Introduction to multi-biomarker profiling: what is the data saying about it?

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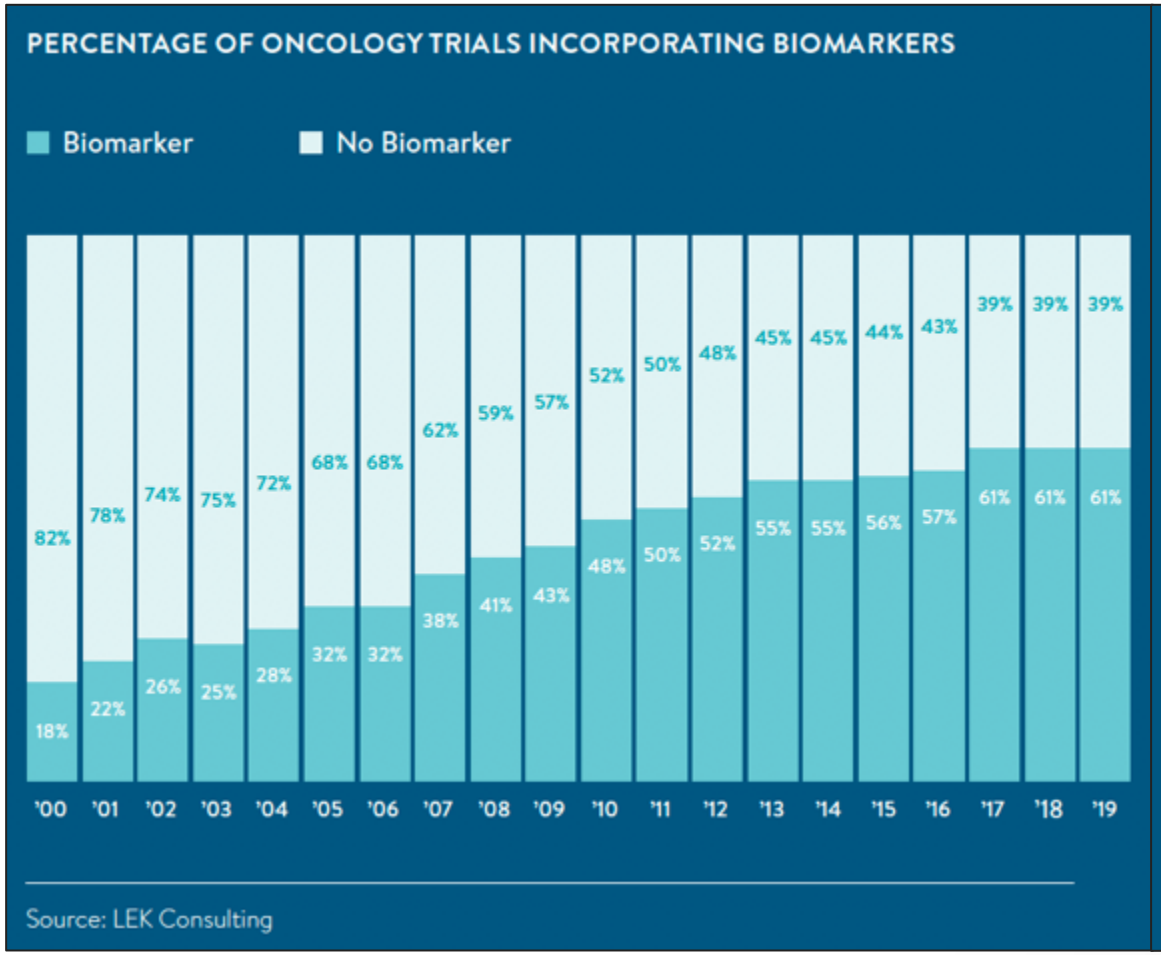
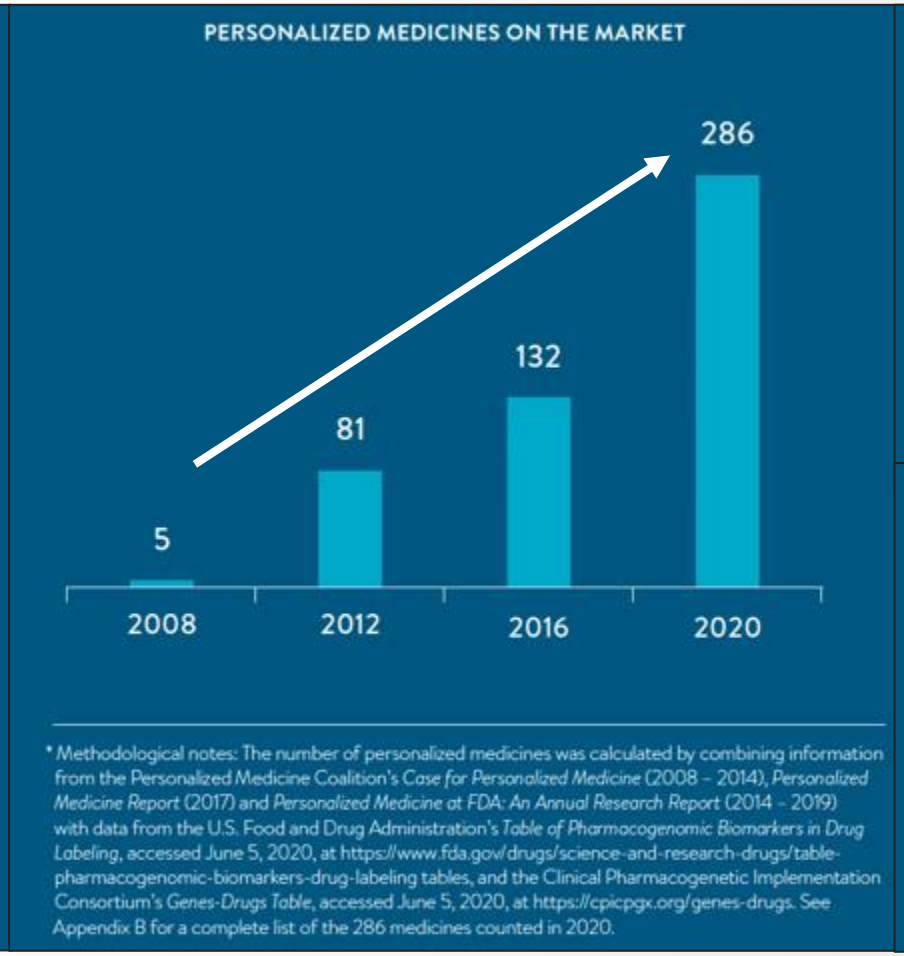
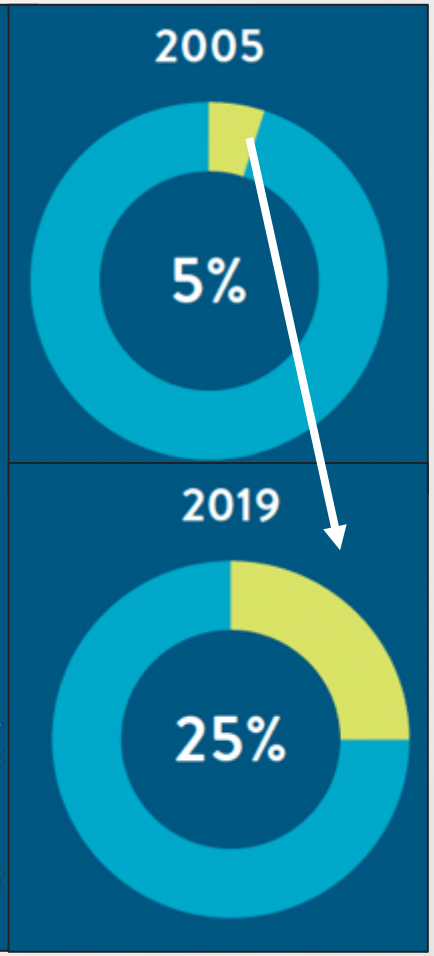
Precision medicine is a biomarker driven story

