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ITAPA Health&Care 2025

The Role of Molecular Diagnostics in today's cancer care

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The world leader in serving science

Slovakia Perspective – Access to NGS

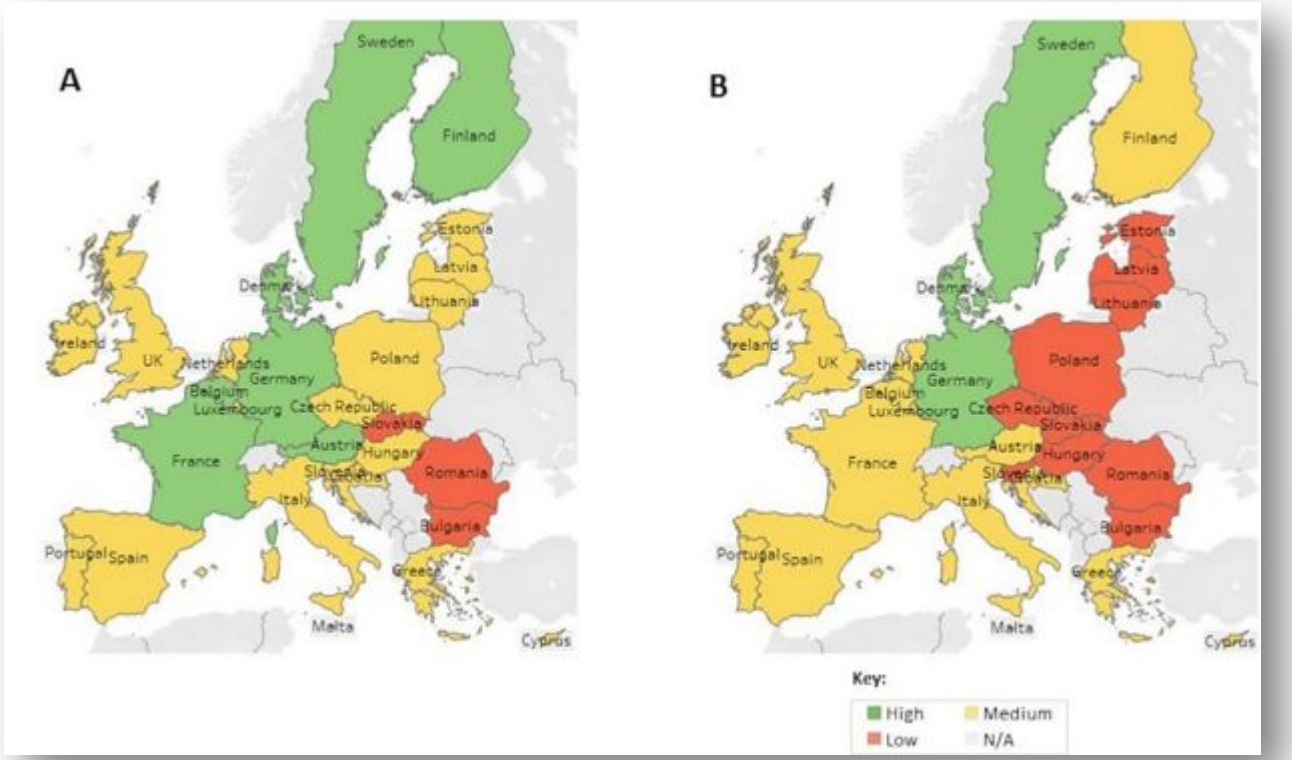


Fig. 1. The current status on quality and access to biomarker testing in Europe: (A) Single biomarker test access; (B) multi-biomarker test access;[1]

Table 2
Access to precision medicines.

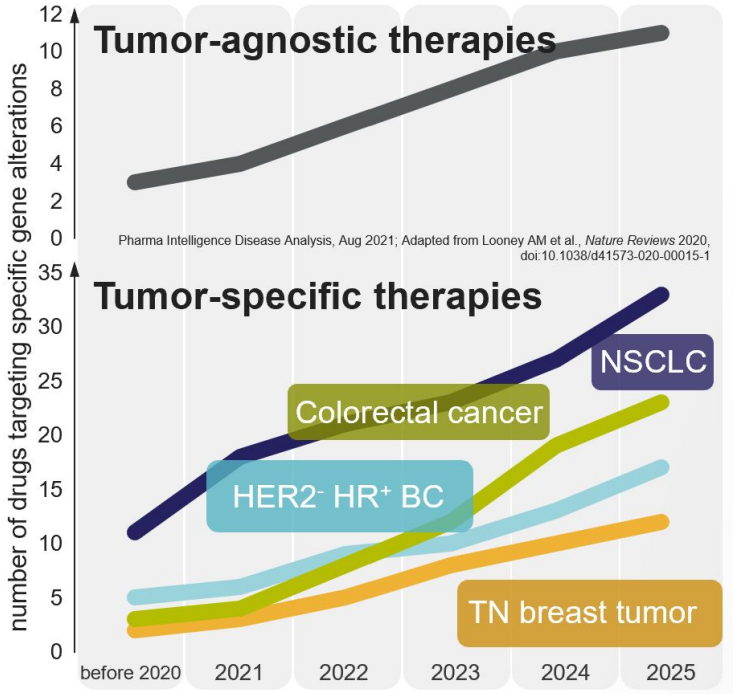
Rank[a]	Country	N. medicines reimbursed	N. medicines available	% reimbursed
1	Germany	35	37	95%
2	Netherlands	35[b]	36	95%
3	UK	29+5[c]	36	95%
4	Spain	31[b]	33	95%
5	Italy	30[b]	33	90%
6	Denmark	29	29	100%
7	Belgium	28	29	95%
8	Croatia	28	28	100%
9	Sweden	27	35	75%
10	France	27	34	80%
11	Bulgaria	26[d]	29	90%
12	Austria	25[e]	33	75%
13	Finland	24	34	70%
14	Ireland	24	33	75%
15	Poland	23	27	85%
16	Romania	22	27	80%
17	Slovenia	20	33	60%
18	Hungary	20	25	80%
19	Greece	19	26	75%
20	Czech Republic	19	25	75%
21	Slovakia	18	31	60%
22	Portugal	18	26	70%
23	Luxembourg	17	26	65%
24	Estonia	17	23	75%
25	Lithuania	15	24	65%
26	Latvia	10	24	40%
27	Cyprus	7	27	25%
28	Malta	7	7	100%

Table 2. Access to Precision Medicine[1]

Publication report from 2021
https://www.efpia.eu/media/589727/unlocking-the-potential-of-precision-medicine-in-europe.pdf

Precision Oncology in 2025: More targets, more testing

More Targeted Therapies
and updated testing guidelines[1]



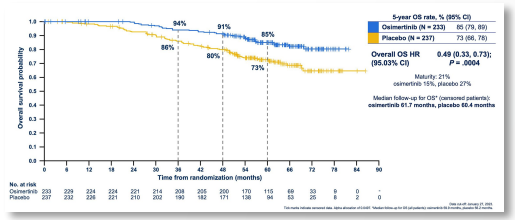
Pharma Intelligence Disease Analysis, Aug 2021; Adapted from Looney AM et al., *Nature Reviews* 2020, doi:10.1038/d41573-020-00015-1

Moving to early stages
Reflex testing as the new standard[2]

Pathologist-initiated reflex testing for biomarkers in non-small-cell lung cancer: expert consensus on the rationale and considerations for implementation

