Héritas
Medicina de precisión

CIRCULO MEDICO DE ROSARIO 1910

Curso

Biología molecular aplicada al diagnóstico médico

2021

Clase:
Oncología de precisión

Círculo Médico de Rosario | Fecha: 26/10/2021

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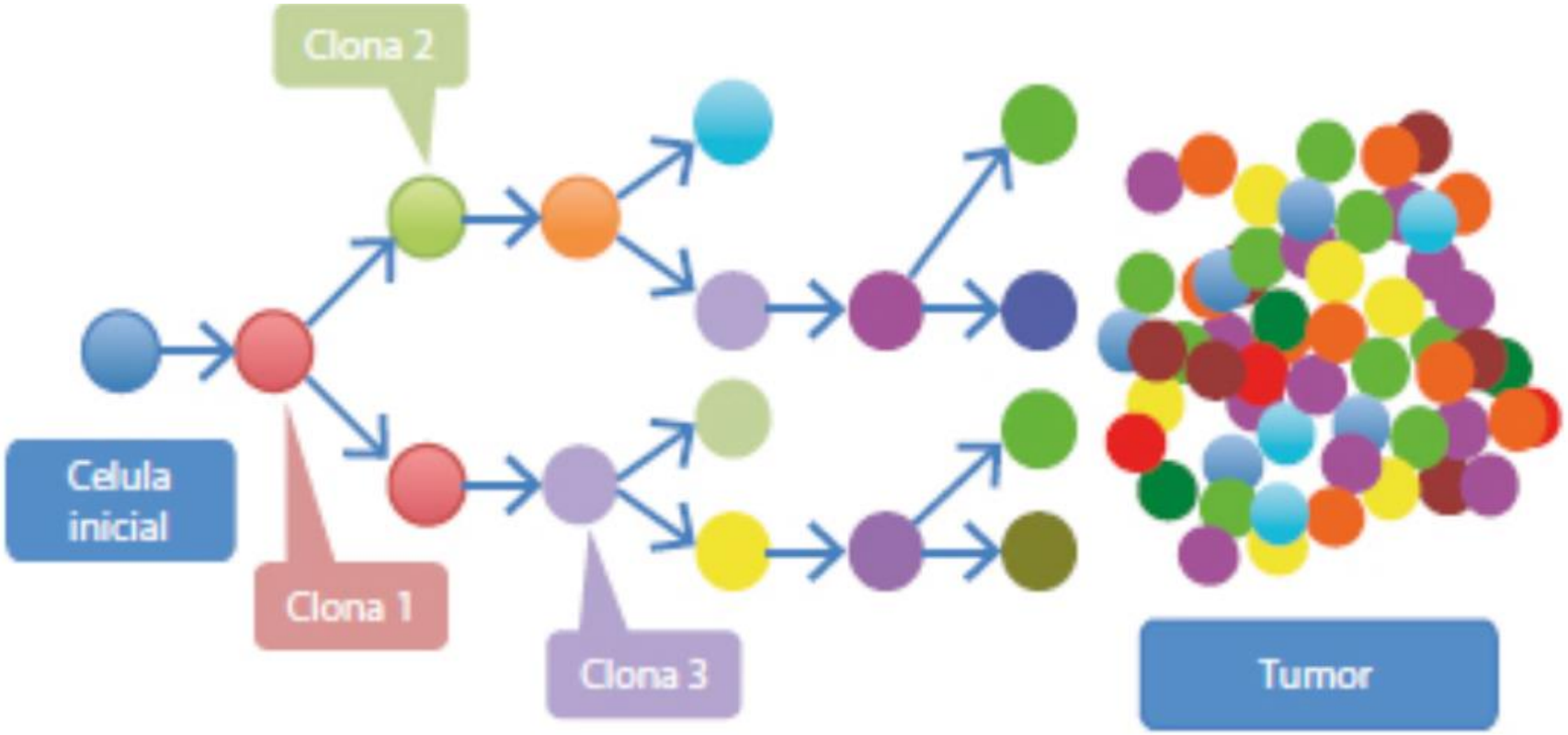

Cáncer: Una enfermedad del Genoma

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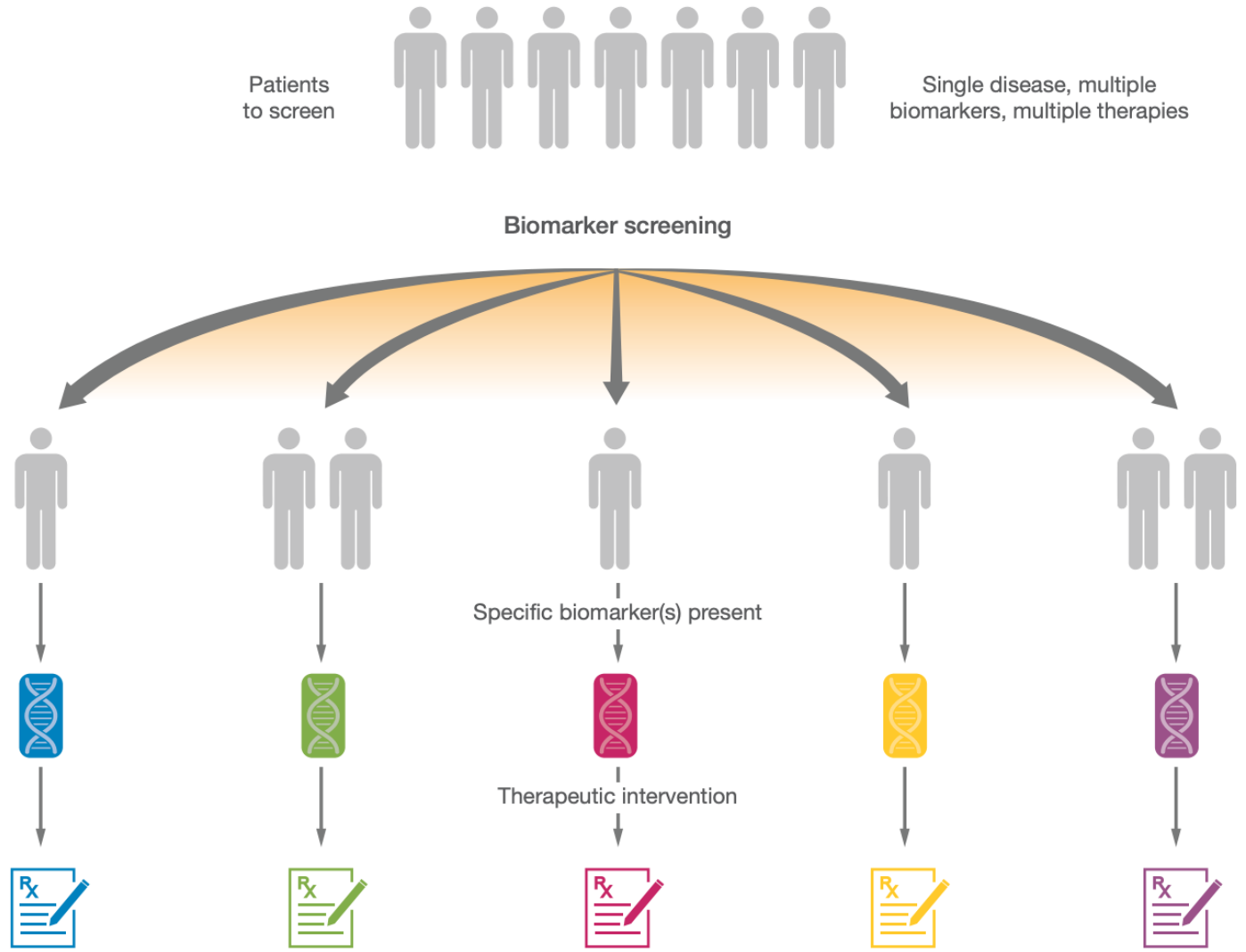
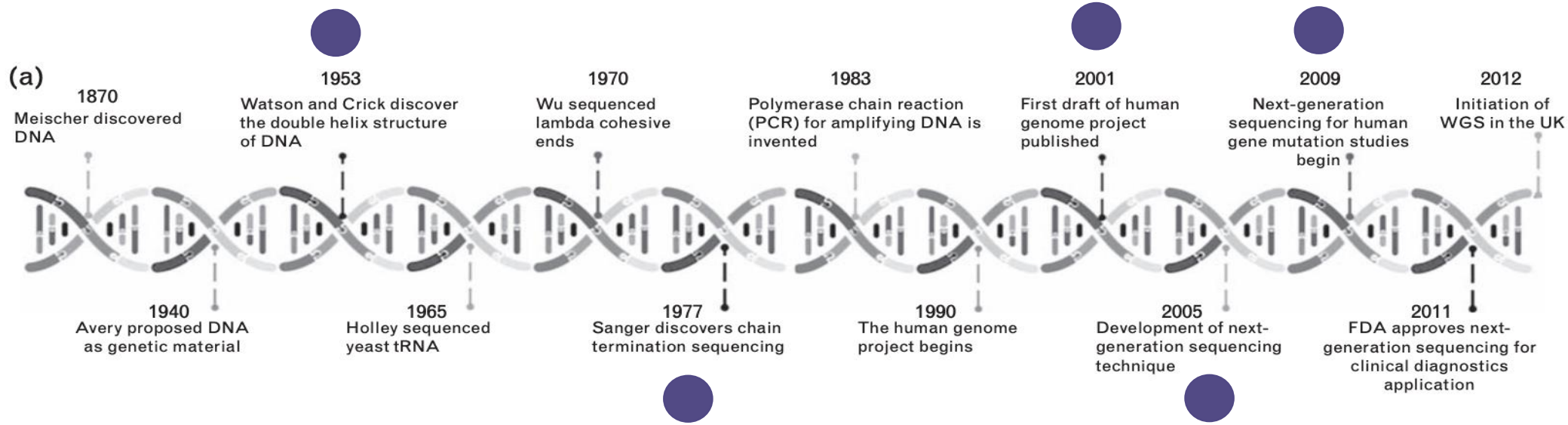


