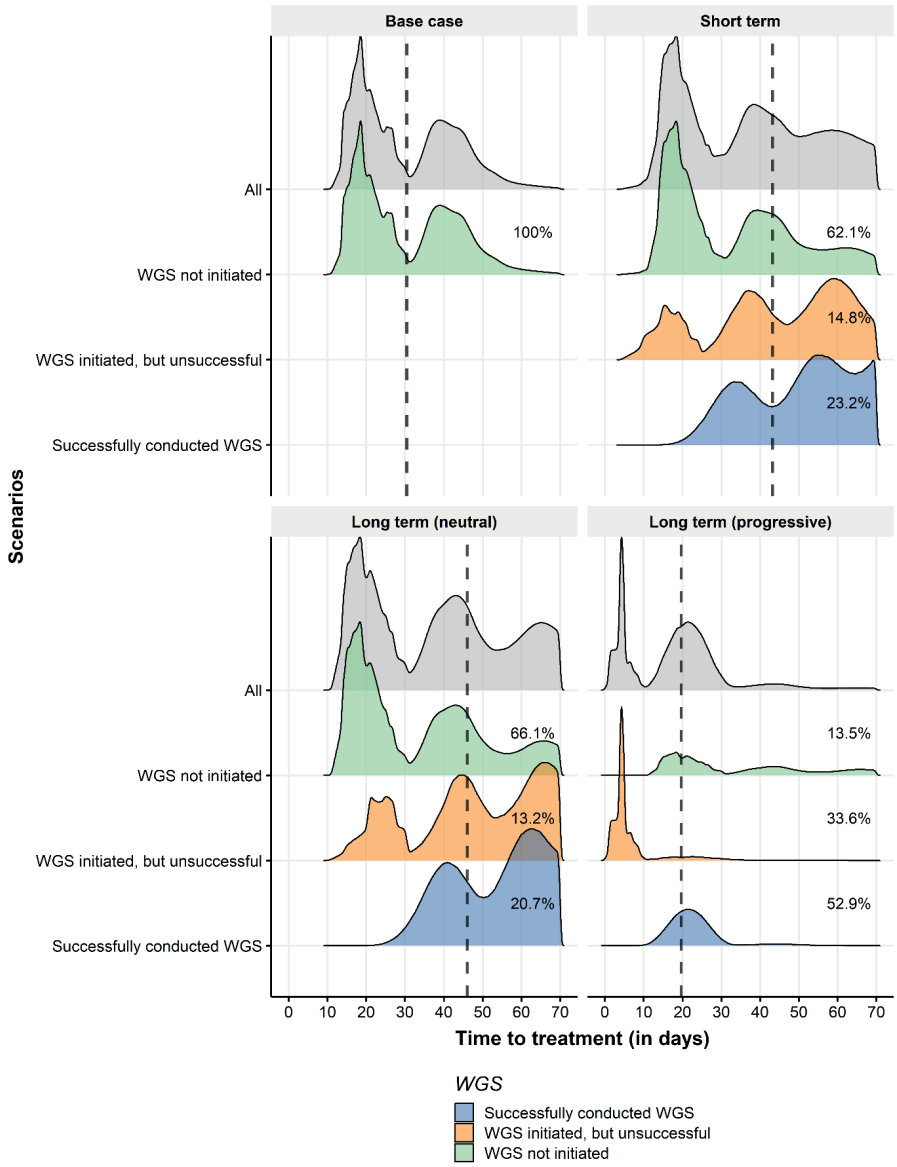

Figure 2. Distribution of the time-to-treatment for the base case and three scenarios. Subgroups reflect patients for whom WGS was not initiated (green), WGS was initiated but not completed successfully (orange), and WGS was successfully conducted (blue). Grey density curves reflect all these subgroups combined. The dashed line illustrates the mean time-to-treatment in each scenario across all subgroups. The percentages shown for each subgroup represent the size of each subgroup. The area under the density curves for each subgroup is reflective of the percentage of patients in each subgroup for each scenario. Patients who did not conclude their diagnostic pathway are not included in this figure.

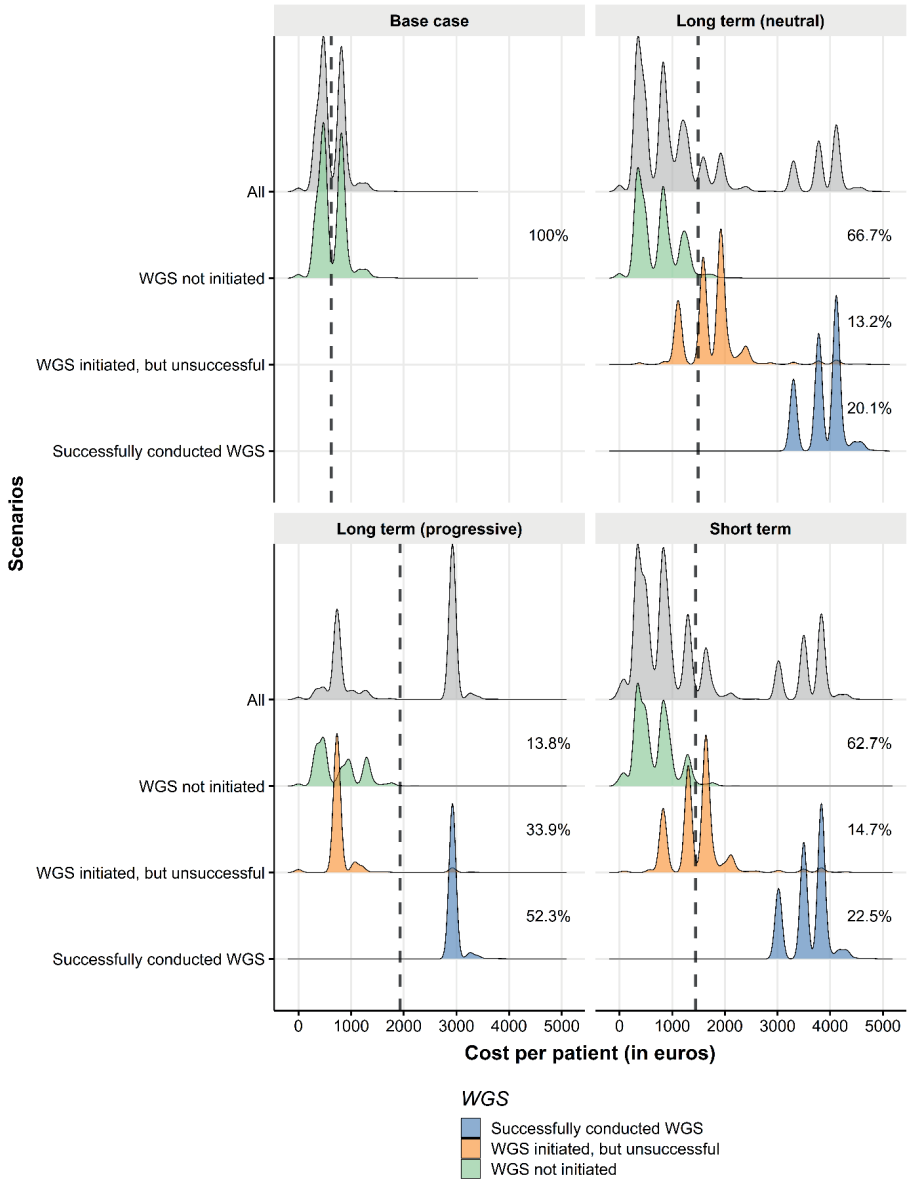

Figure 3. Distribution of the cost per patient for the base case and three scenarios. Subgroups reflect patient groups for whom WGS was not initiated (green), WGS was initiated but not completed successfully (orange), and WGS was successfully conducted (blue). Grey density curves reflect are all these subgroups combined. The dashed line illustrates the mean cost per patient in each scenario across all subgroups. The percentages shown for each subgroup represent the size of each subgroup. The area under the density curves for each subgroup is reflective of the percentage of patients in each subgroup for each scenario.

access to WGS is more limited. Compared to Figure 3 which uses the discounted cost of WGS, Figure S1 shows that the cost distribution for all subgroups for whom WGS was initiated is shifted to the left because of the lower cost of WGS. While scenario 'long term (progressive)' still has the highest mean cost per patient at 1258 euro per patient, this is below the mean cost per patient in scenarios 'short term', 'long term (neutral)', and 'long term (progressive)' shown in Figure 3 which uses the unreduced cost of WGS.

Using the reduced cost of WGS, the total annual diagnostic cost is 4.2 million euros (SD: 54,000 euros) in the base case, 7.8 million euros (SD: 73,000 euros) for scenario 'short term', 11.9 million euros (SD: 88,000 euros) for scenario 'long term (neutral)', and 15.9 million euros (SD: 100,000 euros) for scenario 'long term (progressive)'.

3.4 Aggregate demand

Table 2 lists for each scenario the annual number of biopsies that were sent to the WGS facility for sequencing, the annual number of biopsies that passed quality control, and the annual number of successfully sequenced biopsies. Table 2 also shows the total number of reports that were sent to and discussed in MTBs, as well as the average number of reports received per MTB, as some MTBs receive more reports than other MTBs.

Table 2. The aggregate demand (number of biopsies processed) for WGS for each scenario. Outcomes are averaged across simulation runs.

Scenario	Biopsies sent to WGS facility per year Mean (± SD)	Biopsies passed quality control per year Mean (± SD)	Biopsies successfully sequenced per year Mean (± SD)	Total no. of. reports received by all MTBs per year Mean (± SD)	Reports received per MTB per year Mean (± SD)
Base case	0	0	0	0	0
Short term	1773 (± 37)	1688 (± 36)	1647 (± 35)	1647 (± 35)	235 (± 61)
Long term (neutral)	2255 (± 47)	2147 (± 45)	2094 (± 44)	2092 (± 45)	299 (± 74)
Long term (progressive)	7549 (± 43)	7194 (± 43)	7040 (± 43)	7044 (± 43)	1006 (± 351)

4. Discussion

In this study, we investigated how the cost per patient and time-to-treatment is affected by the nationwide implementation of WGS as a cancer diagnostic and how these outcomes differ among patient subgroups. Additionally, we estimated the aggregate demand for sequencing and analytic capacity with the respect to WGS. When WGS is used upfront for all stage I-IV lung cancer patients, the mean cost per patient (1930 euros) and total annual diagnostic costs (24.5 million euros) were highest while the mean time-to-treatment (20 days) was lowest, compared to the other scenarios. Also, the aggregate demand for WGS was highest when WGS was used upfront for all patients, because of the increased access to WGS and large patient indication. It should be noted that any decision on the use of WGS in a particular setting depends on the clinical utility or need.

Our results show that using an NGS panel prior to WGS makes little difference for the cost per patient and time-to-treatment. Scenario 'short term' only uses a PD-L1 test prior to WGS, scenario 'long term (neutral)' uses both a PD-L1 test and an NGS panel prior to WGS. Our simulation results show that including a PD-L1 test and NGS panel prior to WGS increases the time-to-treatment by three days at similar costs per patient. Therefore, based on our results, using both an NGS panel and WGS in sequence does not seem to efficient use of resources when considering the time-to-treatment and testing cost per patient.