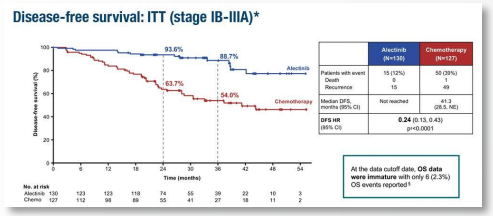
J. R. Gosney[1], L. Paz-Ares[2], P. Jänne[3], K. M. Kerr[4], N. B. Leighl[5], M. D. Lozano[6], U. Malapelle[7], T. Mok[8], B. S. Sheffield[9], A. Tufman[10,11,12], I. I. Wistuba[13,14] & S. Peters[15]

- *"Reflex testing is expeditious and standardises the ordering of biomarker tests to **ensure more patients are tested**."*
- *"Recent clinical and **technological advancements will help** to overcome concerns of increased costs and limited reimbursement."*



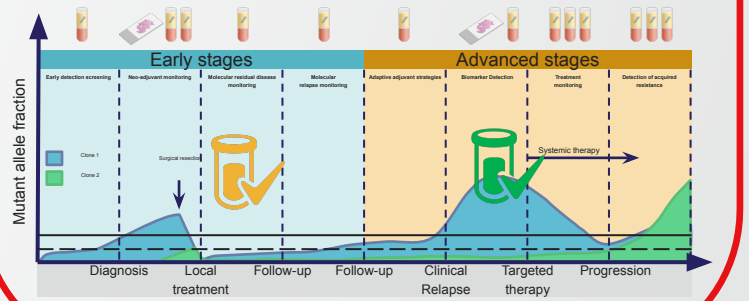
ADAURA trial[3]
EGFR TKI adjuvant

ALINA trial[4]
ALK TKI adjuvant



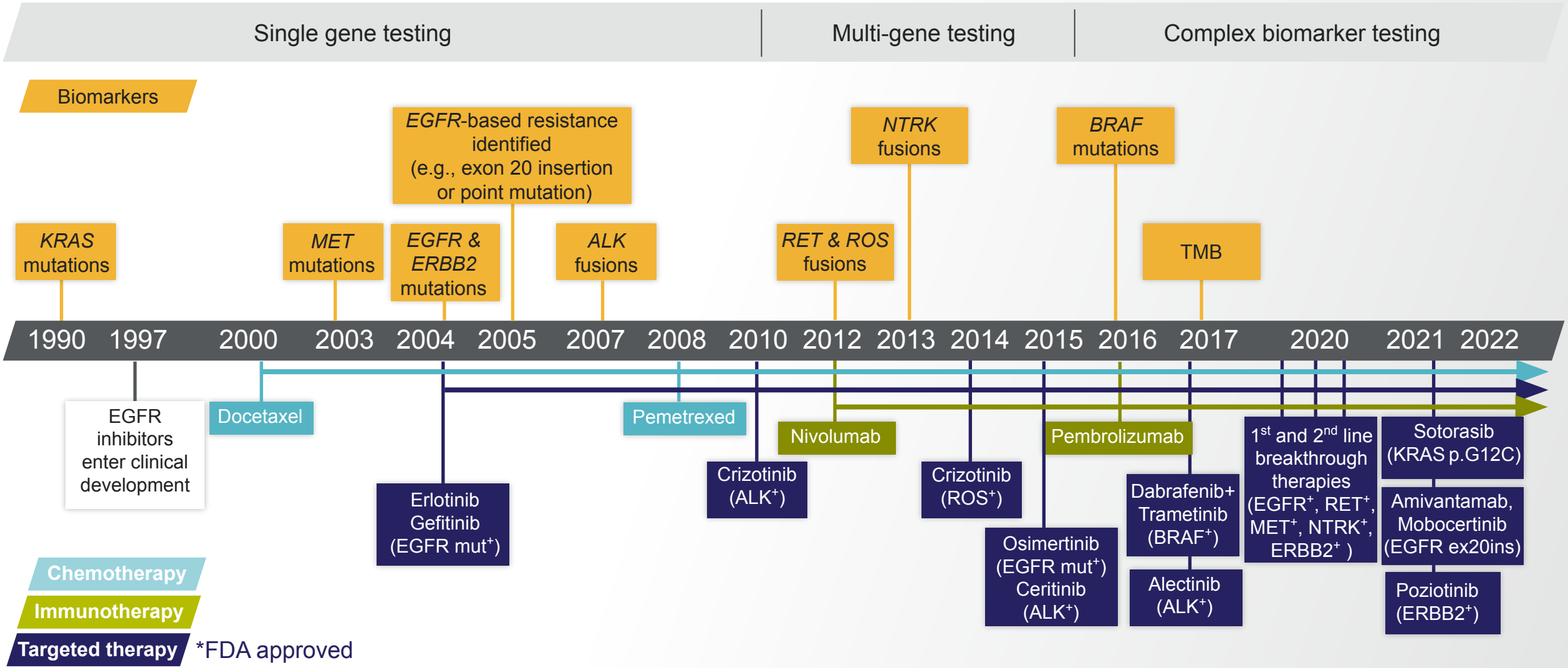
Less invasive diagnostics
Liquid Biopsy

- Liquid biopsy continues a viable salvage pathway in the absence of adequate tissue.[5]
- **Key clinical indications for LBx:**
  - NSCLC @ diagnosis and progression[5]
  - Prostate cancer @ diagnosis[6]
  - Metastatic breast cancer @ progression[7]



1. ESMO webinar series: Update of the Recommendations for the Use of Next-Generation Sequencing (NGS) for Patients with Metastatic Cancer, 22. Nov, 2023; **2.** Gosney et al., https://doi.org/10.1016/j.esmoop.2023.101587; **3.** Tsuboi et al., N Engl J Med 2023; 389:137-147; **4.** Solomon BJ, et al. ESMO Congress 2023, LBA2; **5.** Rolfo et al., Journal of Thoracic Oncology, Volume 16, Issue 10, October 2021, Pages 1647-1662; **6.** Kwan et al., Front Oncol. 2022; 12: 1054497; **7.** Betz et al., Cancers 2023, 15(21), 5169;

Number of clinically relevant biomarkers in NSCLC grows rapidly



TMB = tumor mutation burden

Politi & Herbst, *Clin Cancer Res* 2015, doi:10.1158/1078-0432.CCR-14-2748; **Herbst et al.**, *Nature* 2018, doi:10.1038/nature25183; **Planchard et al.**, *Ann Oncol* 2018, doi:10.1093/annonc/mdy275; Tan et al., *Lancet Oncol* 2016, doi:10.1016/S1470-2045(16)30123-1; **Maus et al.**, *Annu Rev Immunol* 2014, doi:10.1146/annurev-immunol-032713-120136; Skoulidis et al., *N Engl J Med* 2021, doi:10.1056/NEJMoa2103695; **Park et al.**, *J. Clin. Oncol.* 2021, doi: 10.1200/JCO.21.00662; **Le et al.**, *J. Clin. Oncol.* 2022, doi:10.1200/JCO.21.01323; **Thai et al.**, *Lancet* 2021, doi:10.1016/S01406736(21)00312-3

Recommendations for the use of NGS for patients with advanced cancer in 2024

A report from the ESMO Precision Medicine WG[1]

Fig 1. ESMO ESCAT Scale for Clinical Actionability of Molecular Targets[2]

Table 1: List of genomic alterations level I/II according to ESCAT in advanced non-squamous non-small-cell lung cancer[1]

Table 2. List of genomic alterations level I/II according to ESCAT in advanced non-squamous non-small-cell lung cancer