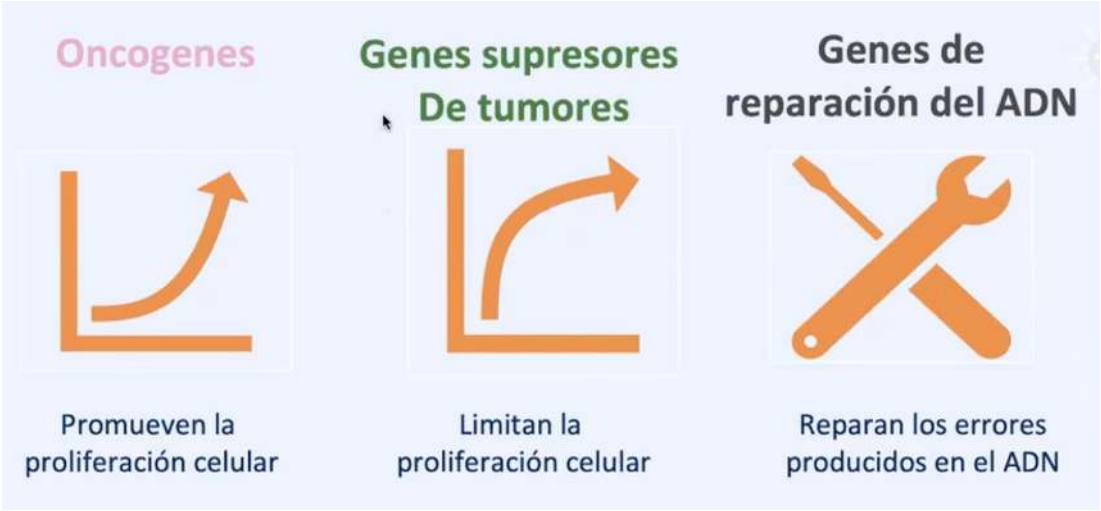
Timeline showing key events in the history of genomics

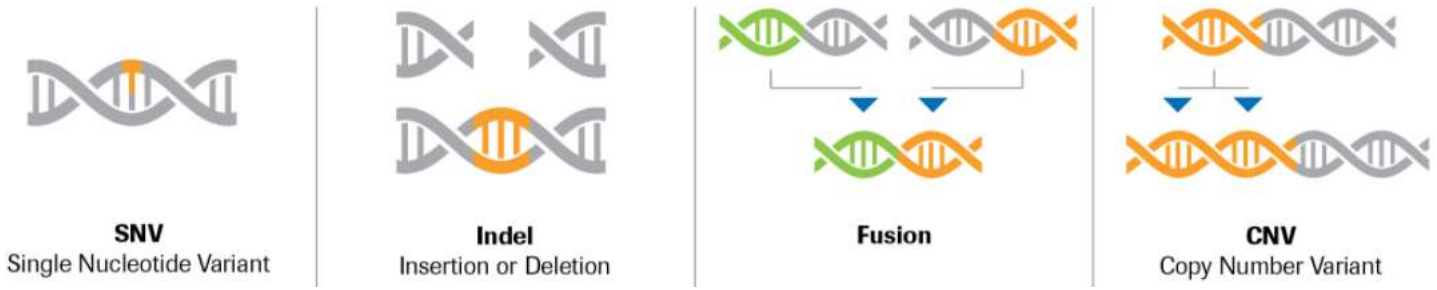


- 1953: Descubrimiento de la estructura de ADN. Premio Nobel Watson – Crick 1962
- 1977: Descubrimiento de método de secuenciación Sanger.
- 1987: Primer secuenciador ABI 370.
- 2001: Proyecto Genoma humano: 2,7 billones USD, 20 Inst., 6 países, 13 años.

- NovaSeq performs whole-genome sequencing more efficiently and cost-effectively than ever.
- Up to 6 Tb and 20 billion reads.
- Configure the system to sequence a trio in one day or up to 48 genomes in ~2 days.

