PAN-TUMOR

Fusion Detection with DNA and RNA

FOUNDATION MEDICINE®

This document covers the capabilities of DNA and RNA sequencing to detect fusions in solid tumors with a focus on FoundationOne®CDx. Key takeaways include:

FoundationOne CDx is validated to detect common fusions[1-3]	Some fusions are detectable only by RNA sequencing[4,5]	Due to RNA instability, RNA sequencing requires a high-quality sample[4-7]

DNA and RNA Next-Generation Sequencing Overview

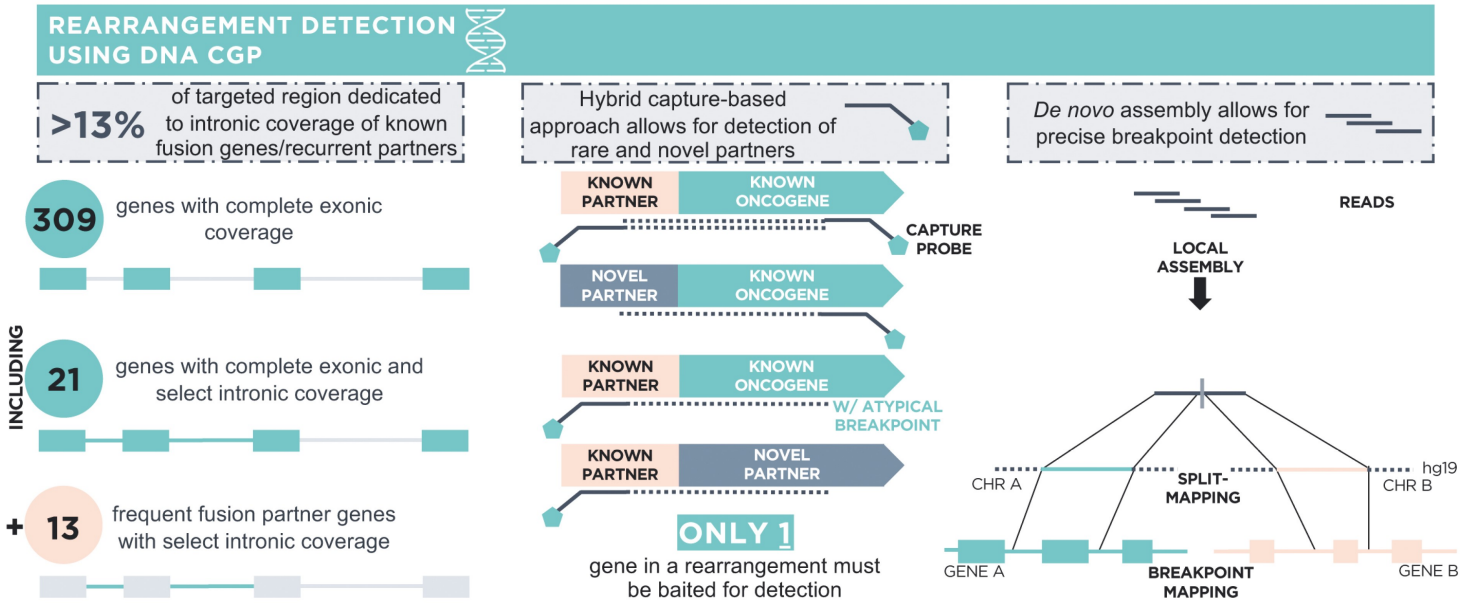
Nucleic acid extraction	*Library preparation*	*Library amplification*	*Sequencing*	*Bioinformatics*
• RNA: lower **stability, quality,** and **quantity** than DNA[4-6] • Use of archival FFPE specimens may reduce sequencing success[7]	RNA must be reverse transcribed to cDNA[4]	Low mRNA expression levels in the cell **can limit alteration detection**[6]		RNA sequencing requires additional bioinformatics expertise[4,6]

Mack et al. used a model based on real-world data to predict the likelihood of a fusion detected by only RNA sequencing, but not DNA sequencing, in non-squamous NSCLC[8]

1.3% Predicted RNA-only fusion detection rate

4.4% Predicted RNA-only fusion detection rate in otherwise driver-negative samples

