Modelling the Impact of Next-Generation Sequencing Based Comprehensive Genomic Profiling Panel on Treatment Practices in Advanced or Metastatic Cancer

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BACKGROUND AND OBJECTIVE

- Recent advancements in the identification of actionable biomarkers and the availability of a greater range of targeted therapies and immunotherapies have drawn attention to key limitations in current testing practices.
- Actionability of single-gene tests (SGT) that rely on polymerase chain reaction (PCR)- and fluorescence in situ hybridization (FISH)-based technologies can be limited by availability of tissue sample for testing and provide information on a select number of genes.
- Small next-generation sequencing (NGS) multigene panels are limited in breadth and the ability to simultaneously detect novel fusions, such as the case with rare mutations like *NTRK*, and emerging biomarkers, including tumor mutational burden (TMB) and microsatellite instability (MSI).
- NGS-based comprehensive genomic profiling (CGP) can test multiple established and emerging biomarkers (i.e., hundreds) in a single, relatively small tissue sample, and has seen increasing adoption in Western Europe and the United States (US).

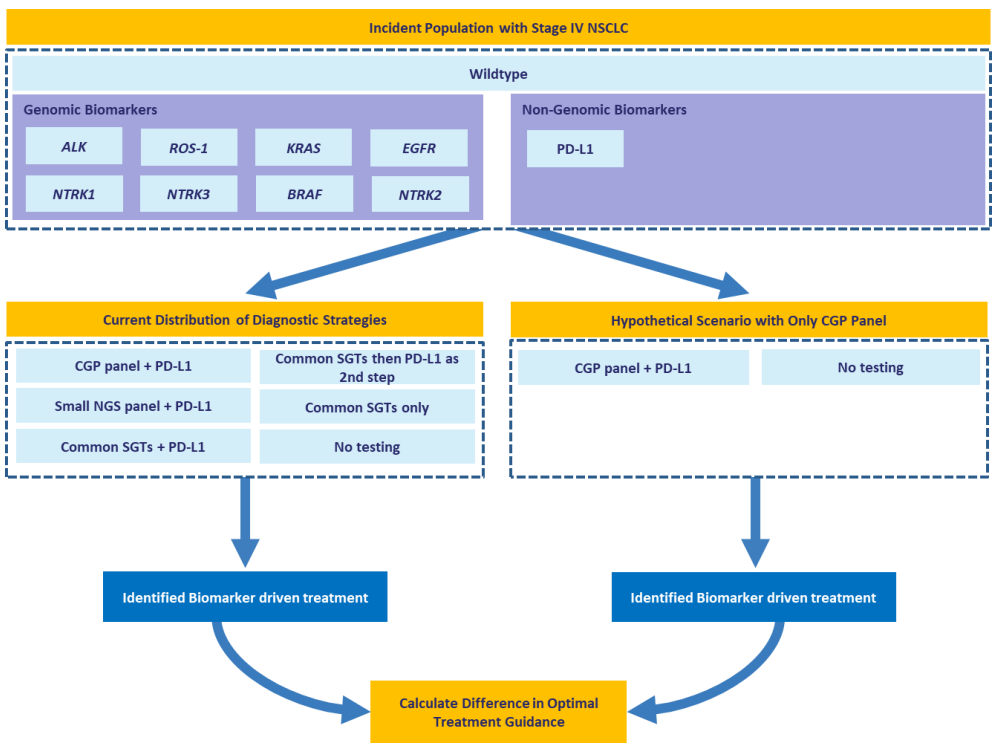
- The primary objective was to evaluate the impact of shifting diagnostic strategies from single-gene and small-panel testing approaches to CGP on treatment guidance for patients with advanced or metastatic cancer in Germany while accounting for variability in real-world testing practices and known correlations in prevalence between actionable biomarkers. Stage IV non-small cell lung cancer (NSCLC) was used in the base-case analysis, while exploratory analyses were conducted on stage IV colorectal cancer (CRC) and emerging biomarkers.

