

Supplementary Materials:

Reflex ROS1 IHC Screening with FISH Confirmation for Advanced Non-Small Cell Lung Cancer—A Cost-Efficient Strategy in a Public Healthcare System

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Figure S1. Decision tree model of testing strategies

(Figure S1 attached separately)

Table S1. Model Parameter inputs.

Probabilities	Base-case	Variation		Source
		Lower Limit	Upper Limit	
Assay Specificity and Sensitivity				
FISH assay Sensitivity	0.96	0.95	0.99	¹
FISH assay Specificity	0.96	0.95	0.99	¹
NGS assay Sensitivity	0.84	0.78	0.99	¹
NGS assay Specificity	0.99	0.98	0.99	^{1, 2}
IHC assay Sensitivity	0.96	0.9	0.99	³ lower limit based on expert opinion
IHC assay Specificity	0.9	0.7	0.96	³ lower limit based on expert opinion
ctDNA Sensitivity	0.89	0.83	0.95	Guardant360
ctDNA Specificity	0.99	0.8	0.99	Guardant360
ROS1 gene rearrangement prevalence	0.015			^{1, 4-8} , expert opinion. Not varied
Diagnostic strategies				
ROS1 FISH				
Proportion of cohort who test positive	0.054	0.025	0.064	
PPV FISH	0.268	0.224	0.601	
NPV FISH	0.999	0.999	0.9998	
ROS1 IHC then FISH				
Proportion testing positive after IHC	0.113	0.135	0.165	
Proportion of cohort who test positive after FISH confirmation	0.157	0.135	0.165	
PPV after IHC then FISH	0.778	0.735	0.935	
NPV after IHC then FISH	0.994	0.992	0.999	
EGFR, ALK wildtype				
Proportion of cohort testing EGFR, ALK positive	0.20			^{9, 10}
Proportion testing positive after IHC	0.116	0.058	0.311	
Proportion testing positive by FISH after IHC	0.183	0.162	0.190	
PPV after IHC then FISH	0.815	0.777	0.948	
NPV after IHC then FISH	0.992	0.990	0.998	
EGFR, ALK, KRAS wildtype				
Proportion of cohort testing EGFR, ALK, KRAS positive	0.45			⁹⁻¹¹
Proportion testing positive after IHC	0.123	0.066	0.316	
Proportion testing positive by FISH after IHC	0.235	0.218	0.241	
PPV after IHC then FISH	0.866	0.836	0.964	
NPV after IHC then FISH	0.989	0.986	0.997	
EGFR, ALK wildtype never-smokers				
Proportion of never smokers	0.20			¹²⁻¹⁵
Proportion of EGFR and ALK positive cases among never-smokers	0.60			¹⁶

Proportion of ROS1 positive cases among never-smokers, EGFR, ALK wild-type cases	0.12			17
Proportion testing positive after IHC	0.203	0.154	0.372	
Proportion testing positive by FISH after IHC	0.562	0.560	0.566	
PPV after IHC then FISH	0.969	0.961	0.992	
NPV after IHC then FISH	0.948	0.936	0.987	
NGS				
Proportion who test positive after NGS	0.022	0.016	0.031	
PPV NGS	0.561	0.373	0.938	
NPV NGS	0.998	0.997	0.9999	
ctDNA				
Proportion who test positive after ctDNA	0.023	0.015	0.209	
PPV ctDNA	0.575	0.059	0.935	
NPV ctDNA	0.998	0.997	0.999	

Table S2. FISH test characteristics

	Disease positive (D+)	Disease negative (D-)	Total
Test Positive (T+)	A - True Positives (TP)	B- False Positives (FP)	A+B (TP+FP)
Test Negative (T-)	C - False negatives (FN)	D -True Negatives (TN)	C+D (FN +TN)
	A+C	B+ D	Cohort (A+B+C+D)

	Probabilities	Variation	
Assay Specificity and Sensitivity		Lower Limit	Upper Limit
FISH assay Sensitivity	0.96	0.95	0.99
FISH assay Specificity	0.96	0.95	0.99
ROS1 gene prevalence	0.015		

