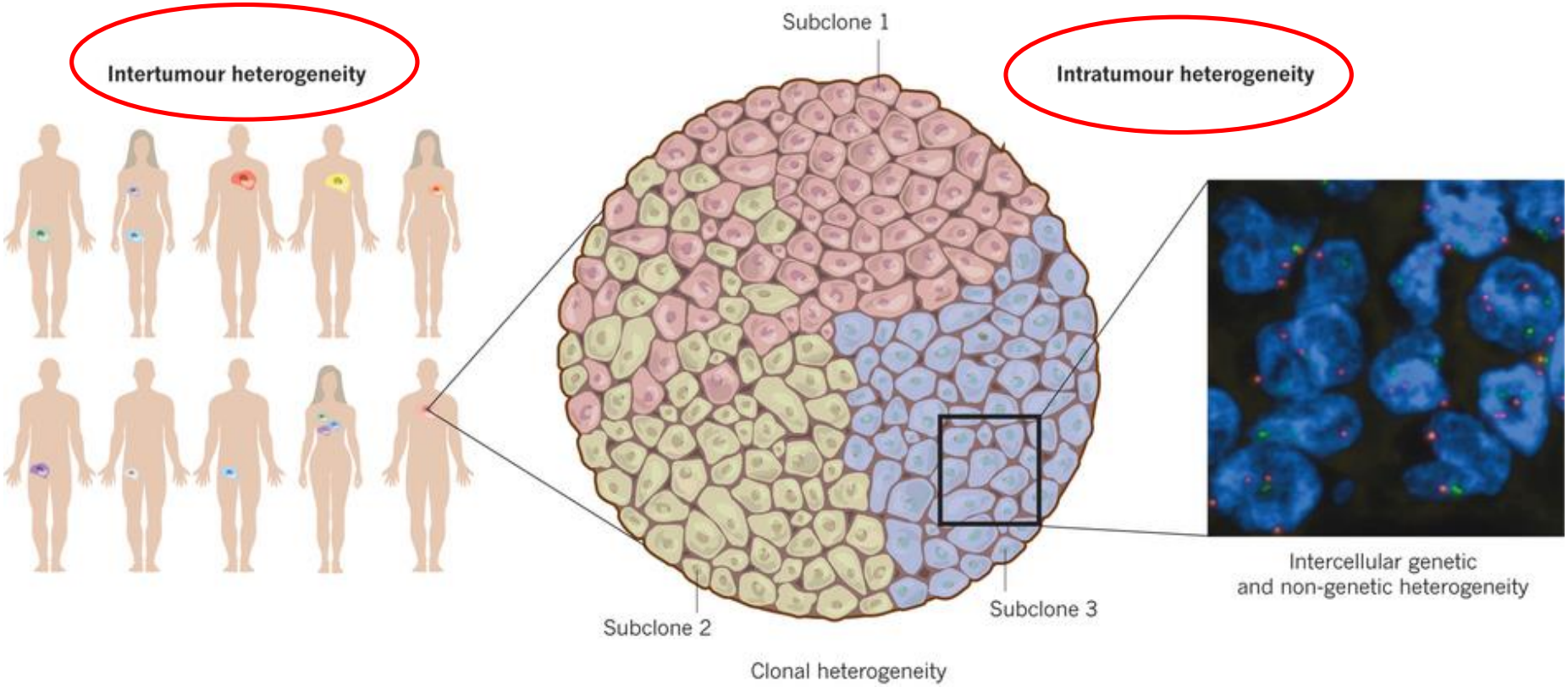
QUALI PERCORSI PER GARANTIRE STANDARDIZZAZIONE E RIPRODUCIBILITÀ DEI PROCESSI IN BIOLOGIA MOLECOLARE

Michelangelo Fiorentino
Laboratorio Unico di Patologia Molecolare dell'area Metropolitana di Bologna
Università di Bologna

Cancer is a heterogeneous disease



From Burrell RA Nature 2013

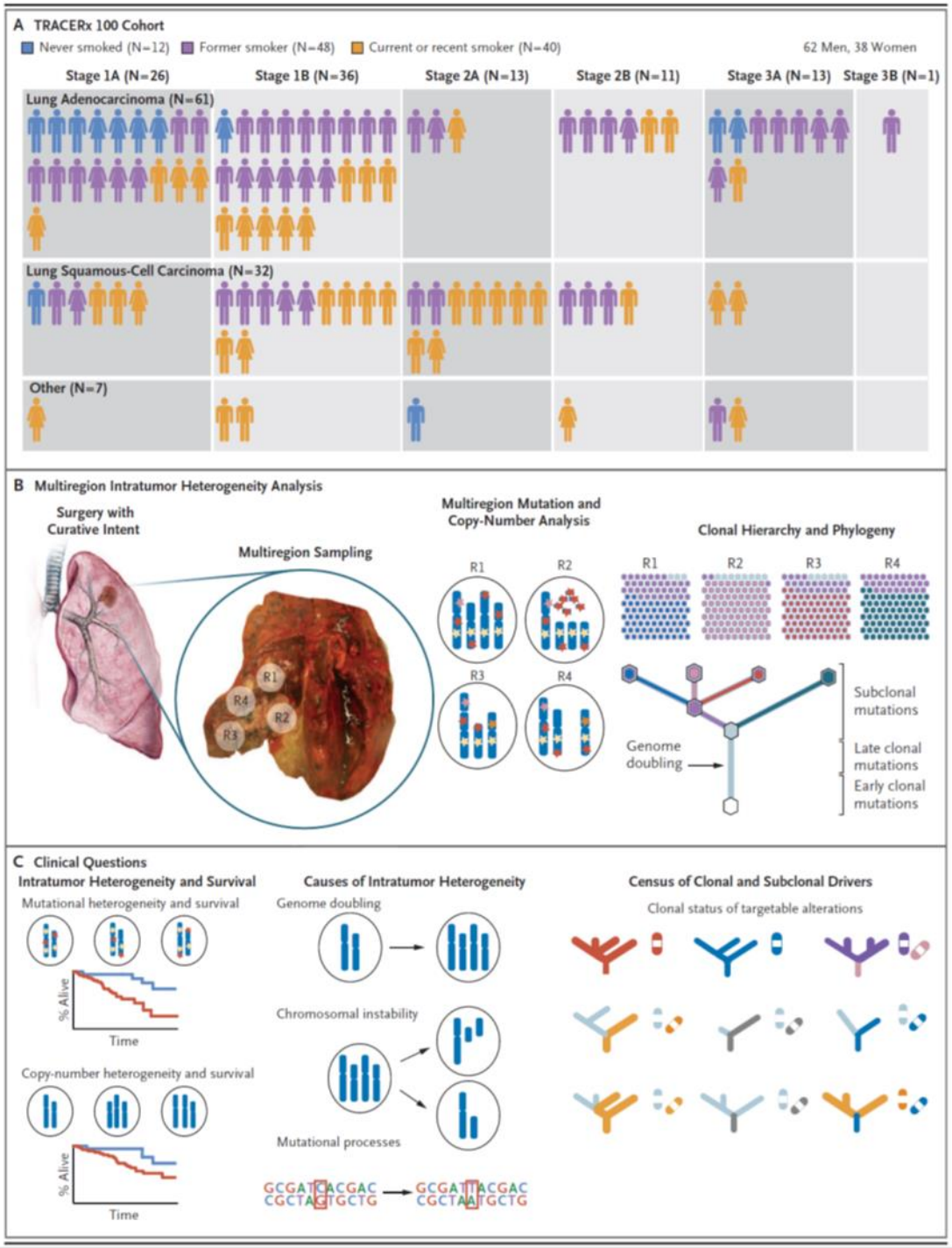
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