Precision Medicine: the right drug to the right patient at the right time - a rapid progression



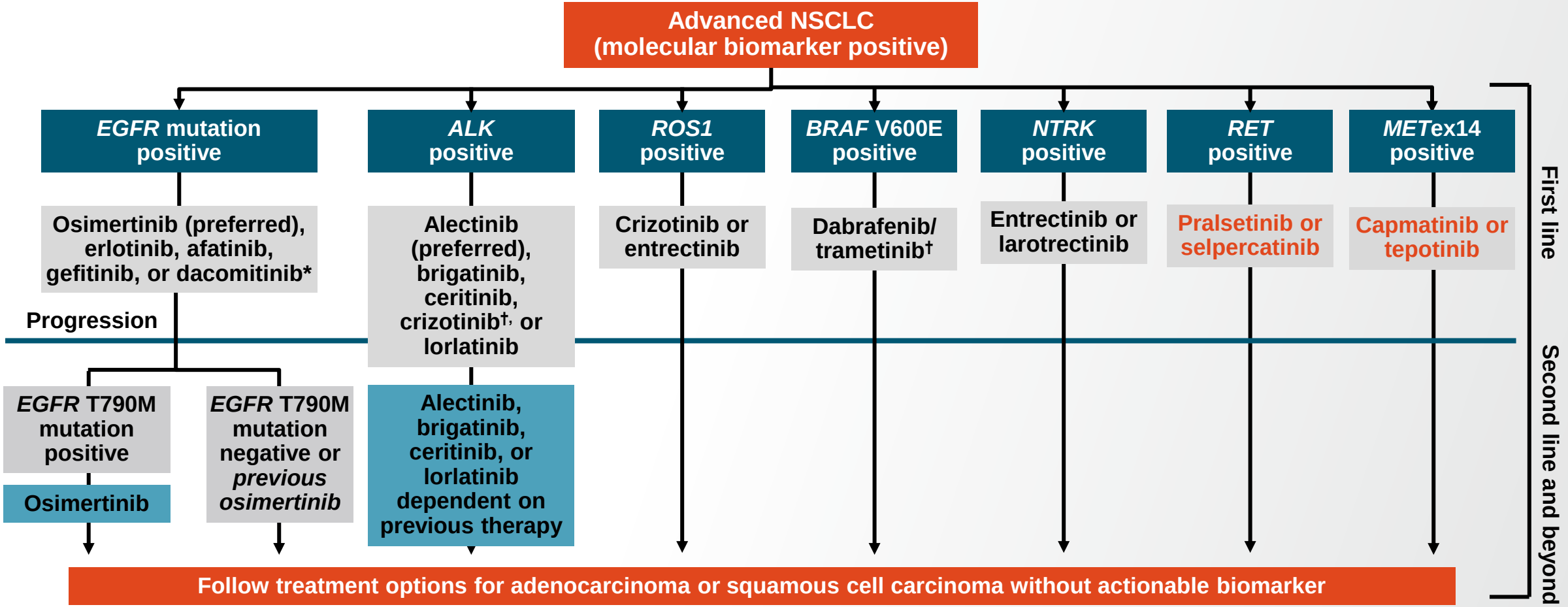




Source: 1. Table of pharmacogenomic biomarkers in drug labelling, Food and Drug Administration, updated December 2019, fda.gov; **2.** Modified from LEK Consulting contribution to PMC annual report 2020.

