

Cancer Interception And Clonal Hematopoiesis



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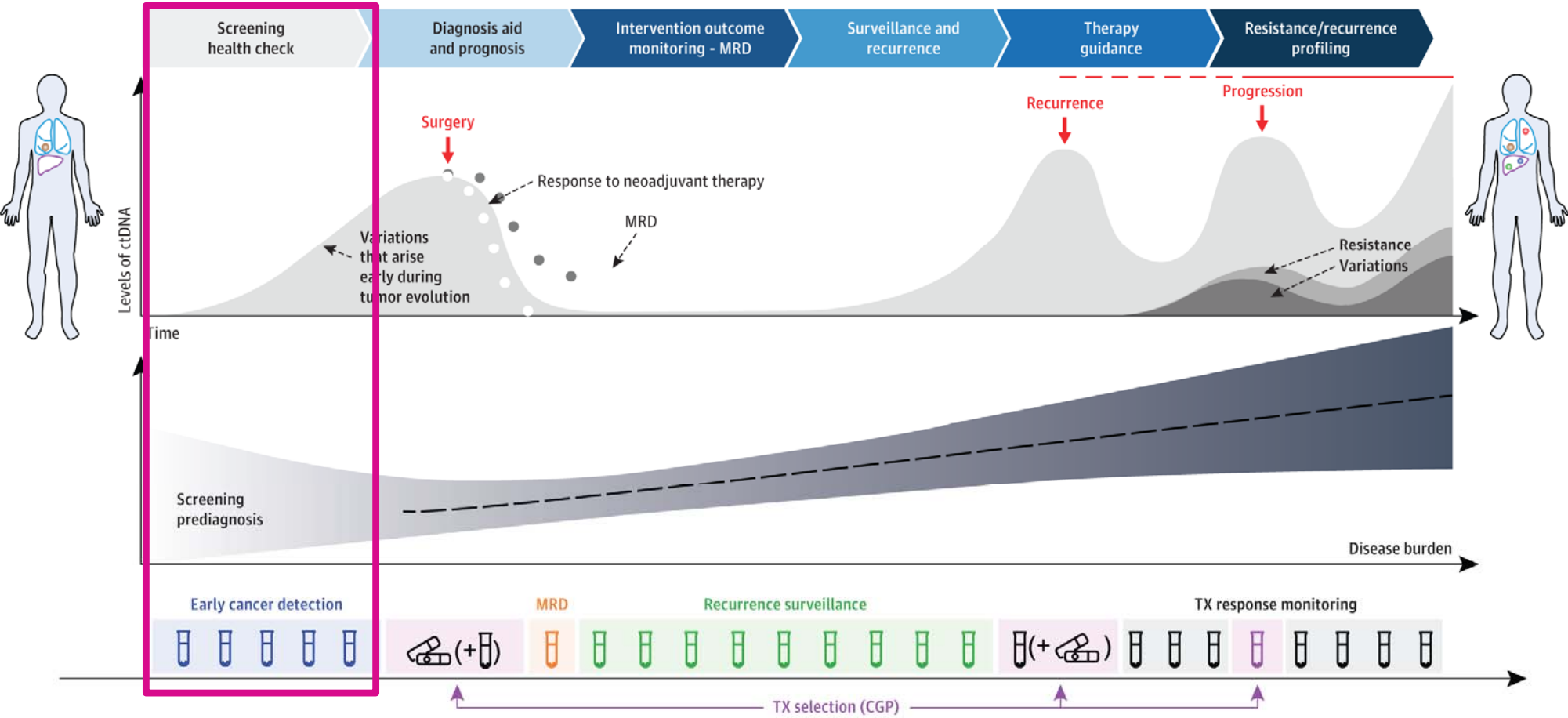
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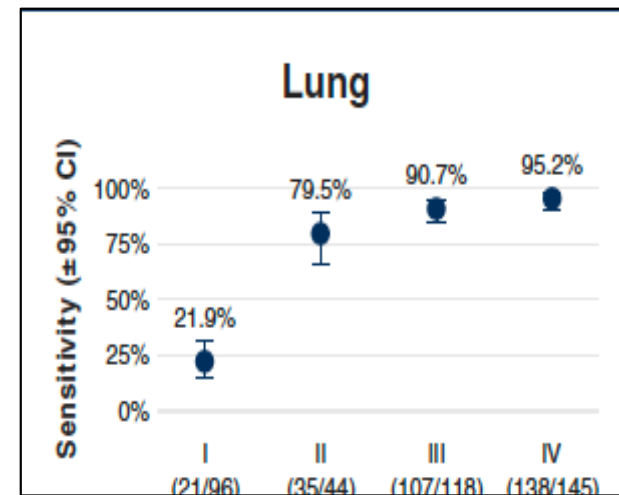
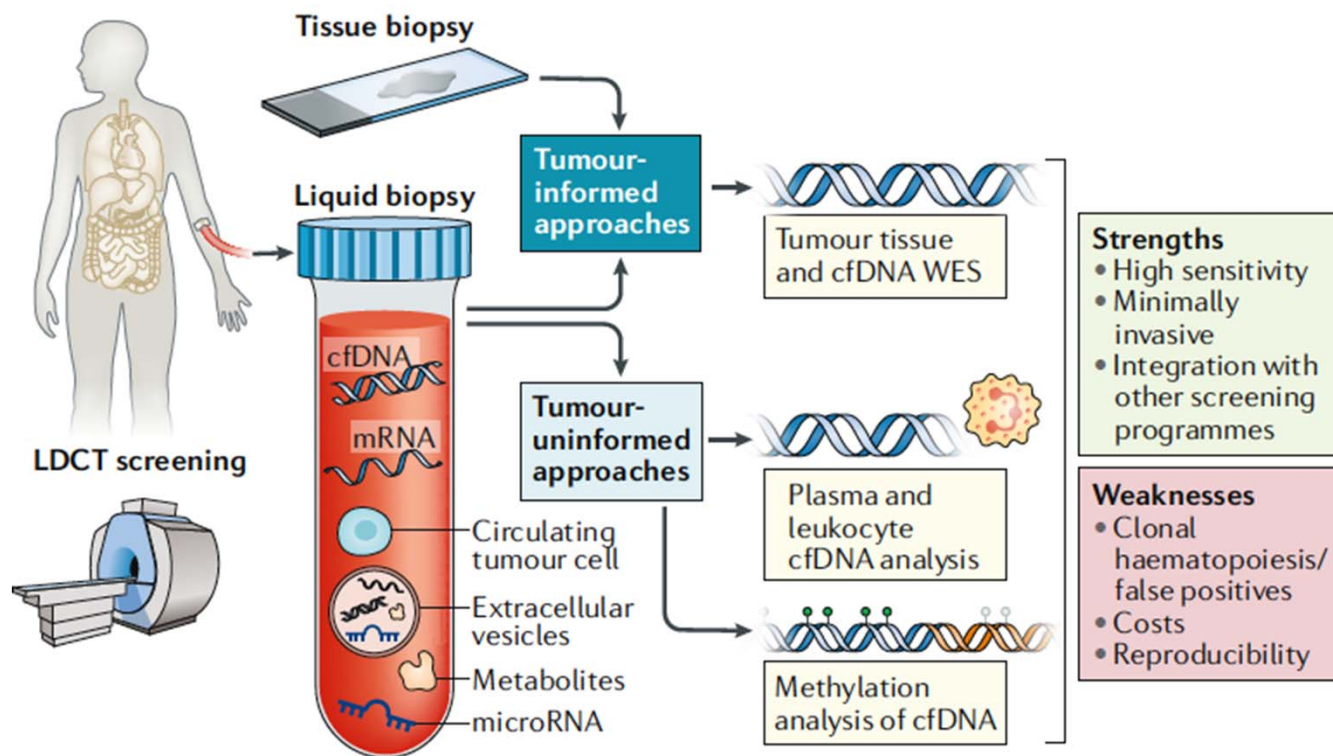
Disclosures

Research grants	Lung Cancer Research Foundation-Pfizer Grant 2019 American Cancer Society NIH SBIR, NCI SeroNet 2020
Personal financial interests	Speaker: MSD, Astra Zeneca, Roche, GuardantHealth
Personal financial interests	Advisory board: Inivata, ArcherDx, EMD Serono, Novartis, BMS, Boston Pharmaceuticals, Esai, BluePrint, CORE2, Pfizer
Non-financial interests	Research Collaboration: GuandantHealth (UMB)
Leadership roles	Chair Educational Committee IALSC - President ISLB (International Society of Liquid Biopsy) - Educational Chair: OLA Oncology Latin American Association Scientific Committee Member at ESO (European School of Oncology).

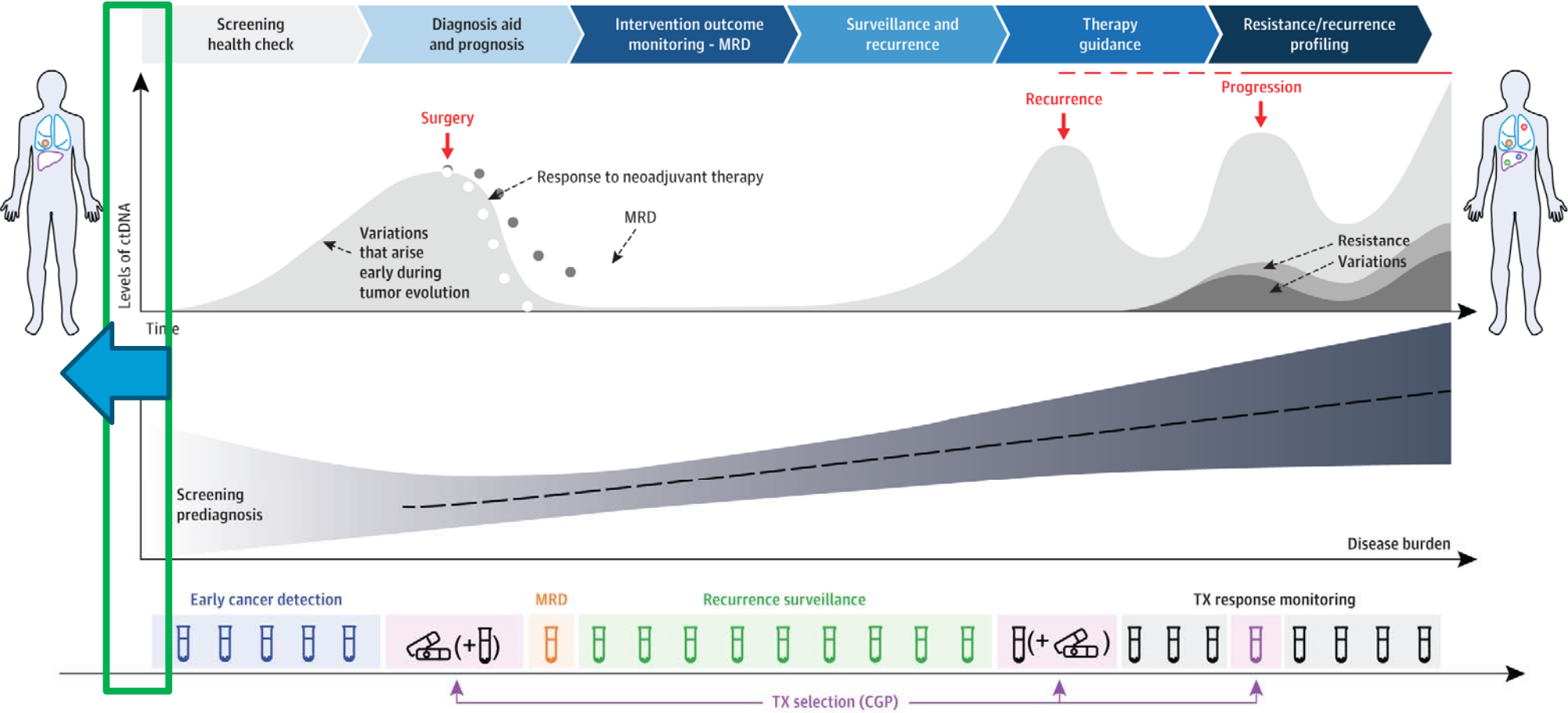
Liquid biopsy can provide clinically-valuable information along the whole patient journey