Gene	Alteration	Estimated prevalence	ESCAT score	Drug class matched	References
EGFR	Common mutations (deletion exon 19, p.L858R)	15% Caucasian 50% Asian 30% LATAM	IA	First-, second- and third-generation EGFR TKIs EGFR-MET bispecific antibodies + third-generation EGFR TKIs EGFR-MET bispecific antibodies + chemotherapy ± EGFR TKIs (after PD on third-generation EGFR TKIs)	Midha et al., *Am J Can Res* 2015[12] Arrieta et al., *J Thorac Oncol* 2015[13] Soria et al., *N Engl J Med* 2018[14] Ramalingam et al., *N Engl J Med* 2020[15] Cho et al., *Ann Oncol* 2023[16] Passaro et al., *Ann Oncol* 2024[17]
	Acquired p.T790M mutation in exon 20	60% after first- or second-generation EGFR TKIs	IA	Third-generation EGFR TKIs	Mok et al., *N Engl J Med* 2017[18] Papadimitrakopoulou et al., *Ann Oncol* 2020[19]
	Exon 20 insertions	2%	IA	EGFR-MET bispecific antibodies or TKIs	Park et al., *J Clin Oncol* 2021[20] Zhou et al., *N Engl J Med* 2023[21]
	Uncommon mutations (p.G719 variants in exon 18, p.L861Q in exon 21, p.S768I in exon 20)	10%	IB	Second- and third-generation EGFR TKIs	Cho et al., *J Clin Oncol* 2020[22] Yang et al., *Front Oncol* 2022[23]
ALK	Fusions	5%	IA	ALK TKIs	Mok et al., *Ann Oncol* 2020[24] Shaw et al., *N Engl J Med* 2020[25] Camidge et al., *J Thorac Oncol* 2021[26] Horn et al., *JAMA Oncol* 2021[27] Solomon et al., *Lancet Respir Med* 2023[28]
KRAS	Mutations (p. G12C)	12%	IA	KRAS ^{G12C} TKIs	Jänne et al., *N Engl J Med* 2022[29] de Langen et al., *Lancet* 2023[30]
RET	Fusions	1%-2%	IA	RET TKIs	Subbiah et al., *Clin Can Res* 2021[31] Griesinger et al., *Ann Oncol* 2022[32] Drilon et al., *J Clin Oncol* 2023[33] Zhou et al., *N Engl J Med* 2023[34]
ROS1	Fusions	1%-2%	IB	ROS1 TKIs	Shaw et al., *Ann Oncol* 2019[35] Shaw et al., *Lancet Oncol* 2019[36] Drilon et al., *JTO Clin Res Rep* 2022[37]
BRAF	Mutations (p. V600E)	2%	IB	BRAF TKIs + MEK TKIs	Planchard et al., *J Thorac Oncol* 2022[38] Riely et al., *J Clin Oncol* 2023[39]
MET	Mutations exon 14 skipping	3%	IB	MET TKIs	Drilon et al., *Nat Med* 2020[40] Wolf et al., *J Clin Oncol* 2021[41] Lu et al., *Lancet Respir* 2021[42] Thomas et al., *J Thorac Oncol* 2022[43] Wolf et al., *Ann Oncol* 2022[44]
	Focal amplifications	5% as primary 15% as mechanism of acquired resistance on EGFR TKIs	IIB	MET TKIs + third-generation EGFR TKIs EGFR-MET bispecific antibodies + third-generation EGFR TKIs	Yu et al., *Ann Oncol* 2021[45] Bauml et al., *J Clin Oncol* 2021[46] Shu et al., *J Clin Oncol* 2022[47] Marmarelis et al., *J Thorac Oncol* 2022[48] Hartmaier et al., *Cancer Discov* 2023[49] Tan et al., *J Clin Oncol* 2023[50]
ERBB2	Hotspot mutations	3%	IIB	Pan-HER TKIs Anti-HER2 ADCs	Hyman et al., *Nature* 2018[51] Li et al., *N Engl J Med* 2022[52]
NRG1	Fusions	<1%	IIB	Anti-HER2/HER3 bispecific antibody	Schram et al., *JCO* 2022[53]

ADC, antibody–drug conjugates; EGFR, epidermal growth factor receptor; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; HER, human epidermal growth factor receptor; LATAM, Latin America; PD, progressive disease; TKIs, tyrosine kinase inhibitors.

1.doi: 10.1016/j.annonc.2024.04.005;2.doi:10.1093/annonc/mdy263

Recommendations for the use of NGS for patients with advanced cancer in 2024

A report from the ESMO Precision Medicine workgroup[1]

Table 7. List of genomic alterations level I/II according to ESCAT in advanced ovarian cancer

Gene/Signature[a]	Alteration	Estimated prevalence	ESCAT score	Drug class matched	References
BRCA1/2	Germline pathogenic/likely pathogenic variants Somatic pathogenic/likely pathogenic variants	15%-17% 5%-7%	IA	PARP inhibitors	Bell et al., *Nature* 2011[109] Mirza et al., *N Engl J Med* 2016[110] Coleman et al., *Lancet* 2017[111] Pujade-Lauraine et al., *Lancet Oncol* 2017[112] Moore et al., *N Engl J Med* 2018[113] González-Martin et al., *N Engl J Med* 2019[114] Ray-Coquard et al., *N Engl J Med* 2019[115] DiSilvestro et al., *J Clin Oncol* 2023[116] González-Martin et al., *Ann Oncol* 2023[117]
HRD[a]	HRD	50% high-grade serous ovarian cancer	IA	PARP inhibitors	Mirza et al., *N Engl J Med* 2016[110] Coleman et al., *Lancet* 2017[111] González-Martin et al., *N Engl J Med* 2019[114] Ray-Coquard et al., *N Engl J Med* 2019[115] González-Martin et al., *Ann Oncol* 2023[117]

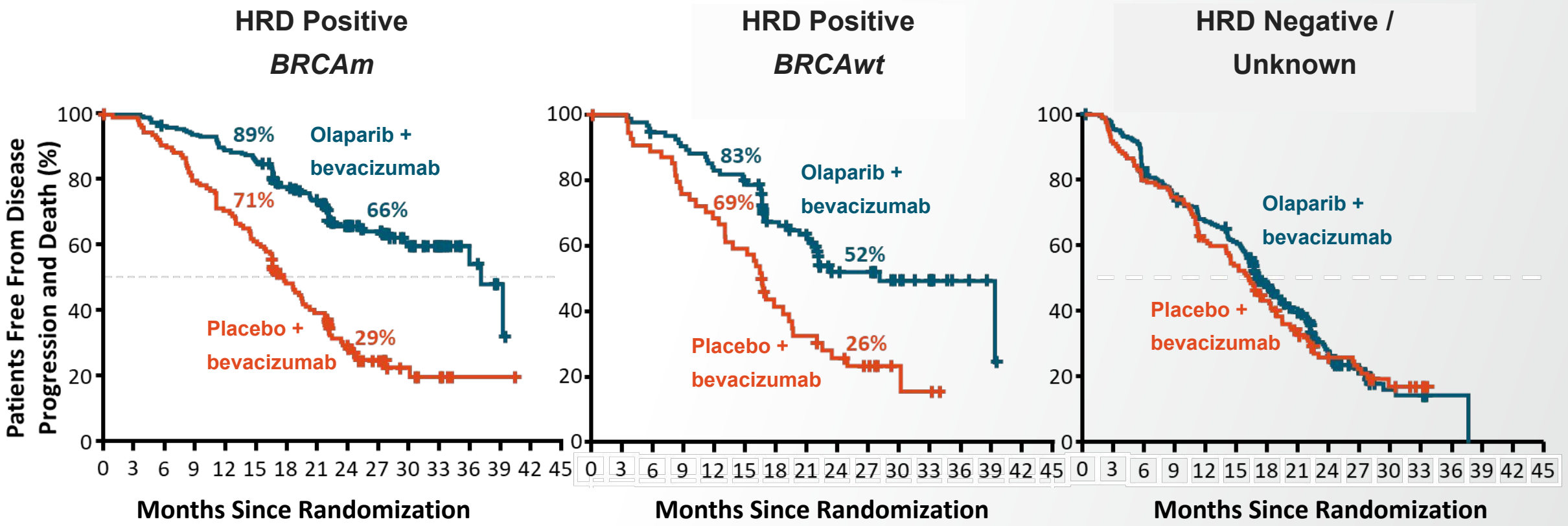
ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; HRD, homologous recombination deficiency; PARP, poly (ADP-ribose) polymerase.
[a]Signature.

