WGS IN CANCER DIAGNOSTICS

AFFORDABLY BETTER

Hartwig MEDICAL FOUNDATION

VINTURA

Written by Vintura on behalf of Hartwig Medical Foundation in collaboration with the medical field

Colophon

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OPENING WORDS

It has now been 16 years since I sat at the oncologist's office with my father, who suffered from oesophageal cancer with metastases in the lymph nodes and liver, to discuss his treatment options. A treatment was available, but side effects would be severe and the chance of successful treatment was only 30%. It was certain the treatment would have significant negative impact on my father's quality of life in the short term, but whether he would benefit from that treatment, was also uncertain. A diabolical dilemma that patients with cancer face to this day.

This personal experience with my father's disease process was the reason for me to delve into oncology research to find ways to better predict the outcome of oncology treatments.

For optimal treatment of cancerpatients, doctors must be optimally informed about the intrinsic characteristics of tumour cells. This is especially true for patients with metastatic disease. In recent years, molecular diagnostics have been increasingly used for this purpose. Molecular diagnostics involves detecting errors in the DNA of tumour cells that underlie the development of cancer and can also be used as points of engagement for targeted treatment.

This detection can be done with single tests looking at only a few DNA mutations, with larger so-called multigene tests, and more recently, also by means of Whole Genome Sequencing (WGS).

WGS maps the DNA of tumour cells and compares it with the DNA present in healthy cells (the germline). Advantages of WGS are that it allows a tumour to be better classified and drugs to be used in a targeted manner, based on the DNA mutations found. There is no patient with the same mutation profile.

WGS for tumour diagnostics is currently performed in routine setting in the Netherlands by Hartwig Medical Foundation (Hartwig), a non-profit, philanthropic foundation. In addition to providing a complete patient report, Hartwig strives to collect anonymised genetic and clinical data of as many patients as possible. Patients must give explicit consent and only encrypted data is recorded and processed. This database is now a unique and valuable source for global research on improving the treatment of future patients.

Hartwig is now successfully using WGS in patient diagnostics an WGS is reimbursed for a specific group of patients. However, WGS can have greater impact if the test is used earlier in the treatment pathway for more patients.

This white paper structurally examines whether and from what point onwards broad use of WGS is efficient. It also elaborates on the important opportunities that broad use of WGS offers for today's patients and for the patients of 'tomorrow', especially if we can make WGS part of a 'learning care system' in oncology.

I wish you a pleasureful and inspirational read ahead!

TABLE OF CONTENTS

SUMMARY AND CONCLUSIONS

The demand for care is increasing and resources (financial and human) are scarce. Problems in delivering care are growing and (radical) decisions are needed. As urgency is growing, making decisions quickly, accurately and efficiently is important. WGS can help us make the right decisions.

In this white paper we investigate an economic evaluation of the use of Whole Genome Sequencing (WGS) and other types of molecular diagnostics. We investigate the situation in 2022 and work with a future scenario up to 2027, in which an ever-larger number of targets are investigated with broad molecular diagnostics and the cost of using WGS decreases. In addition, we investigate how the use of WGS can contribute to making necessary choices in healthcare. Some assumptions were made to calculate the impact on the overall Dutch healthcare system (see also chapter 2).

Although the economic evaluation forms the basis of this white paper, the paper is also connected to existing debates, current literature on positioning and funding of molecular diagnostics and the preconditions for the realisation of its value.

It is efficient to use broad molecular diagnostics (including WGS) from 2025 onwards in almost all patients with metastatic solid tumours

The conclusions of this white paper show that the use of WGS in molecular diagnostics grows equally to the extent of which the use of broad molecular diagnostics for different tumour types is considered necessary. We conclude that the use of broad molecular diagnostics in 2025 is desirable for almost all patients with metastatic disease.

Use of WGS is cost-effective from 2024 onwards compared to current diagnostics

The cost of using WGS will decrease in coming years, following a clearly established trend. A tipping point will occur in 2024 when the cost of WGS will be lower than the cost of the current broad molecular diagnostic tests. This involves savings of ~€50 per patient, and these savings increase over time. The use of WGS for broad molecular diagnostics in patients with metastatic cancer will therefore be cheaper from 2024 onwards than the current way of working.

Use of WGS offers opportunities for substantial alternative cost savings

In addition, the use of WGS offers savings in pharmacogenetic and clinical genetic tests, which are currently often performed separately.

The biggest impact for both patients and the oncology healthcare system lies in effective use of oncology drugs. These drugs represent a large expenditure to society; therefore, effective use is important. In 2022, molecular diagnostics with WGS costed €440 more per patient than current broad molecular diagnostics tests. However, we show that a saving of €1,645 per patient is possible when using WGS, due to its ability to identify inefficient use of prescribed medications.'

Effective use of drugs in oncology has the potential to save more than €41 million per year, provided that the research findings can be applied broadly. Additionally, less patients will suffer unnecessarily from toxic treatments without added value.

Using WGS as part of a learning care system helps structurally improve care

Learning care systems translate scientific insights into clinical practice and translate insights from clinical practice back into scientific insights. Fast broad implementation of WGS can play a crucial role in learning care systems to ensures patients get the best match between tumour and treatment in a timely manner. Preconditions for a learning care system are:

- Implementation of a nationwide and uniform working method of molecular diagnostics,
- Connected to a nationwide and uniform data collection process, and
- Continued use of data for quality improvement of care and molecular diagnostics.

Quality of diagnostics based on your zip code *(zip code diagnostics)* thus becomes a thing of the past.

However, to accommodate WGS, care pathways need to be redesigned to provide alternative collection and storage of biopsies. In addition, a multidisciplinary way of working for treatment advice is needed to interpret the results of molecular diagnostics. Collaboration leading to the concentration of complex molecular diagnostics is a logical next step. It needs to be clarified at which place in the treatment pathway the use of broad molecular diagnostics is the most efficient. Furthermore, reimbursement for molecular diagnostics should be extended.

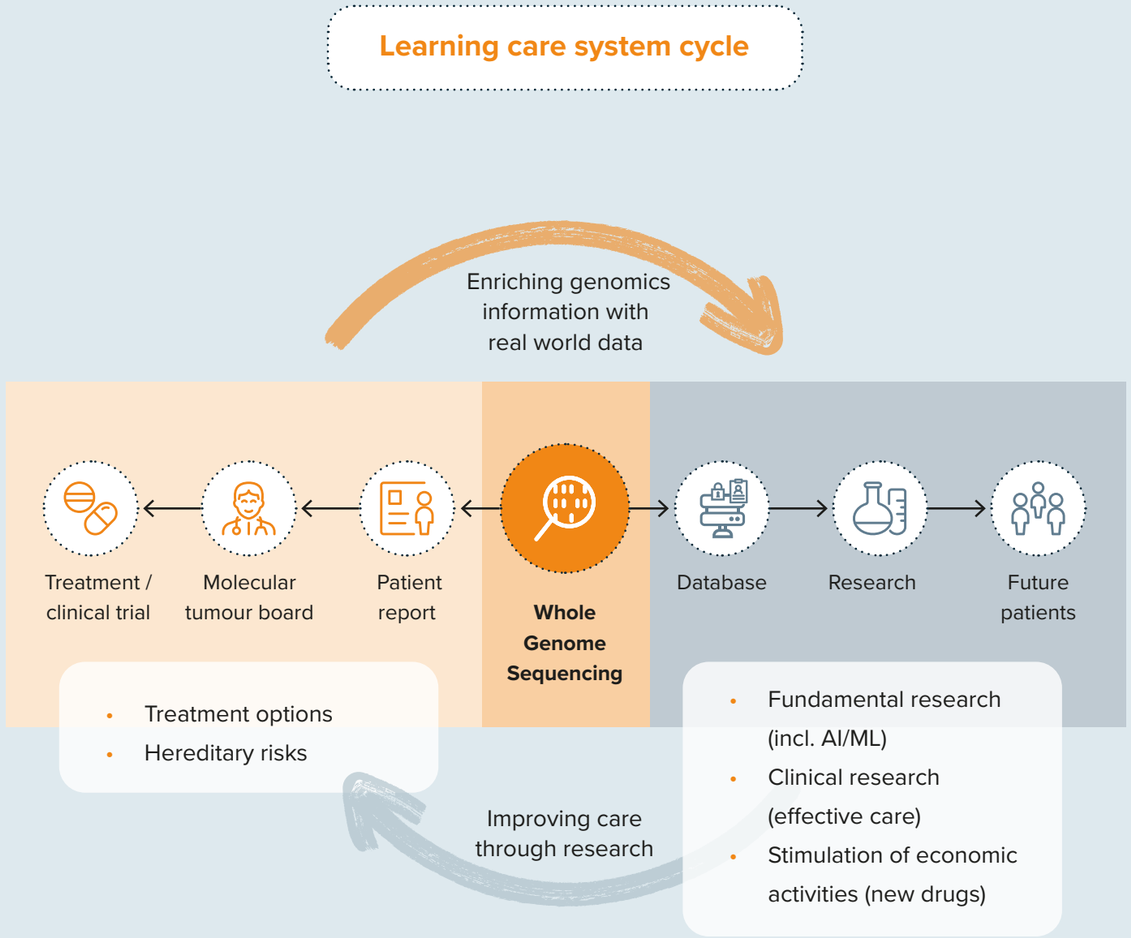
Broad use of WGS helps to make unavoidable choices in healthcare

It is inevitable that we have to make choices in healthcare. The resources at our disposal are scarce (human and financial). If choices are made as well-informed as possible, access to the best oncology care for everyone can be delivered.

The use of WGS in molecular diagnostics allows us to make well-informed choices. In the relatively short term, it is cheaper and more efficient to use WGS to replace the current way of working, therefore it pays to invest sooner rather than later in broad use of WGS in patients with metastatic solid tumours. To realise this added value for the learning care system, it is important to pay sufficient attention to the required change management.

Figure 1

Overview of the learning care system cycle in oncology.



1

INTRODUCTION, RESEARCH QUESTION AND READING GUIDE

Sustainability of the healthcare system is under pressure

In the report ‘Opting for sustainable care’, the Scientific Council for Government Policy (in Dutch: WRR) paints a bleak picture of the future. The number of patients and care activities per patient will increase rapidly in the coming decades under the influence of innovation and the ageing population. If policies remain unchanged, the associated costs will push out other socially important issues such as education and safety.

Due to the increasing number of new therapies, this pressure will continue to increase. Similarly, in oncology, a great deal of progress in available treatments is expected. At the same time, the number of available healthcare professionals and informal carers to deliver the rapidly growing demand for care is decreasing.

Access to care may be compromised for large groups of people because care has become unaffordable or because there is a lack of skilled staff to deliver the care.

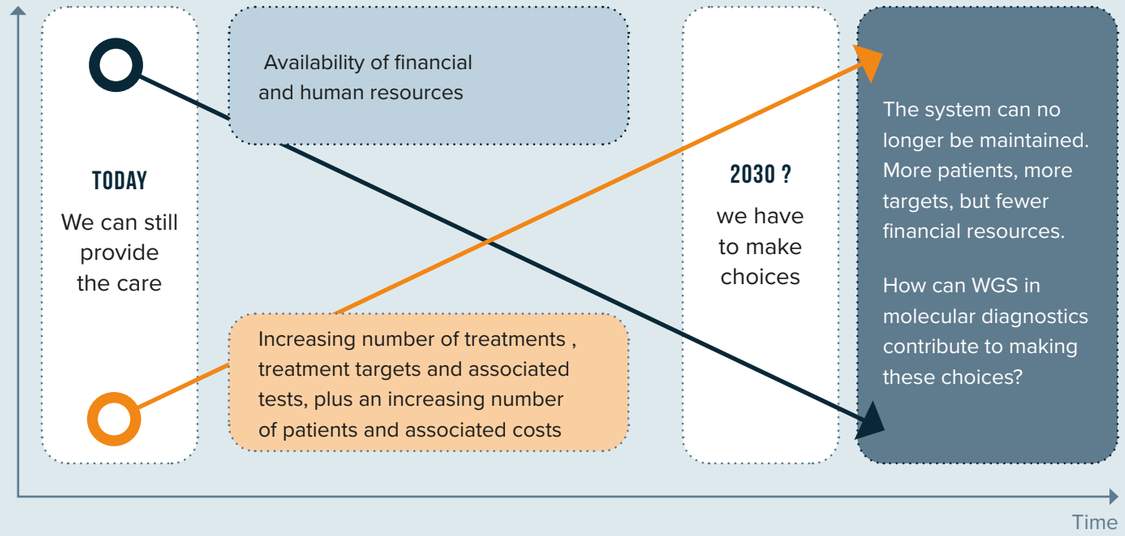
From the recently published Integral Care Agreement[2] (in Dutch: Integraal Zorg Akkoord) and the Cancer in the Netherlands in 2032[3] publication by the Integral Cancer Centre the Netherlands (IKNL), it appears that the number of new patients with cancer will grow from 124,000 in 2021 to 156,000 in 2032. In 2032 there will be 1.4 million Dutch people who live with or after a cancer diagnosis. The cost of treatment per patient is increasing due to the rising cost of (expensive) medication. The average extra lifespan for patients for many indications lags behind top European countries. The impact of cancer on the healthcare budget is increasing more than proportionally.

The Dutch coalition agreement 2021-2025 strongly focuses on Appropriate Care (in Dutch: Passende Zorg).

‘Appropriate care is the norm. This means that care is proven to be effective and overtreatment is prevented. It also means that care is created together with the professional and the patient and that care is delivered in the right place. Care that is common and not complex is available to everyone nearby, while complex care that is rare is centralised.’

Figure 2

Pressure on the healthcare system is increasing due to a reduced availability of financial resources and personnel with an increasing availability of treatment options



To keep good and necessary care accessible to everyone, the available care must be used effectively; the right intervention at the right time in the right place. We must refrain from care that has no added value for the patient and we must reduce overtreatment. Making (radical) choices is inevitable. Appropriate diagnostics offer an opportunity to make these choices in a targeted manner based on thorough information. Connected with systematic data collection in the care process, it also creates a system in which continuous adjustments can be made based on available information.

Different types of diagnostics play a major role in oncology

In oncology, diagnostics plays a major role, as the outcome defines the treatment decision. An effective treatment is clinically effective and meets the patient's wishes.

Determining the primary tumour and mapping the characteristics and extent of malignant disease has a major impact on treatment choices. To place this white paper in the right context, a short introduction to oncology diagnostics is provided.

If malignant cancer is suspected, the following steps in diagnostics are taken. It starts with the patient's story and explanation; subsequently, the following takes place:

1. Anamnesis and physical examination,
2. Blood tests and imaging to determine extent of the disease,
3. Microscopic examination on a biopsy (tissue sample) of the primary tumour or metastasis,
4. Where applicable, a visual examination (endoscopy), for example in the stomach or large intestine, and
5. Molecular research on the tumour tissue.

Information from a single source is not always unambiguous and therefore insufficient for a complete diagnosis. Good integration of all available information is key to achieving a complete diagnosis. This information is usually brought together in a multidisciplinary consultation, during which a conclusion is drawn about the nature, characteristics, and extent of disease after which a treatment plan is formulated and discussed with the patient.

Goals of tissue examination

Tissue examination is an important part of diagnostics. The aim is to determine whether cancer is indeed present and if so, which tumour type it belongs to. Breast cancer metastases in the liver are treated in a different way than colon cancer metastases in the liver. Moreover, different types of cancer may occur in the same organ. In lung cancer, for example, there may be small-cell and non-small-cell lung carcinomas, and here too, several further subdivisions are possible. Each type often requires a different treatment.

Use of molecular diagnostics

The aforementioned tissue examination is known as classic pathology. Molecular research is increasingly successful in identifying specific characteristics of a tumour. This may involve looking for special proteins on or in the tumour cells, but also mapping pieces of the DNA of tumour cells. The DNA of cancer cells is usually markedly different from that of normal cells. The "genome" is dysregulated and contains abnormalities that cause tumour growth.

The entire DNA contains about 25,000 genes, and DNA changes can occur in all of them. Errors can have far-reaching consequences such as unrestrained cell division. But these errors can also become targets for possible treatment. Molecular diagnostics can be used to detect these errors and identify other characteristics of the tumour that are relevant for treatment decisions.

Tests that look at a limited number of genes or more extensive sets of genes/characteristics exist. Recently, however, it has also become possible to map the entire DNA of tumour cells using a single test. This is done with Whole Genome Sequencing (WGS)[4].

Different types of molecular diagnostics and their comparison

In molecular diagnostics for patients with metastatic cancer (or suspicion thereof), different tests are used in different ways.

Stepped molecular diagnostics:

The use of tests that look for a specific mutation and/or tumour characteristic. Usually, testing starts for the most common mutation within a tumour indication. If necessary, the test is followed by a subsequent test for another mutation, so-called stepped diagnostics.

- **Seperate tests:** looking at one or a few DNA changes
- **Small panels:** looking at 2 to 50 genes at a time
- **Large panels:** looking at more than 50 genes at a time and specifically looking for genes for which drugs are available. An example of this is the Oncomine Comprehensive Assay[5].

