Rapidly evolving biomarker landscape – tools to keep pace

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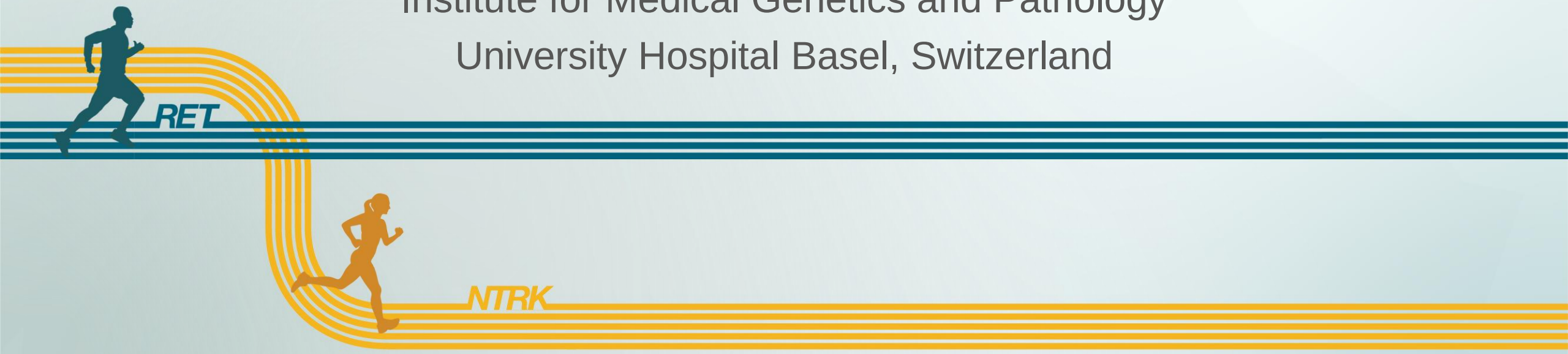
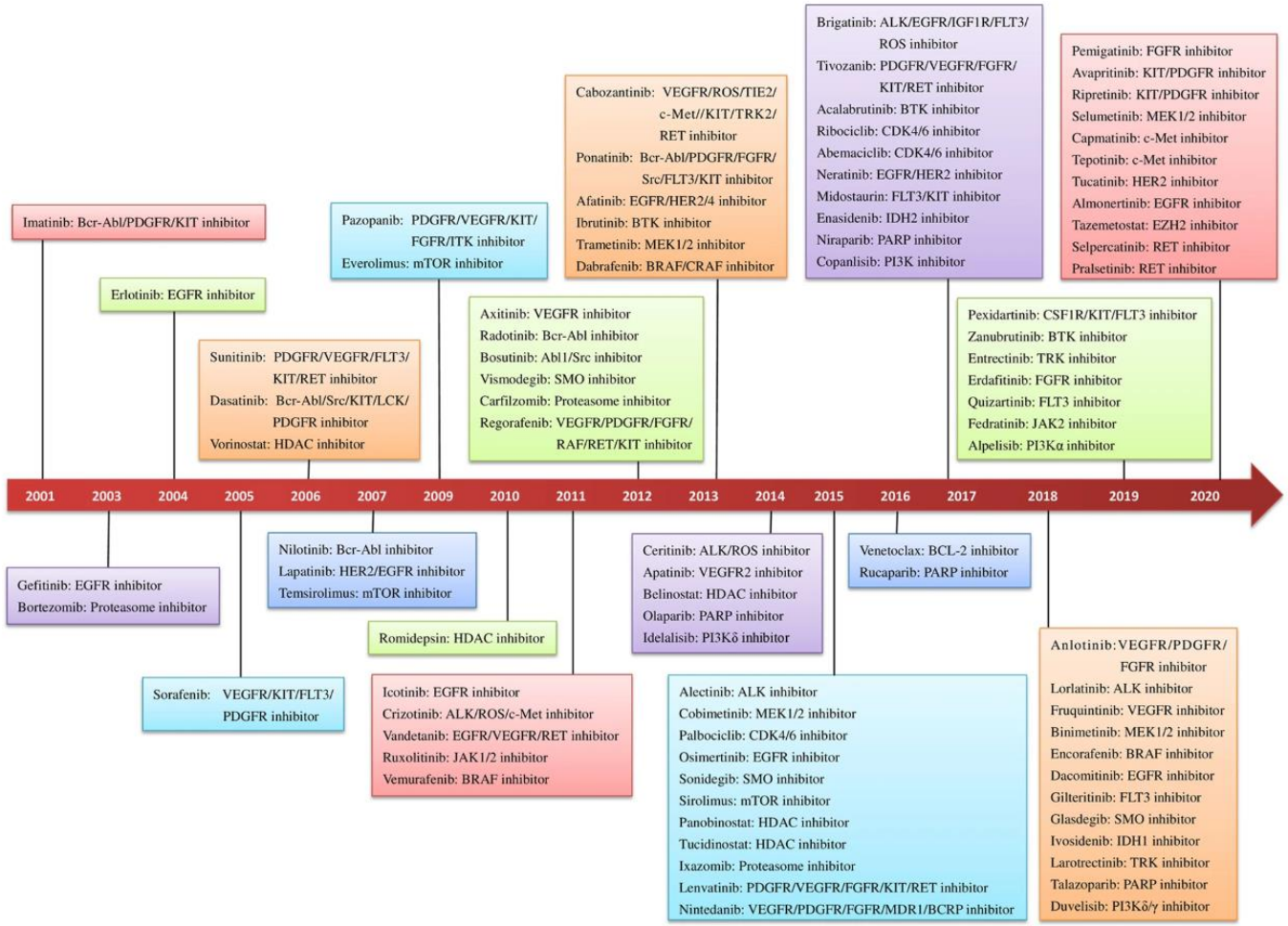
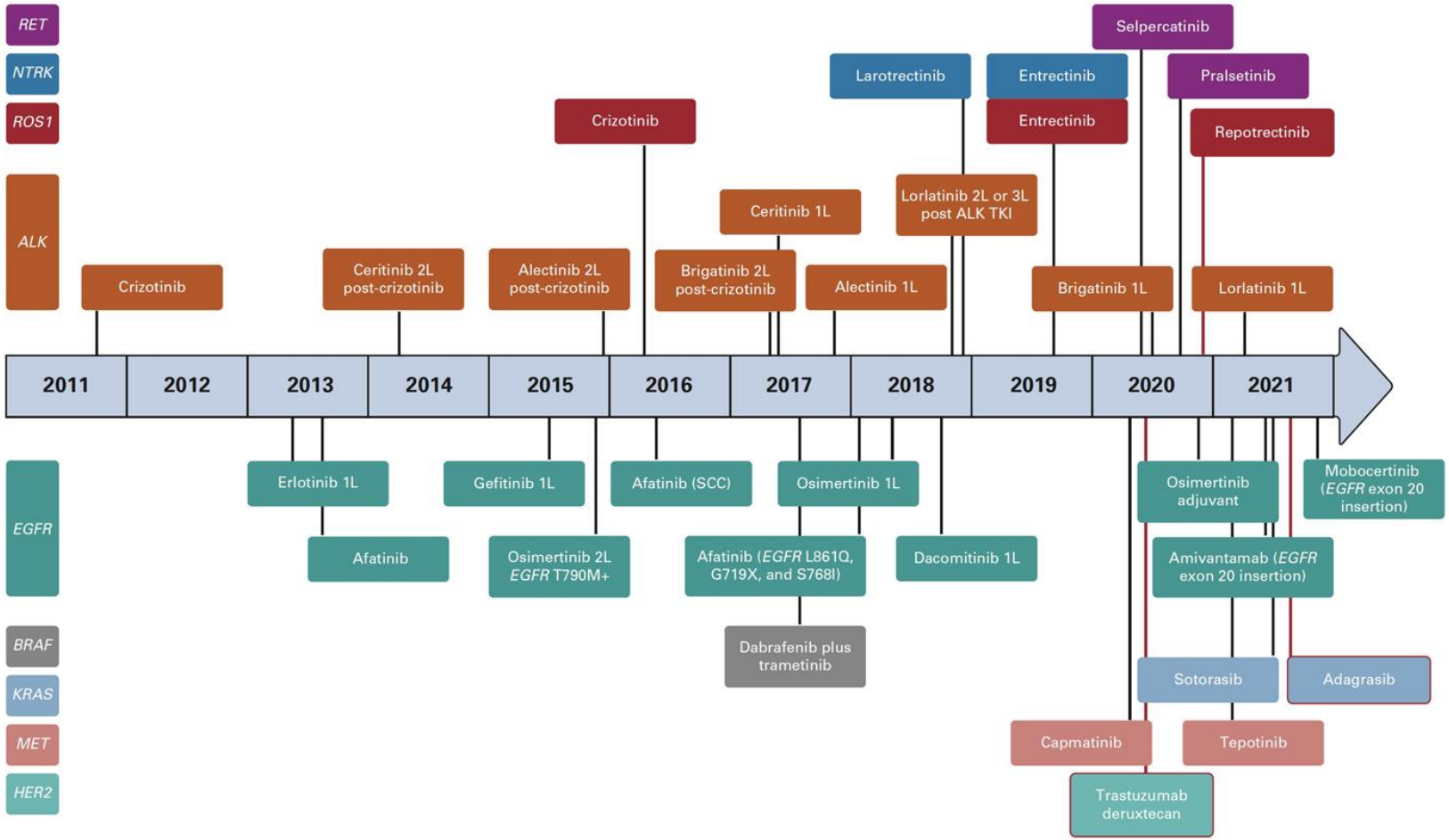