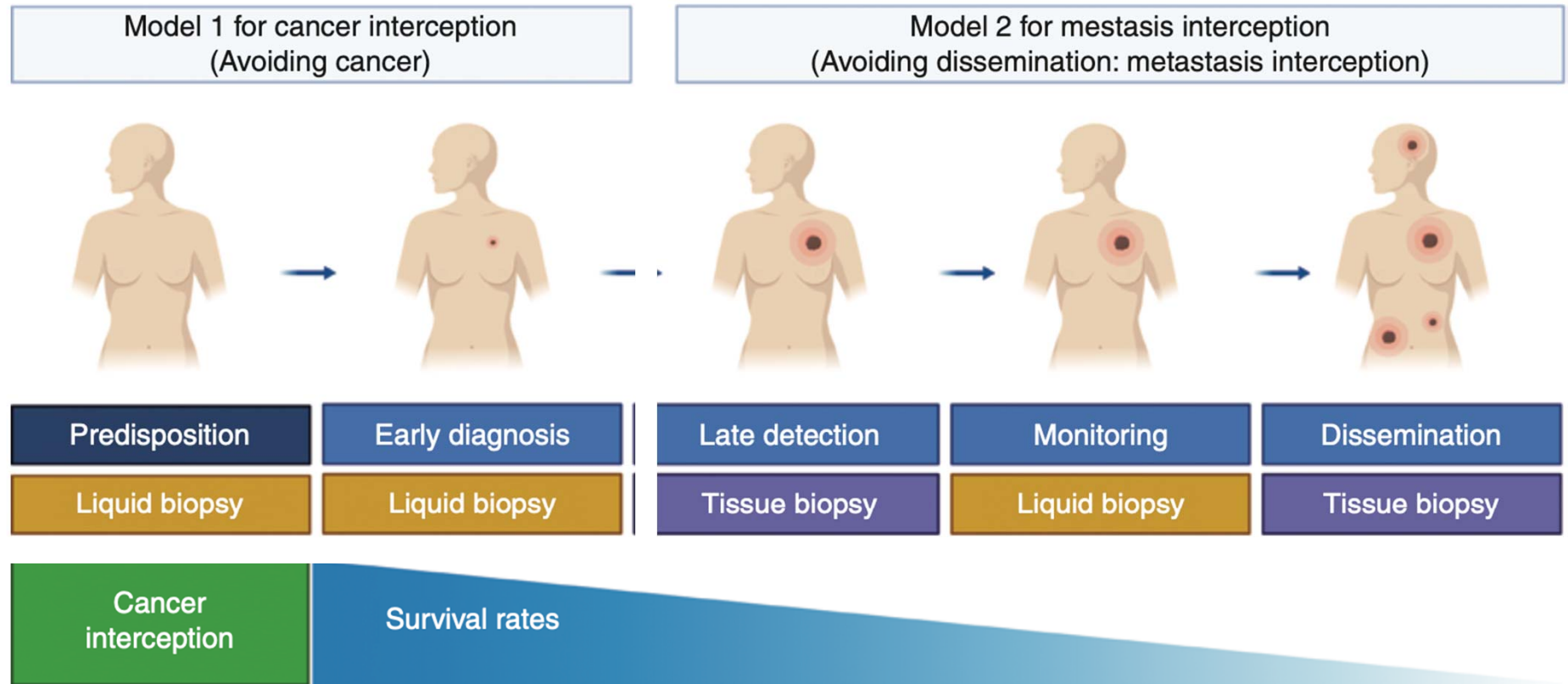
Liquid biopsy & early detection: Strengths and weaknesses of currently used approaches



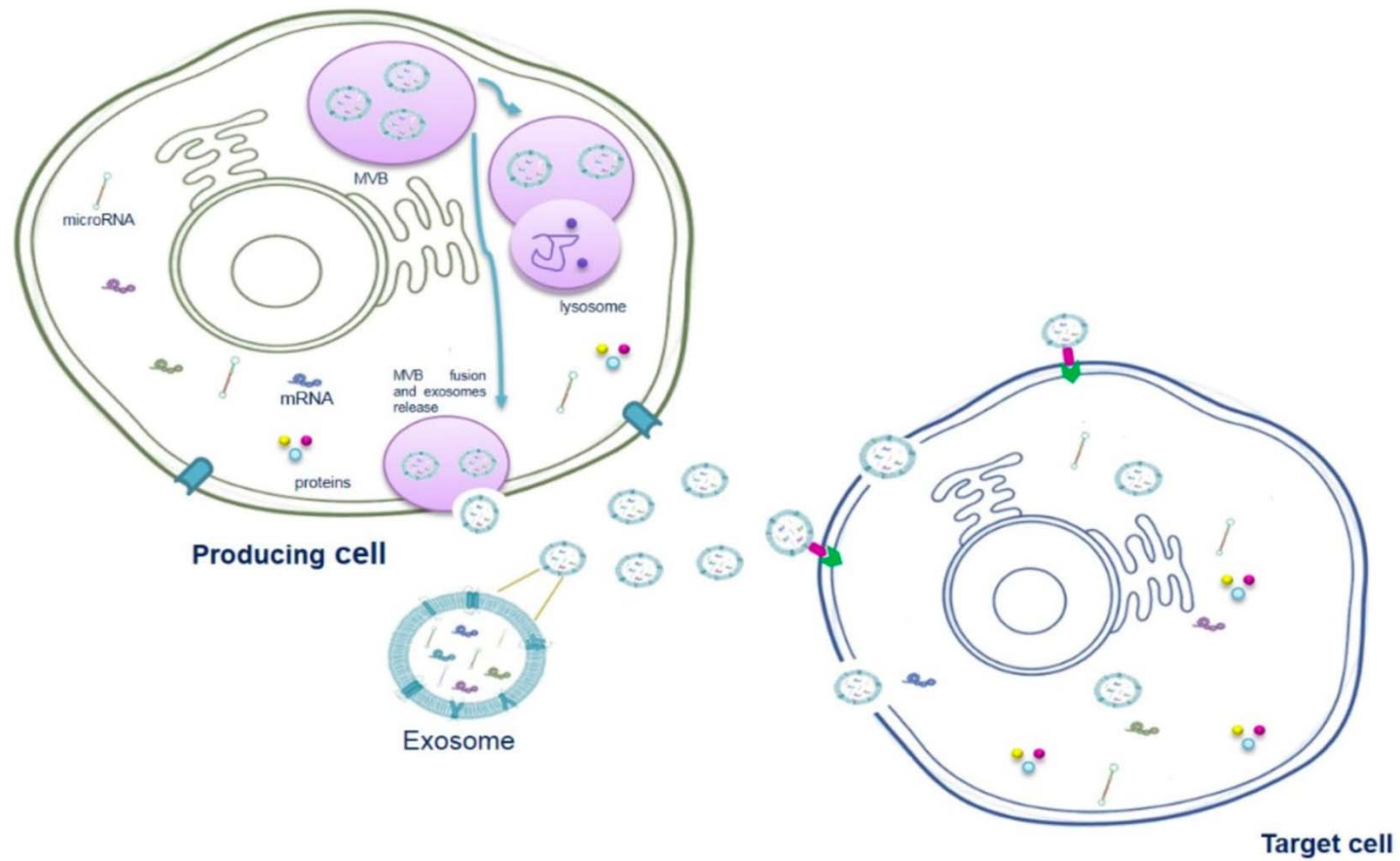
Liquid biopsy can provide clinically-valuable information along the whole patient journey



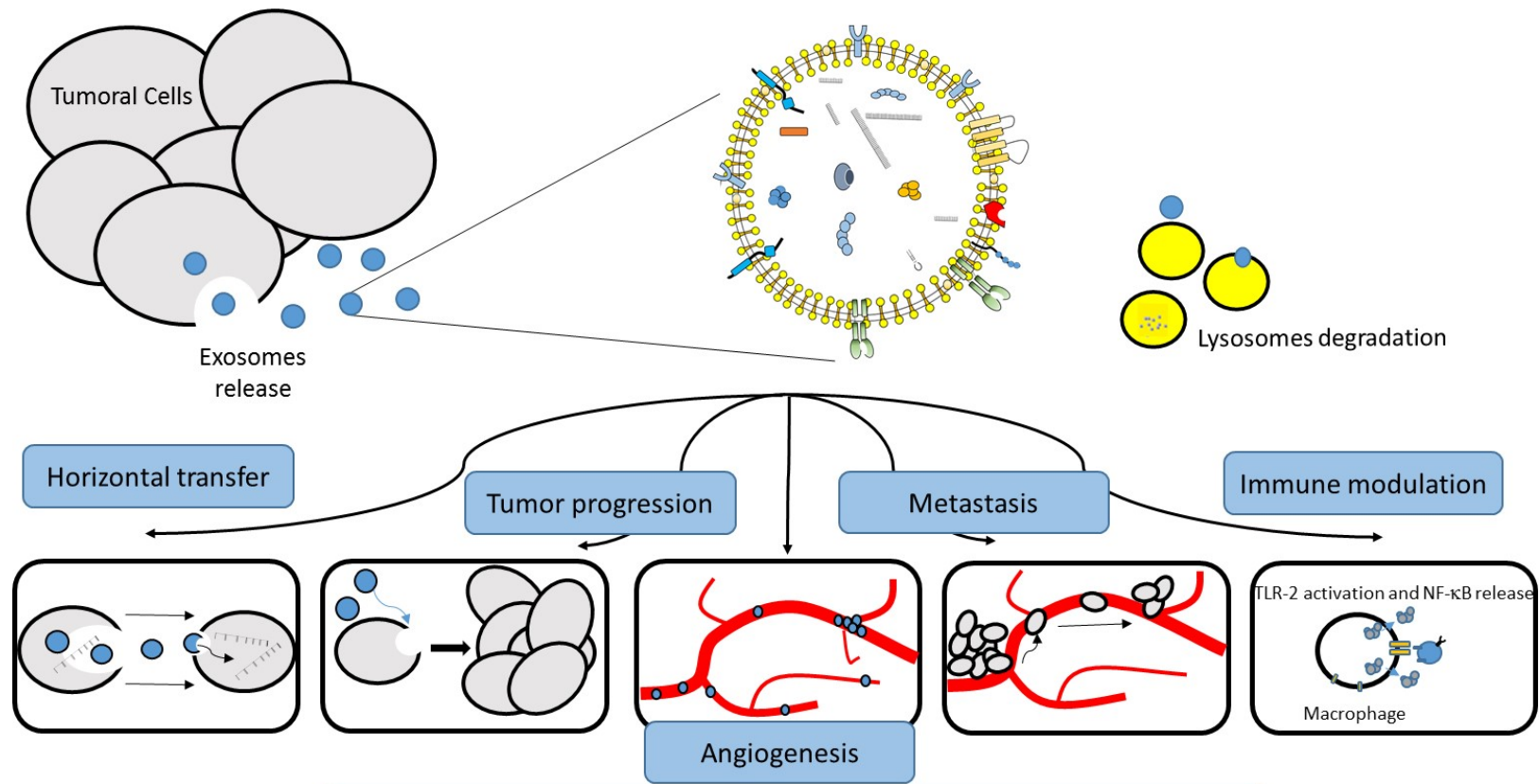
Liquid vs. Tissue Biopsies in Cancer Interception



