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Belgian Health Care Knowledge Centre

SYNTHESIS

NEXT GENERATION SEQUENCING GENE PANELS FOR TARGETED THERAPY IN ONCOLOGY AND HAEMATO-ONCOLOGY

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HEALTH TECHNOLOGY ASSESSMENT

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NEXT GENERATION SEQUENCING GENE PANELS FOR TARGETED THERAPY IN ONCOLOGY AND HAEMATO-ONCOLOGY

MARC VAN DEN BULCKE, LORENA SAN MIGUEL, ROBERTO SALGADO, ELS DE QUECKER, HARLINDE DE SCHUTTER, ANOUK WAEYTENS, PETER VAN DEN BERGHE, SABINE TEJPAR, JEROEN VAN HOUDT, STEVEN VAN LAERE, BRIGITTE MAES, FRANK HULSTAERT

FOREWORD

Personalized Medicine has been announced already years ago as an important breakthrough in oncology. After determining the genetic fingerprint of the tumour a highly targeted medicine is administered, highly efficacious and with very few side-effects. At least this is our hope. In reality this theoretical framework has been realized only a limited number of times, with a few spectacular exceptions such as the treatment of metastatic malignant melanoma characterized by a specific mutation in the BRAF gene. Today, such cases of melanoma can be treated in a highly targeted way using BRAF kinase inhibitors.

Significant advances in sequencing techniques and molecular diagnostics do accelerate this field. Using *Next Generation Sequencing* (NGS) it is possible to sequence a panel of genes in a single run. This way mutations in multiple cancer cell genes can be identified and the targeted drug selected. This approach is currently mainly used for clinical research purposes. Cancer patients in larger centres are more and more tested to evaluate their possible inclusion into clinical trials with new targeted drugs.

The necessary equipment and reagents have become affordable, allowing also smaller centres to invest in this technology. Oncologists may want to use the test results and experiment with off-label targeted drugs. Sometimes this happens outside of a clinical research framework, without the necessary supporting clinical evidence.

How restrictive should the healthcare payer be with such off-label use of such expensive targeted drugs? How reliable are the results of the new tests in the routine practice in smaller centres? These questions were studied in a collaborative project between KCE and the Cancer Centre of the Institute of Public Health. We thank the many experts in the field and representatives of several government institutes who participated in the realisation of the report.

Johan PEETERS
General director WIV-ISP

Raf MERTENS
General director KCE

SUMMARY

TABLE OF CONTENTS

1. INTRODUCTION

1.1. Background

This report on targeted therapy in oncology and the role of panel tests using next generation sequencing (NGS) is the result of a joint project of the Belgian Cancer Centre (KC-CC) and the Belgian Healthcare Knowledge Centre (KCE). A KCE project on the importance of the accuracy of companion diagnostics in routine care was joined with an evaluation of next generation sequencing panel tests in oncology and haemato-oncology. This latter evaluation was requested by RIZIV-INAMI and the pathologists/clinical biologists/geneticists and clinicians exploring this new technology. It is part of the Thematic Working Group 'Personalized Medicine' of the Cancer Centre.

Cancer consists of cells that are proliferating in a non-controlled manner. This is caused by specific alterations in the DNA of these cells (including methylation), which can drive tumour growth. Identifying the specific pathway that drives tumour proliferation allows the use of targeted medicines to block it. In comparison to non-selective forms of chemotherapy, cancer patients treated in a targeted way are more likely to respond. In addition, one avoids that patients who will not respond receive an expensive and potentially toxic treatment. The diagnostic test identifying the target population is called a companion diagnostic.

Examples of targeted drugs in clinical use are trastuzumab (Herceptin) in HER2-amplified breast cancer, imatinib (Glivec) in chronic myelogenous leukaemia and gastrointestinal stromal tumours (GIST), gefitinib (Iressa), erlotinib (Tarceva) and afatinib (Giotrif) in EGFR-mutated non-small cell lung cancer, cetuximab (Erbitux) and panitumumab (Vectibix) in RAS-wild type colorectal carcinoma, and vemurafenib (Zelboraf) in BRAF-mutant melanoma.

Many test methods exist to interrogate the cancer cells at the DNA (gene), the RNA (step between gene and protein) or the protein level. Most methods will however only test for a single marker or pathway. This is different for the new technique of next generation sequencing (NGS) which allows for the simultaneous detection of multiple alterations in DNA or RNA. In this study, we focus on NGS panels to test for alterations/mutations in the tumour cell DNA (somatic DNA) of solid tumours and haematological malignancies. 'Actionable' mutations are alterations that predict for sensitivity or resistance to targeted drug.