Timeline of FDA-Approved Targeted Therapies



Zhong L, et al. *Signal Transduct Target Ther* 2021;6:201.

Timeline of FDA-Approved Targeted Therapies in NSCLC



Tan AC, et al. *J Clin Oncol* 2022;40:611–25.

Approvals & Clinical Practice Guidelines in Oncology[1,2]

Example: nsNSCLC

The **Musts**

EGFR mutations (15%)
KRAS G12C mutation (15%)
METex14 (3%)
BRAF V600E mutation (1%)
HER2 mutation (1%)
ALK rearr. (3%)
ROS1 rearr. (1-3%)
NTRK rearr. (0.2%)
RET rearr. (1-2%)

The **Shoulds**

MET amplification (2%)

Broad molecular profiling (NGS)

1. Ettinger D, et al. *J Natl Compr Canc Netw* 2022;20:497–530; 2. Mosele F, et al. *Ann Oncol* 2020;31:1491–505.

ESMO Recommendations for NGS for Patients With Metastatic Cancers

NGS indicated
Lung adenocarcinoma
Colon cancer
Prostate cancer
Cholangiocarcinoma

Ovarian cancer (BRCA1/2)
CUP (large panels)
TMB in various cancer types

No current indication
Breast, Gastric,
Pancreatic, Liver,
others not mentioned

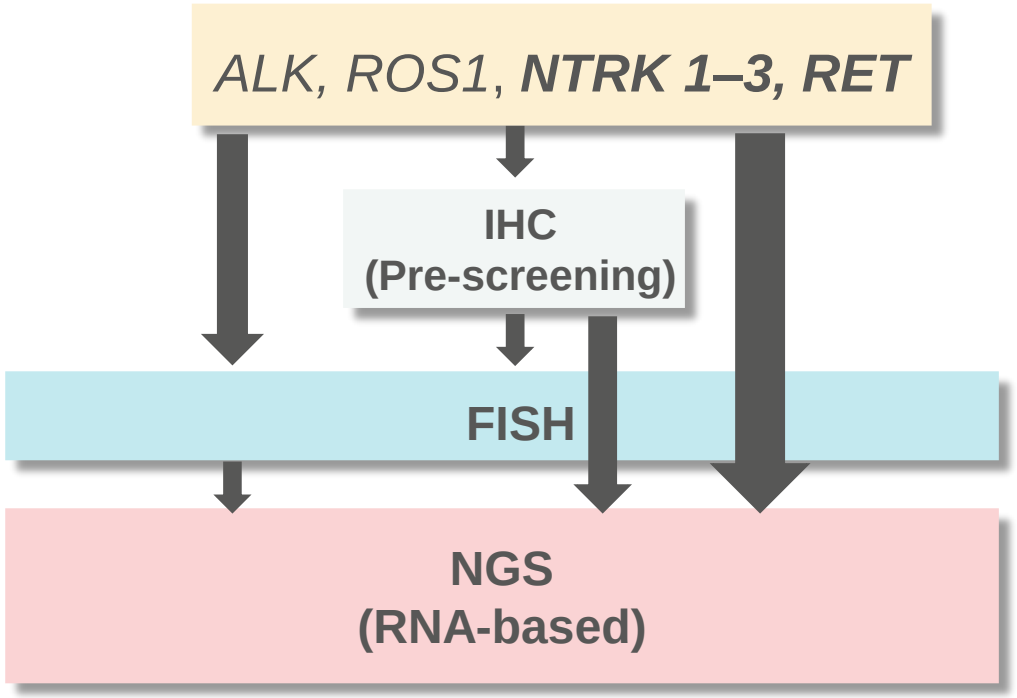
Exceptions for large panel testing
Clinical Research Centers
Informed individual patients

