EDRN virtual Steering Committee meeting

Early Detection Research Network

Clinical Utility trial for biomarker driven management of Indeterminate Pulmonary Nodules

Pierre P. Massion

On behalf of the lung collaborative group

October 28, 2020

Early Detection Research Network

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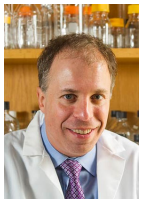
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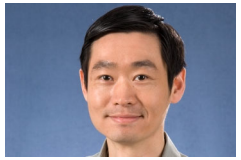
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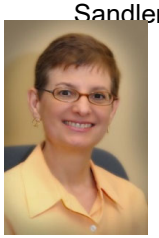
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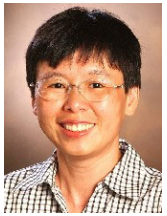
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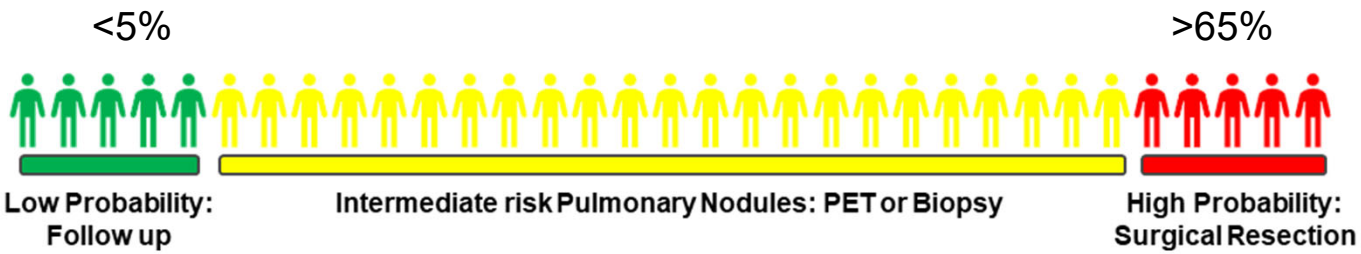
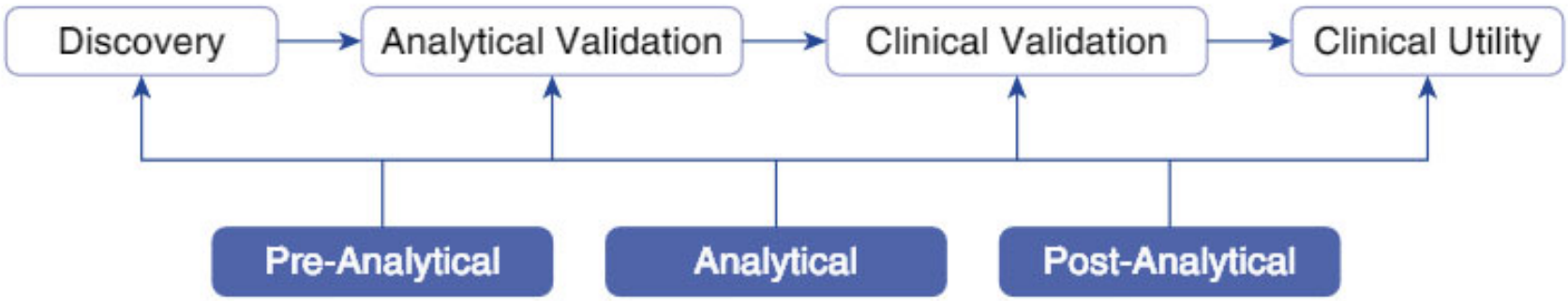
Hypothesis