Table 7. List of genomic alterations level I/II according to ESCAT in advanced ovarian cancer[1]

doi: 10.1016/j.annonc.2024.04.005

Clinical Evidence: PARP Inhibitors in Ovarian Cancer

PAOLA-1: PFS by HRD Status

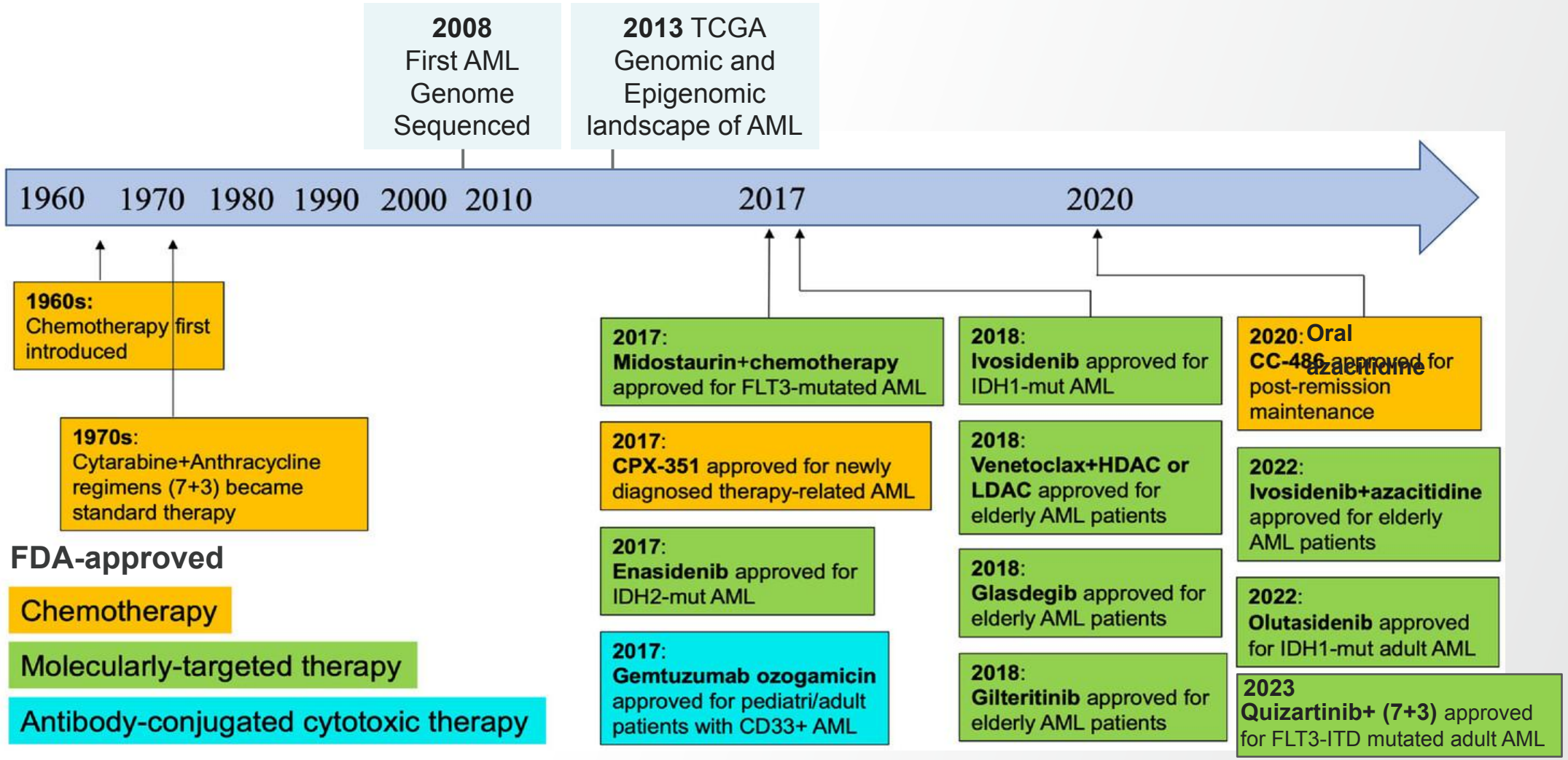


In 2020, based on the phase III PAOLA-1 study, the FDA and EMA approved olaparib plus bevacizumab for the maintenance treatment of HRD positive ovarian cancer

Images credit: clinicaloptions.com

1. Ray-Coquard. ESMO 2019. Abstr. LBA2.2. Ray-Coquard. NEJM. 2019;381:2416.

Genomic profiling enables advancements in the treatment of AML patients



AML patients can benefit from a more individualized treatment approach

Park HJ and Gregory MA, Aging and Cancer Blood 2023 (doi:10.1002/aac2.12065)
Lachowiez CA et al., Cancers 2023 (doi:10.3390/cancers15051617)
Marando L, Huntly BJP., Curr Oncol Rep. 2020 (doi:10.1007/s11912-020-00918-7)

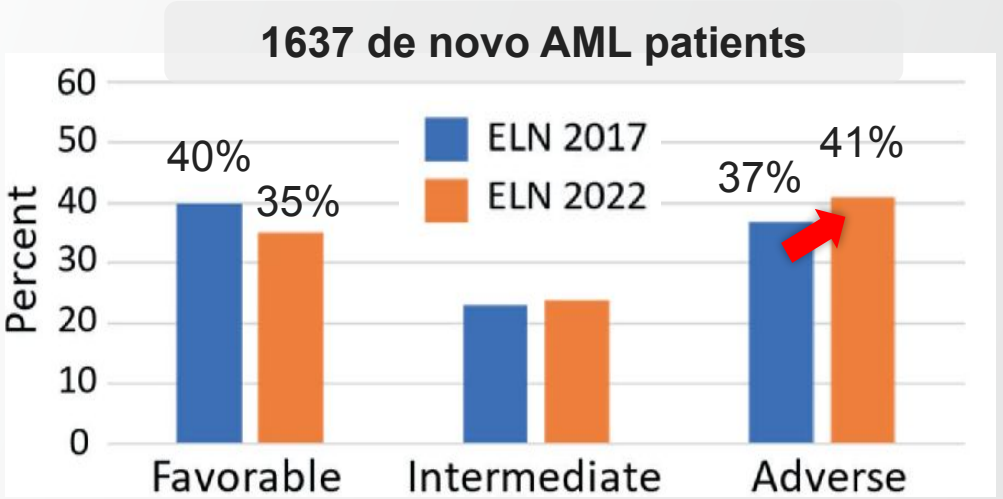
AML: Risk classification based on genetic markers