Exosomal cross-talk



Pleiotropic role of exosomes



Seed and Soil theory



- ✓ A number of recent studies have described **EVs as messengers** with the potential to modulate intercellular communication
- ✓ Several reports suggest that EVs **cargo** that can heavily **influence gene expression in target cells...**
- ✓ **First “soldiers”** in metastastization process
- ✓ **Premetastatic niche**

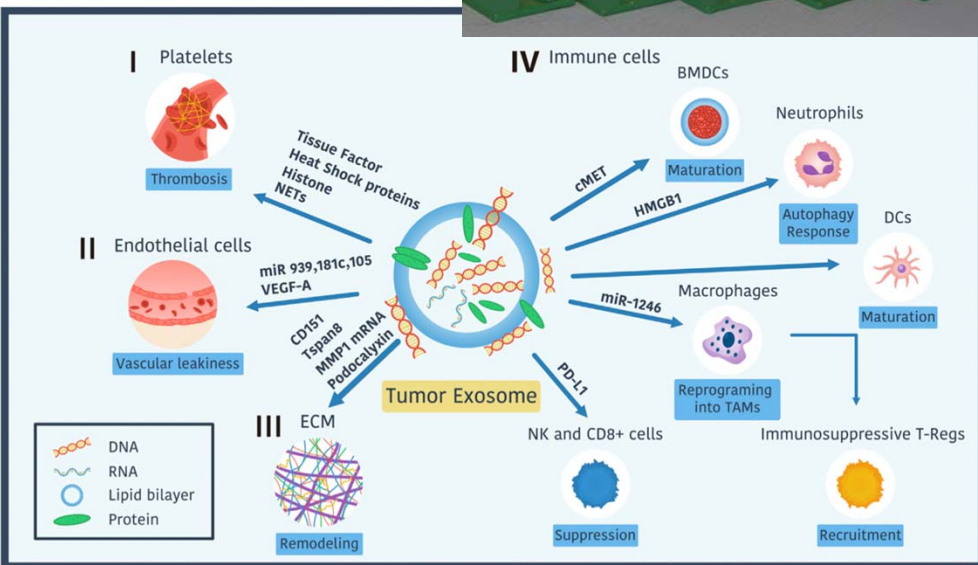
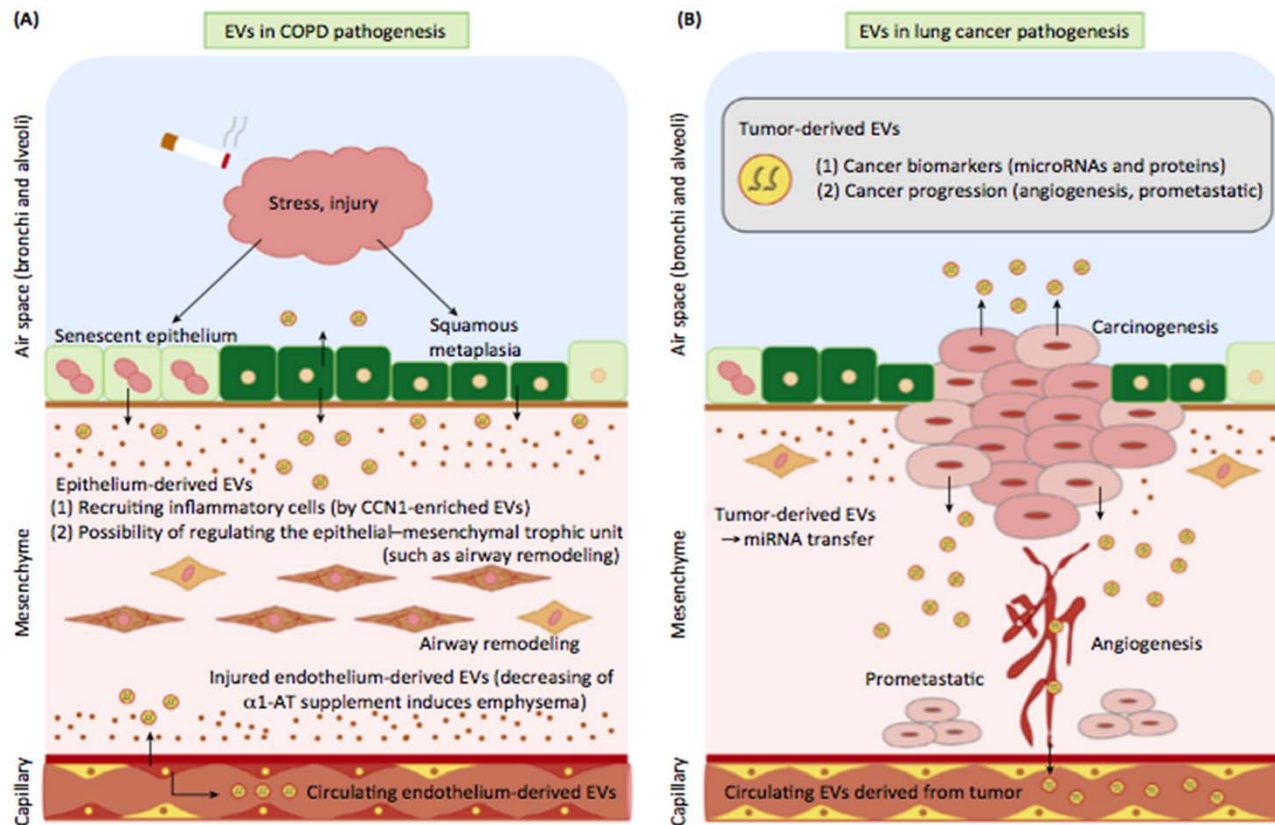


Image from Wortzel et al, Developmental Cell 49, May 6, 2019

The function of extracellular vesicle (EVs) in COPD and lung cancer pathogenesis

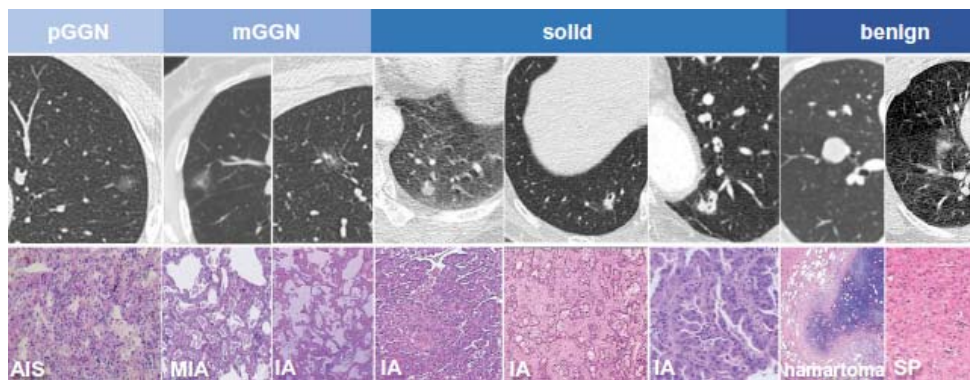


RESEARCH ARTICLE

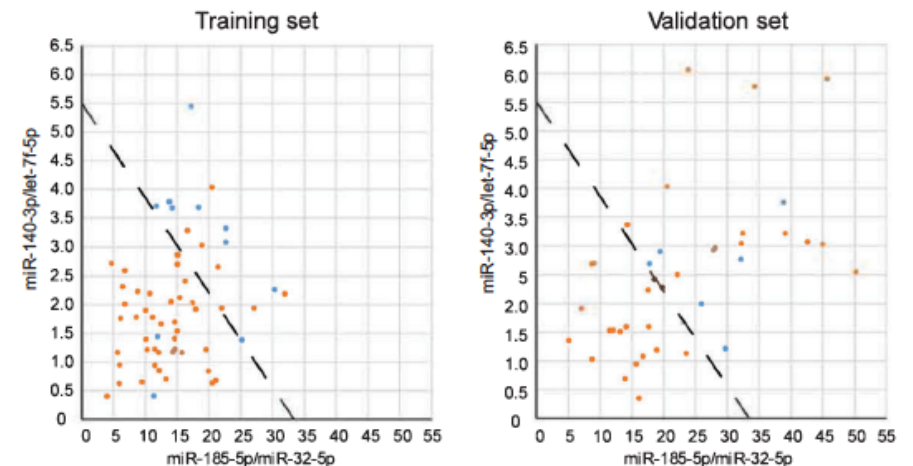
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Plasma extracellular vesicle microRNAs for pulmonary ground-glass nodules

Jia-Tao Zhang^a, Hao Qin^b, Fiona Ka Man Cheung^c, Jian Su^a, Da-Dong Zhang^b, Shi-Yi Liu^b, Xiao-Fang Li^b, Jing Qin^{de}, Jun-Tao Lin^a, Ben-Yuan Jiang^a, Song Dong^a, Ri-Qiang Liao^a, Nie Qiang^a, Xue-Ning Yang^a, Hai-Yan Tu^a, Qing Zhou^a, Jin-Ji Yang^a, Xu-Chao Zhang^a, Ya-Nan Zhang^b, Yi-Long Wu^a and Wen-Zhao Zhong^a



The Support Vector Machine classifier accurately distinguished malignant GGNs and benign nodules



	Training set	Validation set
Sensitivity	85.1%	75.0%
Specificity	59.3%	100.0%

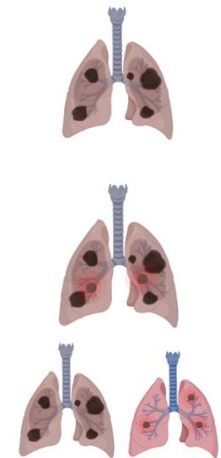
Chronic Obstructive puLmOnaRy disease evolution and inhaled treAtment responses using liquiD biOpsey (COLORADO project)



Objectives:

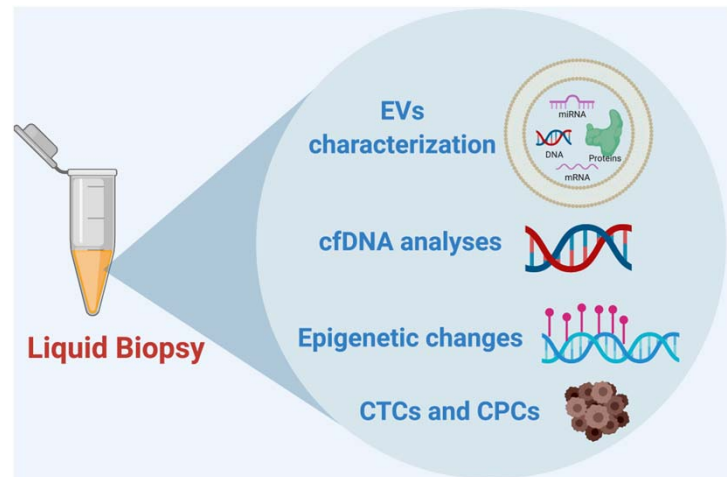
1. Identify the evolution of COPD in real time through the long of the time.
2. Stratify patients into responders and non-responders to the initial inhaled therapies based on liquid biopsy
3. Identify molecular profiles based on liquid biopsy risk of developing cancer in COPD patients.