The aim of this project is to present the current clinical utility of NGS gene panel tests and to define the requirements for implementation of these tests in routine care. A second aim of this project is to evaluate the importance of the diagnostic test accuracy on the patient benefit, harms and the cost-effectiveness of targeted therapy in oncology.

1.2. Research questions

The following research questions are addressed:

- What are the indications for NGS panel testing in haematology/oncology and what should be the characteristics of such panels (level of clinical utility, technical specifications, informed consent and reporting specifications, quality assurance,…) in order to implement this technology in routine clinical care, as an alternative method for the currently accepted single gene markers?
- What is the added value of NGS panel tests compared with current practices; what is the cost for performing NGS panel tests?
- What is the impact of the diagnostic accuracy of the companion diagnostic on the cost-effectiveness of the treatment from a healthcare payer perspective?
- How are targeted therapy and companion diagnostics reimbursed in Belgium (and abroad)?
- What could be options for financing this technology during a transitional period and which further data could be collected during such a period to support the clinical use?

1.3. General approach

The project was managed by the KCE and the KC-CC and supported by a Steering Group and dedicated working groups that included domain experts to document the desired panel composition, the required quality assurance measures, the current testing activity in Belgium, the cost aspects and options for further data collection during a transient research financing phase. The Steering Group included representatives of the RIZIV-INAMI, FOD-VVVL/SPF-SSCE, FAGG-AFMPS, BELAC, WIV-ISP, the College of Oncology, the College of Human Genetics, the Commissions of Pathology and Clinical biology specialists as well as the rapporteurs of the working groups who co-authored this report. Within the short time frame of this project no systematic review of the clinical utility of the markers listed was undertaken.

2. NEXT GENERATION SEQUENCING PANEL TESTS

2.1. Steps of NGS panel tests

In contrast to closed systems, available for single parameter molecular tests, the NGS panel tests still consist of multiple steps that require some manual intervention. These steps, from sample selection and preparation, over sequencing to data analyses and reporting require expert knowledge and specific quality assurance.

Sample selection step. Biopsies or resected malignant tissue typically contain a mix of malignant cells and non-malignant cells. Even within a single tumour not all malignant cells may have the same genetic alterations. It is important to detect also minor tumour populations that drive the tumour proliferation. For solid tumour tissue, areas of malignant cells are first selected by the pathologist and scraped from a slide. In order to be able to detect DNA alterations a sufficiently high proportion of tumor cells should be present among the cells selected for analysis. In addition the quality of the DNA must be good in order run a good quality NGS test. This is more often the case if fresh-frozen tissue samples are used.

NGS platforms. Currently two NGS platforms are mainly used. They employ different technologies but their underlying workflow is similar. The Illumina (MiSeq/NextSeq/HiSeq) performs sequencing by synthesis and the Life Technologies (Ion Torrent Ion Proton/Ion PGM) performs sequencing by monitoring pH. The NGS workflow consists of six steps.

1. **Fragmentation of DNA**. In this step the DNA is fragmented in pieces of a specific length using a physical, chemical or enzymatic process. Separate protocols are needed for formalin fixed paraffin embedded (FFPE) versus blood versus frozen tissue. Fragments of DNA that are too short, as may occur in bad quality FFPE samples, may invalidate the NGS analysis. NGS starting from fresh frozen tissue is less error prone, also because there are no fixation-induced DNA modifications.
2. **Ligation to adaptor sequences**. These are platform-specific sequences that are ligated to the ends of DNA fragments, creating the sequencing library. These adaptors contain primers for a possible PCR amplification and often molecular barcodes that enable pooling of samples from different patients before sequencing.
3. **Immobilisation**. This occurs through the adaptor sequence to a solid surface, such as a bead or a glass slide.
4. **Clonal amplification**. Amplification increases the signal for detection. This can be achieved through emulsion bead PCR or surface cluster PCR. It should be kept in mind that the lower the number of copies of DNA extracted from the tissue, the higher the potential impact of a first round amplification error.
5. **Sequencing**. Cycles of base incorporation by synthesis or ligation are followed immediately by signal detection. Signals are converted to base calls, from which a nucleotide sequence or 'read' is produced. The read length is about 200 bp for NGS panel tests in oncology. Each template DNA region is also sequenced a number of times (depth of coverage). The coverage for cancer genomes is typically 500–1000X. Incomplete coverage, where regions are not sequenced or poorly sequenced, is a problem. The different technologies are all prone to different sequencing errors to varying degrees. For example, the Ion PGM has difficulty accurately sequencing homopolymers greater than 8 bases long, while the Illumina MiSeq has difficulties with GC-rich motifs.
6. **Data analysis**. The bioinformatics processes start from the sequence read generated by the instrument. Due to the short read lengths, there is limited ability to reassemble a genome through overlapping sequences. Therefore, 'resequencing' is used: each read is compared to and aligned with a human reference genome. Differences between the alignment and reference sequence are identified ('variant calling'), filtered and annotated to identify those that may be clinically significant.

