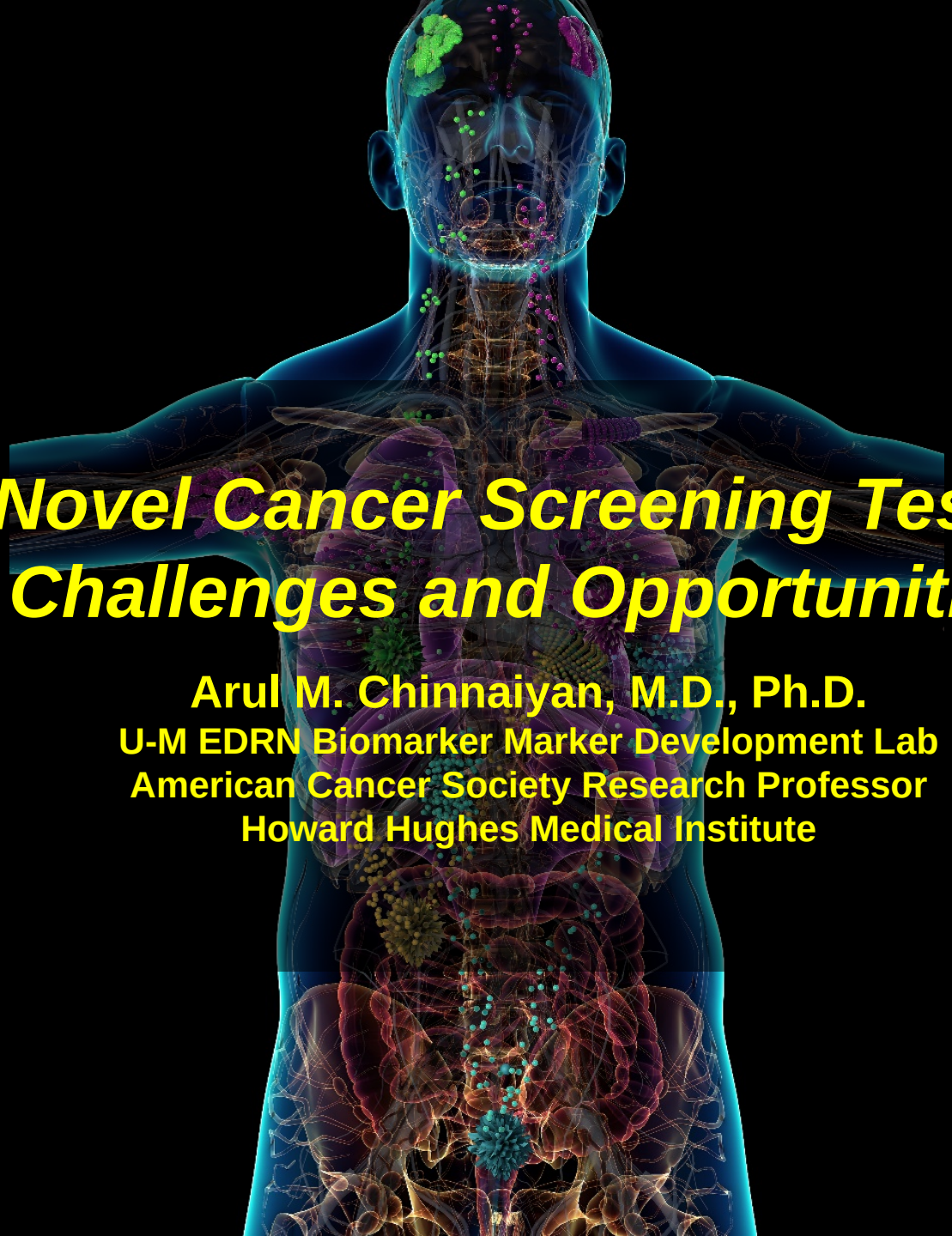

Novel Cancer Screening Tests: Challenges and Opportunities

Arul M. Chinnaiyan, M.D., Ph.D.
U-M EDRN Biomarker Marker Development Lab
American Cancer Society Research Professor
Howard Hughes Medical Institute

MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

Relevant Disclosures

- Tempus- SAB (Scientific Advisory Board)
- Lynx Dx- SAB/co-founder, commercialization of a urine test for prostate cancer
- Co-inventor on IP related to prostate cancer gene fusions (T2:ERG) and long non-coding RNAs (lncRNAs) associated with cancer

Outline

- Challenges with validation of novel cancer screening tests
- Development of a non-invasive early detection test for a specific cancer (prostate cancer)
- Multi-cancer, multi-omics cancer detection

Outline

- Challenges with validation of novel cancer screening tests
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The Case for Early Detection

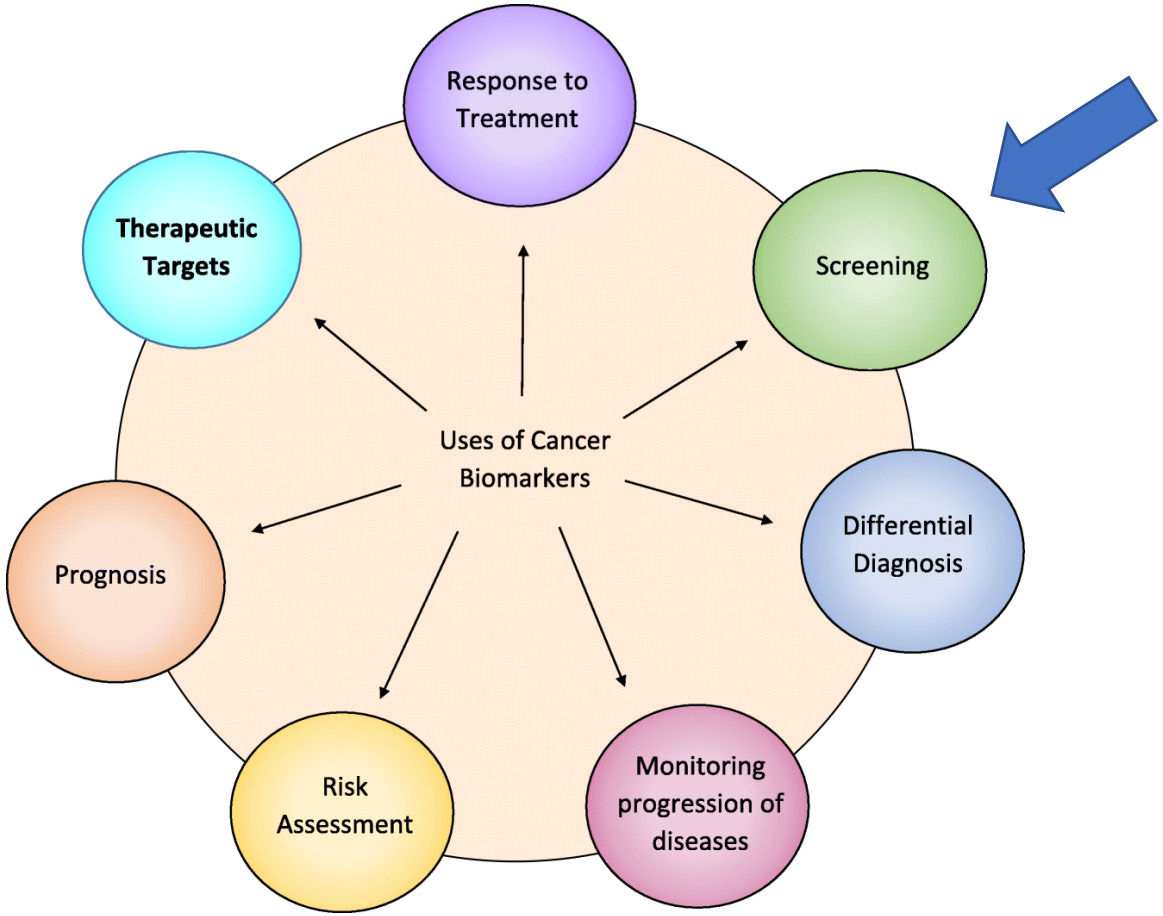
Table 1 | **Projected changes in survival with early detection**

Cancer site	Tumours localized when detected (%)	5-year survival rate (%)	5-year survival rate if all tumours were localized when detected (%)
Colorectal	41	64	90
Lung	19	16	49
Breast	65	87	97
Prostate	65	90	100

Based on data from SEER[1] for cases diagnosed between 1990 and 1999 inclusive. Cases with *in situ* or unstaged disease have been excluded. The favourable overall 5-year survival among breast and prostate cancer patients is partly due to the prevalence of screening for these cancers during the calendar years considered.

Etzioni et al., Nature Reviews Cancer 3, 243-252 (2003)

Cancer Biomarkers by Clinical Use



Townsend et al, *J. of Experimental & Clinical Cancer Research* 2018

Cancer Biomarkers by Validation Level

1st Step – Define clinical need → determine needed performance characteristics!