The results indicate there is a tradeoff between costs and time-to-treatment across implementation scenarios. For example, the cost per patient and total annual diagnostic costs are lowest in the base case where WGS is not used at all, while the mean time-to-treatment is 10 days longer compared to a scenario where all patients are receiving upfront WGS, which has the shortest mean time-to-treatment and highest cost per patient and total annual diagnostic costs. On the one hand, the mean cost per patient for the subgroups for whom WGS was successfully conducted is substantially higher than for other patients. On the other hand, conducting WGS upfront in all patients such as in scenario 'long term (progressive)' means that biopsies of patients are no longer referred to another hospital as no other hospital has a more extensive diagnostic test available.

From an organizational perspective, upfront testing for all patients may also have other benefits, as diagnostic workflows can be simplified through the substitution of current SOC tests. Recently, it has been shown that conducting WGS once is sufficient for almost all patients to identify SOC biomarkers [19]. Besides consequences for the cost-effectiveness of WGS, this also means that the amount of biomarker tests needed

if treatment progression or resistance is detected, is reduced for patients for whom WGS was already conducted. In effect, this increases the degree of substitution that WGS brings and further helps to simplify the diagnostic pathway. This also means that aggregated across multiple treatment lines, the testing costs with WGS upfront will become more favorable, relative to SOC testing costs, than reported here.

Conducting WGS at a higher volume may make it possible to achieve a lower cost per patient, by increasing the utilization rate of sequencing devices [20] and by receiving a volume discount on certain cost drivers of WGS. The likelihood of obtaining and the magnitude of a volume discount is partly dependent on the demand for WGS. It is therefore more likely that this discount can be obtained when the patient indication is largest, such as in the scenario in which WGS used upfront for all lung cancer patients and is less likely when the demand is more limited such as in the other scenarios.

In an additional analysis, we applied a 50% discount on the cost on consumables. This led to a mean cost per patient for scenario 'long term (progressive)' of 1258 euro (Figure S1), down from a mean cost per patient of 1930 euro (Figure 3). This cost of 1258 euro per patient is lower than the mean cost per patient in all scenarios when the original cost of WGS was used. Although a 50% discount is substantial, and may not (immediately) be possible, having a higher demand for WGS leads to an improved bargaining position with suppliers to receive a high volume discount. Thus, conducting WGS upfront in all patients may initially lead to a higher cost per patient and total annual diagnostic costs. However, in the end it may prove to be the approach with the shortest time-to-treatment and most inexpensive of all three implementation scenarios if a substantial volume discount is obtained.

On a more cautionary note, the time-to-treatment of 20 days that may be attained by conducting WGS upfront for all patients is only possible if enough sequencing and analytic capacity is available to meet WGS demand (Table 2). Otherwise, insufficient capacity may cause long delays in the diagnostic pathway to the point that patients may not wait for WGS results but rather start with a suboptimal treatment. Implementation and infrastructure building strategies can help to prevent such bottlenecks by deliberately focusing on genomic workforce education, which has been recognized widely as important for an optimal clinical translation of genomic data [21,22]. Additionally, putting in place infrastructure and tools to improve the efficiency of MTB's, such as the use of clinical decision support systems is underway [23].

It is unlikely that WGS will fully and completely substitute current SOC diagnostics, considering that currently WGS cannot be successfully conducted for 28% of biopsies [24]. This is primarily due to not meeting the tumor cell percentage requirements. Thus, it is likely that SOC biomarker tests, and the corresponding infrastructure and logistics, will need to remain available. These can serve as alternatives in cases where WGS cannot be completed successfully.

To our knowledge, this study is the first systems modeling approach to implementing genomics in healthcare. The main strength of this study is that it quantifies the consequences of multiple implementation scenarios, addressing key uncertainties in the potential future use of WGS, while adopting a whole-systems perspective. Hence, this study is able to go beyond mentioning the cost per patient in a single institute by estimating the time-to-treatment along the entire diagnostic pathway and the total diagnostic costs associated with each scenario. Combined with the estimates for aggregate demand, these outcomes can inform implementation and infrastructure building strategies to prepare the healthcare delivery system for increased use of WGS in oncology. And thus, our results have additional relevance for policy, which is not captured in other studies.

While a systems approach has several strengths, this study also has some limitations. First, the simulation is limited to the diagnostic pathway. Therefore, the consequences of the potentially improved treatment selection and the costs of treatments have not been included and therefore, the results are likely underestimations of the true societal benefit. It is likely that WGS has the potential to improve treatment selection by more accurately predicting which treatment will work best and by helping to prevent potentially ineffective treatment. Hence, it is plausible that increased use of WGS will indirectly lead to patient benefit.

The second limitation of this study is that the results cannot be directly generalized to other tumor streams. We chose to focus only on NSCLC as including other cancer types would lead to increased model complexity due to differences in patient populations and diagnostic pathways. However, NSCLC is a relevant case study as it can be used to illustrate the substitution effects of WGS and has a high incidence. Consequently, how WGS is used for this cancer type can substantially affect the total demand for WGS across all cancer types.

Third, differences in diagnostic yield across biomarker tests were not incorporated, and thus, the study implicitly assumes equal diagnostic yield across all tests. Incorporating differences in diagnostic yield could potentially lead to increased subgroup differences.

There are multiple interesting avenues for future research. A further study could investigate which scenario would be most desirable, creating a target for implementation and infrastructure building strategies. Additionally, it needs to be determined which actions are required to realize that scenario.

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Author contributions

Conceptualization: M.V, V.R, H.K, W.H, M.IJ; Writing-original draft: M.V.; Formal analysis: M.V.; Visualization: M.V.; Writing-review & editing: M.V, V.R, H.K, W.H, M.IJ; Supervision: V.R, H.K, W.H, M.IJ

Ethics Declaration

The need for ethics approval is waived, as the study does not concern medical scientific research and does not include human subjects.[24]

Conflicts of Interest

Dr. van Harten and Dr. Retèl have both received non-restricted research grants from Agendia B.V. and Novartis. All other authors have no conflicts of interest to disclose.

Supplementary information

Supplementary file 1.

Figure S1. Distribution of the cost per patient for the base case and three scenarios, using the cost of WGS that reflects the discounted cost of consumables.

References

[1] Z. Stark, L. Dolman, T.A. Manolio, B. Ozenberger, S.L. Hill, M.J. Caulfied, Y. Levy, D. Glazer, J. Wilson, M. Lawler, T. Boughtwood, J. Braithwaite, P. Goodhand, E. Birney, K.N. North, Integrating Genomics into Healthcare: A Global Responsibility, Am. J. Hum. Genet. 104 (2019) 13–20. https://doi.org/10.1016/j.ajhg.2018.11.014.

[2] K.A. Phillips, M.P. Douglas, D.A. Marshall, Expanding Use of Clinical Genome Sequencing and the Need for More Data on Implementation, JAMA - J. Am. Med. Assoc. 324 (2020) 2029–2030. https://doi.org/10.1001/jama.2020.19933.

[3] E.J. Duncavage, M.C. Schroeder, M. O'Laughlin, R. Wilson, S. MacMillan, A. Bohannon, S. Kruchowski, J. Garza, F. Du, A.E.O. Hughes, J. Robinson, E. Hughes, S.E. Heath, J.D. Baty, J. Neidich, M.J. Christopher, M.A. Jacoby, G.L. Uy, R.S. Fulton, C.A. Miller, J.E. Payton, D.C. Link, M.J. Walter, P. Westervelt, J.F. DiPersio, T.J. Ley, D.H. Spencer, Genome Sequencing as an Alternative to Cytogenetic Analysis in Myeloid Cancers., N. Engl. J. Med. 384 (2021) 924–935. https://doi.org/10.1056/NEJMoa2024534.

[4] R. Rosenquist, E. Cuppen, R. Buettner, C. Caldas, H. Dreau, O. Elemento, G. Frederix, S. Grimmond, T. Haferlach, V. Jobanputra, M. Meggendorfer, C.G. Mullighan, S. Wordsworth, A. Schuh, Clinical utility of whole-genome sequencing in precision oncology, Semin. Cancer Biol. (2021). https://doi.org/10.1016/j.semcancer.2021.06.018.

[5] K.G. Samsom, L.J.W. Bosch, L.J. Schipper, P. Roepman, E. de Bruijn, L.R. Hoes, I. Riethorst, L. Schoenmaker, L.E. van der Kolk, V.P. Retèl, G.W.J. Frederix, T.E. Buffart, J.J.M. van der Hoeven, E.E. Voest, E. Cuppen, K. Monkhorst, G.A. Meijer, Study protocol: Whole genome sequencing Implementation in standard Diagnostics for Every cancer patient (WIDE), BMC Med. Genomics. 13 (2020) 1–7. https://doi.org/10.1186/s12920-020-00814-w.

[6] M. van de Ven, H. Koffijberg, V. Retèl, K. Monkhorst, E. Smit, W. van Harten, M. IJzerman, Real-World Utilization of Biomarker Testing for Patients with Advanced Non–Small Cell Lung Cancer in a Tertiary Referral Center and Referring Hospitals, J. Mol. Diagnostics. 23 (2021) 484–494. https://doi.org/10.1016/j.jmoldx.2021.01.004.

[7] S. Kato, K.H. Kim, H.J. Lim, A. Boichard, M. Nikanjam, E. Weihe, D.J. Kuo, R.N. Eskander, A. Goodman, N. Galanina, P.T. Fanta, R.B. Schwab, R. Shatsky, S.C. Plaxe, A. Sharabi, E. Stites, J.J. Adashek, R. Okamura, S. Lee, S.M. Lippman, J.K. Sicklick, R. Kurzrock, Real-world data from a molecular tumor board demonstrates improved outcomes with a precision N-of-One strategy, Nat. Commun. 11 (2020) 1–9. https://doi.org/10.1038/s41467-020-18613-3.

[8] B. Koopman, A.J. van der Wekken, A. ter Elst, T.J.N. Hiltermann, J.F. Vilacha, M.R. Groves, A. van den Berg, B.I. Hiddinga, L.B.M. Hijmering-Kappelle, J.A. Stigt, W. Timens, H.J.M. Groen, E. Schuuring, L.C. van Kempen, Relevance and Effectiveness of Molecular Tumor Board Recommendations for Patients With Non–Small-Cell Lung Cancer With Rare or Complex Mutational Profiles, JCO Precis. Oncol. (2020) 393–410. https://doi.org/10.1200/po.20.00008.

[9] D.A. Marshall, L.R. Grazziotin, D.A. Regier, S. Wordsworth, J. Buchanan, K. Phillips, M. Ijzerman, Addressing Challenges of Economic Evaluation in Precision Medicine Using Dynamic Simulation Modeling, Value Heal. (2020) 1–8. https://doi.org/10.1016/j.jval.2020.01.016.