- 1) **COPD cohort:** patients with a diagnosis of COPD according to current national and international recommendations and starting an inhaled treatment.
- 2) **COPD & Lung cancer cohort:** patients with a diagnosis of COPD as discussed in #1 and confirmed diagnosis of localized lung cancer (Stage I & II) suitable for lung resection surgery
- 3) **Controls:** adults without COPD or Lung cancer

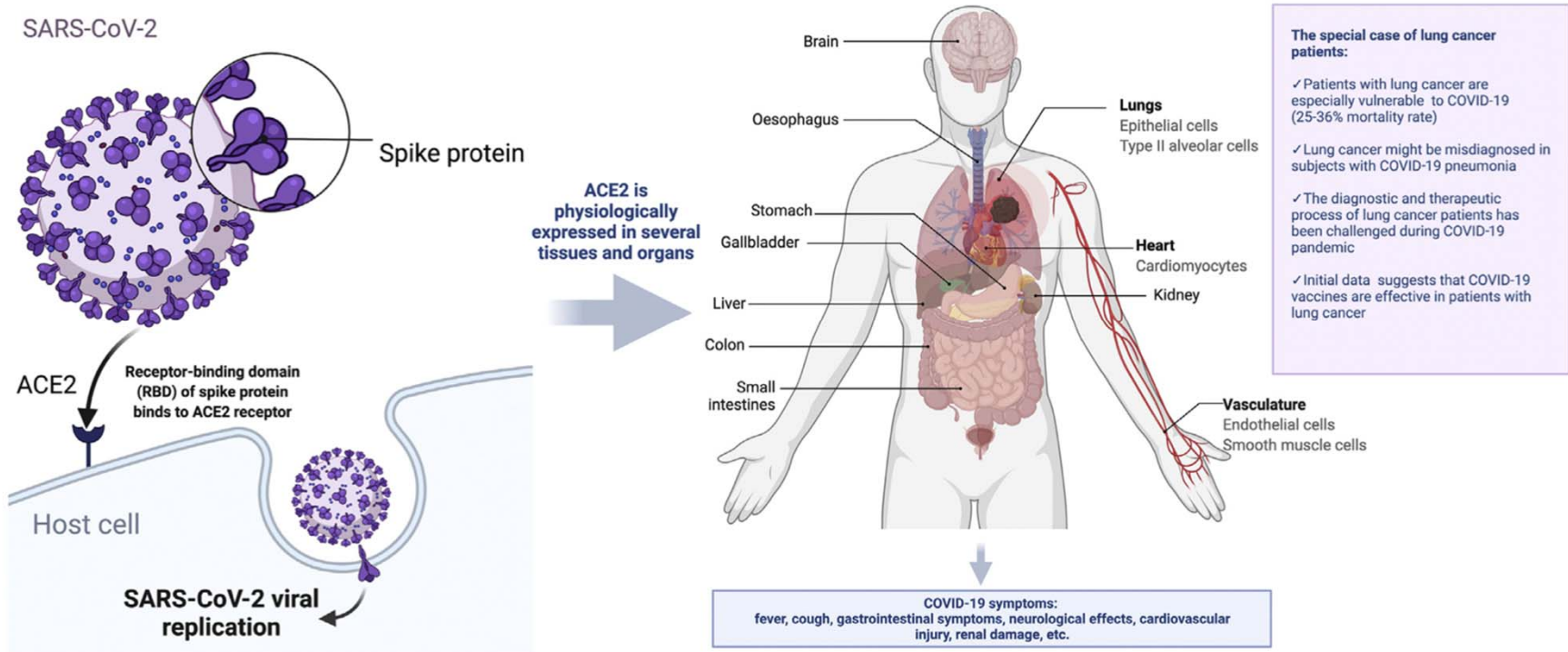


Methodologies:

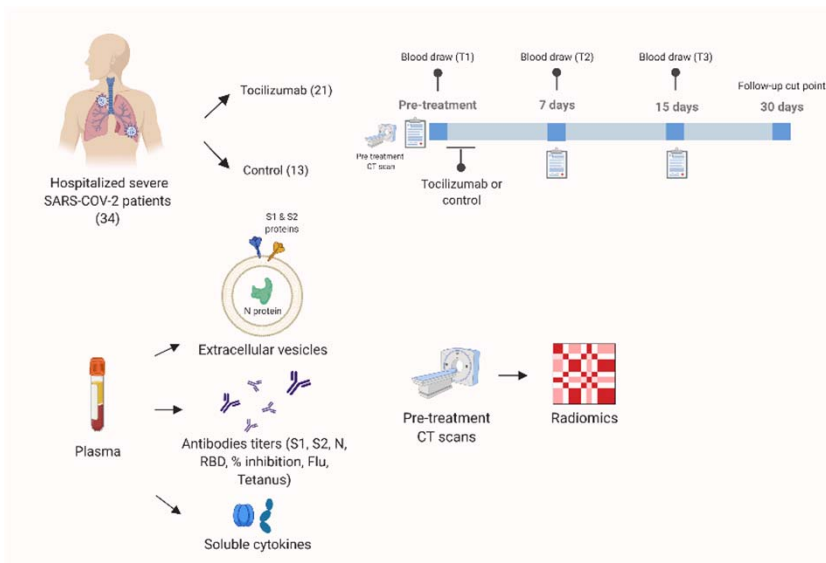
1. Detection and enumeration of Circulating Pulmonary Cells (CPCs) and Circulating Tumor Cells (CTCs)
2. Isolation and characterization of cfDNA
3. Methylation assays
4. Extracellular vesicles (EVs) characterization



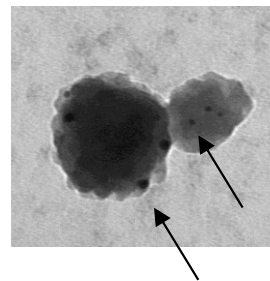
Lung Cancer and Severe Acute Respiratory Syndrome Coronavirus 2 Infection: Identifying Important Knowledge Gaps for Investigation



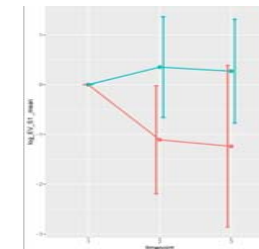
Extracellular vesicles carry COVID proteins and correlate with immune response and outcomes



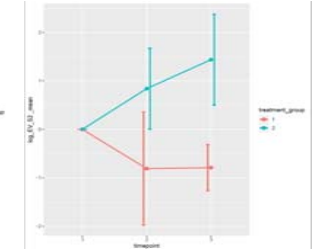
Immunogold CD9 & S2



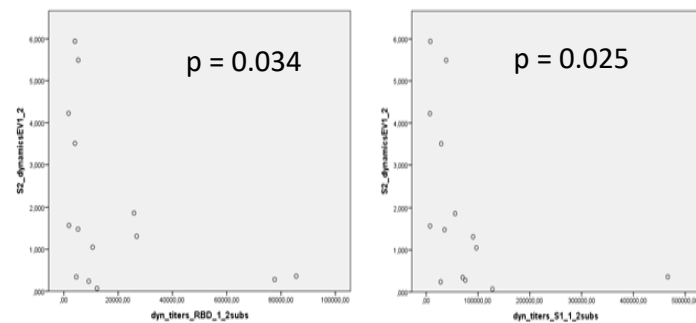
p=0.035



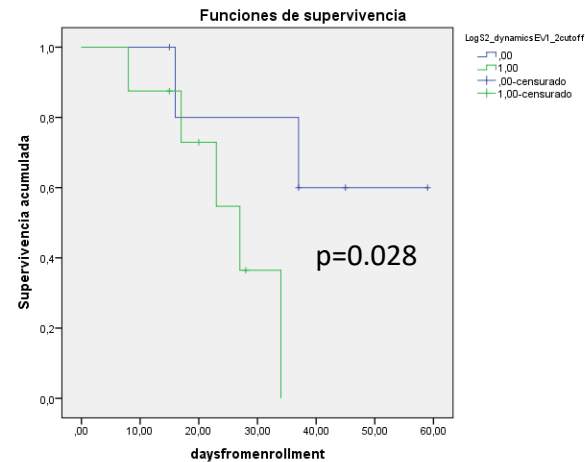
p=0.015



Tocilizumab reduced expression of S1 and S2 in EVs at 7 days in comparison to controls.

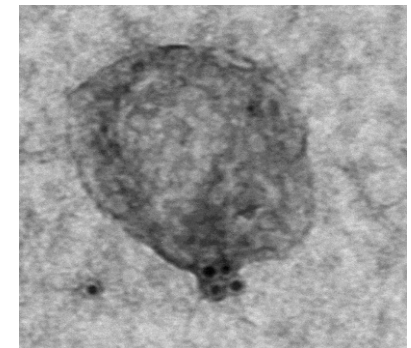


Dynamics of S2 correlates with RBD and S1 antibodies



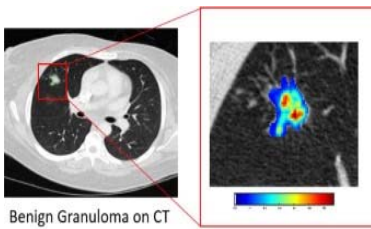
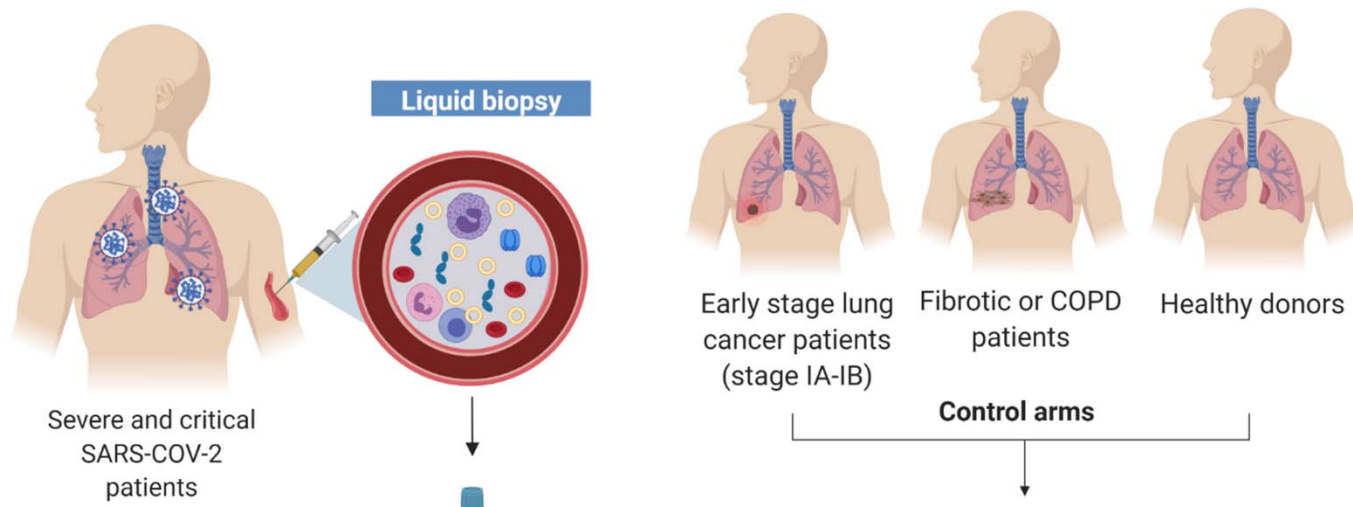
Higher S2 in EVs correlates with poor outcomes