Early Detection Research Network



Biomarker helps stratify risk

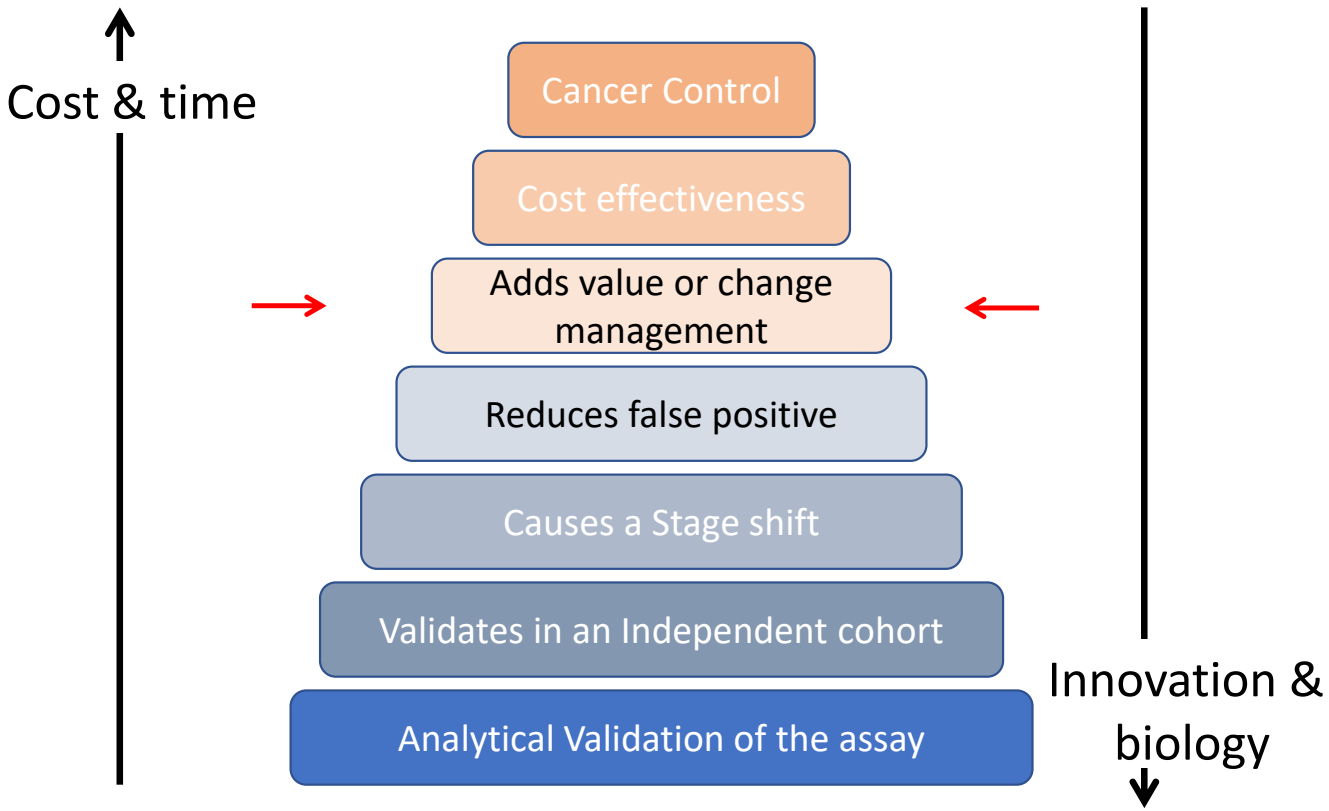
Evaluating Molecular Biomarkers for the Early Detection of Lung Cancer: *When Is a Biomarker Ready for Clinical Use?*



- DISCOVERY in the context it is intended to be used.
- ANALYTICAL VALIDATION - different blood collection tubes, variation in time, permitted for clot formation, …
- CLINICAL VALIDATION: Changes in the clinical context, screened or non screened population, clinical characteristics of cases or controls .
- CLINICAL UTILITY. What does it mean?

Mazzone et al. Evaluating Molecular Biomarkers
American Thoracic Society Policy Statement Oct 2017

Criteria for clinical use of biomarkers



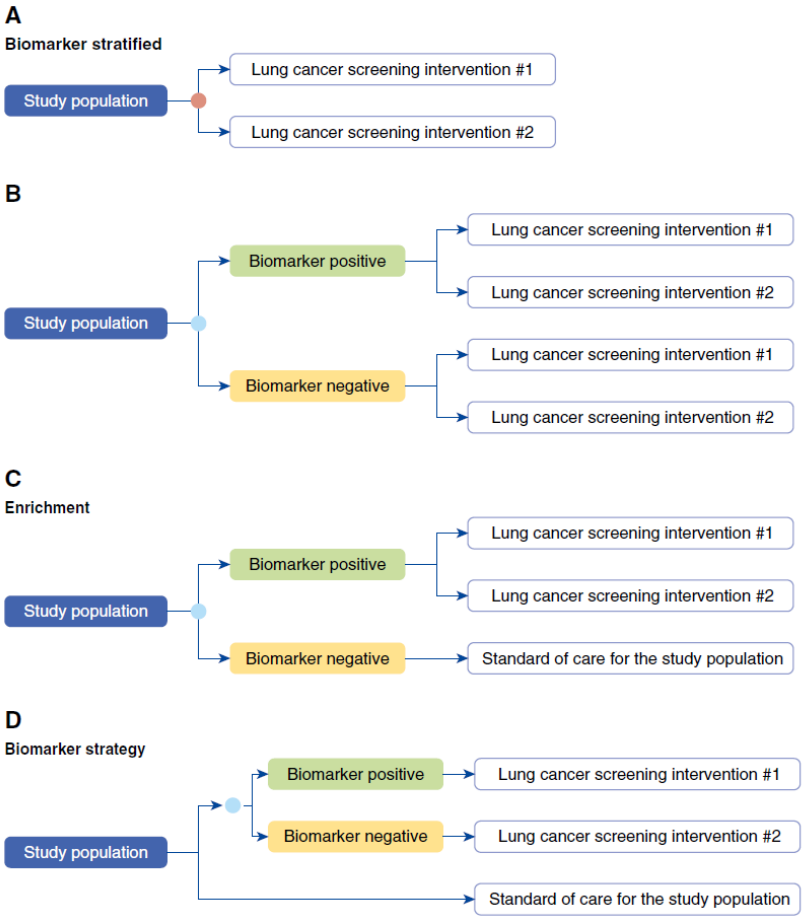
Atwater Seminars in Respiratory and Critical Care Medicine, 2016