[10] K. Degeling, H. Koffijberg, M.J. IJzerman, A systematic review and checklist presenting the main challenges for health economic modeling in personalized medicine: towards implementing patient-level models, Expert Rev. Pharmacoeconomics Outcomes Res. 17 (2017) 17–25. https://doi.org/10.1080/14737167.2017.1273110.

[11] M. van de Ven, M. IJzerman, V. Retèl, W. Van Harten, H. Koffijberg, Developing a dynamic simulation model to support the nationwide implementation of Whole Genome Sequencing in lung cancer, (2021). Manuscript submitted for publication.

[12] J.K. Sabari, F. Santini, I. Bergagnini, W.V. Lai, K.C. Arbour, A. Drilon, Changing the Therapeutic Landscape in Non-small Cell Lung Cancers: the Evolution of Comprehensive Molecular Profiling Improves Access to Therapy, Curr. Oncol. Rep. 19 (2017).

[13] M. van de Ven, M. IJzerman, V. Retèl, W. van Harten, H. Koffijberg, The nationwide implementation of Whole Genome Sequencing in oncoloy in the Netherlands, AnyLogic Cloud. (2021). https://cloud.anylogic.com/model/6f5c67f2-1423-422a-be35-63f0f664cc77?mode=SETTINGS (accessed August 16, 2021).

[14] Netherlands Cancer Registry, Incidence, Lung/bronchus | Non small-cell lung carcinoma | Small-cell lung carcinoma | Other/unspecified lung cancer, (2021). https://iknl.nl/nkr-cijfers?fs%7Cepidemiologie_id=506&fs%7Ctumor_id=200%2C202&fs%7Cregio_id=530&fs%7Cperiode_id=543%2C542%2C541&fs%7Cgeslacht_id=622&fs%7Cleeftijdsgroep_id=655&fs%7Cjaren_na_diagnose_id=665&fs%7Ceenheid_id=681&cs%7Ctype=line&cs%7CxAxis=per (accessed September 24, 2021).

[15] M. van de Ven, V.P. Retèl, H. Koffijberg, W.H. van Harten, M.J. IJzerman, Variation in the time to treatment for stage III and IV non-small cell lung cancer patients for hospitals in the Netherlands, Lung Cancer. 134 (2019) 34–41.

[16] C.T.B. Pasmans, B.B.J. Tops, E.M.P. Steeghs, V.M.H. Coupé, K. Grünberg, E.K. de Jong, E.M.D. Schuuring, S.M. Willems, M.J. l. Ligtenberg, V.P. Retèl, H. van Snellenberg, E. de Bruijn, E. Cuppen, G.W.J. Frederix, Micro-costing diagnostics in oncology: from single-gene testing to whole- genome sequencing, Expert Rev. Pharmacoeconomics Outcomes Res. 21 (2021) 413–414. https://doi.org/10.1080/14737167.2021.1917385.

[17] A.H. Briggs, M.C. Weinstein, E.A.L. Fenwick, J. Karnon, M.J. Sculpher, A.D. Paltiel, Model parameter estimation and uncertainty analysis: A report of the ISPOR-SMDM modeling good research practices task force working group-6, Med. Decis. Mak. 32 (2012) 722–732. https://doi.org/10.1177/0272989X12458348.

[18] R Core Team, R: A language and environment for statistical computing, (2021).

[19] J. van de Haar, L.R. Hoes, P. Roepman, M.P. Lolkema, H.M.W. Verheul, H. Gelderblom, A.J. de Langen, E.F. Smit, E. Cuppen, L.F.A. Wessels, E.E. Voest, Limited evolution of the actionable metastatic cancer genome under therapeutic pressure, Nat. Med. (2021). https://doi.org/10.1038/s41591-021-01448-w.

[20] K. Schwarze, J. Buchanan, J.M. Fermont, H. Dreau, M.W. Tilley, J.M. Taylor, P. Antoniou, S.J.L. Knight, C. Camps, M.M. Pentony, E.M. Kvikstad, S. Harris, N. Popitsch, A.T. Pagnamenta, A. Schuh, J.C. Taylor, S. Wordsworth, The complete costs of genome sequencing: a microcosting study in cancer and rare diseases from a single center in the United Kingdom, Genet. Med. 22 (2020) 85–94.

[21] I. Slade, D.N. Subramanian, H. Burton, Genomics education for medical professionals - the current UK landscape, Clin. Med. (Northfield. Il). 16 (2016) 347–352.

[22] B.L. Burns, G.A. Bilkey, E.P. Coles, F.L. Bowman, J.P. Beilby, N.S. Pachter, G. Baynam, H.J.S. Dawkins, T.S. Weeramanthri, K.J. Nowak, Healthcare system priorities for successful integration of genomics: An Australian focus, Front. Public Heal. 7 (2019) 1–14. https://doi.org/10.3389/fpubh.2019.00041.

[23] D. Tamborero, R. Dienstmann, M.H. Rachid, J. Boekel, R. Baird, I. Braña, L. De Petris, J. Yachnin, C. Massard, F.L. Opdam, R. Schlenk, C. Vernieri, E. Garralda, M. Masucci, X. Villalobos, E. Chavarria, S. Anand, A. Azaro, D. Baars, S. Bajalica-Lagercrantz, J. Balmaña, J. Bergh, M. Bierkens, L. Blomqvist, G.J. Doherty, A. Forest, V. Fornerone, I.G. Funingana, P. Gabaldi, J. Hartman, P. Horak, C. Karlsson, M. Kasanicki, S. Kreutzfeldt, R. Lewensohn, J. Lindberg, C. Lopez, A. Lundqvist, P. Martin-Romano, J.E. Martin, G. Meijer, S. Muñoz, M.N. Camus, C. Nicotra, P. Nuciforo, P. Oberrauch, P. Östling, A. Piris-Giménez, E. Provenzano, E. Rouleau, J. Rowell, O. Saavedra, I.S. Valdivia, G. Scoazec, K. Seamon, M. Tischkowitz, L. van der Kolk, R. van der Noll, D. Vis, A. Vivancos, C. von Gertten, A. Wennborg, L. Wessels, V. Wirta, J. Wolfart, F. Calvo, S. Fröhling, A. Eggermont, G. Apolone, E.E. Voest, C. Caldas, J. Tabernero, I. Ernberg, J. Rodon, J. Lehtiö, Support systems to guide clinical decision-making in precision oncology: The Cancer Core Europe Molecular Tumor Board Portal, Nat. Med. 26 (2020) 992–994. https://doi.org/10.1038/s41591-020-0969-2.

[24] K. Monkhorst, K. Samsom, L. Schipper, P. Roepman, L. Bosch, E. de Bruijn, L.R. Hoes, I. Riethorst, L. Schoenmaker, L. van der Kolk, T. Buffart, K. van der Hoeven, E.E. Voest, E. Cuppen, G. Meijer, Validation of whole genome sequencing in routine clinical practice, ESMO Annu. Meet. 31 (2020) 1189O. https://doi.org/10.1016/j.annonc.2020.08.083.

Supplementary file 1

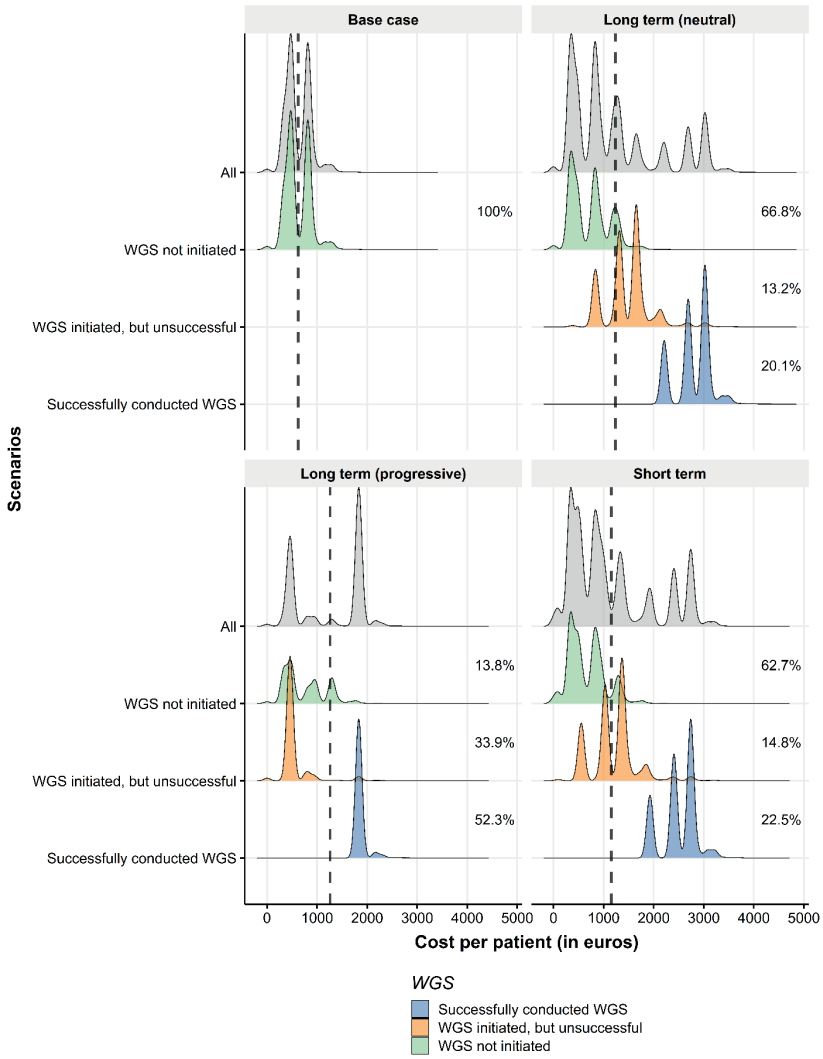

Figure S1. Distribution of the cost per patient for the base case and three scenarios, using the cost of WGS that reflects the discounted cost of consumables. Subgroups reflect patient groups for whom WGS was not initiated (green), WGS was initiated but not completed successfully (orange), and WGS was successfully conducted (blue). Grey density curves are all these subgroups combined. The dashed line illustrates the mean cost per patient in each scenario across all subgroups: 621 euro (base case), 1155 euro (short term), 1236 euro (long term (neutral)), 1258 euro (long term (progressive)). The area under each density curve is reflective of the percentage of patients in each subgroup.

7

Chapter 8

General discussion

1.1 Background

Lung cancer is known as one of the most lethal cancers, particularly due to the late stage of detection [1]. With new systemic targeted treatments, improved survival has been demonstrated. In 2020, a large real-world data analysis indicates survival benefits from targeted treatment [2]. In this personalized approach, selective biomarkers are used to stratify patients into genetic subgroups and to prescribe treatments that are most effective for their genetic subgroup. The role of biomarkers in tumor growth has been especially well-characterized and defined for non-small cell lung cancer (NSCLC).

