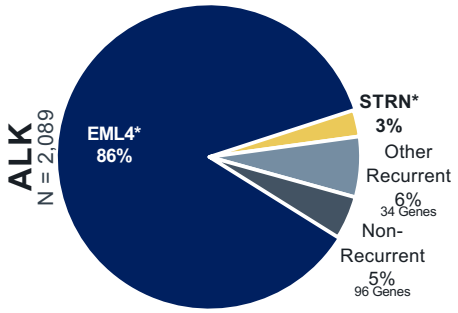
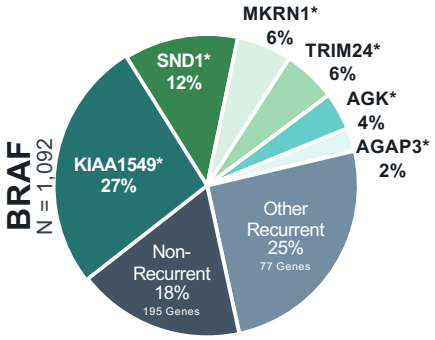
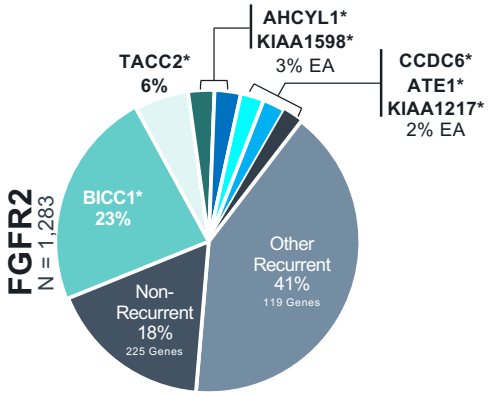
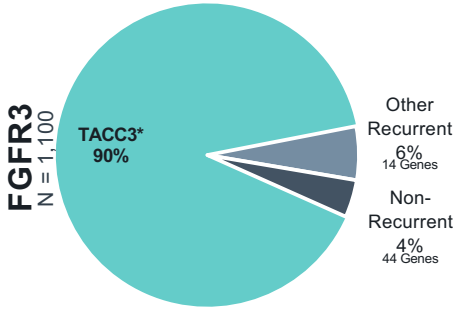
FMI DNA CGP

