



Original research

Institutional variability in testing for actionable genetic alterations in patients with stage IIIB/C or IV non-small cell lung cancer: A real-world study from the German prospective, observational, multicenter CRISP registry (AIO-TRK-0315)

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ABSTRACT

Background: Molecular testing in NSCLC is essential for treatment selection, yet routine implementation remains inconsistent across institutions. Clinical evidence suggests that variability in testing may not be explained by patient or tumor characteristics but might be driven by institutional factors, potentially leading to adverse outcomes. We examined the extent to which variability in AGA testing is attributable to the treating institution. **Methods:** We analyzed 6437 adults with stage IIIB/C or IV NSCLC enrolled in the prospective German real-world registry CRISP (2016–2022). Logistic mixed-effects models with AGA testing as the primary outcome were used to determine institutional variability across 171 institutions. Models included patient, tumor, and treatment-related fixed effects with institutions as random effects. Intraclass correlations (ICC) quantified institutional variability unexplained by other covariates. Institution type was tested in secondary analysis, and overall survival in exploratory analysis.

Findings: AGA testing was performed in 77.9 % of patients (n = 5016). Predicted probabilities for testing use ranged from 30.5 % to 93.2 % across institutions. Institutions significantly influenced testing use (p < 0.001), accounting for 21.4 % of the total variance. Variability significantly differed by institution type and was more

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pronounced in subgroups, e.g., squamous histology (ICC 29.5 %) and KRAS testing (ICC 34.4 %). Absence of AGA testing was independently associated with inferior survival (HRadj 1.11, 95 % CI 1.01–1.23, $p = 0.029$).

Interpretation: Substantial institutional variability exists in AGA testing for NSCLC, which was unexplained by patient or tumor characteristics. This objective evaluation of institution-based variability in testing may emphasize the importance of practice patterns on patient care and may therefore provide an avenue for change.

1. Introduction

Lung cancer affects more than two million patients every year worldwide. In Germany, more than 57,000 newly diagnosed lung cancers were encountered in 2019, where it ranks second among cancers in men and third in women, accounting for 13.3 % and 9.4 % of all newly diagnosed cancers, respectively [1]. Non-small cell lung cancer (NSCLC) accounts for approximately 85 % of lung cancer cases, including tumors of non-squamous (adenocarcinomas) and squamous histology. Biomarker testing for actionable genetic alterations (AGA), such as EGFR and ALK, has become an integral component of personalized treatment strategies for NSCLC. Today, targetable molecular alterations are identified in approximately 60 % of lung adenocarcinoma patients in Western populations and up to 80 % among Asian populations [2]. The most frequent AGA in adenocarcinomas in Germany include KRAS mutations (~30 %), EGFR mutations (10–15 %), ALK rearrangements (4–5 %), and ROS1, RET, BRAF V600E, NTRK, and HER2 alterations, each occurring in less than 5 % of cases [1]. However, despite the importance of AGA testing, its routine application remains inconsistent across healthcare institutions [3–5].

There is clinical evidence for variability in the use of AGA testing, with factors such as patient characteristics, tumor biology, and access to testing technologies all potentially influencing its implementation [5–7]. However, institutional factors, such as hospital type, routine practices, and the availability of resources, may also contribute to this variability [3]. Understanding the extent to which these factors contribute to differences in practice is crucial, as this variation may influence treatment decisions and patient outcomes. In this multicenter analysis, we aimed to test whether variability in AGA testing for NSCLC exists across individual healthcare institutions and different types of institutions, and to investigate to what extent institutional factors, rather than patient or tumor characteristics, play a role in determining AGA testing practices.

2. Methods

2.1. Study design and setting

This multicenter, observational study utilized data from the prospective CRISP registry (“Clinical Research platform Into molecular testing, treatment and outcome of non-Small cell lung carcinoma Patients”), a real-world data platform that prospectively collects clinical and treatment data across multiple institutions in Germany. This study included adult patients with stage IIIB/C NSCLC treated with non-curative intent or stage IV NSCLC, diagnosed between 2016 and 2022, where data on the use of AGA testing were available. Institutions included university hospitals, non-university hospitals, ambulatory health care centers, and practices. Data analyses included patient characteristics such as age, sex, BMI, smoking status, Charlson comorbidity index (CCI), ECOG performance status, as well as tumor-related factors such as tumor location, histology, staging at initial diagnosis, and start year of first-line treatment. Institutions were analyzed on an individual basis and categorized by institution type into four groups: university hospitals, non-university hospitals, ambulatory health care centers, and practices. Ambulatory health care centers refer to multi-disciplinary medical care centers, while practices refer to individual office-based practices. AGA testing was defined as the use of any diagnostic assay to identify AGA in common genes associated with NSCLC,

including EGFR, ALK, ROS1, BRAF V600E, and KRAS. We recorded the proportion of patients who underwent any AGA testing (yes/no, binary variable) and also created separate variables for individual AGA to analyze testing for specific genetic alterations. AGA testing status reflects testing performed at initial diagnosis/baseline, as captured prospectively in the CRISP registry. This manuscript adheres to the STROBE guidelines (Supplement, Table 1) [8].