Current Treatment Paradigm for Molecular Biomarker–Positive Advanced NSCLC

A growing palette of to be tested biomarkers



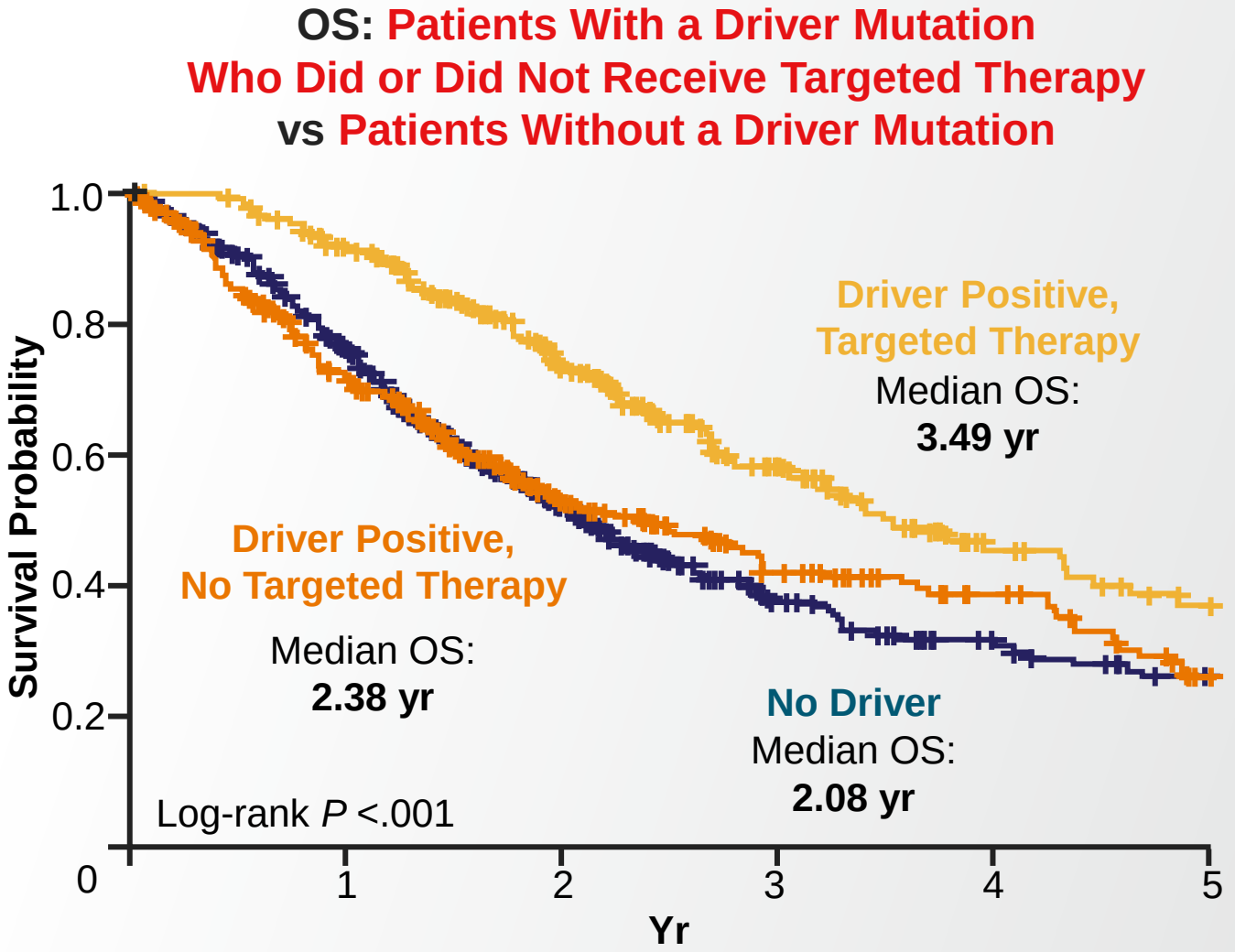
*Afatinib, dacomitinib, erlotinib, gefitinib, osimertinib approved for *EGFR* exon19del, exon 21 L858R; afatinib for *EGFR* G719X, S768I, L861Q.
†Or as second-line after CT.

Afatinib PI. Alectinib PI. Brigatinib PI. Capmatinib PI. Ceritinib PI. Crizotinib PI. Dabrafenib PI. Dacomitinib PI. Entrectinib PI. Erlotinib PI. Gefitinib PI. Larotrectinib PI. Osimertinib PI. Pralsetinib PI. Selpercatinib PI. Tepotinib PI. Trametinib PI.

Slide credit: clinicaloptions.com

The Importance of Genetic Profiling in NSCLC

Key takeaway: NSCLC with an oncogenic driver mutation carries a better prognosis. Forfeited if a patient does not receive corresponding targeted therapy



Kris. JAMA. 2014;311:1998.

Slide credit: clinicaloptions.com

Single-gene testing simply cannot keep up at peace

And that is not just for Lung Cancer

- Equitable delivery of the same quality of care for patients, whether at academic- or community-based medical centers, is essential for community health.
- While waiting for NGS data from outsourced partners, patients are often started on a traditional therapy (e.g., radiation or chemotherapy), which may not only be less effective but also come with harsh side effects.
- 94% of patients had complete biomarker information available at their first consult with an oncologist, compared to just 17% when we were outsourcing testing to a reference lab.