2022 European LeukemiaNet (ELN) recommendations

Status	Genetic abnormality	
Favorable	• *RUNX1-RUNX1T1* • *CBFB-MYH11*	• Mutated *NPM1* without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*
Intermediate	• Mutated *NPM1* with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions)	• *MLLT3-KMT2A* • Cytogenetic abnormalities not classified as favorable or adverse
Adverse	• *DEK-NUP214* • *KMT2A* rearranged • *BCR-ABL1* • *KAT6A-CREBBP* • -5 or del (5q); -7; 17/abn(17p)	• *GATA2, MECOM(EVI1)* • *Complex karyotype, monosomal karyotype* • Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, UTAF1, or ZRSR2* • Mutated *TP53*

12 biomarkers recently added in 2022 (in red)

Comparison between the ELN 2022 and 2017



ELN 2022 recommends testing more genetic biomarkers

Döhner, H., et al. Blood 2022 (https://doi.org/10.1182/blood.2022016867);
Mrózek K. et al. Leukemia 2023 (doi:10.1038/s41375-023-01846-8)

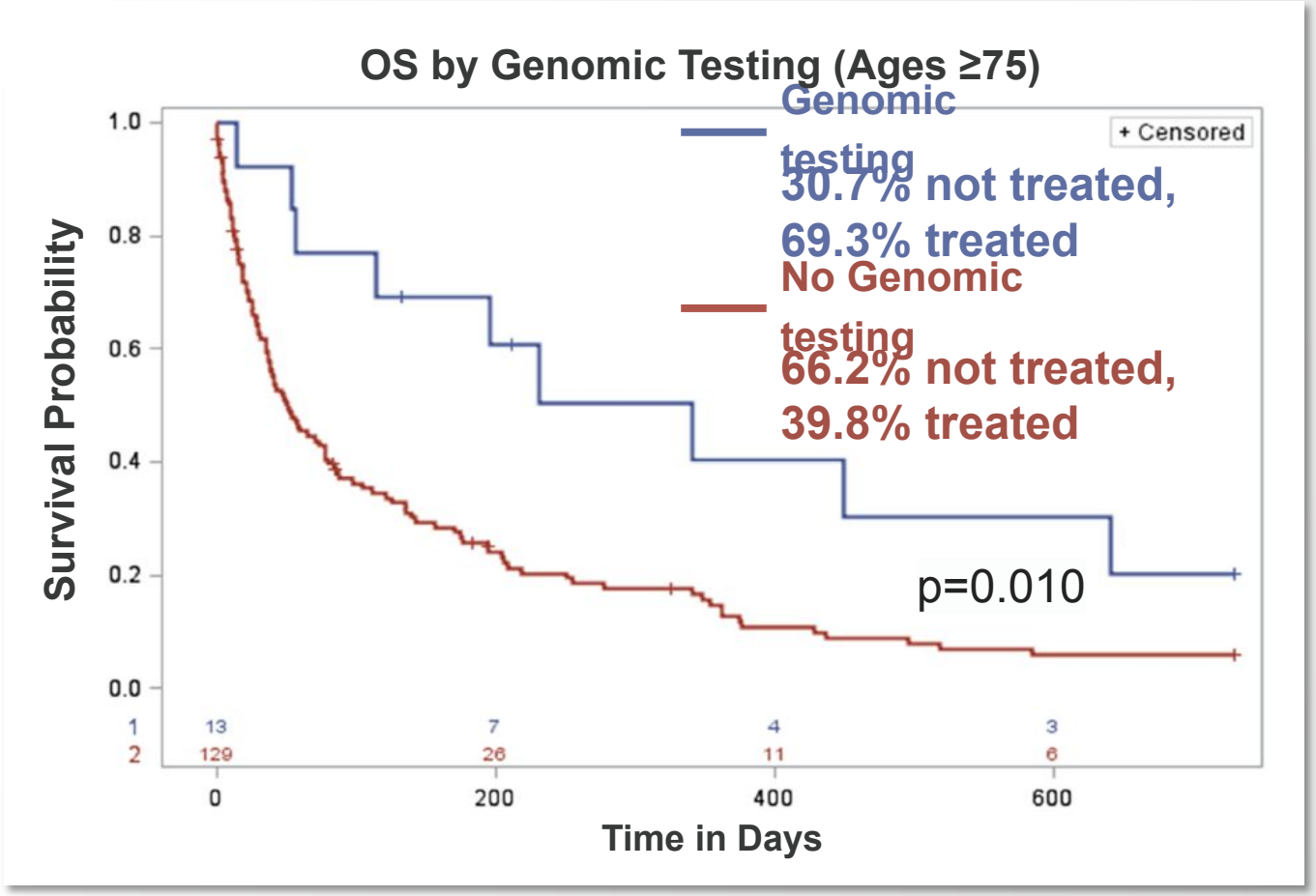
Real-world genomic testing in AML older patients impacts patient outcome – Research Study

629 newly diagnosed adult AML (*Indiana University Health System Enterprise Data Warehouse**)

Only 13% of patients have genomic sequencing reports, with the majority of patients <60 years

Elderly patients (≥75 years) had the highest proportion (46%) of **multiple (≥3) mutations**

Elderly patients who underwent genomic testing have a **longer OS**



**from 2011 to 2018*

Access to genomic testing may increase treatment options, especially for elderly AML patients

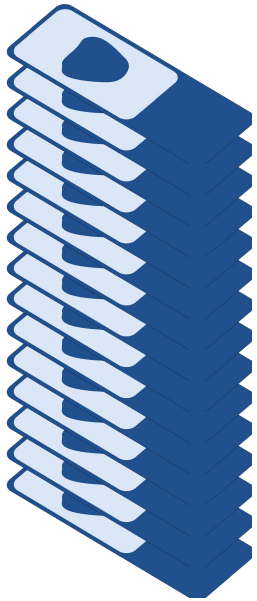
Byrd JC. et al. Cancer Medicine 2023 (doi:10.1002/cam4.6442)

Single-gene testing cannot keep up the pace

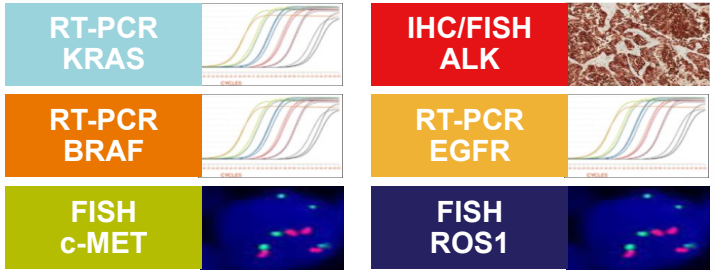
NGS is fundamental to ensure patient care[1,2]

NSCLC

Single gene testing



- × *Insufficient material*
- × *Incomplete testing*
- × *Long time to treatment*



Next-generation sequencing

- ✔ *simple workflow*
- ✔ *One sample*
- ✔ *Multiple markers*

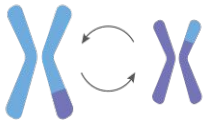
NGS enables parallel detection of relevant biomarkers in a single test

1. Arriola et al., JCO Precision Oncology no. 7 (2023) e2200546
2. Kerr et al., Lung Cancer 154 (2021) 161–175

NGS allows efficient multi-haematologic biomarker testing

One test **for** **Key biomarkers** **across** **Multiple samples** = **Save time**

Mutations (DNA)



Translocations (RNA)