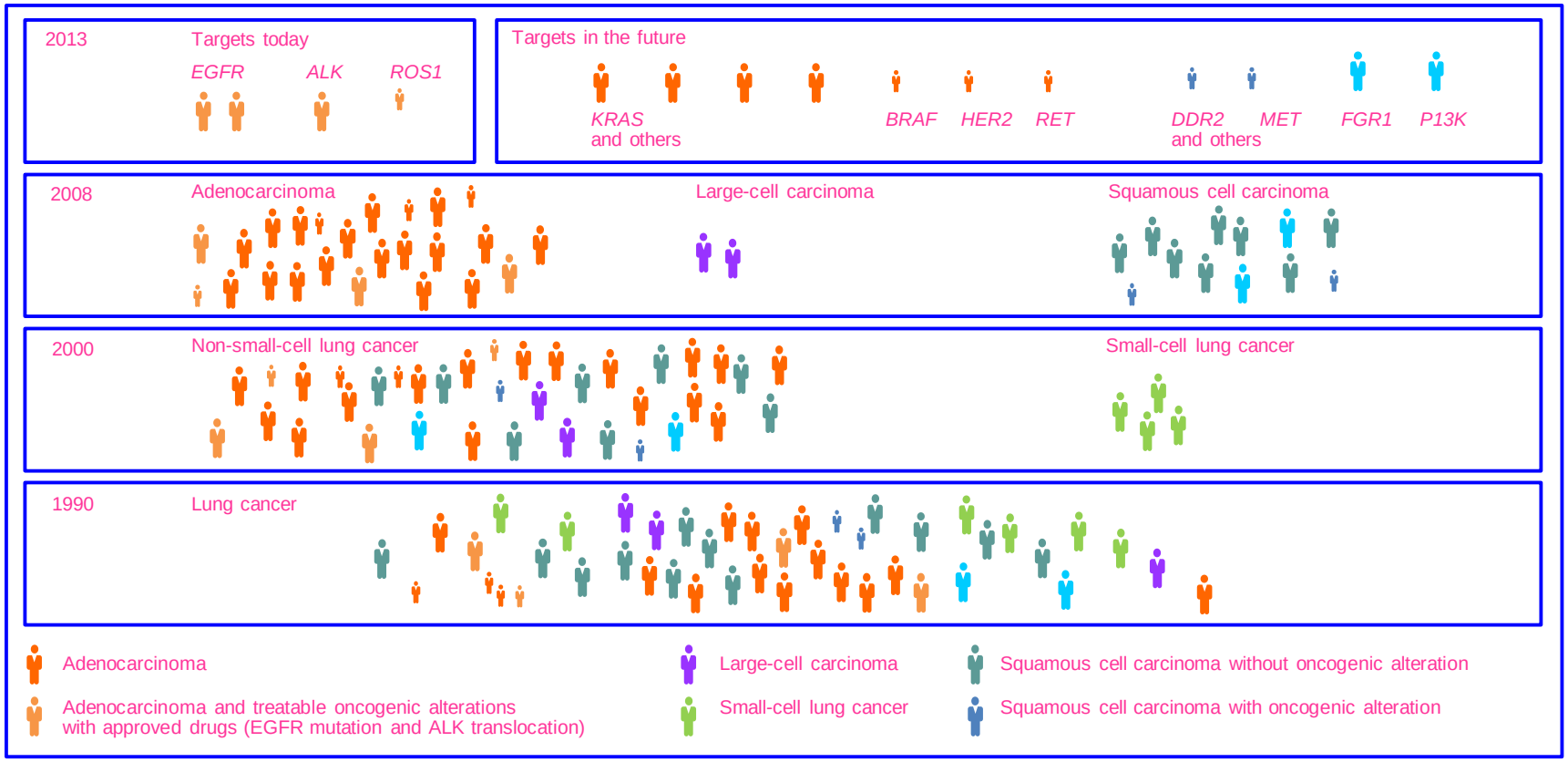
Tracking the Evolution of Non–Small-Cell Lung Cancer

M.Jamal-Hanjani, NEJM 2017:1-13

"Darwinian" evolution of tumor clones



Evolution of biological and pathological understanding in NSCLC



www.thelancet.com Vol 382 August 24, 2013

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2018
Non-Small Cell Lung Cancer
NCCN Evidence Blocks™