Broad molecular diagnostics::

The simultaneous use of one (set of) test(s) in which multiple targets are examined at the same time. A target is a characteristic of a tumour that is a target for drugs. This can be done in two ways:

- **Large panel + Archer + optional single gene tests:** with this set of tests, diagnostics is done on several already known, mutations and / or tumour characteristics. This is performed with an NGS-panel, a fusion gene test via diagnostics Longwood's Archer® FusionPlex® Oncology Research Kit, and possibly some additional single gene tests. In the rest of this white paper we will refer to this combination of tests as 'Large panel + Archer'.
- ***Whole Genome Sequencing (WGS) test*:** with this test, the entire molecular profile of the tumour cells is mapped. In the rest of this white paper we will refer to this test as 'WGS'.

With broad molecular diagnostics, a multitude of treatment options can be identified at once, while with stepped diagnostics this is done in phases. In addition, certain tumour characteristics can only be identified with broad molecular diagnostics, such as tumour mutational burden (TMB) and homologous recombination deficiency (HRD). These characteristics are also important for the choice of treatment[7,8].

The advantages and disadvantages of these different types of molecular diagnostics are presented side by side on the next page (Figure 3).

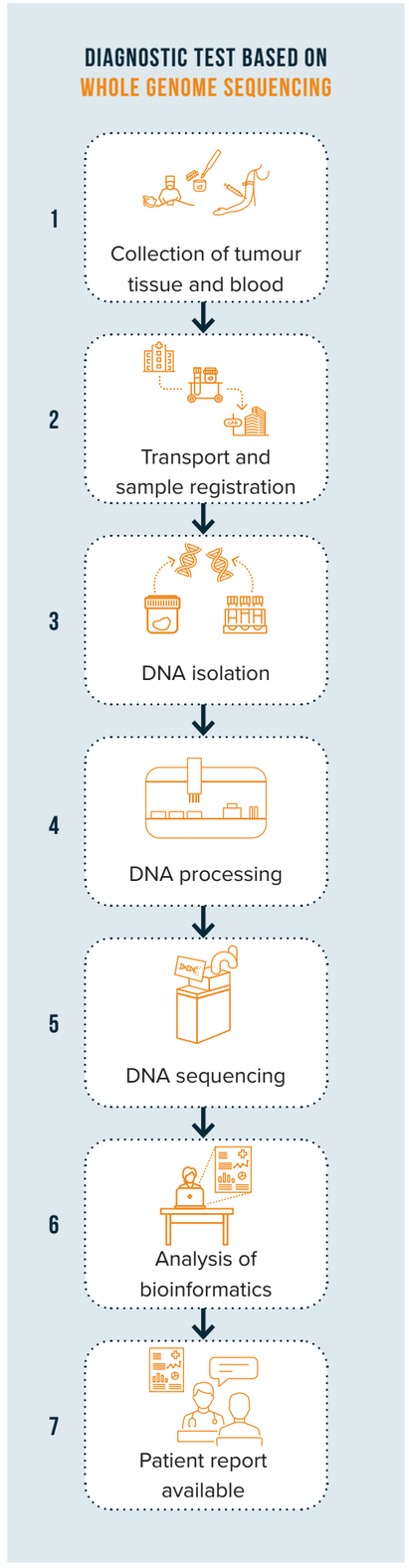


Figure 3

Comparison between stepped molecular diagnostics and broad molecular diagnostics

The colored spheres indicate the amount of diagnostic information (fully white: little, completely black: much)

	SEPARATE TESTS	SMALL AND LARGE PANELS	LARGE PANEL + ARCHER	WHOLE GENOME SEQUENCING
Tissue processing	Formaline-fixed parrafin embedded tissue	Formaline-fixed parrafin embedded tissue	Formaline-fixed parrafin embedded tissue	Fresh-frozen tissue
Amount of molecular information				
Advantages	+ Short lead time test + Low cost per test + Efficient use of resources	+ Provides broader molecular information for specific tumour types + Little tissue required and fits within current way of working + Stepped care, cost-effective	+ Provides broader molecular information for specific tumour types + Little tissue required and fits within current way of working + With a one-time combination of tests, almost all genetic information is available	+ Provides all the genetic information needed for the right treatment with a single test + Short lead time between biopsy, test result, and treatment advice + Rapid implementation of additional targets after validation + Data very suitable for learning care system
Disadvantages	– Provides little molecular information – Multiple biopsies needed if performed more frequently – Detection of complex biomarkers is not possible – Long lead time of diagnostics for sequential testing – Long lead time for validation of new genes in tests	– Only provides information about targeted genes – Detection of complex biomarkers is not possible – Long lead time of diagnostics for sequential testing – Long lead time for validation of new genes in tests	– Costs of this test are higher than costs of small and large panels – Long lead time for validation of new genes in tests	– Other tissue processing required, requires adjustment of the care pathway – Costs of this test is higher than costs of large panel + Archer

Impact of the type of molecular diagnostics chosen on the time to treatment

With stepped molecular diagnostics, the sequence of tests is determined based on the mutation frequency in a specific tumour type. As it is not patient specific, multiple rounds of tests may be required.

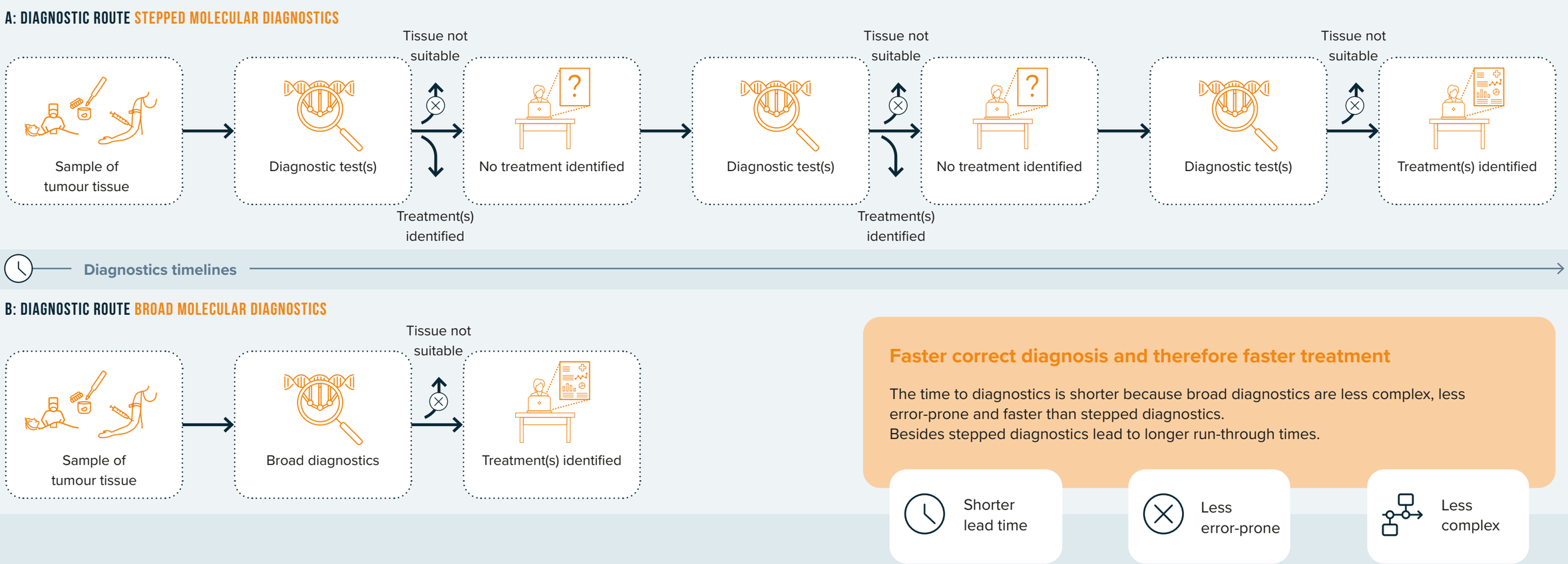
Each round extends the time to identification of the correct treatment. In addition, there is a margin of error for each round, a chance that there is insufficient material for the test, and a chance of delay. The more rounds of testing required, the greater these chances. Also, tumour tissue may run out after multiple tests, requiring a new biopsy. Introduction of a one-off test, like in broad molecular diagnostics, minimises the chance of these possibilities.

Molecular diagnostics in oncology is essential, but not optimally designed everywhere

Appropriate molecular diagnostics is essential for the right treatment choice. Unfortunately, available molecular diagnostics are not used uniformly in the Netherlands. The PATH-report describes practice variation in the use of diagnostic tests[9].

Subsequently, a situation arises where patients do not always receive the right treatment on time, simply because the right molecular diagnostics are not performed (in time). The Dutch Healthcare Institute's (in Dutch: Zorginstituut Nederland or ZIN) molecular diagnostics advisory group[10], led by Prof. Hans Gelderblom, also came to this conclusion based on research[11,12,13]. There is a risk that the hospital in which diagnosis takes place and treatment is provided, determines the treatment available for a patient. This is called zip code diagnostics and is an undesirable development.

Figure 4 A) Diagnostic route stepped molecular diagnostics
B) Diagnostic route broad molecular diagnostics



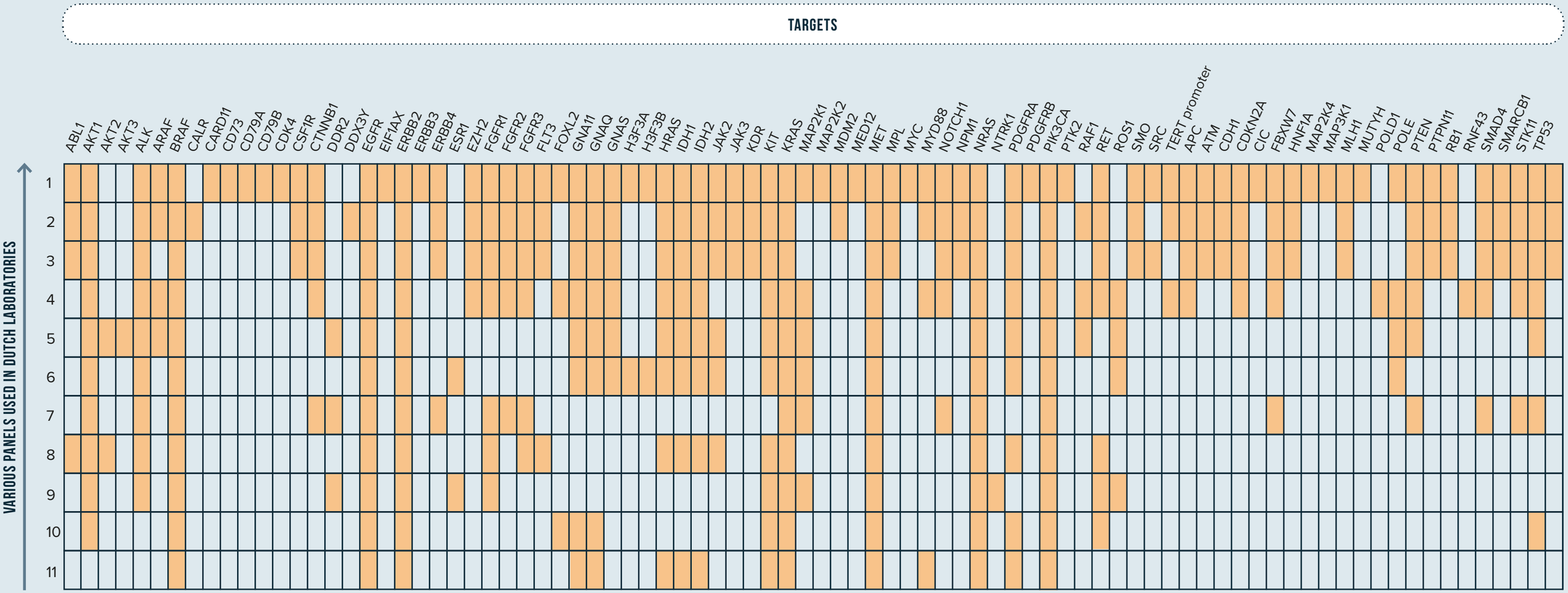
Faster correct diagnosis and therefore faster treatment

The time to diagnostics is shorter because broad diagnostics are less complex, less error-prone and faster than stepped diagnostics.
Besides stepped diagnostics lead to longer run-through times.

- Shorter lead time
- Less error-prone
- Less complex

Figure 5

Practice variation between laboratories in the Netherlands. The horizontal axis shows different targets, the vertical axis shows 11 different panels used in the labs[12].
Panels 1 to 7 are laboratory-developed panels. Panel 8 (Assuragen pan cancer panel), panel 9 (QIAact Lung DNA Panel), panel 10 (Illumina TruSight tumour 15 kit) and panel 11 (Life Technologies Lung-Colon panel) are commercial panels.



Standardising the type of molecular diagnostics ensures that every patient has access to the same diagnostics, regardless of the location where the patient is treated. To put an end to the undesirable zip code diagnostics, uniformity of data analysis and interpretation is also needed. For the latter a good step forward has already been made by introducing molecular tumour boards in various hospitals in the Netherlands, for which multi-disciplinary consultations have been set up in which complex diagnostics and treatment advice are discussed. The Foundation of Oncology Collaboration (in Dutch: SONCOS) has developed a blueprint for this[14].

Insights from science can be introduced more quickly once a uniform type of molecular diagnostics has been rolled out in the Netherlands. Adding new targets in existing panels often has a long lead time. The panels are only adjusted a few times per year and in some cases it takes several years for a target to be added to local tests. Figure 6 shows broad uptake of biomarkers in molecular diagnostics often takes many years[14].

Figure 6

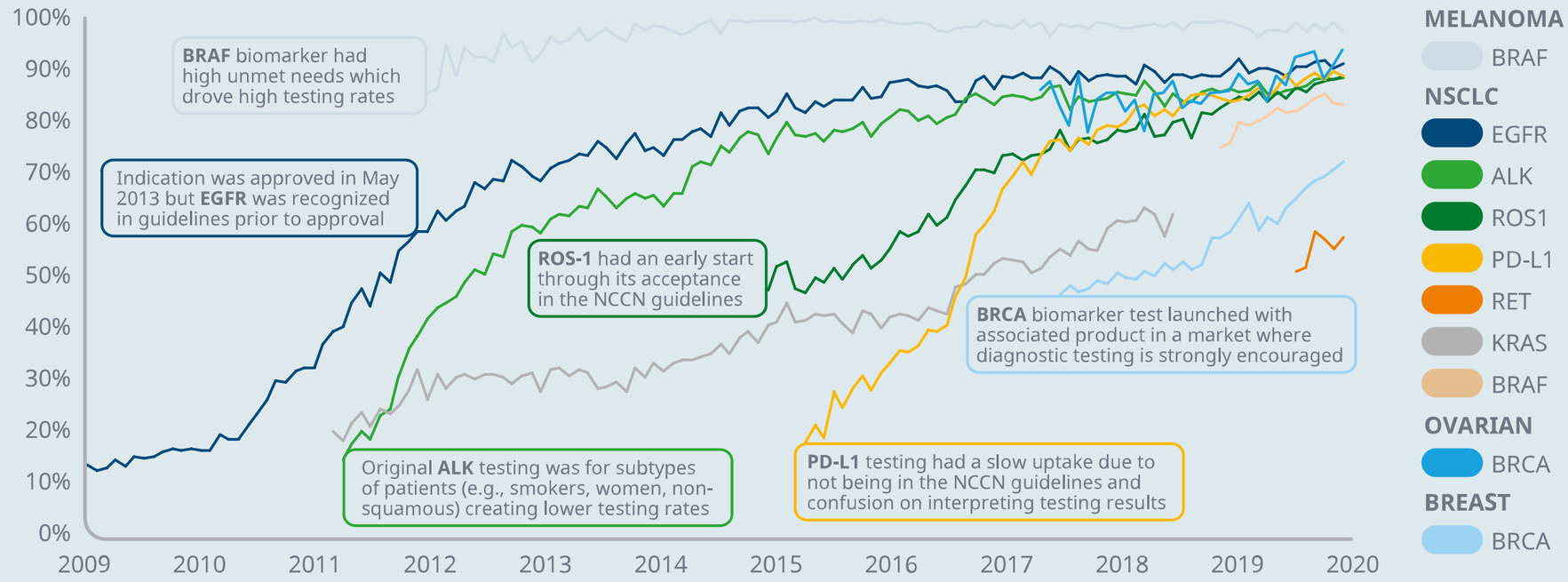
Optimizing Oncology Care Through Biomarker Adoption (IQVIA Institute)[15]

Time between the availability of the therapy and the availability of the applicable molecular tests in clinical practice.

The graph represents the percentage of patients with metastatic disease by cancer type who have been tested for a particular biomarker.

The percentages are based on physician-reported data by a monthly panel of more than 400 oncologists.

For example: When anti-EGFR medication for NSCLC was launched, it took 10 years for >90% of patients to be tested for this mutation.