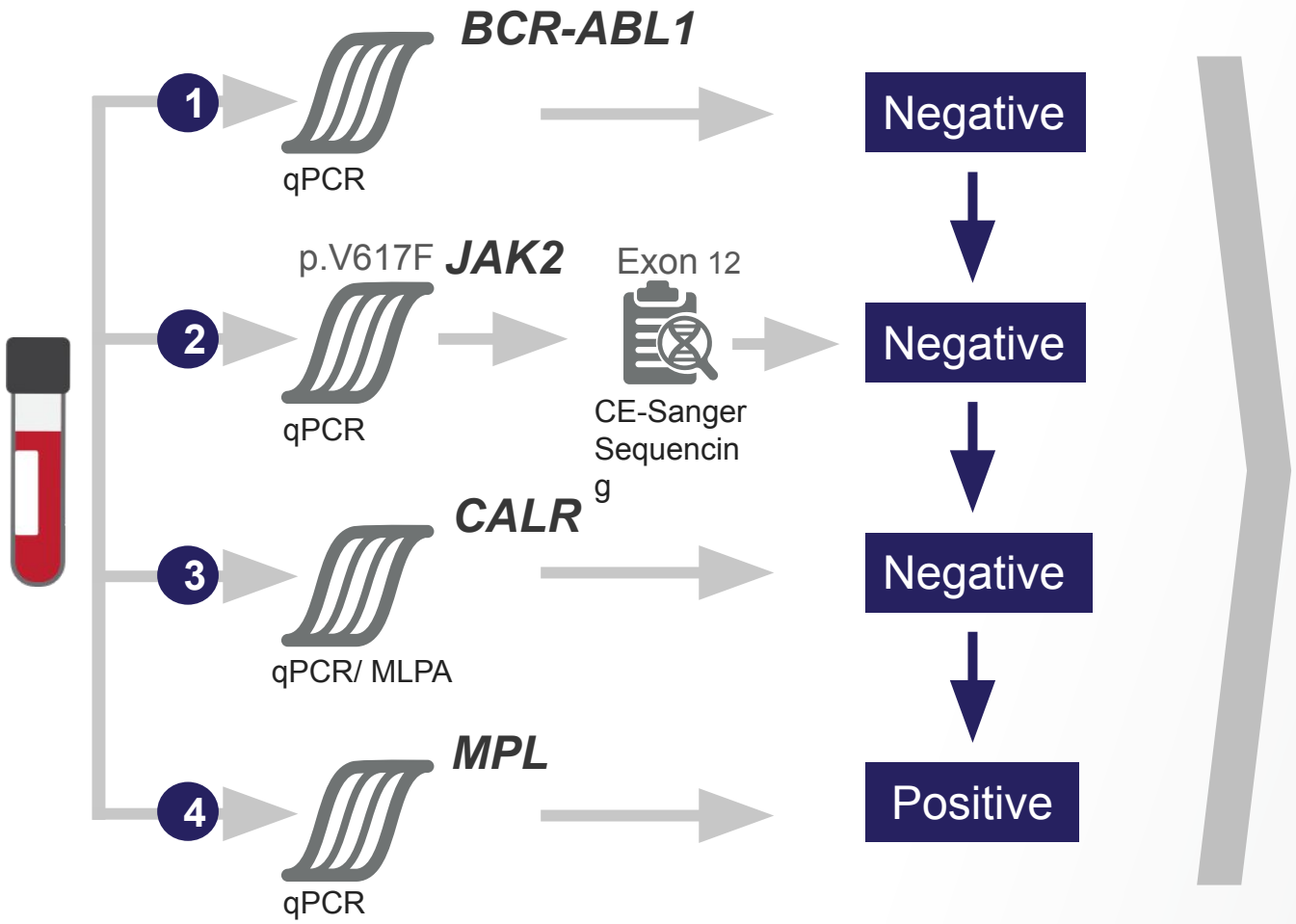
PML-RARA	*RUNX1*
FLT3-ITD	*BCR-ABL*
CALR	*JAK2*
KIT	*IDH1*
TP53	*IDH2*
NPM1	*MPL*
ASXL1	STAG2
CBFB-MYH11	*DEK-NUP214*
KMT2A	*MECOM*
NUP98	CEBPA
DDX41	*SF3B1*
SRSF2	+ more

Diagnostic yield

Myeloproliferative neoplasms (MPN) molecular testing needs to be all-encompassing at the first pass-one

Traditional sequential biomarker testing strategy

MPN sequential testing



Limitations of sequential biomarker testing:

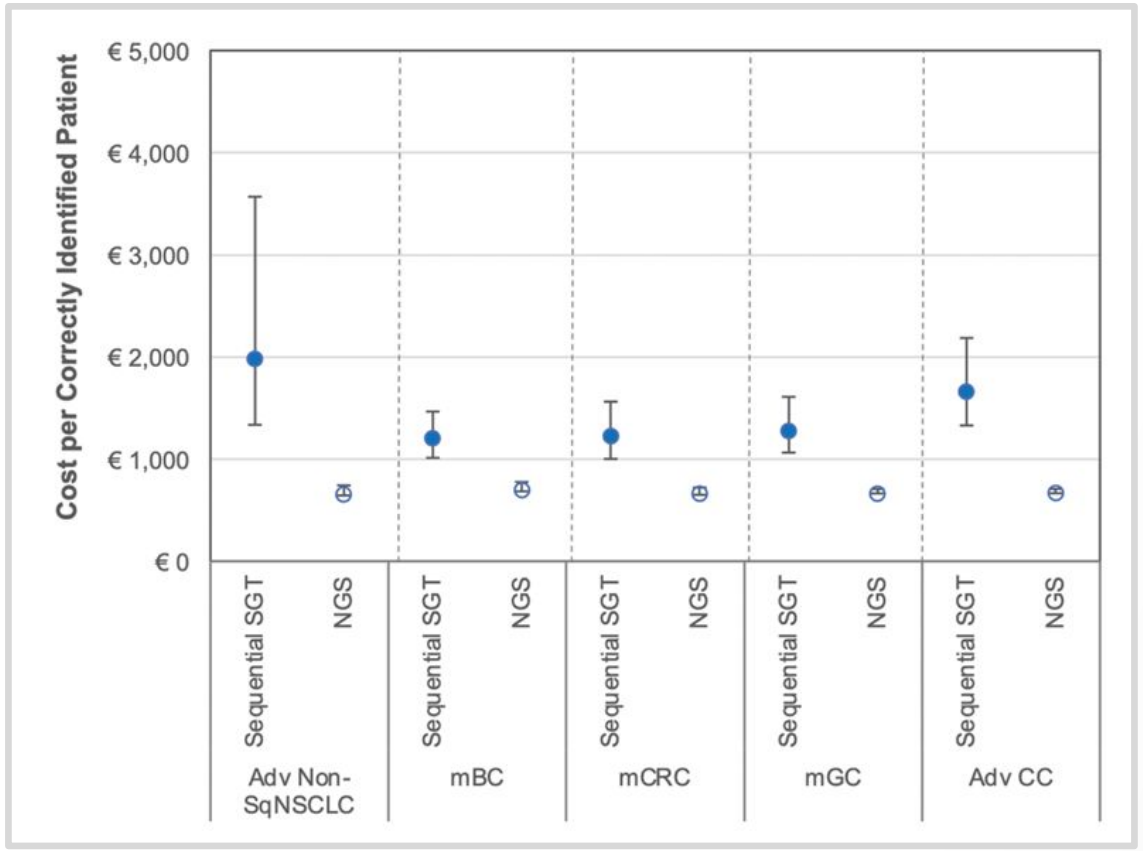
- **increases labor and time** burden for labs
- can **miss co-occurring mutations**