N = 459,751



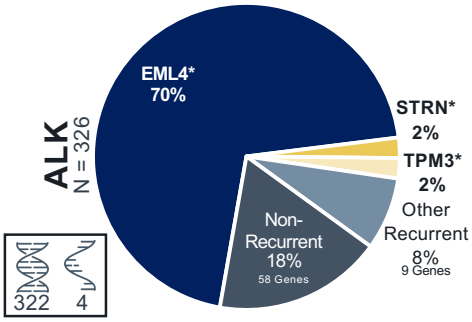


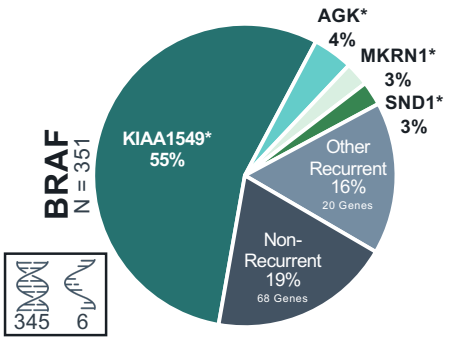


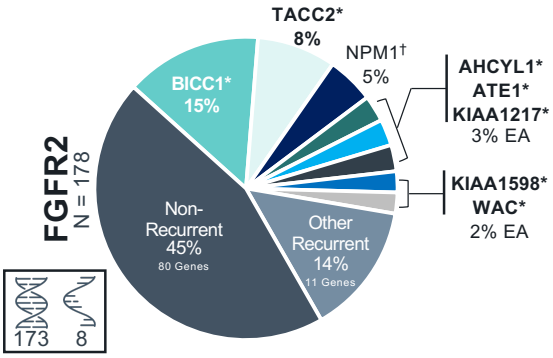


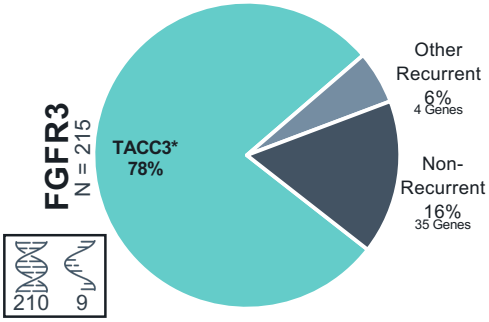
GENIE v13.1

N = 97,592

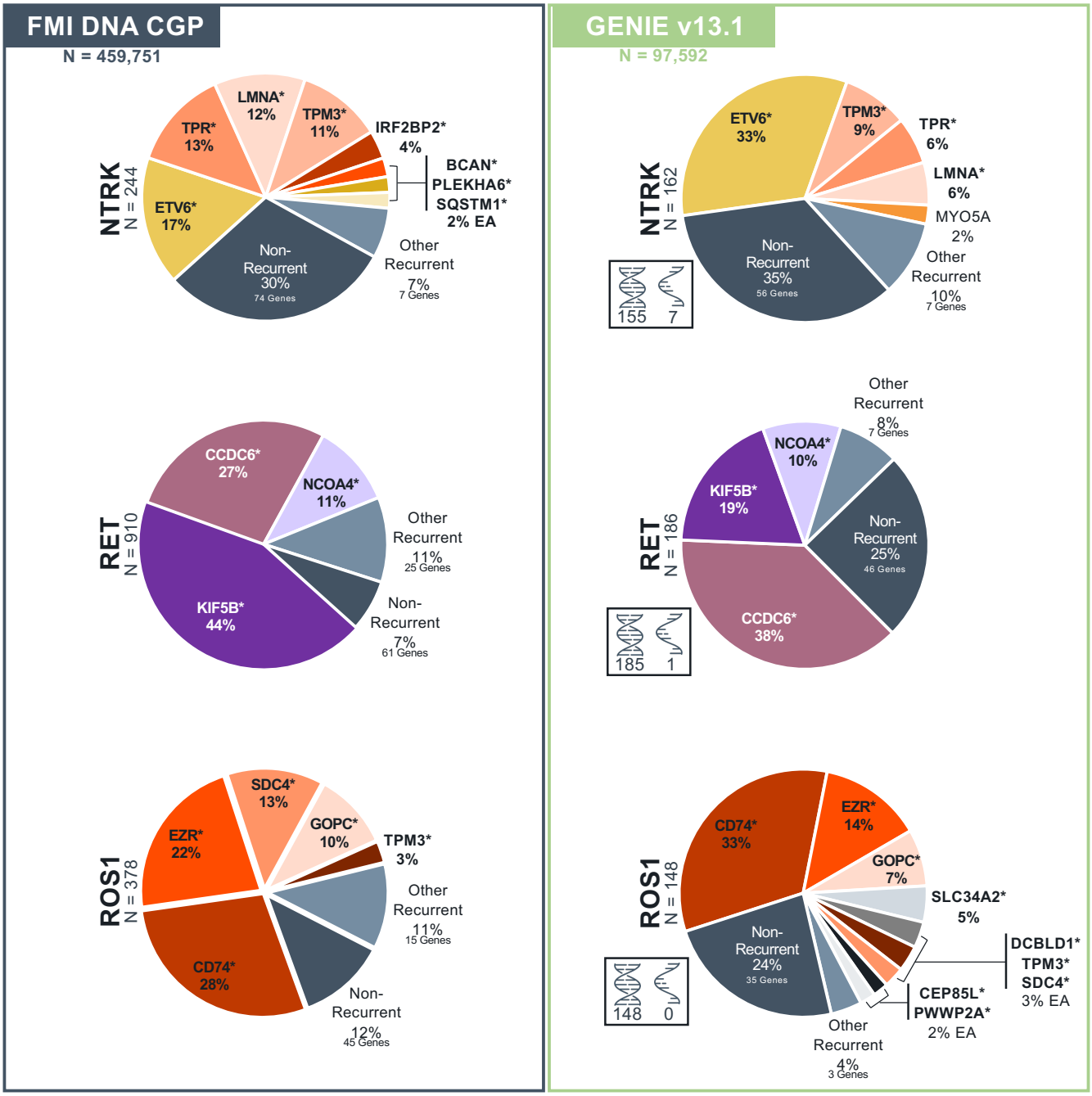




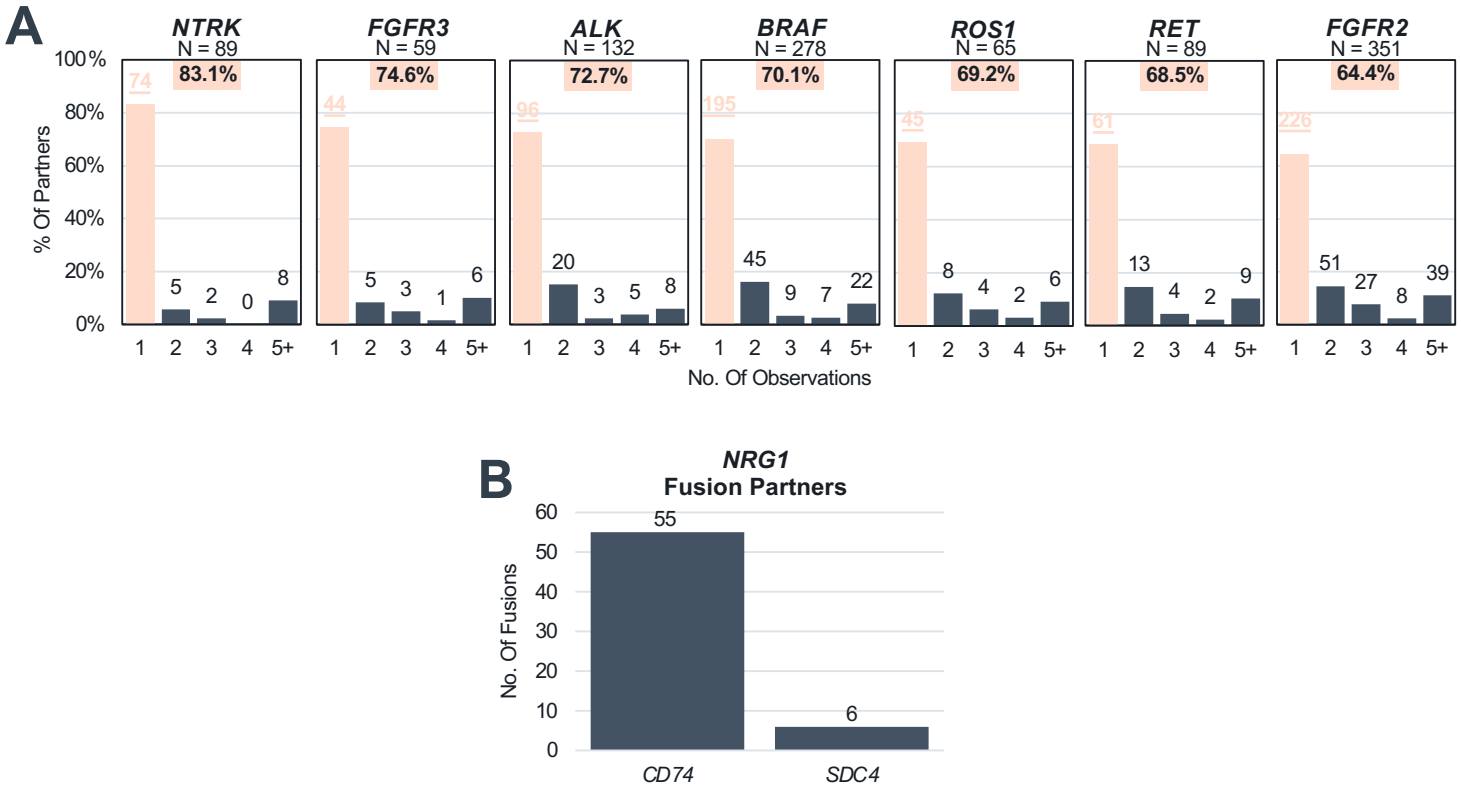




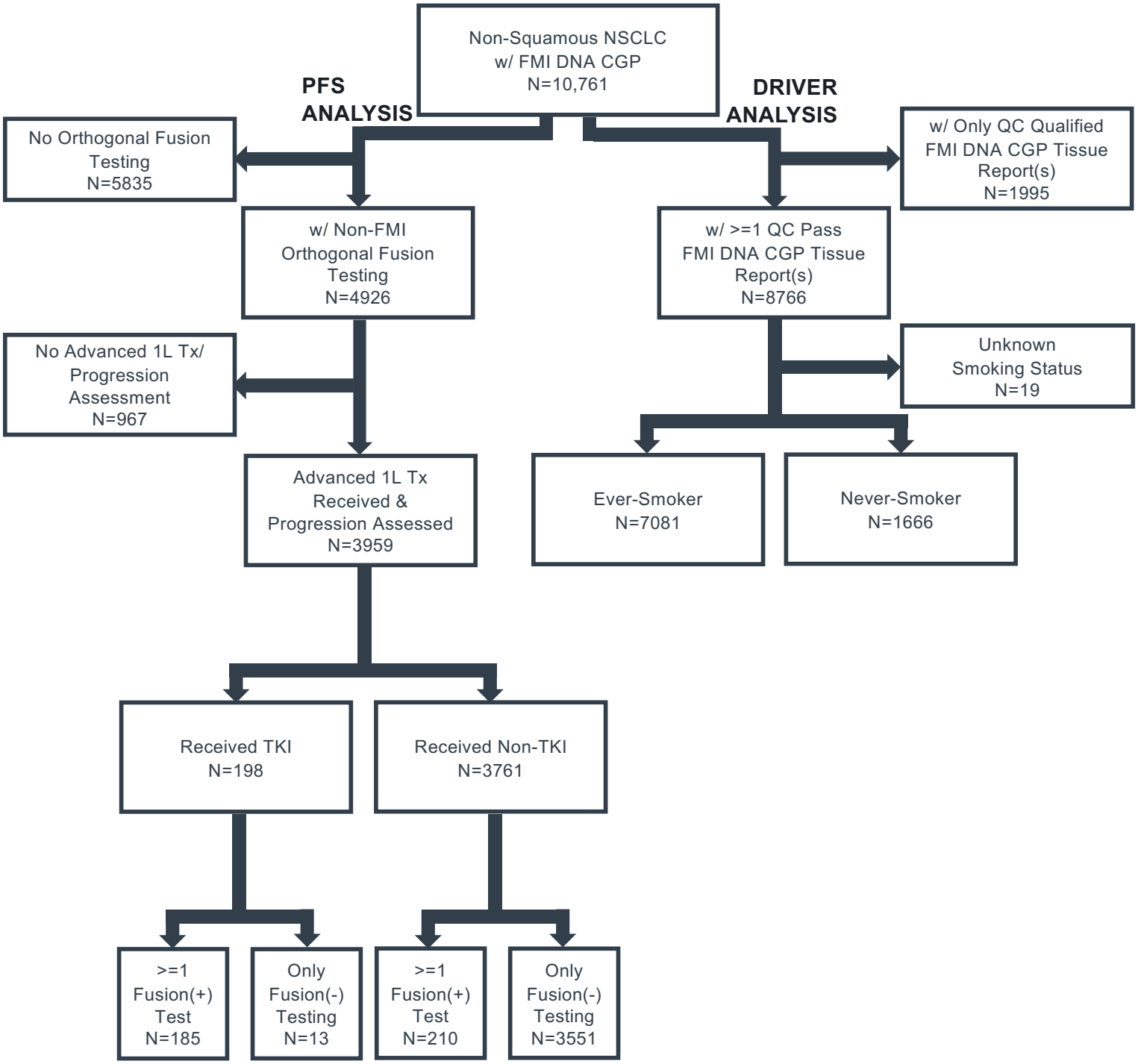
GENE NAME* = OBSERVED AS FUSION PARTNER IN BOTH COHORTS



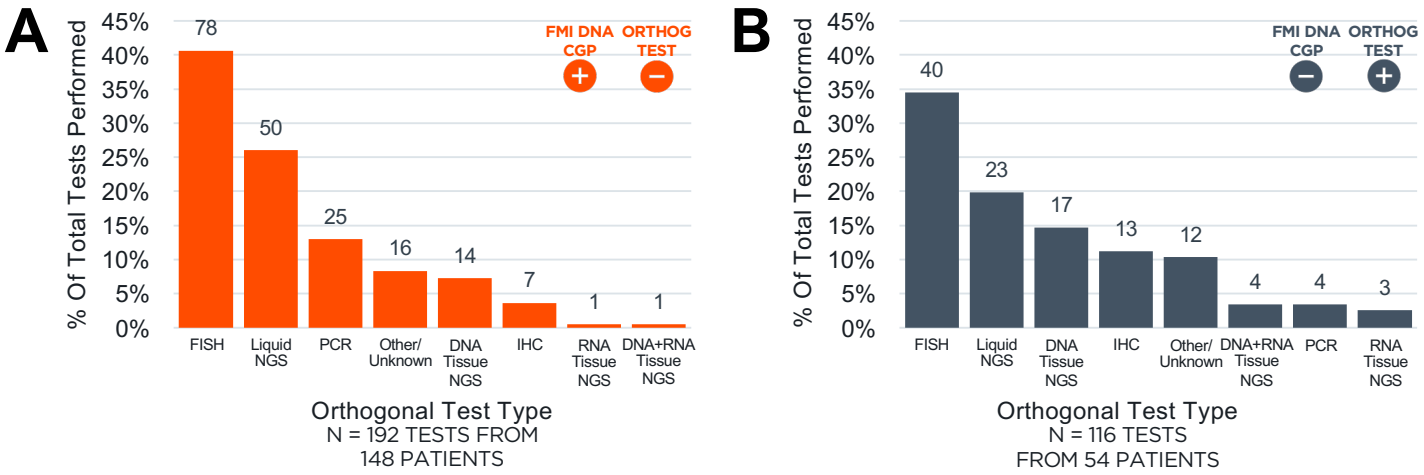
Supplemental Figure 1. FMI DNA CGP Fusion Partner Diversity Prevalence of partner genes involved in *ALK*, *BRAF*, *FGFR2*, *FGFR3*, *NTRK1/2/3, RET*, and *ROS1* fusions. Partner genes representing ≥2% of observed fusions are plotted individually while recurrent partners representing <2% of observed fusions and non-recurrent partners are grouped. Asterisk (*) indicates partner gene was detected using both FMI DNA CGP and non-FMI assays in the AACR GENIE v13.1 data set. Ns below assay names denote the number of unique patients with structural variant profiling in the relevant cohort. Ns adjacent to gene names denote the number of fusion events detected in the relevant cohort. The number of fusion events with DNA and RNA evidence in GENIE is also indicated. (Note that fusions may be supported by both types of evidence.) †While *FGFR2-NPM1* rearrangements were detected on F1CDx/F1, they were considered variants of uncertain significance (VUS). FMI DNA CGP, Foundation Medicine Tissue DNA Comprehensive Genomic Profiling.