An illustrative example in today's diagnostics is the lack of a systematic nationwide test for NTRK fusion gene determination for the tumour-agnostic use of larotrectinib and entrectinib; drugs with a high response rate (70%), extra survival (2 years), and few side effects.

Another recent example concerns the lack of a pharmacogenetic test for the UGT1A1 gene. This gene is associated with the severity of adverse events to irinotecan treatment in colon and pancreatic cancer[16].

To ensure access to oncology care today and in the future, it is important that molecular diagnostics is carried out broadly and uniformly. Zip code diagnostics can lead to limited access or long lead times to the right therapy and inefficient use of (expensive) oncology agents.

Molecular diagnostics will play a more crucial role in the coming years, but unclarity remains about the correct use and associated costs

No patient is the same, each tumour in a patient has unique characteristics. The trend in oncology is personalised medicine; the increasingly precise tailoring of treatment to the patient and tumour characteristics. This requires extensive diagnostics aimed at mapping those unique characteristics and the availability of appropriate treatment options.

Fortunately, an increasing number of drugs are developed that target specific tumour characteristics. The research pipeline of such drugs more than doubled between 2017 and 2020[17]. This was also confirmed in the December 2021 horizon scan, in which 531 new drugs were presented, 64% of which were inpatient drugs, largely in oncology and haematology[18,19]. Usually, these drugs are registered for a specific abnormality in a specific tumour type, but by the end of 2021, 2 drugs (larotrectinib and entrectinib) were registered for specific DNA changes (NTRK fusion gene). These 2 drugs are now also provisionally reimbursed for all types of cancer, provided tumours have these specific DNA changes (tumour-agnostic)[20].

The importance of extensive tumour characterisation in all patients with cancer is greatly increasing due to these developments.

A relevant question is how and when comprehensive molecular diagnostics can best be used. This concerns not only the choice of the type of molecular diagnostics within an indication, but also the costs involved.

Core of the white paper: economic evaluation of WGS and other types of molecular diagnostics

In this white paper we investigate the economic comparison between the use of WGS and other types of molecular diagnostics. This is a broad comparison of costs with an eye on the future. We investigate the situation in 2022 and work with a future scenario up to 2027, in which with broad molecular diagnostics an ever-larger number of targets are investigated and the cost of using WGS decrease.

Reading guide

Chapter 1 outlines the challenges for the healthcare system based on the findings in the recent report by the Scientific Council for Government Policy (in Dutch: WRR). Drastic choices are needed to keep healthcare affordable. This chapter also introduces molecular diagnostics for cancer. The treatment of cancer has developed from “one size fits all” to “precision medicine”. The broader the diagnostics, the greater the chance that the patient will receive the most effective treatment, with the right dosage at the right time.

Chapter 2 compares stepped diagnostics and 2 types of broad diagnostics. The economic evaluation forms the core of this white paper.

On behalf of the Ministry of Health, Welfare and Sport (VWS), the Dutch Healthcare Institute is carrying out an adjacent study of positioning and financing of complex molecular diagnostics[21].

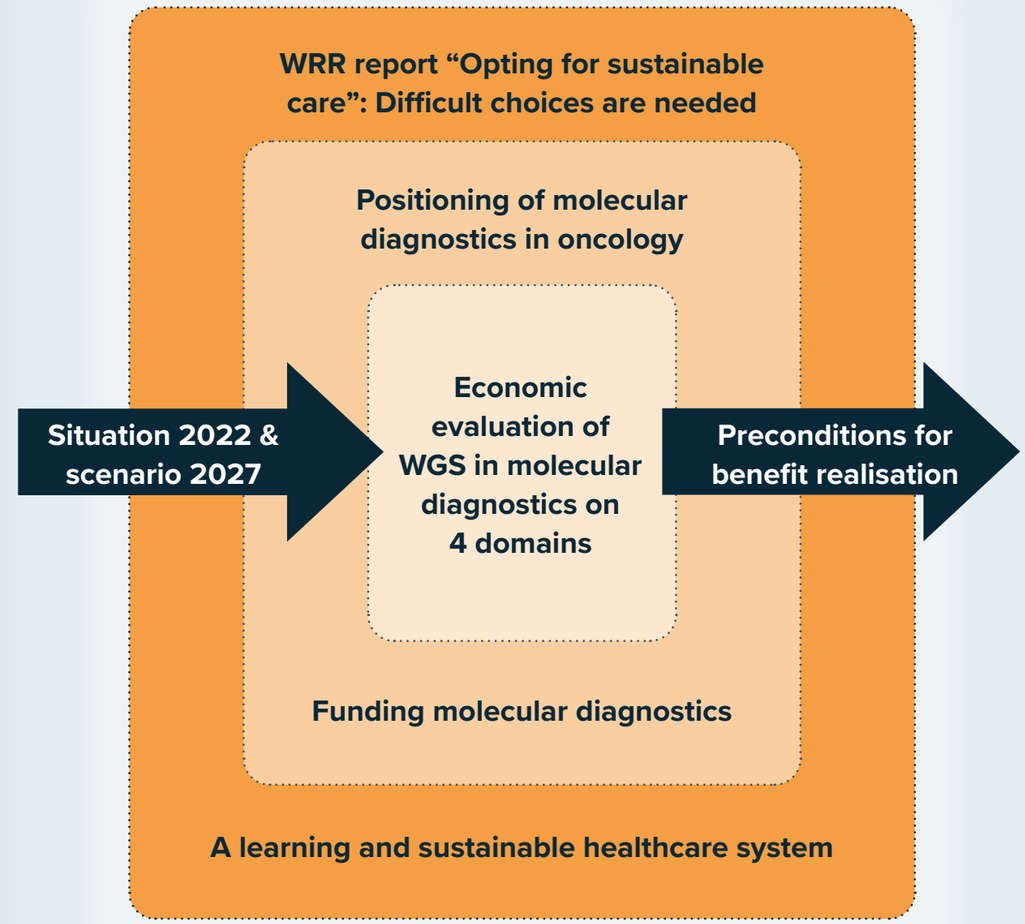
Besides a comparison of the cost of each test, the additional benefits of broad diagnostics with WGS are also described, partly quantitatively and partly qualitatively.

Chapter 3 specifically addresses how the use of WGS can contribute to improving care, reducing overtreatment, and helping to control the cost of expensive drugs. The WGS-data obtained in diagnostics can contribute to a learning care system by enriching data from treatment outcomes.

Chapter 4 describes the preconditions for implementation of WGS in diagnostics for patients with cancer, including funding, adjustment of the care pathway, objections, and obstacles.

Figure 7

Overview of the structure of arguments in this white paper



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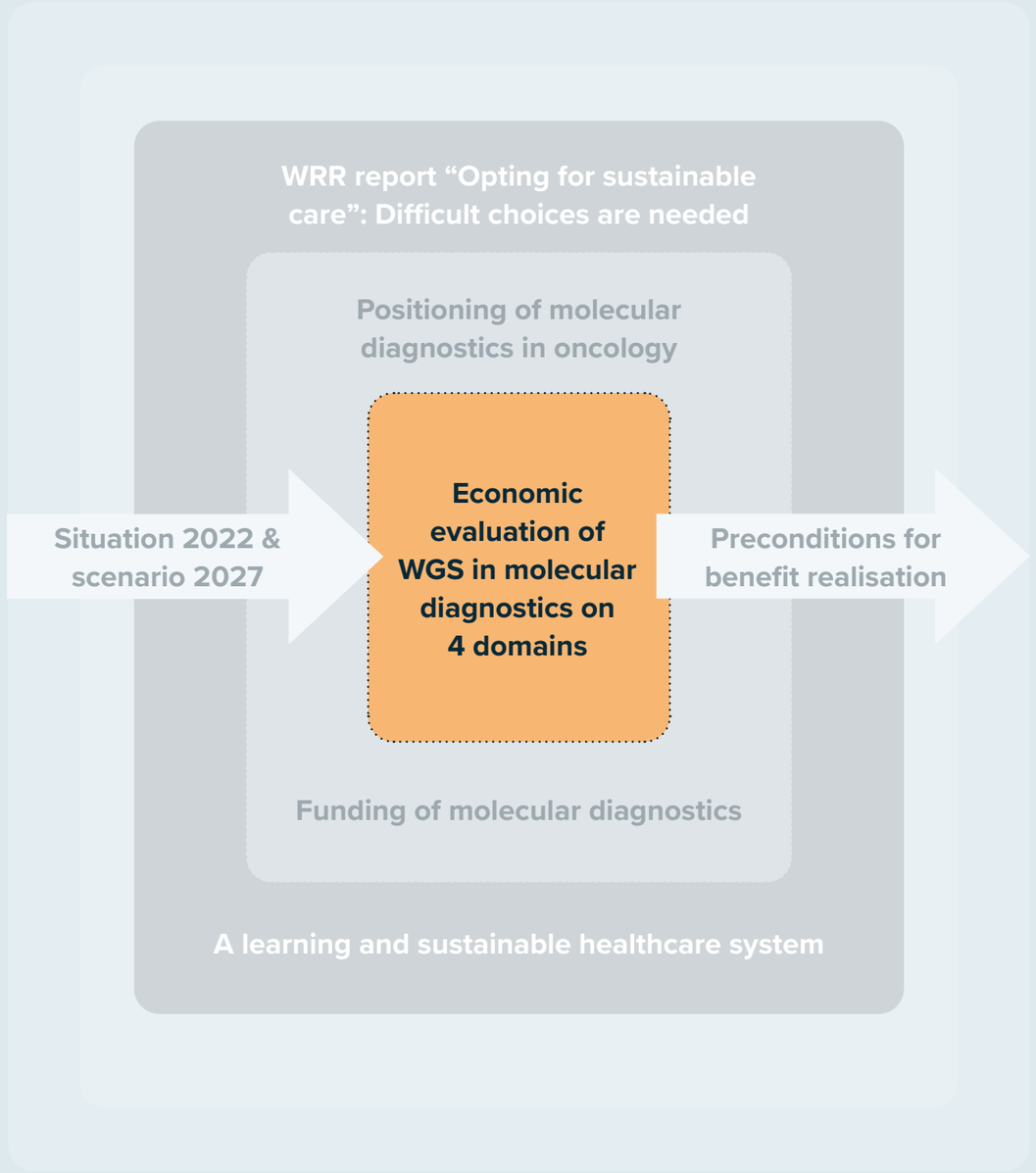
ECONOMIC EVALUATION OF DIFFERENT TYPES OF MOLECULAR DIAGNOSTICS

Traditionally, when evaluating a healthcare innovation, especially for innovative medicines, a health technology assessment (HTA) is used. Here, one compares the current way of working with the new, innovative way. For WGS, this means a test versus test analysis for a single tumour type. As such, this approach has considerable limitations. For example, you must perform a separate analysis for each tumour type and treatment. In addition, the traditional HTA analysis does not take into account the much broader impact of this innovative technology in diagnostics. Therefore, we opted for an economic evaluation in which many more aspects were taken into account and quantified. In addition, it not only provides insight into the current situation, but includes the impact of new drug developments and diagnostics for 2023-2027.

Figure 8

Positioning of the economic evaluation in thewhite paper argumentation



In this white paper we look at the value (costs and benefits) of broad molecular diagnostics with WGS in 2022 and in a future scenario until 2027. We use 3 assumptions for this scenario.

Scenario assumptions 2022-2027

Assumption 1: Increase in the number of targeted therapies.

In the future scenario, we foresee an increase in the number of targeted therapies and associated diagnostic markers. For an increasing number of tumour types, more tumour characteristics will become important for making the right treatment choice.

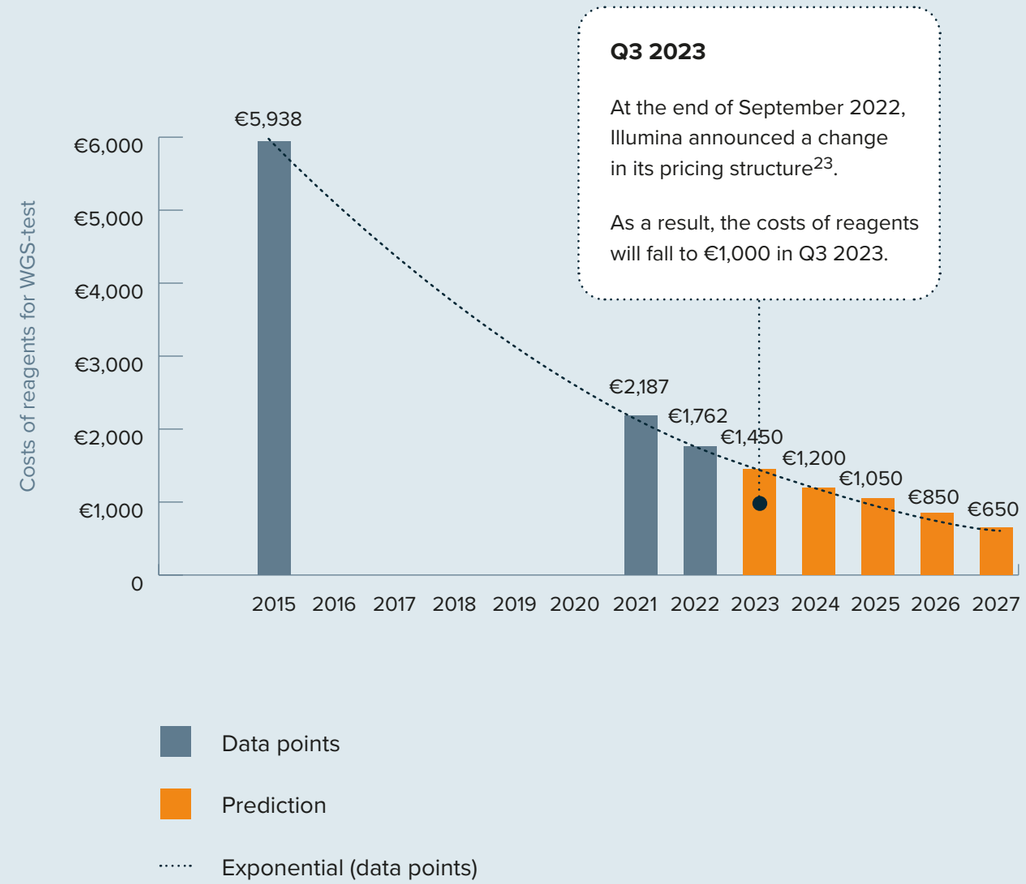
Assumption 2: Cost reduction of reagents.

A second assumption for the future scenario concerns cost reduction of WGS. The CEO of Illumina, Francis deSouza, a company with a dominant market position in equipment and reagents needed to perform WGS, has expressed during interviews that the '$100-Genome' is close[22]. In the implementation of WGS, 4 genomic analyses are performed. The tumour is analysed 3 times because normal cells are also present in the biopsy and additionally, a control analysis on the germline takes place to accurately determine which DNA changes have occurred in the tumour. The $100-Genome means that for WGS in cancer diagnostics the cost of the required reagents will eventually fall to $400.

The cost of reagents currently makes up ~70% of the total cost of a WGS test. Due to the decrease in the cost of reagents, the total cost of a WGS test will also be greatly reduced. In the coming 5 years, we expect a decrease in the cost of reagents per WGS test performed for tumour characterisation from €1,762 in 2022 to €650 in 2027. As a result, the total cost of conducting a WGS test will decrease from €2,500 in 2022 to ~€1,400 in 2027.

Figure 9

Costs of the WGS reagents; gray are the available data points, orange is the future scenario based on extrapolation of an exponential fitting



Assumption 3: Increase in the number of patients with metastatic disease of a solid tumour in the Netherlands.

In the Netherlands, each year approximately 21,000 people are diagnosed with a form of cancer that has already metastasised at the time of diagnosis. The Integral Cancer Centre the Netherlands (IKNL) is responsible for the National Cancer Registry (NKR) and published about this patient group in the report 'A view on metastatic cancer'[24].

In addition, there are patients with a primary tumour who, despite treatment, still get metastases. No exact numbers are known, but the IKNL estimates in the same report that the total number of people who had to deal with metastatic cancer in 2018, was between 35,000 and 39,000. Since 2017, the total number of cancer diagnoses has increased annually by ~1.7%[25].

For certain patients, treatment is not useful or not desired by the patient. Due to old age, condition and comorbidities, systemic therapy is not used in some of these patients. Systemic therapy is therapy that is applied throughout the body and not only locally. You must have a certain health status to tolerate this type of therapy. Before the start of systemic therapy, it is necessary to apply molecular diagnostics. The patient group that qualifies for broad molecular diagnostics is estimated to be 25,000 patients per year[10].

In this report, we work with the assumption that the distribution of all patients with metastases of a solid tumour across the different cancer types is equal to the distribution of people with metastatic cancer at first diagnosis.