N17 BAL

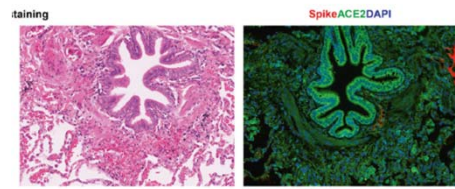


De Miguel-Perez. D. et al. Rolfo C. Under preparation

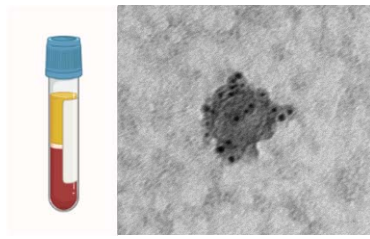
Lung Injury by SARS-COV-2 and Cancer Interception



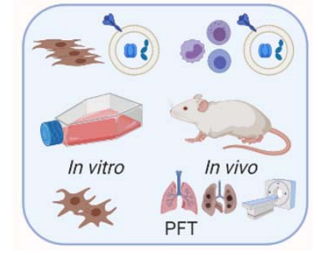
Radiomics



EMT transition



Evs Analysis

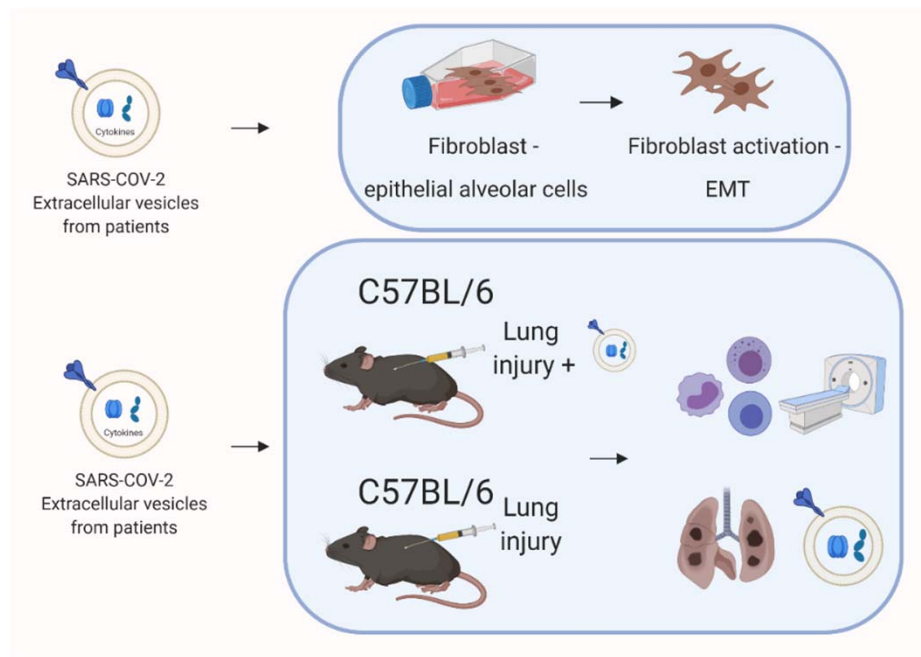


In vitro & In vivo models

Demonstrate the role of SARS-COV-2 convalescent patient derived-EVs in the mechanism of chronic pulmonary dysfunction in *in vitro* and *in vivo* models.

Rationale: Studies have demonstrated that EVs isolated from lung transplant recipients with viral infections are immunogenic and induced chronic pulmonary changes in lung of EVs immunized mice.

- ✓ SA-3A. Determine if SARS-COV-2 EVs induce chronic lung changes in *in vitro* model (Fibroblast activation).
- ✓ SA-3B. Investigate immunogenicity of SARS-COV-2 EVs.
- ✓ SA-3C. Determine if SARS-COV-2 EVs induce chronic lung changes in mice model after lung injury.



SARS-COV-2 Lung Injury and Cancer Interception Working Group



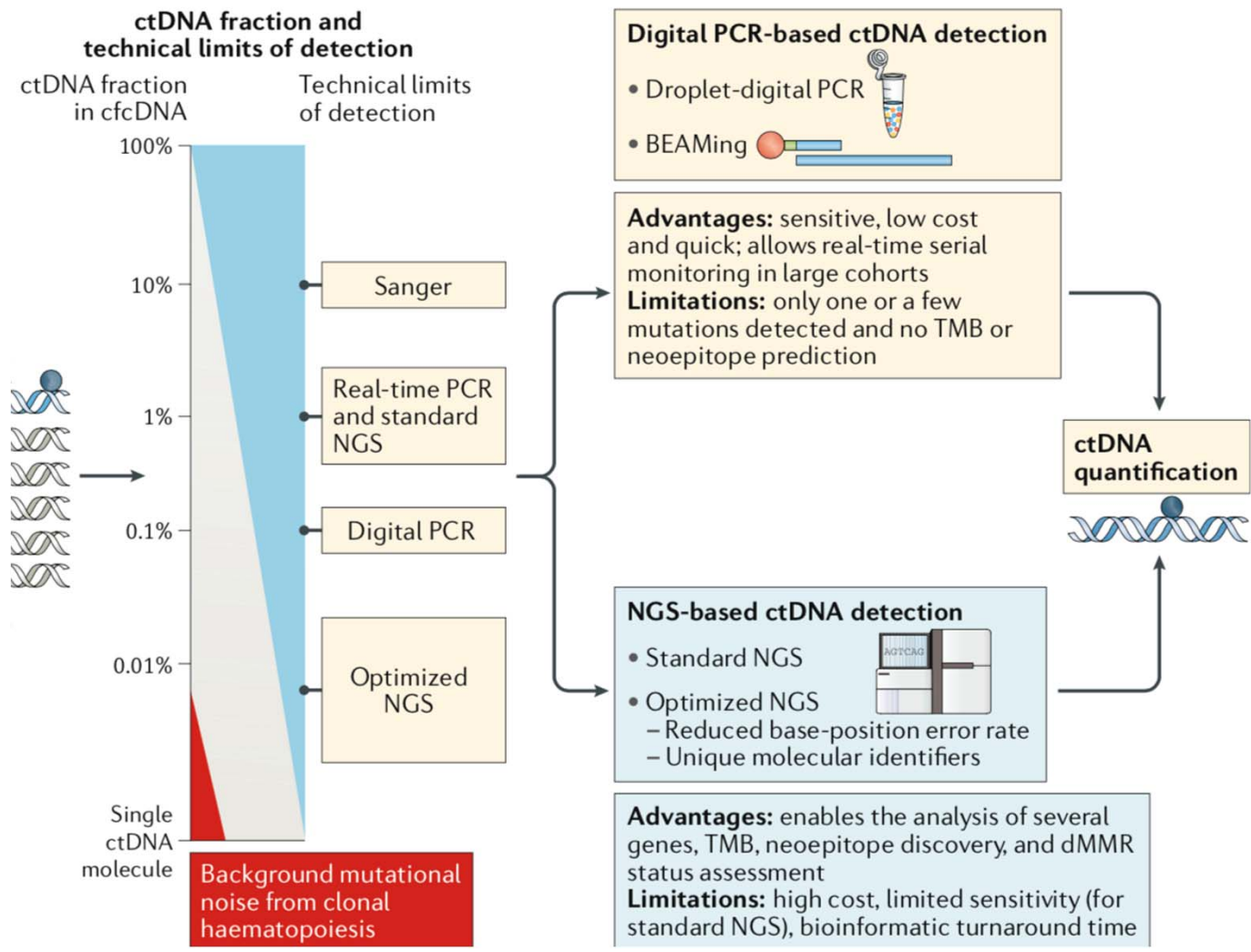
Other projects funding



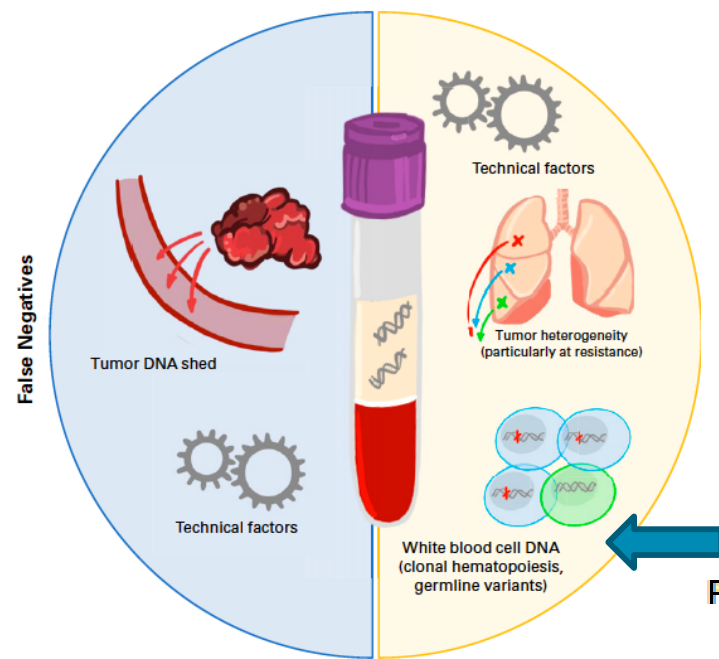
Clonal Hematopoiesis and liquid biopsies



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Sources of false positive and false-negative results in plasma NGS



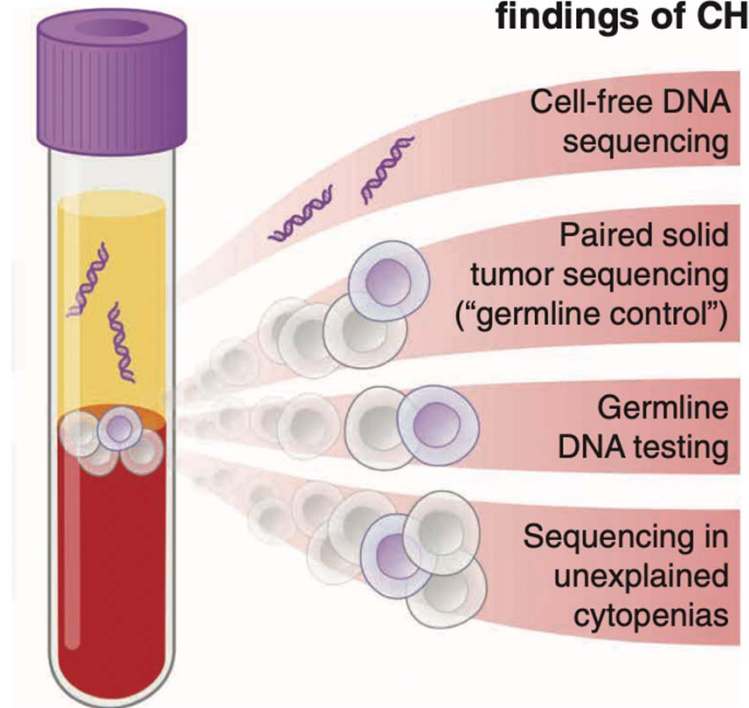
"False Positives" in Liquid Biopsy

Technical Factors:
Sample differences
(> 6 months from tissue to plasma sampling)