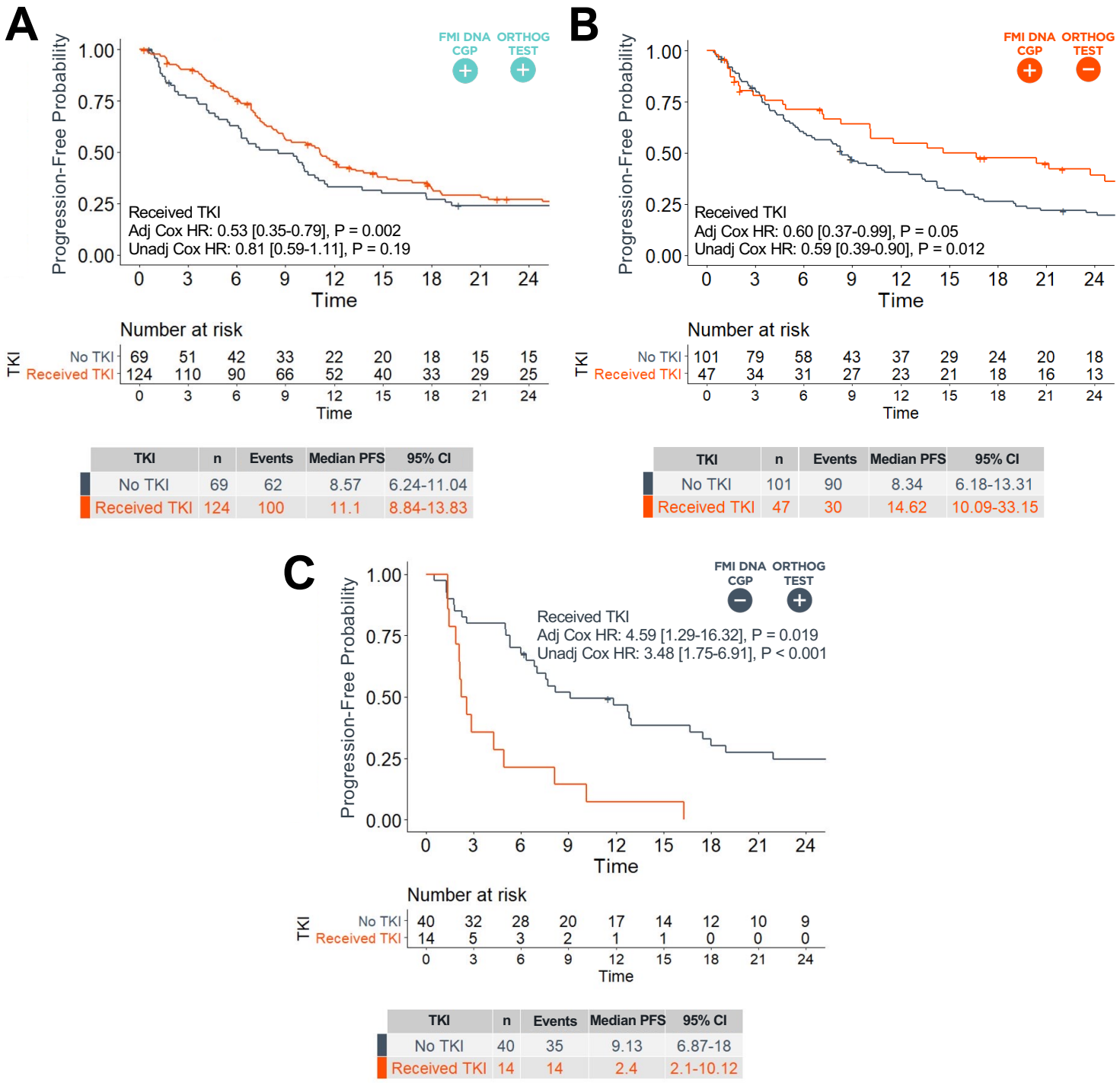
Supplemental Figure 2. FMI DNA CGP Fusion Detection Additional Data (Related To Figure 2). A) Percentage of fusion partners observed a single –versus– multiple times with each clinically actionable fusion gene. The total number of fusion partners observed with each gene is indicated above the plots. The number of fusions partners observed with each gene in each observation category (1-5+) is also indicated. B) No. of detected *NRG1* fusions involving baited gene partners in tissue biopsies profiled using F1CDx (N = 316,152). FMI DNA CGP, Foundation Medicine Tissue DNA Comprehensive Genomic Profiling.



Supplemental Figure 3. CONSORT Diagram For Non-Squamous NSCLC Clinicogenomic Analyses The clinicogenomic cohort consisted of patients with histology/genomics consistent with non-squamous NSCLC who underwent FMI DNA CGP (N = 10,761). (*Left*) For the PFS analysis (**Figure 3**), patients 1) with both tissue-based FMI DNA CGP and fusion testing using an orthogonal method through which 2) an *ALK*, *NTRK*, *RET*, or *ROS1* fusion was identified in >=1 test and who 3) received a matched TKI in the advanced 1L and 4) were assessed for progression were included. (*Right*) For the oncogenic driver analysis (**Figure 4**), patients with qualified reports were excluded due to the possibility of reduced sensitivity for alteration detection. The cohort was divided into ever-smokers and never-smokers based on self-reported smoking history and patients with unknown smoking history were excluded. FMI DNA CGP, Foundation Medicine Tissue DNA Comprehensive Genomic Profiling.



Supplemental Figure 4. Orthogonal Testing Methods For Non-Squamous NSCLC Patients With Discordant FMI DNA CGP And Orthogonal Fusion Testing Results Distribution of orthogonal testing modalities undergone by A) N = 148 patients who were assessed for progression and were found to be fusion-positive on FMI DNA CGP and fusion-negative on orthogonal testing (FMI DNA CGP+/Orthog-) and B) N = 54 patients who were assessed for progression and were found to be fusion-negative on FMI DNA CGP and fusion-positive on orthogonal testing (FMI DNA CGP-/Orthog+). Each testing modality is only counted once per patient. However, a single patient could be counted towards multiple modalities if a patient underwent multiple types of testing such that the sum of all bars may exceed 100%. FMI DNA CGP, Foundation Medicine Tissue DNA Comprehensive Genomic Profiling.