Cost issues
Size of NGS panels
Agreement with payers

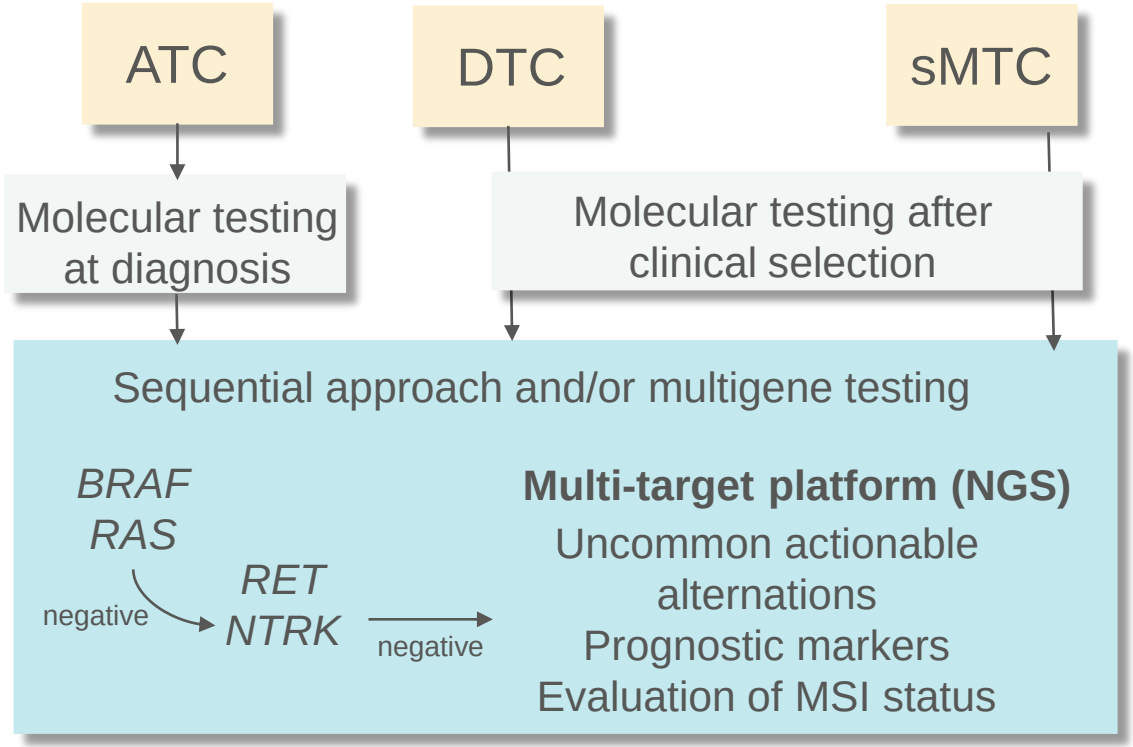
Mosele F, et al. *Ann Oncol* 2020;31:1491–505.