Tipo de mutaciones tumorales





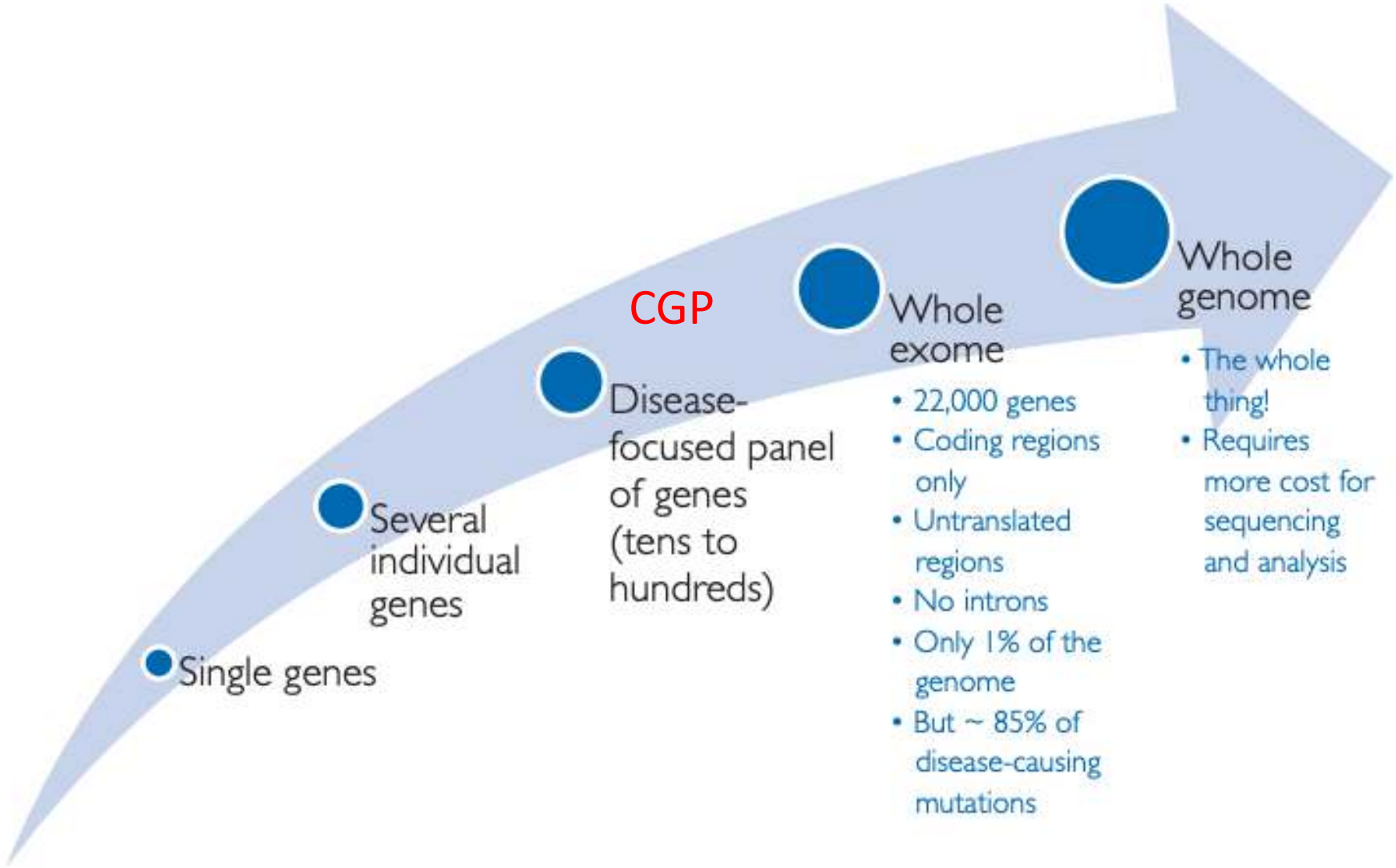
BRAF V600E

EGFR ex 19 del

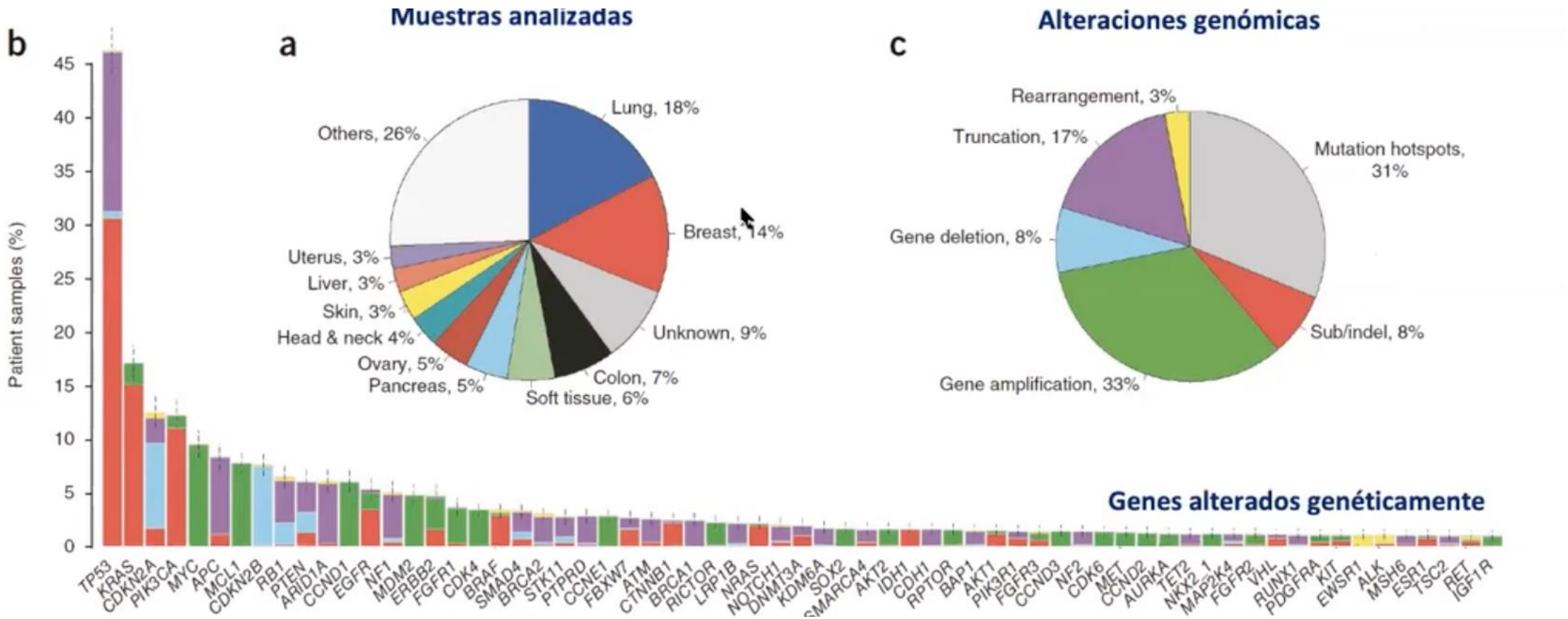
ROS1, NTRK, ALK

ERBB2 (Her2) amp

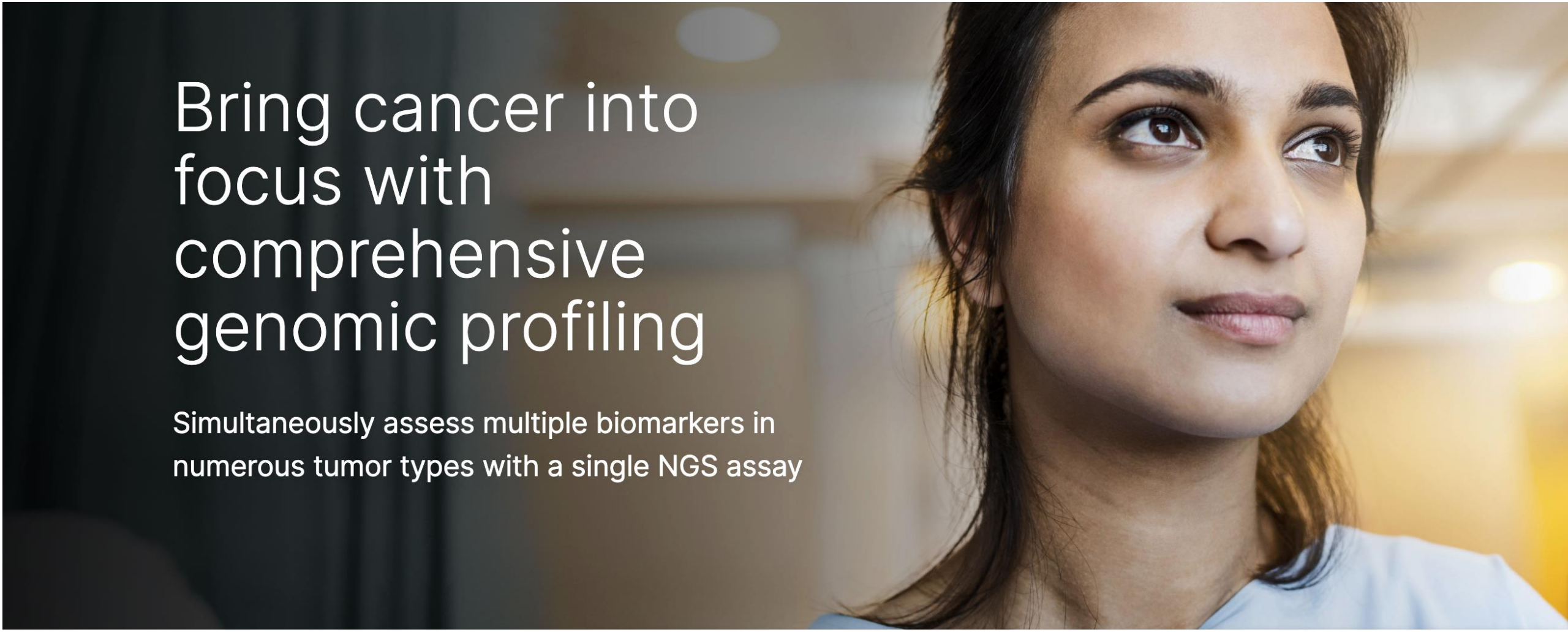
Estrategias de secuenciación NGS



Panel de FM (324 genes, +10.000 muestras)



Frampton and FM, Nature biotechnology, 2013


Bring cancer into focus with comprehensive genomic profiling
Simultaneously assess multiple biomarkers in numerous tumor types with a single NGS assay

Key Benefits of CGP:

- Detect Multiple Biomarkers in a Single Assay

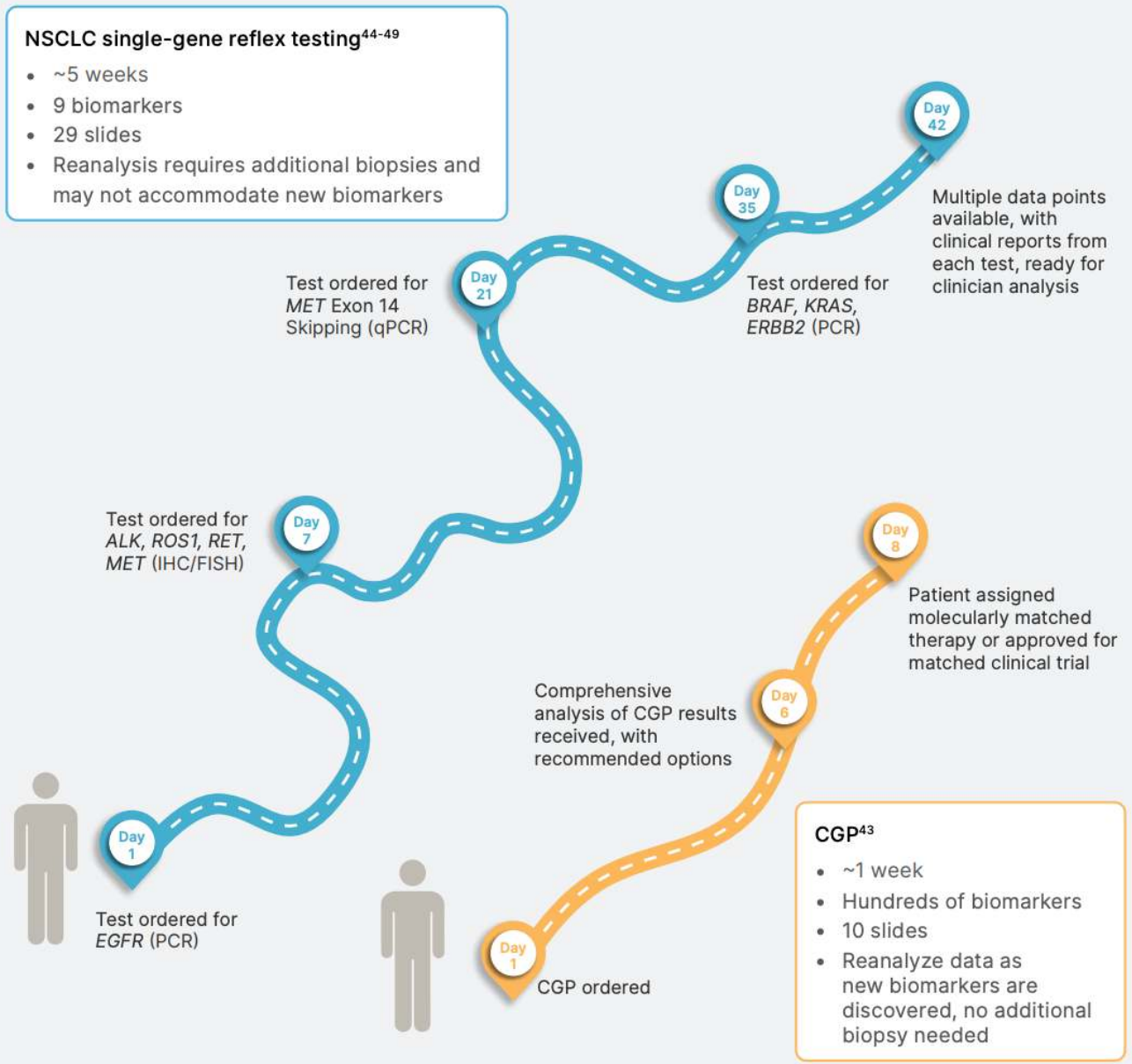
(SNVs, indels, CNVs, fusions, splice variants) genomic signatures (TMB, MSI), maximizing the ability to find clinically actionable alterations.

- Consolidate Testing to Save Time and Precious Samples

- Identify Actionable Alterations

Help identify more effective therapeutic paths and innovative clinical trial options for cancer patients.

Potential patient journeys



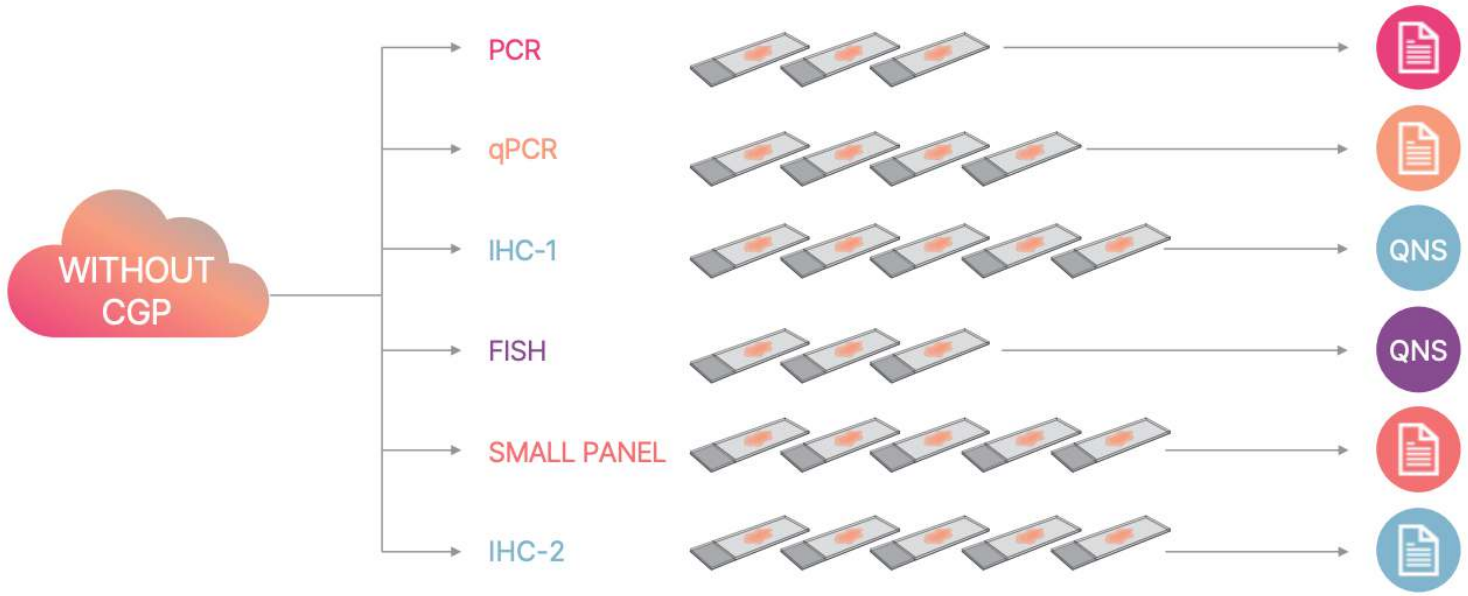
Comparison between a potential journey of a patient receiving in-house CGP with that of a patient receiving single-gene testing. Example illustrates single-gene testing based on an NSCLC patient. Test times and tissue requirements for the NSCLC example compiled from test menus offered by various medical laboratories.