Observed Difference	Candidate Biomarker	Verified Biomarker	Validated Biomarker	Utility Validated	Approved Biomarker
	True comparison between properly matched cases and controls	Repeat of comparison with fully **independent** cases and controls, Blinded	•CLIA or GLP clinical assay •Large study •Blinded •Prospective study, •More than one location	•Intended use •Large study •Randomized •Blinded •Prospective study, •More than one location	•Typically approached with a commercial partner •Based on discussions occurring during final validation studies
Simple statistics •T test, •Wilcoxon rank sum	•Power study •Sensitivity •Specificity •ROC analysis •FDR compensation, etc.	•Power study •Sensitivity •Specificity •ROC analysis •FDR compensation, etc.	**•Demonstrates that marker is truly predictive**	**•Demonstrates that marker provides clinical benefit when used as intended**	

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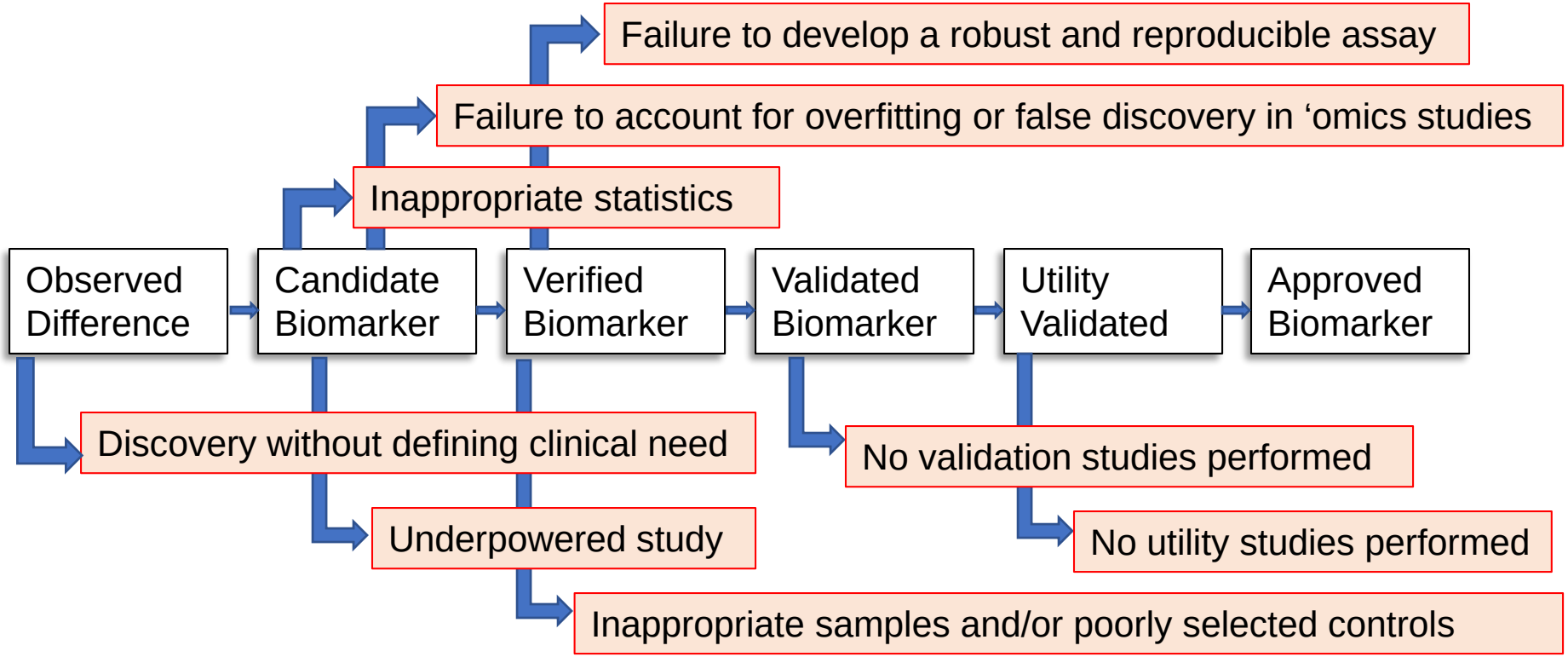
LaBaer et al

Common Pitfalls in Cancer Biomarker Research



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Challenges in Cancer Biomarker Develoment

- Finding validated and clinically useful biomarkers is rare
  - Despite 40,000 papers/year, many claiming > 90% sensitivity and specificity
  - Only a few FDA approved biomarkers per year
    - ***Nationwide – in the USA***
    - ***Industry and Academia***
    - ***All diseases***
  - The challenge is similar to finding a new drug or validated target
- Challenges:
  - Biology
  - Different culture: not just about the *story*, the markers have to work
  - Validation is not sexy
  - Cannot get grants to do validation
  - Journals don't publish negative results
  - Hard to get academic credit or grants for participating in this type of research

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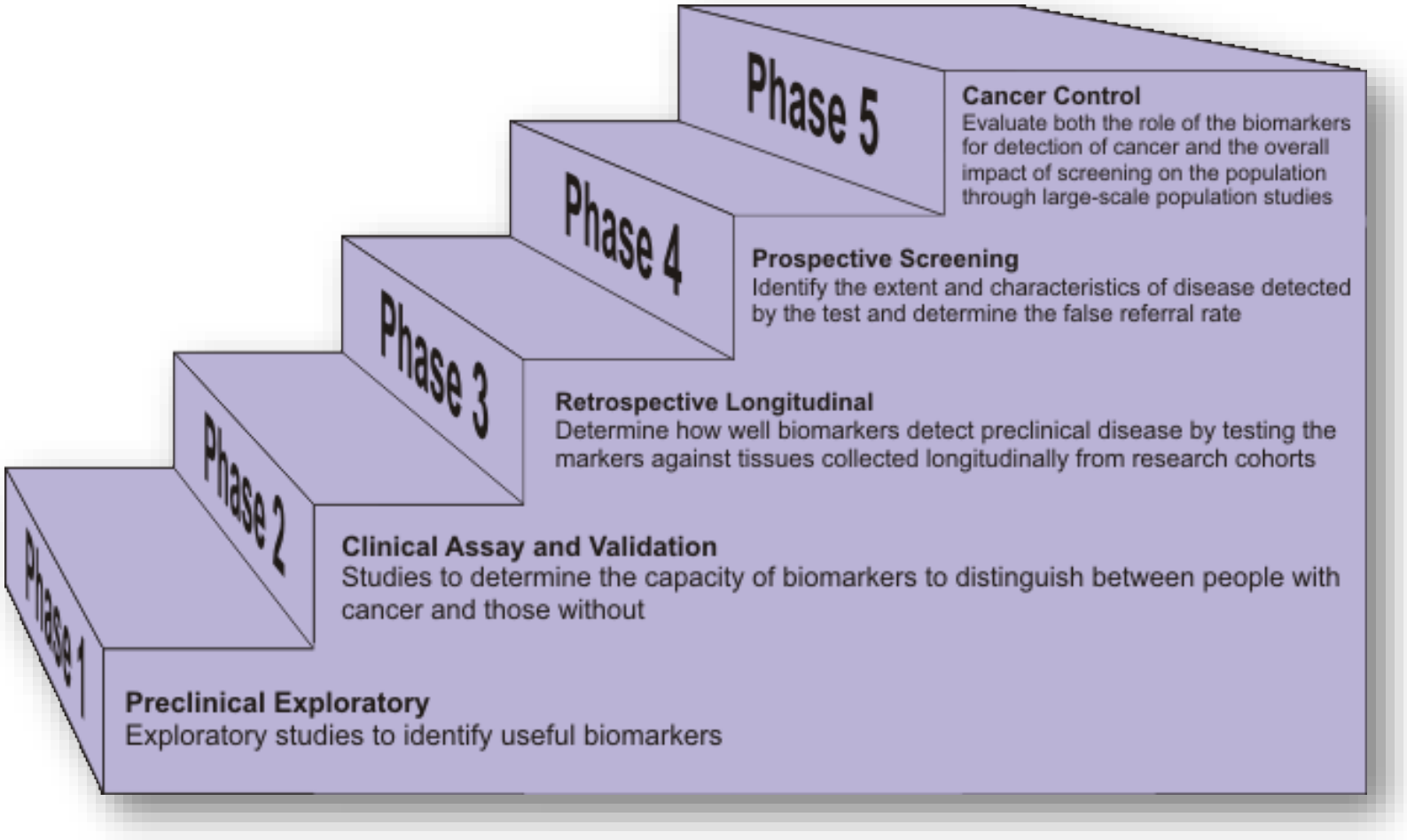
LaBaer et al

Phases of Biomarker Development



PRoBE Study Design:
Prospective-
Specimen-
Collection,
Retr**o**spective-
Blinded-
Evaluation

Pivotal Evaluation of the Accuracy of a Biomarker Used for Classification or Prediction: Standards for Study Design
Margaret Sullivan Pepe et al.,
J Natl Cancer Inst. 2008 Oct 15; 100(20): 1432-1438.