Currently, multiple diagnostic tests are often required for a clinical diagnosis [3]. However, the increasing number of biomarkers used for treatment selection require a more efficient and comprehensive diagnostic testing strategy, such as large Targeted Gene Panels (TGP). These TGPs are found to be costeffective compared to single-gene tests [4,5]. Alternatively, by substituting all DNA-based biomarker tests, Whole Genome Sequencing (WGS) may offer a further efficiency improvement for the diagnostic pathway of NSCLC. Moreover, to the extent that novel treatments have been developed that make use of the additional diagnostic information that WGS generates, the clinical utility of WGS is potentially higher compared to the standard of care (SOC). Although the clinical use of WGS is emerging, the benefits for society as a whole largely depend on the health economic impact which depends on how, for who, and when WGS is used in clinical practice. In particular, the optimal position of WGS in the diagnostic test strategy must be considered and challenges regarding the organization and interpretation, the handling of secondary findings, and the total cost of the service need to be addressed.

This thesis aims to identify the value of WGS from a systems perspective and under which conditions the value of WGS can be realized. The studies presented contribute to the Technology Assessment for Next Generation Sequencing in Personalized Oncology (TANGO) study [6], a large national project investigating the current and potential future clinical and health economic added value of WGS in oncology. For the TANGO project, we developed a systems model which allows a detailed analysis of the consequences of different implementation scenarios of WGS in the Netherlands. For developing the model, we analyzed the diagnostic pathway of NSCLC patients and the variation therein among patients and hospitals in the Netherlands. Using the model, this thesis provides the required policy insight that justify the implementation of WGS following different scenarios. This thesis is unique as it is the first study in the world that develops and applies a systems model for advanced genomics.

1.2 Practice variation in the use of molecular testing

Clinical practice guidelines are used to optimize patient care by providing evidence-based recommendations. Physicians have the freedom to make ad-hoc decisions to address heterogeneity in their patients' needs and preferences, in local clinical circumstances. This freedom to deviate from clinical practice guidelines leads to practice variation, which is a topic that has been researched frequently both in the Netherlands [7–10] and internationally [11]. Practice variation is not a source of ineffiency per se, as it may be result of comparative advantages of certain healthcare providers [12]. Other sources of practice variation in the diagnostic pathway of NSCLC are differences across hospitals in diagnostic strategies and the availability of diagnostic tests, preferred work routines of clinicians, and differences across hospitals in the adoption rate of evidence-based recommendations. In the diagnostic setting, practice variation is expressed through the use, timing, and order of diagnostic tests.

Given that the provided care is tailored to the patients' needs and characteristics, the use, timing, and order of molecular diagnostics are highly varied among patients with NSCLC in the Netherlands (chapter 4). As we have shown, there is no clearly defined SOC in terms of molecular diagnostics, which complicates the health economic comparison with WGS. Furthermore, for most patients with NSCLC, multiple biomarker tests to identify actionable targets are conducted along their entire diagnostic pathway. In our study which covered the entire biomarker testing history of a cohort of patients who were referred to a comprehensive cancer center, the median number of tests per patient was 7. The primary reason is that multiple tests are conducted since most tests currently used in clinical practice only test a subset of all targets. Our results also indicated that the same test for the same target may be conducted more than once for the same patient. This may be due to failed tests or limited confidence of the referral hospital in the results of a test conducted in the referring hospital, at which point the referral hospital may decide to repeat that test. Additionally, a confirmatory test is sometimes needed when a previous test provided an inconclusive result. The current need for multiple different tests at different moments along the care pathway makes it challenging for hospitals to optimize the use of molecular diagnostics.

Practice variation can lead to variation in access to treatment and thus outcomes among hospitals and patients. While the research in this thesis is focused on the diagnostic setting and we did not investigate the effects of practice variation on final outcomes, we did look closely at intermediate outcomes such as delays in the diagnostic pathway. For example, we found considerable variation among hospitals and among patients in the time-to-treatment of patients with stage IIIB or IV

NSCLC across all hospitals in the Netherlands that treat these patients (chapter 3). Moreover, we found substantial differences in the time-to-treatment, the time from diagnosis until treatment initiation, for similar patients that were treated at different hospitals. Hence, we concluded that patient characteristics were not the cause of this variation. As there is not a legally binding maximum time-to-treatment for cancer patients in the Netherlands, maxima of 30 days [13], 6-9 weeks [14], and 7 weeks [15] were recommended by the Dutch Cancer Society (KWF), SONCOS, and healthcare providers and insurers in the so-called "Treeknormen," respectively. Comparing the median time-to-treatment to the recommended maxima, we also concluded that it is likely that most hospitals have designed their diagnostic pathway in a way that an acceptable time-to-treatment can be attained, even though only 53 hospitals (68%) were able to meet the strictest recommended maximum time-to-treatment.

The fact that not all patients could start treatment within the recommended maxima for time-to-treatment is an important finding as the turnaround time of WGS, currently on average 10 working days [16], remains longer compared to current SOC tests, which can be conducted in several days. At the current turnaround time of WGS, it is challenging for hospitals to accommodate WGS in their diagnostic pathway while making sure that the time-to-treatment does not increase substantially unless diagnostic pathways are changed radically. The difficulty of accommodating WGS in the diagnostic pathway also depends on which tests WGS will substitute, as that might help to streamline or create space in the diagnostic pathway in terms of time-to-treatment. Moreover, as the turnaround time of WGS continues to go down over time, this is likely to be less of an issue in the future.

The degree of substitution that WGS brings influences the efficiency gain that WGS can offer in terms of costs, time-to-treatment, and the complexity of the diagnostic pathway. WGS has the promise to replace all current DNA-based biomarker tests. However, additional alterations in the cancer genome may emerge under the pressure of targeted therapy. Thus, when a patient experiences progression or treatment resistance, additional testing may be required to identify these new alterations in patients. This would harm the efficiency gain that WGS offers. Nevertheless, a recent study has shown that for patients treated with targeted therapy the SOC genomic treatment indications remained unchanged over time, as a consequence of a relatively stable cancer genome [17]. The study also concludes that conducting WGS once was enough to maximize all subsequent treatment opportunities for patients. If WGS is conducted before the first-line treatment, the practice variation in terms of the use, timing, and order of molecular diagnostics observed in chapter 3 would be reduced. In turn, that would likely lead to less complex diagnostic pathways that are more efficient both in delays and costs.

The existence of practice variation also has consequences for the national implementation of WGS. Given that there are differences between hospitals in which diagnostic tests are available and how they are used, the likely consequences are differences in outcomes, comparative value, and costs associated with WGS. For example, academic hospitals may already utilize relatively comprehensive and more expensive TGP and general hospitals typically utilize less comprehensive and less expensive test techniques. Thus, the gap between their current SOC and using WGS is different between hospitals. The variation among hospitals means that tailoring the implementation strategy for WGS to one hospital specifically does not generalize well to all other hospitals as it ignores practice variation. Therefore, acknowledging that practice variation exists and including it in the analysis will improve the accuracy and validity of the analysis.

1.3 Scenario analysis to support the implementation of WGS

In chapter 5 we explored the uncertainty around the potential future developments related to WGS. However, there is also uncertainty around how WGS will be used in practice. In chapter 7, we identified the following three sources of uncertainty related to the use of WGS. First, it is unclear which patient subgroup(s) would benefit most from WGS, given the lack of clearly demonstrated clinical utility. Second, WGS can, in theory, replace all current DNA-based biomarker tests, but it is unknown which tests WGS will actually replace. Practice variation in the use of current diagnostic tests makes this matter more complicated. Third, equal access for patients to WGS is important to realize the potential value of WGS. To achieve equal access, enough hospitals need to offer WGS and WGS-based treatments to their patients, but how access to WGS will be guaranteed or managed is not yet established.

Addressing these uncertainties would enable informed decision-making regarding implementation and infrastructure building strategies. In chapter 7, we simulated three scenarios that vary in the patient indication, the degree of substitution of WGS, and the types of hospitals (academic, teaching, general) that offer WGS to their patients. Hence, this chapter quantified under which conditions the value of WGS can be realized.

Our main finding was that the scenario in which upfront testing with WGS was available for all lung cancer patients in all hospitals was the most expensive scenario we considered, both in terms of cost per patient and total annual diagnostic costs, as WGS is substantially more expensive than other diagnostic tests. However, the simulated patients in this scenario had on average the shortest time-to-treatment as testing upfront with WGS reduces the length of the diagnostic pathway. Specifically, starting with the most comprehensive test maximizes the likelihood of finding an

actionable target as soon as possible, and negates the need to conduct several less comprehensive tests sequentially. Moreover, it also eliminates the need to send biopsies of patients to other hospitals to receive more comprehensive testing given that all hospitals used WGS in this scenario. Reducing the complexity and length of the diagnostic pathway, both within hospitals as well as across hospitals, can be labeled as an unintended consequence of making WGS directly and widely available for patients.

The cost of WGS can decrease when the utilization rate of WGS devices increases [18] or when specific cost drivers decrease [19]. One important cost driver is the cost of consumables, responsible for approximately 70% of the total cost per patient of WGS. To illustrate the effects of conducting WGS at scale, we simulated all scenarios with a cost of WGS that included a 50% discount on consumables. Using WGS for a larger group of patients leads to an improved bargaining position with suppliers, thereby increasing the likelihood that such a volume discount is attained. While using the discounted costs, we found that upfront testing for all lung cancer patients resulted in lower costs per patient compared to the scenarios in which WGS was used as a second or subsequent test.

1.4 Potential stumbling blocks for systems models

Systems models take a holistic or "big picture" view of complex systems [20]. Systems models developed with a focus on health technology assessment are not limited to modeling disease progression; any aspect of the technology or system in which the technology will be used, such as clinical, technical, social, and economic aspects, deemed important (enough) can be included in the model. To date, there are only two studies in the field of health technology assessment (HTA) that use a systems model. One study assessed the value of mobile stroke units while considering the disease and population dynamics, and the organization of care and its economics [21]. Another study analyzed the health economic impact of using a sensor for heart failure telemonitoring, taking into account population dynamics and different levels of technology diffusion [22]. Remaining in the healthcare context, systems models are also valuable for public health challenges [23]. Examples are models for cancer screening [24], preventive medicine [25], and a model to support controlling unreasonable growth of medical expenses in public hospitals in China [26]. The wide scope of systems models should be an attractive trait, yet there are few peer-reviewed articles published on developing or applying systems models in a healthcare-specific context, even though there is some guidance that should help with determining when a systems model is useful [27] and for model selection [28].

There are several reasons why there are so few systems models developed for HTA (chapter 6). First, developing a systems model is not necessary for all health technologies that undergo HTA, as many health technologies are relatively simple. Thus, their implementation and use typically do not require substantial reconfiguration of (parts of the) healthcare system. Moreover, there usually is no incentive (why complex if you can access the market with simpler models) to develop a systems model for reimbursement decisions as HTA agencies provide policy recommendations based foremost on the cost-effectiveness and budget impact of the new health technology. Second, developing a systems model is more complex and time-consuming compared with the analyses that are more frequently conducted for HTA. Because of the, by definition, wider scope of systems models compared to cost-effectiveness analyses, conceptualizing the problem, defining model boundaries, and validating the model with stakeholders requires a larger time investment than traditional health economic models. Finally, the added value of a systems model is not always clear. All models can only be useful to the extent that there is data available to parametrize the model. However, a systems model requires different and additional data to reflect the system's interdependencies, such as referral patterns, and provider heterogeneity. Even if it is deemed worthwhile to create a systems model, in practice the systems model may have little added value if the data to fill the model is lacking.