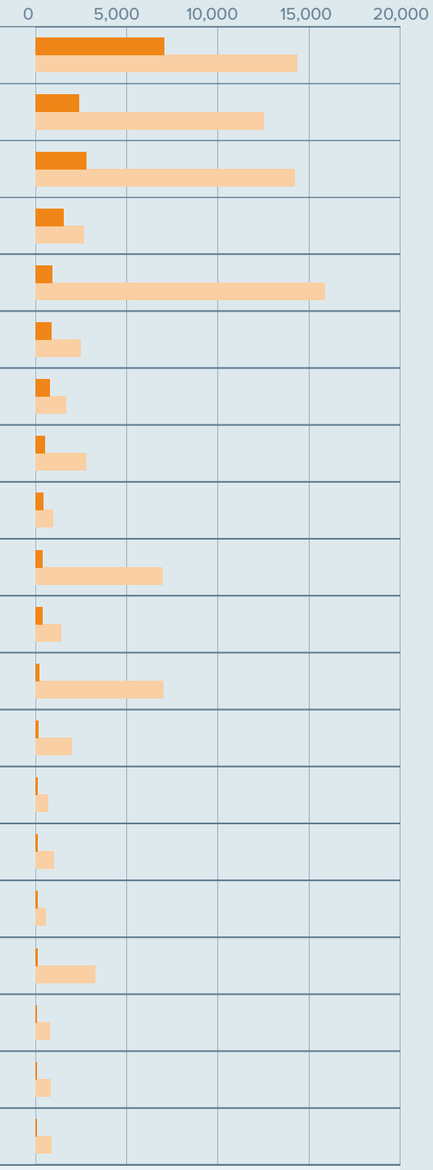
Figure 10:

* *Haematological malignancies, tumours of the central nervous system and squamous cell and basal cell carcinomas of the skin are not considered in this report because they do not or rarely metastasize.*
** *Metastases confirmed by pathologist.*
*** *Rare cancers: the total of all patients with a rare form of cancer.*

Figure 10

Number of patients with metastatic cancer broken down by cancer type[24]

Cancer type	Total diagnoses	Metastatic cancer at diagnosis		PA confirmed**
Lung cancer	14,322	**7,030**	**49%**	43%
Prostate cancer	12,505	**2,366**	**19%**	9%
Colorectal carcinoma	14,196	**2,777**	**20%**	46%
Pancreatic cancer	2,667	**1,534**	**58%**	49%
Breast cancer	15,859	**924**	**6%**	36%
Esophageal cancer	2,453	**875**	**36%**	36%
Stomach cancer	1,669	**767**	**46%**	49%
Kidney cancer	2,766	**505**	**18%**	47%
Bile duct cancer	934	**401**	**43%**	45%
Bladder cancer	6,976	**395**	**6%**	29%
Ovary and fallopian tube cancer	1,384	**386**	**28%**	53%
Melanoma	6,900	**207**	**3%**	78%
Uterine cancer	1,968	**167**	**8%**	54%
Liver cancer	709	**130**	**18%**	19%
Bone, cartilage and soft tissue cancer	988	**127**	**13%**	38%
Renal pelvis and ureteral cancer	565	**107**	**19%**	39%
Head and neck cancer	3,279	**95**	**3%**	33%
Cancer of the endocrine glands	796	**86**	**11%**	43%
Cervical cancer	836	**69**	**8%**	39%
Testicular cancer	848	**63**	**7%**	24%
Primary tumour unknown	1,356	**1,356**	**100%**	63%
Other cancer types	3,904	**664**	**17%**	46%
Total of all rare cancers***	15,014	**2,297**	**15%**	49%
Total of all cancers*	97,970	**21,031**	**21%**	41%



Based on these 3 assumptions, 4 domains are investigated in the economic evaluation.

1

Direct cost-comparison of different types of molecular diagnostics

For a number of major indications of metastatic solid tumours, we look at the tests needed to arrive at a complete diagnosis and treatment proposal, and how they compare in terms of costs. We show how this situation changes in the future with an increasing number of treatment targets and decreasing cost of WGS.

2

Additional benefits of WGS in the field of pharmacogenetics and germline diagnostics

In addition to molecular diagnostics at the tumour level, we describe additional benefits for 'secondary use' of the already available WGS information for pharmacogenetics (alignment of drug dosage) and germline diagnostics (hereditary of cancer genes) for clinical genetics.

3

Impact of the identification of the number of *non-responders* to the efficient use of drugs

The effective use of drugs and associated costs are also investigated. The use case for this is non-small cell lung cancer (NSCLC). We investigate whether using WGS can prevent inefficient use of drugs and what the economic impact is.

4

Impact of shorter lead time and higher quality of molecular diagnostics

In addition to financial benefits, we investigate the qualitative advantage of a higher and uniform quality of molecular diagnostics, including shorter lead time to correct diagnosis.

Wide implementation of WGS requires changes in the care pathway. We will discuss two of the most frequently mentioned concerns about these changes; the need for freshly frozen tumour tissue instead of in formalin (formalin-fixed paraffin embedded), and the higher demands on the minimum percentage of tumour cells that must be present in a biopsy. This is discussed in Chapter 4.

For domains 1-3, we not only make a direct comparison (diagnostic test A versus diagnostic test B per patient) but we also look at the impact of this on the total Dutch healthcare system in oncology. There are preconditions associated with scaling up from patient-level to system-level. We use data from previously presented analyses and case studies, supplemented with several assumptions about incidence (how common is a certain tumour type) and costs. In some areas, we make several assumptions to come to system-level values. These assumptions are explained in the text. In addition, we use the aforementioned estimate that 25,000 patients per year are treated with systemic therapy for metastatic solid tumours[10].

The overview below shows the number of assumptions that were needed to calculate the impact on the Dutch healthcare system. The number of full circles indicates the number of assumptions.

Domain	Number of assumptions	
Direct costs	●○○○○	Very few
Pharmacogenetics	●●●○○	Average
Clinical genetics	●●●●○	Many
Non-responders	●●○○○	Few

1

Direct cost-comparison of different types of molecular diagnostics

The comparison between the direct costs of the different types of molecular diagnostics is made by answering the following 2 questions.

1. **When is which type of molecular diagnostics needed?** There is a tipping point in molecular diagnostics when so many targets must be investigated that the use of broad molecular diagnostics is more effective than the use of stepped molecular diagnostics. When would this tipping point be reached?
2. **What is the cost difference between these types of molecular diagnostics?** We compare the cost of current stepped molecular diagnostics in different indications to the cost of broad molecular diagnostics with large panel + Archer and the cost of broad molecular diagnostics with WGS.

After answering these two questions, we can calculate the impact of the use of broad molecular diagnostics with WGS on the entire patient population (the number of patients for which broad molecular diagnostics is required multiplied by the cost difference between the 3 types of molecular diagnostics).

1. When is which type of molecular diagnostics needed?

There are several reasons to choose broad molecular diagnostics. This may be due to (the combination of) the search for a large number of targets, the size of the genes to be investigated, or the relevance of fusion genes and/or complex biomarkers for diagnosis. In various oncology indications, such as lung cancer, it is already necessary to use broad molecular diagnostics. With the increase of drugs targeting specific tumour characteristics, the tipping point at which broad molecular diagnostics is a necessity is expected to be reached soon[26]. This is a development which is currently also seen abroad[27].

The Dutch Healthcare Institute is researching the use of broad molecular diagnostics per oncology indication (tumour type). This involves creating a list of targets that must be known for different oncology indications to give a patient the right treatment. In this white paper we use the list currently under development by the Dutch Society for Medical Oncology (NVMO) and the Dutch Association of Doctors for Lung Diseases and Tuberculosis (NVALT) which will also be used as input for the Dutch Healthcare Institute. This list shows for which indications at what point in time it is necessary to use broad molecular diagnostics.

In a response to the Dutch House of Representatives (in Dutch: Tweede Kamer) about this list of minimally clinically necessary targets to be drawn up by NVMO, the following is noted:

> *Project group 1 is working on a list of minimally necessary molecular diagnostic tests (and associated treatments). This number is expected to be so high with the diagnosis of metastatic cancer that broad testing is necessary for virtually all types of cancer*[10].

Figure 11 shows that for a number of indications the use of broad molecular diagnostics is already desirable. This is due to the number of targets that needs to be investigated. The increase in targets means that within a few years almost all newly diagnosed metastatic tumours will require broad molecular diagnostics. This is accompanied by an increase in the number of patients for whom broad molecular diagnostics should be used (Figure 12). A conservative estimate is that by 2025, broad molecular diagnostics will be necessary for all metastatic tumours to effectively test all relevant targets. However, based on the results of the above-mentioned project group, this could also be earlier.

Figure 11

The number of targets to be investigated per indication determines the tipping point from stepped molecular diagnostics to broad molecular diagnostics[28]

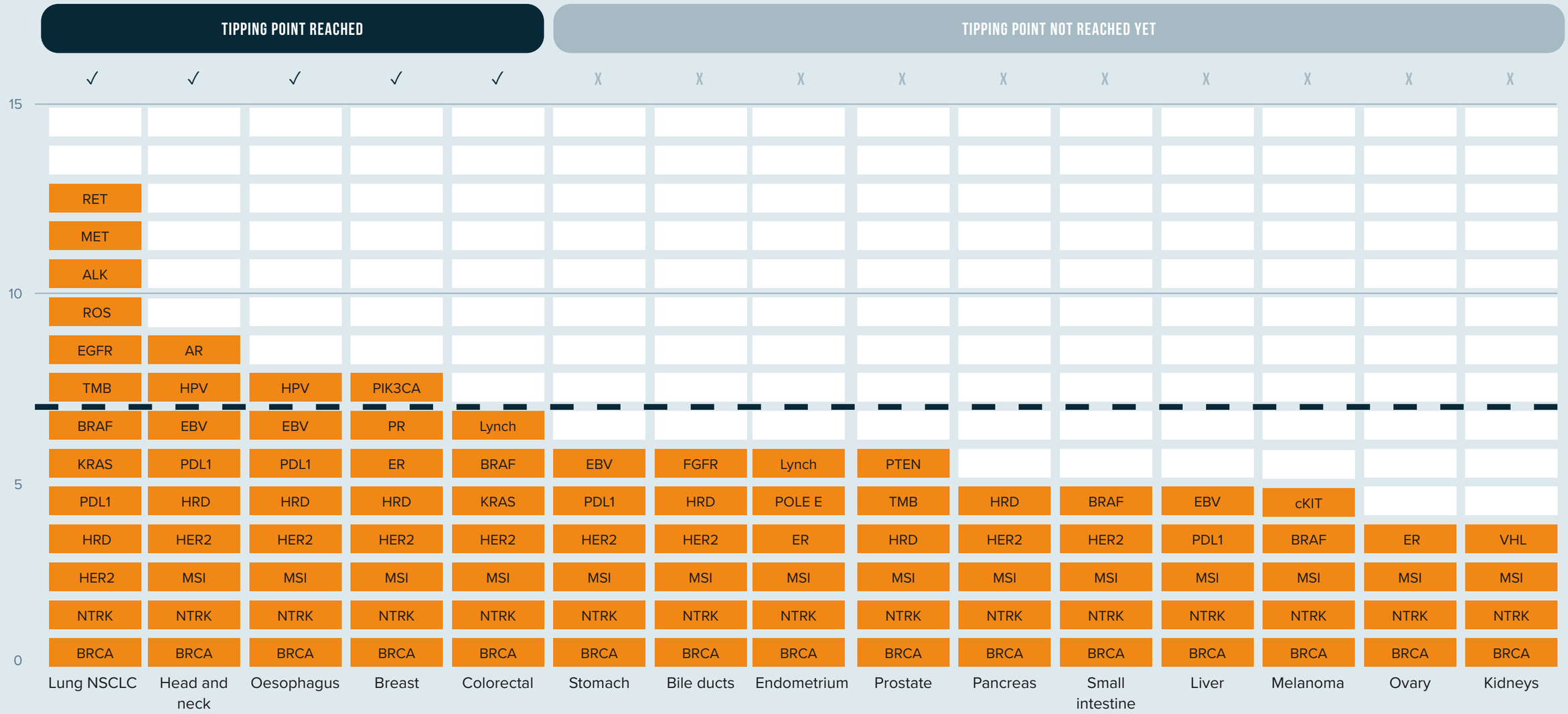
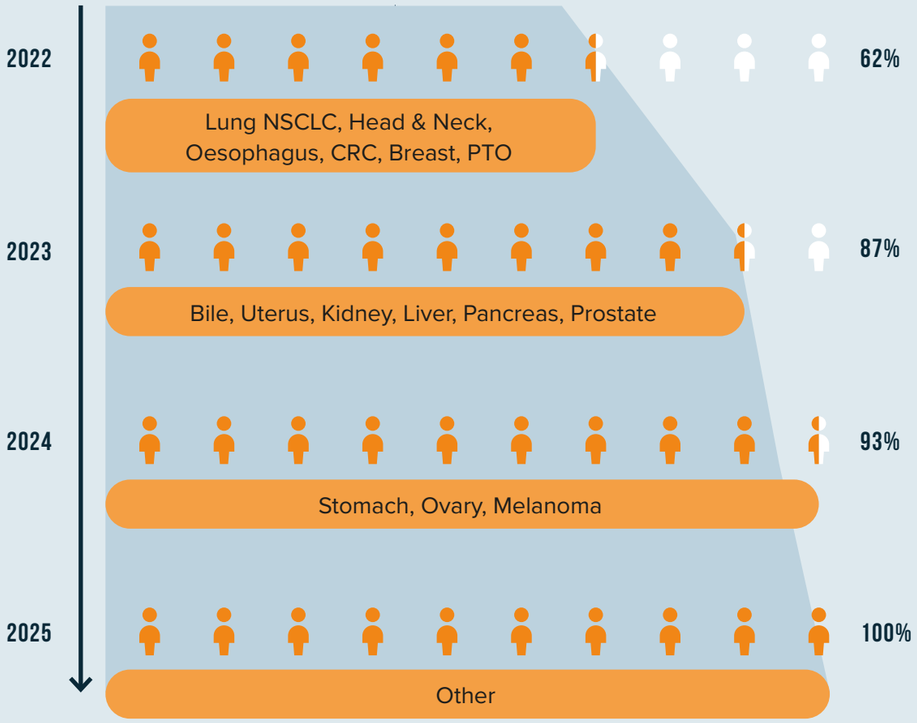


Figure 12

Prediction of the **percentage of patients with metastatic solid tumours** where broad molecular diagnostics are necessary based on the increasing number of targets for which treatments exist[24]



% of the total patient population with metastatic solid tumours

In 2025, it will be necessary for almost all newly diagnosed metastatic solid tumours to use broad molecular diagnostics due to the increasing number of molecular targets that require testing.

2. What is the cost difference between these different types of molecular diagnostics?

In the white paper, we mapped the actual cost of molecular diagnostics in the indications Primary Tumour Unknown (PTO), non-small cell lung carcinoma (NSCLC), melanoma, gastrointestinal stromal tumour (GIST) and colorectal carcinoma (CRC). Together, these tumour types represent about half of the total patient group eligible for broad molecular diagnostics (25,000 patients)[10,24,29]. The tests done on this patient population over one year were mapped and the average diagnostic costs per patient were calculated.

This cost comparison is made based on data from the pathology laboratory of *hospital A* and has been validated with the data from *hospital B*. All patients who underwent molecular diagnostics were included in this dataset. This concerns a total of more than 800 patients. To estimate the cost of WGS, the microcosting study by Pasmans et al., was used.[30,31.]

The results of the evaluation show that at present the cost of broad molecular diagnostics and the current cost of stepped molecular diagnostics are already similar to each other for the indications PTO and NSCLC[32]. For other indications, stepped molecular diagnostics is still cheaper because the number of targets that must be tested according to guidelines is still limited.

Types of molecular diagnostics for metastatic tumours

For the economic evaluation, the cost prices of three different types of molecular diagnostics were compared.

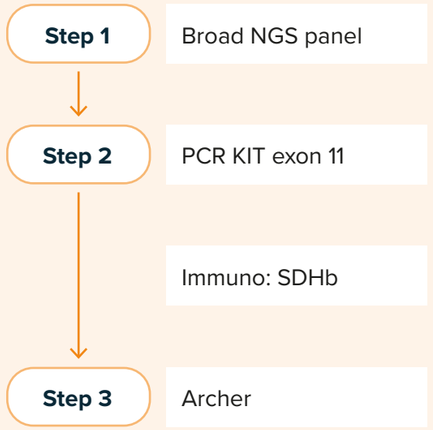
1. Stepped molecular diagnostics
2. Broad molecular diagnostics with large panel + Archer
3. Broad molecular diagnostics with WGS

Example of stepped molecular diagnostics

In Gastrointestinal Stroma Tumour (GIST), the following stepped molecular diagnostics strategy exists, see Figure 13. If no mutation is found in the first step, the second step of diagnostics is carried out. This process of stepped diagnostics for patients with GIST may vary slightly per hospital.

The cost of the stepped molecular diagnostics for the different indications has been calculated as explained in 'Technical explanation of the economic evaluation' and is shown in Figure 14. In addition, the cost of broad molecular diagnostics with large panel + Archer and with WGS are also plotted here. In 2022, the costs of large panel + Archer are around €2,060 and the cost of WGS have been estimated at €2,500. This puts the difference in costs between a large panel + Archer and WGS at €440.