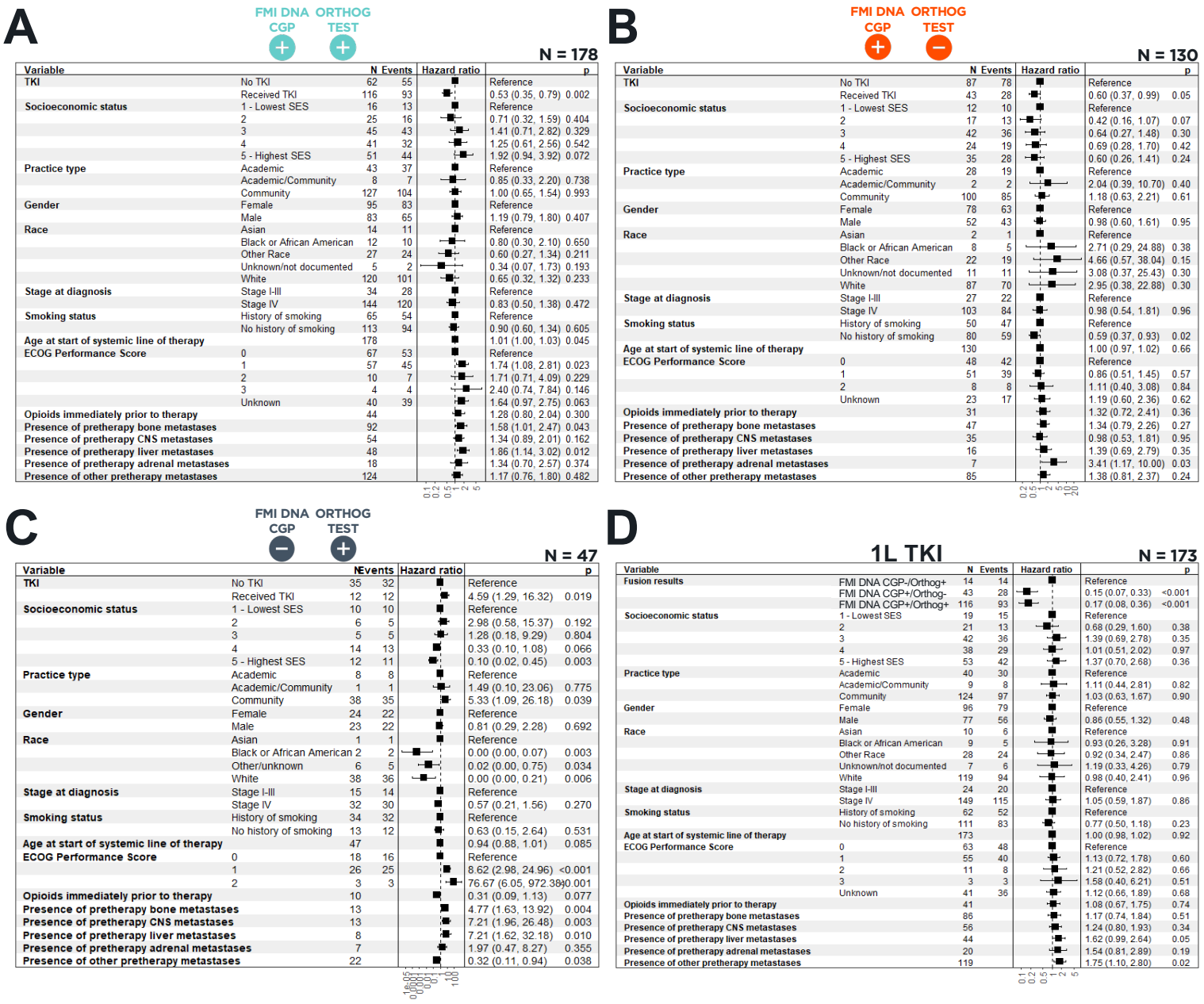


TKI	n	Events	Median PFS	95% CI
No TKI	69	62	8.57	6.24-11.04
Received TKI	124	100	11.1	8.84-13.83

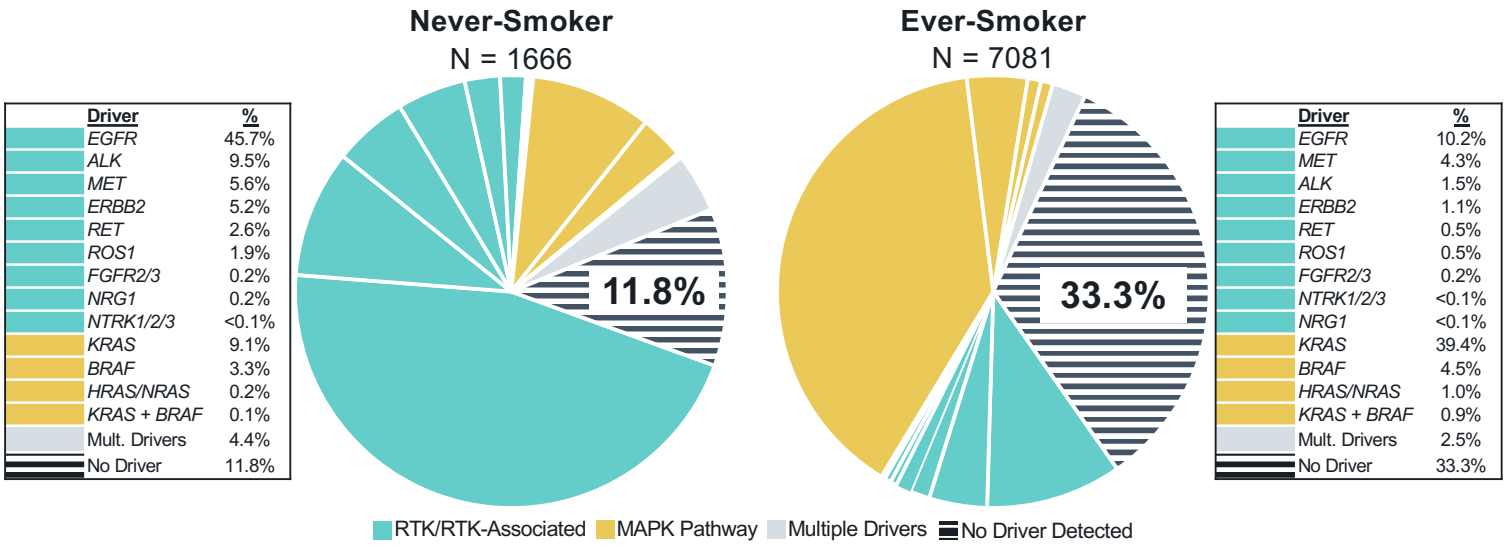
TKI	n	Events	Median PFS	95% CI
No TKI	101	90	8.34	6.18-13.31
Received TKI	47	30	14.62	10.09-33.15