METHODS

Model Concept

- A decision model was developed in Excel® to predict expected treatment guidance based on available information from testing in a genetically heterogenous population with cancer when administered a mix of common diagnostic strategies, ranging from SGTs to NGS-based large multigene panels.
- Utilization of common diagnostic strategies was based on data for Germany from the Ipsos Oncology Monitor,[1] a physician-based syndicated patient record form-tracking study capturing usage of anti-cancer drugs and testing rates across many cancer types.
- The model estimated changes in treatment guidance and number of biopsies if the current mix of common diagnostic strategies (i.e., sequential SGTs, small NGS panels, CGP, and programmed death-ligand 1 [PD-L1] testing) were to be shifted towards higher utilization of CGP.

Figure 1. Model Concept Diagram



Abbreviations: CGP = comprehensive genomic profiling; NGS = next-generation sequencing; NSCLC = non-small cell lung cancer; PD-L1 = programmed death-ligand 1; SGT = single-gene test

Population

- Patients may present with multiple actionable biomarkers, including common and rare genetic alterations (e.g., *NTRK1*, *NTRK2*, *NTRK3*, *RET*), and/or expression-based biomarkers such as PD-L1.
- Prevalence of PD-L1 positivity in wildtype patients was 51.4%,[1] and other than epidermal growth factor receptor (*EGFR*), which has been shown to have a negative correlation with PD-L1 (prevalence of PD-L1 positivity in patients with *EGFR* was 27.5%),[1-2] it was assumed that prevalence of PD-L1 positivity in genetic alterations was the same as wildtype.[1]
- Having driver mutations in multiple genes at once is rare and it was, therefore, assumed patients could only present with one mutation at a time.
- The incidence of treated stage IV NSCLC in Germany was 22.55 per 100,000[3-4] and it was assumed that 78.6% of those patients underwent testing[1] based on German testing frequencies from Ipsos.

Diagnostic Strategies

- Common diagnostic strategies were designed based on European Society of Medical Oncology (ESMO) recommendations for testing[5] and market research,[6] and frequencies were based on Ipsos data from Germany.[1]
- CGP panels and small panels have the advantage over SGT strategies in detecting rare genetic alterations, such as *NTRK1*, *NTRK2*, and *NTRK3*.
- Patients with *KRAS* mutations, indicative of low likelihood of response to targeted therapies, received chemotherapy or proceeded to a subsequent step in testing (if available).
- Based on rates of re-biopsy for diagnostic purposes in Germany, it was assumed that approximately 10% of patients administered SGTs would require re-biopsy (due to the tissue from the first biopsy being insufficient), while patients administered small panel and CGP strategies required only a single biopsy.[7]

Treatment Guidance

- Detected genomic alterations may lead to guidance of administering targeted therapies, while detection of threshold PD-L1 expression may lead to administering checkpoint inhibitor immunotherapies.
- For patients with multiple actionable biomarkers, detected genetic alterations took precedence over PD-L1 expression in guiding treatment.[8]

Exploratory Analysis: Emerging Biomarkers for Treatment

- Tests for emerging biomarkers *MET*, *RET*, and TMB were added to the CGP as these biomarkers were either targeted by a new treatment in the pipeline or were supported by evidence showing a potential link to response to certain treatments.
- Prevalence of *MET* and *RET* was 4% and 1.5%, respectively.[9-10]
- Due to limited data on the correlation between TMB and single-gene alterations, it was assumed that the likelihood of high TMB was the same across all patients, with the prevalence of 35%.[11]

Exploratory Analysis: CRC

- We evaluated the impact on treatment guidance from increasing CGP testing in newly diagnosed patients with stage IV CRC who may present with multiple actionable biomarkers (*KRAS*, *NRAS*, *BRAF*, and MSI).
- Prevalence of *KRAS*,[12] *NRAS*, and *BRAF* was 46%, 7%, and 8%, respectively.[13]
- A positive correlation was found between MSI and *BRAF* vs. *BRAF* wildtype, and the modeled prevalence of MSI in patients with *BRAF* was 21.2%,[14] while the prevalence of MSI in other patients was assumed to be the same as the general population with mCRC at 5% (1% to 10% range).[5,15]
- Following ESMO guidelines, patients harboring *KRAS* and *NRAS* were not recommended for *EGFR* targeted therapy and received chemotherapy or a subsequent step in testing if available; patients positive for *BRAF* were recommended for bevacizumab.[5]
- The incidence of stage IV CRC was 12.66 per 100,000[3,16] and was assumed that 87.7% of patients would take gene mutation testing based on German testing frequencies.[1]

METHODS (CONT.)