		Base Case	Variation	
Population (Cohort)	Cohort*	1000.00		
Disease positive (D+)	ROS1 positive cases**	15.00		
Disease negative (D-)	ROS1 negative cases	985.00		
A, TP	Sensitivity X (D+)	14.40	14.25	14.85
C, FN	(D+) - TP	0.60	0.75	0.15
D, TN	Specificity X (D-)	945.60	935.75	975.15
B, FP	(D-) - TN	39.40	49.25	9.85
Total Test positive (T+)	TP+ FP (A+B)	53.80	63.50	24.70
Total Test negative (T -)	TN + FN (C+D)	946.20	936.50	975.30

		Base Case	Variation	
PPV	A/(A+B)	0.268	0.224	0.601
NPV	D/(C+D)	0.999	0.999	0.9998
Proportion testing positive	Total T+/Cohort	0.054	0.064	0.025

*Assuming 1000 patients with advanced non-squamous NSCLC

** Based on ROS1 fusion prevalence

Table S3. IHC screening (followed by FISH confirmation) test characteristics

	Probabilities	Variation	
Assay Specificity and Sensitivity		Lower Limit	Upper Limit
FISH assay Sensitivity	0.96	0.95	0.99
FISH assay Specificity	0.96	0.95	0.99
IHC assay Sensitivity	0.96	0.90	0.99
IHC assay Specificity	0.9	0.70	0.96
ROS1 gene prevalence	0.015		

		Base Case, IHC first	Variation		Base Case, IHC then FISH	Variation	
Population (Cohort)	Cohort*	1000.00			112.90		
Disease positive (D+)	ROS1 positive cases**	15.00			14.40		
Disease negative (D-)	ROS1 negative cases	985.00			98.50		
A, TP	Sensitivity X (D+)	14.40	13.50	14.85	13.82	13.68	14.26
C, FN	(D+) - TP	0.60	1.50	0.15	0.58	0.72	0.14
D, TN	Specificity X (D-)	886.50	689.50	945.60	94.56	93.58	97.52
B, FP	(D-) - TN	98.50	295.50	39.40	3.94	4.93	0.98
Total Test positive (T+)	TP+ FP (A+B)	112.90	309.00	54.25	17.76	18.61	15.24
Total Test negative (T-)	TN + FN (C+D)	887.10	691.00	945.75	95.14	94.30	97.66

IHC		Base Case	Variation	
PPV	A/(A+B)	0.128	0.044	0.274
NPV	D/(C+D)	0.999	0.998	0.9998
Proportion testing positive	Total T+/Cohort	0.113	0.309	0.054

FISH after IHC		Base Case	Variation	
PPV	A/(A+B)	0.778	0.735	0.935
NPV	D/(C+D)	0.994	0.992	0.999
Proportion testing positive	Total T+/Cohort	0.157	0.165	0.135

*Assuming 1000 patients with advanced non-squamous NSCLC

**Based on ROS1 fusion prevalence

Table S4. NGS test characteristics

	Probabilities	Variation	
Assay Specificity and Sensitivity		Lower Limit	Upper Limit
NGS assay Sensitivity	0.84	0.78	0.999
NGS assay Specificity	0.99	0.98	0.999
ROS1 gene prevalence	0.015		

		Base Case	Variation	
Population (Cohort)	Cohort*	1000.00		
Disease positive (D+)	ROS1 positive cases**	15.00		
Disease negative (D-)	ROS1 negative cases	985.00		
A, TP	Sensitivity X (D+)	12.60	11.70	14.99
C, FN	(D+) - TP	2.40	3.30	0.02
D, TN	Specificity X (D-)	975.15	965.30	984.02
B, FP	(D-) - TN	9.85	19.70	0.99
Total Test positive (T+)	TP+ FP (A+B)	22.45	31.40	15.97
Total Test negative (T-)	TN + FN (C+D)	977.55	968.60	984.03

		Base Case	Variation	
PPV	A/(A+B)	0.561	0.373	0.938
NPV	D/(C+D)	0.998	0.997	0.99998
Proportion testing positive	Total T+/Cohort	0.022	0.031	0.016