Comprehensive Genomic Profiling

Empowering broader access to precision oncology[1]

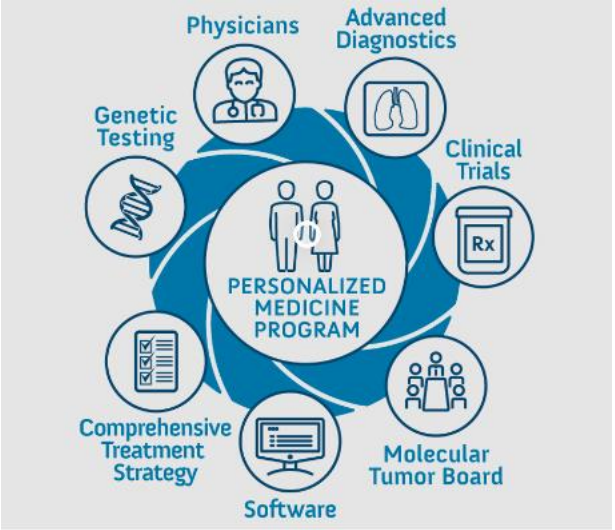
Comprehensive Genomic Profiling (CGP) helps maximize the ability to detect actionable genomic alterations

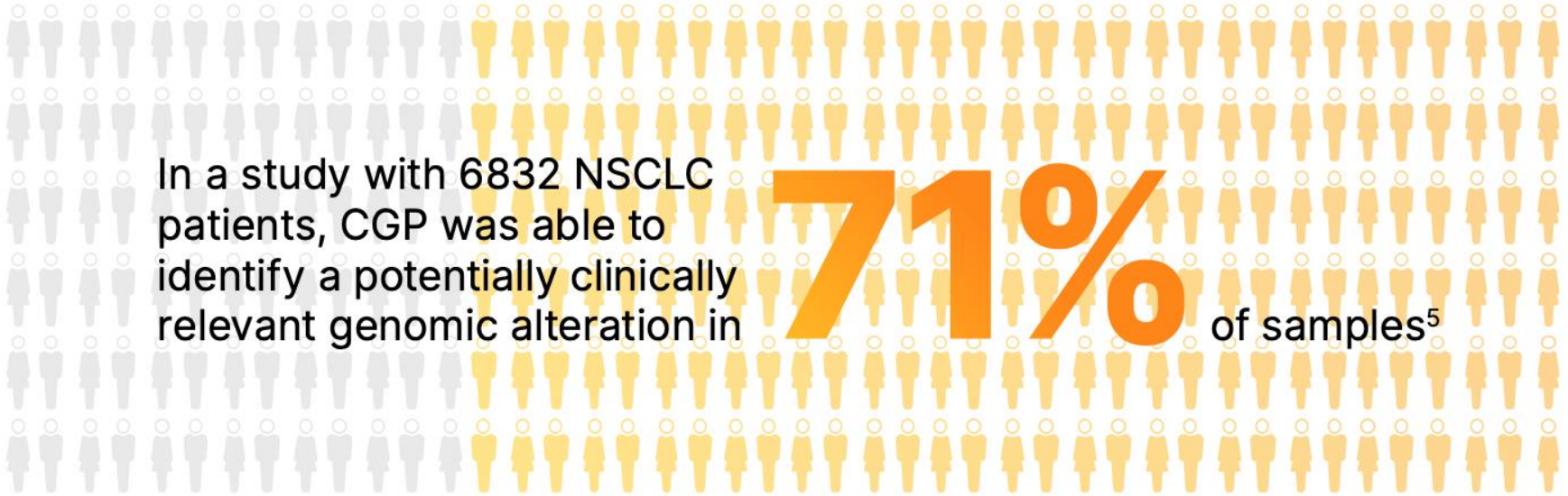
CGP provides actionable information for therapy selection from one test, one workflow, and one report



A comparison of potential workflows for patient sample analysis without (top) or with (bottom) CGP. Without CGP testing (top), the sample is spread across multiple tests, each one yielding a separate report, or none at all for tests that may require additional sample (QNS, quantity not sufficient). The CGP workflow (bottom) requires one test with as few as five slides and generates a single actionable report that provides information on hundreds of biomarkers and includes guidance for possible therapies and clinical trials.

MTB





A missed biomarker is a missed opportunity

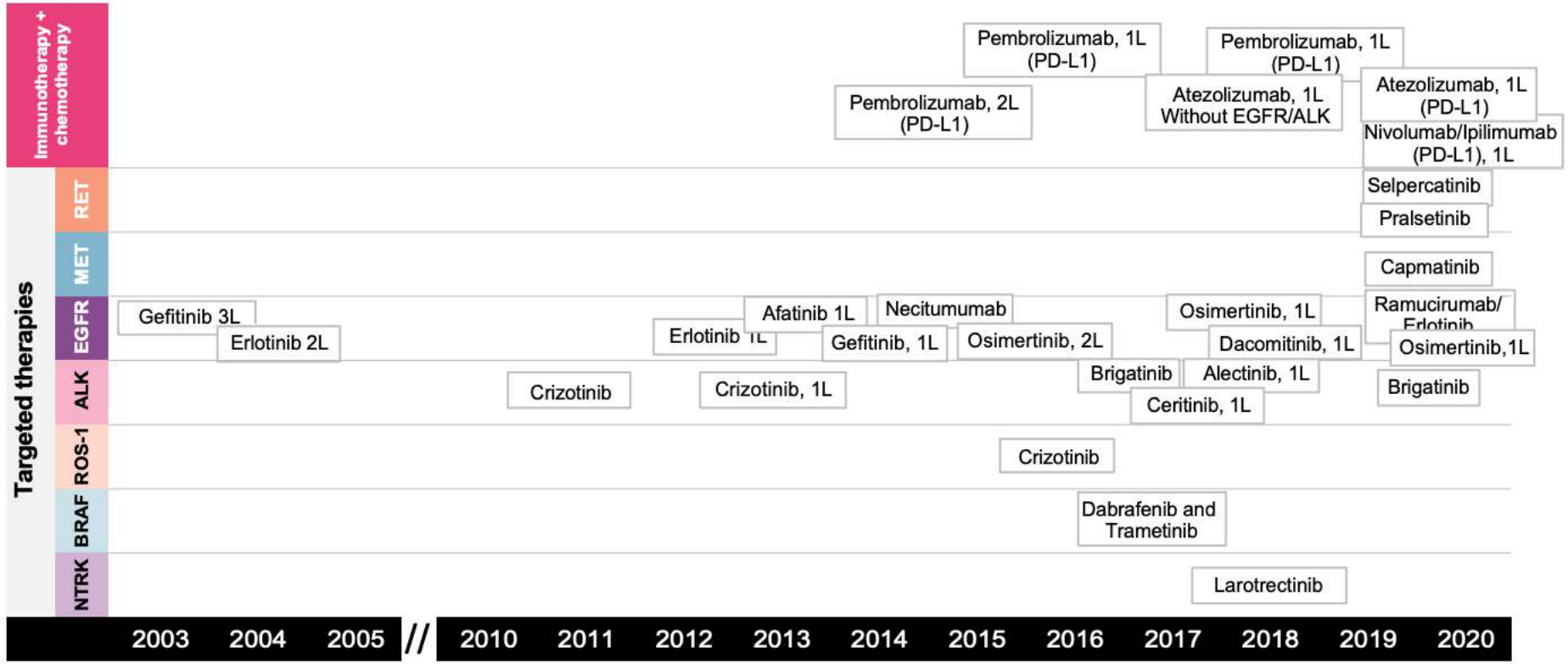
CGP provides a single test that uses minimal biopsy samples for deep analysis of biomarkers and molecular signatures linked to therapies, guidelines, and clinical trials. Data from CGP tests can be reanalyzed as new discoveries emerge, without the need to rebiopsy or to rerun the test.

With CGP, every discovery is a potential opportunity.

5. Zehir A, Benayed R, Shah RH, et al. Nat Med. 2017;23(6):703-713. doi:10.1038/

Approved biomarker-driven therapies available for NSCLC

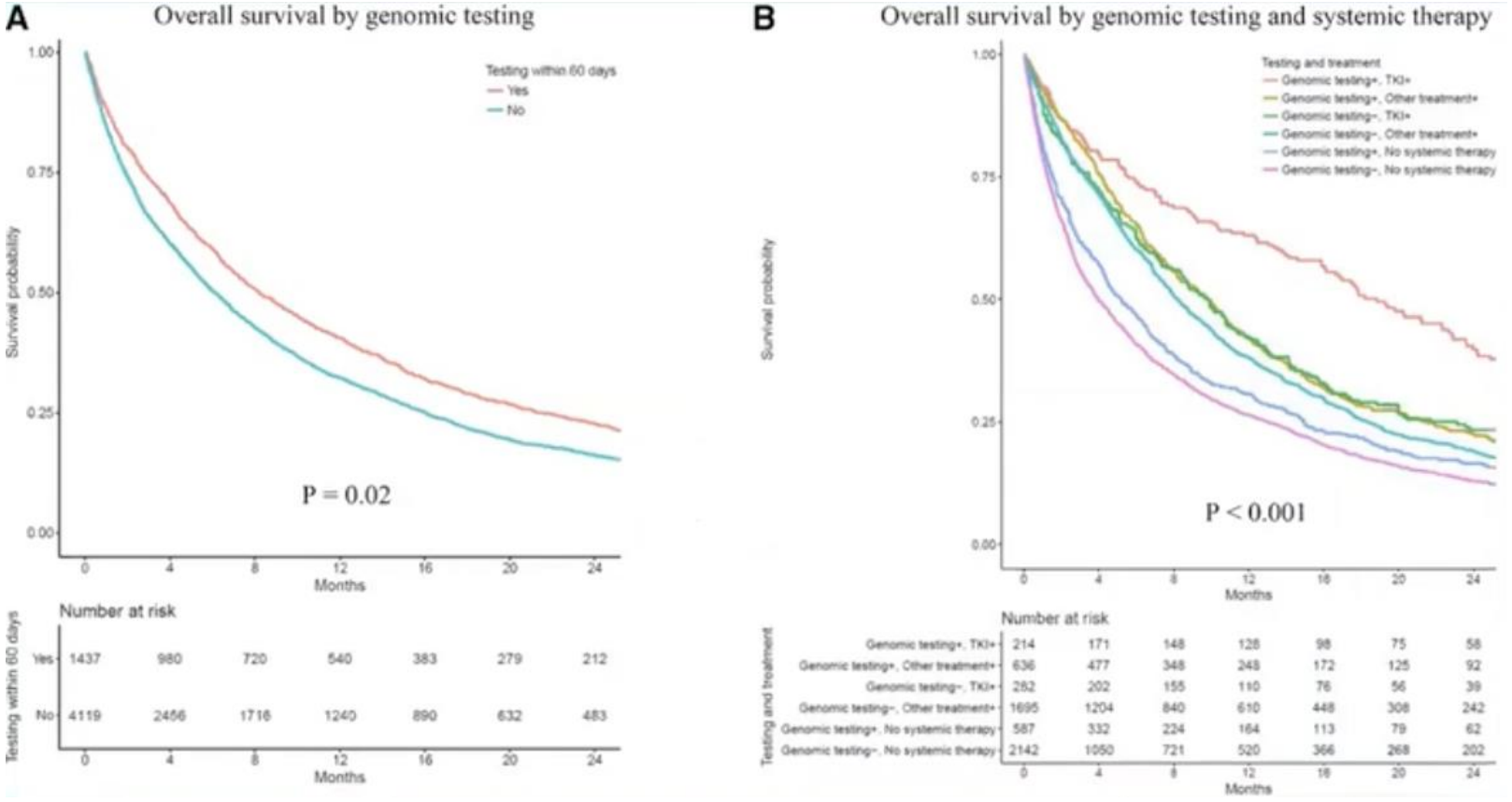
55% gaining US FDA approval in just the past 3 years



US FDA-approved indications of NSCLC treatments since 2003. Abbreviations: 1L, first-line; 2L, second-line; ALK, anaplastic lymphoma kinase; BRAF, murine sarcoma viral oncogene homolog B; del19, deletion in exon 19; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; NSCLC, non–small cell lung cancer; NTRK, neurotropic tropomyosin receptor kinase; PD-L1, programmed-death ligand 1; ROS1, c-ros1 oncogene; SqCC, squamous cell carcinoma.