Table 1. Model Inputs for NSCLC Analysis

Epidemiology	Prevalence	Ref	Epidemiology	Prevalence	Ref
ALK	7.0%	17	*RET*	1.5%	9,18
EGFR	22.0%		*MET*	3.0%	19
ROS-1	2.0%		*NTRK1*	3.3%	20
BRAF	3.0%		*NTRK2*	0.2%	
KRAS	25.0%		*NTRK3*	0.08%	
Test Accuracy	**Sensitivity**		**Specificity**		**Ref**
FISH	100%		100%		21
PCR	99%		87%		22-23
KRAS PCR	97%		95%		24
PD-L1 IHC	93%		99%		25
Small/large panels	Assume the same as SGTs				

Note: *FISH* is used for testing *ALK*, *ROS-1*, *NTRK1–3*; PCR is used for testing *EGFR*, *KRAS*, and *BRAF*; IHC is used for testing PD-L1. Abbreviations: *ALK* = anaplastic lymphoma kinase; *EGFR* = epidermal growth factor receptor; *FISH* = fluorescence in situ hybridization; IHC = immunohistochemistry; PCR = polymerase chain reaction; Ref = reference; TMB = tumor mutational burden

Table 2. Diagnostic Strategies for NSCLC Analysis

Diagnostic Strategy	Description	Frequency in Current Market
CGP panel + PD-L1	*ALK*, *EGFR*, *ROS-1*, *KRAS*, *BRAF*, *NTRK1*, *NTRK2*, and *NTRK3*	24.4%
Small NGS panel + PD-L1	Same as CGP panel	27%
Common SGTs + PD-L1	*ALK*, *EGFR*, *ROS-1*, and *BRAF*	25.1%
Common SGTs then PD-L1 as 2nd step if negative at 1st step		1.0%
Common SGTs only		1.0%
No testing	—	21.5%

Note: Diagnostic strategy utilizations were calculated through Ipsos data, in which the frequency of single gene mutation test was calculated. Then Excel® Solver was used to calibrate diagnostic strategy utilization to match each single gene mutation test frequency.
Abbreviations: *ALK* = anaplastic lymphoma kinase; CGP = comprehensive genomic profiling; NGS = next-generation sequencing; PD-L1 = programmed death-ligand 1; SGT = single-gene test

Table 3. Diagnostic Strategies for CRC Analysis

Diagnostic Strategy	Description	Frequency in Current Market
CGP panel	*KRAS*, *NRAS*, *BRAF*, and MSI	1.0%
Small NGS panel + MSI as 2nd step if negative at 1st step	*KRAS*, *NRAS*, and *BRAF*	10.0%
Common SGTs only	*KRAS*, *NRAS*, and *BRAF*	9.6%
Common SGTs + MSI in parallel		67.1%
No testing	—	12.4%

Note: *First and second generation TKIs. Abbreviations: CGP = comprehensive genomic profiling; MSI = microsatellite instability; NGS = next-generation sequencing; SGT = single-gene test

RESULTS

Base-case Analysis: NSCLC

- The model forecasted that higher use of CGP panels increased the number of patients receiving optimal treatment guidance from predictive biomarker status from 684/1,000 to 705/1,000 patients (3.2% increase), driven by the testing of rare biomarkers.
- Increasing the utilization of CGP lowered the need for re-biopsies, potentially decreasing overall biopsy requests from 813/1,000 to 786/1,000 patients (3.3% decrease).

Exploratory Analysis: Emerging Biomarkers for Treatment

- With the inclusion of *MET*, *RET*, and TMB in CGP, the model forecasted that the higher use of CGP panels would increase the number of patients receiving optimal treatment guidance from 631/1,000 to 701/1,000 patients (11.1% increase).

Exploratory Analysis: CRC

- The number of patients receiving optimal treatment guidance from an increase use of CGP would increase from 747/1,000 to 790/1,000 patients (5.8% increase), mostly driven by higher frequency of MSI testing.