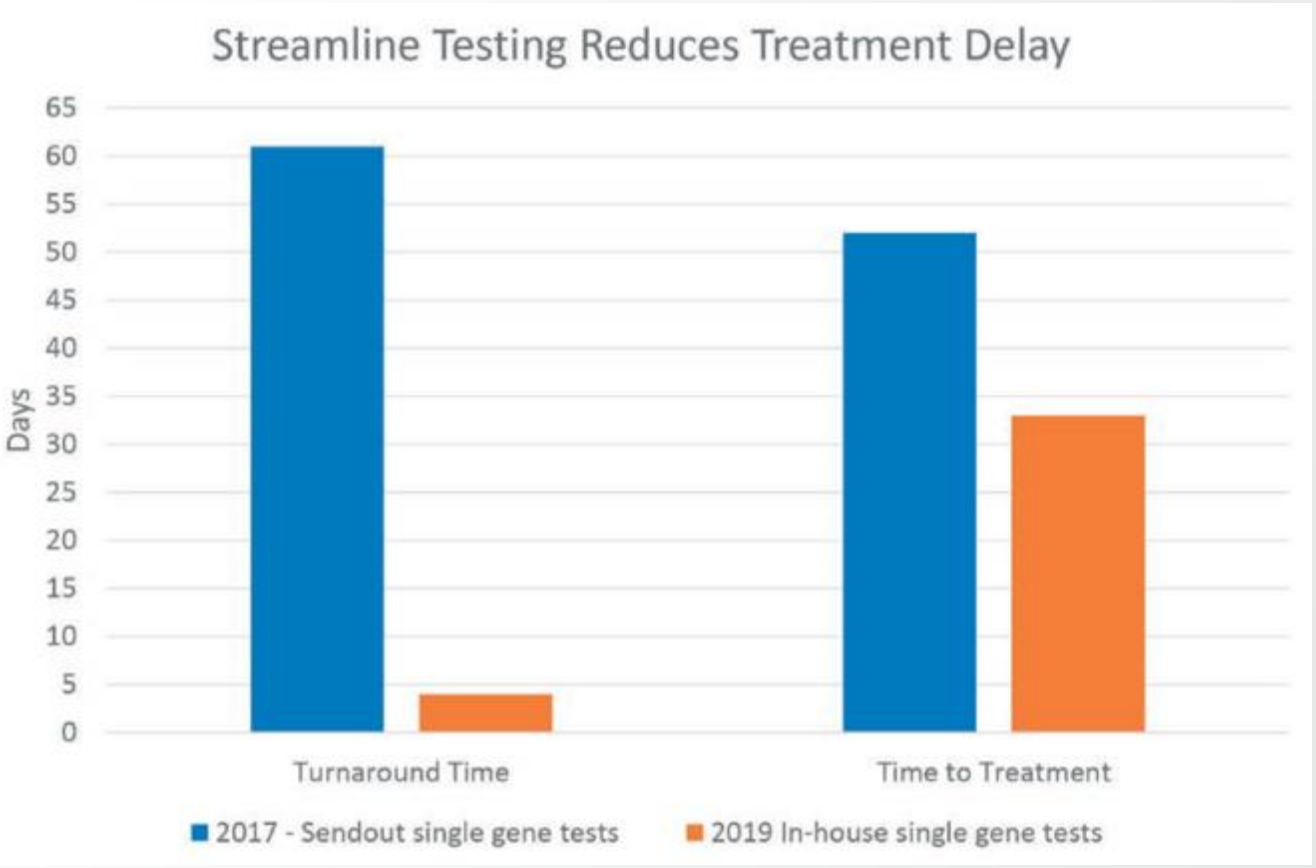


Figure 1: Comparison of turnaround time for test results and time to treatment for patients using outsourced single-gene testing (2017) and in-house single gene tests (2019)

Beharry A. et al., Journal of Precision Medicine | Volume 7 | Issue 2 | June 2021