Citations: >400

Source: Pepe et al, *J. Natl. Cancer Inst.* 93, 1054-1061, 2001 >1300 citations

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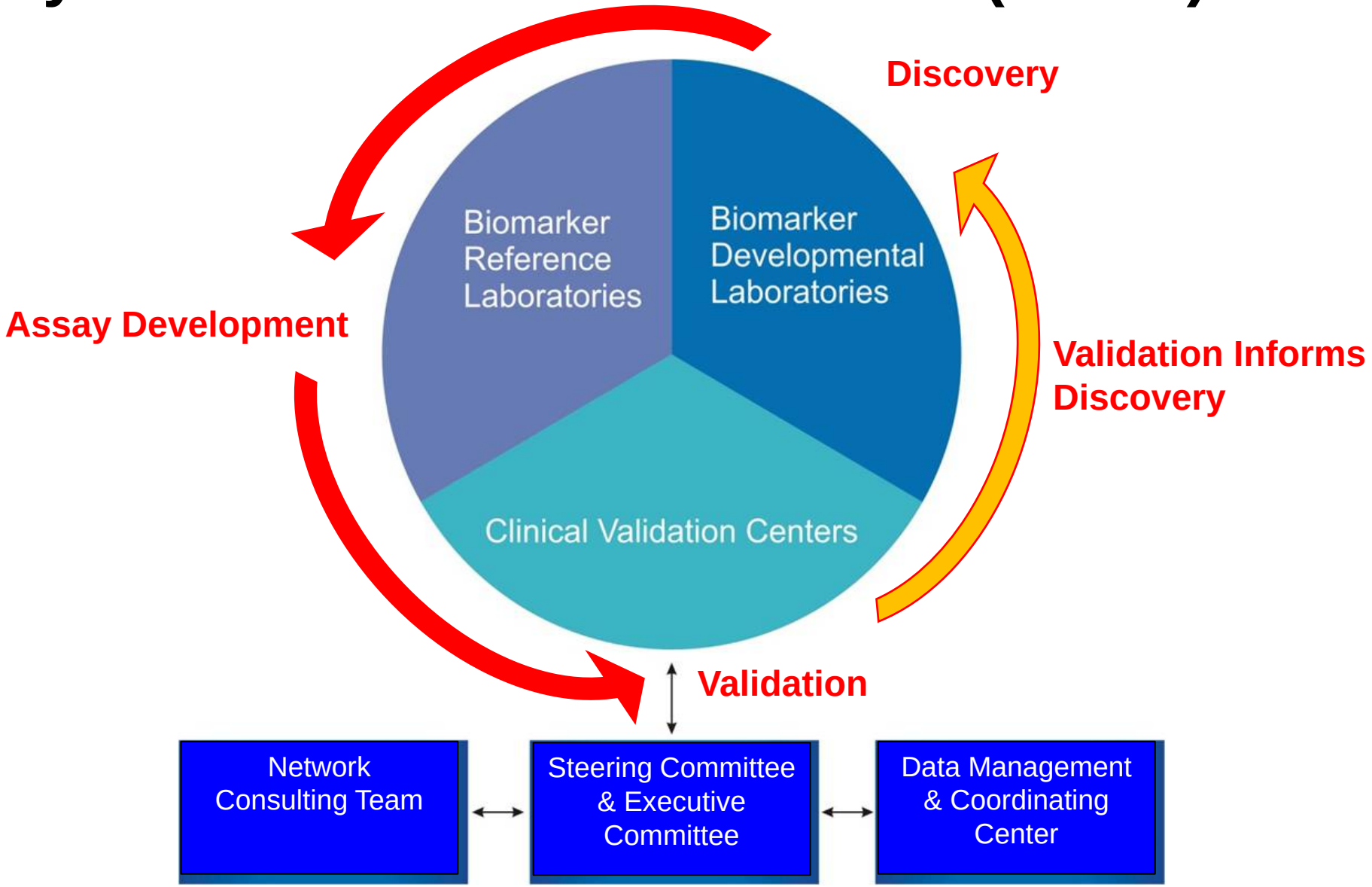
Infrastructure for Cancer Biomarker Development: Early Detection Research Network (EDRN)



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Outline

- Challenges with validation of novel cancer screening tests
- Development of a non-invasive early detection test for a specific cancer (prostate cancer)
- Multi-cancer, multi-omics cancer detection

Background

- Prostate cancer (PCa) poses a massive clinical and financial burden on patients and the healthcare system.
- Each year, approximately one million prostate biopsies are performed, 175,000 men are diagnosed with PCa, and 32,000 men die of the disease.

Figure 3. Leading Sites of New Cancer Cases and Deaths – 2019

Estimated New Cases

Male		
Prostate	174,650	20%
Lung & bronchus	116,440	13%
Colon & rectum	78,500	9%
Urinary bladder	61,700	7%
Melanoma of the skin	57,220	7%
Kidney & renal pelvis	44,120	5%
Non-Hodgkin lymphoma	41,090	5%
Oral cavity & pharynx	38,140	4%
Leukemia	35,920	4%
Pancreas	29,940	3%
All sites	870,970	

Estimated Deaths

Male		
Lung & bronchus	76,650	24%
Prostate	31,620	10%
Colon & rectum	27,640	9%
Pancreas	23,800	7%
Liver & intrahepatic bile duct	21,600	7%
Leukemia	13,150	4%
Esophagus	13,020	4%
Urinary bladder	12,870	4%
Non-Hodgkin lymphoma	11,510	4%
Brain & other nervous system	9,910	3%
All sites	321,670	

American Cancer Society

Background: PSA Screening

- The etiology of these hardships can in many cases be traced back to current prostate-specific antigen (PSA)-based methods of PCa diagnosis.

- PSA is a marker of prostate epithelial *cells*, not prostate *cancer.*

- The high rate of false positive PSA tests (i.e. elevated PSA in the absence of cancer) results in frequent unnecessary biopsies (up to 80%) and a cascade of negative outcomes for patients and undue burden on the healthcare system.

- This is compounded by the broad biological and clinical heterogeneity of PCa, as a significant proportion of screen-detected cancers are indolent (~50%) and will not harm a patient during their lifetime (i.e. overdiagnosis).

Moyer 2012, Fenton 2018, Grossman 2018

Background: PSA Screening

- Harms of overdiagnosis:
  - Unnecessary surveillance
    - Serial prostate biopsy
    - Serial imaging
    - Frequent conversion to treatment
  - Unnecessary treatment
    - Treatment-associated side effects
    - Erectile dysfunction
    - Urinary incontinence
  - Mental/emotional burden
  - Cost and resource burden

Table. Estimated Effects After 13 Years of Inviting Men Aged 55 to 69 Years in the United States to PSA-Based Screening for Prostate Cancer[a]

Effect	No. of Men
Men invited to screening	1000
Men who received at least 1 positive PSA test result	240
Men who have undergone 1 or more transrectal prostate biopsies	220[b]
Men hospitalized for a biopsy complication	2
Men diagnosed with prostate cancer	100
Men who initially received active treatment with radical prostatectomy or radiation therapy	65
Men who initially received active surveillance	30
Men who initially received active surveillance who went on to receive active treatment with radical prostatectomy or radiation therapy	15
Men with sexual dysfunction who received initial or deferred treatment	50
Men with urinary incontinence who received initial or deferred treatment	15
Men who avoided metastatic prostate cancer	3
Men who died of causes other than prostate cancer	200
Men who died of prostate cancer despite screening, diagnosis, and treatment	5
Men who avoided dying of prostate cancer	1.3

Schroder 2014, Fenton 2018

Where does that leave us?

- There is consensus regarding the need for a test that can reduce the number of men who undergo unnecessary prostate biopsies, i.e. negative biopsies or those detecting low-grade cancer.