Table 4. Base-case Results (based on incident cohort of 1,000)

Patients Receiving Optimal Treatment	Change	Ref Market (N)	New Market (N)
Overall % patients receiving guidance of optimal treatment	3.2%	684	705
With treatment guidance based on detected mutation	3.4%	284	294
With treatment guidance based on PD-L1 expression	3.8%	187	195
Without actionable biomarkers	2.3%	212	217
Patient NOT receiving optimal treatment guidance	-21.2%	102	81
Overall Treatment Distribution	**Change**	**Ref Market (N)**	**New Market (N)**
Chemotherapy	-0.5%	236	235
EGFR-targeted TKI*	-4.9%	220	209
ALK/*ROS-1*-targeted TKI	-	71	71
BRAF inhibitor with and without *MEK* inhibitor	-4.8%	29	28
IO	1.7%	211	215
NTRK-targeted TKI	52.9%	18	28

*First- and-second generation TKIs; Abbreviations: *ALK* = anaplastic lymphoma kinase; *EGFR* = epidermal growth factor receptor; IO = immuno-oncology; PD-L1 = programmed death-ligand 1; TKI = tyrosine kinase inhibitor

DISCUSSION

Model Strengths

- Explicitly captures genetic heterogeneity and correlation between genetic alterations and other actionable biomarkers like PD-L1
- Reflects treatment decisions when faced with competing actionable biomarkers in accordance with clinical guidelines
- Modeled diagnostic strategies designed to reflect the common practices of SGTs and NGS done in parallel or in sequence and are grounded in real-world data on testing frequencies
- Forecasts the potential effect of higher detection of rare and novel biomarkers (e.g., *NTRK*, *MET*, *RET*, and TMB) on treatment guidance

Limitations

- Testing accuracy was based on commercially available tests; in reality, testing accuracy can be highly variable among laboratory developed tests and in the detection of novel fusions, as hybrid capture-based CGP has the advantage over amplicon-based NGS panels in detecting more novel fusion partners.
- The model forecasts changes in treatment guidance; however, test results are not always utilized by physicians when deciding on treatments.

CONCLUSIONS

- The utilization of CGP tests to inform first-line treatment in metastatic cancer can be increased and potentially lead to more patients being matched with optimal treatments and lower the need for re-biopsy for testing.
- The impact of CGP in oncology benefits from a modeling approach can be assessed to capture genetic heterogeneity and treatment decisions when dealing with multiple actionable biomarkers.

- All references can be found in the printed handout.

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Abstract

Objectives: This study aims to evaluate the impact of shifting diagnostic strategies from current practice to next generation sequencing (NGS) based comprehensive genomic profiling (CGP) on the treatment guidance for patients with advanced or metastatic cancer in Germany while accounting for variability in real-world diagnostic practices and correlation between multiple actionable biomarkers.

Methods: A decision model was developed in Excel® that examined multiple diagnostic strategies, including common single gene tests, small and CGP panels, and PD-L1 testing, in parallel or in sequence, with frequencies based on Ipsos Healthcare chart review data. CGP panels detected rare mutations including known and novel fusions with NTRK and emerging biomarkers for advanced therapies. The model factored sensitivity and specificity of tests to predict observed diagnoses versus actual patient characteristics. For patients positive for multiple actionable biomarkers, biomarkers for targeted therapy took precedence over PD-L1 in driving treatment. The base case analysis evaluated the impact of CGP panels on the fraction of non-small cell lung cancer (NSCLC) patients receiving optimal treatments. Scenarios of alternative cancer indications were also evaluated.

Results: The model predicted that higher use of CGP panels in NSCLC can increase detection of genetic biomarkers for targeted therapy from 684/1,000 to 705/1,000 patients and detection of NTRK can improve by as much as 52.9%. When considering emerging biomarkers in NSCLC, optimal treatment guidance can increase by 11%. Analysis in colorectal cancer (CRC) showed optimal treatment guidance can increase by 5.8%, driven by higher frequency of MSI testing.

Conclusions: CGP panels can lead to more patients being matched with optimal treatments in the current market. Assessing the impact of NGS in oncology benefits from a modeling approach that captures genetic heterogeneity and treatment decisions when dealing with multiple actionable biomarkers.

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