2.2. Statistical analysis

2.2.1. Primary analysis

In the primary analysis, we used a logistic mixed-effects model with AGA testing as the primary outcome (dependent variable) and random effects for individual institutions to assess variability in AGA testing across institutions in Germany [9]. Covariates were included as fixed effects in all statistical models to adjust for potential confounding effects on the use of AGA testing, including patient, tumor, and treatment characteristics. We used the random effects’ variances and the model residuals to calculate the intraclass correlation coefficient (ICC). The ICC represents the percentage of variance in AGA testing that could not be explained by the covariates of the model but can be accounted for by the institution. In our mixed-effects model, the ICC helps to understand how much of the overall variation in AGA testing is explained by institutions. The ICC ranges from 0 % to 100 %. If the ICC is high (closer to 100 %), much of the variance in AGA testing that is unexplained by the covariates can be attributed to the institution [10]. To plot variability across institutions, we obtained predicted probabilities for the use of AGA testing from models without fixed effects, using individual institution and institution type as random effects, respectively.

2.2.2. Secondary analysis

In secondary analysis, we added the institution type (university hospitals, non-university hospitals, ambulatory health care centers, and practices) to the primary model. This was done to analyze whether differences in AGA testing exist across different institution types.

2.2.3. Sensitivity analyses

Sensitivity analyses were performed to assess the robustness of the primary analysis. We performed analyses in more homogenous subgroups such as subgroups by tumor histology and tumor staging. In addition, we tested the primary model while considering experience levels of different institutions by adding the number of patients recruited per year as a fixed effect. Additionally, we applied case volume restrictions by including only institutions that had treated a minimum of 100 NSCLC cases since the start of their recruitment. Institutional variability in AGA testing was further examined in subgroups defined by testing modality, analyzing patients with NGS-based testing and those tested with other non-NGS methods (e.g., PCR, Sanger sequencing). Finally, with an exploratory intent, we evaluated the impact of AGA testing on overall survival using a multivariable Cox regression model that included the same covariates as the primary model. For this survival analysis, we used the outcome dataset with a minimum follow-up time of 12 months, resulting in a reduced sample size ($n = 5503$).

Variables with a non-linear relationship were categorized into clinically relevant groups (Table 1). Unless otherwise specified, results of adjusted analyses are presented as random effect variances with 95 % confidence intervals (CI) and odds ratios (OR) with 95 % CI for fixed effects. A two-sided p -value of < 0.05 was considered statistically

significant. Analyses were performed in SAS and Rstudio.

3. Results

In total, 7774 patients were prospectively enrolled into the CRISP platform and screened for eligibility until 30.06.2022. After excluding cases with missing data, a total of 6437 patients from 171 institutions

were included into this study (Fig. 1). AGA testing was performed in 77.9 % of patients (n = 5016). Table 1 displays detailed patient characteristics.

In the primary model, factors significantly associated with the use of AGA testing were a low performance status (ECOG ≥ 2 vs. ECOG 0; OR 0.73, 95 % CI 0.58 – 0.93), older age (70–75 years vs. <59 years; OR 0.77, 95 % CI 0.61 – 0.97), non-squamous tumor histology vs. squamous

Table 1
Patient characteristics.