Figure 13
Stepped molecular diagnostics GIST



Technical explanation of the economic evaluation

Data specification

The cost of the molecular and immunological determinations include direct and indirect personnel costs, reagent costs, other material costs (including required machines and lab equipment), and overhead (45% of personnel costs). Costs for the innovation of tests are not included. Where any costs were missing, an estimate of these costs was made which was then validated with interviewees in the hospital concerned.

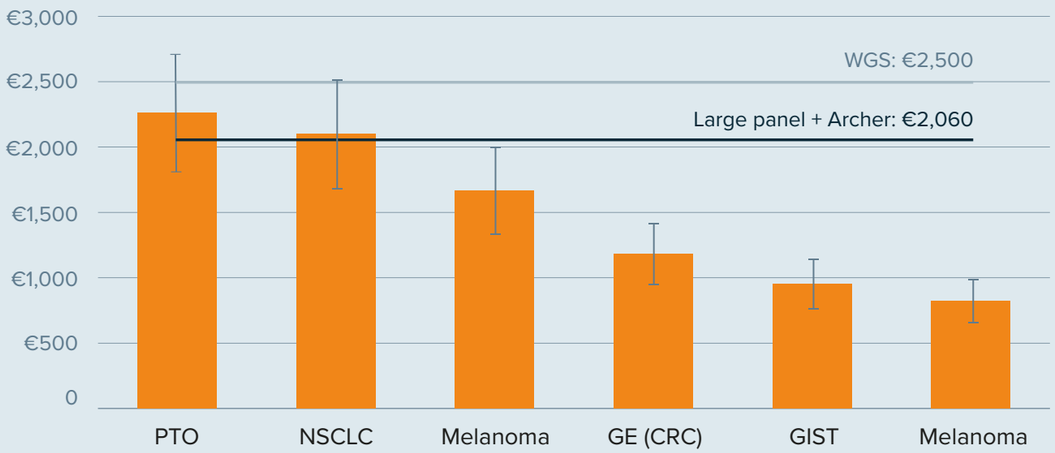
To correct for possible differences between hospitals and to ensure confidentiality of the data, a bandwidth of costs is displayed. All analyses have been validated by staff from the pathology departments.

Molecular Determination	Definition	Admin code
No test in the examined routings fell under this admin code	Simple molecular diagnostics - determinations on sections with tissue and/or cells due to frequently requested determinations for the presence of HPV	050513
FISH: FGFR1 FISH: MET RT-PCR MET exon14del PCR KIT exon 11	Pathological examination - simple molecular diagnostics on tissues and/or cells on a limited number of genes and/ or microorganisms (excluding HPV)	050541
Hotspot panel	Pathological examination - complex molecular diagnostics on tissues and/ or cells on a limited number of genes	50543
Broad NGS panel Archer	Pathological examination - complex molecular diagnostics on tissues and/or cells on multiple genes	50544
Immunological determinations (MLH1, MSH2, PMS2, CEA, Her2, PDL1 22C3, BRAF, TRKpan, Her2 DISH, MSH6, SDHb) are not covered by these admin codes		

The evaluation was done based on a dataset from 2021.

Figure 14

Cost of the current type of molecular diagnostics (stepped diagnostics) compared to cost of broad molecular diagnostics in 2022. For melanoma, two different routes are included; the medical urgency determines which route is applied. For more urgent cases, more targets are tested in step 1.



For some indications, the costs of broad molecular diagnostics (with large panel + Archer) in 2022 are (almost) equal to the costs of stepped molecular diagnostics. For most indications, stepped molecular diagnostics is still cheaper. For these tumour types, a limited number of drugs are available and only a few targets need to be tested.

Technical explanation of the economic evaluation

Current cost of stepped molecular diagnostics

The costs for the different tests of stepped diagnostics have been calculated. Next, the percentage of patients receiving the different tests was determined and used to calculate an average price per patient. Below is an example of the calculation of the cost for GIST (the same procedure was followed for other indications).

Current cost of large panel + Archer

The average price for broad molecular diagnostics with large panel + Archer (and any individual tests) was estimated by adding up the cost of a large NGS panel, a test on Archer fusion genes, and some individual tests. In this approach, all patients receive all tests. The total costs add up to €2,060.

Current cost price WGS

The current price of the WGS test in 2022 is €2,500 per patient[30].

Stepped diagnostics GIST	% of patients who go through this step	Cost range per determination	Cost per patient
Broad NGS panel	100%	€600 - €900	€600 - €900
PCR KIT exon 11	27%	€750 - €950	€203 - €257
Immuno: SDHb	27%	€20 - €40	€5 - €11
Archer	15%	€950 - €1,250	€143 - €188
Average cost of stepped molecular diagnostics per patient			**€950 - €1,355**

Note: These numbers are illustrative and include a range to ensure confidentiality and accommodate for differences between hospitals

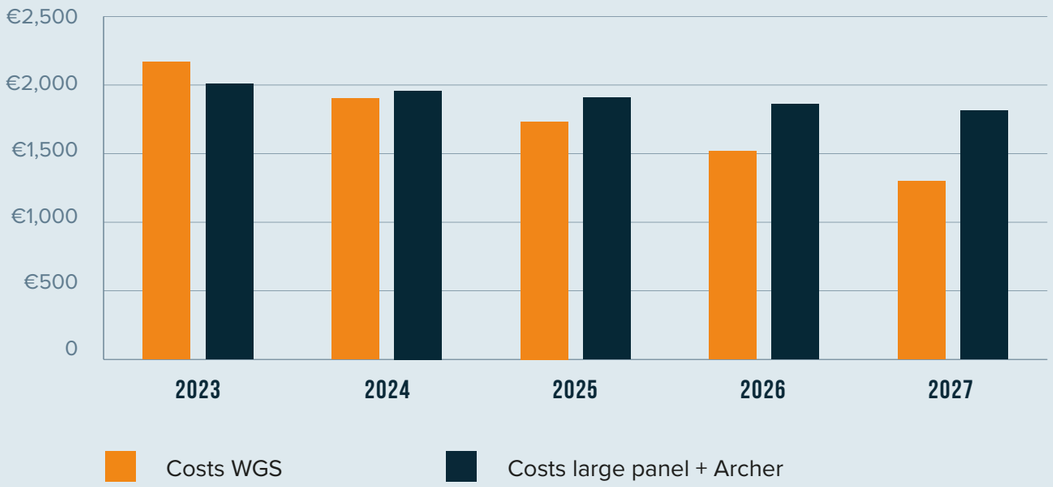
Plotting the future scenario up to 2027

If we model the cost development of both large panel + Archer and WGS up to 2027, we see that in 2024 the price of WGS (€ 1,902) is lower than the price of a large panel + Archer (€ 1,958). Other decreases in costs are not included in this evaluation as there are still many uncertainties. In 2024, the tipping point is reached and it becomes cheaper to use WGS instead of a large panel + Archer.

From 2024, it is cheaper to use WGS for broad molecular diagnostics, instead of large panel + Archer.

Figure 15

Comparison between the two types of broad molecular diagnostic



Technical explanation of the economic evaluation

Decrease in WGS cost

The decrease in cost of WGS is based on:

- Cost reduction of reagents (~70% of total costs), as explained in Chapter 2
- Cost reduction of 2.5% in other costs (~30%).

Decrease in price of large panel + Archer

The price decrease of large panel + Archer is based on a cost decrease of 2.5% per year with a baseline of € 2,060 in 2022. This was chosen because with a large panel, a smaller percentage of the total costs are reagent costs. As a result, the price drop for this type of broad diagnostics will be lower.

Figure 16

Cost of the reagents for WGS; gray is the available data points, orange is the future scenario based on extrapolation of an exponential fitting

Budget impact on the Dutch healthcare system: different types of molecular diagnostics

Multiplying the estimated number of patients requiring broad molecular diagnostics over time by the price difference between broad molecular diagnostics with large panel + Archer and broad molecular diagnostics with WGS over time, brings us to the impact of the use of WGS on the entire patient population.

Example 2022: 25,000 patients (patient group eligible for broad molecular diagnostics) * 62% (% requiring broad diagnostics) * €440 (cost difference large panel + Archer and WGS) = € 6,829,300.

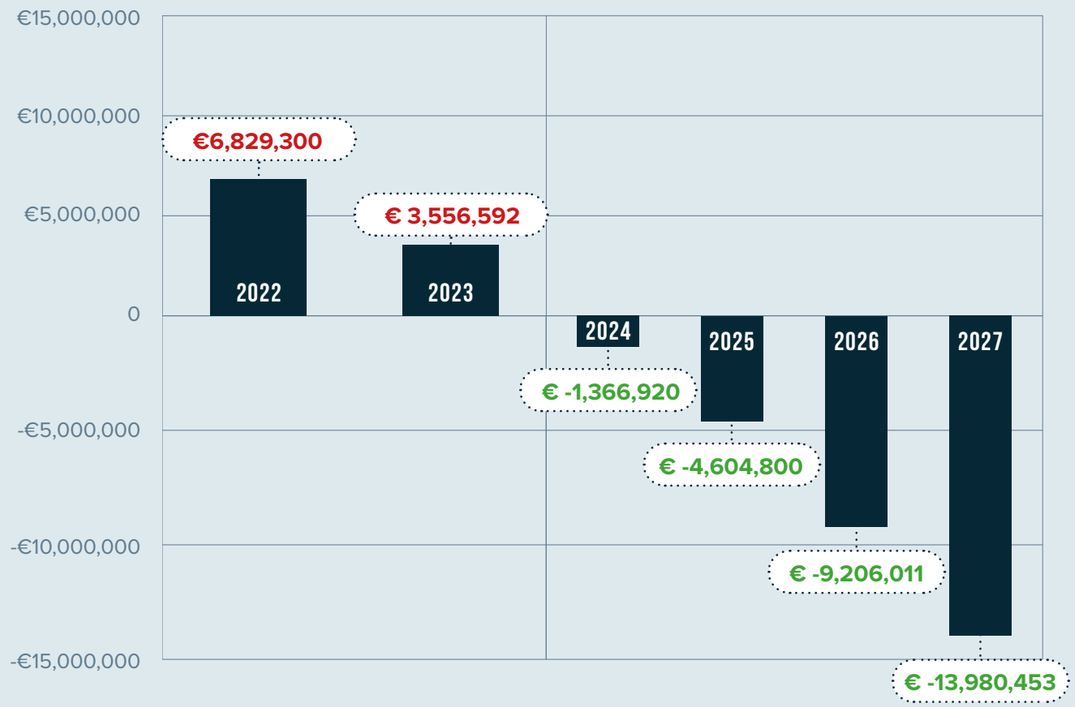
The budget impact for the use of WGS in the indications where broad molecular diagnostics is necessary thus comes to a total extra cost of €6.8M in 2022, equal to €273 per patient, compared to the use of broad molecular diagnostics with a large panel + Archer for these patients. In 2023, these extra costs will drop to €3.6M or €140 per patient. This drop is caused by the decreasing price difference between large panel + Archer and WGS.

In 2024, we see a tipping point in the costs. From this moment on, the cost of using WGS is lower than the cost of using broad molecular diagnostics with large panel + Archer. In 2024, the use of WGS in broad molecular diagnostics costs €1.4M less than the use of a large panel + Archer, equal to €53 per patient. In 2027, this cost difference will have risen further to €14M, or €515 per patient, in favour of WGS.

In 2022, the extra cost of using WGS in broad molecular diagnostics will amount to approximately €6.8M. From 2024 onwards, the cost of using WGS in broad molecular diagnostics is lower than the cost of using a broad panel + Archer. The saving in 2027 amounts to €14M.

Figure 17

Budget impact of the broad use of WGS per year from 2022 to 2027.
Calculated by multiplying the patient population requiring broad molecular diagnostics by the price difference between ‘large panel + Archer’ and ‘WGS’



2

Additional benefits of WGS in the field of pharmacogenetics and germline diagnostics

There are additional diagnostic test results that are available with a WGS-report at no extra cost, whereas for other types of molecular diagnostics, these results would need to be obtained via additional tests. This includes diagnostic tests for pharmacogenetics and the mapping of germline mutations for clinical genetics.

Pharmacogenetics establishes the interaction between medicinal products and the genetic profile of the patient. This is a relatively new field that studies whether the patient's genetic profile also plays a role in the effectiveness and tolerability of treatments. Traditionally, only so-called drug-drug interactions were looked at, but it is becoming increasingly clear that the patient's genetic profile and the drug-gene interactions[33] play an important role in the tolerability of the medication and the effectiveness of the treatment.

A recent example of this is the screening for the UGT1A1 gene when using irinotecan, a chemotherapy mainly used in the treatment of colon and pancreatic cancer. The presence of a specific variant of this gene increases the risk of severe side effects because the patient is less likely to break down the chemotherapy. Pre-estimating the patient's metabolism by genetic screening helps to determine the correct dosage in advance and minimise the risk of (severe) side effects[34]. During a Dutch Society for Medical Oncology conference, 71% of oncologists expressed their desire to introduce this additional test as soon as possible[35].

Another example of pharmacogenetics is the presence of dihydropyrimidine dehydrogenase (DPD) deficiency with 5-fluorouracil (5-FU) treatment. Genetic profiling of this gene can also predict the patient's response to treatment. By downwards adjustment of the dosage for specific patients, serious side effects can be prevented as much as possible[36]. This is already included in the treatment guideline and a specific test for this is currently carried out separately.

Inclusion of these tests in the guidelines will prevent many serious treatment-related side effects. However, including the UGT1A1 gene test in current stepped molecular diagnostics involves additional costs. A single test for UGT1A1 costs €83[34] and the average costs of such tests (for other genes) are about €75 per test[37].

If broad diagnostics with WGS is used, these targets are automatically analysed, but it is also possible to draw up a complete pharmacogenetic passport for side effects or dosages of other medications that patients with cancer often receive (such as pain relief). This currently untapped but relevant information can be quickly incorporated into clinical practice at no extra costs. This not only saves testing costs, but also avoids suffering and extra care needed for patients by preventing predictable and therefore unnecessary side effects.

The impact on the Dutch healthcare system: in the field of pharmacogenetics

Most patients with cancer suffer from treatment-related effects. One of the causes is the interaction between oncolytics and the tumour; drug-gene interactions. Research in this field is rapidly evolving, understanding is limited on the prevention of these interactions and the impact on costs. UGT1A1 is now in play, while the DPD gene has taken years to get properly into the system. Standardised analysis of this DPD gene is now consistently done, but healthcare (and especially the patient) has long suffered from poor implementation and varied interpretation between hospitals.

Germline diagnostics

WGS can also be used to trace germline mutations, which can be used to determine the hereditary risk of cancer. In the current care pathway, patients are referred to the clinical genetics department where individual DNA tests are performed. Patients with a suspicion of hereditary predisposition are referred to this department, including patients in whom ultimately no germline mutation is found. With WGS, this information is already available. As a result, only the molecular interpretation and counselling is required and the need for additional DNA testing at the clinical genetics department is eliminated.

It is estimated that in 5-15% of patients with metastatic cancer a relevant genetic (cancer) predisposition mutation is present and clinical genetics research may be desired (depending on patient preference)[38]. However, referral does not always occur. From healthcare consumption data we estimated that referral takes place in almost 3% of cases[39]. The cost of germline diagnostics for clinical genetics is estimated at ~€1,665[40]. With WGS, it is possible to detect all patients with a suspicion of clinical predisposition, allowing more targeted referral of patients. This increases the number of correctly referred patients and prevents referrals that (afterwards) were proven unnecessary. The estimated percentage of "incorrect" referrals amount to 50% of the current number of referrals[41]. Use of WGS avoids the costs incurred for patients where no clinical predisposition appears to be present.

Budget impact on the Dutch healthcare system: in the field of clinical genetics

Although a referral to clinical genetics is desirable for 5-15%[38] of patients, today only about 3% of patients are referred. If we multiply the cost of clinical genetic research (~€1,665[40]) by this 3%[39], this amounts to a total cost of €1.2M per year, or €47 per patient, of the total patient population. These costs can be avoided by using broad diagnostics with WGS in oncology diagnostics, which also greatly improves clinical genetic care without additional costs as more patients are adequately diagnosed.

Use of WGS to prevent referrals to clinical genetics has an annual savings potential of €1.2M, or €47 per patient. Taking these additional financial benefits into account for clinical genetics (€1.2M) will increase the attractiveness of using WGS in 2022. The extra cost of using WGS instead of a large panel + Archer will then be €5.7M in 2022, or €227 per patient instead of €6.8M.

The tipping point, where the use of WGS costs less than the use of broad molecular diagnostics with a large panel + Archer, will remain in 2024 but the difference in costs in the years before is smaller.

The size of the additional benefit for pharmacogenetics depends on the number of new markers (such as UGT1A1) for drug tolerability. The more markers, the greater the additional benefit. There is insufficient insight into the size of this additional benefit, and it is therefore not included in Figure 19. The realised magnitude of the additional benefit of clinical genetics depends on the speed of implementation in clinical practice. In this white paper we distinguish between the direct cost comparison and a comprehensive comparison including the potential additional benefits of using WGS for broad molecular diagnostics.