Both **false positive and false negative variant calls** may be made due to errors in alignment, alignment with an unsuitable reference sequence or too stringent or lenient filtering. Correct annotation is highly dependent on the accuracy of information obtained from interrogated databases, such as those containing known disease-causing mutations, common polymorphisms or mutations in cancer.

False positives and negatives also occur more frequently when the coverage and the number of reads are low and in case of bad quality DNA, as can be seen after prolonged tissue fixation and storage.

The bioinformatics pipeline used to analyze, interpret and report NGS results needs to be validated and revalidated each time modifications are made.

There are several international guidelines and standards that can be used when implementing NGS panel tests, for example, from the College of American Pathologist (CAP). The consensus document of Eurogentest can be used for **reporting of the results**. It is essential to use the mutation nomenclature according to the Human Genome Variation Society.

To **validate the complete system**, FFPE-samples with different levels of neoplastic content and different levels of cellularity representing a wide variety of tumour types should be included to:

- determine the limit of detection of the platform,
- determine the uniformity of coverage,
- determine the depth of coverage required to confidently detect mutations within a tumour,
- all this in addition to classical parameters such as the accuracy, analytical sensitivity and analytical specificity.

2.2. Availability of NGS panels

NGS panel tests can be performed in a laboratory of a hospital or can be offered as a commercial service whereby the sample is shipped to the central facility, often abroad.

Regulatory status. NGS panels are available as reagent kits, currently mostly still marketed for research use only (RUO). None of the oncology NGS panel tests currently has obtained market approval by the Food and Drug Administration (FDA) in the US. All NGS kits are based on PCR amplification of the genes of interest, or their hotspot regions. Their product inserts state that these kits can be used starting from FFPE materials, and this claim remains to be validated.

Panel size. Different levels of acceptance of gene alterations exist:

- Level 1: well accepted actionable mutations with proven clinical utility
- Level 2: alteration being validated in ongoing clinical trials phase 2/3
- Level 3: known alteration but clinical significance not known
- Level 4: newly identified alteration

Clinical oncologists tend to favor limited gene panels (restricted to actionable mutations) or intermediate size gene panels (including non-actionable recurrent or prognostic mutations as well). Centers with a strong academic and clinical trial setting may opt for a wider gene panel approach, including level 2. For targeted therapy trials, many pharmaceutical companies will only recruit centres where cancer patients had their tumour already tested with a (broad enough) NGS panel test. This accelerates and facilitates the identification of eligible patients and limits the costs and time of centralized companion diagnostic testing. This strategic advantage is to be seen in a highly competitive clinical research environment with significant research and economic implications for the concerned larger hospitals and their staff. It is important to note that this clinical research use is currently still the main use of NGS panel tests.

Commercial or custom-made panel. Arguments in favor of commercial standard panels, in comparison with home-designs, are their immediate availability, their prior optimization (for example with regard to a more uniform coverage), and their wider user community. However, also commercial IVD kits require sufficient validation by the laboratory that wants to use the kit. The cost of commercial panels is lower than that of custom panels by the same manufacturers, which are tested only *in silico*.

While the panels marketed by Illumina and Ion Torrent/Life Technologies are specifically designed for their own sequencing platforms, the independent manufacturers Agilent and Multiplicom provide kits which are adapted to either platform. Finally, the match of the gene panel with the local needs can be less than optimal.

Panels for solid tumours and haematological malignancies. The commercial gene panels for solid tumours show extensive overlap, and cover many cancer genes relevant for lung, colorectal, breast, thyroid and brain tumours, and melanoma, GIST and gynecological malignancies. Many laboratories opt for a single design or a few panels for solid tumours. Many hematological samples are directly processed without fixation. Therefore, there is less of a concern about FFPE-related artifacts in haematological malignancies. Second, the spectrum of mutations in hematological malignancies is wide, distinct from the solid tumour spectrum, and not always covered by commercially available panels, for example for lymphoid neoplasms no panels are commercially available yet. Custom panels require extensive further validation before these can be used in the clinic.