Diagnostic biomarkers for lung cancer

Pepe, JNCI 2001- EDRN

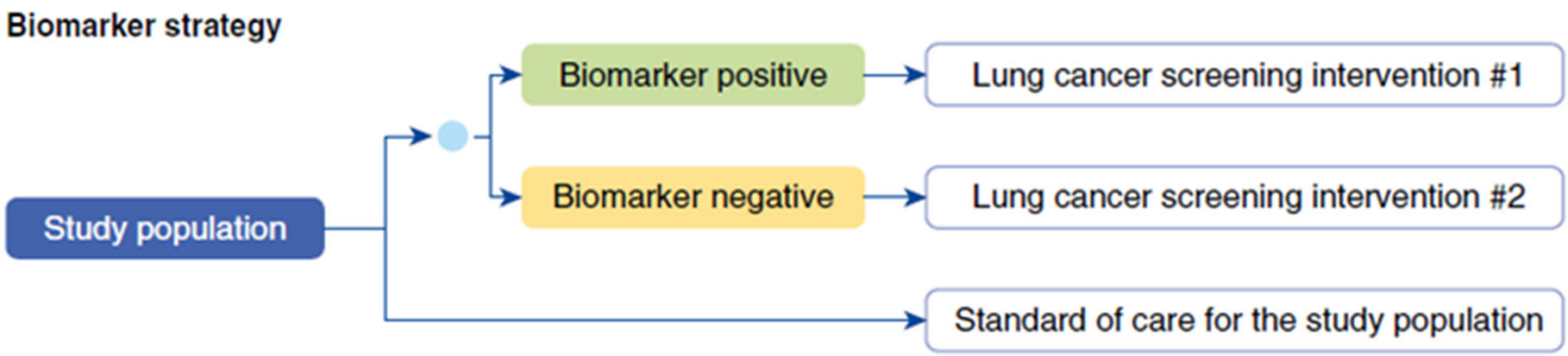
Candidates	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5
	Discovery, Prediction	Assay validation	Retro-longitudinal	Prospective Utility	Cancer Control
SERUM/PLASMA					
Proteomic profiling	x	x	x		
Autoantibodies	x	x	x	x	
Specific antigens /proteins	x	x	x	x	
miRNA	x	x	x	x	
DNA methylation Blood	x	x		x	
Nucleosomal fragmentation cfDNA	x	x			
Circulating Tumor DNA	x			x	
TUMOR/airway epith	x	x	x		
Preinvasive histo/cytology					
DNA methylation	x	x	x		
RNA airway signature	x	x	x	x	
MS profiling	x	x			
Chromosome aberrations	x	x			
SPUTUM/EBC					
DNA Methylation Sputum	x	x	x		
DNA CN -FISH	x	x			
VOCs	x	x	x		
Imaging biomarkers					
Radiomics				x	
Deep Learning				x	