Single-gene testing simply cannot keep up at peace

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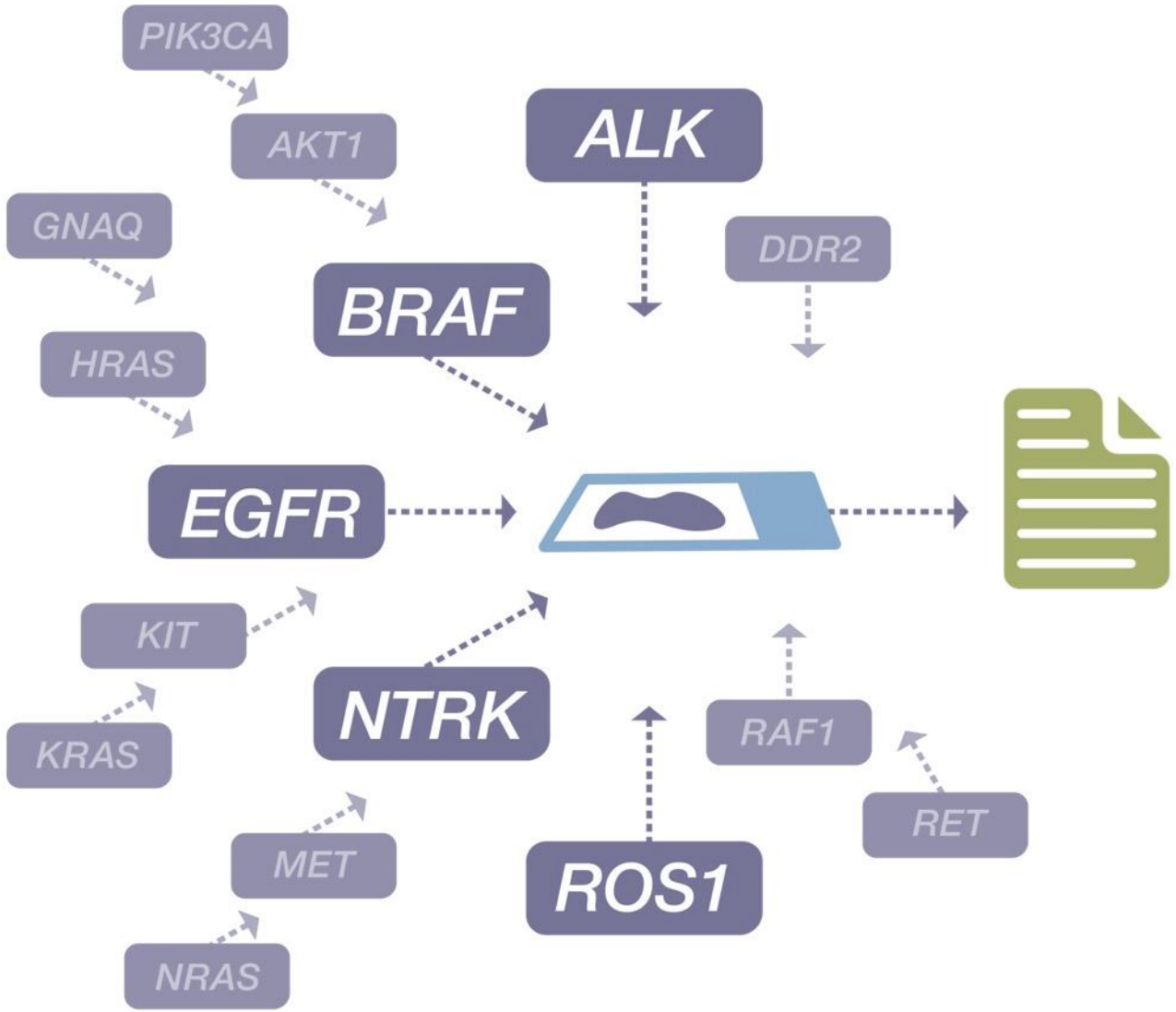
	< 2020	2020	2021	2022	2023	2024
Tumour Agnostic Approvals	3	3	4	5	12	15
Tumour-Specific Approvals						
NSCLC	5	6	7	7	8	14
HER2- HR+ BC	2	2	2	4	5	5
TNBC	1	1	2	5	5	5
CRC	3	4	4	4	7	7
Ovarian Cancer	2	2	2	2	3	3

WHY SO MUCH TALKING ABOUT NEXT GEN-SEQUENCING (NGS)?



With NGS, we are able to detect all biomarkers associated with approved targeted therapies, and many others currently in clinical trials.

Assay Success Rate: EU Leading Medical Center

IJC International Journal of Cancer

Cancer Epidemiology | Free Access

Combined targeted DNA and RNA sequencing of advanced NSCLC in routine molecular diagnostics: Analysis of the first 3,000 Heidelberg cases

Anna-Lena Volckmar, Jonas Leichsenring, Martina Kirchner, Petros Christopoulos, Olaf Neumann, Jan Budczies, Cristiano Manuel Morais de Oliveira, Eugen Rempel, Ivo Buchhalter, Regine Brandt, Michael Allgäuer, Suranand Babu Talla, Moritz von Winterfeld, Esther Herpel, Benjamin Goeppert, Amelie Lier, Hauke Winter, Tilman Brummer, Stefan Fröhling, Martin Faehling, Jürgen R. Fischer, Claus Peter Heußel, Felix Herth, Felix Lasitschka, Peter Schirmacher, Michael Thomas, Volker Endris, Roland Penzel, Albrecht Stenzinger ... See fewer authors

First published: 17 January 2019 | https://doi.org/10.1002/ijc.32133 | Citations: 24

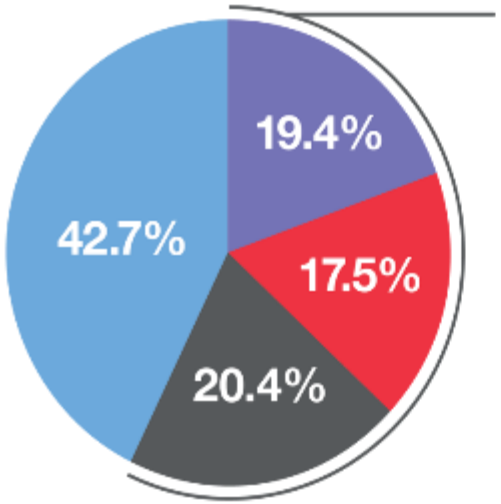
Abstract

Tyrosine kinase inhibitors currently confer the greatest survival gain for non-small cell lung cancer (NSCLC) patients with actionable genetic alterations. Simultaneously, the increasing number of targets and compounds poses the challenge of reliable, broad and timely molecular assays for the identification of patients likely to benefit from novel treatments. Here, we demonstrate the feasibility and clinical utility of comprehensive, NGS-based genetic profiling for routine workup of advanced NSCLC based on the first 3,000 patients analyzed in our department. Following automated extraction of DNA and RNA from formalin-fixed, paraffin-embedded tissue samples, parallel sequencing of DNA and RNA for detection of mutations and fusion genes, respectively, was performed using PCR-based enrichment with an ion semiconductor sequencing platform. Overall, 807 patients (27 %) were eligible for currently approved, EGFR-/BRAF-/ALK- and ROS1-directed therapies, while 218 additional cases (7 %) with *MET*, *ERBB2 (HER2)* and *RET* alterations could potentially profit from off-label treatments. In addition, routine capturing of comutations, e.g. *TP53* (55%), *KEAP1* (11%) and *STK11* (11%), as well as the precise typing of fusion partners and involved exons in case of actionable translocations including *ALK* and *ROS1*, are prognostic and predictive tools currently gaining importance for further refinement of therapeutic and surveillance strategies. The reliability, low dropout rates (<5%), minimal tissue requirements, fast turnaround times (6 days on average) and lower costs of the diagnostic approach presented here compared to sequential single-gene testing, highlight its practicability in the routine setting in order to support individualized decisions in patient care as well as clinical and translational research.