Need for international standards. Currently, there is no generally approved minimum set of genes and DNA regions that should be tested for a specific tumour type, other than the few actionable genetic alterations appearing in practice guidelines and required for the reimbursement of targeted drugs. An important effort in this regard, “The Cancer Genomics

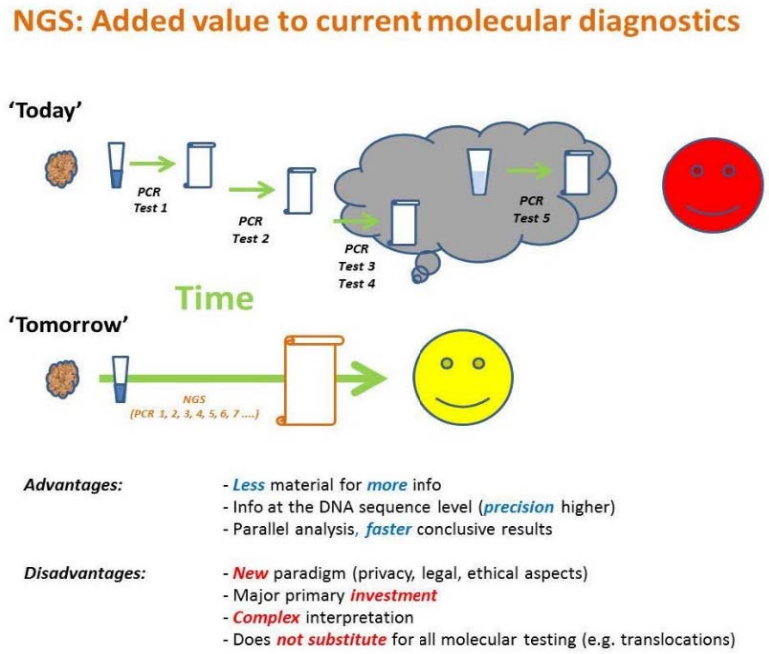
Resource List 2014", was published recently by Zutter M. et al. (2014), for the College of American Pathologists. A table with NGS panels used in Belgium today and their overlap is available in the appendix of the report.

Different panels, from different providers or home-made, tested on different platforms may have only partially overlapping sequenced regions. This is not acceptable from a good clinical practice perspective and requires further standardization in order to avoid the reporting of different results on the same case when analyzed in different laboratories.

There is a need for a multidisciplinary National Committee (preferentially embedded in an international consortium) that regularly updates the clinically relevant markers in oncology and interacts with the National Federal Authorities and reimbursement institutions.

2.3. Advantages of NGS panel tests for the laboratory

Figure 1 – Advantages and disadvantages of NGS



The conventional "gene-by-gene" analysis, by PCR, Sanger sequencing, Pyrosequencing, … is time-consuming, requires a rather large amount of DNA, has high turn-around-times (especially if reflex testing is used), and is expensive in the use of reagents, equipment, personnel, validation and quality control. These problems are becoming increasingly important as more and more single gene analyses are implemented (Figure 1).

The introduction of a targeted-NGS analysis can partly overcome these problems, as it is a single, multiplex assay, analyzing a broad panel of genes (or gene regions) at once (massively parallel), requiring only a limited amount of DNA. As many different gene tests can be consolidated on the NGS platform, a single workflow can replace many single tests, reducing hands-on-time and turn-around-times. In addition, the panel can be designed so that potentially relevant genes are already included in the panel, reducing the need for future additional validation and implementation costs.

However, NGA panel tests cannot replace all present molecular tests.

In the long-term however, it may be expected that tumours (both solid and hematological) will be profiled both at the DNA and RNA level, either in a single or in two separate massively parallel analyses, as well as for copy number variations, methylation status, etc. In addition, the analysis of several tissue or liquid biopsies, sequentially during the course of the therapy (and not exclusively at diagnosis) might be indicated in the future, at least for some patients. These issues are beyond the scope of this report but might be taken into account when deciding on the modalities and the degree of flexibility of the reimbursement strategy.

2.4. Points of attention

An **increased use of targeted drugs off-label** has already been observed in routine care in case the NGS panel test identifies a mutation in a gene that would otherwise not have been interrogated. Any potential health effects or the possible budget impact of increased off-label use of targeted drugs are however not well documented.

