REAL-WORLD DATA FROM THE PROSPECTIVE, MULTICENTER CRISP REGISTRY (AIO-TRK-0315)

INSTITUTIONAL VARIABILITY IN TESTING FOR ACTIONABLE GENETIC ALTERATIONS IN PATIENTS WITH STAGE IIIB/C OR IV NSCLC

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BACKGROUND

While molecular testing in advanced NSCLC is essential for guiding targeted therapies, routine implementation has remained inconsistent.[1–4] Previous studies have reported variability in overall testing rates,[1,2,5] but institutional variability has not been objectively quantified. There is clinical evidence for variability in its use that may not be explained by patient and tumor characteristics but might be driven by institutional culture. Variability in the use of testing may contribute to adverse outcomes. We analyzed whether and to what extent variability in AGA testing is attributable to the treating institution.

METHODS

We analyzed 6,437 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.

RESULTS

AGA testing was performed in 77.9 % of patients (n = 5,016). Mean predicted probabilities for use of AGA testing ranged from 30.5 % to 93.2 % across individual institutions. Institutions were significantly associated with the use of AGA testing ($p < 0.001$), accounting for more than one fifth of the total variance in its use (ICC 21.4 %). Variability in AGA testing significantly varied among institution types such as university vs. non-university hospital, ambulatory health care centers, and practices ($p = 0.028$). 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 %, $p < 0.001$). Absence of AGA testing was an independent risk factor for inferior survival (HRadj 1.11, 95 % CI 1.01 to 1.23, p = 0.029).

CONCLUSION

We demonstrated significant institutional variability in the use of AGA testing in NSCLC, which was independent of patient and tumor-related factors. These findings matter at the patient level. For example, a newly diagnosed patient with metastatic NSCLC harboring an ALK rearrangement may or may not receive appropriate AGA testing depending on where they present. In such cases, patients risk being treated with chemo(-immuno) therapy instead of targeted therapy, thereby missing the survival and QoL-benefits achievable with effective targeted treatment. Ensuring consistent molecular diagnostics across institutions should therefore be regarded as a public health priority.

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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 ± StD)	66.3 ± 9.54	64.6 ± 9.36	65.9 ± 9.62	67.1 ± 8.93	67.5 ± 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 ± StD)	45.9 ± 26.60	44.3 ± 27.51	45.1 ± 27.56	51.7 ± 27.39	46.4 ± 24.07
BMI (kg/m²)					
Mean ± StD	25.1 ± 5.39	25.2 ± 6.95	25.0 ± 5.03	25.0 ± 4.97	25.2 ± 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 (%)					
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 %)

Figure 1: Flow chart

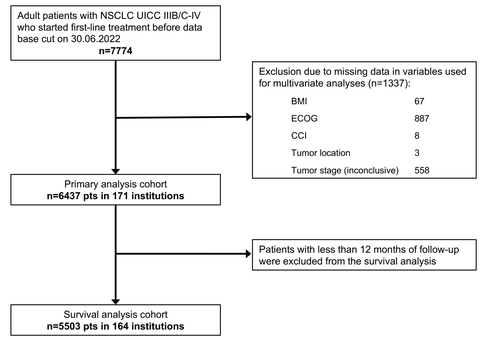

Table 2: Institutional experience by institution type

	Total	University hospital	Non-university hospital	Ambulatory health care center	Practice
Institutions (N)	171	22	64	25	60
Recruited patients per year					
Mean ± StD	7.7 ± 7.90	10.2 ± 10.21	9.0 ± 8.91	5.3 ± 4.46	6.4 ± 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 <= pat/year < 20)	35 (20.5 %)	7 (31.8 %)	15 (23.4 %)	4 (16.0 %)	9 (15.0 %)
high (pat/year >= 20)	13 (7.6 %)	2 (9.1 %)	8 (12.5 %)	0 (0.0 %)	3 (5.0 %)

Figure 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 were derived from the primary multivariable-adjusted mixed-effects model. Each dot represents one of the 172 participating institutions; vertical lines indicate the 95 % confidence interval for the predicted probability. 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-, provider-, 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.