	Total	University hospital	Non-university hospital	Ambulatory health care center	Practice
Patients (N)	6437	1040	2696	720	1981
Sex, female, n (%)	2642 (41.0 %)	429 (41.3 %)	1103 (40.9 %)	294 (40.8 %)	816 (41.2 %)
Age (mean $\pm$ StD)	66.3 $\pm$ 9.54	64.6 $\pm$ 9.36	65.9 $\pm$ 9.62	67.1 $\pm$ 8.93	67.5 $\pm$ 9.55
ECOG at LOT, n (%)					
0	2079 (32.3 %)	392 (37.7 %)	882 (32.7 %)	255 (35.4 %)	550 (27.8 %)
1	3383 (52.6 %)	513 (49.3 %)	1467 (54.4 %)	349 (48.5 %)	1054 (53.2 %)
≥ 2	975 (15.1 %)	135 (13.0 %)	347 (12.9 %)	116 (16.1 %)	377 (19.0 %)
Smoking status, n (%)					
Current Smoker	1924 (29.9 %)	276 (26.5 %)	762 (28.3 %)	242 (33.6 %)	644 (32.5 %)
Ex-Smoker	3303 (51.3 %)	584 (56.2 %)	1453 (53.9 %)	315 (43.8 %)	951 (48.0 %)
Never Smoker	729 (11.3 %)	124 (11.9 %)	285 (10.6 %)	70 (9.7 %)	250 (12.6 %)
Unknown to site	481 (7.5 %)	56 (5.4 %)	196 (7.2 %)	93 (12.9 %)	136 (6.9 %)
Pack years (mean $\pm$ StD)	45.9 $\pm$ 26.60	44.3 $\pm$ 27.51	45.1 $\pm$ 27.56	51.7 $\pm$ 27.39	46.4 $\pm$ 24.07
BMI (kg/m ²)					
Mean $\pm$ StD	25.1 $\pm$ 5.39	25.2 $\pm$ 6.95	25.0 $\pm$ 5.03	25.0 $\pm$ 4.97	25.2 $\pm$ 5.06
Obesity, n (%)	875 (13.6 %)	150 (14.4 %)	361 (13.4 %)	99 (13.8 %)	265 (13.4 %)
Missing, n (%)	67 (1.0 %)	22 (2.1 %)	24 (0.9 %)	5 (0.7 %)	16 (0.8 %)
Any comorbidity, n (%)	5455 (84.7 %)	887 (85.3 %)	2264 (84.0 %)	616 (85.6 %)	1688 (85.2 %)
Charlson comorbidity index [0–24], n (%)					
0	3600 (55.9 %)	655 (63.0 %)	1470 (54.5 %)	393 (54.6 %)	1082 (54.6 %)
1	1651 (25.6 %)	232 (22.3 %)	712 (26.4 %)	194 (26.9 %)	513 (25.9 %)
2	641 (10.0 %)	84 (8.1 %)	276 (10.2 %)	71 (9.9 %)	210 (10.6 %)
3	304 (4.7 %)	28 (2.7 %)	139 (5.2 %)	39 (5.4 %)	98 (4.9 %)
4	114 (1.8 %)	16 (1.5 %)	51 (1.9 %)	10 (1.4 %)	37 (1.9 %)
≥ 5	127 (2.0 %)	25 (2.4 %)	48 (1.8 %)	13 (1.8 %)	41 (2.1 %)
Tumor histology, n (%)					
Adenocarcinoma	4731 (73.5 %)	818 (78.7 %)	2000 (74.2 %)	494 (68.6 %)	1419 (71.6 %)
Squamous	1338 (20.8 %)	155 (14.9 %)	556 (20.6 %)	177 (24.6 %)	450 (22.7 %)
Large cell	106 (1.6 %)	16 (1.5 %)	37 (1.4 %)	16 (2.2 %)	37 (1.9 %)
Other	262 (4.1 %)	51 (4.9 %)	103 (3.8 %)	33 (4.6 %)	75 (3.8 %)
Tumor stage at inclusion, n (%)					
IIIB/C	417 (6.5 %)	34 (3.3 %)	168 (6.2 %)	67 (9.3 %)	148 (7.5 %)
IVA	2430 (37.8 %)	299 (28.8 %)	1010 (37.5 %)	285 (39.6 %)	836 (42.2 %)