Testing for Rearrangements

Algorithm for molecular diagnostics of predictive markers in NSCLC[1–3]



Algorithm for molecular diagnostics of predictive markers in thyroid cancer[4]



1. Matter MS, et al. *Transl Lung Cancer Res* 2020;9:2645–55; 2. Belli C, et al. *Ann Oncol* 2021;32:337–50;
3. Marchiò C, et al. *Ann Oncol* 2019;30:1417–27; 4. Macerola E, et al. *Front Oncol* 2022;12:901004.

Methods for Biomarker Analysis

Histological subtype

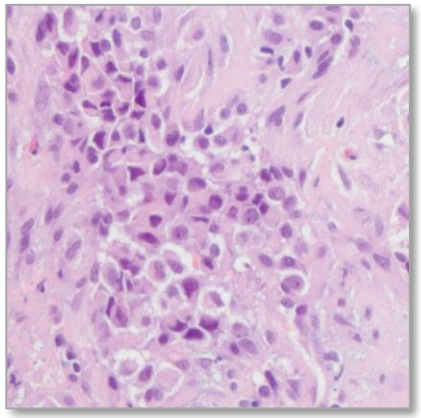
ALK/ROS1/NTRK/RET/MET/PD-L1

ALK/ROS1/RET/NTRK/MET

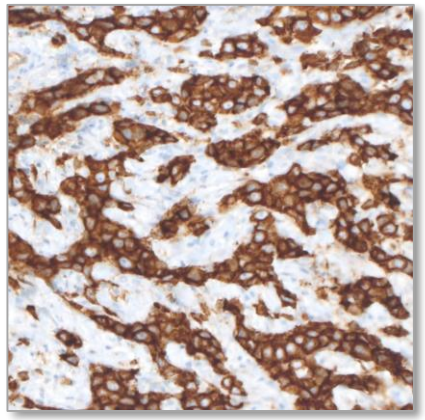
- Predictive mutations
- Rearrangements
- "Mutational burden"

- Resistant mutations
- Monitoring

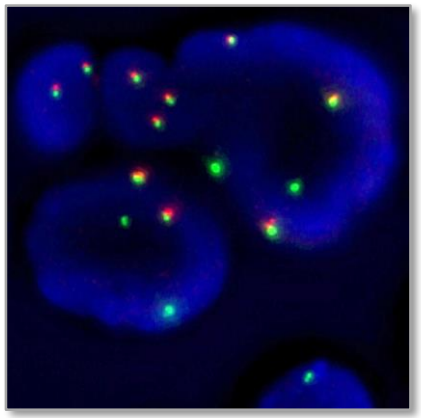
Histology/ cytology



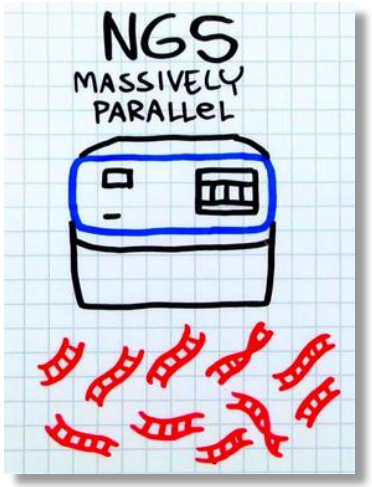
IHC



FISH



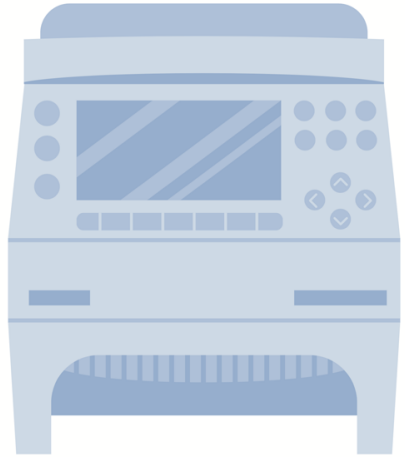
NGS (DNA/RNA)



Liquid biopsies (ctDNA)

Next Generation Sequencing (NGS)