WBC contamination:
Germline Variants
Clonal Hematopoiesis

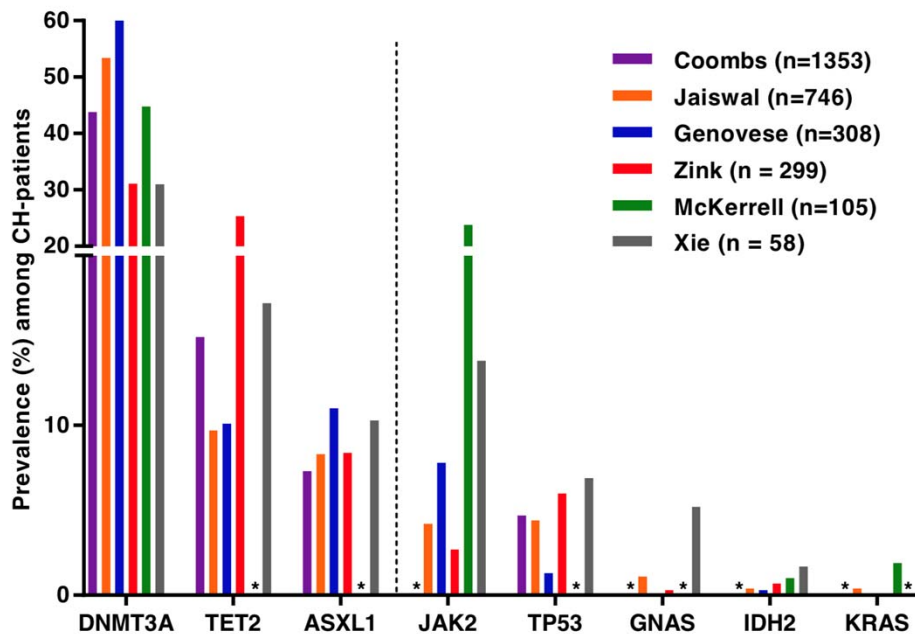
Tumor Heterogeneity:
Positive Plasma & Negative Tissue
(assumes tissue is "Gold standard")

Source of incidental findings of CH



A new problem: Clonal Hematopoiesis

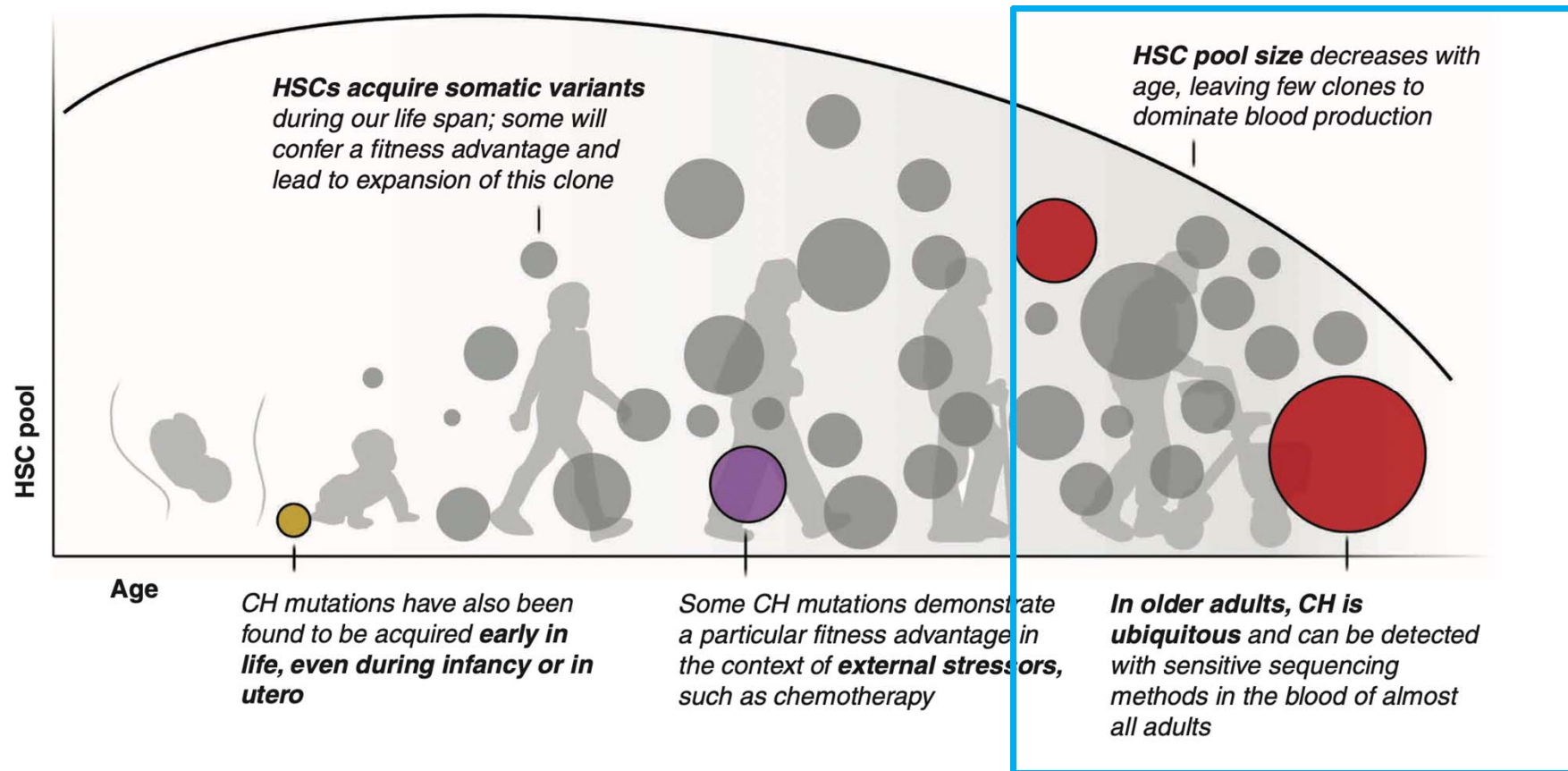
► Genes commonly mutated



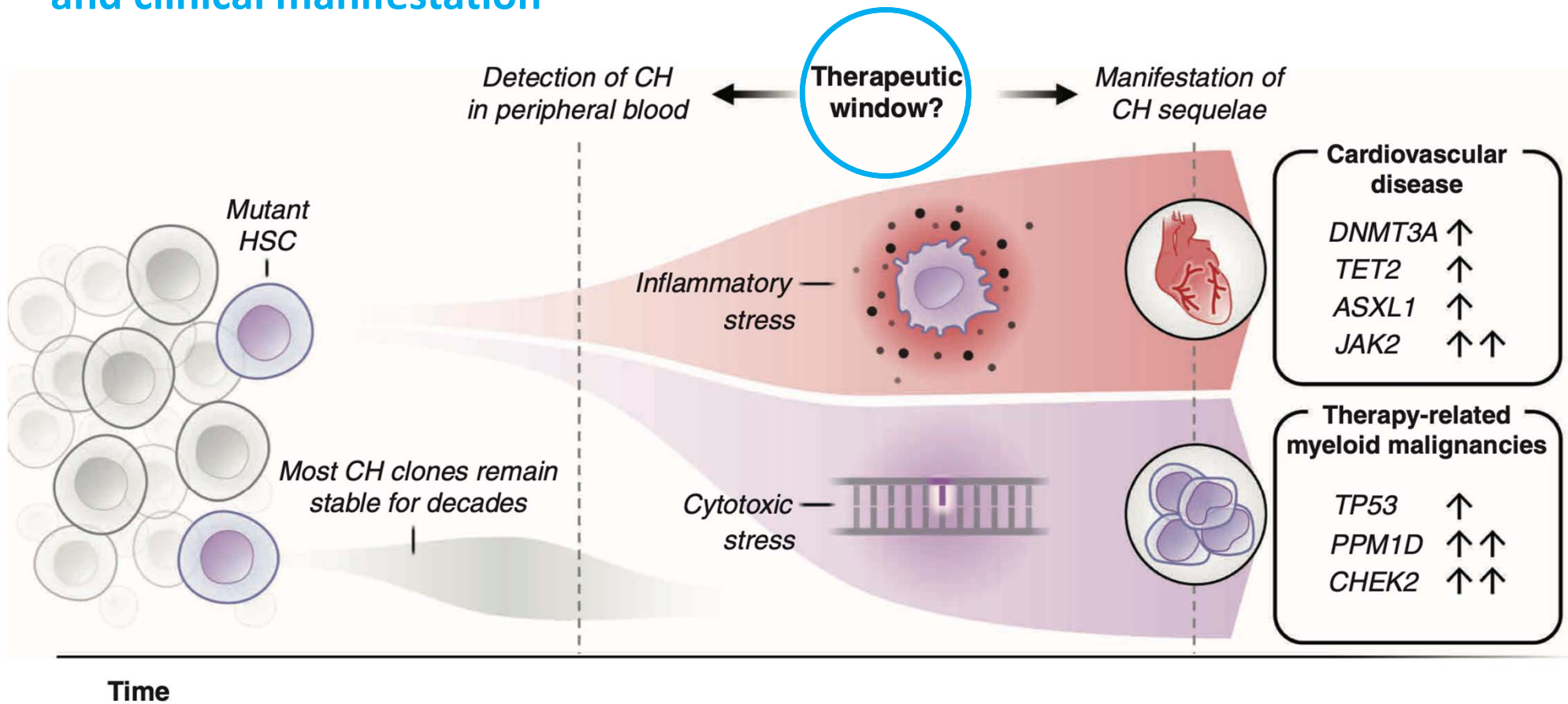
Clonal hematopoiesis (CH) is the somatic acquisition of genomic alterations in hematopoietic stem and/or progenitor cells, leading to clonal expansion.

- A **large proportion of cfDNA is derived from peripheral blood cells (PBC)**, therefore somatic mutations within non-malignant hematopoietic cells, known clonal hematopoiesis (CH).
- CH might be a recurring source of discordance between tumor genotyping and plasma cfDNA genotyping.