IVB	3590 (55.8 %)	707 (68.0 %)	1518 (56.3 %)	368 (51.1 %)	997 (50.3 %)
Tumor stage: primary diagnosis vs. inclusion, n (%)					
Same as at inclusion	5534 (86.0 %)	845 (81.3 %)	2398 (88.9 %)	630 (87.5 %)	1661 (83.8 %)
Different from stage at inclusion	798 (12.4 %)	150 (14.4 %)	255 (9.5 %)	84 (11.7 %)	309 (15.6 %)
Unknown	102 (1.6 %)	45 (4.3 %)	40 (1.5 %)	6 (0.8 %)	11 (0.6 %)
Metastatic sites, n (%)					
Brain	1521 (23.6 %)	326 (31.3 %)	660 (24.5 %)	148 (20.6 %)	387 (19.5 %)
Bone	1988 (30.9 %)	418 (40.2 %)	820 (30.4 %)	209 (29.0 %)	541 (27.3 %)
Lung - contralateral	1528 (23.7 %)	235 (22.6 %)	631 (23.4 %)	161 (22.4 %)	501 (25.3 %)
Lymph node - extrathoracic	842 (13.1 %)	187 (18.0 %)	331 (12.3 %)	107 (14.9 %)	217 (11.0 %)
Lymph node - thoracic	159 (2.5 %)	36 (3.5 %)	51 (1.9 %)	18 (2.5 %)	54 (2.7 %)
Liver	956 (14.9 %)	156 (15.0 %)	384 (14.2 %)	117 (16.3 %)	299 (15.1 %)
Pleura metastases	1004 (15.6 %)	154 (14.8 %)	432 (16.0 %)	99 (13.8 %)	319 (16.1 %)
Pleural effusion	490 (7.6 %)	49 (4.7 %)	206 (7.6 %)	69 (9.6 %)	166 (8.4 %)
Skin	77 (1.2 %)	11 (1.1 %)	31 (1.1 %)	9 (1.3 %)	26 (1.3 %)
Adrenal gland	1081 (16.8 %)	217 (20.9 %)	474 (17.6 %)	94 (13.1 %)	296 (14.9 %)
Pericardial effusion	103 (1.6 %)	12 (1.2 %)	41 (1.5 %)	12 (1.7 %)	38 (1.9 %)
Other	626 (9.7 %)	148 (14.2 %)	249 (9.2 %)	80 (11.1 %)	149 (7.5 %)
Type of first-line treatment, n (%)					
Chemotherapy	2127 (33.0 %)	343 (33.0 %)	837 (31.0 %)	294 (40.8 %)	653 (33.0 %)
CPI mono	1062 (16.5 %)	201 (19.3 %)	432 (16.0 %)	105 (14.6 %)	324 (16.4 %)
Chemotherapy + CPI	2352 (36.5 %)	324 (31.2 %)	1071 (39.7 %)	242 (33.6 %)	715 (36.1 %)
TKI	707 (11.0 %)	152 (14.6 %)	296 (11.0 %)	55 (7.6 %)	204 (10.3 %)
Other treatment	189 (2.9 %)	20 (1.9 %)	60 (2.2 %)	24 (3.3 %)	85 (4.3 %)
Any palliative radiotherapy, n (%)	2603 (40.4 %)	521 (50.1 %)	1112 (41.2 %)	278 (38.6 %)	692 (34.9 %)
Missing n (%)	43 (0.7 %)	21 (2.0 %)	16 (0.6 %)	0 (0.0 %)	6 (0.3 %)
Area of radiation, n (%)					
Brain	1209 (18.8 %)	276 (26.5 %)	514 (19.1 %)	122 (16.9 %)	297 (15.0 %)
Bone	956 (14.9 %)	209 (20.1 %)	412 (15.3 %)	96 (13.3 %)	239 (12.1 %)
Thorax	777 (12.1 %)	134 (12.9 %)	335 (12.4 %)	80 (11.1 %)	228 (11.5 %)
Other	356 (5.5 %)	92 (8.8 %)	145 (5.4 %)	26 (3.6 %)	93 (4.7 %)
Missing	18 (0.3 %)	7 (0.7 %)	4 (0.1 %)	2 (0.3 %)	5 (0.3 %)