With the implementation of WGS, (significant) benefits for patients and finances can be realised in both pharmacogenetics and clinical genetics. These benefits are added on top of the direct cost comparison in molecular tumour diagnostics.

Figure 18

Patient-level overview of the cost comparison between WGS and large panels with and without additional benefits of pharmacogenetics and clinical genetics from 2022 to 2027

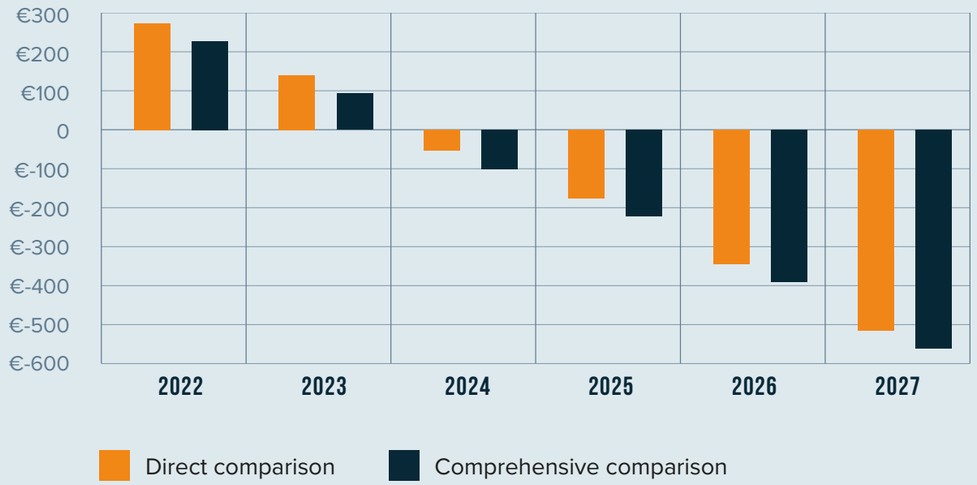
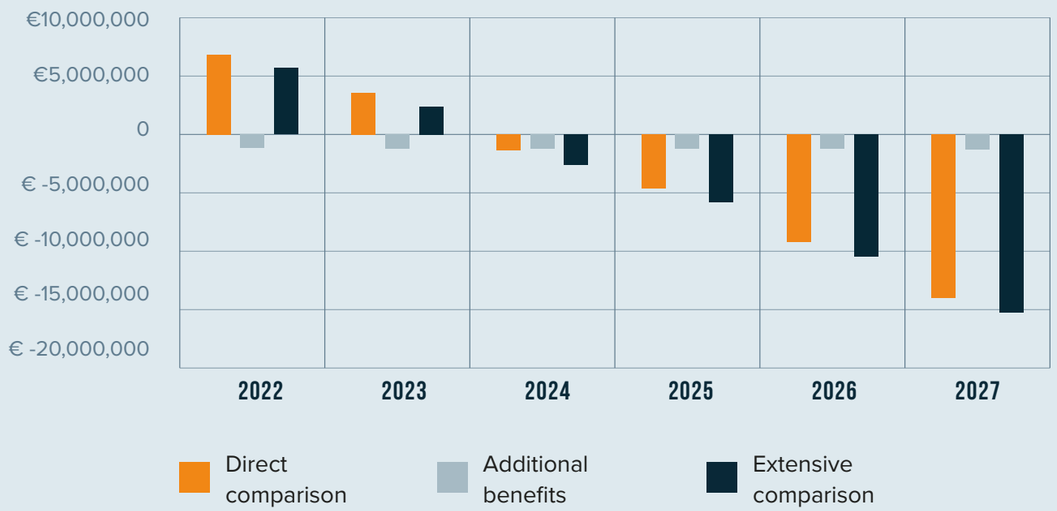


Figure 19

Healthcare system-level overview of the cost comparison between WGS and large panels with and without additional benefits of pharmacogenetics and clinical genetics from 2022 to 2027



3

Impact of the identification of the number of non-responders to the efficient use of drugs

Getting the right treatment is essential for the patient. Reducing overtreatment is becoming increasingly urgent given the pressure on the healthcare system. There is still large untapped potential to better choose the right treatment and thus increase effectiveness of drugs. Good tumour characterisation with molecular diagnostics can contribute to this. We demonstrate this potential with a use case of non-responders to immunotherapy (check-point inhibitors) in non-small cell lung carcinoma (NSCLC).

A non-responder is a patient who does not benefit from medication after two to three months of treatment after which treatment is discontinued. In this use case, we look at the percentage of non-responders who could have been predicted prior to treatment.

In the Van de Haar et al. publication WGS data of 75 NSCLC patients was used. The WGS data was used for diagnostics to make treatment choices for patients, but it was also the source for finding markers (genetic characteristics) that could predict non-response. Thus, the WGS-knife cuts two ways. On the one hand, by its nature (most complete DNA test), it brings into focus all treatment options for today's patients. On the other hand, it is a unique source for further research, that through the same comprehensiveness, can provide greater efficiency of (expensive) treatments. This requires a 'central' storage of WGS data (which is already available in the Netherlands through the publicly accessible Hartwig Medical database). This data infrastructure enables a system in which measurement of treatment effectiveness and the identification of groups of non-responders can become a structural part of the healthcare system.

Technical explanation of the economic evaluation

Per Van de Haar et al., (under revision) it appears that a subset of NSCLC patients with specific characteristics does not respond to monotherapy nivolumab or pembrolizumab. Treatment with these products is currently determined on the basis of PDL1 expression (by immunohistochemistry):

- **PDL1 expression >50%** immunotherapy as monotherapy in the first line of treatment.
- **PDL expression 1-50%** first-line treatment with immunotherapy in combination with chemotherapy or chemo monotherapy first line. Followed by immunotherapy upon progression, when they have not been previously treated with immunotherapy. Patients with an EGFR, ALK or ROS mutation are first given targeted therapy.

In our use case we investigate 3 different patient groups that fit the patient characteristics as described by Van der Haar et al.

- Nivolumab in locally advanced or metastatic NSCLC in adults, as monotherapy after prior chemotherapy treatment.
- Pembrolizumab monotherapy as a first-line treatment of metastatic NSCLC with PDL1 expression with a tumour proportion score (TPS) ≥ 50% without EGFR or ALK-positive tumour mutations in adults.
- Pembrolizumab monotherapy in locally advanced or metastatic NSCLC with PDL1 expression with a TPS ≥ 1% and with at least one prior chemotherapy used in adults. If EGFR- or ALK-positive tumour mutations are present, the approved treatments before starting pembrolizumab treatment should also have been given.

In the recent study by Van de Haar et al., on treatment effectiveness of immunotherapy in NSCLC, WGS data was used to investigate a predictive marker that identifies non-responders to treatment[42]. This was demonstrated in a retrospective study context. A prospective validation study is yet to be conducted.

The study looks at the use of nivolumab and pembrolizumab, which are both immunotherapies that target the PD-1 receptors in metastatic NSCLC. Every year, more than 7,000 people are diagnosed with this type of cancer. The above-mentioned study shows that by using WGS, non-response could be predicted before treatment in 27% of cases.

The money for treating these patients has therefore been used inefficiently. Calculation of this impact is based on the number of patients treated[43], the average treatment duration, and the number of treatment cycles leading up to non-response[44,45,46], the price per cycle[47], and the non-response rate. It is important to note, that it is not about direct savings, but about preventing inefficient use of scarce financial resources. After all, we could also use these resources to pay for treatments that do work and are not unnecessarily toxic to the patient.

Technical explanation of the economic evaluation

The total costs are calculated in four steps. To illustrate this, the calculation of nivolumab is explained below.

1. Calculating the number of non-responders

The number of patients expected to use nivolumab (low: 3,063, high: 4,928) for this indication multiplied by the percentage of these patients expected to be non-responders (27%). This gives a range of 817 to 1,314 patients.

2. Calculating the number of milligrams (mg) of drug

The average amount of drugs used by non-responders was calculated by multiplying the average number of treatment cycles until the first response assessment at week 6 by the average volume of drug per kilogram (kg) multiplied by body weight (the average weight according to the Dutch Statistics Bureau (CBS) in the Netherlands in 2020 was 78.1 kg). The drug volume per patient was then multiplied by the total number of non-responders, which adds up to a range of 574,129 mg to 923,704 mg.

3. Calculate price per milligram

The list price, as laid down in the Pharmaceutical Compass (in Dutch: Farmaceutisch Kompas), deducted by the average negotiated discount after lock procedure (45%).

4. Calculating the total costs of inefficiently used dugs

The discounted price per mg (€8.14) multiplied by the total drug volume for non-responders gives a range of €4,675,839 to €7,522,865

In this evaluation a time of 6 weeks was included in the first response assessment. In practice, however, this sometimes only happens after 8 to 12 weeks. We have chosen 6 weeks to make a cautious approach to the costs.

Figure 20

Cost-saving for non-responders NSCLC

	NIVOLUMAB	PEMBROLIZUMAB		
NSCLC subpopulation	**2L stage III-IV after chemo**	**1L PDL1 ≥ 50%; EGFR- or ALK+**	**2L PDL1 ≥ 1% after chemo; EGFR+ or ALK+**	
Average number of patients treated*	**3,996 patients** *(3,063 – 4,928)*	**666 patients** *(615 – 717)*	**882 patients** *(615 – 1148)*	Total: 5,543 patients
Non-responder rate	✕ **27%**	✕ **27%**	✕ **27%**	
Average number of non-responders	**1,065 patients** *(817 – 1,314)*	**178 patients** *(164 – 191)*	**235 patients** *(164 – 306)*	
Average amount (mg) until discontinuation of treatment per patient**	✕ **703 mg**	✕ **400 mg**	✕ **312 mg**	
Average mg total	**748,917 mg** *(574,129 – 923,704)*	**71,038 mg** *(65,575 – 76,501)*	**73,435 mg** *(51,234 – 95,636)*	
Costs per mg***	✕ **€8,14** *(€14,81*55%)*	✕ **€20,89** *(€37,98*55%)*	✕ **€20,89** *(€37,98*55%)*	
Total costs of inefficient use of treatment	**€6.1M** €4.7M – €7.5M	**€1.5M** €1.4M – €1.6M	**€1.5M** €1.1M – €2.0M	Total: €9.1 million
Average per patient	**€1,527**	**€2,228**	**€1,740**	Weighted average: €1,645 per patient

* Patient numbers according to label studies

** It is common to do the first response assessment after 6 weeks, so this was used as duration of treatment.

*** List price (source: Farmaceutisch Kompas) deducted by the average negotiated discount after lock procedure (45%). Source: letter to parliament 'Progress letter financial arrangements 2020'

Uncertainties still remain about the identification of non-responders. Studies are conducted with small groups of patients and a prospective estimate has its limitations. Other treatments have often already been given based on progressive insight and (early) evidence from practice, thus studies on therapies lag behind reality, as in the use case around PD-1 monotherapy for NSCLC. However, several similar studies are taking place of which the results point in the same direction. Identification of non-responders is possible if there is sufficient information for such research. The markers can be identified quickly and retrospectively using WGS.

There is large potential to identify non-responders through the use of WGS. In this example, €1,645 per patient is inefficiently used, which could be avoided. Annually, an inefficient use of €9.1 million could be prevented in an average of ~5,500 patients. Validation of these findings with a prospective study is yet to take place.

Technical explanation of the economic evaluation

Variable	**Sources** *(method and sources have been validated with oncologists)*	
% non-responders	*under revision*	Van de Haar et al.
Number of patients	Budget impact analyses by Dutch healthcare Institute (ZIN)	Nivolumab: *https://www.zorginstituutnederland.nl/publicaties/adviezen/2015/12/08/pakketadvies-nivolumab-opdivo* Pembrolizumab*: *https://www.zorginstituutnederland.nl/over-ons/publicaties/adviezen/2016/12/14/pakketadvies-pembrolizumab-keytruda*
List price of drugs		
Average treatment duration	Time to the first response assessment	*https://www.nvmo.org/bom/pembrolizumab-met-chemotherapie-als-eerstelijns-behandeling-voor-gemetastaseerd-plaveiselcelcarcinoom-van-de-long/*
Average volume of drug, per month/kg	Studies submitted by label	Nivolumab: *https://www.nejm.org/doi/full/10.1056/nejmoa1504627* Pembrolizumab: • *https://www.nejm.org/doi/full/10.1056/nejmoa1606774 (1L)* • *https://www.thelancet.com/article/S0140-6736(15)01281-7/fulltext (2L)*
Average weight of Dutch people 2020	Dutch Statistics Bureau (CBS)	*https://opendata.cbs.nl/statline/#/CBS/nl/dataset/81565NED/table?fromstatweb*
Negotiated discount on drugs	Letter to Dutch Parliament: Progress letter financial arrangements 2020	*https://www.rijksoverheid.nl/documenten/kamerstukken/2020/12/18/kamerbrief-over-voortgangsbrief-financiele-arrangementen-2020*

* A budget impact analysis for pembrolizumab (indication 1L PDL1 ≥ 50%; EGFR or ALK+) was not available. Therefore, the same budget impact analysis as for pembrolizumab was used (indication 2L PDL1 is ≥ 1% after chemo; EGFR+ or ALK+).

Budget impact on the Dutch healthcare system: identification of non-responders

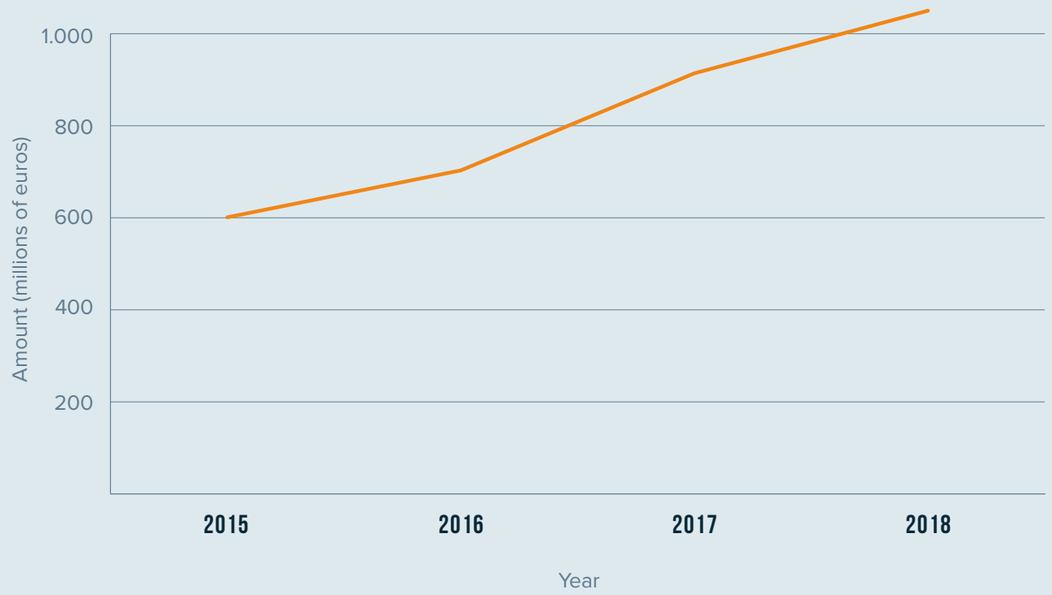
The use case in NSCLC shows that a saving of ~€1,645 per patient can be realised as 27% of patients were given a treatment that was not effective. For other indications, the percentage is still unknown. Suppose this percentage applies to every indication. If we extrapolate this to the total Dutch population, this amounts to €41.1M per year in avoidable overtreatment costs. This is a big amount – about 4% of the total expenditure on oncolytics in 2018[48] in the Netherlands. This expenditure has been rising for years and is the largest cost implication for expensive drugs[49].

At a time when efficiency is essential, this use case highlights the potential to reduce overtreatment. The use of WGS, combined with the construction of data infrastructure, enables a system in which such choices become a structural part of the healthcare system.

Extrapolation of the use case around the identification of non-responders shows that there is great potential to reduce overtreatment costs exceeding €41M per year. By using WGS, coupled with the availability of appropriate clinical data, we can start to exploit this potential.

Figure 21

Spending on oncolytics in the Netherlands, 2015 to 2018. Source: Vektis[49]



4

Impact of shorter lead time and higher quality of molecular diagnostics

Patients who are diagnosed with metastatic cancer face a very unpredictable time with uncertainty about the severity of disease and treatment options. Many patients struggle with questions such as: “What are the chances of healing, and how much time do I have left?” This is why it is important for patients to rapidly receive a complete diagnosis based on the latest scientic insights.

It is important for a patient that both diagnostics and treatment meet the latest (scientific) insights (state of science and practice).

Molecular diagnostics with WGS uses software (a bioinformatic pipeline) that guarantees uniformity of test results, regardless of where they are performed.

Impact of shorter lead time for patients

WGS is the technology that measures all characteristics of DNA, including characteristics of which relevance remains unknown, but can therefore be used for research. For tumour analysis for diagnostic purposes, only those characteristics are reported that have been found to be relevant according to the current ‘state of science and practice’ by the Dutch Healthcare Institute.