NIH

NATIONAL CANCER INSTITUTE

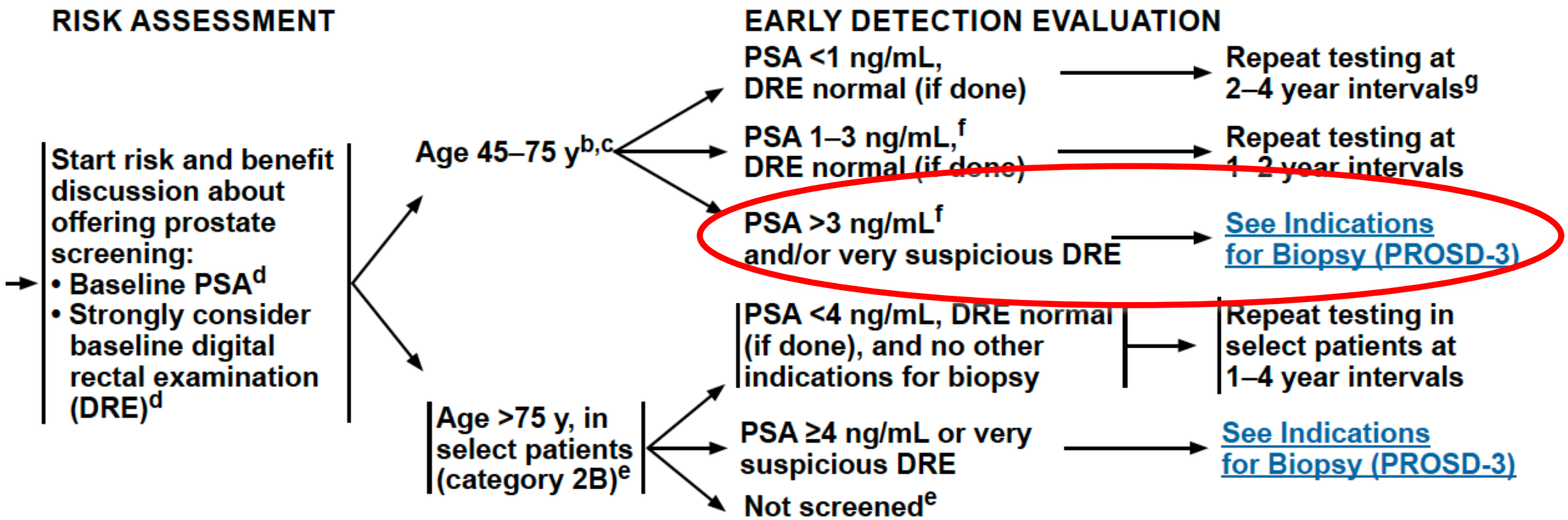
American Urological Association

NCCN National Comprehensive Cancer Network®

U.S. Preventive Services TASK FORCE

Moyer 2012, Davies 2018, NCCN 2019

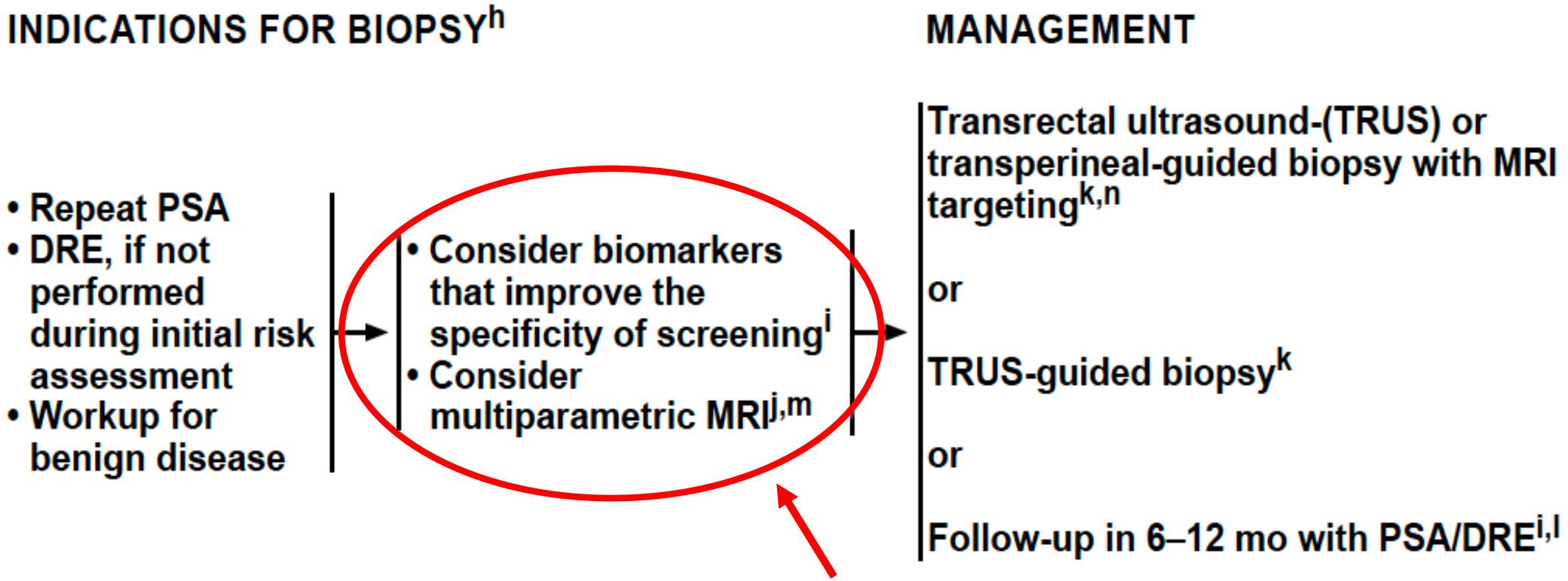
Current Standard



National Comprehensive Cancer Network®

NCCN 2019

Current Standard



The NCCN now offers that clinicians consider alternatives to immediate biopsy: biomarkers or multiparametric MRI.

NCCN 2019

Current Standard

Percent-free PSA, PHI, EPI score, 4Kscore, PCA3/T2:ERG

INDICATIONS FOR BIOPSY[h]

- Repeat PSA
- DRE, if not performed during initial risk assessment
- Workup for benign disease

→

- Consider biomarkers that improve the specificity of screening[i]
- Consider multiparametric MRI[j,m]

→

MANAGEMENT

Transrectal ultrasound-(TRUS) or transperineal-guided biopsy with MRI targeting[k,n]

or

TRUS-guided biopsy[k]

or

Follow-up in 6–12 mo with PSA/DRE[i,l]

NCCN 2019

URINE

SERUM

PCA3

T2:ERG

PSA

MPS

CLINICAL WORKFLOW

ELEVATED PSA → UROLOGIST REFERRAL → MPS → PERFORM TEST

\+ → BIOPSY

\- → PREVENTED BIOPSY

MPS: My Prostate Score

PCA3

- long non-coding RNA with highly PCa specific expression
- Most validated non-invasive biomarker for PCa outside of serum PSA

TMPRSS2:ERG FUSION (T2:ERG)

- Highly PCa specific gene fusion discovered by our group
- Most specific and validated tissue biomarker of prostate cancer

MLabs
Expertise Delivered Personally

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VALIDATION STUDIES

PERFORMANCE OF PCA3 AND T2:ERG HAS BEEN VALIDATED AND TESTED IN NEARLY 4,000 PATIENTS

Publication	Validation Cohort Size
Tomlins, S. A. *et al. Eur. Urol.* (2016)	1244
Sanda, M. G. *et al. JAMA Oncol.* (2017)	561
Leyten, G. H. J. M. *et al. Eur. Urol.* (2014)	443
Tomlins, S. A. *et al. Sci. Transl. Med.* (2011) *T2:ERG Only	1312
Lin, D. W. *et al. Clin. Cancer Res.* (2013)	387
Salami, S. S. *et al. Urol. Oncol.* (2013)	45

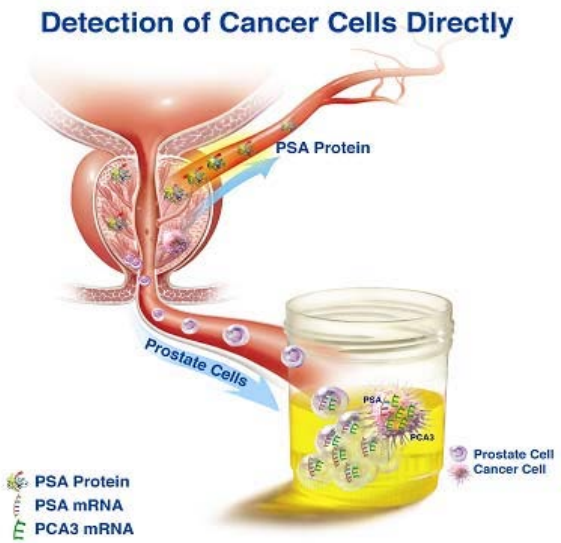
Research

JAMA Oncology | Original Investigation

Association Between Combined *TMPRSS2:ERG* and *PCA3* RNA Urinary Testing and Detection of Aggressive Prostate Cancer

Martin G. Sanda, MD; Ziding Feng, PhD; David H. Howard, PhD; Scott A. Tomlins, MD, PhD; Lori J. Sokoll, PhD; Daniel W. Chan, PhD; Meredith M. Regan, DSci; Jack Groskopf, PhD; Jonathan Chipman, MS; Dattatraya H. Patil, MBBS, MPH; Simpa S. Salami, MD; Douglas S. Scherr, MD; Jacob Kagan, PhD; Sudhir Srivastava, PhD; Ian M. Thompson Jr, MD; Javed Siddiqui, MS; Jing Fan, MS; Aron Y. Joon, MS; Leonidas E. Bantis, PhD; Mark A. Rubin, MD; Arul M. Chinnayian, MD, PhD; John T. Wei, MD; and the EDRN-PCA3 Study Group

JAMA Oncol. 2017;3(8):1085-1093. doi:10.1001/jamaoncol.2017.0177
Published online May 18, 2017.



MiPS= Mi Prostate Score
(PCA3+ TMPRSS2-ERG + urinary PSA+ serum PSA)