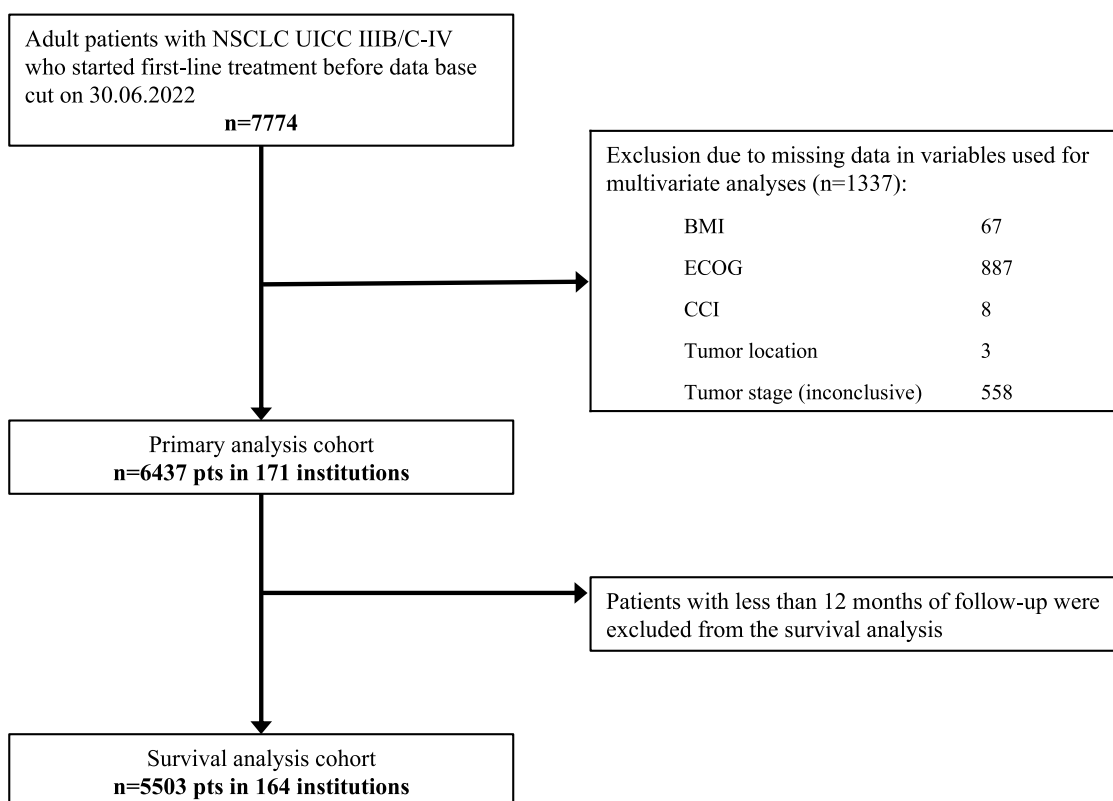


Fig. 1. Flow chart.

NSCLC (OR 12.62, 95 % CI 10.72 – 14.85), and tumor staging, with IVA versus IIIB/C (OR 2.80, 95 % CI 2.13 – 3.68), and IVB versus IIIB/C (OR 2.77, 95 % CI 2.12 – 3.61).

3.1. Institutional variability

The adjusted mean predicted probabilities for the use of AGA testing ranged from 30.5 % to 93.2 % across individual institutions, which can be interpreted as the predicted probability that an average patient would receive AGA testing at each institution. There was statistically significant variability in AGA testing across institutions ($p < 0.001$). According to the ICC, 21.4 % of the total variance in testing was attributable to the institution, independent of patient-, tumor-, or treatment-related covariates.

3.2. Institution type

Across different institution types, 1040 (16.2 %) patients were treated at 22 university hospitals, 2696 (41.9 %) patients at 64 non-university hospitals, 720 (11.2 %) patients at 25 ambulatory health care centers, and 1981 (30.8 %) patients in 60 practices. Table 2

provides an overview of institutional experience and patient recruitment rates across different types of institutions. Institution type was a significant factor influencing the observed institutional variability in AGA testing ($p = 0.028$). University hospitals generally had a higher adjusted mean predicted probability for the use of AGA testing (87.3 %, 95 % CI 85.1–89.2 %) compared to non-university hospitals (75.8 %, 95 % CI 74.1–77.3 %), ambulatory health care centers (72.0 %, 95 % CI 68.7–75.2 %), and practices (78.1 %, 95 % CI 76.2–79.9 %). Fig. 2 provides a graphical visualization of each individual institution's predicted probability for the use of AGA testing (2a), as well as the distribution grouped by institution type (2b).

3.3. Sensitivity analyses

Institutional variability in AGA testing was particularly pronounced in certain subgroups, such as patients with squamous histology (ICC 29.5 %, $p < 0.001$) and in the testing for KRAS mutations (ICC 34.4 %, $p < 0.001$). For other mutations, institutional variability in testing was more consistent (e.g. EGFR: ICC 19.4 %, $p < 0.001$; ALK: ICC 19.3 %, $p < 0.001$; Supplemental Tables S1 to S5). In testing modality-stratified subgroup analyses, institutional variability in AGA testing remained

Table 2
Institutional experience by institution type.

	Total	University hospital	Non-university hospital	Ambulatory health care center	Practice
Institutions (N)	171	22	64	25	60
Recruited patients per year					
Mean $\pm$ StD	7.7 $\pm$ 7.90	10.2 $\pm$ 10.21	9.0 $\pm$ 8.91	5.3 $\pm$ 4.46	6.4 $\pm$ 6.46
Median (25–75 % quantiles)	4.7 (2.0–10.9)	6.3 (3.7–15.6)	7.4 (2.0–13.7)	3.8 (1.8–7.8)	4.4 (1.9–8.1)
Institutional experience, n (%)					
low (<10 pat/year)	123 (71.9 %)	13 (59.1 %)	41 (64.1 %)	21 (84.0 %)	48 (80.0 %)
medium (10 $\leq$ pat/year < 20)	35 (20.5 %)	7 (31.8 %)	15 (23.4 %)	4 (16.0 %)	9 (15.0 %)
high (pat/year $\geq$ 20)	13 (7.6 %)	2 (9.1 %)	8 (12.5 %)	0 (0.0 %)	3 (5.0 %)

Footnote: Institutional experience reflects number of patients recruited into the CRISP registry by institution type.