Study design for clinical utility of LC screening biomarker



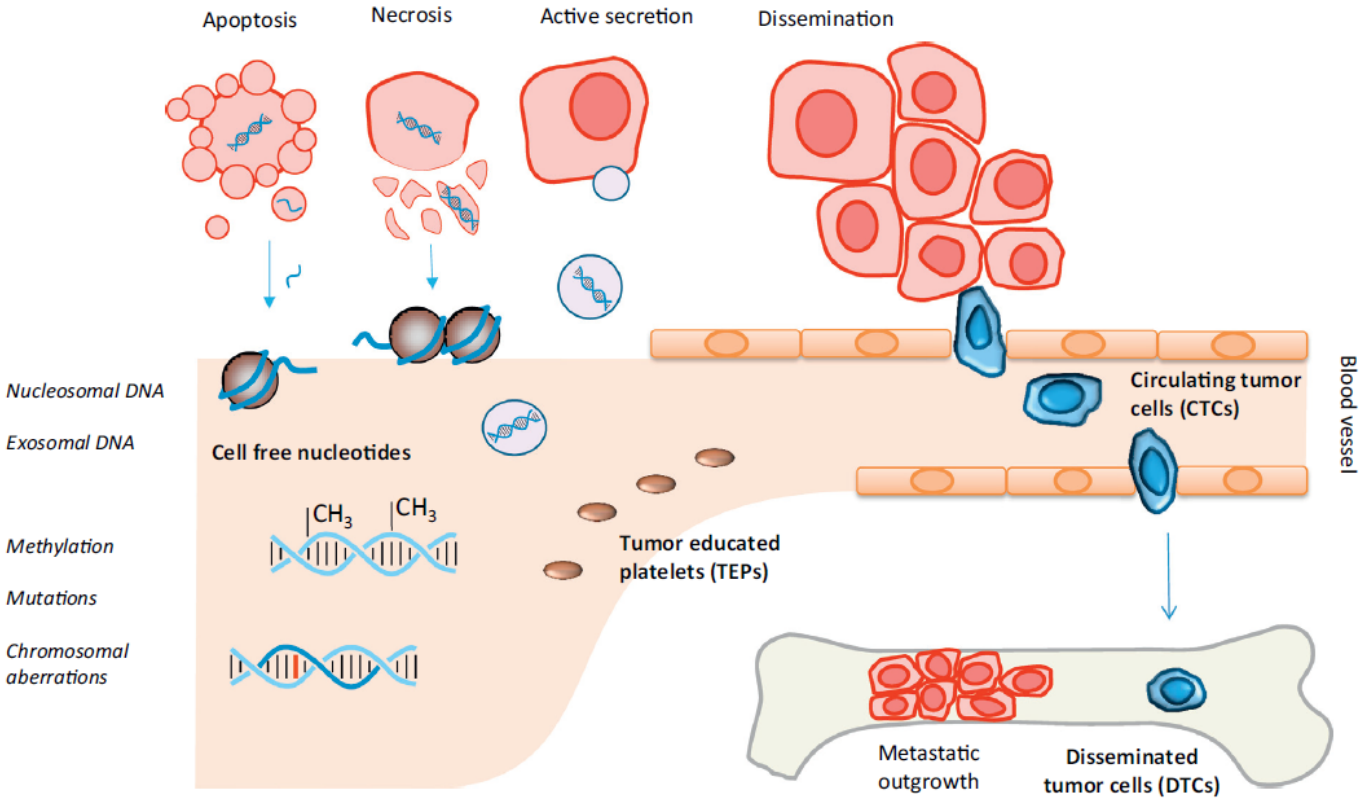
Mazzone et al. AJRCCM Oct 2017

Clinical utility of a diagnostic biomarker --Study Design



Mazzone et al. AJRCCM Oct 2017

Liquid Biopsy biomarkers.



- NGS: Targeted, Safe Seq, Capp-Seq,…
- Dig PCR: dd PCR, Beaming
- RT PCR
- MS: ultra Seq