Coexisting *JAK2* and *CALR* variants were reported
(frequency non-accurate, <1% to 6.8%)

Vannucchi AM, Guglielmelli P, Hematology Am Soc Hematol Educ Program 2022 (doi:10.1182/hematology.2022000339)
Haberichter K et al. CAP TODAY 2019

NGS identifies more patients in a more cost-efficient manner

NGS is more cost efficient than single-gene testing[2]



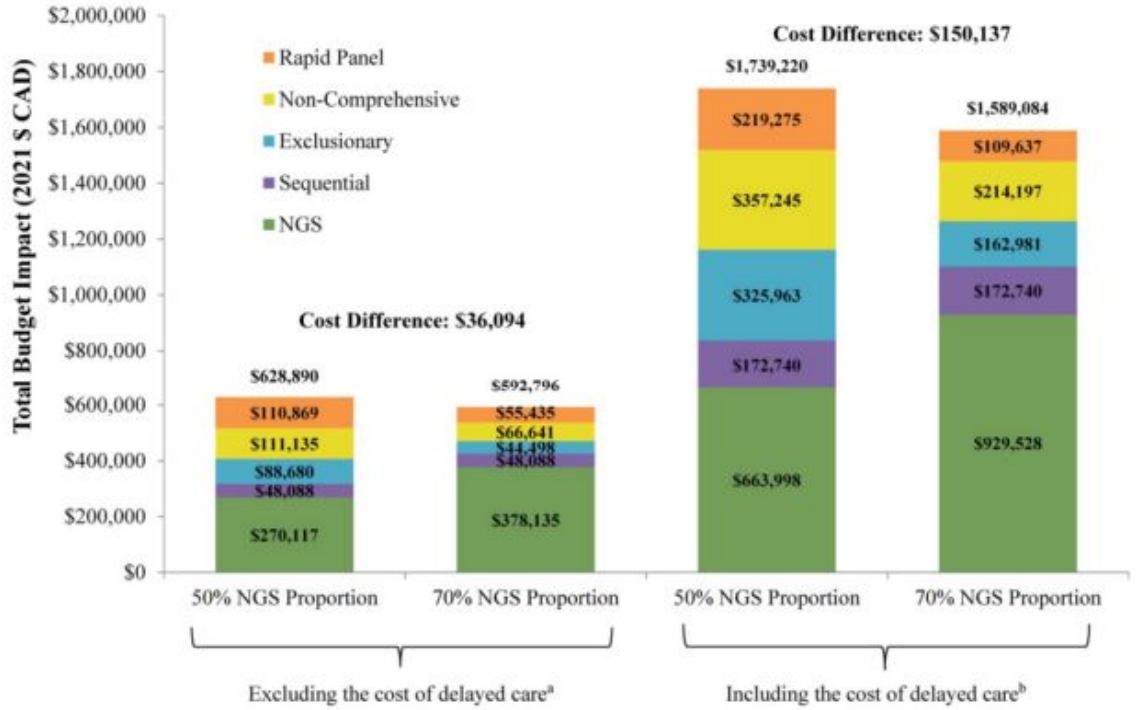


Figure 2. Total budget impact of increasing the proportion of patients tested with NGS from 50% to 70%. **Abbreviations:** NGS = next-generation sequencing. **Notes**: a. Costs include gene testing costs, rebiopsy costs, costs for interventional radiologist and oncologist visits, and costs of PD-L1 testing. b. Total costs include genetic testing costs, medical costs associated with testing, and estimated costs of delayed care. The estimated costs associated with delaying treatment were calculated as the time to initiation of appropriate targeted therapy times estimated weekly cost during the pre-diagnosis phase.

Compared to Single-gene testing, NGS identifies more patients positive for actional biomarkers and potentially reduces the economic burden on the healthcare system[1,2]

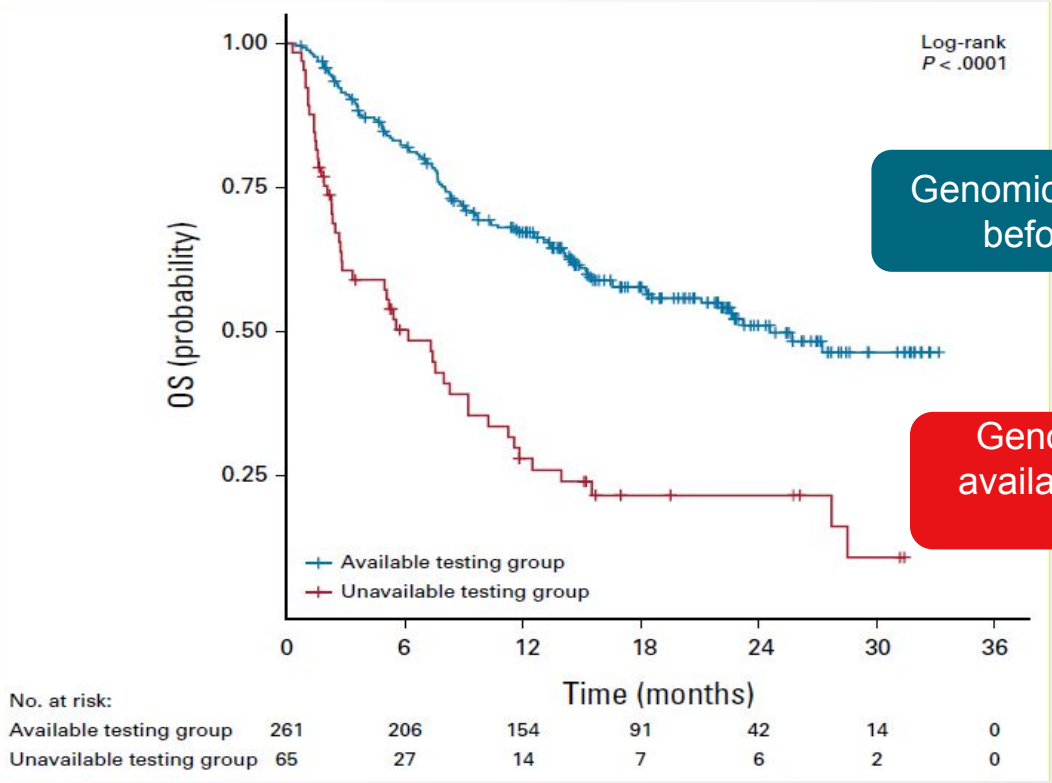
1. Sheffield BS et al.Curr. Oncol. 2023 (doi:10.3390/curroncol30020180)
2. 2023 Publ in The Oncolist, Genomic Testing Cost Calculator Stenzinger A. Et al., The Oncologist, 2023, 28, e242-253

Patient survival is positively influenced by timely genomic testing

Patients with genomic profile available for 1st line therapy decision have **4x longer median overall survival (aNSCLC)**

80% (n=261)genomic profile **available** before 1L
Median overall survival **24.6 months**

20% (n=144) **unavailable** before 1L
Median overall survival **6.2 months**



Genomic profile available before treatment

Genomic Profile Not available for treatment decision

Figure: association between availability of molecular genotyping results and overall survival in patients with advanced nonsquamous non–small-cell lung cancer[1]

Patients treated based on molecular test results have better clinical outcomes

1. Aggarwal C et al. JCO Precis Oncol 2023 (doi:10.1200/PO.23.00191)

Long turnaround times result in suboptimal outcomes

Turn-around time (TAT) is a key factor for therapy initiation and clinical trials recruiting