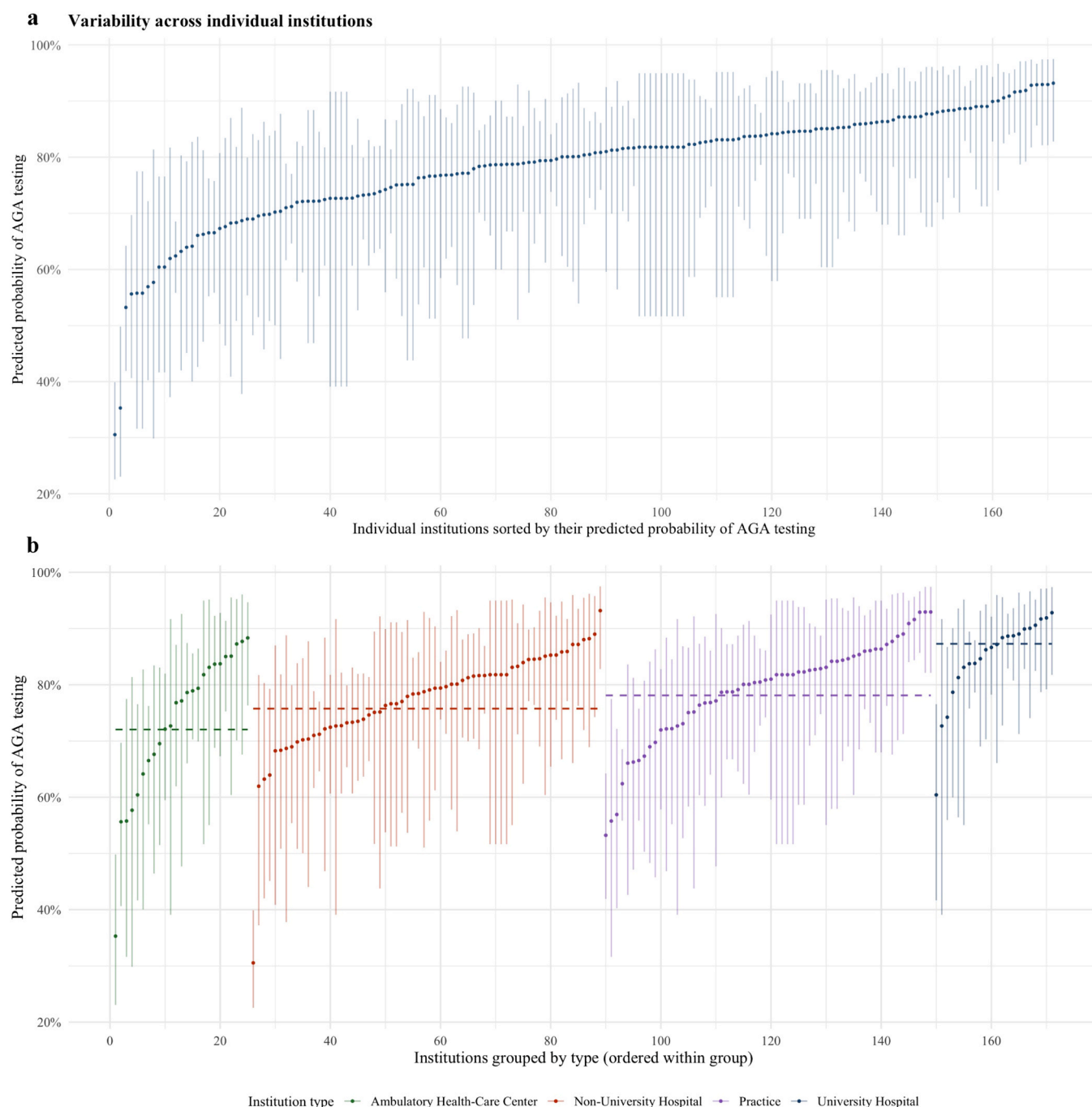


Fig. 2. Institutional variability in the use of AGA testing across individual institutions. Predicted probabilities for the use of AGA testing (mean and 95 % confidence interval) across individual institutions. For each of the 171 institutions, the dot marks the mean of the predicted probability of AGA testing, and the vertical bar shows its 95 % confidence interval. The figures illustrate how AGA testing practices vary substantially between institutions – even within the same institution type. The observed variability could not be explained by the covariate model accounting for patient-, tumor-, and treatment-related factors that may have influenced the use of AGA testing in NSCLC. Figure 2a shows individual institutions sorted by their adjusted mean predicted probability of AGA testing, regardless of institution type. Figure 2b displays the same institutions grouped by institution type (university hospital, non-university hospital, ambulatory health care center, and practice) and ordered within each group according to their predicted probability of AGA testing. Horizontal dashed lines indicate the model-derived overall mean predicted probability of AGA testing separately for each institution type in Figure 2b.

robust, with an ICC of 40.1 % for NGS-based testing and 33.6 % for other non-NGS methods. Overall, we found significant institutional variability in AGA testing across all subgroup and sensitivity analyses (Supplemental Tables S1 to S15). The lowest institutional variability was observed in a subgroup analysis of 16 institutions that had treated a minimum of 100 NSCLC cases since the start of their recruitment (ICC 13.7 %, $p < 0.001$, $n = 2323$ patients).