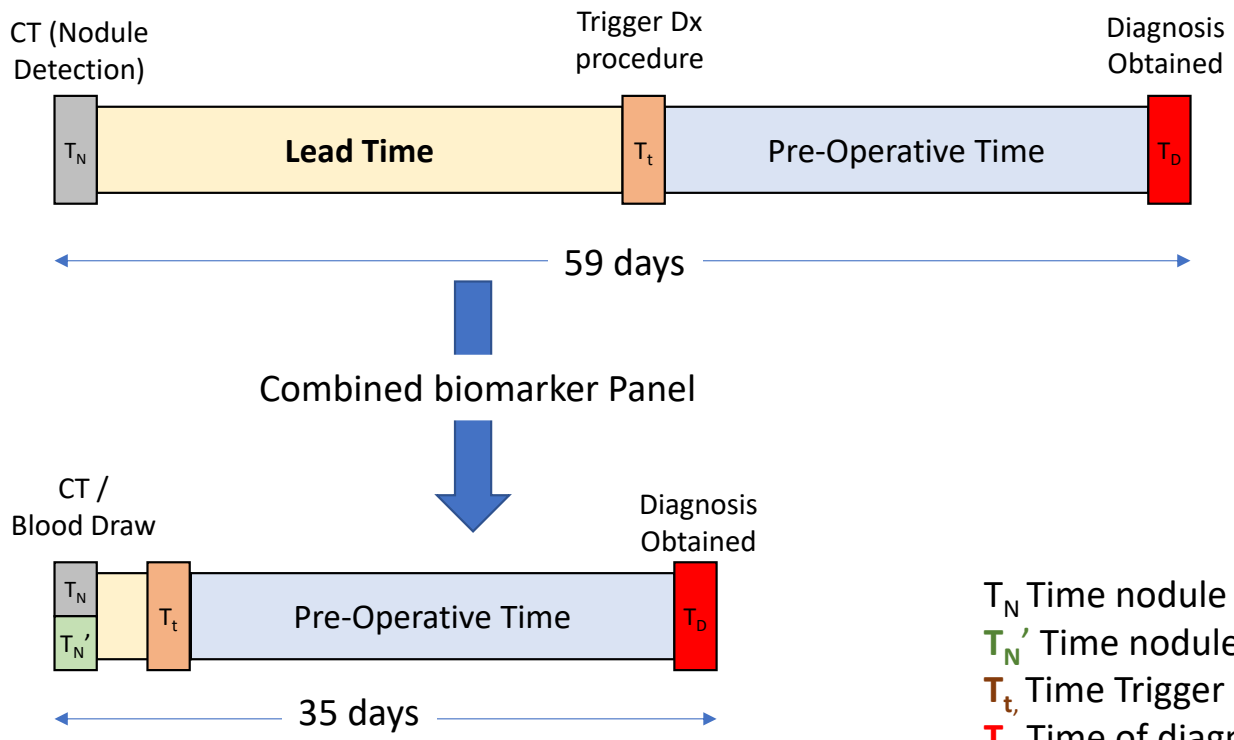
- Need to detect and localize cancer

Elazezy Comp Struch Biotech J 2018

Liquid biopsy biomarker performance stage1 LC

Moiety	Signature	Assay	Sensitivity	Specificity	AUC
ctDNA Lung CLIP		NGS	39	95+	82%
ctDNA Grail		NGS	40	95+	?
CTCs		EPCAM	30	90	
Meth cfDNA		NGS	50	92	
cfDNA nucl Fragm		NGS			?
hsCYFRA 21-1	single	BSI	85	99	92

Clinical utility of the model: hsCYFRA 21-1 and Radiomics Reduced Time to diagnosis tested on 106 patients from VUMC.



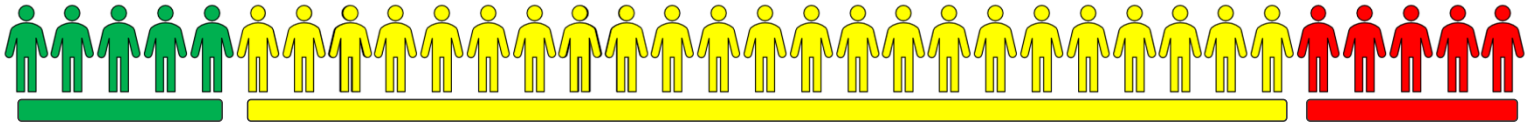
T_N Time nodule detection
T_N' Time nodule detection with BM
T_t, Time Trigger a diagnostic procedure
T_D Time of diagnosis