NCCN Guidelines Index
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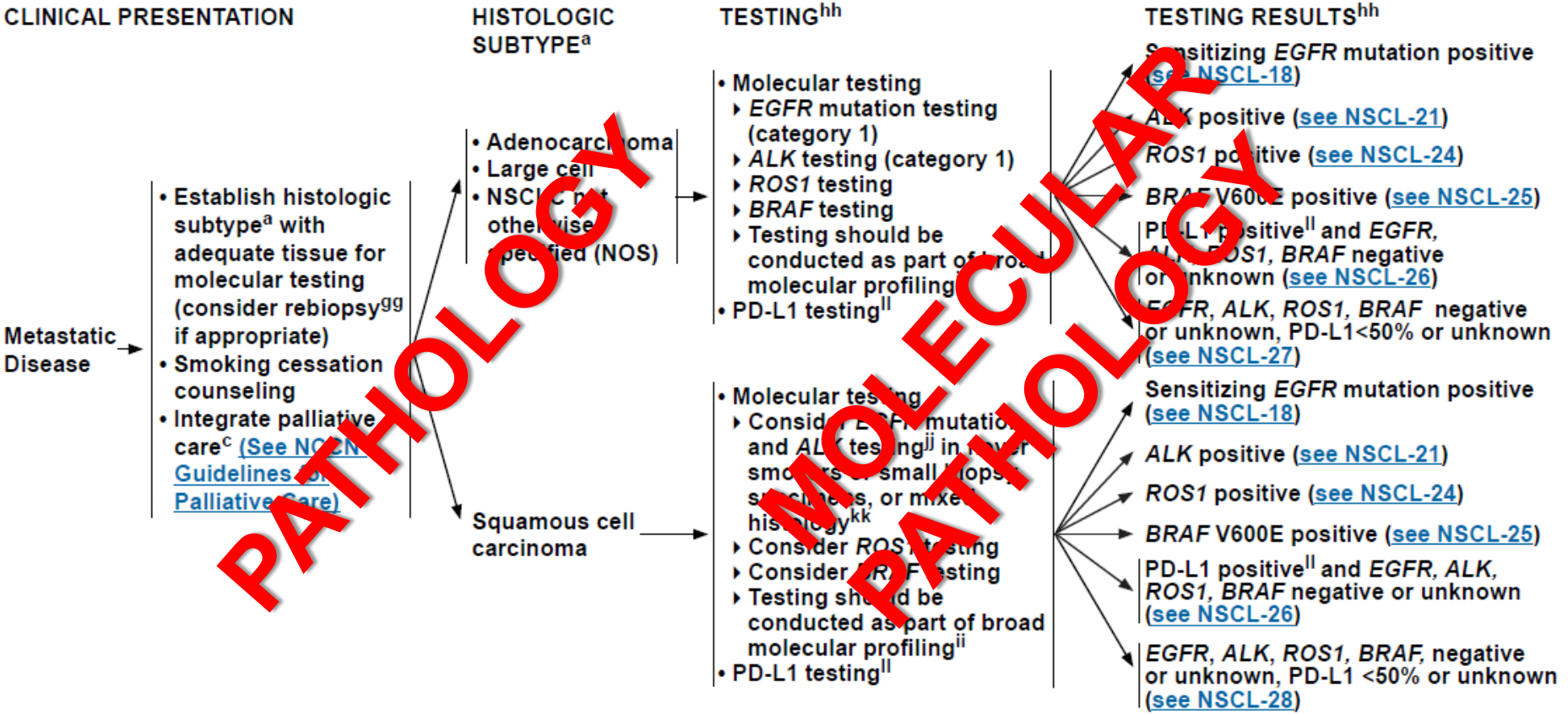
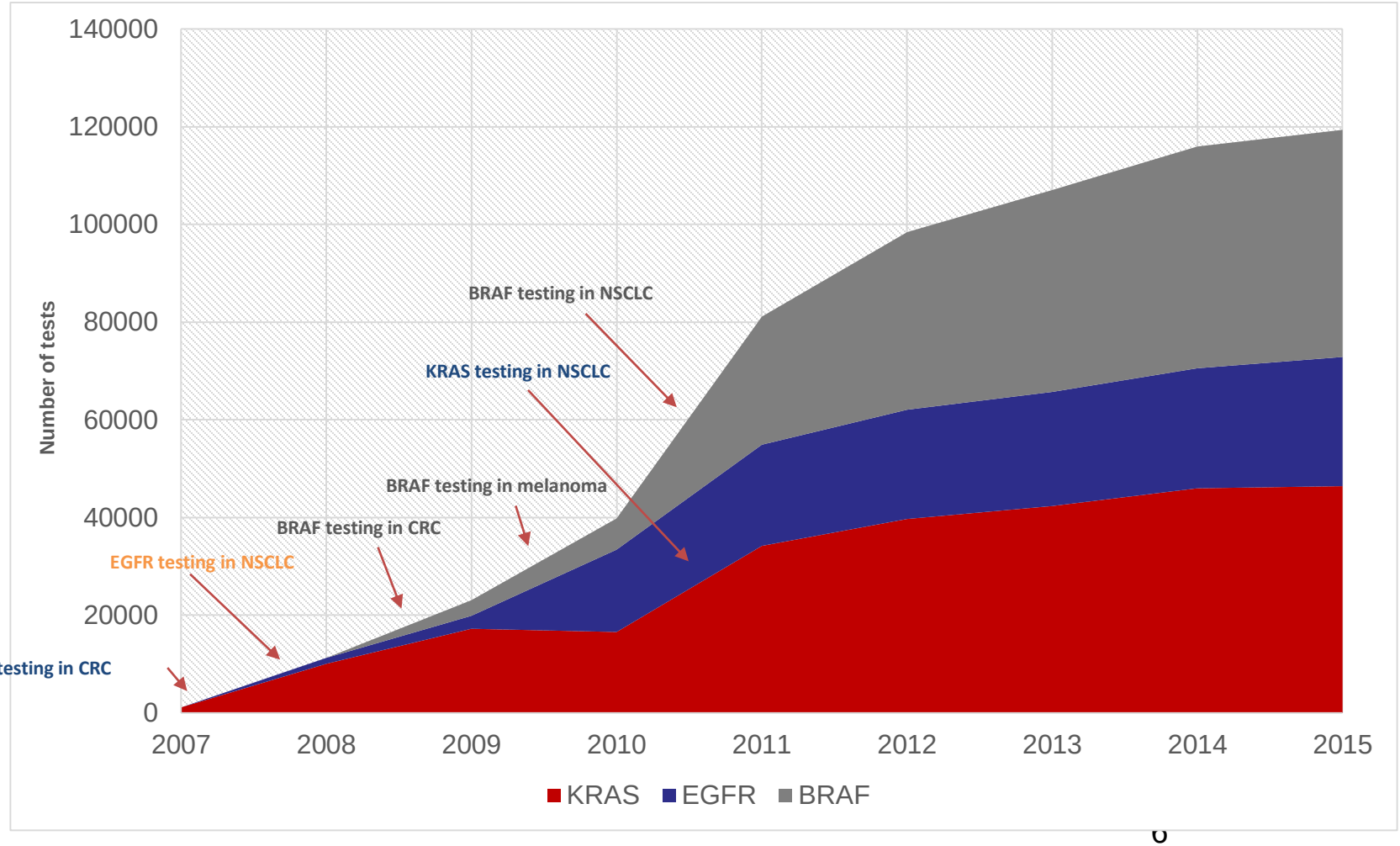
Discussion