However, with each subsequent scientific finding about a treatable target, no extra measurement is required, simply adjusting the reporting software is sufficient. This is usually ready within a few weeks and immediately applicable nationwide.

In molecular testing with a large panel, the additional measurements must first be determined, then a (new) customised test must be developed or procured for it, and then it must be validated in the lab. As indicated earlier, this can take months to years.

Pathology laboratories now spend part of their time validating and adapting tests to incorporate new developments. The long lead time for implementation is partly caused by the fact that adjustments are ‘hoarded’ because of the laborious and expensive follow-up process. It is estimated that analysts spend about 5% of their time validating these modified or new molecular diagnostic tests[52]. In a large diagnostic lab, this easily adds up to 1 FTE, which can be prevented with the implementation of WGS. At 46 laboratories (national estimate in the Netherlands), this translates to reduction of inefficient use of scarce professionals[53] and significant financial savings.

The use of WGS can prevent unnecessary anxiety for patients because there is greater certainty about the most up-to-date diagnosis – and therefore the most appropriate treatment choice – and doctors can treat based on the latest (scientific) insights.

Patient story

Astrid Nollen-De Heer, patient advocate

Astrid was cured of cancer thanks to an innovative drug she received as part of a study. The drug that healed her was registered shortly thereafter. Nevertheless, it was still months before patients in the Netherlands were given access to this medicine, because of discussions about price and reimbursement. It motivated her to work as a patient advocate to improve the treatment of cancer in the Netherlands and empower patients. She does so with great knowledge of the organisation and financing of healthcare in the Netherlands.

Astrid observes that ‘zip code healthcare’ exists in the Netherlands: access to treatments depends on the diagnostic technique used, which in turn depends on the hospital where you are treated as a patient. Reluctance to use innovative and effective diagnostics and treatments is still too often driven by financial incentives.

According to her, the timeliness of an appropriate diagnosis is crucial. It prevents a patient from undergoing treatments that only weaken him or her, further impairing the quality of life and the chance of survival.

In order to achieve a timely appropriate diagnosis, broad molecular diagnostics with WGS plays a major role. Astrid therefore advocates that this broad molecular diagnostics test is made available to more patients at an earlier stage so under- and overtreatment are prevented. There should be no ‘zip code diagnostics’.

This calls for new standards for the wider and earlier application of WGS. Use of WGS in every patient, even at the earliest disease stage, is too much and not efficient. But only using WGS in patients who are in a very advanced stage of their disease is too little and too late.

According to Astrid, not using WGS or, not using it in time for fear of finding a mutation for which only expensive therapies exist, is not ethical. You should not withhold appropriate treatment from patients.

At the same time, WGS can also accelerate the understanding that no appropriate therapy is available. This provides clarity and contributes to the patient’s quality of life in the last phase of their life.

Difference in effectiveness between different types of diagnostics

The advantages of different types of molecular diagnostics have already been mentioned previously. In the WIDE study involving more than 1,000 Dutch patients, it was shown that WGS finds all targets that are found with all other molecular tests[50]. Furthermore, additional clinical benefits of molecular diagnostics with WGS have been demonstrated for specific tumour types. Schippers et al., published a study on WGS in 83 patients diagnosed with sarcoma[51]. Patients underwent both the normal diagnostic route and diagnosis with WGS; both routes were compared. Heterogeneous and diagnostically complex tumour type in which up to 70 different subtypes have been defined.

The study showed that the use of WGS, compared to the standard diagnostic route, has clinical consequences for 24% of patients. Additionally, for 12 out of 83 patients (14%), genetic profiling of tumour cells led to a different than initial diagnosis and for 8 of those patients (10%) this led to identification and start of another treatment option. This included optimising therapy in response to the re-diagnosis, preventing overtreatment with incorrect therapy, or deciding not to start a therapy based on the genetic profile.

The study by Schippers et al., showed that diagnosis with WGS makes a difference for the treatment of patients with sarcoma. The right diagnosis is very important for the selection of the right treatment. The researchers stated that determining the genetic profile with stepped molecular diagnostics is often done with a particular diagnosis in mind. As a result, targets can be missed unknowingly. WGS offers the possibility to do a complete, unbiased genetic characterisation of the tumour cells. This had clinical consequences for 24% of the patients in this study and would lead to a change in treatment for 10% of them.

3

HOW A LEARNING CARE SYSTEM WITH WGS DATA CAN HELP US MAKE BETTER CHOICES

The treatment guidelines we apply in medicine are evidence-based. Solid scientific research is needed before a treatment is included in guidelines. When deciding which care to include in the basic insurance, the Dutch Healthcare Institute carries out an assessment. This assessment determines whether there is a solid (scientific) basis to include a care activity in the basic insurance package. This is called the assessment of ‘current state of science and practice’.

Conducting this assessment has several major challenges.

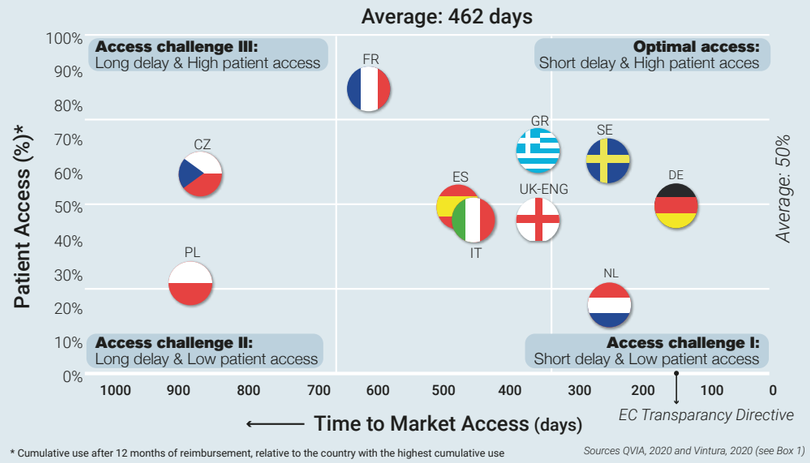
1. Applying insights from scientific research into clinical practice takes a long time because the turnaround time of a study takes years due to the lack of an efficient research infrastructure.
2. In addition, due to lack of standardised outcomes (parameters) and systems, it is difficult to evaluate clinical practice based on real-world insights. This complicates a rapid and thorough evaluation of the effect of medicines for (certain) patient groups. Implementing, improving, and tightening the clinical protocols thus takes longer than strictly necessary.

This becomes evident in Vintura’s Patient Access Indicator[54]; in research of 10 European countries, the Netherlands ranks as one of the slowest to implement new innovations after market access approval. One of the delaying steps is the introduction of additional molecular diagnostics required in hospitals. The NTRK inhibitor is an example of this; the drug has been available to Dutch patients for some time, but the patients are not found due to absence of adequate molecular diagnostics.

Figure 22

Vintura Patient Access Indicator, 2019, EFPIA

Within Europe, there are big inequalities in time to market access and patient access to new oncology therapies.



* Cumulative use after 12 months of reimbursement, relative to the country with the highest cumulative use

Sources QVIA, 2020 and Vintura, 2020 (see Box 1)

A learning care system can contribute to addressing these challenges. In a learning care system, data from current clinical practice, such as outcomes of diagnosis and treatment, are used to gain insights that help improve future patient's treatments (Figure 23). Of course, this system must be properly set up on the basis of privacy legislation, ethical guidelines, and data processing guidelines. The WGS data created for the treatment of today's patient, simultaneously generates a rich source for further research. This data is already present and does not require additional (research) funding. Combined with outcome data research can thus be accelerated.

A learning care system breaks the silos between care and research, making it easier to evaluate drug efficacy because the required data from clinical practice is available quickly. This is how we arrive at a system where outcomes from today's treatments contribute to improving treatment choices for tomorrow's patients at an increasingly rapid pace.

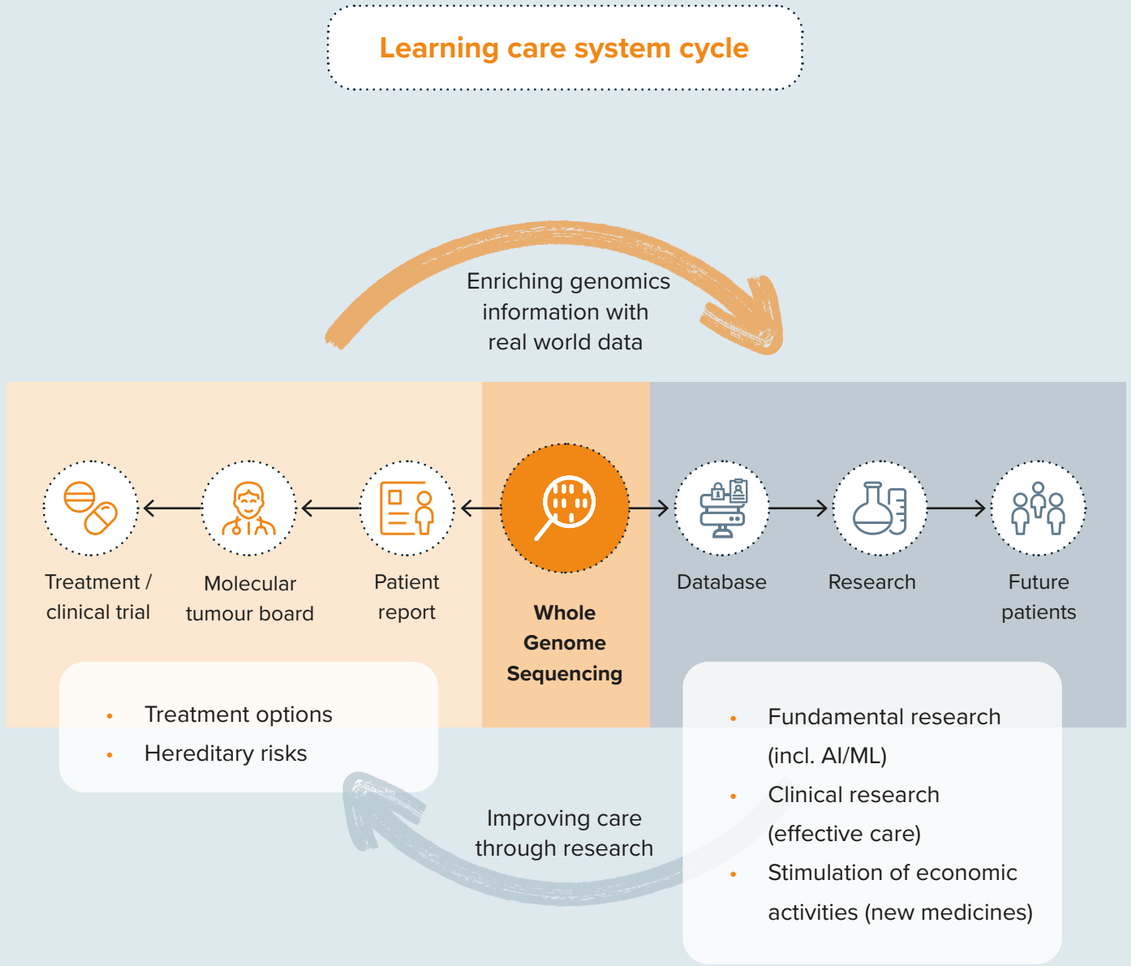
Setting up a learning care system in oncology has already been successfully done on a limited scale. The collaboration between the CPCT Foundation, Hartwig Medical Foundation, 44 hospitals, and researchers from academic research centres over a five-year period have produced a database of rich (and uniform) genetic and clinical data from more than 5,500 patients. As such:

- A control arm for assessment and research into the effectiveness of new drugs is available.
- An algorithm has been developed to 'predict' the primary tumour in patients with a Primary Tumour Unknown (PTO), which can be used for 1,500 patients per year[55].
- The accuracy of diagnostics for sarcoma patients (~1,100 patients per year[3]) can be significantly improved (24%). This leads to 10% other treatment choices[51].
- The effectiveness of existing expensive drugs can be predicted and groups of non-responders can be recognized like for NSCLC patients (~5,500 per year) where in 27% of patients there is reason to expect immunotherapy to fail[42].

This is not the only database developed in this area. IKNL and the DICA Foundation (Dutch Institute for Clinical Auditing) have been collected clinical data for many indications in the Netherlands for years, and several additional databases exist in the Netherlands for the melanoma indication. The development of a nationally uniform method to collect a complete clinical dataset is a necessity.

Figure 23

Overview of the learning care system cycle in oncology.



4

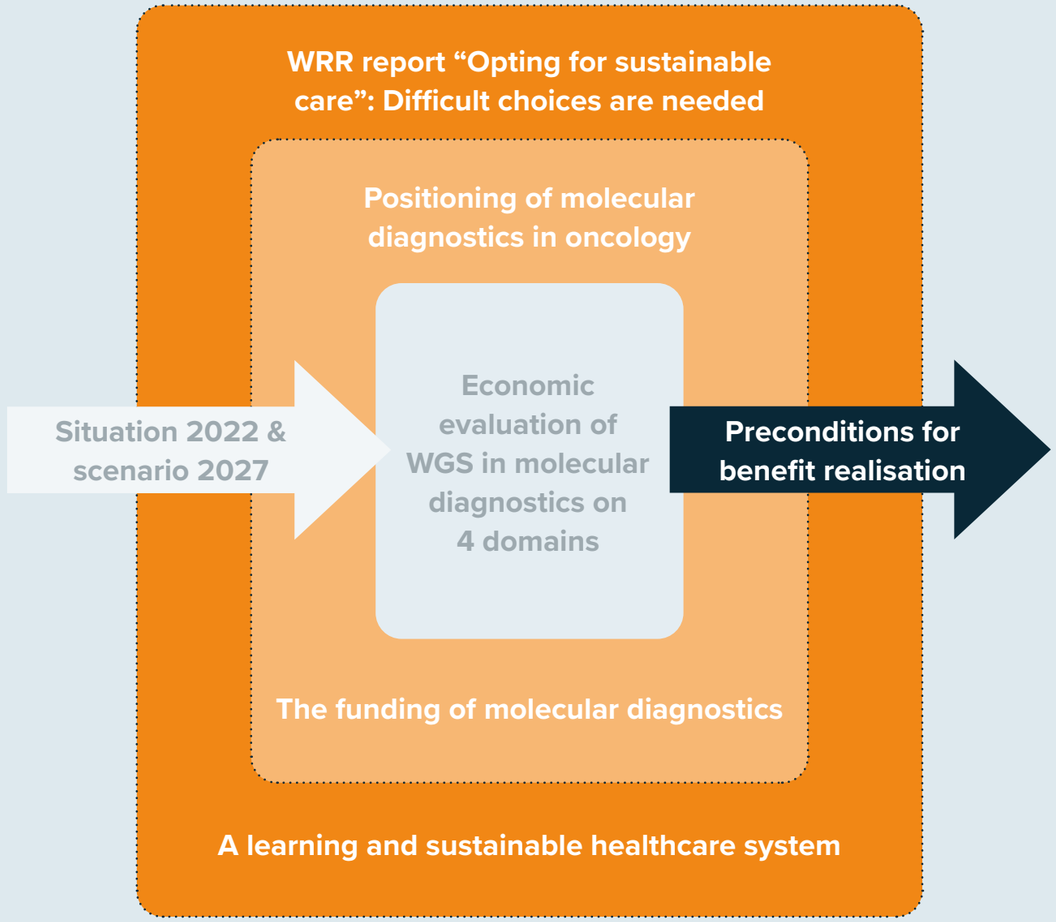
PRECONDITIONS FOR THE USE OF BROAD MOLECULAR DIAGNOSTICS WITH WGS AND THE IMPACT ON THE HEALTHCARE SYSTEM

The challenge of ensuring acces to molecular diagnostics

Patients do not always have equal access to molecular diagnostics. Because this field is still in full development, there is not always agreement among professionals on how and when the different types of molecular diagnostics can best be used. The extra costs and limited budgets also play a role in not implementing new insights, which can lead to underdiagnosis. Knowledge, expertise, and available resources are not equally present in every hospital, and institutions run into funding problems.

Figure 24

Overview of the impact of using WGS on the healthcare system in the white paper argumentation



In 2021 the Dutch Healthcare Institute recommended to concentrate centres for complex molecular diagnostics[56]. This ensures that molecular diagnostics is available to every patient, is carried out in a uniform manner, and the information is processed optimally for the patient's benefit. The concentration of centres can also contribute to creation of a learning care system. The latter is important because the developments in the field of molecular diagnostics are rapid and new insights are constantly emerging about which molecular diagnostics are suitable for which patients at what time. Combining data and insights about treatment and outcomes also helps to continuously improve and adjust the standards of care for diagnosis and treatment of cancer. After diagnosis, the patient can be treated in his/her own hospital (preferably nearby).

The Minister has endorsed the Dutch Healthcare Institute's advice and supports the establishment of a Diagnostic Advisory Committee (DAC, in Dutch abbreviated as: cieBOD) that examines the value and positioning of predictive diagnostic tests in Dutch oncology practice. This examination will be completed by September 2023[56]. Based on the results of the DAC, steps towards standardisation and concentration of molecular diagnostics can be taken and the opportunity can be seized to also create a learning care system.