Kammer et al Submitted 2020

Conclusions

The incidentally detected IPN population: roughly 1.6 million per year

Clinical Risk Model

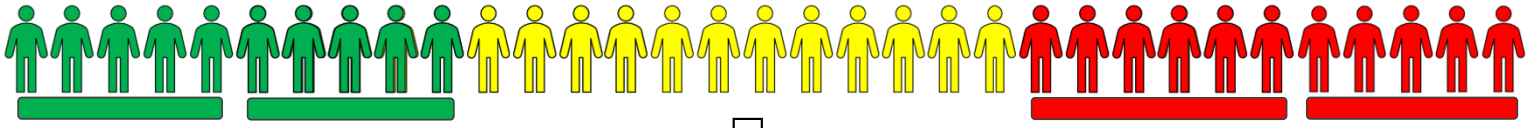


Low Probability: Follow up

Intermediate risk Pulmonary Nodules: PET or Biopsy

High Probability: Surgical Resection

Combined Biomarker Model

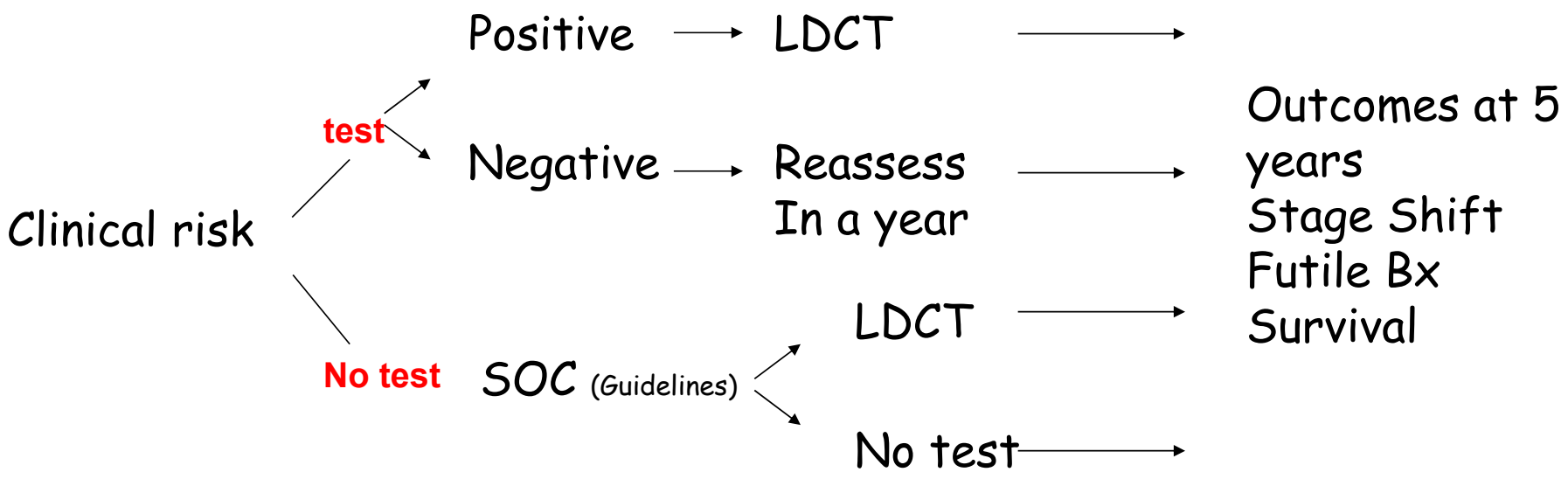


Rule Out 30%

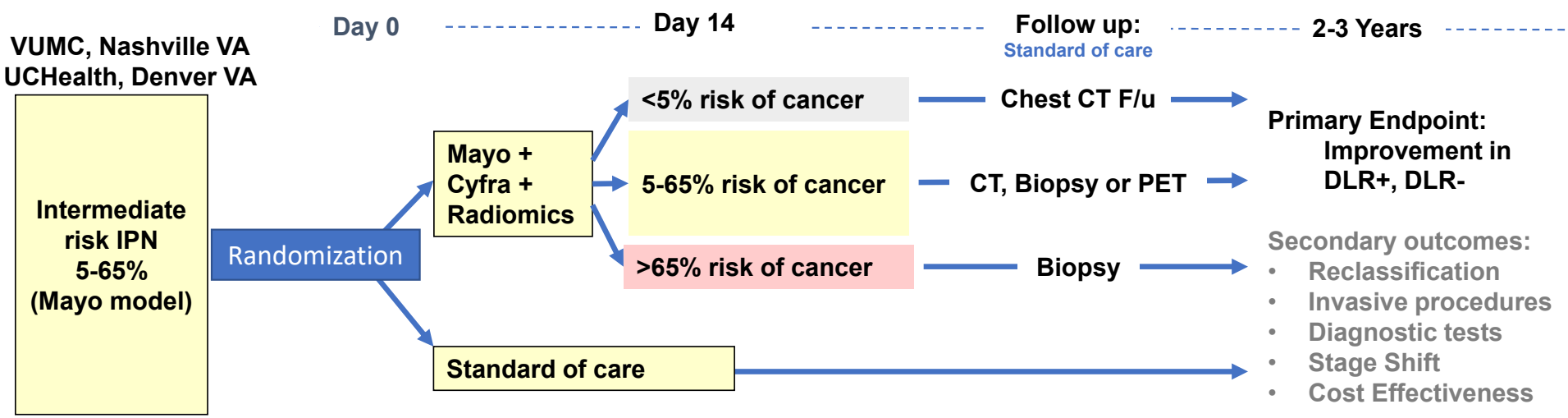
Rule In 45%

Lower rate of unnecessary biopsy/thoracotomy/PET

Study Design : Clinical utility of a risk biomarker



Biomarker-informed management of IPNs

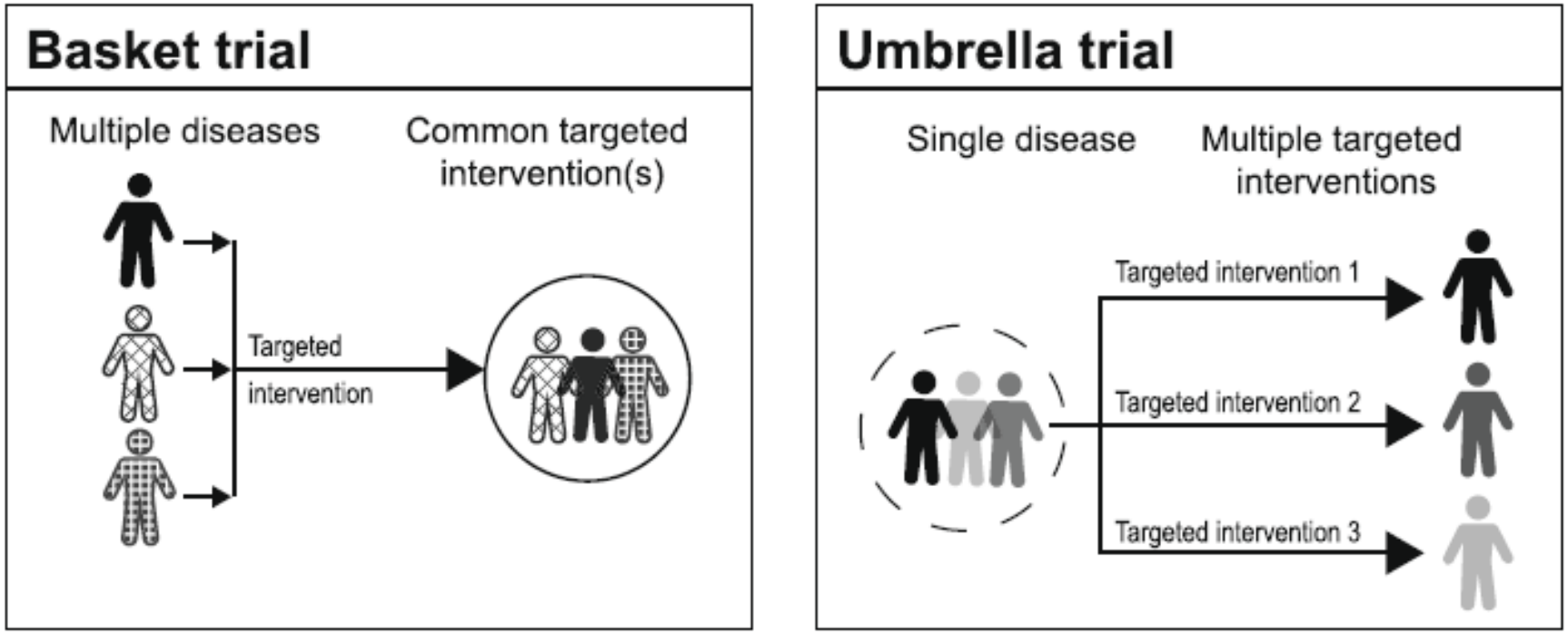


Randomized IIB
440 patients

Follow up 2-3 years

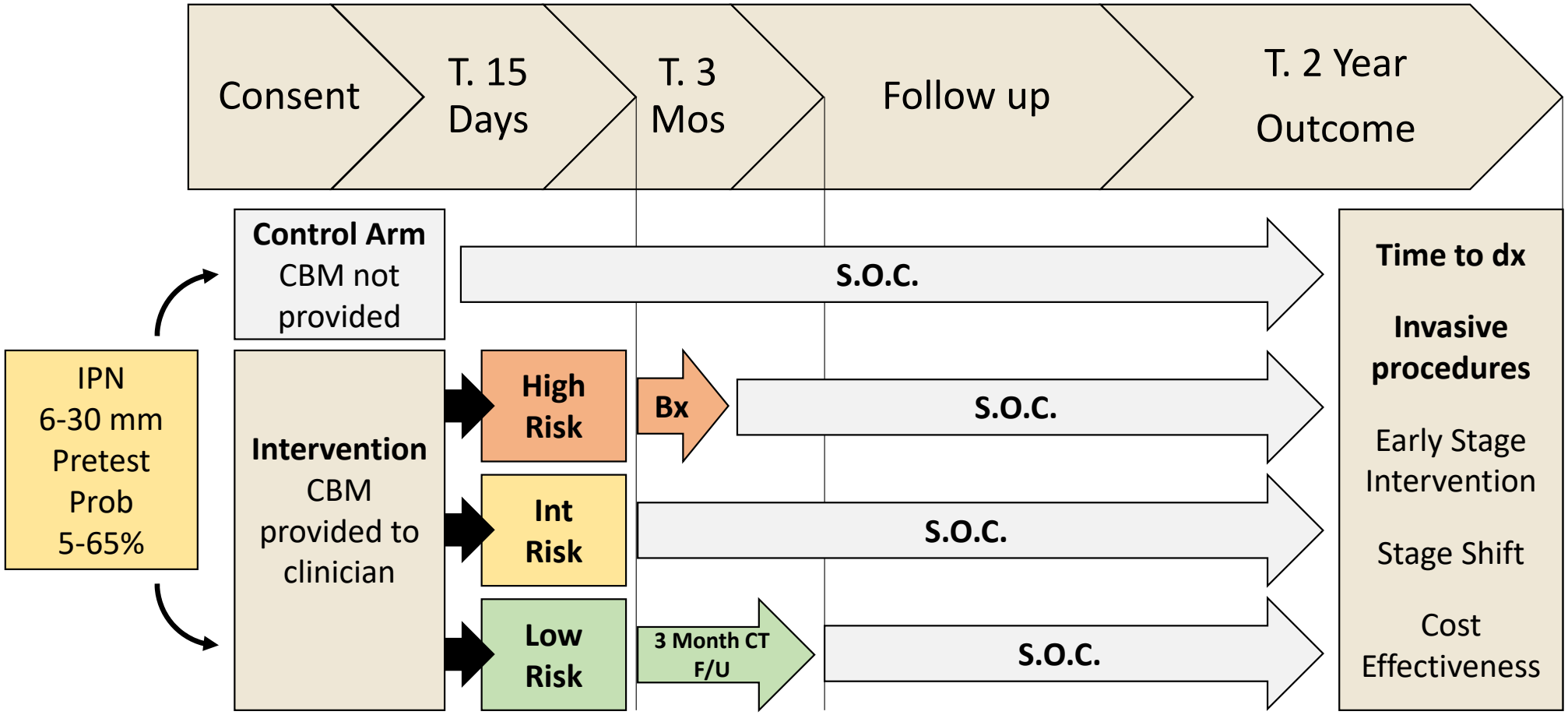
Safety: Minimize FP
Minimize FN

Master protocols



Park et al Trials 2019

Proposal of a Master protocol: Biomarker driven trial for the management of IPNs