*Assuming 1000 patients with advanced non-squamous NSCLC

**Based on ROS1 fusion prevalence

Table S5 Biomarker informed selection of *EGFR*, *ALK* wildtype samples for ROS1 IHC screening and FISH confirmation

	Probabilities	Variation	
Assay Specificity and Sensitivity		Lower Limit	Upper Limit
FISH assay Sensitivity	0.96	0.95	0.99
FISH assay Specificity	0.96	0.95	0.99
IHC assay Sensitivity	0.96	0.90	0.99
IHC assay Specificity	0.9	0.70	0.96
Proportion of cohort testing <i>EGFR</i> , <i>ALK</i> positive	0.2		

		Base Case, IHC first	Variation		Base Case, after FISH	Variation	
Population (Cohort)	Cohort*	800.00			92.90		
Disease positive (D+)	ROS1 positive cases	15.00			14.40		
Disease negative (D-)	ROS1 negative cases	785.00			78.50		
A, TP	Sensitivity X (D+)	14.40	13.50	14.85	13.82	13.68	14.26
C, FN	(D+) - TP	0.60	1.50	0.15	0.58	0.72	0.14
D, TN	Specificity X (D-)	706.50	549.50	753.60	75.36	74.58	77.72
B, FP	(D-) - TN	78.50	235.50	31.40	3.14	3.93	0.78
Total Test positive (T+)	TP+ FP (A+B)	92.90	249.00	46.25	16.96	17.61	15.04
Total Test negative (T -)	TN + FN (C+D)	707.10	551.00	753.75	75.94	75.30	77.86

IHC first		Base Case	Variation	
PPV	A/(A+B)	0.155	0.054	0.321
NPV	D/(C+D)	0.999	0.997	0.9998
Proportion testing positive	Total T+/Cohort	0.116	0.311	0.058

FISH after IHC		Base Case	Variation	
PPV	A/(A+B)	0.815	0.777	0.948
NPV	D/(C+D)	0.992	0.990	0.998
Proportion testing positive	Total T+/Cohort	0.183	0.190	0.162

*Based on proportion of patients who test positive for *EGFR*, *ALK* in a 1000 patient cohort

Table S6. Biomarker informed selection of *EGFR*, *ALK*, *KRAS* wildtype samples for ROS1 IHC screening and FISH confirmation

	Probabilities	Variation	
Assay Specificity and Sensitivity		Lower Limit	Upper Limit
FISH assay Sensitivity	0.96	0.95	0.99
FISH assay Specificity	0.96	0.95	0.99
IHC assay Sensitivity	0.96	0.90	0.99
IHC assay Specificity	0.9	0.70	0.96
Proportion of cohort testing <i>EGFR</i> , <i>ALK</i> positive	0.2		
Proportion of cohort testing <i>EGFR</i> , <i>ALK</i> , <i>KRAS</i> negative	0.55		

		Base Case, IHC first	Variation		Base Case, after FISH	Variation	
Population (Cohort)	Cohort*	550.00			67.90		
Disease positive (D+)	ROS1 positive cases**	15.00			14.40		
Disease negative (D-)	ROS1 negative cases	535.00			53.50		
A, TP	Sensitivity X (D+)	14.40	13.50	14.85	13.82	13.68	14.26
C, FN	(D+) - TP	0.60	1.50	0.15	0.58	0.72	0.14
D, TN	Specificity X (D-)	481.50	374.50	513.60	51.36	50.83	52.97
B, FP	(D-) - TN	53.50	160.50	21.40	2.14	2.68	0.54
Total Test positive (T+)	TP+ FP (A+B)	67.90	174.00	36.25	15.96	16.36	14.79
Total Test negative (T -)	TN + FN (C+D)	482.10	376.00	513.75	51.94	51.55	53.11

IHC first		Base Case	Variation	
PPV	A/(A+B)	0.212	0.078	0.410
NPV	D/(C+D)	0.999	0.996	0.9997
Proportion testing positive	Total T+/Cohort	0.123	0.316	0.066