TKI	n	Events	Median PFS	95% CI
No TKI	40	35	9.13	6.87-18
Received TKI	14	14	2.4	2.1-10.12

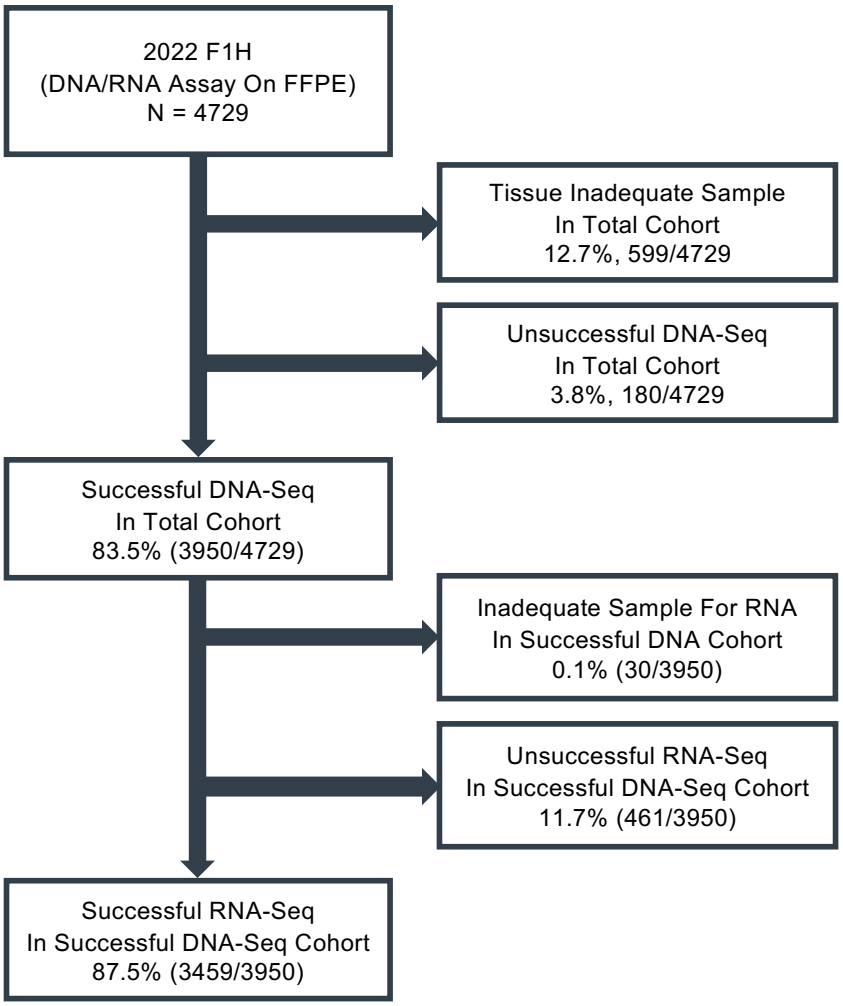
Supplemental Figure 5. Non-Squamous NSCLC rwPFS Associations According To Fusion Testing Results And 1L Therapy Class Received Patients with non-squamous NSCLC who were assessed for progression and underwent both FMI DNA CGP and additional fusion testing were stratified by 1L therapy class (i.e., matched TKI versus other). Unadjusted Kaplan-Meier plots are shown for patients who (A) had *ALK*, *NTRK*, *RET*, or *ROS1* fusions detected on both FMI DNA CGP and orthogonal testing (FMI DNA CGP+/Orthog+), (B) had *ALK*, *NTRK*, *RET*, or *ROS1* fusions detected on FMI DNA CGP but not orthogonal testing (FMI DNA CGP+/Orthog-) or (C) had *ALK*, *NTRK*, *RET*, or *ROS1* fusions detected on orthogonal testing but not FMI DNA CGP (FMI DNA CGP-/Orthog+). Analyses are indexed to the start of 1L therapy. In addition to univariable Cox model HRs, adjusted HRs are presented for a multivariable Cox model that includes established prognostic variables (see **Supplementary Figure 6**). FMI DNA CGP, Foundation Medicine Tissue DNA Comprehensive Genomic Profiling; HR, Hazard Ratio; TKI, Tyrosine Kinase Inhibitor; rwPFS, Real-World Progression Free Survival.