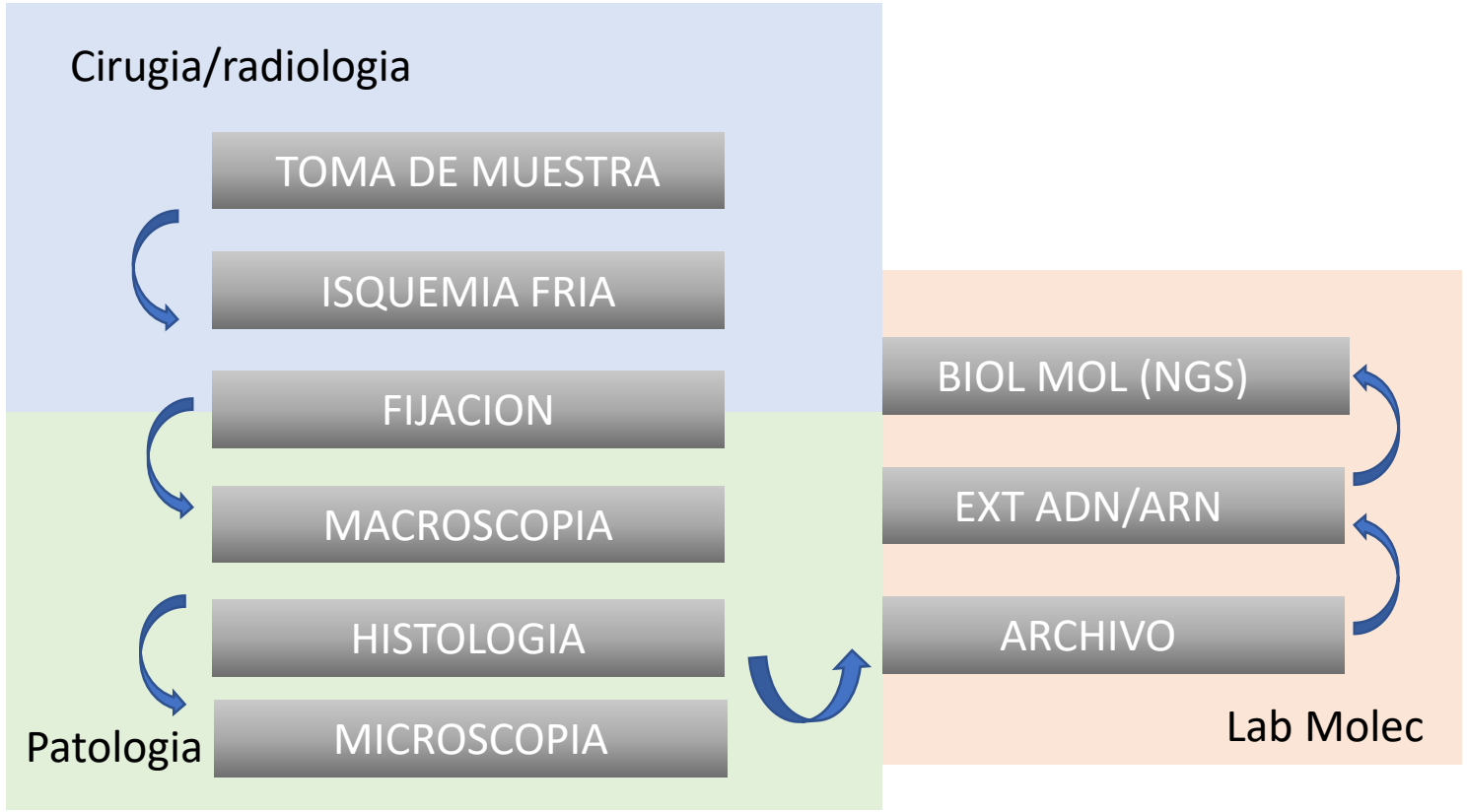
https://www. fda.gov/drugs/resources-information-approved-drugs/hematologyoncology-cancer-approvals-safety-notifications. Updated February 9, 2021. Accessed December 1, 2020.

Asociación entre testo genómico y sobrevida: terapia administrada dentro de los 60 dias del diagnótico



Kehl KL et al. J Natl Cancer Inst, Volume 111, Issue 4, April 2019

La importancia de la calidad de la muestra

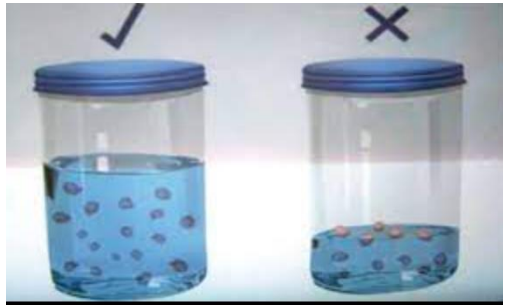


"In the era of precision oncology
proper processing
of patient tissue
is the real starting point
for targeted therapy"
(Kim S et al. JMD 2017)

La importancia de la calidad de la muestra

- Isquemia fría: menor a 1 h (ideal 15 minutos). DOCUMENTAR

- Fijación: Formol buffer/neutro 10%. Entre 6 – 72 hs. DOCUMENTAR
  Ratio formol:pieza >10:1



- Procesamiento histológico: Usar alcoholes y xilenos limpios.

La importancia de la calidad de la muestra

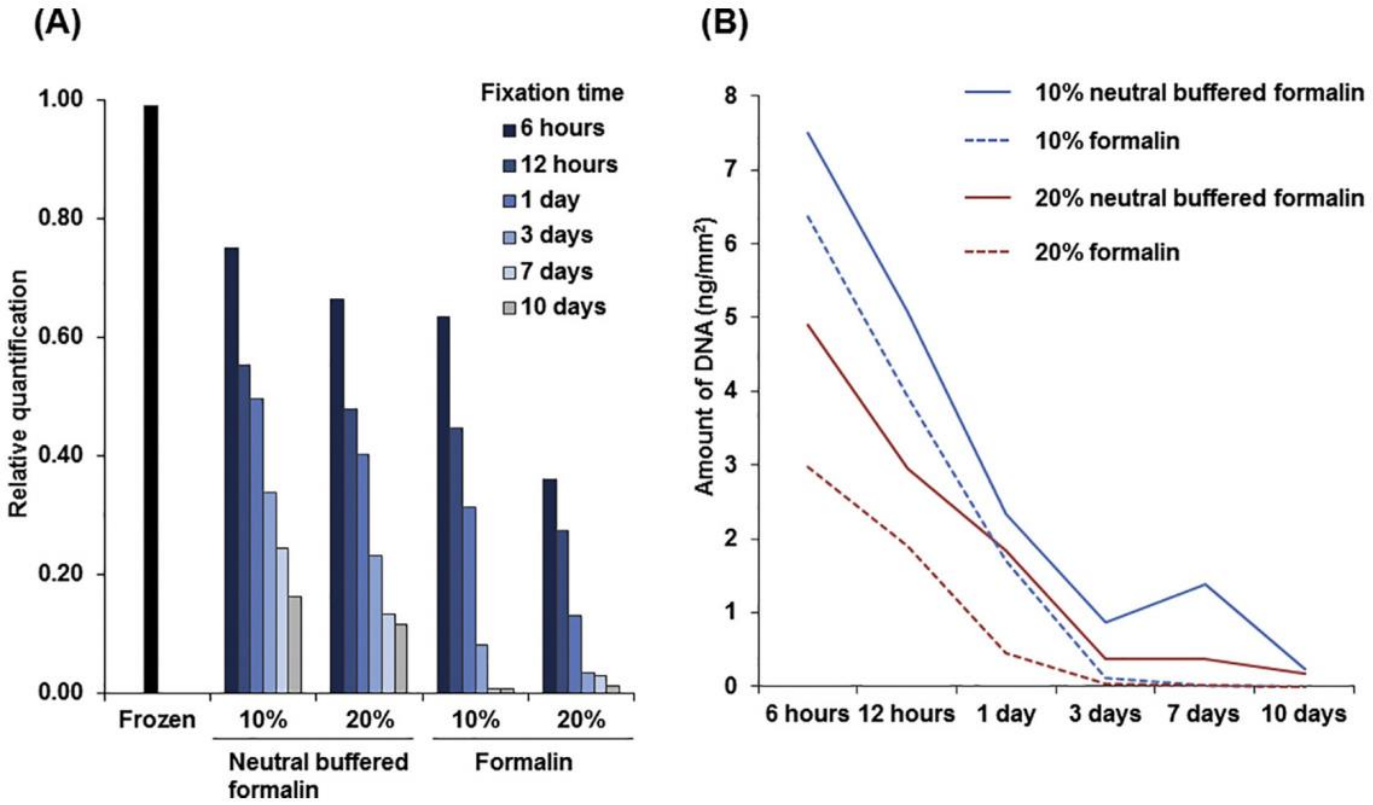
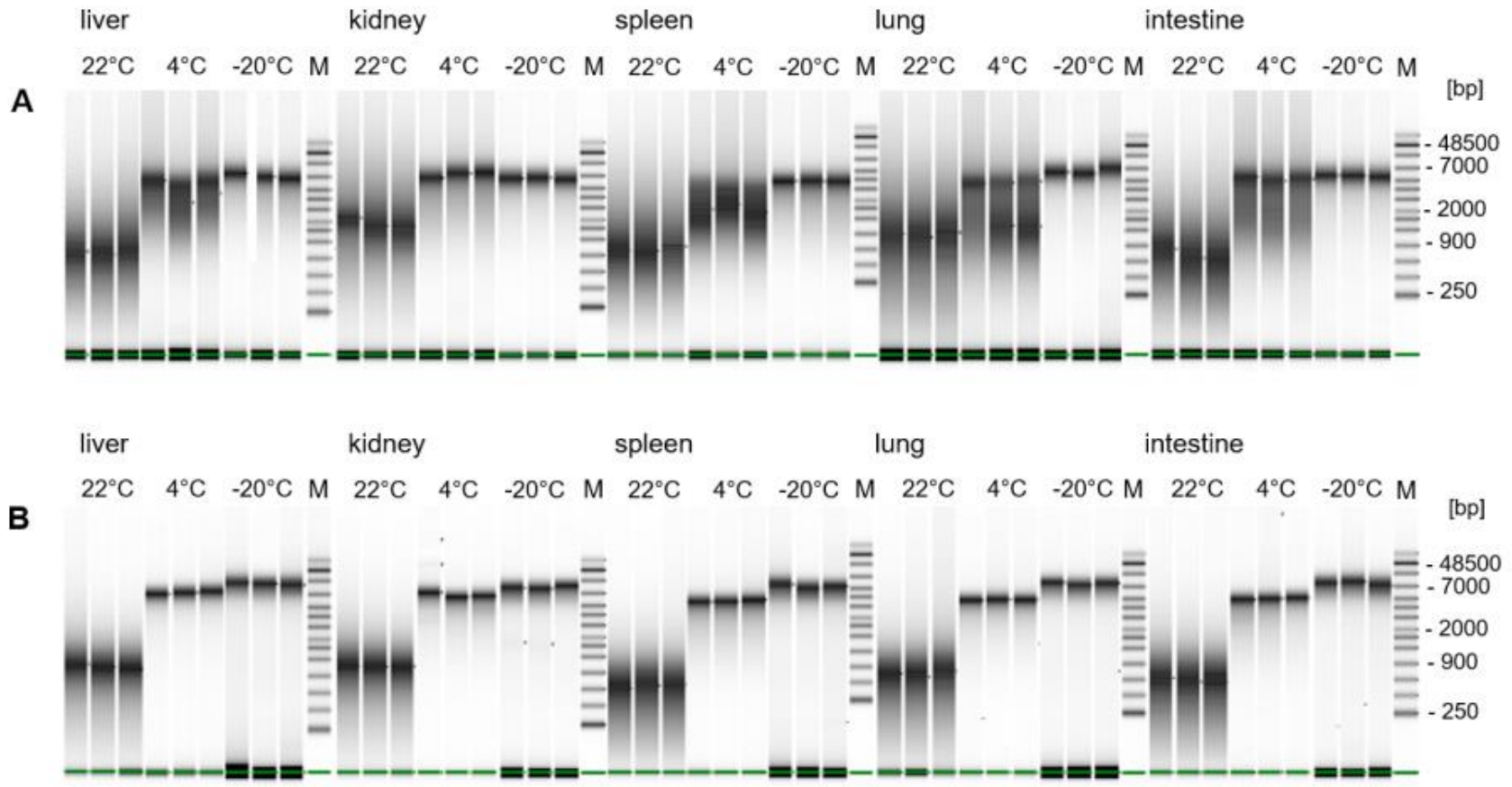