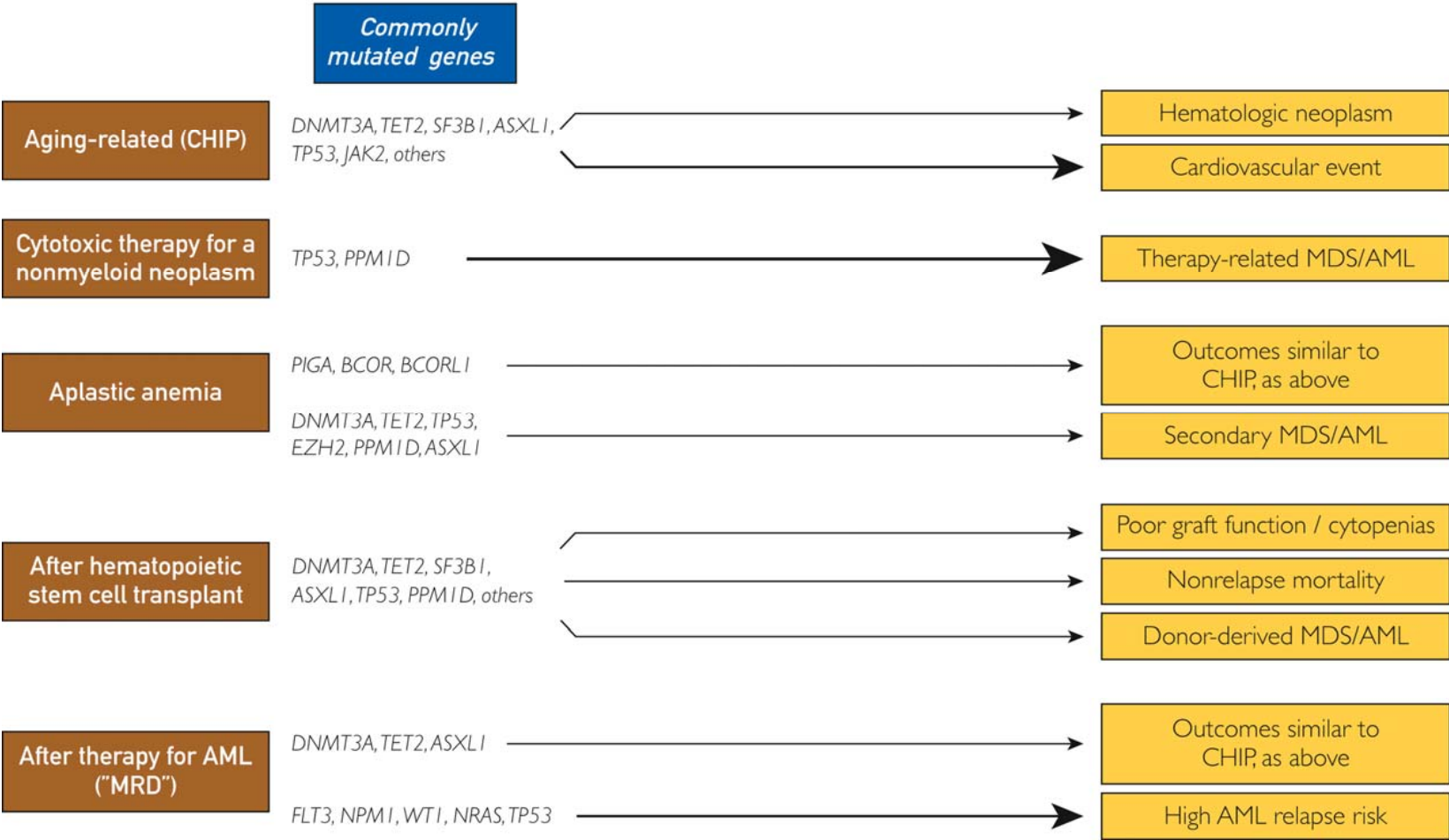
CHIP: context dependent mechanism

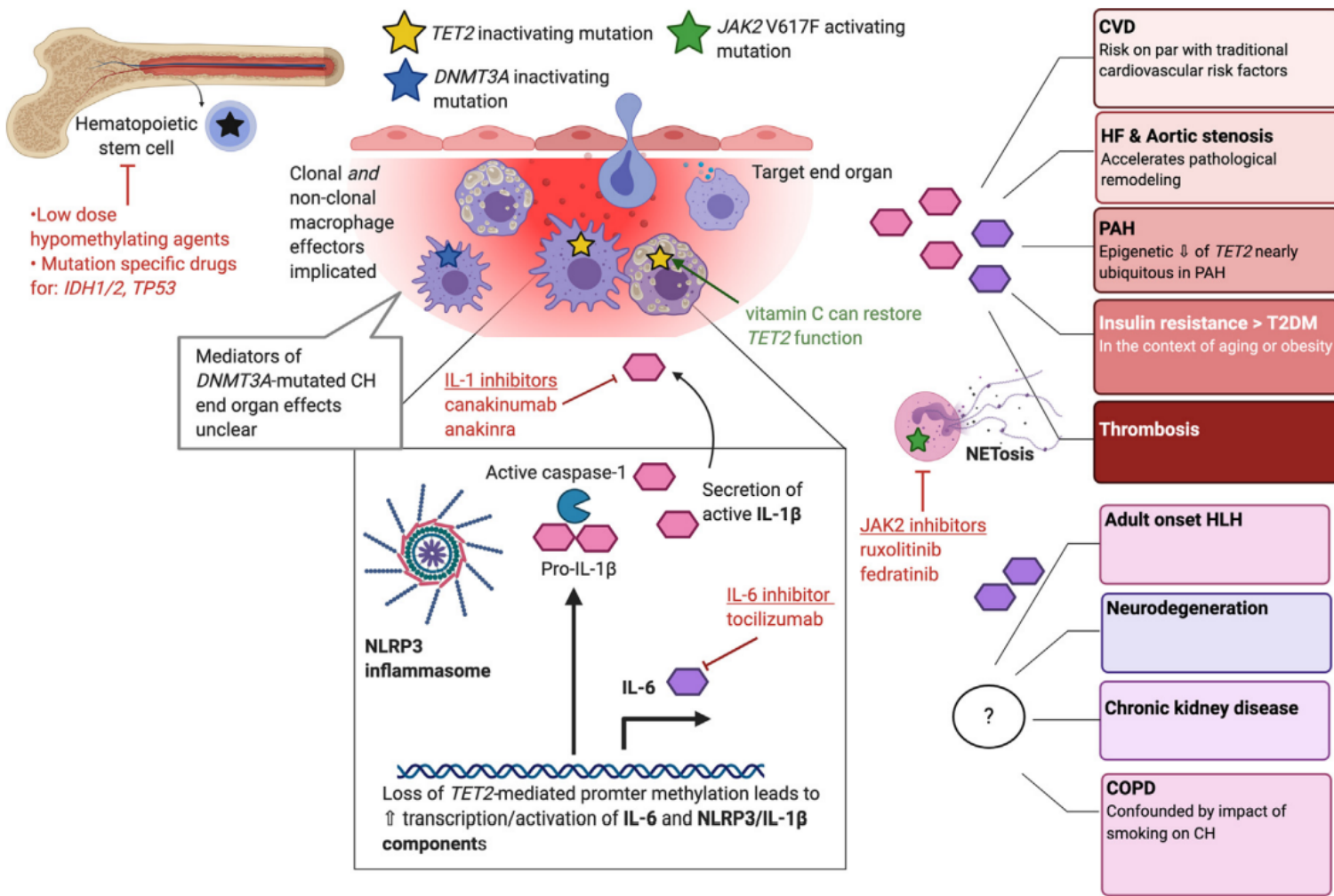


Latency between detection of clonal hematopoiesis in the peripheral blood and clinical manifestation



Clonal hematopoiesis: potential consequences





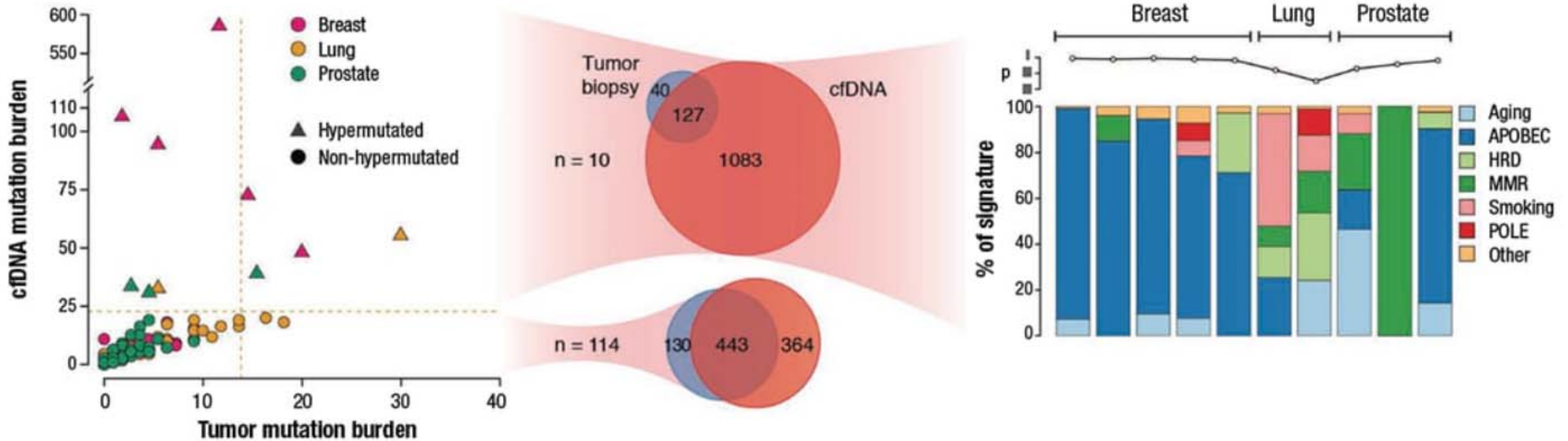
Cardiometabolic

Other

Impact of CHIP on cardiometabolic and other diseases

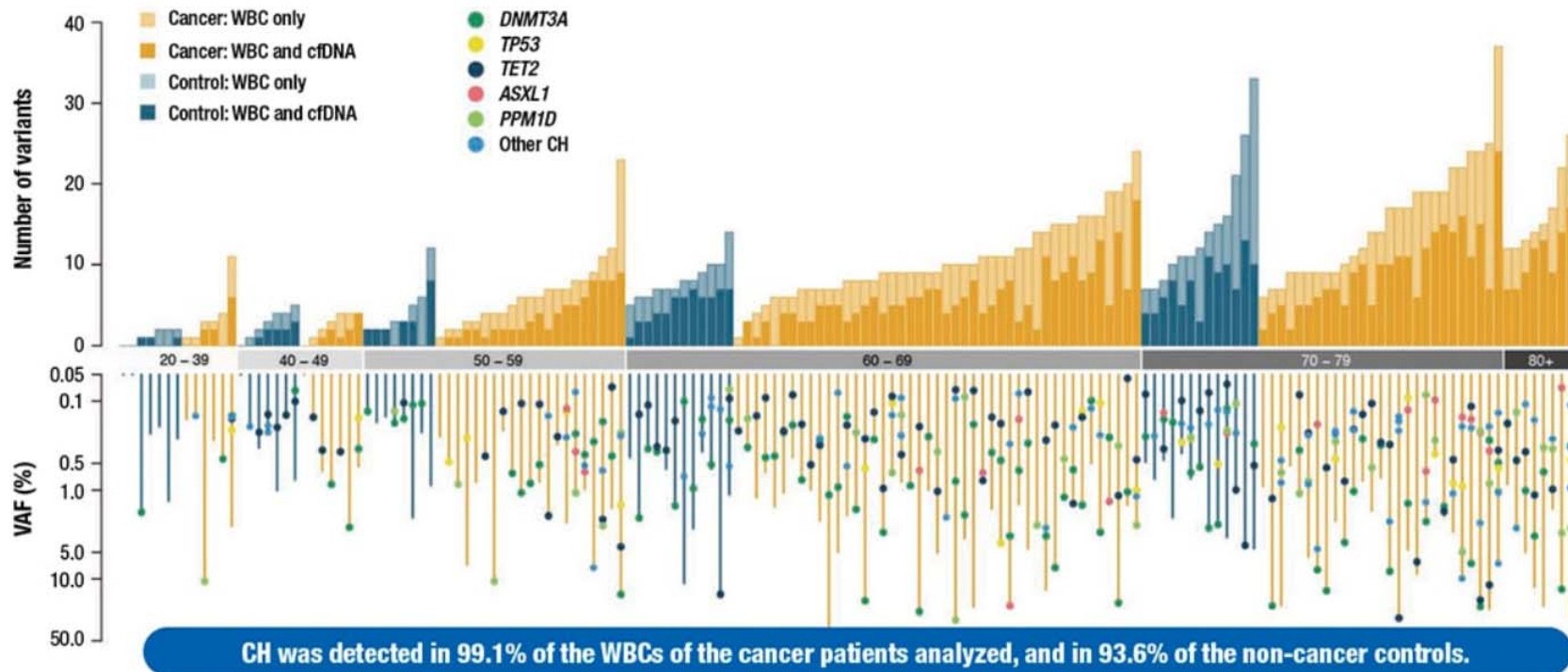
Clonal hematopoiesis can be found at the younger ages