3.4. Association between AGA testing and overall survival

Absence of biomarker testing was associated with inferior survival. After adjusting for all fixed covariates of the primary model, patients who did not undergo AGA testing had a significantly higher risk of death (HRadj 1.11, 95 % CI 1.01–1.23, $p = 0.029$).

4. Discussion

This large multicenter, real-world analysis is the first to demonstrate a substantial institutional variability in AGA testing for patients with advanced/metastatic NSCLC across multiple institutions in Germany. While some patient and tumor characteristics are important factors influencing AGA testing practices, our data suggest that one-fifth of the total variability in testing can be attributed to the institution itself, independent of these covariates. This is particularly reflected in the overall higher predicted testing probabilities observed at university hospitals compared to other institution types. However, substantial variability remained within and across all institution types.

While our study quantifies significant institutional variability in AGA testing, it does not allow for direct conclusions regarding the underlying causes. This variability may be related to institutional policies, local routines, resource availability, or other unmeasured structural or cultural factors. Plausible examples include the presence or absence of standardized testing workflows, use of pathologist-initiated reflex testing for biomarker panels [11,12], integration of molecular tumor boards [13], and whether AGA testing is centralized in high-volume pathology institutes. These factors are potentially modifiable through local quality-improvement initiatives. However, they were not captured in this registry, and their contribution to the measured variability in AGA testing remains hypothetical in the context of our study.

Previously published CRISP data demonstrated increasing overall testing rates from 83.2 % in 2015 and 2016–94.2 % in 2019 [14]. Calendar year was included as a fixed effect in all models to adjust for these changes over time, yet substantial institutional variability in AGA testing persisted. However, while calendar year was adjusted for, our analysis does not formally test whether institutional variability changed over time.

It is worth noting that the highest institutional variability in AGA testing was observed among lung cancer patients with squamous histology and in testing for KRAS mutations. The higher institutional variability in AGA testing among patients with squamous tumors may be explained by the lower prevalence of actionable genetic alterations in this subtype compared to non-squamous NSCLC [15–18], which may lead clinicians to be more hesitant in performing AGA testing in this population. In addition, KRAS testing showed the greatest overall institutional variability, likely due to the relatively recent availability of targeted therapies for KRAS mutations. Since the approval of the first KRAS G12C inhibitor for second-line treatment of KRAS G12C-mutant NSCLC in February 2022 in Germany, there has been increased focus on KRAS testing [14,19]. However, differences in institutional readiness and awareness may contribute to the observed variability in testing practices for this mutation. It is important that tests are rapidly implemented after targeted therapies become available, to avoid delays between drug availability and test access [3].

Moreover, our survival analysis and similar studies demonstrated that the absence of AGA testing was associated with inferior overall survival [6,7,20]. These survival findings should be interpreted cautiously given the inclusion of both stage IIIB/C patients treated with non-curative intent and stage IV patients, as prognostic differences and treatment pathways may influence the observed association. While this exploratory finding cannot demonstrate causality between testing and survival, it aligns with established evidence from clinical trials and real-world studies showing survival benefits of matched targeted therapies in AGA-positive disease. These studies highlight the clinical significance of AGA testing in guiding targeted therapies. Therefore, addressing institutional variability in AGA testing practices is essential to ensure that all patients with AGA-positive NSCLC benefit from the range of targeted therapy options available. The clinical relevance becomes more evident when considering the implications from a patient perspective. For example, a newly diagnosed patient with metastatic

NSCLC harboring an ALK rearrangement – a molecular subtype with highly effective targeted treatment options – may not undergo appropriate AGA testing depending on the institution they present to. In such cases, the patient may receive first-line chemotherapy or chemo-immunotherapy instead of ALK-directed therapy. Clinical trials have demonstrated that patients treated with third-generation tyrosine kinase inhibitors can achieve a median overall survival exceeding five years, with a subset of patients responding for a decade or longer [21, 22]. In contrast, median survival under chemo-immunotherapy in this population is typically less than two years, often accompanied by increased toxicity and reduced quality of life [23,24]. Based on national incidence data and our findings, several hundred ALK-positive patients in Germany may be affected by insufficient AGA testing each year, depending on the institutions they seek care from. Therefore, ensuring consistent AGA diagnostics should now be considered a public health priority. Supporting this view, a large real-world study from France found that the presence of an AGA influenced first-line treatment decisions in 51% of over 8000 patients with advanced NSCLC [20]. Moreover, when patients with EGFR mutations were included in the analyses, AGA presence was significantly associated with higher objective response rates both in first-line and second-line treatment, as well as with improved PFS and OS in the first-line setting [20]. More recent data from a large US clinicogenomic database further support the clinical relevance of comprehensive molecular profiling, showing that patients with AGA had substantially longer overall survival when treated with matched targeted therapies compared with those who did not receive such treatments [25].