Fig. 1. DNA quality and quantities in FFPE samples prepared with various formalin reagents and fixation times.
A: FFPE DNA was obtained in samples prepared in the indicated formalin reagents for the indicated fixation times. DNA quality was evaluated by relative quantification values (see Methods). DNA extracted from frozen tissues was used as a high-quality control. B: Amount of long DNA was assessed in samples prepared in the indicated formalin reagents for the indicated fixation times as shown in (A).

Amemiya K et al, Clinica Cj=himica, Acta 2019

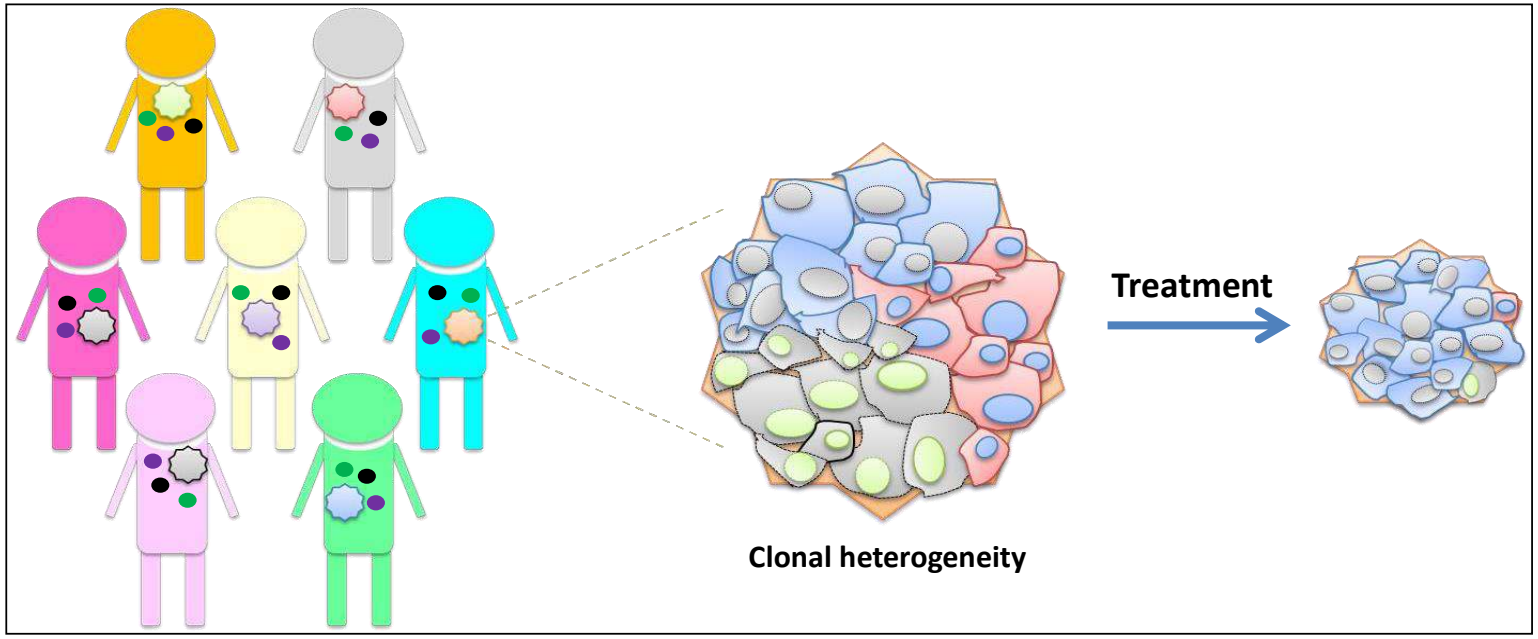
Almacenamiento de tacos en archivo

FFPE almacenados por 9 años a distintas temp.