Rejection Rate of Amplicon-based NGS: **<5%**

Assay Success Rate: US Reference Lab

Multicentric feasibility study, US[1]

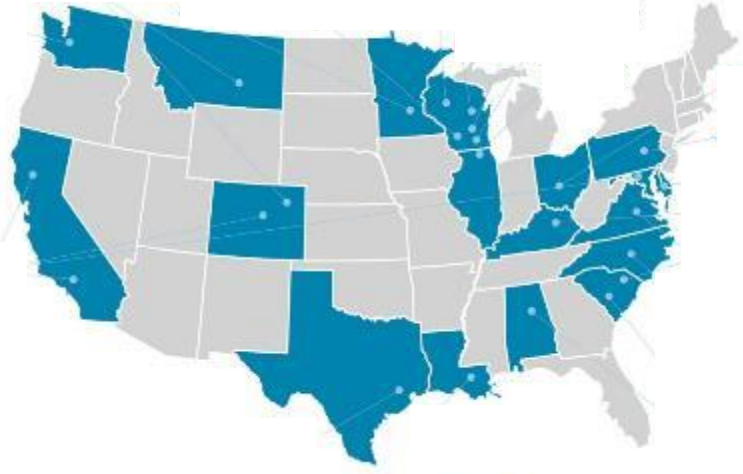


57.3% of all samples had less than 25 mm² tumor area

Tumor area

- ≤4 mm²
- >4 mm² and ≤10 mm²
- >10 mm² and ≤25 mm²
- >25 mm²

21,722
NSCLC samples



COMPREHENSIVE GENOMIC PROFILING: FEASIBILITY STUDY

21,734 *Total Tested Samples*

20,493 *Eligible Samples for Amplicon-based NGS* ⇨ **94.3%**

9,281 *Eligible Samples for Hybrid Capture-based NGS* ⇨ **42.7%**

TAT

7-day

21-day

1. S Tomlins, et al. **ASCO-2020** (Abstract 3574); 2. A. Volckmar, et al., **Int J Cancer. 2019.** DOI: 10.1002/ijc.32133.

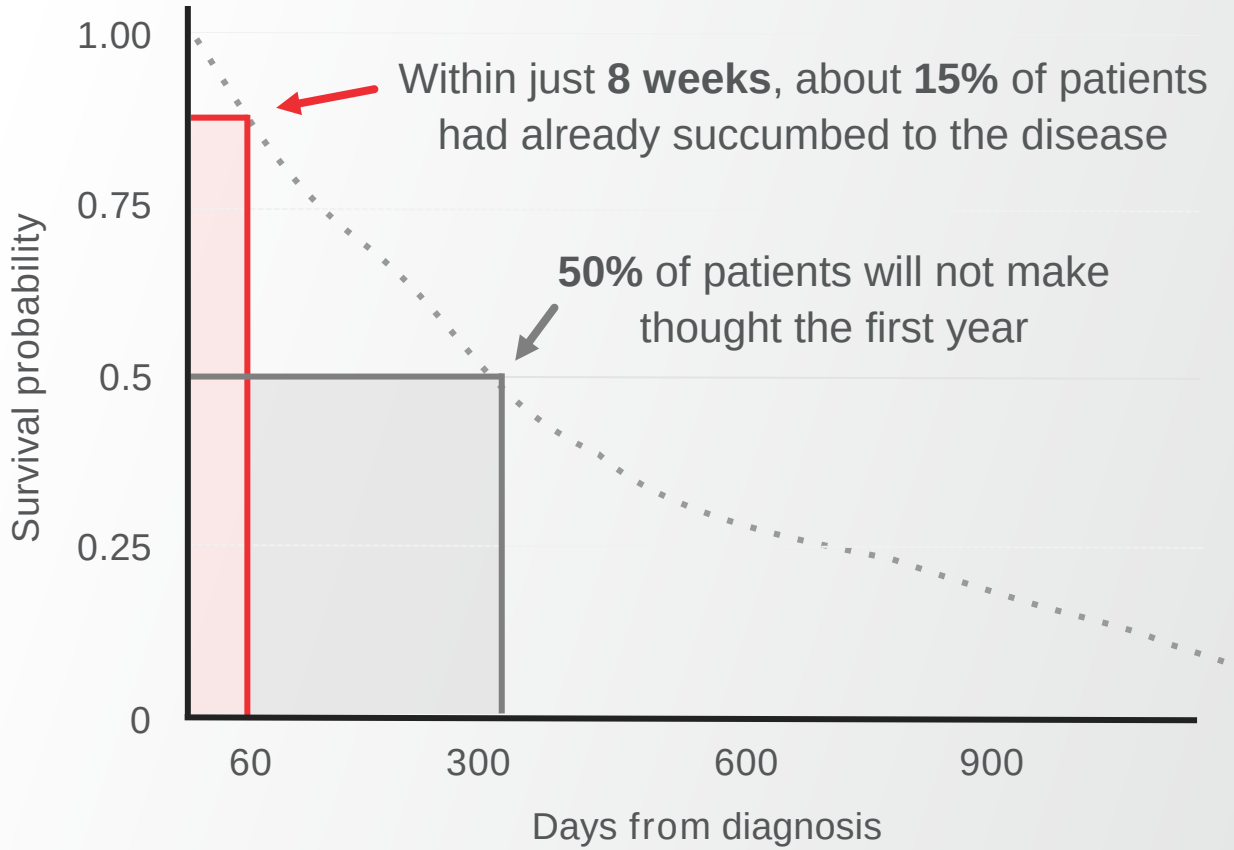
Why is timely delivery of results so important in the routine clinical setting?