Testing environment – EGFR, KRAS, BRAF

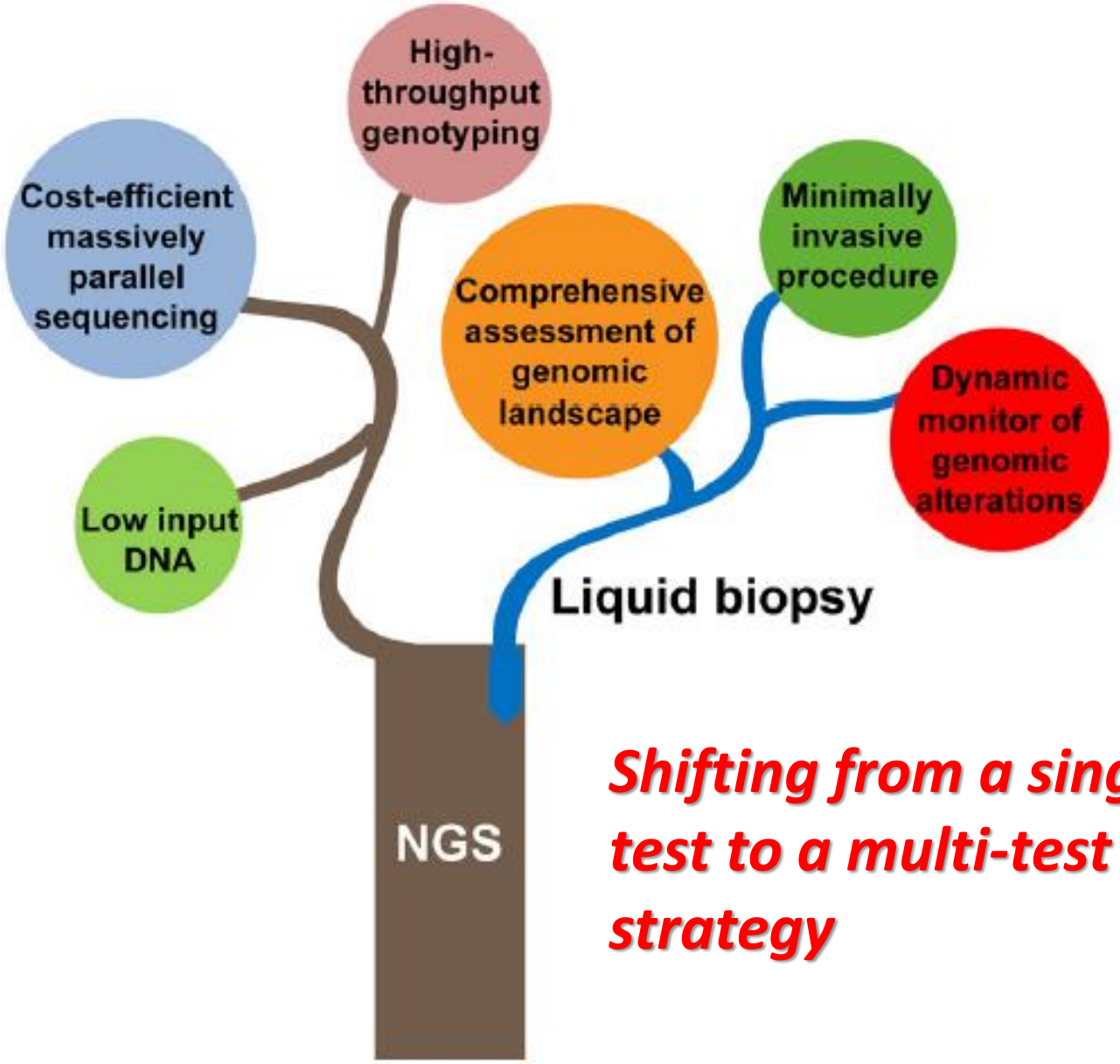
- **Evolution of EGFR, KRAS & BRAF testing in NSCLC, CRC and melanoma since 2007:**



Source: INCa

Solutions

- Rationalization of methodologies
- External Quality controls
- Establishment of Tumor Molecular Boards



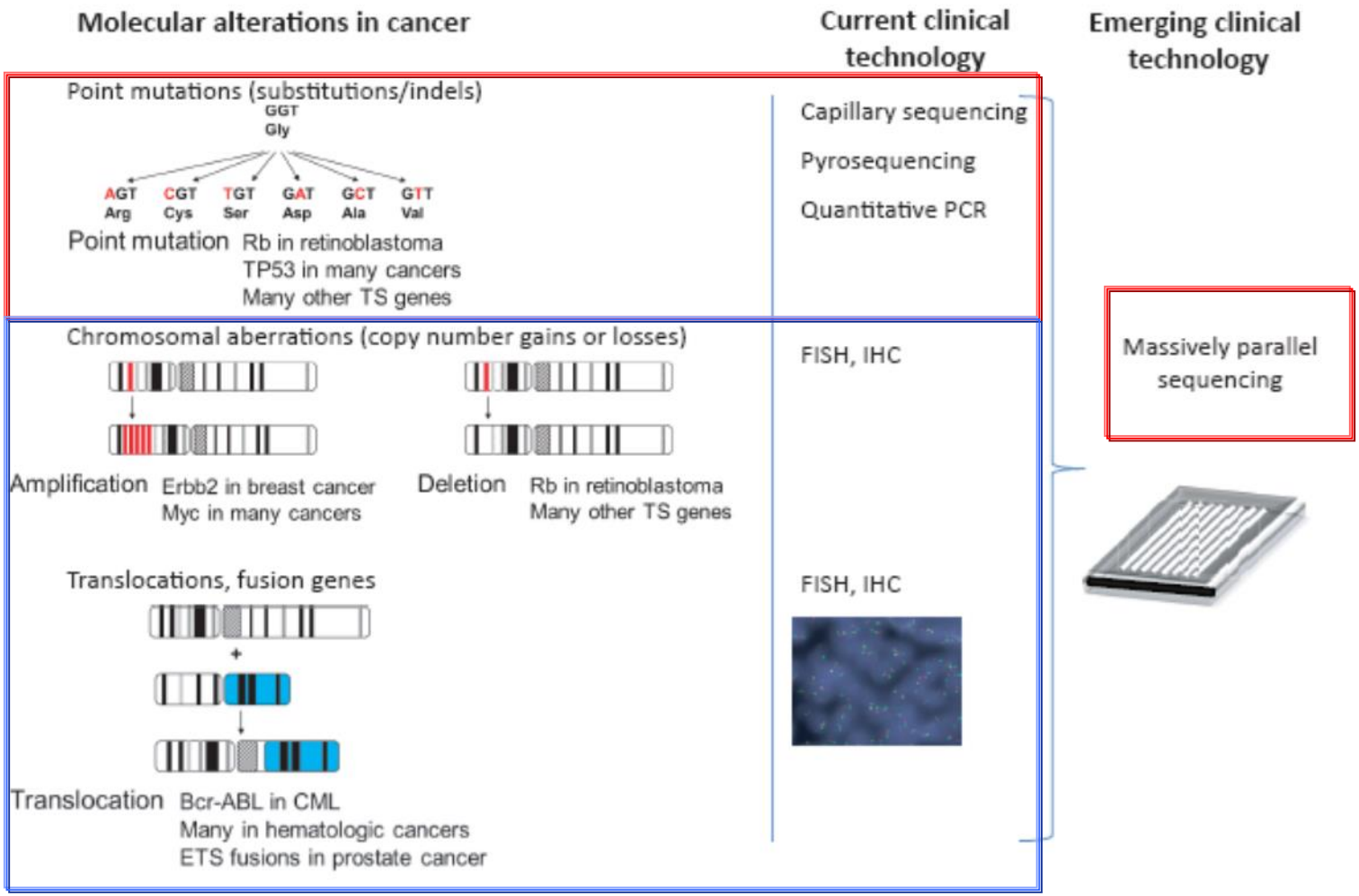
Shifting from a single-test to a multi-test strategy