Whereas somatic mutations that characterize a tumour have no direct hereditary character, this is different for germline mutations that may be discovered by accident if the specific gene is part of the panel. Especially with large panels, the handling of **accidental germline findings** may need to be defined. In the near future somatic BRCA1- and 2-mutations will have to be included in gene panels of daily practice, as this marker will be guiding the treatment selection of serous high grade ovarian cancer. Pre-test genetic

counselling of ovarian cancer patients therefore seems necessary when such panel test is offered. The logistics that will be needed if this principle would also become standard practice for more common types of cancer is out of the scope of this report.

2.5. Regulations, Quality Assurance and Education

In contrast to the FDA which requires demonstration of safety and effectiveness of devices (including *in vitro* devices), the European Conformité Européenne (**CE) mark** procedure requires the pre-market evaluation of safety and 'performance' of a device. The term 'performance' is however not defined. The intended-use statements and performance characteristics are often expressed in analytical terms only. A few NGS panels for the detection of hereditary (not somatic) DNA mutations have obtained FDA approval. Each step in the process was subjected to a very extensive degree of validation exceeding by far the requirements for obtaining a CE mark.

For the Belgian medical laboratories of pathology and clinical biology, participation in the external quality assessment (**EQA) schemes** organized by the Belgian Scientific Institute of Public Health (WIV-ISP) is mandatory to obtain reimbursement for routine testing as specified by the Belgian nomenclature.

Additionally, **ISO 15189 accreditation**, granted by BELAC, is mandatory to obtain reimbursement for tests performed by molecular biological techniques, as described in article 33bis of the Belgian nomenclature. Guidelines are needed to guide and further standardize the accreditation process for NGS panel tests. The EQA participation needed in the context of the ISO 15189 accreditation is currently not controlled nor standardized by the IPH. The laboratories can decide themselves which EQA scheme(s) fits their needs. According to the experience of the experts, some EQA schemes are more difficult to pass than others.

One of the aims of EQA is the inter-laboratory comparison of the Belgian laboratories. Therefore, there may be a need for streamlining the selection, control and reporting of a common and appropriate EQA programme in a transparent way by WIV-ISP and BELAC.

It is important to note that up to now no specific NGS panel EQA for oncology or haemato-oncology has been performed. However, all EQA results for IHC/molecular tests used as a companion diagnostic for targeted therapy are of relevance as these data are an indication of test accuracy in routine use (versus phase 3 trial central lab).

As many health professionals were trained before molecular diagnostics in oncology were introduced in routine care, there is a more general need for **education** in this field. Genomics-related patient care, especially when larger gene panels are used, necessitates a multidisciplinary approach, with the instalment of so called "molecular advisory boards" or "molecular sequencing boards" that includes expert clinicians, molecular pathologists or clinical biologists whenever it concerns solid tumour and/or haematological testing, scientist, ethicist and bio-informaticians whenever applicable.