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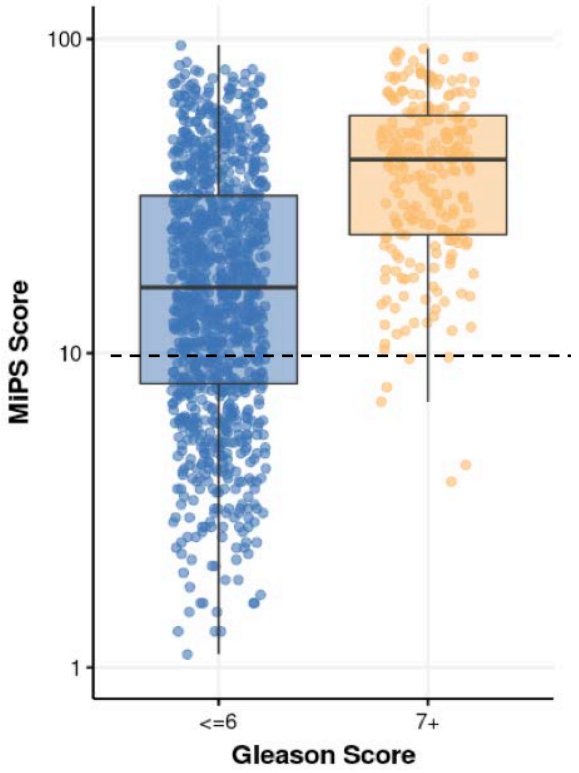
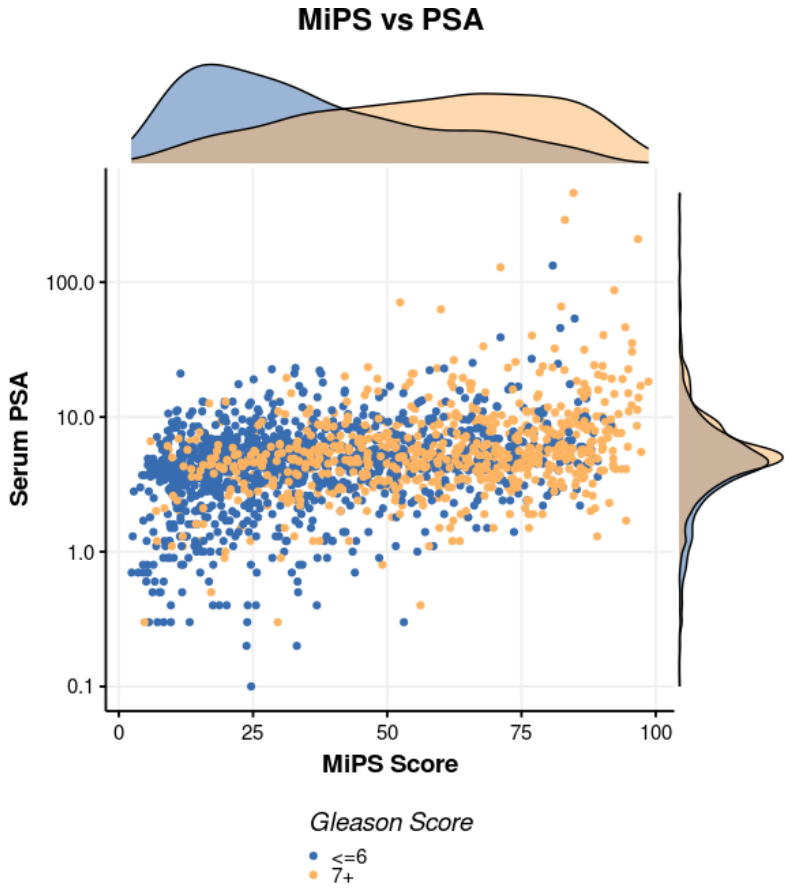
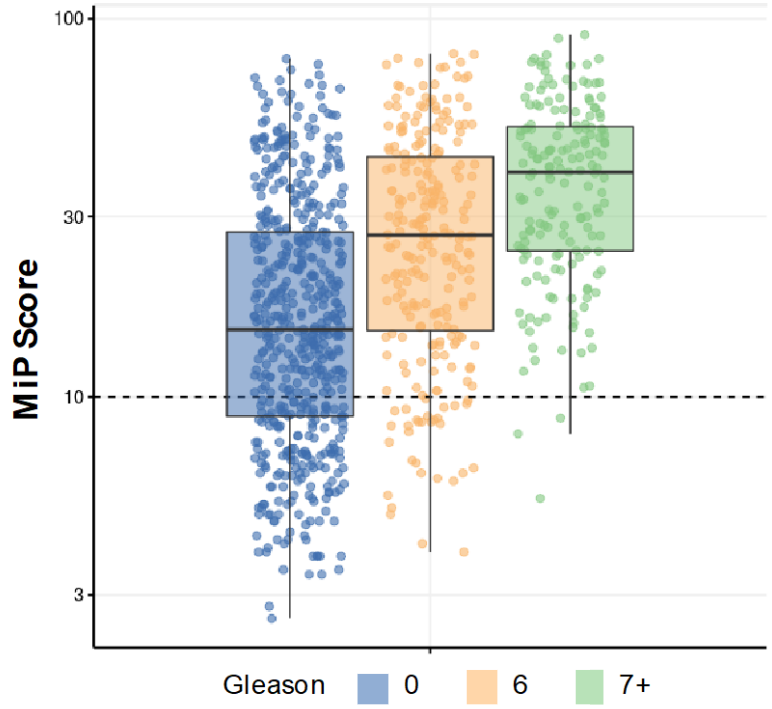
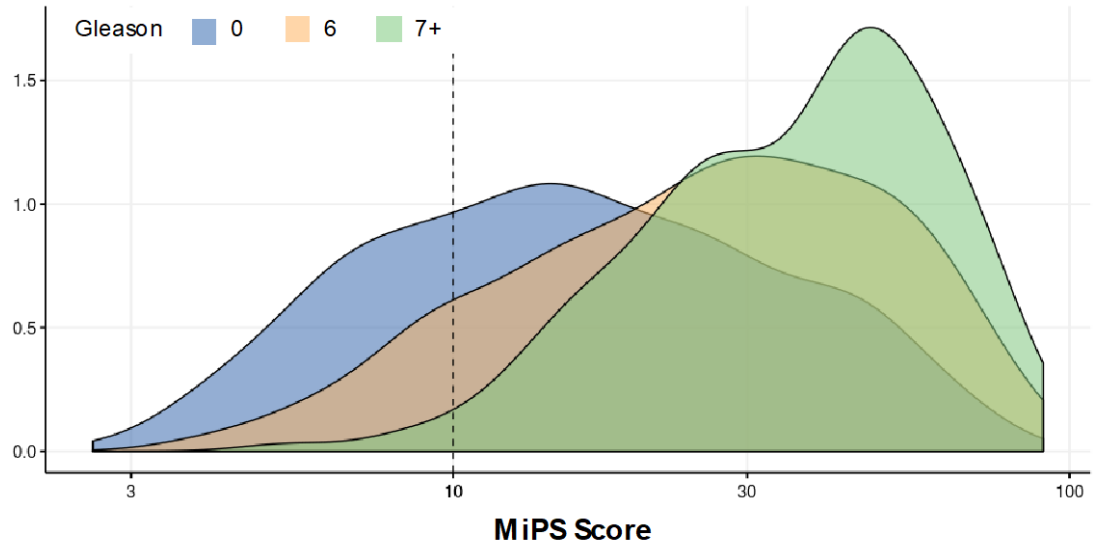
MPS IS ABLE TO SEPARATE HIGH-GRADE CANCERS FROM LOW-GRADE AND NORMAL SIGNIFICANTLY BETTER THAN PSA





MPS is a powerful rule-out test for high-grade prostate cancer





Validation Cohort:

1,244 Samples

30% biopsies prevented

- Sensitivity: 97%
- NPV: 98%

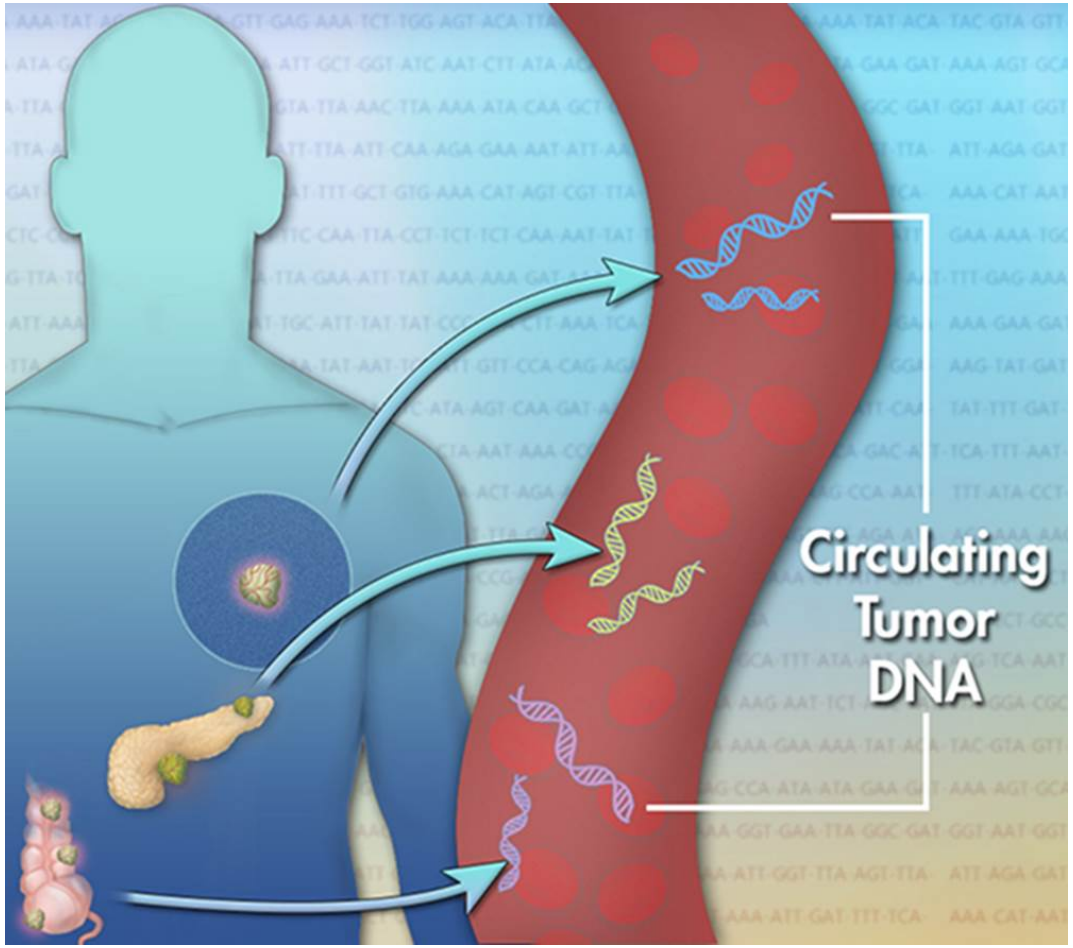
- Specificity: 33%
- NPV: 26%

Tomlins et al, *Euro. Urol*. 2016

Outline

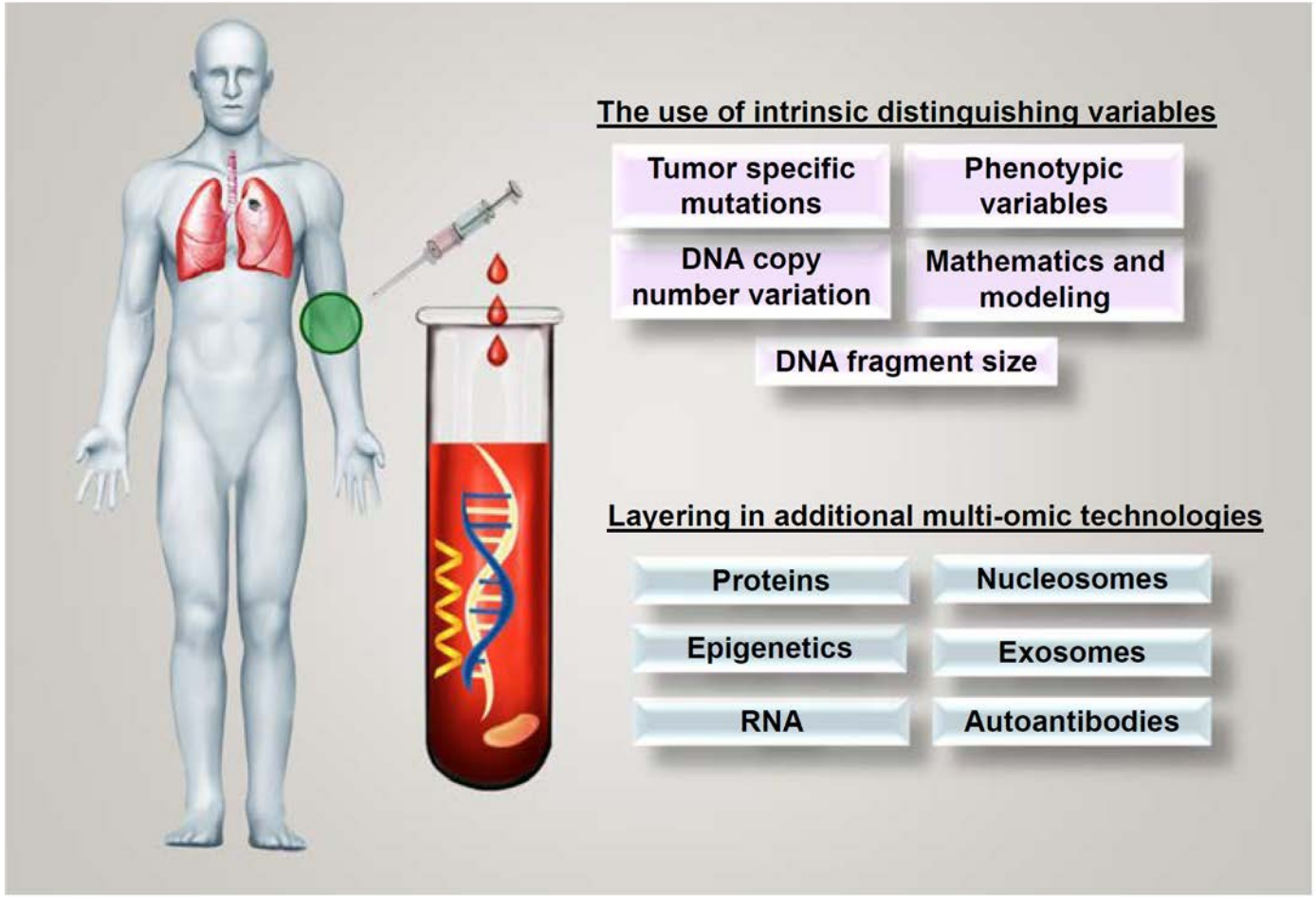
- Challenges with validation of novel cancer screening tests
- Development of a non-invasive early detection test for a specific cancer (prostate cancer)
- Multi-cancer, multi-omics cancer detection

Multi-cancer, multi-omics cancer detection (“liquid biopsy”)



NIH

Integrative analysis of ctDNA with other multi-omic technologies

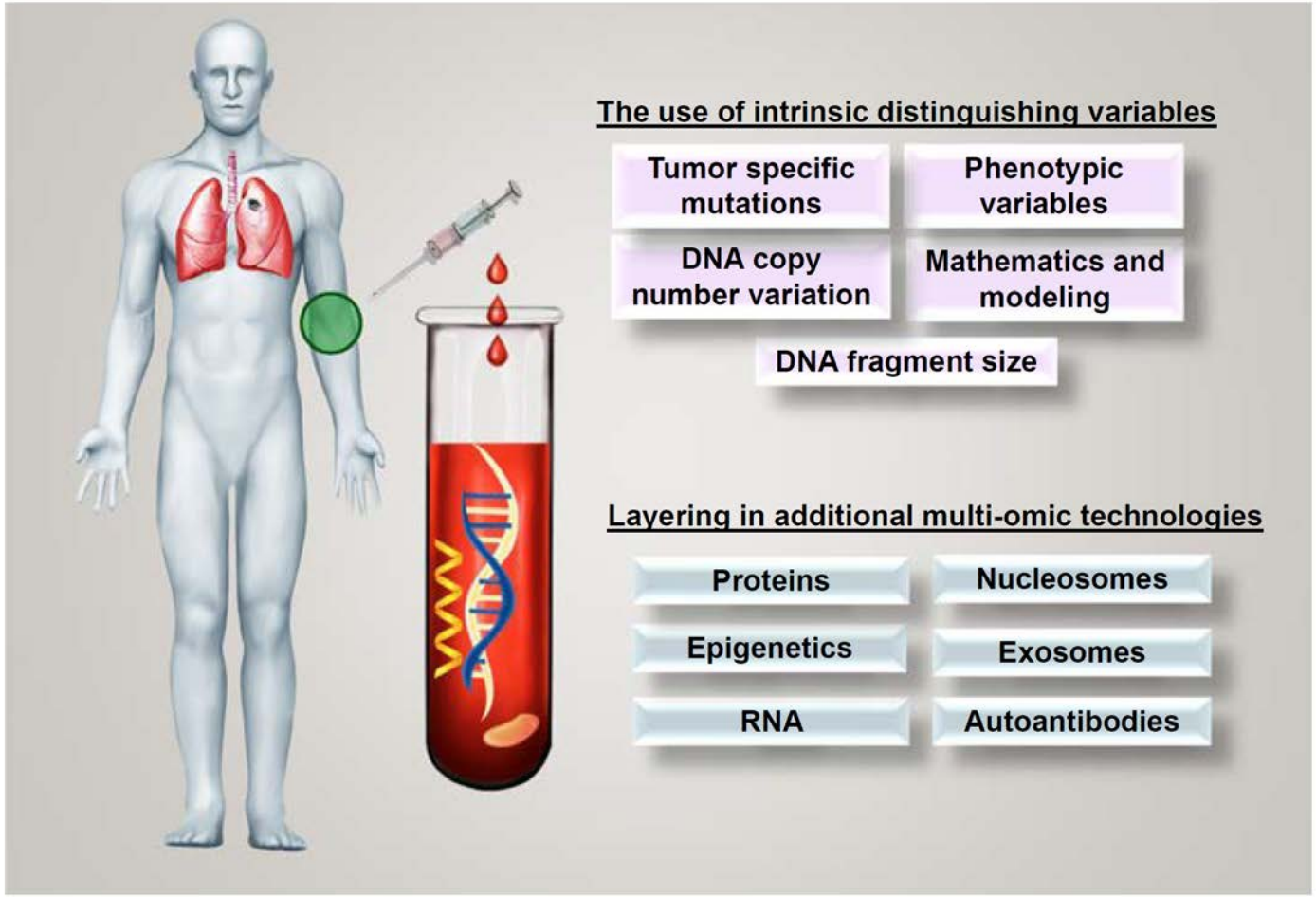


Campos-Carrillo et al, *Pharmacology & Therapeutics* 2020

The race to develop early detection tests for cancer

GRAIL	Multi-cancer, deep NGS sequencing, machine learning, and DNA methylation
Thrive. Earlier Detection	Multi-cancer, CancerSEEK, DNA mutations + protein biomarkers, FDA Breakthrough Device designation
GUARDANT HEALTH	DNA mutations, colon cancer (LUNAR-2)
freenome	Multi-omics test, AI, colon cancer

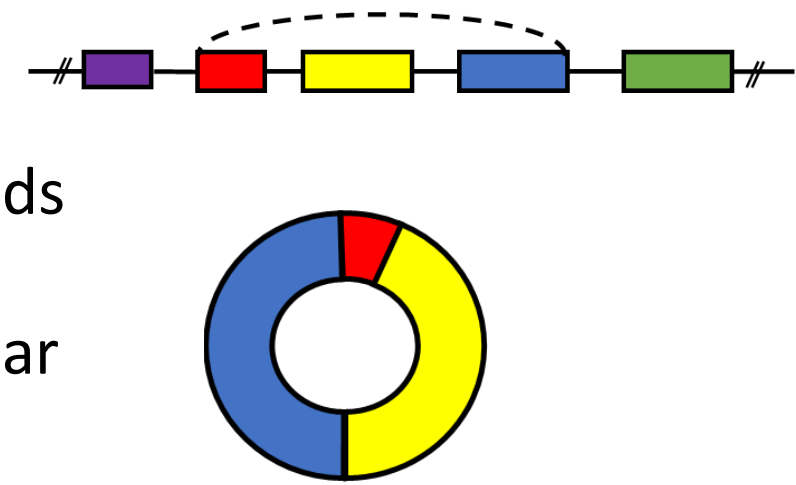
Integrative analysis of ctDNA with other multi-omic technologies