Zhang J Hematol Oncol 2017

Next-Generation Sequencing (NGS) technologies

…..by the mid-2000s……

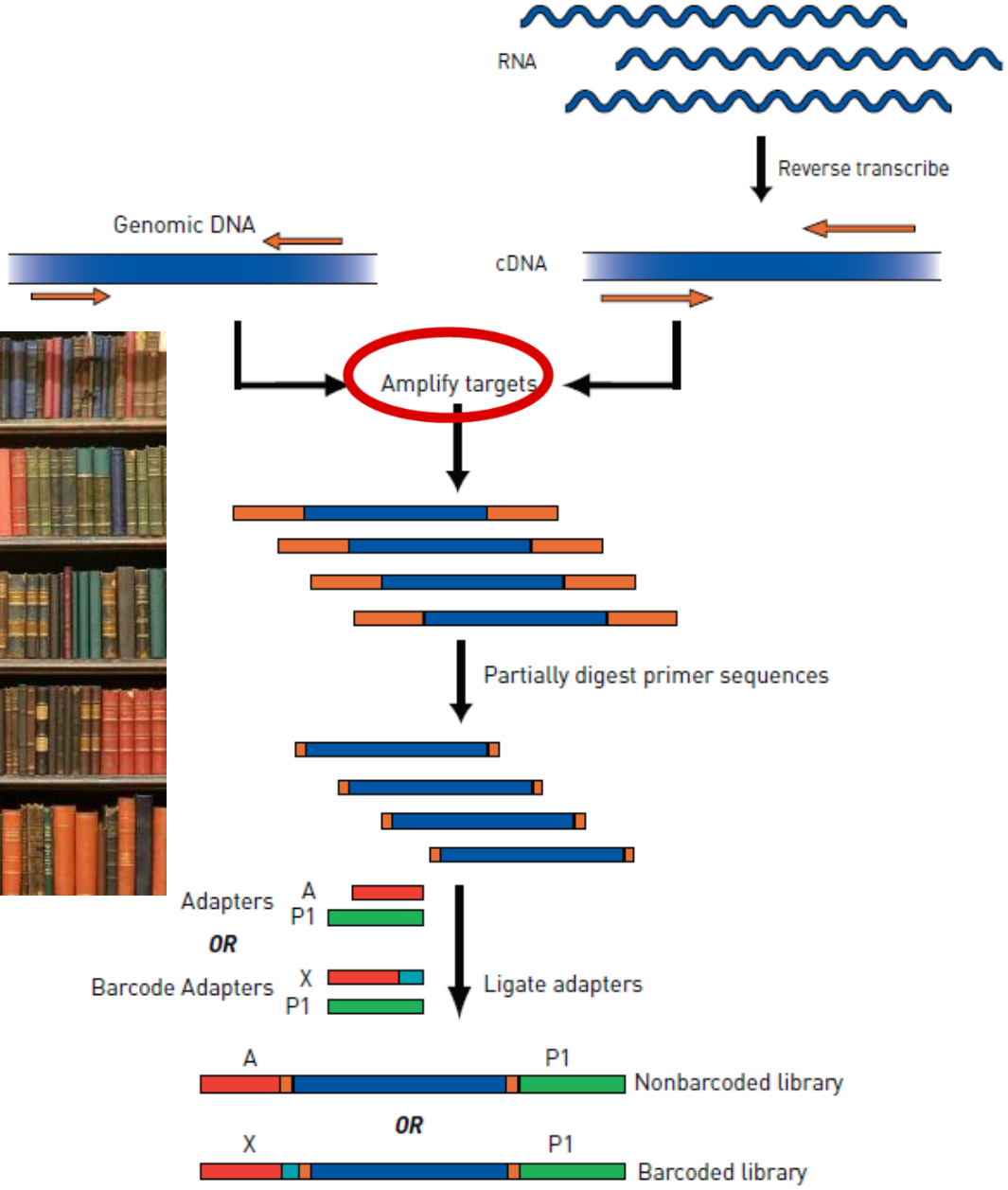
PAST SINGLE GENE STRATEGIES ARE MERGING INTO NGS PANELS