3. ECONOMIC ASPECTS

3.1. Impact of test accuracy on cost-effectiveness

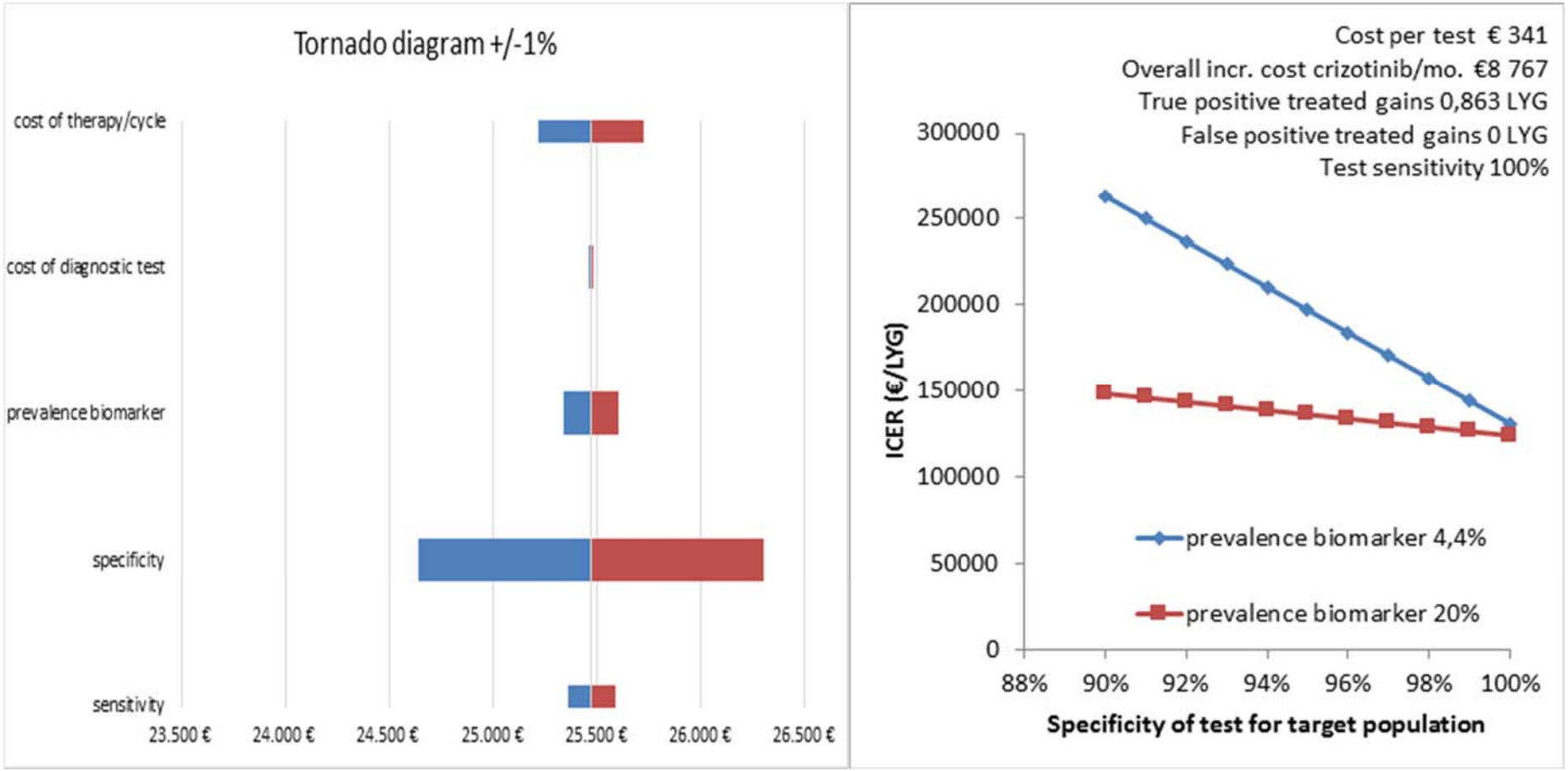
We studied the impact of changes in test accuracy (i.e. diagnostic sensitivity and specificity) on the economic value of test-intervention combinations. The assumption is that tests used in clinical routine might be less accurate than the centralised tests of the confirmatory trials used for the evaluation of the cost-effectiveness of the drug during the reimbursement procedure. Many EU countries including Belgium still lack an integrated reimbursement review of the drug and the companion diagnostic, despite the recommendation formulated in KCE report 20, 2006. The first steps at RIZIV-INAMI to include in the drug reimbursement dossier information on predictive markers of targeted drugs were recently taken.

A systematic literature search was used, but only few reports were identified on this subject. We adapted published examples to the Belgian situation for trastuzumab in HER2+ early breast cancer and crizotinib in ALK translocation positive non-small cell lung cancer. Detailed methods are given in the full report.

The tornado diagram (figure2a) illustrates a 1% change in input parameters if trastuzumab is given to all IHC2+/3+ early breast cancer cases, a situation whereby both test sensitivity and specificity show room for improvement. The figure illustrates that maintaining a high test specificity in routine care is crucial for the cost-effectiveness of the targeted treatment, much more than the cost of the test or even the cost of the drug. This finding is important as in most evaluations only the cost of the test and the drug are studied and discussed. A very high test specificity is even more important if the target pathway is present only in a minor subset of the samples, as is the case for ALK translocation, seen in only 4.4% of the non-small cell lung cancers (figure 2b).

Rare false positives for actionable mutations have been reported for NGS panel tests. This is more likely to occur when the panels are large, the coverage and the number of reads are low, and the quality of the DNA is low, as can be seen after fixation and storage. Multiple testing has to be addressed::the fact that multiple genes are tested simultaneously in panel tests increases the probability of false positive results. The increase in probability depends on the number of tests performed simultaneously and the probability to obtain a false positive result per gene. Unless all actionable DNA alterations identified using NGS are first confirmed using an orthogonal technique, it seems prudent to select small panels if one wants to minimise the risk of reporting false positive actionable gene alterations.

Figure 2a and 2b – Test specificity and impact on incremental cost-effectiveness ratio (ICER)



Left: impact of input parameters on ICER of trastuzumab in early breast cancer; right: impact of test specificity on ICER of crizotinib in NSCLC.