We also encountered some of these challenges during the development of the systems model (chapter 6). Chapter 6 described the model development process, the model structure, and the inputs that were used to parametrize the model. Our model was designed to inform organizational decisions regarding the use of WGS, we naturally focused on the flow of patients and information among the stakeholders involved. Conceptualizing the model and setting the model boundaries required an understanding of the disease dynamics, WGS, diagnostic pathways, and the changes that WGS may bring to those pathways. Therefore, we have used multiple interactive discussions with stakeholders, before and during model development, to build trust, increase transparency, and ensure our model structure was designed in a way that it could produce informative results.

Another challenge was the degree of detail that needed to be reflected in the model so that the model can support the national implementation of WGS. The degree of detail reflected in the model was partly by design, as we have aimed to match the degree of detail reflected in the model with the sort of decisions the model will inform. For instance, the model omits highly technical details of the sequencing process, as the model will be used for tactical and strategic purposes. Omitting details where possible not only reduces the computational burden of the model, it also makes the model less complex [29] and less difficult to understand and validate by stakeholders.

The degree of detail was also partly constrained by data availability, as real-world evidence databases typically do not register detailed information regarding referral patterns and the use and timing of diagnostic tests. Thus, assumptions had to be made. Nonetheless, the systems model developed in chapter 6 led to a better understanding of the system at hand and could address policy-relevant questions.

Moreover, developing a systems model is a time-consuming task. That is costly in itself, but the fact that it is time-consuming can also have consequences for the potential downstream value of the developed systems model. In fast-evolving fields such as healthcare in general and oncology more specifically, the systems model may be overtaken by the real world and the danger is that the model is outdated before it is finished. This is not necessarily systems model specific but is a consequence of the time investment required for model development. To prevent that the model becomes outdated before it is finished, the model developer needs to be vigilant for important changes or developments that have implications for the model. This may be achieved by staying in close contact with domain experts and discussing the model and exploring potentially impactful changes from within clinical practice. These real-world changes can have consequences for the model structure, input parameters, or implications based on the model outcomes.

On a more technical note, developments in the real world may impose substantial changes to the model structure, even to the extent that a different modeling approach would be better. This 'risk' is more prominent for systems models compared to more conventional health economic models, as those models typically reflect disease progression, which is less likely to change structurally. Using modeling software in which multiple types of models can be developed is one way to prevent a sort of model type lock-in and alleviates the amount of sunk costs that went into the model development process.

1.5 Exploring potential future developments related to WGS

WGS has not yet been widely implemented in oncology as there are uncertainties around the required infrastructure and expertise, costs and reimbursements, and unknown clinical utility. For instance, the number of available therapies that can be prescribed based on information that only WGS can provide may increase over time, thereby increasing the clinical utility of WGS. Additionally, clever decision support systems may be developed, reducing the burden on clinicians, pathologists, clinical biologists, geneticists, and bioinformaticians to provide clinical interpretations of the genetic information that WGS produces.

In chapter 5, we explored the potential future developments that either facilitate or impede the use of WGS as a molecular diagnostic in oncology. By eliciting the belief of a diverse group of national and international experts, we found that the implementation of WGS as a clinical diagnostic in oncology is heavily dependent on the price, clinical utility, and turnaround time. Instead of pooling elicited values of each expert, we pooled the probability distribution of each expert. Therefore, our study not only revealed the uncertainty at the group level but also presented the uncertainty or lack of consensus across the group of experts. We concluded that establishing a clear clinical benefit can also have consequences for other barriers and facilitators. For instance, demonstrating a clinical benefit of WGS for cancer patients can result in a knock-on effect for the reimbursement status of WGS.

Exploring what the potential future developments are for WGS is important as it can lead to a better understanding of what uncertainties are most impactful for the implementation of WGS and it leads to an improved ability to anticipate future changes. Anticipating future changes is crucial for disruptive health technologies such as WGS, as, by definition, these lead to a large shift in how healthcare is provided. Reconfiguring the healthcare system to accommodate the new health technology is often a slow, complex, and expensive process, and undoing the implementation is typically not feasible.

The scenarios drafted in chapter 5 were input for the implementation scenarios that were simulated in chapter 7.

1.6 Remaining challenges and future perspectives

Based on the research in this thesis, it is apparent that simulation modeling can support complex processes such as the national implementation of WGS in oncology. There are, however, several challenges left unanswered and these challenges have enough merit to warrant additional discussion.

The inclusion of real-world evidence and practice variation in the systems model that was developed in this thesis has been a key component of its added value. As discussed earlier, the degree of included practice variation was partly limited by design as we did not want to include unimportant details and partly by data availability. Registry data are often lacking in the amount of details that is included in the data, the lack of coverage of hospitals and patient population, or both. Moreover, data such as referral patterns are not of primary interest for registries and are therefore hardly registered. In addition to data not being registered, in some cases, data are registered but unavailable to researchers as they are deemed business-sensitive information. If we

want to improve the healthcare system and the values of systems models, we need both an improved registration of practice variation as well as easier data access for researchers.

There are also some interesting avenues for future research. Primarily, the systems model was developed with a focus on lung cancer: both the patient population and diagnostic pathways were based on the lung cancer setting. It would be interesting to investigate how feasible it is to tweak the model so that it can include other tumor streams as well. Is it then still possible to have the current level of details, or would the model need to be more generic?

Another interesting open end is a dimension of the value of WGS that is not often discussed, namely the potential of WGS to reduce the downtime of test platforms. Diagnostic tests need to be clinically validated as part of quality control and when new tests are implemented in hospitals. When tests are being validated, they are not available for healthcare. This constrains the resource pool of the hospitals. Given the scope of WGS, it is likely that fewer new tests will be added to the diagnostic strategy which require subsequent clinical validation. This is an interesting advantage that WGS may provide and it would potentially streamline the diagnostic pathway further.

It would also be interesting to compare the outcomes of a constrained with the outcomes of an unconstrained analysis of the implementation of WGS, illuminating the consequences of relaxing the constraints [30]. An example of such an unconstrained analysis could be a cost-effectiveness analysis of WGS [31]. However, the endpoints in this thesis and the cost-effectiveness analysis are substantially different, making the comparison not possible in this case.

1.7 Conclusions

WGS has a large potential to transform the way healthcare is provided. It has become clear that nationally implementing WGS, a complex and disruptive technology, in a rapidly evolving healthcare system is challenging and fraught with uncertainties and that a one-size-fits-all approach is likely suboptimal. By, first exploring current clinical practice, and subsequently investigating how the implementation of WGS would have different consequences across different local circumstances, we have made progress toward a more custom-sized approach and have made inroads towards including the organization of care when health technologies are assessed.

The main method of analysis in this thesis, the systems model, is a simplified reflection of a part of the real-world healthcare system. The healthcare system is constrained, and our analysis aimed to capture that key characteristic by including

practice variation, referral patterns, capacity constraints, and constraints in the access to WGS. In this thesis, we were able to obtain the required evidence on practice variation for NSCLC patients. Combined with the developed systems model, we were able to address the aim of the thesis, which was to identify the value of WGS from a systems perspective and under which conditions the value of WGS can be realized.

Decision-makers are confronted with a dilemma: either (1) implement WGS even though the cost of WGS is higher compared to SOC and the benefit of WGS is not clear, or (2) adopt a wait-and-see tactic during which knowledge gaps can potentially be filled or the cost of WGS may decrease. The first strategy is potentially more expensive if WGS remains to have no additional clinical benefit, but is unlikely to lead to health loss, as WGS is at least on par with current SOC in terms of diagnostic yield. The second strategy is more conservative as no money would be spent on a potentially cost-ineffective technology, but it may potentially lead to health foregone. Even if WGS have additional clinical benefit, the use of WGS may initially be limited, as the healthcare system would not yet be ready to accommodate WGS. In this thesis, we have shown that upfront testing with WGS for all lung cancer patients may be the least expensive approach, if, due to the high patient volume, discounts may be obtained from suppliers. Therefore, if decision-makers accept initially higher costs per patient, they can pave the way to less complex diagnostic pathways, shorter time-to-treatment, and lower costs per patient by using WGS upfront for all lung cancer patients.

Implementing upfront testing with WGS for all lung cancer patients can be organized with various degrees of centralization of care. On one end of the spectrum could all WGS-based care be centralized in academic hospitals, which potentially limits access to care but may have benefits for the quality of care. On the other end of the spectrum could all WGS-based care be given in all hospitals, and while this may be beneficial for patient access, it may have detrimental effects on the quality of care. Instead, an approach in which biopsies for WGS are taken at the local hospital and are tested in one of a few WGS facilities, and if required, patients are referred to specialized hospitals if needed for their care. Regardless of the degree of centralization, the national implementation of WGS requires national coordination to realize the potential value of WGS.

References

[1] Netherlands Cancer Registry, Survival, Non small-cell lung carcinoma, Stage at time of diagnosis, TNM, (2021). https://iknl.nl/nkr-cijfers?fs%7Cepidemiologie_id=507&fs%7Ctumor_id=202&fs%7Coverlevingssoort_id=511&fs%7Cklassificatie_stadium_id=616&fs%7Cstadium_id=659&fs%7Cjaren_na_diagnose_id=665%2C666%2C667%2C668%2C669%2C670%2C671%2C672%2C673%2C674%2C675&cs%7Ctype= (accessed December 19, 2021).

[2] N. Howlader, G. Forjaz, M.J. Mooradian, R. Meza, C.Y. Kong, K.A. Cronin, A.B. Mariotto, D.R. Lowy, E.J. Feuer, The Effect of Advances in Lung-Cancer Treatment on Population Mortality, N. Engl. J. Med. 383 (2020) 640–649. https://doi.org/10.1056/nejmoa1916623.

[3] E.N. Imyanitov, A.G. Iyevleva, E.N. Levchenko, Molecular testing and targeted therapy for non-small cell lung cancer: Current status and perspectives, Crit. Rev. Oncol. Hematol. 157 (2021) 103194. https://doi.org/10.1016/j.critrevonc.2020.103194.

[4] L. Steuten, B. Goulart, N.J. Meropol, D. Pritchard, S.D. Ramsey, Cost Effectiveness of Multigene Panel Sequencing for Patients With Advanced Non–Small-Cell Lung Cancer, JCO Clin. Cancer Informatics. (2019) 1–10. https://doi.org/10.1200/cci.19.00002.

[5] N.A. Pennell, A. Mutebi, Z.-Y. Zhou, M.L. Ricculli, W. Tang, H. Wang, A. Guerin, T. Arnhart, A. Dalal, M. Sasane, K.Y. Wu, K.W. Culver, G.A. Otterson, Economic Impact of Next-Generation Sequencing Versus Single-Gene Testing to Detect Genomic Alterations in Metastatic Non–Small-Cell Lung Cancer Using a Decision Analytic Model, JCO Precis. Oncol. (2019) 1–9. https://doi.org/10.1200/po.18.00356.