It is extremely important to promptly provide physicians with a clinically meaningful molecular report to inform the most appropriate treatment decision.

Clinical deterioration is observed in up to 20% of advanced-stage cancers within the first weeks of diagnosis, greatly reducing the treatment options.

TAT is also a key factor in patients recruiting for clinical trials, time to target accrual represent one of the barriers for trials success

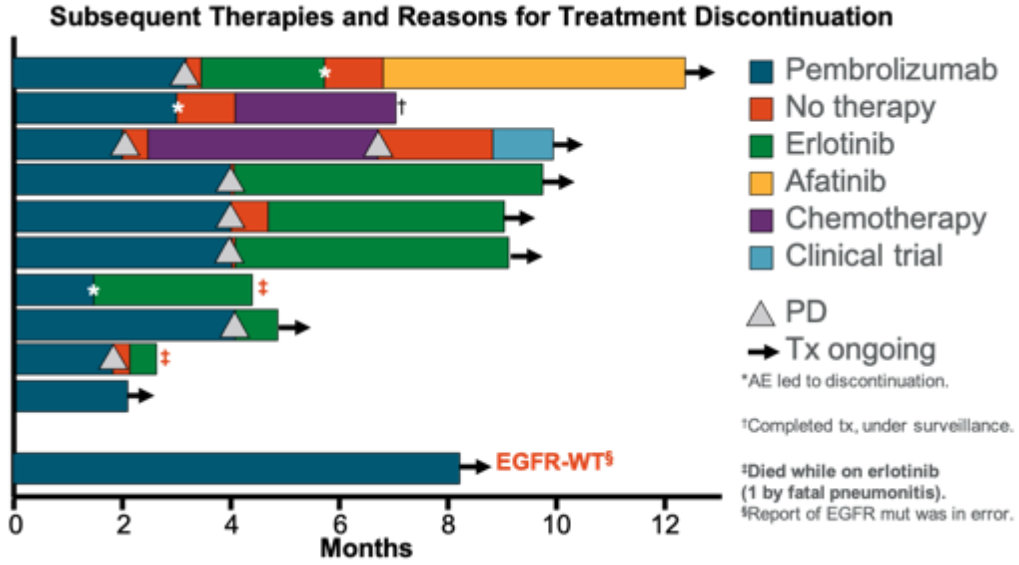
Overall Survival data of stage IV NSCLC



https://www.cancer.org/cancer/lung-cancer/detection-diagnosis-staging/survival-rates.html

MAKE A MISTAKE AND YOUR PATIENTS PAY FOR IT

Lack of efficacy with immune checkpoint inhibition in EGFR mutation–positive NSCLC[1], along with Potential Toxicity with Sequential Use of Immunotherapy Followed by a TKI[2]



Study Setting: Retrospective review of patient records to identify severe toxicity with ICI and EGFR TKI, regardless of sequence, in patients with EGFR-mutated NSCLC (N=126).

In patients treated with osimertinib within 3 months of ICI, 24% developed a severe irAE; conversely, no severe irAEs were identified if osimertinib was given before ICI.[2]

Pt No.	ICI	Days on ICI	Days to irAE Onset After 1st Osi Dose	irAE	Hospitalized?
1	Nivolumab	14	24	G3 pneumonitis	**Y**
2	Pembrolizumab + CT*	21	15	G3 pneumonitis	N
3	Nivolumab + ipilimumab	392	167	G3 pneumonitis	**Y**
4	Pembrolizumab	126	14	G3 colitis	**Y**
5	Pembrolizumab	126	15	G3 pneumonitis	**Y**
6	Nivolumab	68	39	G4 hepatitis	**Y**

Source: 1. Lisberg. Et al . J Thorac Oncol. 2018;13:1138; **2.** Modified from Schoenfeld et al.. Ann Oncol. 2019;30:839.