FISH after IHC		Base Case	Variation	
PPV	A/(A+B)	0.866	0.836	0.964
NPV	D/(C+D)	0.989	0.986	0.997
Proportion testing positive	Total T+/Cohort	0.235	0.241	0.218

*Cohort of patients testing *EGFR*, *ALK*, *KRAS* wildtype

Table S7. Clinical selection of *EGFR*, *ALK* wildtype samples in never-smokers for ROS1 IHC screening and FISH confirmation

	Probabilities	Variation	
Assay Specificity and Sensitivity		Lower Limit	Upper Limit
FISH assay Sensitivity	0.96	0.95	0.99
FISH assay Specificity	0.96	0.95	0.99
IHC assay Sensitivity	0.96	0.90	0.99
IHC assay Specificity	0.9	0.70	0.96
Proportion of never smokers	0.2		
Proportion of <i>EGFR</i> , <i>ALK</i> positive among never-smokers	0.6		
Proportion of <i>ROS1</i> positive cases among never-smokers, <i>EGFR</i> , <i>ALK</i> negative cases	0.12		

		Base Case, IHC first	Variation		Base Case, after FISH	Variation	
Population (Cohort)	Cohort*	80.00			16.26		
Disease positive (D+)	ROS1 positive cases**	9.60			9.22		
Disease negative (D-)	ROS1 negative cases	70.40			7.04		
A, TP	Sensitivity X (D+)	9.22	8.64	9.50	8.85	8.76	9.12
C, FN	(D+) - TP	0.38	0.96	0.10	0.37	0.46	0.09
D, TN	Specificity X (D-)	63.36	49.28	67.58	6.76	6.69	6.97
B, FP	(D-) - TN	7.04	21.12	2.82	0.28	0.35	0.07
Total Test positive (T+)	TP+ FP (A+B)	16.26	29.76	12.32	9.13	9.11	9.19
Total Test negative (T -)	TN + FN (C+D)	63.74	50.24	67.68	7.13	7.15	7.06

IHC first		Base Case	Variation	
PPV	A/(A+B)	0.567	0.290	0.771
NPV	D/(C+D)	0.994	0.981	0.9986
Proportion testing positive	Total T+/Cohort	0.203	0.372	0.154

FISH after IHC		Base Case	Variation	
PPV	A/(A+B)	0.969	0.961	0.992
NPV	D/(C+D)	0.948	0.936	0.987
Proportion testing positive	Total T+/Cohort	0.562	0.560	0.566

*Based on proportion of *EGFR*, *ALK* wildtype never-smokers

**Based on estimated *ROS1* fusion prevalence among *EGFR*, *ALK* wildtype never-smokers

Table S8. ctDNA test characteristics

	Probabilities	Variation	
Assay Specificity and Sensitivity		Lower Limit	Upper Limit
ctDNA Sensitivity	0.89	0.83	0.95
ctDNA Specificity	0.99	0.80	1.00
ROS1 gene prevalence	0.015		

		Base Case	Variation	
Population (Cohort)	Cohort*	1000.00		
Disease positive (D+)	ROS1 positive cases**	15.00		
Disease negative (D-)	ROS1 negative cases	985.00		
A, TP	Sensitivity X (D+)	13.35	12.45	14.25
C, FN	(D+) - TP	1.65	2.55	0.75
D, TN	Specificity X (D-)	975.15	788.00	984.02
B, FP	(D-) - TN	9.85	197.00	0.99
Total Test positive (T+)	TP+ FP (A+B)	23.20	209.45	15.24
Total Test negative (T -)	TN + FN (C+D)	976.80	790.55	984.77

		Base Case	Variation	
PPV	$A/(A+B)$	0.575	0.059	0.935
NPV	$D/(C+D)$	0.998	0.997	0.9992
Proportion testing positive	Total T+/Cohort	0.023	0.209	0.015