Campos-Carrillo et al, *Pharmacology & Therapeutics* 2020

circRNAs

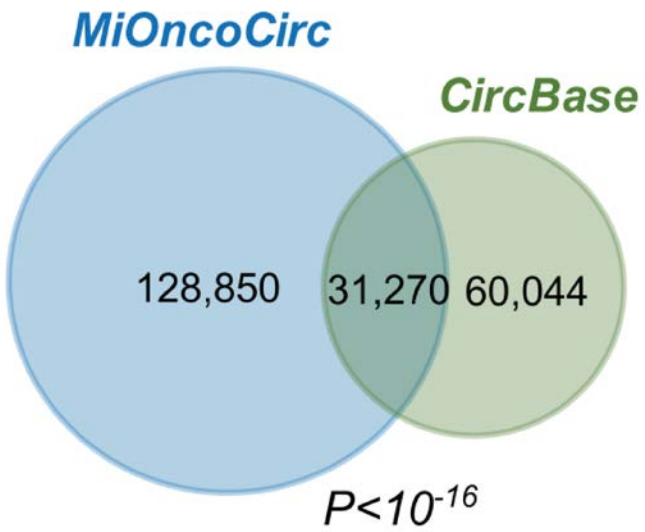
- Class of non coding RNA formed from pre-mRNAs through backsplicing (first characterized >25 years ago)
- Single-stranded and covalently closed; lack Poly A
- RNA seq based technologies have discovered thousands of circRNAs
- Often expression does not correlate with cognate linear RNA
- Varied biological roles have been suggested (e.g., miRNA sponges, EMT, tumorigenesis)
- Due to their covalently closed structure are resistant to exonucleases
- Due to enhanced stability can be found in biospecimens such as plasma

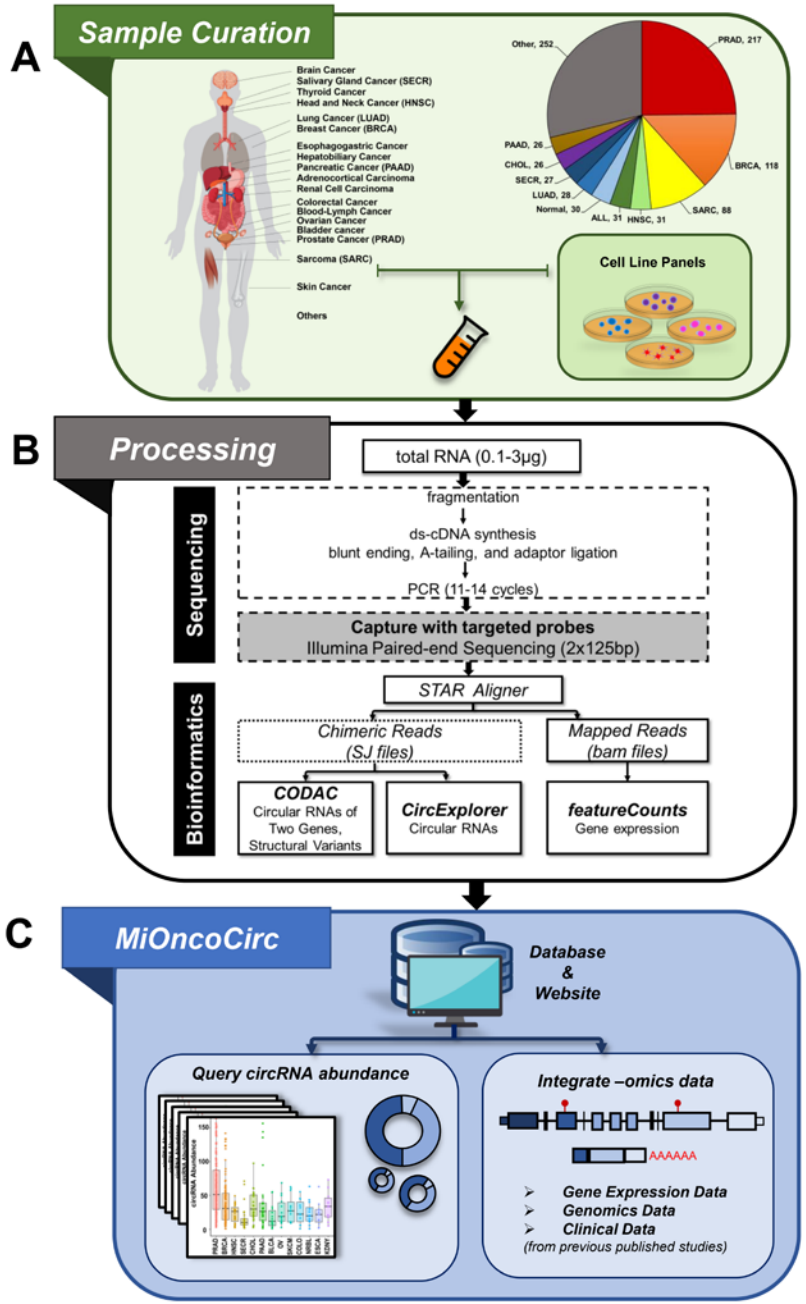


Circular Exonic RNA

Building the MiOncoCirc Compendium with Exome Capture RNA-Seq

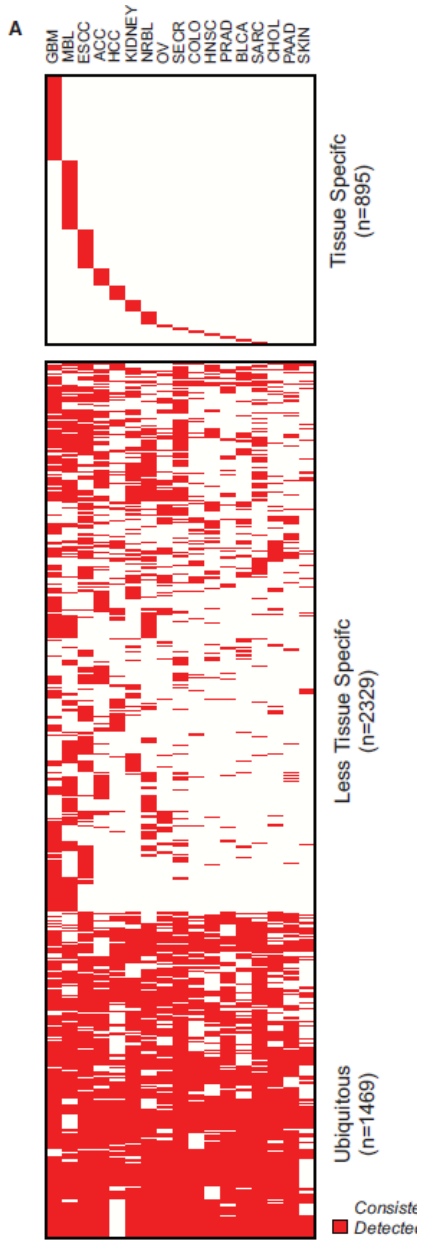
>2000 tumors, >30 tumor types, > 30 metastatic sites

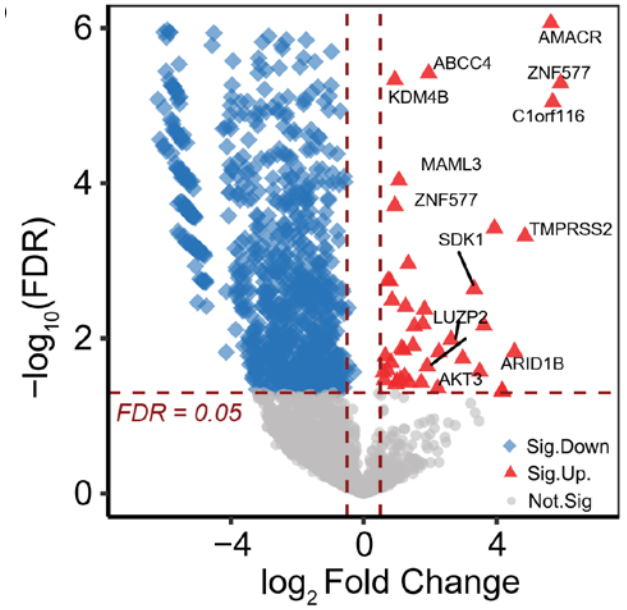




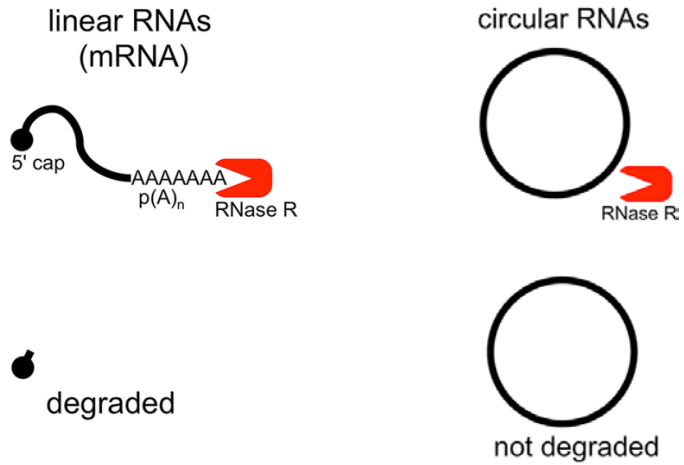
Vo et al *Cell* 2019

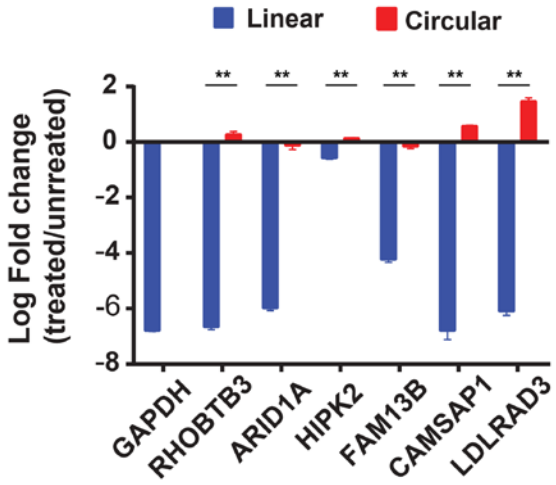
Expression Patterns and Characteristics of circRNAs in Cancer