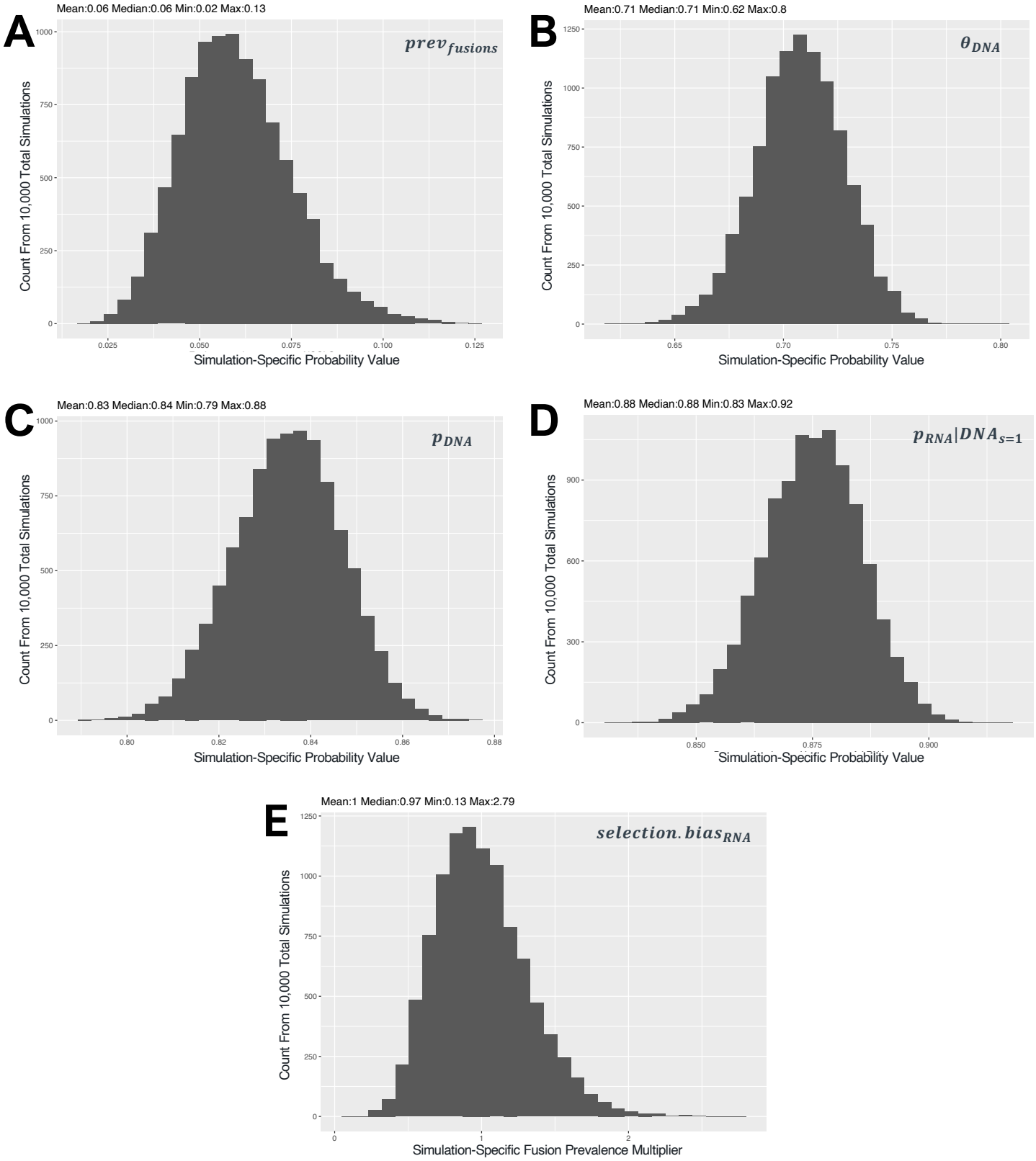
Supplemental Figure 6. Multivariable Cox Models For Non-Squamous NSCLC rwPFS On 1L Therapy rwPFS for (A) patients who had *ALK*, *NTRK*, *RET*, or *ROS1* fusions detected on both FMI DNA CGP and orthogonal testing (FMI DNA CGP+/Orthog+; N = 178) stratified by receipt of a matched TKI in 1L; (B) patients who had *ALK*, *NTRK*, *RET*, or *ROS1* fusions detected on FMI DNA CGP but not orthogonal testing (FMI DNA CGP+/Orthog-; N = 130) stratified by receipt of a matched TKI in 1L; (C) patients who had *ALK*, *NTRK*, *RET*, or *ROS1* fusions detected on orthogonal testing but not FMI DNA CGP (FMI DNA CGP-/Orthog+; N = 47) stratified by receipt of a matched TKI in 1L; and (D) all patients who received a matched TKI for *ALK*, *NTRK*, *RET*, or *ROS1* fusions in 1L stratified by fusion testing results (N = 173). Patients who were negative for *ALK*, *NTRK*, *RET*, or *ROS1* fusions by both FMI DNA CGP and orthogonal testing (FMI DNA CGP-/Orthog-) were excluded from this analysis. Adjustment variables included clinical characteristics which could impact prognosis. Missing Socioeconomic Status and ECOG Performance Score were not imputed, therefore patients missing either of these values were also excluded. For binary variables (pretherapy opioids and pretherapy metastases), the N column shows the number of patients positive for that characteristic. In all analyses, either missing values were imputed or cases with missing values were excluded, as noted above. FMI DNA CGP, Foundation Medicine Tissue DNA Comprehensive Genomic Profiling; HR, Hazard Ratio; TKI, Tyrosine Kinase Inhibitor; rwPFS, Real-World Progression Free Survival.



Supplemental Figure 7. An Oncogenic Driver Is Not Detected In A Minority (12-33%) Of Non-Squamous NSCLC Using DNA CGP Tumors were classified as having an oncogenic driver if activating alterations were detected in select RTK/MAPK pathway genes (see **Supplementary Table 3**). The distribution of detected oncogenic drivers in ever-smoker and never-smoker subpopulations is shown. MAPK, Mitogen-Activated Protein Kinase; RTK, Receptor Tyrosine Kinase.



Supplemental Figure 8. FoundationOne®Heme (F1H) DNA/RNA Analyte Sequencing Success Rates (2022)



Supplemental Figure 9. Parameter Distributions For Probabilistic Sensitivity Analysis Distributions of individual parameter draws with summary statistics used to generate the probabilistic sensitivity analysis (see **Figure 5B**). Distributional parameters are defined in **Supplementary Table 3**. **A:** $prev_{fusions}$ **B**: θ_{DNA} **C:** p_{DNA} **D**: $p_{RNA}|DNA_{s=1}$ **E:** $selection.bias_{RNA}$.