From MacConaill et al. Cancer Discovery 2011

LIBRARY PREPARATION FROM 10 ng DNA or RNA

a **library** is a collection of DNA/cDNA fragments

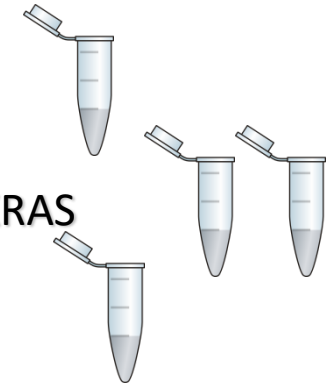


NGS and SANGER : different way of thinking

Sanger: Pz. 1 KRAS

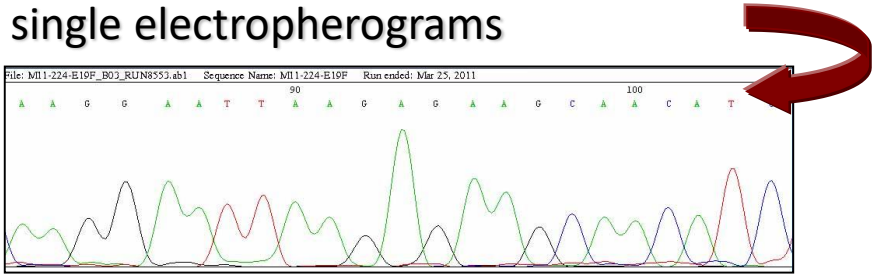
Pz 2 EGFR KRAS

Pz 3 BRAF



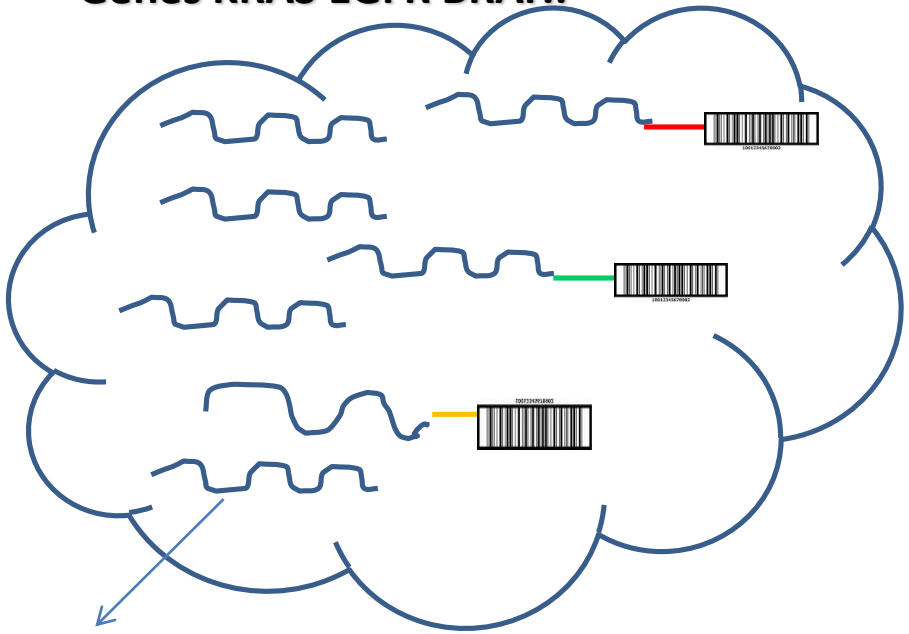
gDNA: single gene PCR mix reactions, purifications, seq PCR , purifications, CE……

single electropherograms



NGS: Pz. 1+ 2+3 → **Library**

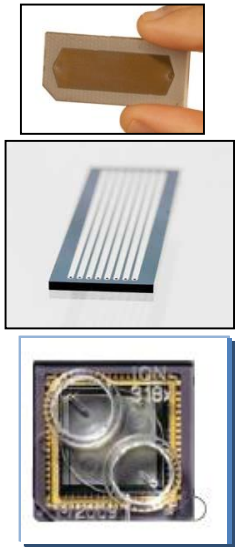
Genes KRAS EGFR BRAF..

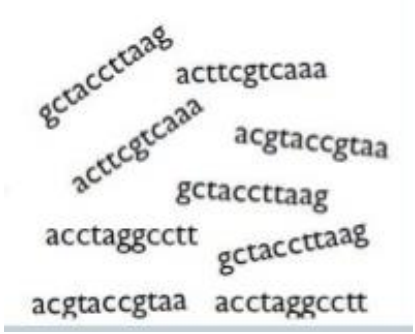


Amplicons or DNA fragments

NGS

platforms





STANDARDIZARION IN NGS SEQUENCING IS CHALLENGING

- **PRE-ANALYTICAL BIAS** (tumor enrichment) Allele fraction is impacted by tumor enrichment
- **ANALYTICAL BIAS** (choice of NGS assay methods) Differences in platform chemistries, technologies (probe capture versus PCR targeting), target gene selection
- **POST-ANALYTICAL BIAS** (Data analysis, mapping and variant calling), different software.
- **CLINICAL BIAS** (tumor Board attendants and composition and rules engine), evidence based decisions?

What is NCI-MATCH?

THIS PRECISION MEDICINE TRIAL EXPLORES TREATING PATIENTS BASED ON THE MOLECULAR PROFILES OF THEIR TUMORS

NCI-MATCH[1] IS FOR ADULTS WITH:

- solid tumors (including rare tumors), lymphomas, and myeloma
- tumors that no longer respond to standard treatment

ECOG-ACRIN cancer research group | NIH NATIONAL CANCER INSTITUTE

NATIONAL CANCER INSTITUTE

NCI-Children's Oncology Group Pediatric MATCH Trial*

This precision medicine clinical trial, funded by NCI and conducted by COG, matches children and adolescents with treatment based on genetic changes in their tumors.

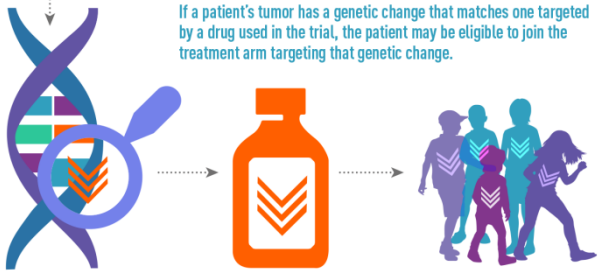
Pediatric MATCH is for patients ages 1 to 21 who have both:

- Solid tumors, including lymphomas and brain tumors, or histiocytoses
- Tumors that no longer respond to standard treatment or that have come back after treatment

ABOUT **200-300** PEDIATRIC PATIENTS ARE EXPECTED TO **BE SCREENED** EACH YEAR

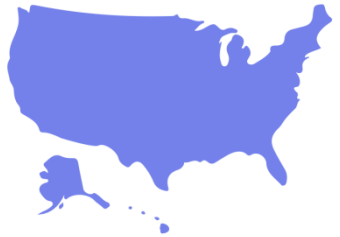
TUMOR TISSUE WILL UNDERGO TESTING FOR CHANGES IN MORE THAN 160 GENES

If a patient's tumor has a genetic change that matches one targeted by a drug used in the trial, the patient may be eligible to join the treatment arm targeting that genetic change.



Talk with your pediatric oncologist about whether this trial would be an option for your child.