- ‘High’ sensitivity in comparison with classic Sanger sequencing
- Analysis of 10–500 genes at a time (gene panels)
- 5–10 ng tumor DNA; ≈ 200 tumor cells
- 10–30 ng RNA: ≈ 500–1000 tumor cells (fusion → overexpression)
- (10%–) 20% tumor cell content



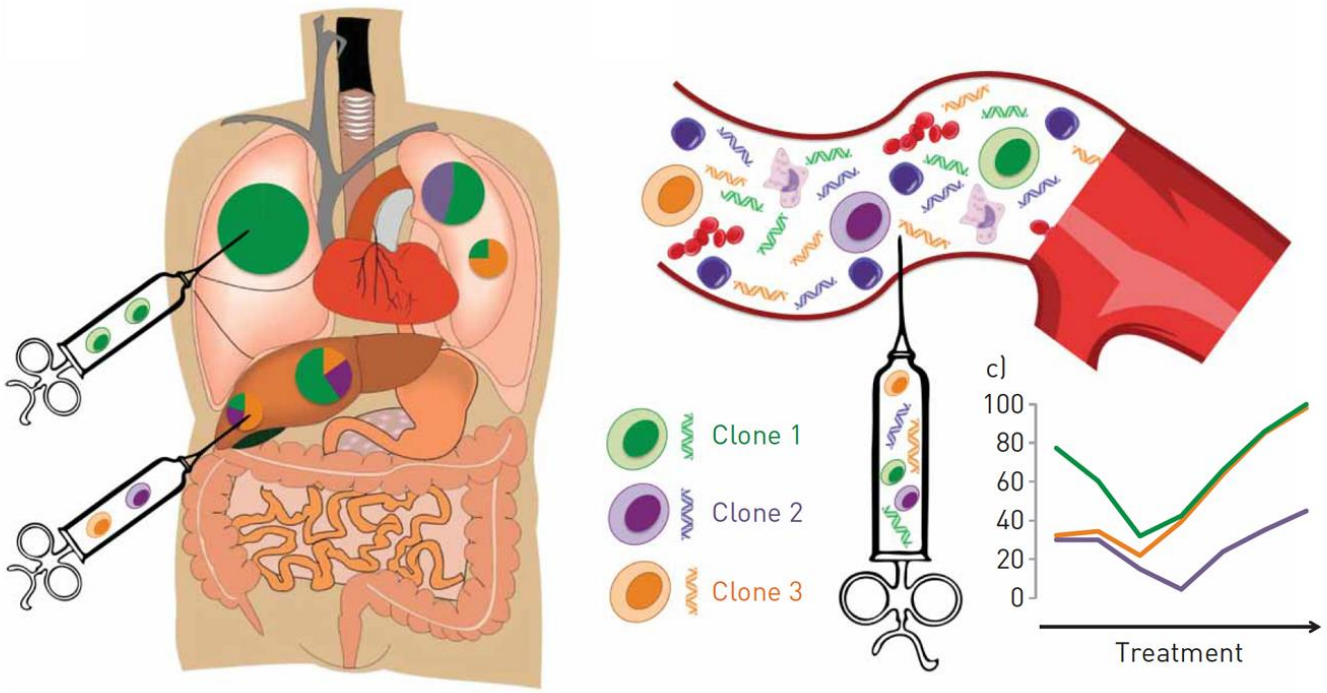
Fully Automated System Based on Real-Time PCR

- Advantages:
  - Real-time PCR-based
  - *EGFR*, *KRAS*, *BRAF* (40%)
  - Convenient
  - Affordable
  - Fast TAT (1–2 days)

- Disadvantages:
  - Not comprehensive
  - Tissue consumption
  - 50–60% negative results
  - → re-analyses

Liquid Biopsies (Plasma ctDNA)[1]

Capturing spatial and temporal heterogeneity[2]



Limited sensitivity (70–80%)