3.2. Billing codes and NGS needs for Belgium

The Belgian Cancer Registry analysed the tests for characterisation of breast, colon, rectal, lung, prostate cancer and haematological malignancies diagnosed in 2010 or 2011, for which immunohistochemistry (IHC) or molecular tests were charged around the incidence date. The study population was selected from the database of the Belgian Cancer Registry and linked with the grouped administrative databases from the health insurance, provided by the Intermutualistic Agency.

Overall, the reimbursed amount is about evenly split into IHC and molecular techniques. Breast cancer accounts for half and haematological malignancies for a quarter of these diagnostic expenses, followed by lung cancer and colorectal cancer. Billing of somatic DNA alterations using article 33 at higher fees per test continued in 2010-11 in some genetic centres.

In addition, the evolution of test volume and expenditure was checked for oncology related tests in Article 33bis. These codes were created in the nomenclature of reimbursed activities to allow laboratories other than the centres for human genetics to bill molecular tests on human DNA.

In some cases the strong increase in test volume cannot be explained by medical needs. In contrast with all existing guidance both IHC and ISH tests are performed for nearly all cases of breast cancer in Belgium. If ISH would be performed in the 38.3% of samples with IHC 1+/2+/3+ and reimbursed according to the 130 euros tariff of France, the yearly budget would drop from over 3.3 mio euros to under 1 mio euros. ISH is reimbursed at 340 euros in Belgium. This deserves further investigation as does the large volume of immunoglobulin or T-cell rearrangement tests (1.2 mio euros).

The current budget spent on molecular tests which can be performed with NGS DNA panel tests amounts to about 2.5 mio euros for solid tumours and 2 mio euros for hemato-oncology.

The Article 33bis billing codes cannot cope with the speed of change ongoing in the field of oncology/haematology. The currently available budget in Article 33bis open for tests that can be performed using a NGS panel is over 4.5 mio euros. Another 2 mio euros can for example be made available if HER2 IHC and ISH tariffs are aligned with the rates in France and the ISH test is no longer used to confirm HER2 IHC negative samples.

Based on calculations for France, the number of NGS panel tests per year for Belgium is estimated at 7000 to 10000, replacing many of the current techniques. The cost for a NGS panel test limited to DNA alterations of direct clinical utility varies by platform and yearly test volume. An overall reimbursement fee of 250 euros to 400 euros should cover all costs provided 1000 samples per year are tested, allowing a reasonable test turnaround time of 10 (working) days maximum.

The (unaudited) microcosting results provided by five Belgian laboratories are in line with cost calculations performed in centres in Canada and the UK. In Canada, a laboratory performing a 38 gene panel on 1000 samples per year using an Illumina platform, calculated a cost, excluding validation, of 413 Canadian dollars, about 290 euros. The laboratory in the UK calculated for a 50 gene panel tested in over 1000 samples per year on an Ion Torrent platform a cost of 339 BPB, about 410 euros. This includes an very extensive validation.

Seven to ten centres in Belgium would thus be able to provide all necessary NGS panel tests for a yearly budget of 2 to 4 mio euros. This could be achieved without any increase of the budget spent under Article 33bis.

4. INTRODUCING NGS PANEL TESTS

In this rapidly evolving field of oncology there is a need for the health insurance to cope in an efficient way with new markers, technologies and testing algorithms. These markers are an essential part of the characterisation of tumours reported to the cancer registry. Registration of the test results in a standard and automated way should become routine practice and can be realized if one makes it a condition for test reimbursement as shown in the table 1 below.

Table 1 – Proposed system for the registration and billing of markers for the characterisation of malignancies during the diagnostic workup

steps in registration and reimbursement process	unique ticket confirming registration (sequential number generated upon registration)	ID of oncology center	ID of lab performing test	technology class (IHC, ISH, PCR, NGS small panel, NGS large panel,...) nomenclature code determining reimbursed amount based on activity-based cost	detailed test ID (HER2 ISH, ALK FISH, NRAS, BRAF V600,..) can be pseudocode	test result in standardised format
step 1		request for test by oncology center to lab				
step 2		result obtained at oncology center from lab				
step 3		result reported by oncology center to cancer registry				
step 4	unique ticket confirming registration automatically sent back to oncology center					
step 5	oncology center bills the test including the unique ticket					
step 6	reimbursement by health insurance agency, after check					

Because of the rapid changes in clinically relevant markers and technologies, the current codes and tariffs for reimbursement are quickly outdated. In addition, generic codes do not offer the required transparency to document evolutions in specific marker use over time.