The methods used in this study have certain limitations. As this was not a confirmatory statistical analysis, no adjustment for multiple testing was applied. Approximately 17 % of initially eligible patients were excluded due to missing covariates and complete-case analyses without multiple imputation were performed, which may introduce selection bias. The use of registry data may have limited our ability to account for unmeasured factors that could have influenced the use or clinical necessity of AGA testing. As previously noted, our data do not allow us to determine the specific reasons for the observed institutional variability, other than institution type. Additionally, our data do not allow any conclusions regarding potential relationships between the observed institutional variability and adverse outcomes.

Finally, this study was conducted only within the German healthcare system, which features high nationwide participation in clinical registries, such as the nNGM (national Network for Genomic Medicine) and CRISP, and standardized reimbursement for molecular testing. These features may limit generalizability to other European countries with different molecular testing reimbursement models and lower registry participation rates, where institutional variability may be even greater. Nevertheless, the mixed-effects modeling approach used here could be applied to other national registries for quantifying institutional variability in AGA testing. Despite these limitations, institutional variability in AGA testing in Germany has not been objectively demonstrated before, and we therefore believe our findings add important value to the discussion about standardized guidelines for the use of AGA testing in NSCLC. Results were robust across several sensitivity analyses, including subgroups by histology and restrictions to higher-volume centers, which strengthens confidence in the findings.

In conclusion, our study demonstrated significant institutional variability in the use of AGA testing in NSCLC. This variability could not be explained by patient- or tumor-related characteristics and may partly reflect institutional culture or other unmeasured structural factors. Given the critical role of AGA testing in personalized treatment selection and patient outcomes, efforts to standardize testing practices across institutions are needed. Reducing institutional disparities in testing could improve the consistency and quality of care for patients with NSCLC, ultimately leading to better clinical outcomes.

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CRediT authorship contribution statement

Martina Jänicke: Writing – review & editing, Software, Resources, Methodology, Investigation, Formal analysis, Data curation. **Martin Sebastian:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Annette Fleitz:** Writing – review & editing, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Eberhardt Wilfried E. E.:** Writing – review & editing, Validation, Resources, Project administration, Funding acquisition, Data curation, Conceptualization. **Stefan Zacharias:** Writing – review & editing, Validation, Supervision, Software, Resources, Methodology, Investigation, Formal analysis. **Michael Thomas:** Writing – review & editing, Validation, Resources, Project administration, Funding acquisition, Data curation, Conceptualization. **Christian Grah:** Writing – review & editing, Validation, Data curation. **Frank Griesinger:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Funding acquisition, Data curation, Conceptualization. **Corinna Elender:** Writing – review & editing, Validation, Data curation. **Jörg Wiegand:** Writing – review & editing, Validation, Data curation. **Konrad Kokowski:** Writing – review & editing, Validation, Data curation. **Henning Pelz:** Writing – review & editing, Validation, Data curation. **Horst-Dieter Hummel:** Validation, Data curation. **Marcel Reiser:** Writing – review & editing, Validation, Data curation. **Althoff Friederike C:** Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Arnd Nusch:** Writing – review & editing, Validation, Data curation. **Paula Ludwig:** Writing – review & editing, Resources, Funding acquisition. **Annika Groth:** Writing – review & editing, Resources, Funding acquisition.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: FCA reports having received a research grant from Novartis, research funding from Gilead Sciences, speaker's honoraria from Roche, Amgen, MSD, and neoConnect GmbH, support for attending meetings and/or travel from Amgen, Johnson & Johnson/Janssen and Daiichi Sankyo, and consultant fees from IQVIA and Johnson & Johnson/Janssen, outside of the submitted work.

HDH has nothing to disclose.

KK has nothing to disclose.

CE has nothing to disclose.

CG has nothing to disclose.

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Legal entity responsible for the study

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Authors' contributions

Study concept and design: FCA, MS, FG, WEE, MT, AF, MJ, SZ. Acquisition, analysis or interpretation of data: All authors. Drafting of the manuscript: FCA, MS, AF, SZ. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: FCA, AF, SZ, MJ. Obtained funding: MS, FG, WEE, MT. Administrative, technical or material support: All authors. Study supervision: AF, MJ, SZ, MS.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.ejca.2026.116265](https://doi.org/10.1016/j.ejca.2026.116265).

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