[6] Technology Assessment of Next Generation Sequencing in Personalized Oncology - TANGO Project, (2021). https://zenodo.org/communities/tango-wgs/?page=1&size=20 (accessed December 21, 2021).

[7] L. Keikes, M. Koopman, M.M. Stuiver, V. Lemmens, M.G.H. van Oijen, C.J.A. Punt, Practice variation on hospital level in the systemic treatment of metastatic colorectal cancer in the Netherlands: A population-based study., J. Clin. Oncol. 37 (2019) 6612–6612. https://doi.org/10.1200/jco.2019.37.15_suppl.6612.

[8] K. Schreuder, J.H. Maduro, P.E.R. Spronk, N. Bijker, P.M.P. Poortmans, T. van Dalen, H. Struikmans, S. Siesling, Variation in the Use of Boost Irradiation in Breast-Conserving Therapy in the Netherlands: The Effect of a National Guideline and Cofounding Factors, Clin. Oncol. 31 (2019) 250–259. https://doi.org/10.1016/j.clon.2018.11.033.

[9] A.K.E. Elfrink, N.F.M. Kok, L.R. van der Werf, M.F. Krul, E. Marra, M.W.J.M. Wouters, C. Verhoef, K.F.D. Kuhlmann, M. den Dulk, R.J. Swijnenburg, W.W. te Riele, P.B. van den Boezem, W.K.G. Leclercq, D.J. Lips, V.B. Nieuwenhuijs, P.D. Gobardhan, H.H. Hartgrink, C.I. Buis, D.J. Grünhagen, J.M. Klaase, M.T. de Boer, M.G.H. Besselink, C.H.C. Dejong, T.H. van Gulik, J. Hagendoorn, F.J.H. Hoogwater, M.S.L. Liem, I.Q. Molenaar, G.A. Patijn, K. Bosscha, E.J.T. Belt, M. Vermaas, M.F. Gerhards, N.T. van Heek, S.J. Oosterling, H. Torrenga, H.H. Eker, E.C.J. Consten, P. van Duijvendijk, Population-based study on practice variation regarding preoperative systemic chemotherapy in patients with colorectal liver metastases and impact on short-term outcomes, Eur. J. Surg. Oncol. 46 (2020) 1742–1755. https://doi.org/10.1016/j.ejso.2020.03.221.

[10] J. Verstijnen, S. Damude, H.J. Hoekstra, S. Kruijff, A.J. ten Tije, W.J. Louwman, E. Bastiaannet, M.M. Stuiver, Practice variation in Sentinel Lymph Node Biopsy for melanoma patients in different geographical regions in the Netherlands, Surg. Oncol. 26 (2017) 431–437. https://doi.org/10.1016/j.suronc.2017.08.006.

[11] A.N. Corallo, R. Croxford, D.C. Goodman, E.L. Bryan, D. Srivastava, T.A. Stukel, A systematic review of medical practice variation in OECD countries, Health Policy (New. York). 114 (2014) 5–14. https://doi.org/10.1016/j.healthpol.2013.08.002.

[12] A. Chandra, D.O. Staiger, Identifying Sources of Inefficiency in Healthcare, Q. J. Econ. 135 (2020) 785–843. https://doi.org/10.1093/qje/qjz040.

[13] Dutch Cancer Society, Wachttijden [waiting times], (2017). https://www.kanker.nl/algemene-onderwerpen/ zorg-in-het-ziekenhuis/zorg/wachttijden (accessed October 23, 2018).

[14] SONCOS, Multidisciplinaire normering oncologische zorg in Nederland [Multidisciplinary standardization of oncological care in the Netherlands], 2020. https://www.soncos.org/wp-content/uploads/2020/03/SONCOS-normeringsrapport-versie-8-1.pdf.

[15] Nederlandse Zorgautoriteit [Dutch Healthcare Authority], Regeling Wachttijden en wachttijdbemiddeling medisch specialistische zorg - NR/REG-1823 [Regulations on waiting times and waiting time mediation for medical specialist care - NR/REG-1823], (2017). https://puc.overheid.nl/nza/doc/PUC_2034_22/1/ (accessed October 2, 2021).

[16] P. Roepman, E. de Bruijn, S. van Lieshout, L. Schoenmaker, M.C. Boelens, H.J. Dubbink, W.R.R. Geurts-Giele, F.H. Groenendijk, M.M.H. Huibers, M.E.G. Kranendonk, M.G.M. Roemer, K.G. Samsom, M. Steehouwer, W.W.J. de Leng, A. Hoischen, B. Ylstra, K. Monkhorst, J.J.M. van der Hoeven, E. Cuppen, Clinical Validation of Whole Genome Sequencing for Cancer Diagnostics, J. Mol. Diagnostics. 23 (2021) 816–833. https://doi.org/10.1016/j.jmoldx.2021.04.011.

[17] J. van de Haar, L.R. Hoes, P. Roepman, M.P. Lolkema, H.M.W. Verheul, H. Gelderblom, A.J. de Langen, E.F. Smit, E. Cuppen, L.F.A. Wessels, E.E. Voest, Limited evolution of the actionable metastatic cancer genome under therapeutic pressure, Nat. Med. (2021). https://doi.org/10.1038/s41591-021-01448-w.

[18] K.J.M. van Nimwegen, R.A. van Soest, J.A. Veltman, M.R. Nelen, G.J. van der Wilt, L.E.L.M. Vissers, J.P.C. Grutters, Is the $1000 Genome as Near as We Think? A Cost Analysis of Next-Generation Sequencing, Clin. Chem. 62 (2016) 1458–1464. https://doi.org/10.1373/clinchem.2016.258632.

[19] K. Schwarze, J. Buchanan, J.M. Fermont, H. Dreau, M.W. Tilley, J.M. Taylor, P. Antoniou, S.J.L. Knight, C. Camps, M.M. Pentony, E.M. Kvikstad, S. Harris, N. Popitsch, A.T. Pagnamenta, A. Schuh, J.C. Taylor, S. Wordsworth, The complete costs of genome sequencing: a microcosting study in cancer and rare diseases from a single center in the United Kingdom, Genet. Med. 22 (2020) 85–94.

[20] P.L. Mabry, D.H. Olster, G.D. Morgan, D.B. Abrams, Interdisciplinarity and Systems Science to Improve Population Health. A View from the NIH Office of Behavioral and Social Sciences Research, Am. J. Prev. Med. 35 (2008) S211–S224. https://doi.org/10.1016/j.amepre.2008.05.018.

[21] P.L. Kolominsky-Rabas, A. Djanatliev, P. Wahlster, M. Gantner-Bär, B. Hofmann, R. German, M. Sedlmayr, E. Reinhardt, J. Schüttler, C. Kriza, C. Niederländer, H.U. Prokosch, R. Lenz, P. Baumgärtel, O. Schöffski, M. Emmert, F. Meier, A. Aisenbrey, W. Voigt, J. Höllthaler, A. Metzger, M. Miethe, Technology foresight for medical device development through hybrid simulation: The ProHTA Project, Technol. Forecast. Soc. Change. 97 (2015) 105–114. https://doi.org/10.1016/j.techfore.2013.12.005.

[22] P.L. Kolominsky-Rabas, C. Kriza, A. Djanatliev, F. Meier, S. Uffenorde, J. Radeleff, P. Baumgärtel, I. Leb, M. Sedlmayr, S. Gaiser, P.B. Adamson, Health Economic Impact of a Pulmonary Artery Pressure Sensor for Heart Failure Telemonitoring: A Dynamic Simulation, Telemed. e-Health. 22 (2016) tmj.2015.0226.rev. https://doi.org/10.1089/tmj.2015.0226.rev.

[23] H. Rutter, N. Savona, K. Glonti, J. Bibby, S. Cummins, D.T. Finegood, F. Greaves, L. Harper, P. Hawe, L. Moore, M. Petticrew, E. Rehfuess, A. Shiell, J. Thomas, M. White, The need for a complex systems model of evidence for public health, Lancet. 390 (2017) 2602–2604. https://doi.org/10.1016/S0140-6736(17)31267-9.

[24] G. Ruile, A. Djanatliev, C. Kriza, F. Meier, I. Leb, W.A. Kalender, P.L. Kolominsky-Rabas, Screening for breast cancer with Breast-CT in a ProHTA simulation, J. Comp. Eff. Res. 4 (2015) 553–567. https://doi.org/10.2217/cer.15.42.

[25] T.O. Tengs, N.D. Osgood, L.L. Chen, The cost-effectiveness of intensive national school-based anti-tobacco education: Results from the Tobacco Policy Model, Prev. Med. (Baltim). 33 (2001) 558–570. https://doi.org/10.1006/pmed.2001.0922.

[26] W. Yu, X. Liu, F. Zhao, M. Li, L. Zhang, Control of unreasonable growth of medical expenses in public hospitals in Shanghai, China: A multi-agent system model, BMC Health Serv. Res. 20 (2020) 1–16. https://doi.org/10.1186/s12913-020-05309-z.

[27] D.A. Marshall, L. Burgos-Liz, M.J. Ijzerman, N.D. Osgood, W. V. Padula, M.K. Higashi, P.K. Wong, K.S. Pasupathy, W. Crown, Applying dynamic simulation modeling methods in health care delivery research - The SIMULATE checklist: Report of the ISPOR simulation modeling emerging good practices task force, Value Heal. 18 (2015) 5–16. https://doi.org/10.1016/j.jval.2014.12.001.

[28] D.A. Marshall, L. Burgos-Liz, M.J. Ijzerman, W. Crown, W. V. Padula, P.K. Wong, K.S. Pasupathy, M.K. Higashi, N.D. Osgood, Selecting a dynamic simulation modeling method for health care delivery research - Part 2: Report of the ISPOR dynamic simulation modeling emerging good practices task force, Value Heal. 18 (2015) 147–160. https://doi.org/10.1016/j.jval.2015.01.006.

[29] R. Axelrod, Advancing the art of simulation in the social sciences, Complexity. 3 (1997) 16–22. https://doi.org/10.1002/(SICI)1099-0526(199711/12)3:2<16::AID-CPLX4>3.0.CO;2-K.

[30] F.M. Bozzani, A. Vassall, G.B. Gomez, Building resource constraints and feasibility considerations in mathematical models for infectious disease: A systematic literature review, Epidemics. 35 (2021) 100450. https://doi.org/https://doi.org/10.1016/j.epidem.2021.100450.

[31] M.J.H.G. Simons, V.P. Retèl, B.L.T. Ramaekers, R. Butter, J.M. Mankor, M.S. Paats, J.G.J.V. Aerts, Z.A. Mfumbilwa, P. Roepman, V.M.H. Coupé, C.A. Uyl-de Groot, W.H. van Harten, M.A. Joore, Early Cost Effectiveness of Whole-Genome Sequencing as a Clinical Diagnostic Test for Patients with Inoperable Stage IIIB,C/IV Non-squamous Non-small-Cell Lung Cancer, Pharmacoeconomics. 39 (2021) 1429–1442. https://doi.org/10.1007/s40273-021-01073-y.