FoundationOne CDx Was Designed to Detect Fusions and Rearrangements with DNA Sequencing[1,2,8]



FoundationOne CDx has Multiple Companion Diagnostic Claims for Fusions and Rearrangements[1-3]

FoundationOne CDx is the only tissue-based test with FDA-approved companion diagnostic claims to detect *ROS1, NTRK, ALK, FGFR2*, and *RET* fusions across multiple tumor types.

	n	Comparator test	PPA, % (95% CI)	NPA, % (95% CI)
ALK rearrangements[1]	159	IHC and FISH	92.9 (85.1-97.3)*	100 (95.2-100)
ROS1 fusions[2]	291	Externally validated NGS assay, PCR	73.9 (59.7-84.4)	99.2 (97.1-99.8)
FGFR2 fusions and rearrangements[1]	181	Externally validated NGS assay	100 (95.7-100)	100 (96.3-100)
RET fusions[2]	209^	PCR, NGS, FISH[3]	90.1 (81.0-95.1)	100 (97.3-100)
NTRK1/2/3 rearrangements[1]	275	RNA sequencing	84.1 (69.9-93.4)	100 (98.4-100)

*2 specimens harbored *ALK* rearrangements detected by FoundationOne CDx classified as negative based on study protocol
^Excludes patients with unevaluable FoundationOne CDx results

Foundation Medicine Tissue DNA CGP Fusion Detection is Associated with rwPFS in NSCLC[8]

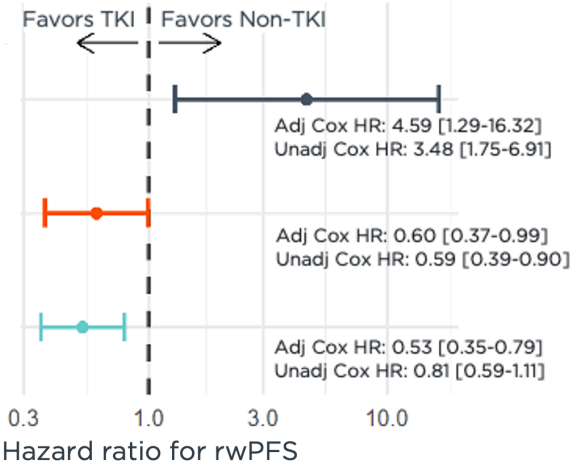
When a fusion was not detected by Foundation Medicine DNA CGP, rwPFS was shorter on targeted therapy

When Foundation Medicine DNA CGP detected a fusion, rwPFS on targeted therapy was similar even if other testing did not identify the fusion

Discordant result
Fusion detected only by other testing

Discordant result
Fusion detected only by Foundation Medicine

Concordant result
Fusion detected by both testing methods



Have questions about fusions? Contact your Medical Science Liaison:
http://www.foundationmedicine.com/contact

Abbreviations
Adj = adjusted, CI = confidence interval, CGP = comprehensive genomic profiling, FISH = fluorescence in situ hybridization, IHC = immunohistochemistry, HR = hazard ratio, NGS = next-generation sequencing, NPA = negative percent agreement, NSCLC = non-small cell lung cancer, PCR = polymerase chain reaction, PPA = positive percent agreement, rwPFS = real world progression-free survival, TKI = tyrosine kinase inhibitors, Unadj = unadjusted.

References
1. Milbury CA, et al. *PLoS ONE*. 2022;17(3): e0264138; 2. FoundationOne®CDx Technical Information. Foundation Medicine; 2023. Accessed February 19, 2024. https://www.F1CDxLabel.com. 3. Subbiah V, et al. *Lancet Oncol*. 2022;23(10):1261-1273. 4. Heyer EE, Blackburn J. *Bioessays*. 2020;42(7):e2000016. 5. Aref-Eshghi E, et al. *Cancer Genet*. 2021;258-259:110-119. 6. Bekaii-Saab TS, et al. *Ann Oncol*. 2021;32(9):1111-1126 7. Rapoport BL, et al. *Karger Publishing: Fast Facts: Comprehensive Genomic Profiling,* 2020. DOI: 10.1159/isbn.978-3-318-06819-1. 8. Mack PC, et al. *Oncologist*. 2024. doi:10.1093/oncolo/oyae028.

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