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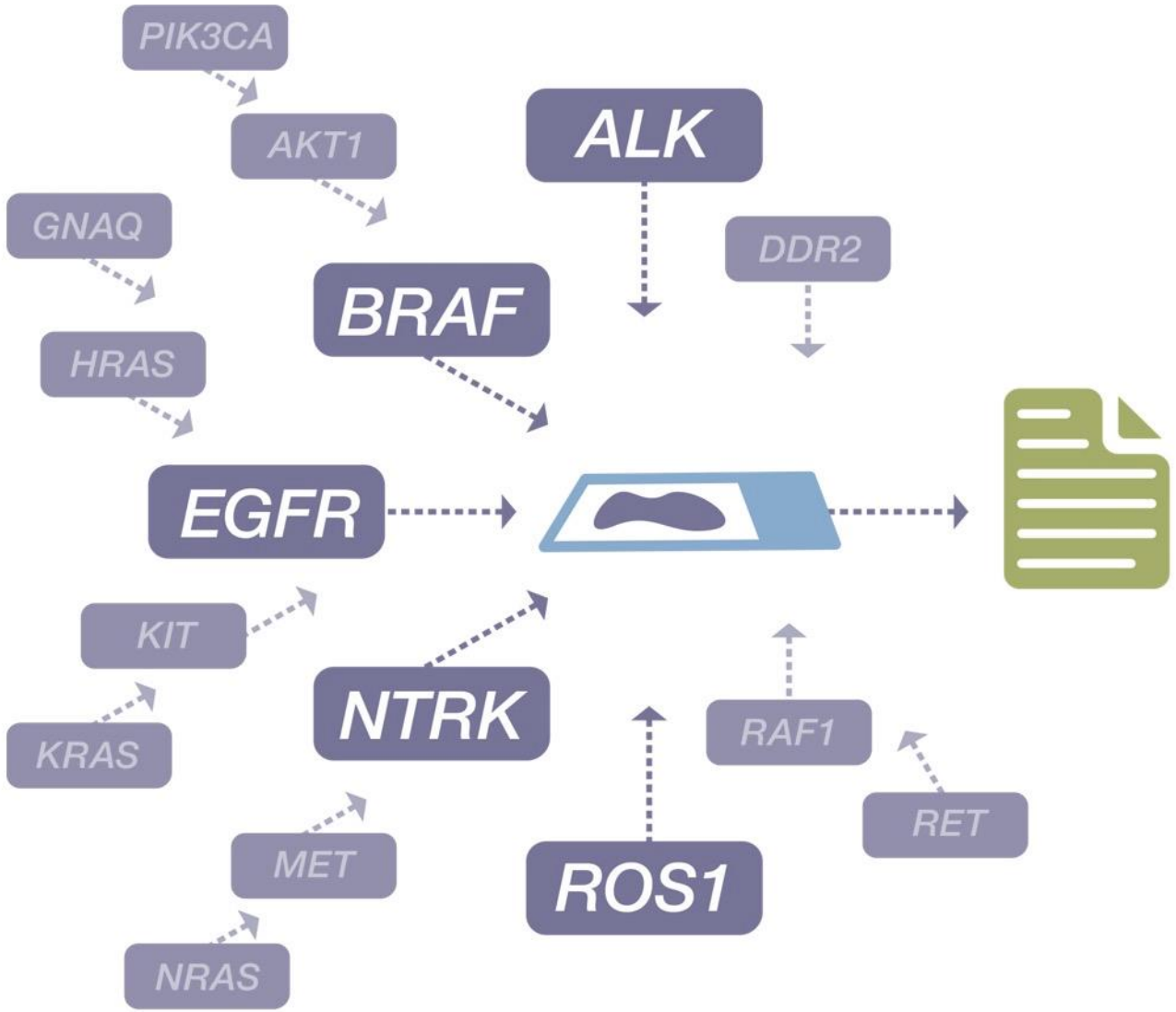

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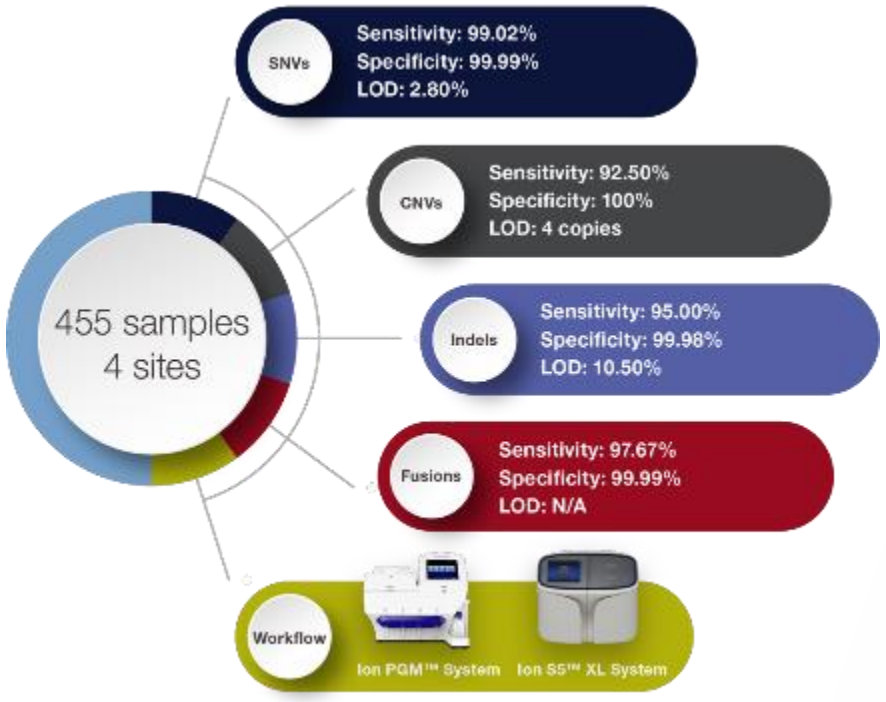
Success Rate: NCI-MATCH

NCI-MATCH Trial

Improving clinical cancer trials with genetic screening

Comprehensive Assay, with robust performance proven in large clinical oncology trials such as NCI MATCH, is a game changer in comprehensive genomic profiling.



Source: *Analytical validation of the NGS assay for a nationwide signal-finding clinical trial molecular analysis for therapy choice clinical trial; C-J Lih et al; The Journal of Molecular Diagnostics Vol. 19, No. 2, March 2017*

Oncomine Comprehensive Assay (OCA)

1,100+
sample collection sites

6,500
patients screened

93%
successful case results*

Scaling molecular profiling technologies to clinical settings

Standardized NGS assay and platform across multiple independent clinical sequencing sites

Use one standardized test to stratify patients into multiple clinical trials

Quick turnaround time, sample-to-results in 14 days with sensitivity of achieving 96.98%+ using FFPE specimens

20 treatment arms; 6,500 patients screened across 1,100 centers throughout the United States

Agenda Overview

1

Multi-biomarker solution for tumor agnostic genomic profiling

Gareth Williams, Medical Director and co-founder

Oncologica UK Ltd, UK

2

Multicentric study to evaluate in-house solution for CGP

Massimo Barberis, Director of Histopathology and Molecular Diagnostics Unit

European Institute of Oncology, Italy