The challenge of structural funding of WGS

In a detailed recommendation from 2015, the Dutch Healthcare Institute explained the meaning of the 'state of science and practice' test, necessary for reimbursement of a treatment, including diagnostics. It is tested whether the 'treatment policy' (diagnostics, treatment), in view of its beneficial and unfavourable consequences (side effects, safety), leads to (more) relevant value for the patient compared to the standard of care.

This requires scientific evidence on the added value, combined with experiences gained in practice. Studies are necessary to arrive at this evidence. In principle, studies are not reimbursed under the Health Insurance Act (in Dutch: ZVW) but other funding, such as subsidies, are available.

The innovative and rapidly evolving playing field of molecular diagnostics, and WGS in particular, can be complex. The more WGS combined with a clinical patient database is used widely, the faster a learning system is created in which this diagnostic test can be used with increasing effectiveness and focus. However, because a learning system also has the characteristics of a study, broad funding of WGS from the Health Insurance Act currently remains a problem.

For patients whose primary tumour is unknown, a preliminary reimbursement title has been set up for the funding of WGS from the Health Insurance Act. This is a temporary construction that, after three years and positive evaluation, should lead to structural funding from the Healthcare Insurance Act for this group of patients. In addition, two motions have unanimously been adopted by the House of Representatives to also implement funding for the use of WGS in out-treatment patients who are still in good condition. For the broad deployment of WGS as part of a learning system, further funding steps are necessary.

The impact of implementing WGS in the care pathway

Changes in the current care pathway are needed to use broad molecular diagnostics with WGS. Important changes are described next, often seen as objections to the widespread introduction of WGS.

The use of WGS has a major impact on the care pathway as biopsies must be stored in a different way for processing

To perform WGS, a freshly frozen biopsy is required. The pathology labs are currently working largely with formalin-fixed paraffin embedded (FFPE) biopsies. Broad implementation of WGS means a new way of working in which the care pathway must be adjusted. This was successfully set up in 44 hospitals in the period 2016-2021. There is certainly an impact on the care pathway, but it is manageable, which is also one of the findings from the WIDE study[38].

Processing FFPE biopsies will continue to be necessary for histological and immunochemical determinations. Therefore, it is a matter of specifically collecting a biopsy for molecular analysis (freshly frozen) in addition to a biopsy for histological analysis (FFPE). This is similar to blood samples, where different types of blood tubes are needed for different tests, and several tubes are often taken in parallel during one procedure.

In addition, this freshly frozen route is also necessary for other work/tests that are carried out in pathology labs, such as biobank storage for research and for other emergency diagnostics.

Suitable tumour tissue for WGS is not always available

In the WIDE study, WGS was used in 1,000 patients. The results of this have been compared to other types of broad molecular diagnostics in regard to the quality of diagnostics and usability in the care pathway. One of the outcomes is the percentage at which WGS produces clinically useful results. This percentage is 70% for WGS and is currently 84% for other types of broad molecular diagnostics. The difference is caused by the amount of tumour cells present in the biopsy. For WGS this should be at least 20% and for other types of broad molecular diagnostics 10% is sufficient. For 14% of patients it is therefore necessary to perform a large panel + Archer or to perform a 'deeper' WGS analysis. The latter is associated with higher testing costs.

The Netherlands Cancer Institute (NKI)/Antoni van Leeuwenhoek (AvL) and Hartwig Medical Foundation are currently working together to close the gap from 70% to 84% and find solutions that allow some form of molecular diagnostics (based on tumour DNA in the blood) to be applied for the remaining (100% - 84%) 16% of patients for whom both WGS and current broad molecular diagnostics are not satisfactory. The objective is that the most complete diagnostics test is automatically carried out for each patient, depending on the properties of the available patient material.

The impact of concentration on the organisation of care

To achieve high-quality and efficient use of complex molecular diagnostics for oncology in the Dutch healthcare system, concentration of infrastructure is required. It seems possible to perform complex molecular diagnostics for all patients (approximately 25,000 per year) in a handful of laboratories[24,57]. Standardisation of WGS in a few laboratories, with large tests volumes in a few locations, enables economies of scale and cost reduction. In the Netherlands, there has long been a trend of scaling up laboratories for hospitals, for example: PathologieDNA and LabPON. The concentration of WGS in a few locations matches this trend.

Molecular tumour boards have already been set up in oncology expertise centres. Here, the 'technical' result of the test is discussed in a multidisciplinary consultation with pathologists and oncologists and treatment advice is designed for the treating physician (possibly in another hospital) and patient. This greatly reduces the chance of zip code diagnostics and differing treatment recommendations. It also contributes to making unambiguous choices based on the latest scientific insights.

Available data can also be used at policy level; insight into the cancer patient population, their indications, and treatments can help to properly estimate the budget impact of (new) medication and to conduct sharper price negotiations (the data for the control arm of the study is already available).

Continuously improving business operations based on a wide amount of data is something that is self-evident in many industries and leads to major improvements in terms of quality and costs. In healthcare, however, this is not yet common practice. By using broad diagnostics based on WGS in oncology, combined with a central data storage, there is an excellent opportunity to implement such a system.

The impact of implementing WGS in the care pathway

Of course, in addition to advantages, there are also objections and obstacles to the use of WGS. These objections and obstacles should not be underestimated due to the impact on logistics of pathology departments and the knowledge required to interpret the WGS test results. Molecular diagnostics with WGS has already found its way into a growing number of centres, including the NKI/AvL since 2021 and Erasmus MC (EMC) since 2019. Objections and obstacles do not outweigh the positive impact that the use of WGS can have on the Dutch healthcare system. Below we explain the most common objections.

WGS is an unnecessary broad diagnostic tool

The term broad molecular diagnostics says it all; WGS looks broadly at the genome. For some indications, this is momentarily unnecessary and individual tests are currently (still) cheaper. We advocate to not yet use WGS in these indications.

However, broad molecular diagnostics is already desirable in several indications in which many treatment targets are known. We need personalised-diagnostics to support our personalised-medicine so the right treatment decision can be made.

The cost of WGS will not fall (as fast) as predicted

The assumption in our scenario is based on the cost reduction in WGS between 2015 and 2021 from €6,676 to €2,500 – Simons et al., 2021[58] which is almost €600 per year. In our scenario, we take into account a decrease in the costs of reagents that starts at €300 per year, and later flattens out. This is half of what it was in previous years, and therefore a relatively conservative estimate. In addition, Illumina announced a change in the pricing structure at the end of September 2022[23], which reduces the costs of reagents per WGS test from €1,762 in 2022 to €1,000 from Q3 2023. This confirms our assumption about the cost reduction.

We won't see the benefits of identification of non-responders, they will just receive a different treatment

Patients with cancer in the Netherlands fortunately have access to innovative medicines to combat their disease. This improves quality and duration of their life. However, medications prescribed are often expensive and cause serious side effects.

One of the worst choices is to treat patients with an expensive and toxic agent of which we could have already known in advance will not improve or extend their life. This is inefficient and wasteful in all areas.

Let us therefore make efficient choices. There is a lot of potential for this as we have shown in the analyses.

As the tumour evolves, a new round of molecular diagnostics is needed

In August 2021, Van de Haar et al., published a study on tumour evolution and the emergence of new therapeutic targets[59]. In this study, 231 patients with metastatic solid tumours were examined. In a second round of molecular diagnostics with WGS on the metastasis, no new biomarkers for treatment (in clinical trials) were detected in 91% of patients. In more than 80% of patients, no new treatment targets for small molecule therapy or hormone therapy were found. This shows that for a large proportion of patients, a second round of molecular diagnostics on the metastases does not provide any new insights compared to the first round of molecular diagnostics on the primary tumour.

We don't want to invest in technology for which the results are only used for research

The use of WGS makes it possible to choose the right treatment option for a unique patient. The awareness that every patient, and therefore every cancer, has a unique profile, is increasing. This also requires good treatment choices based on complete information. A WGS analysis of the genome can contribute to this and thus improve treatments. In addition, WGS results also indicates whether patients are eligible for inclusion in clinical trials, though this is not the main purpose.

Deployment of WGS requires large investments and these are not included

WGS pricing also includes a component that covers equipment depreciation. However, it is important to realise that scaling up helps to make optimal use of equipment investments, which is why we also advocate concentration of complex diagnostics with WGS.

The required centralisation or concentration cannot be implemented in practice

Concentration of hospital laboratories has been a trend for many years. Concentrating diagnostics doesn't mean directly that care is also concentrated. Care can still be provided in a local setting. Another trend in healthcare is the formation of centres of expertise. With increasing complexity of diseases and treatments, there is a concentration of experts in a few centres.

The broad use of WGS matches this trend. Concentration of complex care in a few locations ensures quality and efficiency. This concentration does not have a major impact on the lead time for WGS tests, which (according to the WIDE study) can be carried out within 11 working days, which is often faster than current broad diagnostics in various centres[60].

Linking broad molecular diagnostics with WGS to regional centres of expertise for medical oncology ensures high-quality and efficient diagnostics are used in treatment paradigms by medical experts.

CLOSING WORDS

This white paper shows the results of an economic evaluation of the use of WGS technology in molecular diagnostics. It concludes that this technology is becoming suitable for more and more indications due to falling costs. As a passionate pathologist told me once “A WGS test is a wonderful tool to add to the pathology toolbox”. The use of WGS offers something extra compared to other instruments, because it maps out all characteristics of the tumour at once. In doing so, it also captures information about increased risk of side effects for certain medications and also provides access to data (if desired) that provides insight into a possible hereditary predisposition to cancer.

In a scientific article where various molecular tests were compared, the WGS test was given the predicate “one test to rule ‘m all”. However, diagnostics consist of more than just the WGS test results. It is essential to combine WGS test results with results from histology, imaging (scan), pre-treatment, etc. to arrive at a complete diagnosis. Discussion of all results in a molecular tumour board completes the integral patient approach.

In addition to the comprehensiveness and versatility of WGS tests for today’s patient, the WGS data provides a unique source of knowledge for identifying non-responders. This data helps to recognise, prior to treatment, whether a particular drug will work or not, or whether it has a high or a low chance of being effective. This increases chances to reduce overtreatment and spares patients unpleasant side effects of non-efficacious drugs. Finally, better stratifying patient groups for treatment also provides guidance to contain the increasing costs of expensive cancer drugs (€1.5 billion).

Overall, there is substantial evidence to embrace this technology and use it widely in the Dutch healthcare sector.

Hans van Snellenberg, Director Hartwig Medical Foundation

LIST OF ABBREVIATIONS

5-FU	5-fluorouracil
AvL	Antoni van Leeuwenhoek
CRC	Colorectal carcinoom
DPD	Dihydropyrimidine dehydrogenase
EMC	Erasmus Medisch Center
FFPE	Formaline-fixed paraffine embedded
GIST	Gastro-intestinale stromal tumour
HRD	Homologous Recombination Deficiency
HTA	Health Technology Assessment
IKNL	Integral Cancer Centre The Netherlands
MDO	Multidisciplinary consultation
MSI	Microsatellite instability
NKI	Netherlands Cancer Institute
NKR	National Cancer Registration
NSCLC	Non-small cell lung carcinoma
NVMO	Dutch Society for Medical Oncology
PATH	Predictive Analysis for Therapy (RadboudUMC)
PTO	Primary Tumour Unknown
SONCOS	Foundation of Oncology Collaboration
TMB	Tumour Mutational Burden
VWS	Ministry of Health, Welfare and Sport
WGS	Whole Genome Sequencing
WRR	Scientific Council for Government Policy
ZIN	Dutch Healthcare Institute
ZVW	Health Insurance Act

RESEARCH JUSTIFICATION, STAKEHOLDERS AND INTERVIEWEES

This research was carried out by Vintura on behalf of Hartwig Medical Foundation. The departments of clinical pathology and medical oncology of hospital A and hospital B have made a substantive contribution by sharing knowledge and relevant data and insights. Hospital A and hospital B are both leading oncology treatment centres in the Netherlands.

The analyses and results in this research are based on data from the hospitals mentioned above and are further substantiated with scientific publications, public data, and expert opinion. Where assumptions have been made, this has been indicated.

This research involved 19 people, both with interviews and by contributing to this paper. The insights from interviews were used to execute the analyses and to place them in the right context. The interviews were conducted with various stakeholders from hospital A and hospital B (medical manager, medical oncologist, pathologist, head of laboratory, clinical molecular biologist), as well as the Dutch Healthcare Institute, health insurers, and patient representatives.

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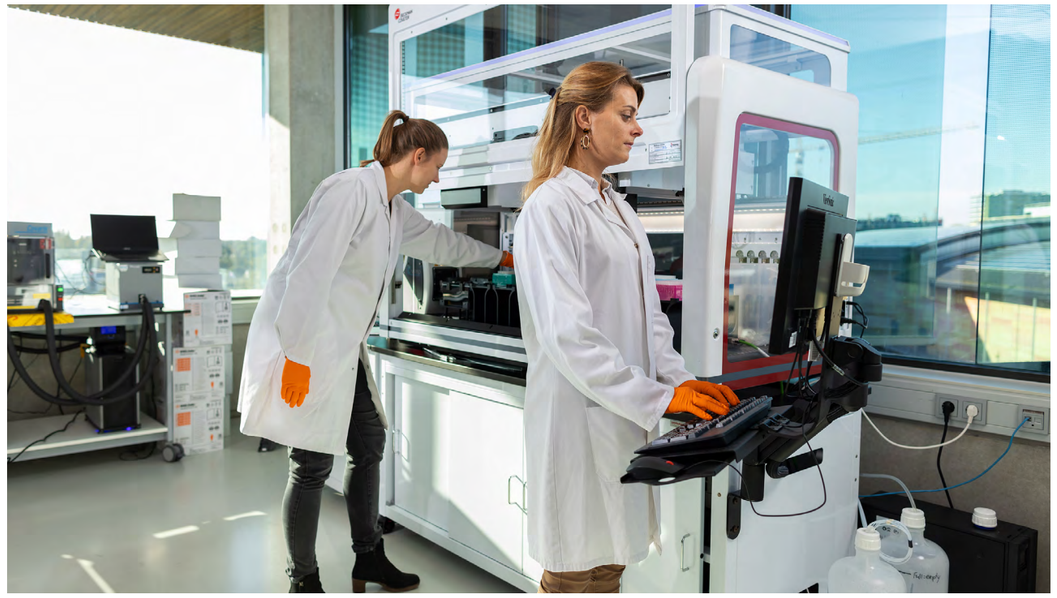
All digital sources were consulted in 2022.

Hartwig Medical Foundation is a Dutch non-profit foundation that aims to improve the care for patients with cancer and to contribute to ensuring that every patient with cancer receives the treatment that best suits her or him. This is done by promoting cancer research and performing complete DNA analyses in patients with cancer.

Every year, 120,000 people in the Netherlands are diagnosed with cancer. Every year, 45,000 people die from the disease. Cancer is an individual disease; it is caused by errors in the DNA. There are no two patients who have the same tumour. Tailor-made treatments are becoming increasingly important for good cancer care.

Hartwig Medical Foundation contributes to the following:

- Oncologists and pathologists are getting increasingly superior diagnostic tools to better diagnose and treat patients. This contributes, alongside a patient report that is understandable, to collaborative decision making and mapping of off-label options and ongoing trials in addition to standard treatment
- Patients with metastatic cancer today have access to the most comprehensive molecular diagnostics and treatment options
- The healthcare system receives the information to more quickly assess the effectiveness of new drugs using the complete DNA analysis and clinical data from a national DNA database
- Researchers receive the genetic and clinical data to accelerate basic, translational, and clinical research by giving them access to a national nationwide DNA database, complemented by clinical data and connected to other relevant data from national databases such as IKNL, NKR, DICA and PALGA.



Some figures (January 2023):

- Hartwig Medical Foundation is founded in **2015**, has **35** employees and is still growing
- The Hartwig Medical Database contains genetic and treatment data for more than **5,500** patients
- More than **250** research groups from **more than 20** countries have worked with the data or are still working with it
- More than **50** research groups have based their results on this data published in world-leading scientific journals
- **44** Dutch hospitals have used the complete DNA test in a study context
- More than **10** hospitals use the complete DNA test for their standard diagnostics, this number is growing.

Visit the website, or check LinkedIn and Twitter for the latest news on improving care for patients with cancer.

VINTURA

WE CREATE MEANINGFUL IMPACT IN HEALTHCARE TOGETHER!

Vintura is an international team of passionate consultants with a shared ambition: making an impact in healthcare and life sciences.

Vintura supports global life sciences companies, hospitals and health insurers in bringing innovative medicines to market, improving the delivery of care and optimising healthcare systems. Our company vision is based on the Value-Based Healthcare (VBHC) principles: a framework for restructuring healthcare systems to create value for patients – through a process of continuous learning and improvement.

We do so based on our core values:

- Being ambitious and courageous in finding the best solutions,
- Being empathetic and sincere to create maximal acceptance and commitment.

Our presence and experience in the international markets allows us to support and understand our global clients and create new insights to arrive at solutions which have a real impact. They are practical, effective and meaningful.