THE TRIAL IS OFFERED IN THE U.S. AT ABOUT **—200—** CHILDREN'S ONCOLOGY GROUP SITES

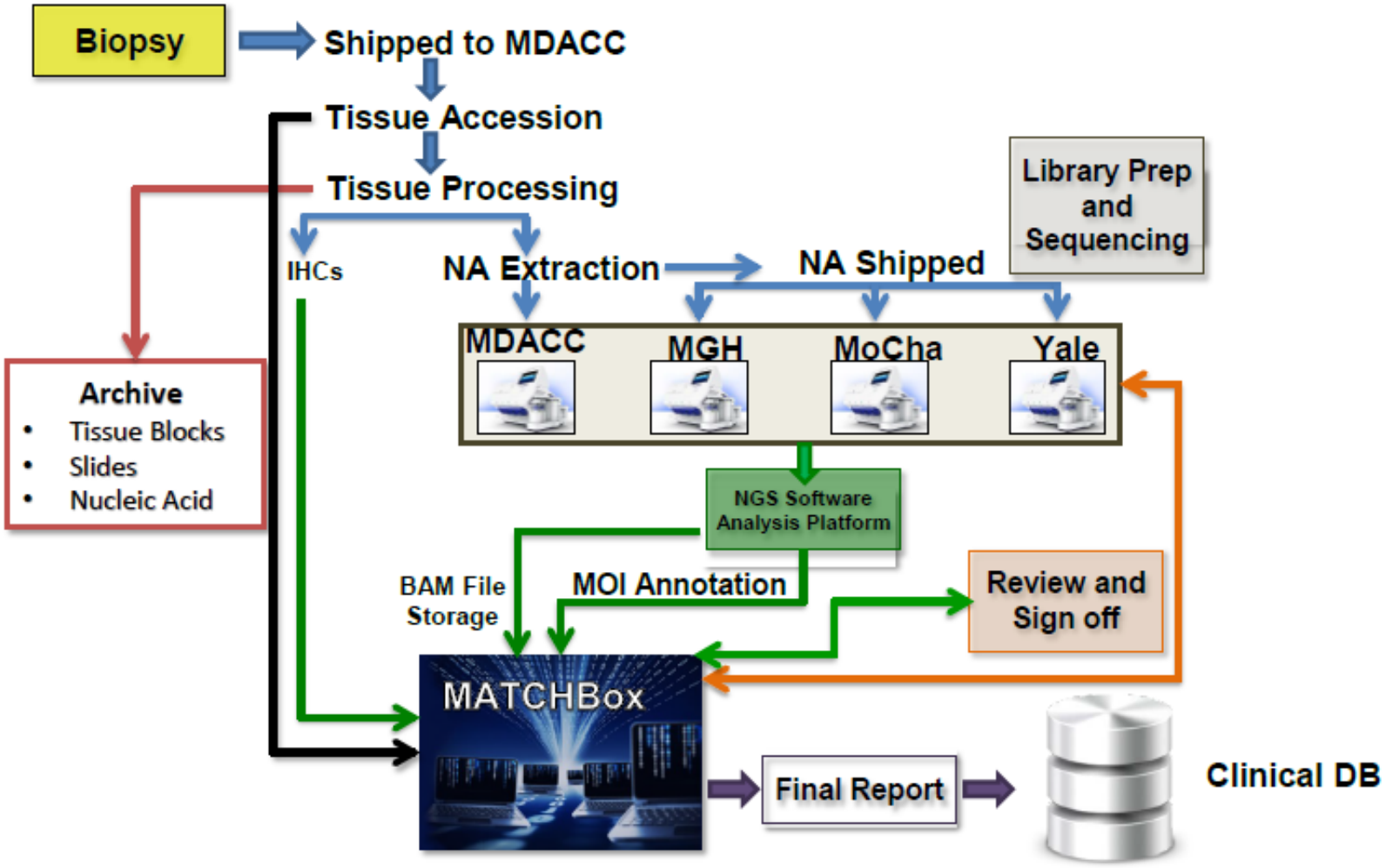


Call NCI's Contact Center (formerly known as the Cancer Information Service) to learn more about the trial or trial locations at 1-800-4-CANCER (1-800-422-6237) for assistance in English and Spanish.

*The Pediatric Molecular Analysis for Therapy Choice (MATCH) trial is being led jointly by NCI and the Children's Oncology Group (COG), part of the NCI-sponsored National Clinical Trials Network (NCTN).

cancer.gov/pediatricmatch

Standardization requires a network of clinical laboratories



Laboratory Network Activities *on a Regional ER basis?*

- **Feasibility** of NGS panels (testing overall performance of assay platforms)
- **Validation** Plan (testing analytical performance)
- **Lock SOPs** and Complete Validation Plan Key lab