8

Summary

1.1 Background

In recent years, cancer treatments have been developed that are more effective for specific genetic subgroups of patients. This personalized approach stratifies patients into genetic subgroups based on the presence of biomarkers and prescribes treatments that match their genetic subgroup. This progress particularly has relevance for the largest and very lethal subgroup of lung cancer, non-small cell lung cancer (NSCLC), as the role of biomarkers for treatment selection in NSCLC has rapidly advanced over the last decade. However, the number of available biomarkers and diversity of the available diagnostic test techniques in different hospitals, together with the challenges of efficiently planning the tests lead to a complex and non-uniform diagnostic pathway for patients with advanced NSCLC.

Advances in genomics have increased the demand for more comprehensive testing. Whole Genome Sequencing (WGS) can be used to test all DNA-based biomarkers in one single test, compared to the current standard of care where multiple tests are performed sequentially. WGS is the most comprehensive type of genome sequencing and offers a substantial amount of (additional) diagnostic information. Consequently, the clinical utility of WGS is potentially higher compared to current single and multi-gene tests if novel treatments are available that make use of the additional diagnostic information that WGS generates. Moreover, WGS can replace most, if not all, current molecular diagnostic tests, thereby simplifying and increasing the efficiency of the diagnostic pathway.

While benefits of WGS emerge, the implementation of WGS into healthcare is slowly moving forward. This slow progress is due to the complexity and disruptive nature of WGS as it can replace many of the current molecular diagnostics. This requires consideration of the optimal position of WGS in the diagnostic pathway from a clinical and health economic perspective. It also requires reconfiguration of the healthcare delivery system to maximize its value. Furthermore, a wide range of interrelated factors, such as clinical, technical, social, and economic factors can play a role in realizing the value of WGS. It is, therefore, important that the implementation of WGS is investigated from a systems perspective, which the presence of interdependencies, potentially at multiple levels in the system, and aims to quantify them. Hence, this thesis aimed to identify the value of WGS from a systems perspective and under which conditions the value of WGS can be realized.

1.2 Summary

The studies presented in this thesis were part of the Technology Assessment of Next Generation Sequencing in Personalized Oncology (TANGO) study in which the comparative advantage of WGS compared to the standard of care molecular diagnostics was assessed.

Chapter 2 was an expert review of early technology assessment of the use of WGS in personalized oncology, listing the ongoing national initiatives that aim to implement WGS into routine clinical practice. This chapter also introduced the TANGO study and concluded that wider use of WGS is dependent on various factors such as identification of sufficient actionable targets, evidence on the health benefit of treatments for these targets, organizational factors, Ethical, Legal and Societal Implications, and cost-effectiveness.

Chapter 3 was a population-based study on the variation in time-to-treatment for patients with stage III or IV across all hospitals in the Netherlands using patient-level data. The study showed that time-to-treatment varied substantially between and within hospitals. The time-to-treatment was within range as recommended in current guidelines in the Netherlands. With further advances in molecular diagnostics and precision oncology we expect variation in time-to-treatment to increase and this needs to be considered in designing optimal cancer care delivery.

Chapter 4 investigated the costs, turnaround times, and utilization of biomarker testing for patients with advanced NSCLC based on data from a large tertiary referral site and from the hospitals the patients were referred from. This resulted in a unique real-world cohort of which the entire biomarker-testing history was known. The results indicated substantial variation in test utilization and sequences. Targeted gene panels were most frequently conducted, followed by testing PD-L1 with immunohistochemistry. Typically, most common biomarkers were tested within the first tests, and emerging biomarkers are tested further down the test sequence. At its current cost level, replacing current biomarker testing with WGS would have led to cost savings for only 2% of patients.

Chapter 5 aimed to anticipate potential future developments that may affect the implementation of WGS, by reviewing existing literature, drafting scenarios describing potential future developments, and eliciting probabilities for these scenarios from a diverse group of experts. Price, clinical utility, and turnaround time of WGS were ranked as the most important aspects. Nine scenarios were developed

and scored on likelihood by eighteen experts. The scenario about introducing WGS as a clinical diagnostic with a lower price, shorter turnaround time, and improved degree of actionability, scored the highest likelihood.

Chapter 6 described the systems model that was developed to inform organizational decisions regarding the use of WGS and to quantify how these decisions affect the value of WGS. This model was the main method of analysis for this thesis and was partly populated with results from the other chapters. The developed systems model can complement conventional health economic evaluations to investigate how the organization of the diagnostic processes can influence the actual use and impact of WGS. Our analyses showed that insufficient capacity to provide WGS and referral patterns can substantially impact the duration of the diagnostic pathway and thus should be considered in the implementation of WGS.

There is still uncertainty regarding which subgroups of patients WGS will be used, which hospitals will offer WGS to their patients, and the position of WGS in the diagnostic pathway for the near future. To address that uncertainty, chapter 7 aimed to analyze multiple implementation scenarios. The emphasis of this study was on the time-to-treatment, costs, and aggregate demand for WGS. The results indicated there is a tradeoff between costs and time-to-treatment across implementation scenarios, as the most comprehensive tests are relatively more expensive and result in shorter diagnostic pathways. If a 50% volume discount for the costs of consumables for WGS is obtained, upfront testing for all lung cancer patients can be the least expensive strategy of all strategies evaluated.

1.3 Conclusion

WGS has a large potential to transform the way healthcare is provided. It has become clear that nationally implementing WGS, a complex and disruptive technology, in a rapidly evolving healthcare system is challenging and fraught with uncertainties and that a one-size-fits-all approach is likely suboptimal. By, first exploring current clinical practice, and subsequently investigating how the implementation of WGS would have different consequences across different local circumstances, we have made progress toward a more custom-sized approach and have made inroads towards including the organization of care when health technologies are assessed. The healthcare system is constrained, and our analysis aimed to capture that key characteristic by including practice variation, referral patterns, capacity constraints, and constraints in the access to WGS. We were able to address the aim of the thesis, which was to identify the value of WGS from a systems perspective and under which conditions the value of WGS can be realized.

Decision-makers are confronted with a dilemma: either (1) implement WGS even though the cost of WGS is higher compared to current standard and the benefit of WGS is not clear, or (2) adopt a wait-and-see tactic during which knowledge gaps can potentially be filled or the cost of WGS may decrease. In this thesis, we have shown that upfront testing with WGS for all lung cancer patients may be the least expensive approach, if, due to the high patient volume, discounts may be obtained from suppliers. Therefore, if decision-makers accept initially higher costs per patient, they can pave the way to less complex diagnostic pathways, shorter time-to-treatment, and lower costs per patient by using WGS upfront for all lung cancer patients.

Samenvatting

1.1 Achtergrond

De laatste jaren zijn er kankerbehandelingen ontwikkeld die effectiever zijn voor specifieke genetische subgroepen. Bij deze gepersonaliseerde aanpak worden patiënten op basis van de aanwezigheid van biomarkers in genetische subgroepen ingedeeld en worden behandelingen voorgeschreven die bij hun genetische subgroep passen. Deze ontwikkeling is met name relevant voor de grootste en zeer dodelijke subgroep van longkanker, niet-kleincellige longkanker (NSCLC), aangezien de rol van biomarkers voor de selectie van behandelingen bij NSCLC de laatste tien jaar snel is toegenomen. Het aantal beschikbare biomarkers en de diversiteit van de beschikbare diagnostische testtechnieken in verschillende ziekenhuizen, tezamen met de uitdagingen om de tests efficiënt te plannen, leiden echter tot een complex en niet-uniforme diagnostisch traject voor patiënten met gevorderd NSCLC.

De vooruitgang in de genomica heeft de vraag naar uitgebreidere tests doen toenemen. Whole Genome Sequencing (WGS) kan worden gebruikt om alle op DNA gebaseerde biomarkers in één enkele test te testen, in vergelijking met de huidige standaard waar meerdere tests achtereenvolgens worden uitgevoerd. WGS is de meest uitgebreide vorm van genoomsequencing en biedt een aanzienlijke hoeveelheid (aanvullende) diagnostische informatie. Daardoor is het klinisch nut van WGS mogelijk hoger in vergelijking met de huidige tests die één of een aantal genen testen. Een voorwaarde hiervoor is dat er nieuwe behandelingen beschikbaar zijn die gebruik maken van de aanvullende diagnostische informatie die WGS genereert. Bovendien kan WGS de meeste, zo niet alle, huidige moleculaire diagnostische tests vervangen, waardoor het diagnostisch traject wordt eenvoudiger en efficiënter wordt.

Terwijl de voordelen van WGS duidelijker worden, vordert de implementatie van WGS in de gezondheidszorg langzaam. Deze trage vooruitgang is te wijten aan de complexiteit en het ontwrichtende karakter van WGS, aangezien WGS veel van de huidige moleculaire diagnostiek kan vervangen. Hierdoor moet er scherp gekeken worden naar de optimale positie van WGS in het diagnostisch traject vanuit een klinisch en gezondheidseconomisch perspectief. Het vereist ook een hervorming van het zorgsysteem om de waarde van WGS te maximaliseren. Verder kan een breed scala aan onderling samenhangende factoren, zoals klinische, technische, sociale en economische factoren een rol spelen bij het realiseren van de waarde van WGS. Het is daarom belangrijk dat de implementatie van WGS wordt onderzocht vanuit een systeemperspectief, dat de aanwezigheid van onderlinge afhankelijkheden, mogelijk op meerdere niveaus in het systeem, tracht te kwantificeren. Dit proefschrift was dan ook bedoeld om de waarde van WGS te identificeren vanuit een systeemperspectief en onder welke voorwaarden de waarde van WGS kan worden gerealiseerd.

1.2 Samenvatting

De studies gepresenteerd in dit proefschrift maakten deel uit van de Technology Assessment of Next Generation Sequencing in Personalised Oncology (TANGO) studie waarin het comparatieve voordeel van WGS ten opzichte van de standaard moleculaire diagnostiek werd beoordeeld.

Hoofdstuk 2 was een expert review van een vroege *technology assessment* van het gebruik van WGS in de precisie-oncologie, waarin ook de lopende nationale initiatieven, die tot doel hebben WGS in de dagelijkse klinische praktijk te implementeren, werden benoemd. In dit hoofdstuk werd ook de TANGO studie geïntroduceerd en werd geconcludeerd dat een breder gebruik van WGS afhankelijk is van verschillende factoren, zoals de identificatie van voldoende genetische subgroepen, informatie over de kosteffectiviteit en mogelijke gezondheidsvoordelen van behandelingen voor deze subgroepen, organisatorische factoren, en ethische, juridische en maatschappelijke problematiek.

Hoofdstuk 3 was een onderzoek naar de variatie in de tijd tot behandeling voor patiënten met stadium III of IV in alle ziekenhuizen in Nederland met behulp van gegevens op patiëntniveau. Uit het onderzoek bleek dat de tijd tot behandeling aanzienlijk varieerde zowel tussen en binnen ziekenhuizen. De tijd tot behandeling was binnen het bereik zoals aanbevolen in de huidige richtlijnen in Nederland. Met verdere toename in het gebruik van moleculaire diagnostiek en precisie-oncologie verwachten we dat de variatie in tijd tot behandeling zal toenemen en hiermee moet rekening worden gehouden bij het formuleren van optimale kankerzorg.