The Problem

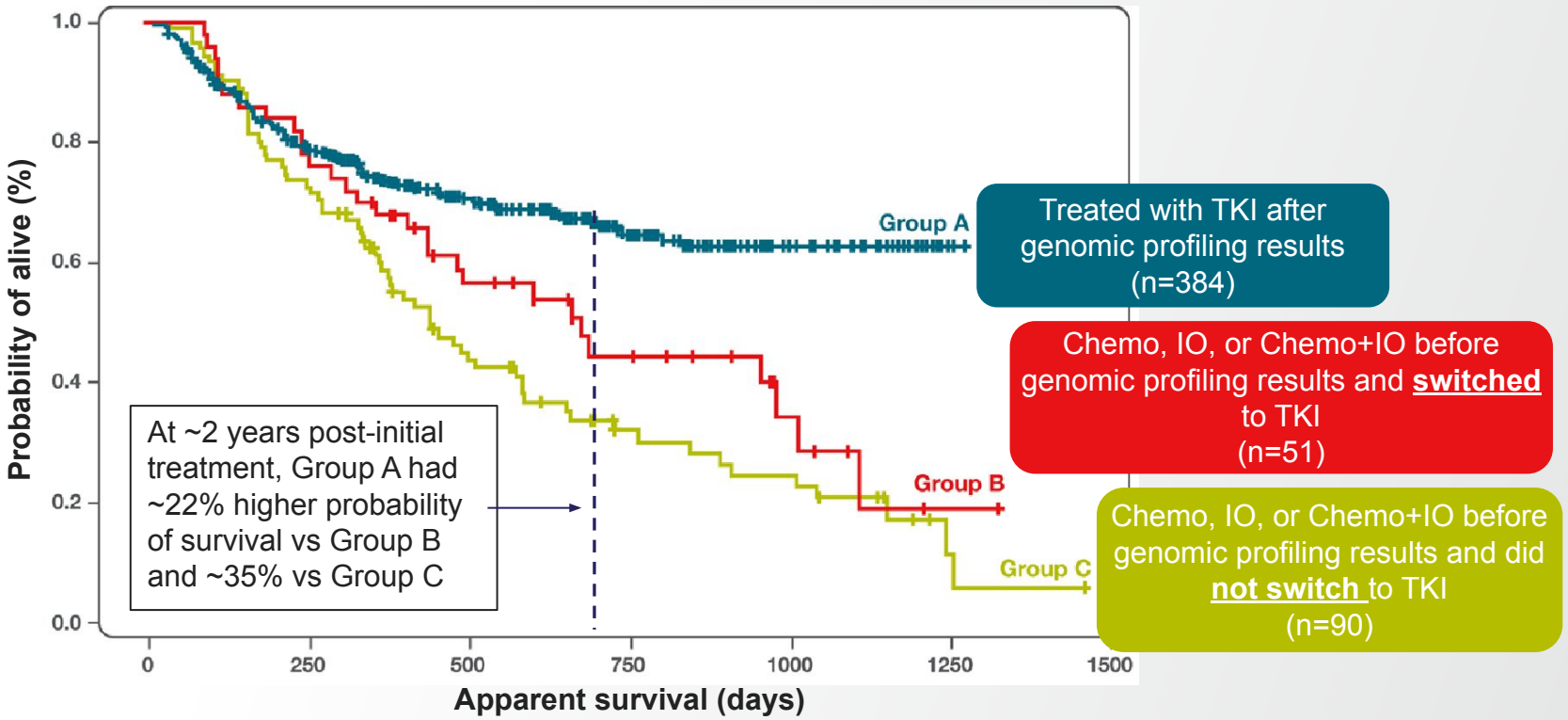
22.4 days

Average TAT of NGS-based tumor biomarker results in U.S.[1]

The Consequences

27%

NSCLC patients are treated *before* molecular profiling results are delivered.[2]



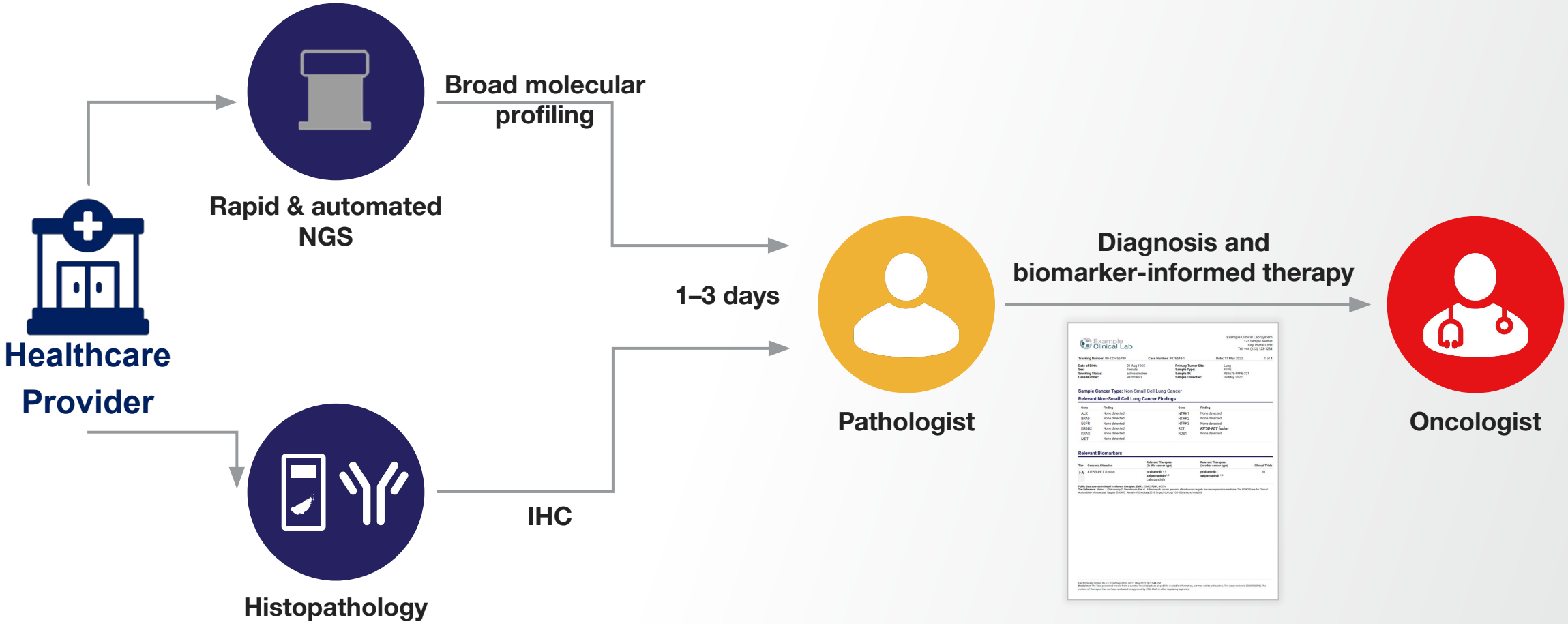
Patients treated based on molecular test results have better clinical outcomes[2] – but results are needed faster, closer to the patient.

TAT: turn-around time; NGS: next-generation sequencing, NSCLC: non-small cell lung cancer

1. Smith RE et al., AMP 2021-Poster ST59 ; 2. Smith RE, et al., J Clin Oncol 40, 2022 suppl 16; abstr 1530

Your path to democratizing access to NGS testing

Rapid and easy-to-use point-of-care NGS can help to enable broad access to molecular profiling



Adapted from Sheffield BS et al. (2022). Current Oncology, 29(3), 1326–1334.

Thank you