Therefore, we propose a system as proposed in Table 1, for the financing of selected IHC markers and all molecular markers that are of relevance for the characterisation of tumours during the diagnostic workup. The steps include an obligatory registration at the cancer registry as a condition for billing each test. Also a pathway for billing tests in case no tumour is confirmed should be foreseen.

In this concept the pathologist, clinical biologist or geneticist at the hospital the patient is seen and diagnosed (the oncology center in the table above) is in control of ordering the tests at the hospital laboratory in the local hospital or to ship the sample for testing at an external laboratory. This external laboratory will send the bill to the ordering hospital, as is the rule now for clinical biology tests (article 24). This way one avoids that tests are performed (and billed) multiple times by different laboratories.

As already recommended in KCE report no 20, laboratories performing molecular tests for oncology should offer the full panel for a given tumour. Service level agreements between laboratories should facilitate outsourcing.

The financing system should reward the appropriate collection, storage, and (if needed) shipment of the sample as well as the use of an appropriate testing algorithm. Therefore it is suggested a lump sum is provided for the pathologist/clinical biologist/geneticist preparing/shipping the sample and another fee for the selection of tumour cells for analysis and interpretation of the tests (IHC, ISH, cytogenetic, PCR, NGS…) during the diagnostic evaluation of a new cancer. In addition to the lump sum, an amount should be paid for each test performed. In order to stimulate the use of the most cost-effective diagnostic algorithm and to avoid overuse of tests, the amount paid per test should cover the actual cost, not more, and this amount should be re-evaluated on a regular base as technology platforms change.

RECOMMENDATIONS[a]

To RIZIV-INAMI, the Cancer Registry, WIV-ISP, BELAC, the healthcare professionals and their scientific associations:

- **NGS gene panels are a valuable and potentially budget neutral alternative to some of the current sequential gene tests in oncology and haemato-oncology provided the test quality is assured and the testing is centralized appropriately.**
- **As the sensitivity and especially the specificity of the companion diagnostics (NGS or other technique) in routine care have a major impact on the incremental cost-effectiveness ratio of the targeted treatment, companion diagnostics should be co-evaluated during reimbursement decisions of targeted therapy. The demonstrated clinical sensitivity and specificity of the approved companion diagnostic should be identical or highly similar to the one used in the trials demonstrating the efficacy of the drug.**
- **Targeted drugs should only be reimbursed if the companion diagnostic was approved for this purpose and performed in a laboratory that passed the yearly EQA for this test, organized by WIV-ISP.**
- **Further standardisation of the ISO 15 189 accreditation process by BELAC in this field is recommended using test specific guidance documents (including bioinformatics) and should be fully integrated with the external quality assessment organized by WIV-ISP. A training of the technical auditors is recommended.**
- **The involved commissions at RIZIV-INAMI should be advised by a independent multidisciplinary committee of experts (preferentially embedded in an international consortium) to define for billable immunohistochemistry or molecular tests:**
  - **the actionability (including thresholds of variant allelic fractions),**
  - **the level of evidence, including the evidence supporting 'off-label' (but on-target) use of targeted drugs**
  - **the specifications for test equivalence,**
  - **the need for pre-test counseling,**
  - **the test turnaround time**
  - **the adequate reporting format.**

[a] The KCE has sole responsibility for the recommendations.

- **For reimbursement decisions, evaluations of effectiveness and cost-effectiveness remain essential. For the billable markers the amount reimbursed could be based on the level of test complexity, but also more global financing systems should be explored. These should include the diagnostic testing as well as the selection of a targeted therapy and the registration of the relevant results.**
- **The results of these markers (specific immunohistochemistry and molecular tests) should automatically be made available to the cancer registry in a standard format, in collaboration with the Healthdata.be initiative. Registration of the test result at the cancer registry should be a condition for reimbursement of the test.**
- **Education in molecular diagnostics (including NGS) of the healthcare professionals is highly recommended during the residency training as well as in a continuous and documented manner during the full professional career.**

Research agenda:

- **Develop cancer type specific guidance for the molecular and immunohistochemical analyses (from sampling to reporting) of the tumor tissue sample(s).**
- **Develop guidance for the off-label (but on target) use of targeted drugs.**
- **Develop guidance for pre-test counseling, testing and reporting of hereditary mutations in the context of NGS somatic mutation panels in oncology and haemato-oncology.**

COLOPHON

Title:	Next generation sequencing gene panels for targeted therapy in oncology and haemato-oncology – Synthesis
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