Groelz D et al, Plos ONE 2018

The issue with tissue: heterogeneity



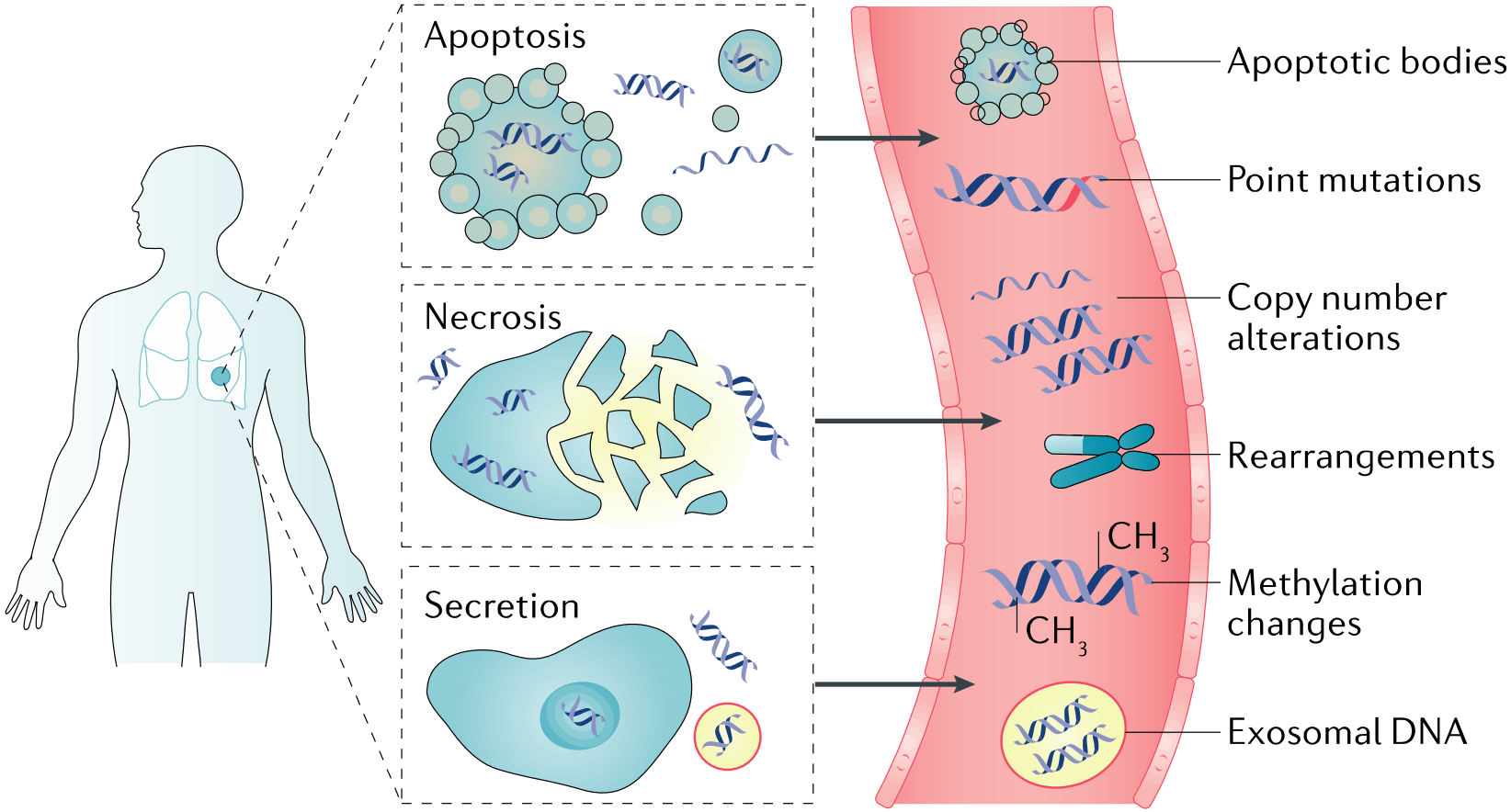
Inter-tumor heterogeneity

Intra-tumor heterogeneity

Courtesy: Andrew Nixon, PhD

BIOPSIA LIQUIDA

cfDNA: cfDNA normal + ctDNA



ctDNA vida media:
16 min a 2.5hs

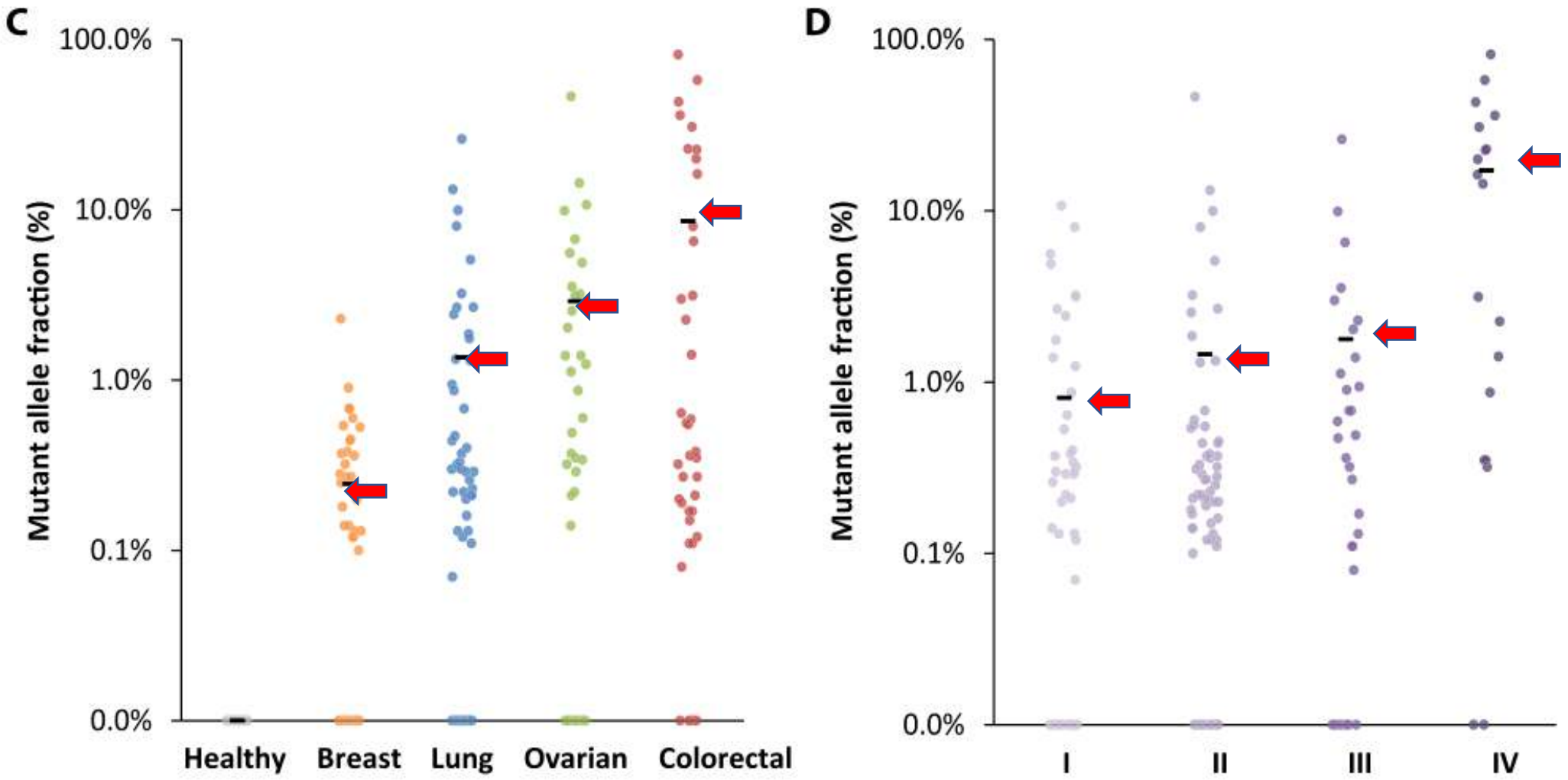
Ventajas:

- Foto a tiempo real
- Monitoreo en tiempo
- No invasivo
- Menos heterogéneo que tejido

Desventajas:

- Escaso material en plasma
- Mutaciones a muy baja AF.

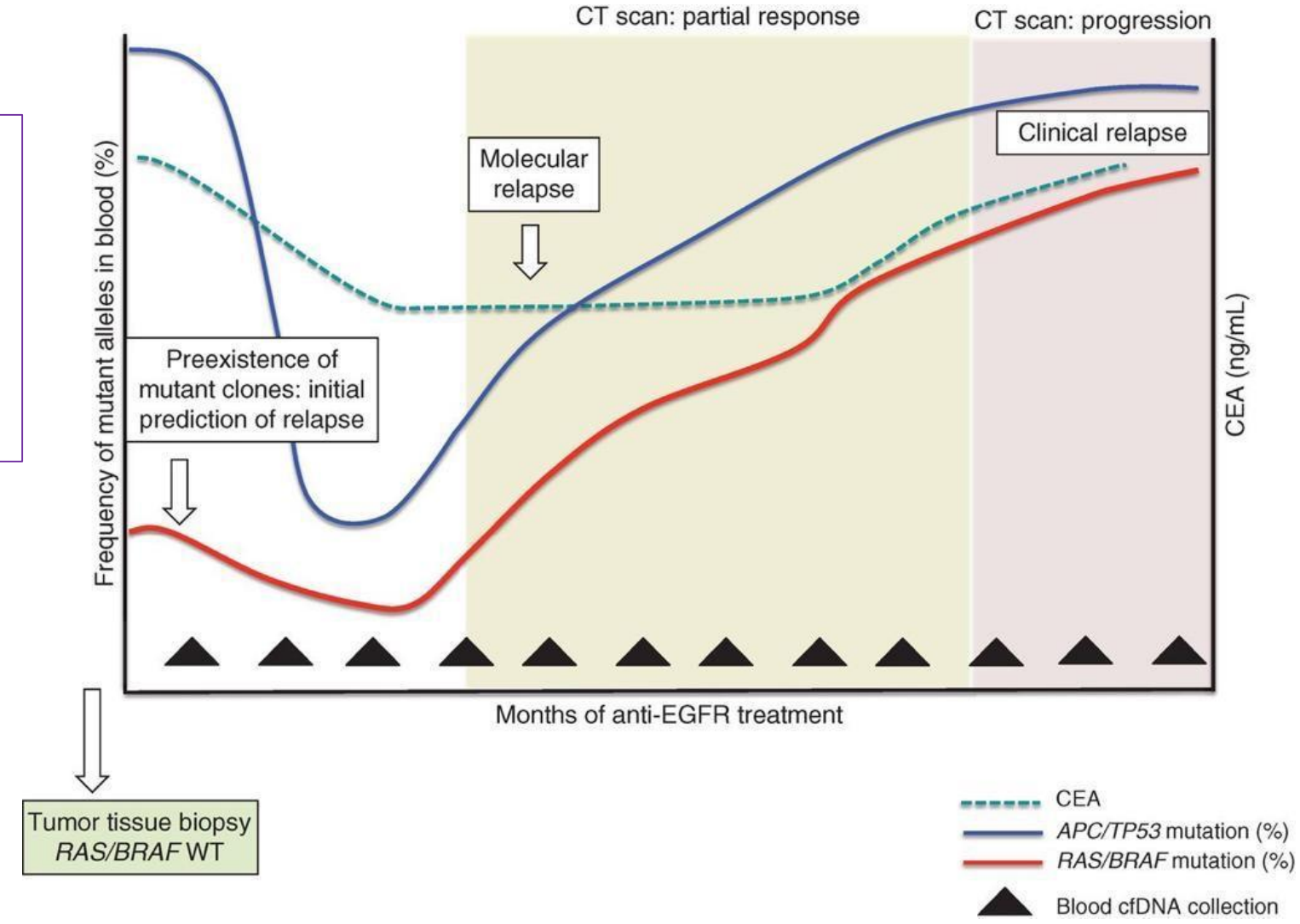
BIOPSIA LIQUIDA



Phallen *et al.*, *Sci. Transl. Med.* **9**, eaan2415 (2017) 16 August 2017

BIOPSIA LIQUIDA

Biomarcadores en plasma predicen anticipadamente, varias semanas antes que CT scan,
el fallo terapéutico.



BIOPSIA LIQUIDA

Liquid biopsy is recommended today

7 NCCN Clinical Practice Guidelines recommend use of liquid biopsy[60-66]

Different tumor types may have specific use cases for liquid biopsy, such as when:

- Patient is medically unfit for a tissue biopsy[60,62,63,65,66]
- Insufficient material is available[60]
- Tissue biopsy is unavailable[64-66]

Liquid biopsy is complementary to tissue

+15%

more clinically relevant mutations identified in mNSCLC when analysis from liquid biopsy is added to tissue[67-69]

Clinical trials benefit from liquid biopsy

↓3x

decrease in screening time

↑2.3x

increase in enrollment rate in advanced gastrointestinal cancer compared to CGP from tissue only[72]

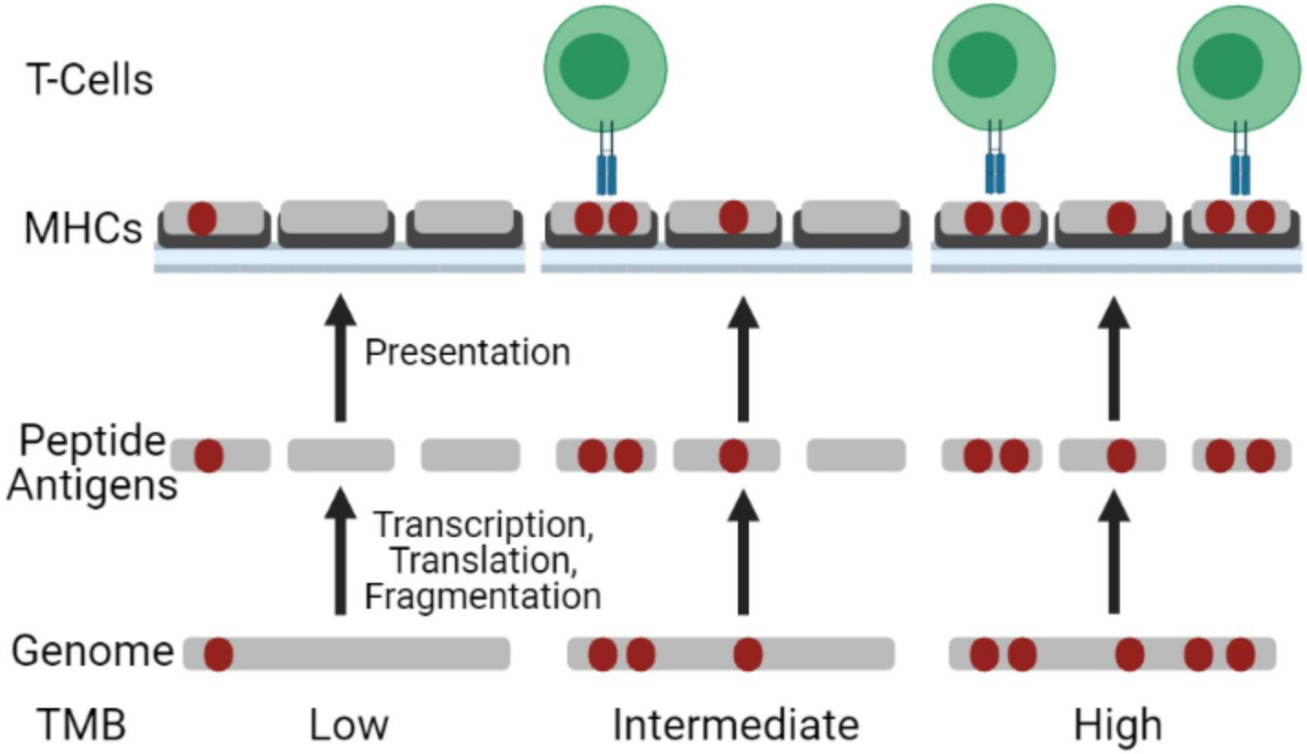
67. Aggarwal C, et al. JAMA Oncol. 2019;5(2):173-180. doi:10.1001/jamaoncol.2018.4305
68. Leighl NB, et al. Clin Cancer Res. 2019;25(15):4691-4700. doi:10.1158/1078-0432.CCR-19-0624
69. Palmero R, Taus A, Viteri S, et al. JCO Precision Oncology. 2021;5:93-102. doi:10.1200/PO.20.00241
72. Nakamura Y, et al Nat Med. 2020;26(12):1859-1864. doi:10.1038/s41591-020-1063-5