Hoofdstuk 4 onderzocht de kosten, doorlooptijden en het gebruik van biomarker testen voor patiënten met gevorderd NSCLC op basis van gegevens van een grote tertiair ziekenhuis en van de ziekenhuizen van waaruit de patiënten werden verwezen. Dit resulteerde in een uniek cohort waarvan de hele geschiedenis van het testen van biomarkers bekend was. De resultaten lieten zien dat er aanzienlijke variatie in testgebruik en volgordes was. Genenpanels werden het vaakst uitgevoerd, gevolgd door het testen van PD-L1 met immuunhistochemie. Doorgaans werden de meest voorkomende biomarkers getest in de eerste aantal tests, en de meer recent ontdekte biomarkers werden later getest. Op het huidige kostenniveau zou het vervangen van de huidige biomarkertests door WGS voor slechts 2% van de patiënten tot kostenbesparingen hebben geleid.

Het doel van hoofdstuk 5 was om te anticiperen op mogelijke toekomstige ontwikkelingen die van invloed kunnen zijn op de implementatie van WGS, door bestaande literatuur te bestuderen, scenario's op te stellen die mogelijke toekomstige

ontwikkelingen beschrijven en waarschijnlijkheden voor deze scenario's uit te vragen bij een diverse groep experts. De prijs, het klinisch nut en de doorlooptijd van WGS werden als de belangrijkste aspecten genoemd. Er werden negen scenario's gedefinieerd en door achttien experts gescoord op waarschijnlijkheid. Het scenario over het introduceren van WGS als klinische diagnostische test waarin de prijs lager en de doorlooptijd korter waren en ook meer genetische subgroepen kan identificeren, werd als het meest waarschijnlijk geacht.

Hoofdstuk 6 beschrijft het systeemmodel dat is ontwikkeld om organisatorische beslissingen over het gebruik van WGS te informeren en om te kwantificeren hoe deze beslissingen de waarde van WGS beïnvloeden. Dit model was de belangrijkste analysemethode voor dit proefschrift en werd gedeeltelijk gevuld met de resultaten uit de andere hoofdstukken. Het ontwikkelde systeemmodel is een aanvulling op conventionele gezondheidseconomische evaluaties en kan worden gebruikt om te onderzoeken hoe de organisatie van diagnostische processen het daadwerkelijke gebruik en de impact van WGS kan beïnvloeden. Onze analyses toonden aan dat onvoldoende capaciteit om WGS uit te voeren en verwijzingspatronen een aanzienlijke impact kan hebben op de duur van het diagnostische traject. Deze factoren moeten dus worden overwogen bij de implementatie van WGS.

Er is voor de nabije toekomst nog onzekerheid over voor welke subgroepen van patiënten WGS zal worden gebruikt, welke ziekenhuizen WGS aan hun patiënten zullen aanbieden en de positie van WGS in het diagnostisch traject. Om die onzekerheid te verminderen, was hoofdstuk 7 bedoeld om meerdere implementatiescenario's te analyseren. De nadruk van dit onderzoek lag op de tijd tot behandeling, de kosten en de totale vraag naar WGS. De resultaten gaven aan dat er een afweging is tussen kosten en tijd tot behandeling in alle implementatiescenario's, aangezien de meest uitgebreide tests relatief duurder zijn en resulteren in een korter diagnostisch traject. Als een volumekorting van 50% voor de kosten van verbruiksmaterialen voor WGS wordt verkregen, kan vooraf testen voor alle longkankerpatiënten de goedkoopste strategie zijn van alle geëvalueerde strategieën.

1.3 Conclusie

WGS heeft een groot potentieel om de manier waarop zorg wordt verleend te transformeren. Het is duidelijk geworden dat het nationaal implementeren van WGS, een complexe en ontwrichtende technologie, in een snel evoluerend zorgsysteem een uitdaging met veel onzekerheden is en dat een one-size-fits-all-aanpak waarschijnlijk niet optimaal is. Door eerst de huidige klinische praktijk te verkennen en vervolgens te onderzoeken hoe de implementatie van WGS verschillende gevolgen zou hebben voor verschillende lokale omstandigheden, hebben we vooruitgang geboekt omtrent

een meer op maat gemaakte aanpak en in het opnemen van de organisatie van de zorg in gezondheidseconomische evaluaties. Het zorgsysteem heeft te maken met restricties en onze analyse was erop gericht om dat belangrijke kenmerk op te nemen in de analyse door praktijkvariatie, verwijzingspatronen, capaciteitsbeperkingen en beperkingen in de toegang tot WGS op te nemen. Hierdoor hebben we het doel van het proefschrift te behaald, namelijk het identificeren van de waarde van WGS vanuit een systeemperspectief en te onderzoeken onder welke voorwaarden de waarde van WGS kan worden gerealiseerd.

Beleidsmakers worden geconfronteerd met een dilemma: ofwel (1) WGS implementeren terwijl de kosten van WGS hoger zijn in vergelijking met de huidige standaard en het voordeel van WGS niet duidelijk is, of (2) een afwachtende houding aannemen waarbij aanvullende kennis mogelijk kan worden opgedaan of de kosten van WGS kunnen dalen. In dit proefschrift hebben we aangetoond dat het vooraf testen met WGS voor alle longkankerpatiënten de goedkoopste benadering kan zijn, als vanwege het hoge patiëntvolume, kortingen kunnen worden verkregen van leveranciers. Als beleidsmakers dus in eerste instantie hogere kosten per patiënt kunnen accepteren, kan dat uiteindelijk leiden tot een minder complex diagnostisch traject, kortere tijd tot behandeling en lagere kosten per patiënt door WGS vooraf te gebruiken voor alle longkankerpatiënten.

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Curriculum Vitae

Michiel van de Ven was born on the 7th of March 1991 in Rosmalen, the Netherlands. After a break of about two years following his graduation of high school (Sint-Janslyceum in 's-Hertogenbosch), Michiel started as a bachelor student in the Economics and Business Economics program at Utrecht University in Utrecht. He finished this program in 2015. Michiel continued his education by enrolling in an Economics and Business Economics master program at the Erasmus University with a specialization in Health Economics. During this time, Michiel wrote his thesis during a research internship at the Dutch Healthcare Authority (NZa), where he investigated the impact of market power of care providers on prices. He obtained his master's degree in 2016.

In July 2017, Michiel started as a PhD candidate at the department of Health Technology and Services Research at the University of Twente. His PhD project mainly focused on the national implementation of Whole Genome Sequencing for lung cancer patients. This PhD project was part of the Technology Assessment of Next Generation Sequencing in Personalized Oncology (TANGO) study in which the comparative advantage of WGS compared to SOC molecular diagnostics is assessed. The results of this PhD project are described in this dissertation.

Besides the PhD project, Michiel was involved in several side activities. For example, he was involved sin various roles with the International Society for Health Economics and Outcomes Research (ISPOR) Student Chapter, and he co-organized LOLAHESG 2019, a Dutch and Belgian health economics conference.

Michiel has continued his career at OPEN Health in Rotterdam, the Netherlands as a health economic modeler.

List of publications

Thesis publications

Published

Van de Ven, M., Retèl, V. P., Koffijberg, H., van Harten, W. H., & IJzerman, M. J. (2019). Variation in the time to treatment for stage III and IV non-small cell lung cancer patients for hospitals in the Netherlands. *Lung Cancer*, *134*, 34-41.

van de Ven, M., Koffijberg, H., Retèl, V., Monkhorst, K., Smit, E., van Harten, W., & IJzerman, M. (2021). Real-World Utilization of Biomarker Testing for Patients with Advanced Non–Small Cell Lung Cancer in a Tertiary Referral Center and Referring Hospitals. *The Journal of Molecular Diagnostics*, *23*(4), 484-494.

Simons, M., Van De Ven, M., Coupé, V., Joore, M., IJzerman, M., Koffijberg, E., Frederix, G., Uyl – De Groot, C., Cuppen, E., van Harten, W. & Retèl, V. (2021). Early technology assessment of using whole genome sequencing in personalized oncology. *Expert review of pharmacoeconomics & outcomes research*, *21*(3), 343-351.

van de Ven, M., Simons, M. J., Koffijberg, H., Joore, M. A., IJzerman, M. J., Retèl, V. P., & van Harten, W. H. (2021). Whole genome sequencing in oncology: using scenario drafting to explore future developments. *BMC cancer*, *21*(1), 1-12.

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Developing a dynamic simulation model to support the nationwide implementation of Whole Genome Sequencing in lung cancer. van de Ven, M., IJzerman, M.J., Retèl, V.P., van Harten, W., Koffijberg, H. (*BMC Medical Research Methodology*)

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Nationwide Implementation of Whole Genome Sequencing in Lung Cancer: A Dynamic Simulation Model to Analyze the Impact of Implementation Scenarios on Time-to-Treatment, Costs, and Aggregate Demand. van de Ven, M., Koffijberg, H, Retèl, V.P., van Harten, W., IJzerman, M.J. (Genome Medicine)

Non-thesis publications

Pending submission

Analysis of variation in clinical practice over time using process mining. Relijveld, S., van de Ven, M., Geleijnse, G., Hans, E.W., Koffijberg, H.

Conference contributions

Retèl, V., van Harten, W., Joore, M., IJzerman, M., Koffijberg, E., Coupé, V., Frederix, G., Feenstra, T., Uyl-de Groot, C., Eekhout, I., Vijver, M. V. D., Aerts, J., Eertwegh, A. V. D., Smit, E., Sleijfer, S., Voest, E., Ploem, C., Gevers, S., Bredenoord, A., ... Cuppen, E. (2017). Whole Genome Sequencing in Personalized Oncology - Poster. In *Whole Genome Sequencing in Personalized Oncology* https://doi.org/10.5281/zenodo.3274283

Retel, V., Coupe, V. M., Feenstra, T., IJzerman, M. J., Koffijberg, H., Joore, M., ... & van Harten, W. (2018, June). A Conceptual Model for Technology Assessment of Next Generation Sequencing in Personalized Oncology (TANGO). In *17th Biennial European Conference*. SMDM.

van de Ven, M., Simons, M., van Harten, W. H., Retel, V. P., Koffijberg, E., Joore, M., & IJzerman, M. (2019). PCN377 Where do we go with whole genome sequencing in oncology? Using scenario drafting to explore future developments. *Value in health*, *22*, S509-S510.

van de Ven, M., IJzerman, M., Retel, V., van Harten, W. H., & Koffijberg, E. (2020). PCN45 Systems Models to Identify Implementation Requirements for Disruptive and Complex Health Technologies: A Conceptual Model Reflecting the Organization of Whole-Genome Sequencing in Lung Cancer. *Value in Health*, *23*, S429.

Degeling, K., Koffijberg, H., van de Ven, M. Short course: Discrete Event Simulation in R to Support Healthcare Decision Making. Society for Medical Decision Making, 43rd Annual North American Meeting, 2021.