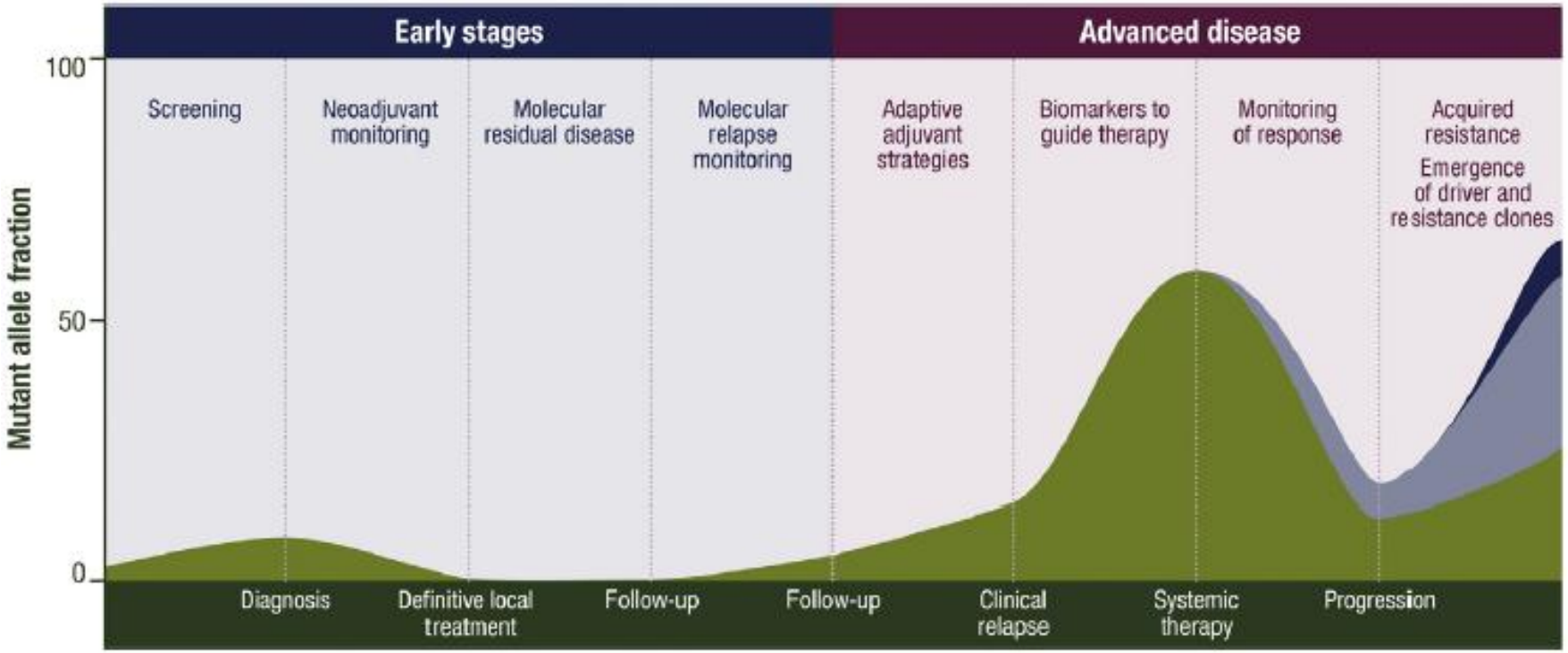
NGS panels:
Hybrid capture
Amplicon sequencing

Targeted assays:
ddPCR, Cobas, BEAMing

- Resistance mutations[3]
- "Plasma first" vs "tissue first"[4]
- Minimal residual disease
- Monitoring

1. Pascual J, et al. *Ann Oncol* 2022;33:750–68; 2. Guibert N, et al. *Eur Respir Rev* 2020;29:190052;
3. Schmid S, et al. *Lung Cancer* 2020;147:123–9; 4. Rolfo C, et al. *J Thorac Oncol* 2021;16:1647–62.

Clinical applications of ctDNA assays



Pascual J, et al. *Ann Oncol* 2022;33:750–68.

Take Home Messages

- Biomarker testing in cancer is a highly dynamic field
- Rapidly increasing number of predictive biomarkers
- Technical progress (e.g. NGS, cfDNA)
- Fit for the present and near future with the current tools
- Testing algorithms adapted to local situation (drug availabilities, reimbursement, economic situation)

The Power of Diagnostics

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