Biomarcadores agnósticos de la histología tumoral

TMB: Tumor Mutational Burden
MSI: Microsatellite Instability

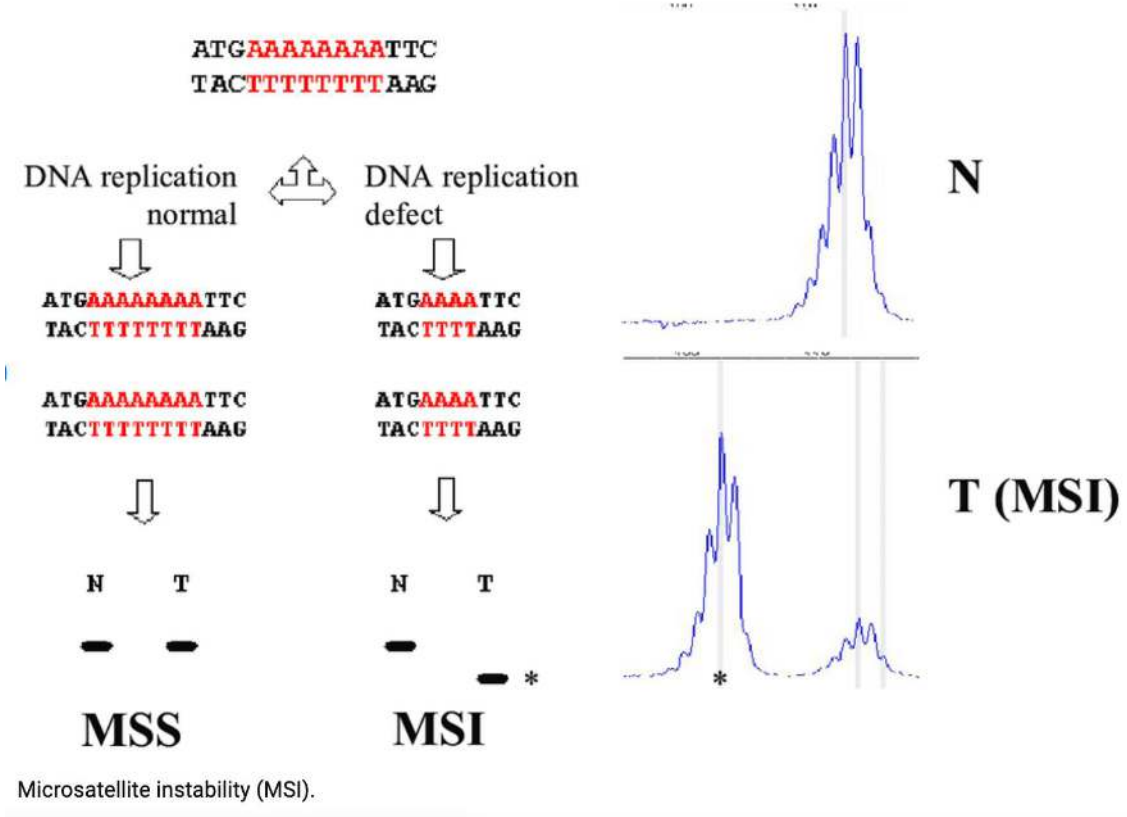
TMB: Tumor Mutational Burden

Mutaciones somáticas en el tumor que se acumulan y se expresan como neoatígenos y son reconocidas por el sistema inmunológico.



TMB HIGH>>>> Buen candidato para recibir tratamiento con Inmunoterapia anti PD-1

MSI: Microsatellite Instability



Deficiencia en el mecanismo de reparación genera MSI

MSI HIGH>>>> Buen candidato para recibir tratamiento con Inmunoterapia

TMB and MSI are both FDA approved tissue-agnostic biomarkers for pembrolizumab

May 2017

High MSI[1]

MSI was the first instance of the FDA approving a drug 'based on a tumour's biomarker without regard to the tumour's original location'

FDA approved pembrolizumab for patients with unresectable or metastatic solid tumours that are MSI-H or mismatch repair deficient (dMMR)

June 2020

High TMB[2]

FDA approved pembrolizumab for patients with unresectable or metastatic solid tumours with TMB-H (≥ 10 muts / Mb) after progression on prior treatment and with no satisfactory alternative treatment options

FoundationOne CDx assay approved as a companion diagnostic to identify TMB-H patients

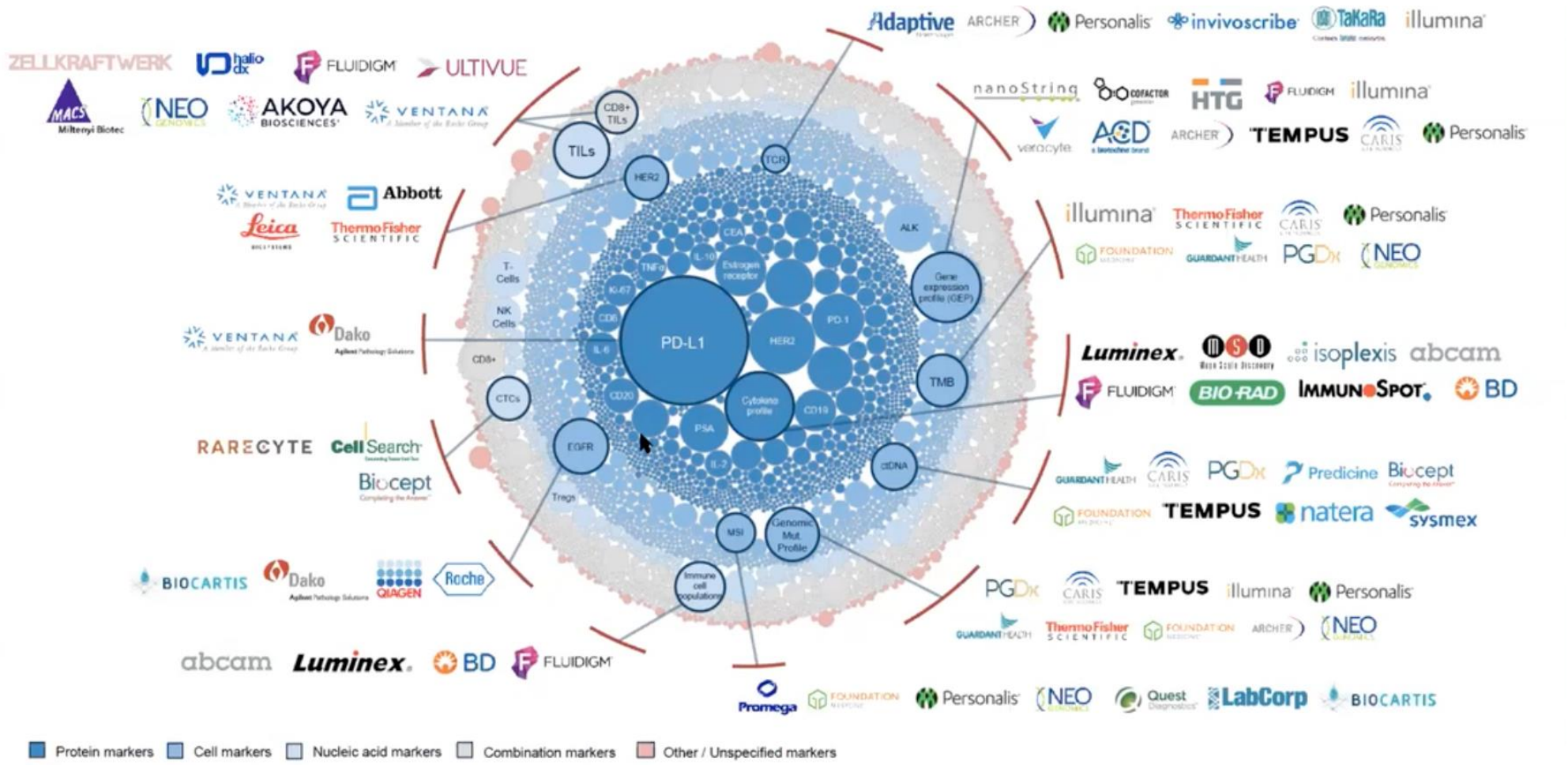
FDA approvals were granted based on clinical evidence of durable response to pembrolizumab in patients with solid tumours with high MSI or high TMB[1-3]

FDA: US Food and Drug Administration; MSI(-H): (high) microsatellite instability; muts / Mb: mutations / megabase; TMB(-H): (high) tumour mutational burden. 1. FDA website (2017) Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pembrolizumab-first-tissuesite-agnostic-indication (Accessed August 2020); 2. FDA website (2020) Available at: https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-pembrolizumab-adults-and-children-tmb-h-solid-tumors (Accessed August 2020); 3. Marabelle, A., et al. *Annals Oncol*. 2019;30(suppl_5):v475-v532.

Projected approval of tumor-agnostic treatments targeting actionable genomic drivers from ongoing clinical trials

Thomas et al, Nature Research 2020

Oncology biomarkers 2021



A change in paradigm

Increasing number of biomarkers

+

Increasing number of molecularly targeted therapies and clinical trials

+

CGP testing

= potential for improved patient outcomes

Transformación de la oncología

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¡Muchas gracias!

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