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ABSTRACT

Introduction: Personalized medicine-based treatments in advanced cancer hold the promise to offer substantial health benefits to genetic subgroups, but require efficient biomarker-based patient stratification to match the right treatment and may be expensive. Standard molecular diagnostics are currently very heterogeneous, and tests are often performed sequentially. The alternative to whole genome sequencing (WGS) i.e. simultaneously testing 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 (HTA) 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 modeling, 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.

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 testing 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

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Article highlights

- A comprehensive early Health Technology Assessment approach is described to support decision making on Whole Genome Sequencing for cancer diagnostics, using the combination of real-world data, various modeling approaches, and expert elicitation to address uncertainty.
- Multidisciplinary and multi-stakeholder collaboration is necessary to analyze on the appropriate mode of implementation in the healthcare system of disruptive technologies such as Whole Genome Sequencing
- Wider use of Whole Genome Sequencing 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.

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, so-called early Health Technology Assessment (HTA) can be used for these types of complex questions in an early stage of development and technology introduction. 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 toward WGS. However, stakeholders had concerns about data safety, secondary findings, data sharing, and other practical aspects [34–37]. Additionally, a modeling 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 Organization 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 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.

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 three 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 Organization for Research and Treatment of Cancer questionnaire (EORTC-QLQ-C30), EuroQol 5D-5 L, 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
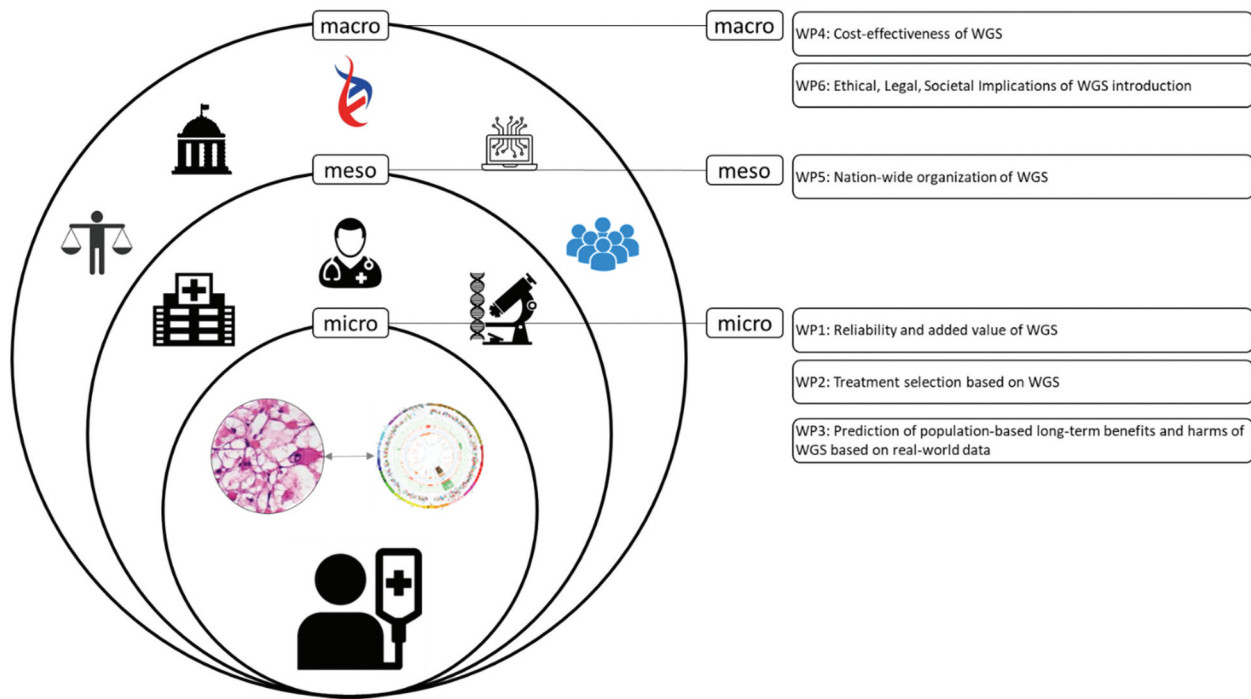
Figure 1. Design 'Technology Assessment of Next Generation Sequencing in Personalized Oncology' (TANGO) study.

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

Work package (WP)	Key challenges addressed
WP1	• Comparison of 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

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, while 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 stepwise 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 next 5 years.

Subsequently, a cost-effectiveness 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 cost-effectiveness 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 into the cost-effectiveness 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 cost-effectiveness 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 a 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 toward 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 to immunotherapy, and of 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 rapid 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 QOL. 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, nation-wide data sets and linkages between pathology, WGS and clinical data are necessary to monitor and evaluate these types 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, HRQoL 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 1,200 patients, is: to demonstrate feasibility of WGS-based diagnostics in routine practice, to 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, and 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, immunogenomic 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

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