*Assuming 1000 patients with advanced non-squamous NSCLC

**Based on ROS1 fusion prevalence

Table S9. Variable Definitions

<u>Name</u>	<u>Description</u>	<u>Root Definition</u>	<u>Low</u>	<u>High</u>
cCTDNA	Cost of ctDNA	3300	0.2	0.2
cEGFRALK	Cost of EGFR + ALK	340	0.2	0.2
cFISH	Cost of FISH	400	0.2	0.2
cIHC	Cost of IHC	100	0.2	0.2
cKRAS	Cost of KRAS testing	200	0.2	0.2
cNGS	Cost of NGS	1000	0.2	0.2
cNo_Rebiopsy	Cost of no re-biopsy	120	0	120
cRe_Biopsy	Cost of re-biopsy	1500	0	1500
NPV_FISH	NPV FISH reflex	0.999	0.999	0.9998
NPVafterctDNA	NPV after ctDNA testing	0.998	0.997	0.999
NPVafterIHC	NPV after IHC (TP)	0.994	0.992	0.999
NPVafterIHCEGFRALKKRASneg	NPV after EGFR, ALK, KRAS	0.989	0.986	0.997
NPVafterIHCEGFRALKneg	NPV after EGFR, ALK	0.992	0.99	0.998
NPVNever smoker	NPV after Never-smoker, EGFR, ALK	0.948	0.963	0.987
NPVNGS	NPV after NGS	0.998	0.997	0.9999
pEGFRALKKRASpos	Proportion EGFR, ALK, KRAS positive	0.45	0	0.45
pEGFRALKpos	Proportion EGFR, ALK positive	0.2	0	0.2
pEGFRALKposamongneversmokers	Proportion Never-smokers, EGFR, ALK positive	0.6	0	0.6
pFISHposafterIHCEGFRALK	Proportion FISH positive after IHC (EGFR, ALK wt)	0.183	0.162	0.19
pFISHposafterIHCEGFRALKKRAS	Proportion FISH positive after IHC (EGFR, ALK, KRAS wt)	0.235	0.218	0.241
pFISHposafterIHCEGFRALKwtneversmoker	Proportion FISH positive after IHC (Never-smoker, EGFR, ALK wt)	0.562	0.56	0.566
pFISHpositiveafterIHC	Proportion FISH positive after IHC (all comers)	0.157	0.135	0.165
pIHCposafterEGFRALK	Proportion IHC positive if EGFR ALK wt	0.116	0.058	0.311
pIHCposafterEGFRALKKRAS	Proportion IHC positive if EGFR ALK, KRAS wt	0.123	0.066	0.316
pIHCposamongEGFRALKwtneversmokers	Proportion IHC positive if Never-smoker, EGFR ALK wt	0.203	0.154	0.372
pNever smoker	Proportion of neversmokers	0.2	0	0.2
PPV_FISH	PPV FISH	0.268	0.224	0.601
PPVafterctDNA	PPV after ctDNA testing	0.575	0.059	0.935

PPVafterIHC	PPV FISH after IHC	0.778	0.735	0.935
PPVafterIHCEGFRALK	PPV FISH after IHC (EGFR, ALK wt)	0.815	0.777	0.948
PPVafterIHCEGFRALKKRAS	PPV FISH after IHC (EGFR, ALK, KRAS wt)	0.866	0.836	0.964
PPVneversmoker	PPV FISH after IHC (Never-smokers, EGFR, ALK wt)	0.969	0.961	0.992
PPVNGS	PPV after NGS	0.561	0.373	0.938
pTestpositivectDNA	Proportion ROS1 positive with ctDNA (TP+FP)	0.0232	0.015	0.209
pTestpositiveFISH	Proportion ROS1 positive after FISH (TP+FP)	0.0538	0.025	0.064
pTestpositiveIHC	Proportion IHC positive (TP+FP)	0.113	0.054	0.309
pTestpositiveNGS	Proportion NGS positive (TP+FP)	0.022	0.016	0.031
TATclinician	Time to clinician visit	14	0.2	0.2
TATctDNA	Turnaround time ctDNA	7	0.2	0.2
TATEGFRALK	Turnaround time for EGFR, ALK testing	7	0.2	0.2
TATFISH	Turnaround time FISH	7	0.2	0.2
TATIHC	Turnaround time ROS1 IHC	4	0.2	0.2
TATKRAS	Turnaround time KRAS	21	0.2	0.2
TATNGS	Turnaround time NGS	21	0.2	0.2

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