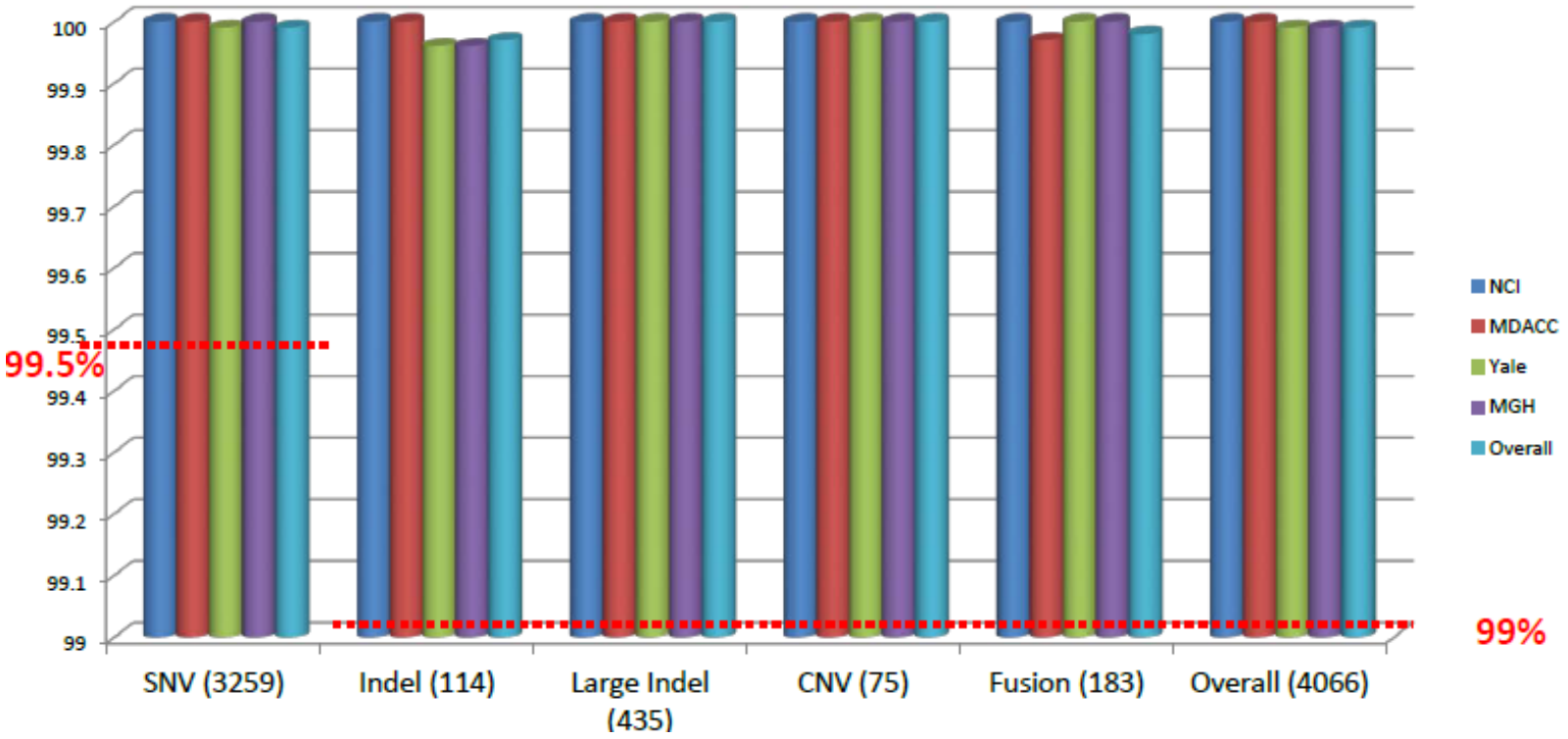
SPECIFICITY SHOUD BE >95%

Specificity

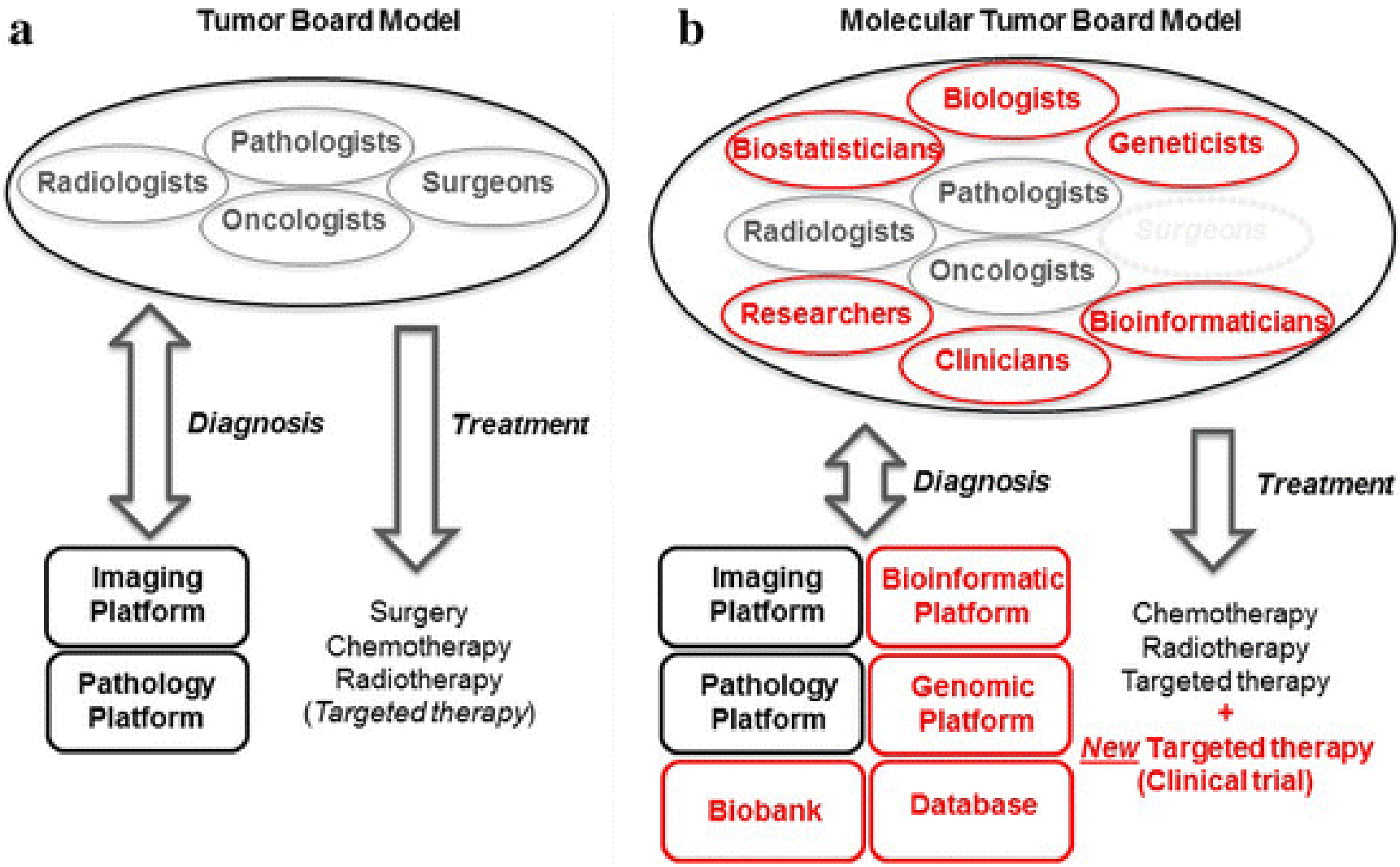
Critical Parameter for Intended Use

True Negative / (True Negative + False Positive) over 4066 MOI loci

Acceptance criteria met by all laboratories



Reproducibility across 16 specimens	Nucleic Acid	Type	Mean Concordance
Positive Concordance	DNA	Intra-Operator	96.20
	RNA	Intra-Operator	100
	DNA	Within lab Inter-Operator	96.20
	RNA	Within lab Inter-Operator	100
	DNA	Cross lab Inter-Operator	96.29
	RNA	Cross lab Inter-Operator	100
Overall Concordance	DNA	Intra-Operator	99.99
	RNA	Intra-Operator	100
	DNA	Within lab Inter-Operator	99.99
	RNA	Within lab Inter-Operator	100
	DNA	Cross lab Inter-Operator	99.99
	RNA	Cross lab Inter-Operator	100



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MCC Molecular Tumor Board

- MTB is a **free** statewide service available to physicians at UK HealthCare & regional affiliates.
- Forum for expert clinicians, pathologists & scientists to discuss and analyze tumor genotypes & molecular abnormalities in order to recommend patient specific targeted therapies.

Meetings occur 1st and 3rd Tuesdays at 12:00 pm in CC457.
Physicians can participate in person or via teleconference.
CE credit is available for clinicians & pharmacists.

HealthCare
MARKEY CANCER CENTER
An NCI-Designated Cancer Center

A bad assay is just as harmful as a bad drug (D. Hayes)