Supplemental Table 1. Summary Of Intronic Coverage On FoundationOne®CDx For Rearrangement Detection

EXONIC + SELECT INTRONIC COVERAGE N = 21

ALK Introns 18,19	***BCL2*** 3' UTR	***BRAF*** Introns 7-10	***BRCA1*** Introns 2,7,8,12,16,19,20	***BRCA2*** Intron 2
EGFR Introns 7, 15, 24-27	***FGFR1*** Introns 1, 5, 17	***FGFR2*** Introns 1, 17	***FGFR3*** Introns 17	***KIT*** Intron 16
KMT2A (MLL) Introns 6-11	***MSH2*** Intron 5	***MYC*** Intron 1	***NOTCH2*** Intron 26	***NTRK1*** Introns 8-11
NTRK2 Intron 12	***PDGFRA*** Introns 7, 9, 11	***RAF1*** Introns 4-8	***RARA*** Intron 2	***RET*** Introns 7-11
		ROS1 Introns 31-35		

SELECT INTRONIC COVERAGE ONLY N = 13

Gene	Introns Covered	Solid Tumor Common Fusion Partner Gene(s)
BCR	8, 13, 14	*NTRK2* (CNS Tumors)
CD74	6-8	*NRG1* (NSCLC); *NTRK1* (Pan-Solid); *ROS1* (NSCLC, Pan-Solid)
ETV4	8	*TMPRSS2* (Prostate)
ETV5	6, 7	*TMPRSS2* (Prostate)
ETV6	5, 6	*NTRK3* (Pan-Solid)
EWSR1	7-13	Multiple Partners (Sarcoma, Prostate)
EZR	9-11	*ROS1* (NSCLC, Pan-Solid)
MYB	14	*NFIB* (Adenoid Cystic Carcinomas)
NUTM1	1	*BRD4* (NUT Midline Carcinoma)
RSPO2	1	Multiple Partners, e.g., *EIF3E* (CRC)
SDC4	2	*NRG1* (Pan-Solid); *ROS1* (NSCLC)
SLC34A2	4	*ROS1* (NSCLC)
TMPRSS2	1-3	*ERG, ETV1, ETV4, ETV5* (Prostate)

Supplemental Table 2. Non-Squamous NSCLC Patient Cohort Clinical Characteristics

	Total Cohort
	N=10761
Age At Diagnosis, Years, Median (IQR)	67.0 [60.0;74.0]
Sex, *n* (%)	
Female	5971 (55.5%)
Male	4790 (44.5%)
Self-Reported Race, *n* (%)	
Asian	361 (3.35%)
Black or African American	722 (6.71%)
Hispanic or Latino	8 (0.07%)
Other Race	1502 (14.0%)
White	7166 (66.6%)
Unknown/Not Documented	1002 (9.31%)
AJCC Stage At Diagnosis, *n* (%)	
I	1330 (12.4%)
II	843 (7.83%)
III	2084 (19.4%)
IV	6164 (57.3%)
Other/Unknown/Not Documented	340 (3.16%)
Smoking History, *n* (%)	
History Of Smoking	8643 (80.3%)
No History Of Smoking	2095 (19.5%)
Unknown/Not Documented	23 (0.21%)
Practice Type, *n* (%)	
Academic	1270 (11.8%)
Academic/Community	608 (5.65%)
Community	8883 (82.5%)
Socioeconomic Status, *n* (%)	
1 - Lowest SES	1459 (13.6%)
2	1865 (17.3%)
3	2187 (20.3%)
4	2248 (20.9%)
5 - Highest SES	2073 (19.3%)
Unknown	929 (8.63%)
ECOG PS At Diagnosis, *n* (%)	
0	2179 (20.2%)
1	2253 (20.9%)
2	578 (5.37%)
3+	153 (1.42%)
Unknown	5598 (52.0%)

Supplemental Table 3. Parameter Inputs For Deterministic And Probabilistic Sensitivity Analyses

Parameter Description		Base Case Estimate	Min	Max	Distribution	Justification
$prev_{fusions}$	Estimated NCCN driver fusion prevalence in the NSCLC patient population	6.0%	1.6%	10.4%	Beta(15,235)	Based on combined fusion prevalence estimates for *ALK*, *RET*, *ROS1*, and *NTRK1/2/3* from the literature (see **Methods**)
θ_{DNA}	Probability of detecting an oncogenic driver alteration on DNA CGP	70.8%	66.7%	88.2%	Beta(354,146)	6,194/8,747 patients observed with driver alterations on FMI DNA CGP (4,724/7,081 Ever-Smoker & 1,470/1,666 Never-Smoker; see **Figure 4**)
p_{DNA}	Probability of DNA CGP assay technical success	83.5%	80%	90%	Beta(835,165)	Calculated based on experience w/ FoundationOne Heme (see **Supplementary Figure 6**)
$p_{RNA}\|DNA_{s=1}$	Probability of RNA CGP assay technical success given prior DNA CGP assay technical success	87.5%	85%	92%	Beta(875,125)	Calculated based on experience w/ FoundationOne Heme (see **Supplementary Figure 6**); 92% UB based on **Benayed et al.**[14]
$selection.bias_{RNA}$	Multiplier for enrichment of fusion-positive patients in the cohort without a driver identified on DNA CGP	1	1	1.2	Gamma(10,10)	BC and LB selection bias assumed as 0 (x1 multiplier for fusion prevalence). UB based on % fusion-positive patients from MSK-IMPACT versus reflex to MSK-Fusion testing (~x1.2) [**Benayed et al.**[14]]

BC, Base Case; FMI DNA CGP, Foundation Medicine Tissue DNA Comprehensive Genomic Profiling; LB, Lower Bound; UB, Upper Bound

Supplemental Table 4. NSCLC RTK/MAPK Oncogenic Driver Alterations

Gene	Classification	Activating Alteration Types
ALK	RTK	RE
EGFR	RTK	MUT
ERBB2	RTK	MUT
FGFR2	RTK	RE
FGFR3	RTK	RE
MET	RTK	MUT, AMP
NRG1	RTK-Associated	RE
NTRK1	RTK	RE
NTRK2	RTK	RE
NTRK3	RTK	RE
RET	RTK	RE
ROS1	RTK	RE
BRAF	MAPK	MUT
HRAS	MAPK	MUT
KRAS	MAPK	MUT
NRAS	MAPK	MUT

AMP, Amplification; MUT, Mutation (Substitutions & Short Insertions/Deletions); RE, Rearrangement; MAPK, Mitogen-Activated Protein Kinase; RTK, Receptor Tyrosine Kinase

Supplemental Table 5. Fusion Partner Genes Detected Using FMI DNA CGP & Non-FMI Assays In AACR Project GENIE v13.1.xlsx

Supplemental Table 6. Estimates From One-Way Sensitivity Analysis Corresponding to Figure 5A

Parameter	Expected % Of Patients With RNA-Only Fusion Result		
	Base Case	Min	Max
$prev_{fusions}$	1.28	0.34	2.22
θ_{DNA}		1.46	0.52
p_{DNA}		1.23	1.38
$p_{RNA}\|DNA_{s=1}$		1.24	1.35
$selection.bias_{RNA}$		1.28	1.54