Get on the train and test clinical utility of your biomarker

Conclusions

- BM has multiple layers of evidence. Long path before demonstrating clinical Utility.
- The industry will probably not sponsor RCTs unless the FDA sets the bar higher. We argue that biomarker research of early detection should reach 'evidence' based on randomized controlled trials or observational cohort studies
- Liquid biopsies are not ready for early detection of lung cancer. The field is progressing fast and many candidates are promising.
- Combination of approaches, utilization of AI strengths and statistical modeling will help us make rapid progress.
- We propose a Master protocol to test candidate biomarkers in a randomized clinical trial allowing biomarker to inform clinical management of IPS.

Acknowledgments

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- Tobias Peikert & Brian Bartholmai
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- Ruben Pio, Luis Montuenga
- Karin Rodland

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- Bluestargenomics

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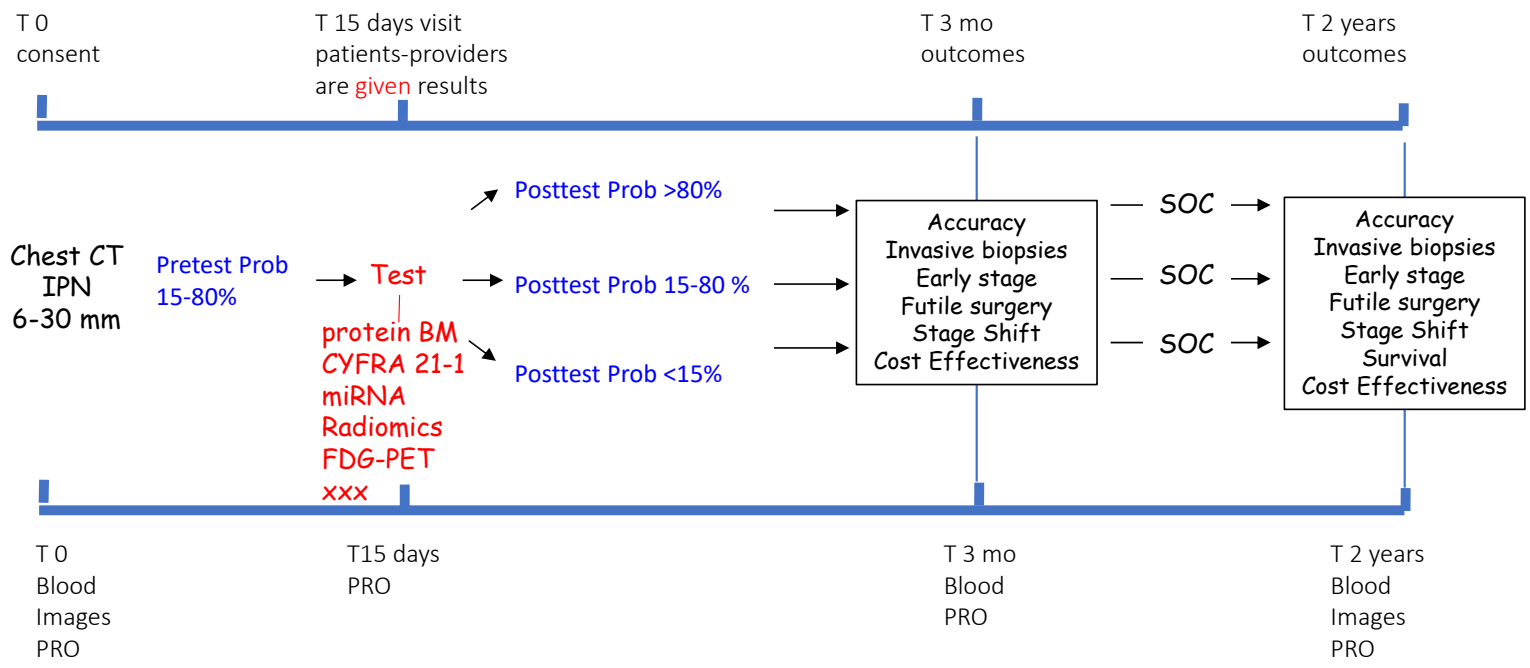
- DECAMP DoD

•Patients

Proposal of a Master protocol: Biomarker driven trial for the management of IPNs.



4 questions for the discussion

1. An umbrella trial design for IPN requires parties to agree to compare their BM to other platforms. What are the caveats and solutions?
2. What are new funding mechanisms conceivable for the NCI beside partnership with the industry?
3. Is the natural history of EDNR progression to get into clinical utility trials?
4. How do we enforce inclusion of health disparity populations inclusion in these trials?