10 hypermutated samples accounted for 60% of all cfDNA mutations and 75% of biopsy subthreshold mutations and VUSO across the entire cohort



Extensive variability in the rate of CHIP among healthy controls and cancer patients in each age category

Extensive variability in the rate of CH among the healthy controls and cancer patients in each age category



Spectrum of clonal hematopoiesis identifiable in ctDNA

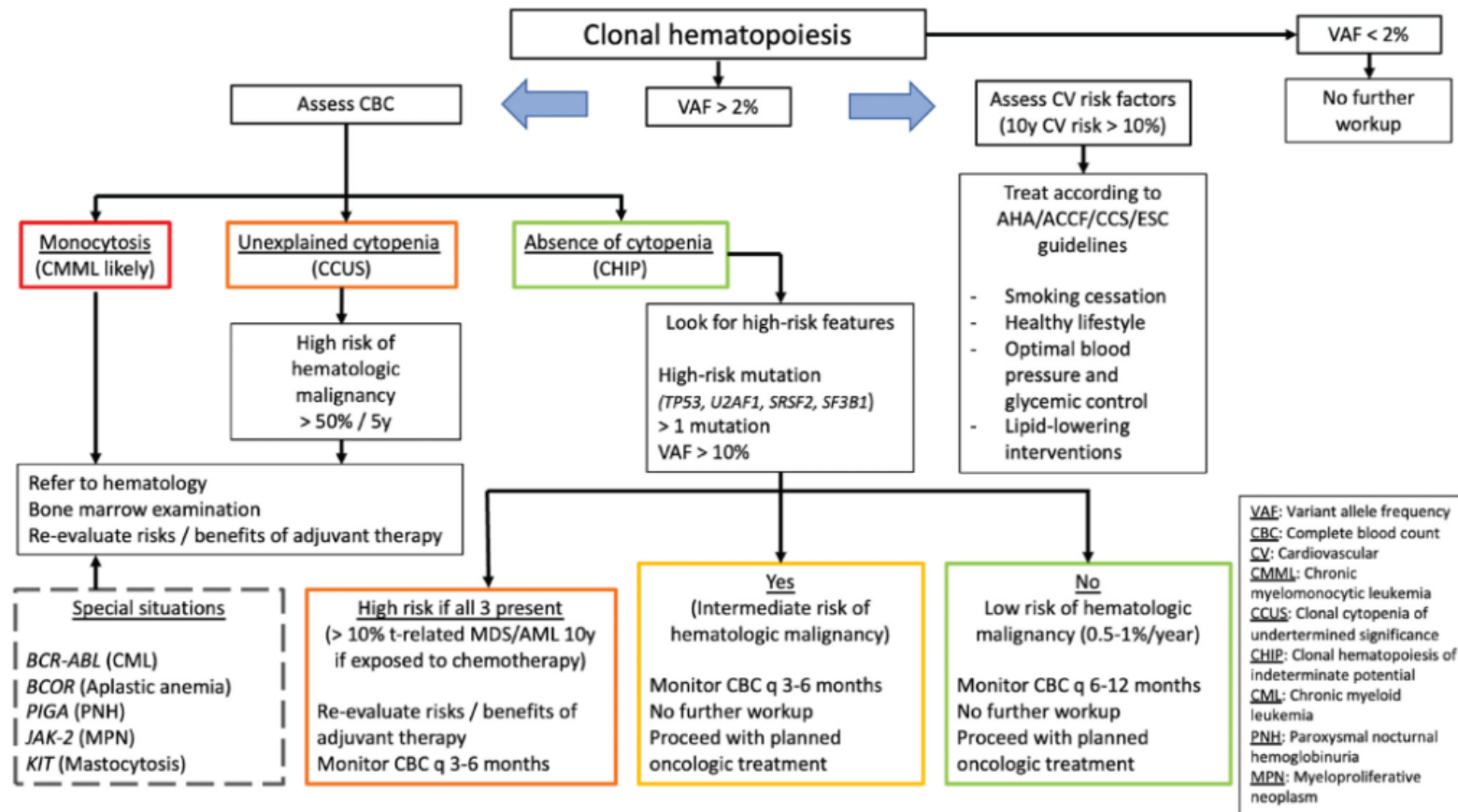
The acquisition of somatic mutations leading to the clonal expansion of hematopoietic stem cells

	ARCH	CHIP	CCUS	MDS (Low risk)	MDS (High risk)	sAML
VAF	< 2%	> 2%	> 2%	> 2%	>> 2%	>>> 2%
No of lesions	+	+	++	+++	++++	++++
Cytopenias	-	-	+	+	++	++
Dysplasia	-	-	-	+	+	+
BM blasts	< 5%	< 5%	< 5%	< 5%	5-19%	> 20%
BM failure						
Prognosis						

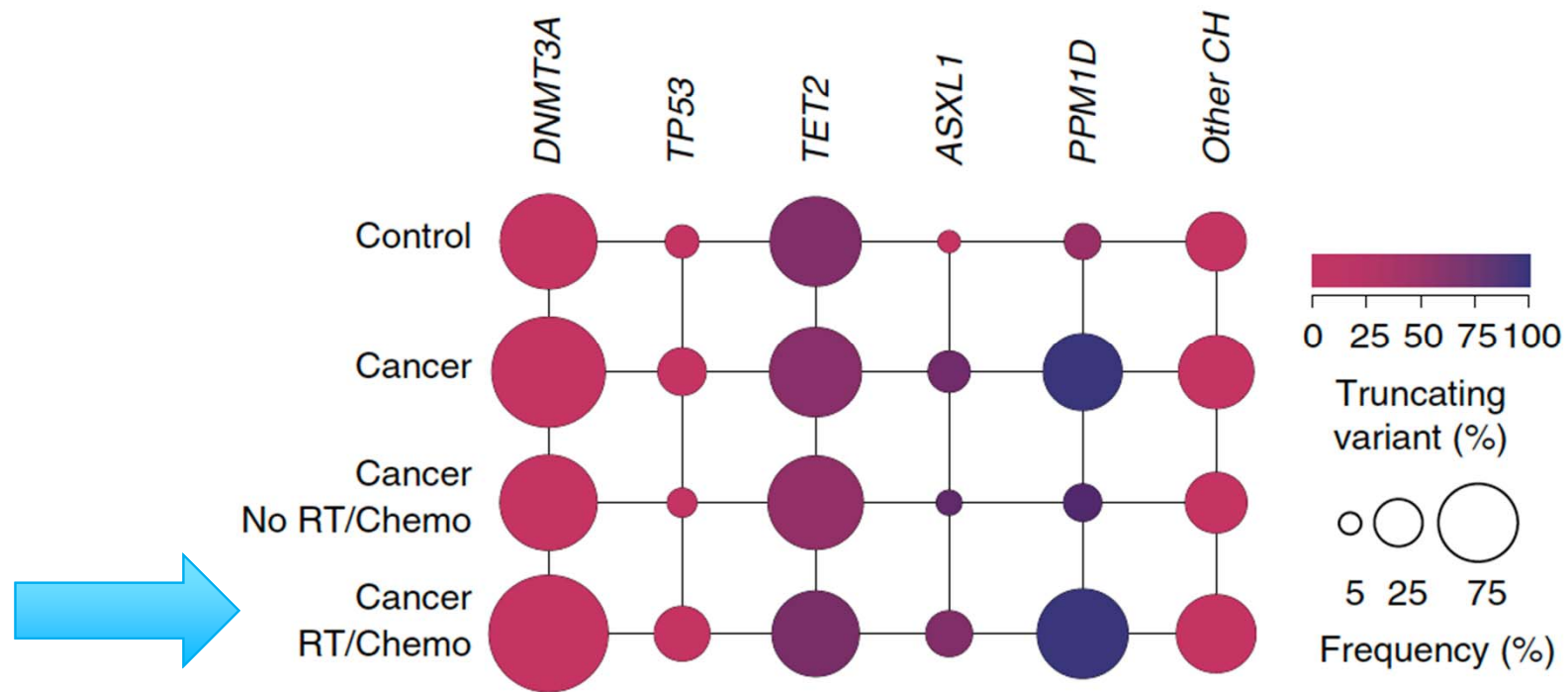
ARCH: Age-related clonal hematopoiesis
 CHIP: Clonal hematopoiesis of indeterminate potential
 CCUS: Clonal cytopenia of undetermined significance
 MDS: Myelodysplastic syndrome
 sAML: Secondary acute myeloid leukemia
 VAF: Variant allele frequency
 BM: Bone marrow

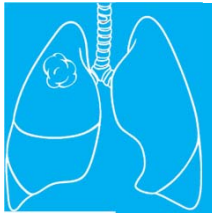


Proposed algorithm for dealing with clonal hematopoiesis detected in ctDNA



Clonal expansion





Center for Thoracic Oncology

CTO As facilitator of International Multidisciplinary Expert Clonal Hematopoiesis in Lung Cancer Early Detection

Biomarker Lab:
Liquid Biopsy Group



Christian Rolfo

computational
cancer genomics



Zeynep Gümüş

CHIP Clinic
Hematology



Bridget Marcellino

Molecular
Pathology



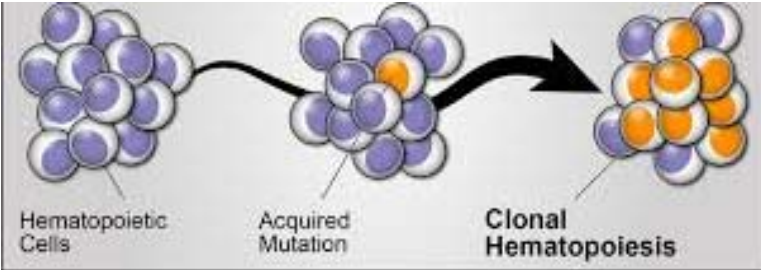
Umberto Malapelle



Marina Garassino



Natasha Leighl



Take Home Message

- **Cancer Interception is the new frontier of liquid biopsy**
- **Thinking beyond ctDNA...**
- **Clonal hematopoiesis is not just a confounding factor for liquid biopsy interpretation**
- **CHIP need to be followed in a multidisciplinary manner**
- **Possible use as biomarker**



**Join us in 2023
Madrid, Spain**



**Save the Date
19-21, November
2023**

Thanks



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