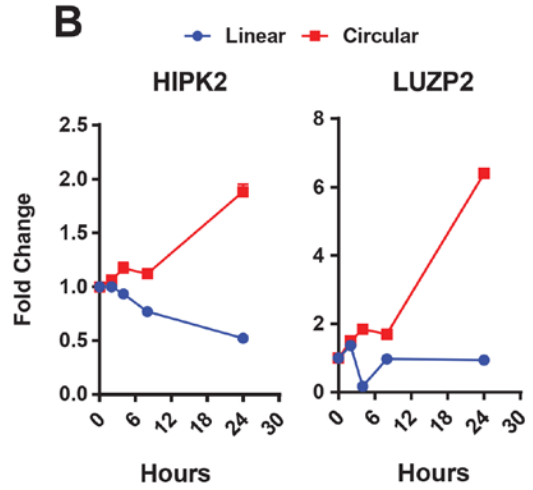


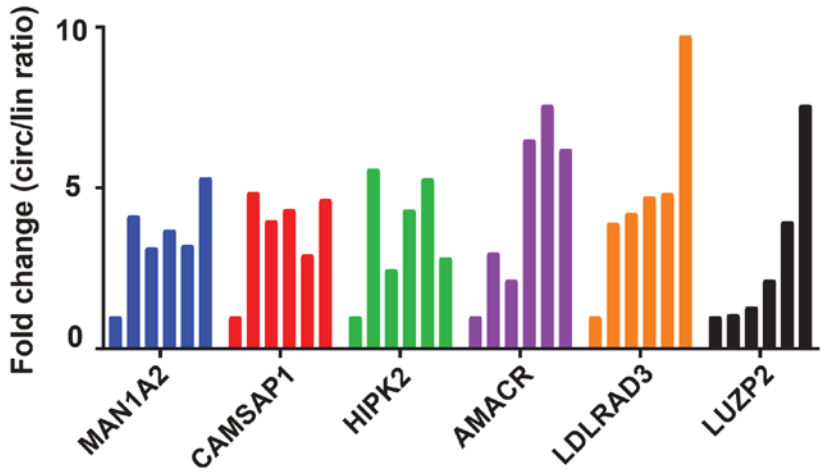


Assess the Stability of CircRNAs in Extracellular Spaces





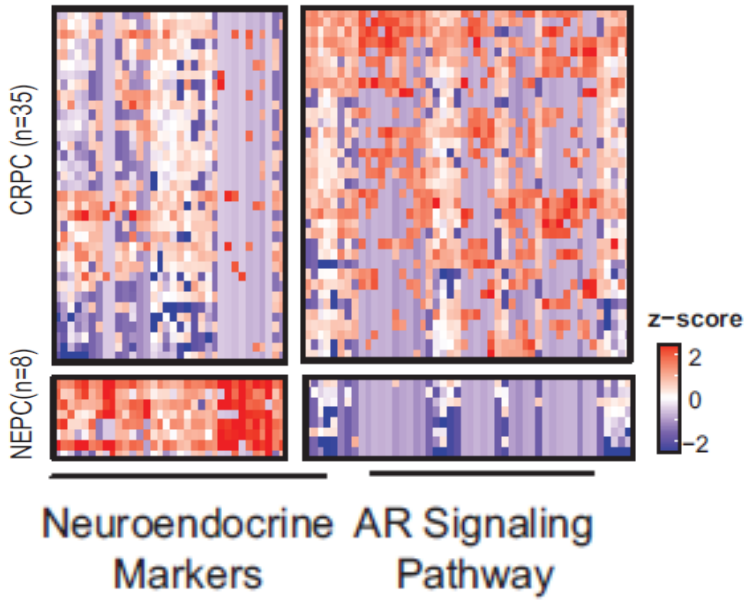


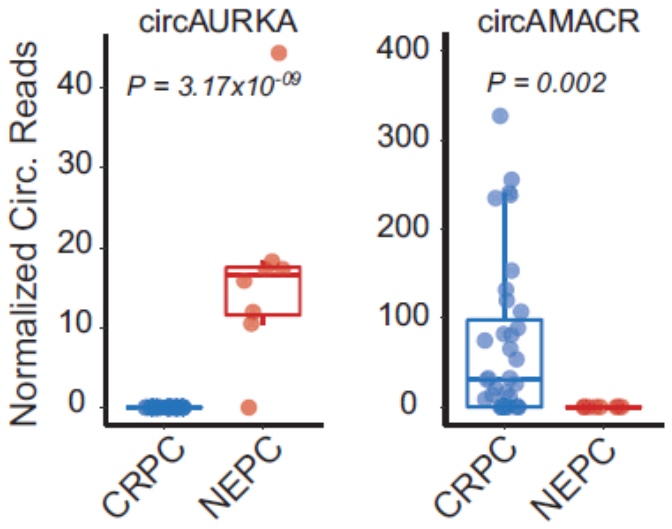


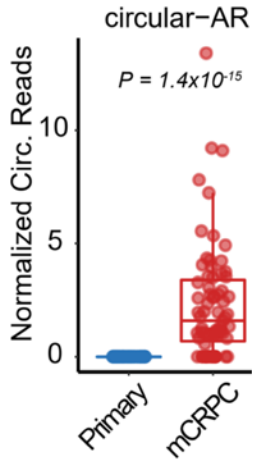
Incubate RNA in human plasma → *"Mimic" circulating RNAs in blood*

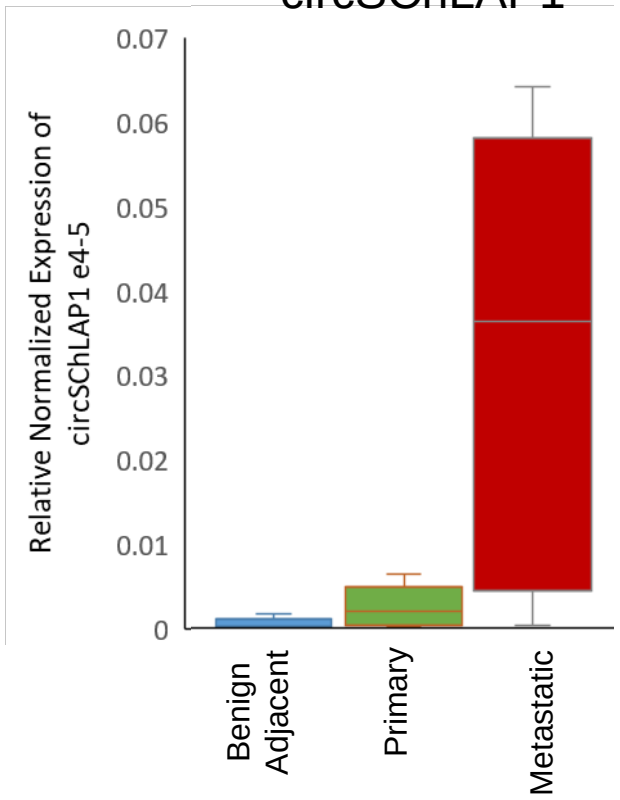
Samples were harvested at 0, 15, 30, 45, 60, and 75 min.

circRNA biomarkers of prostate cancer

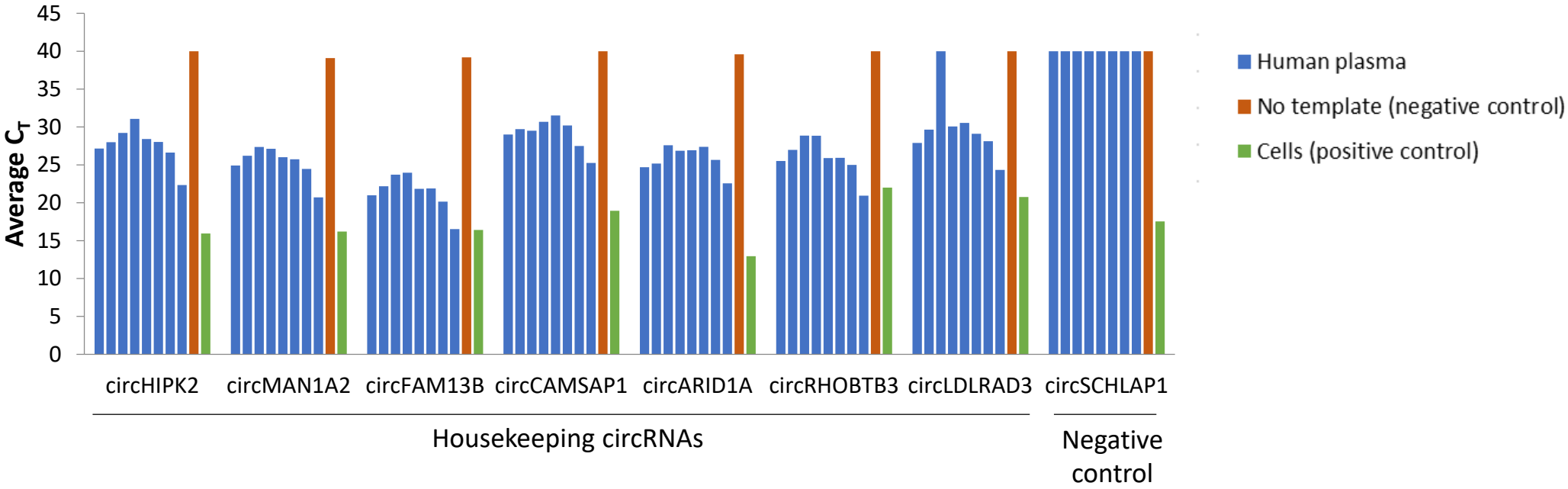




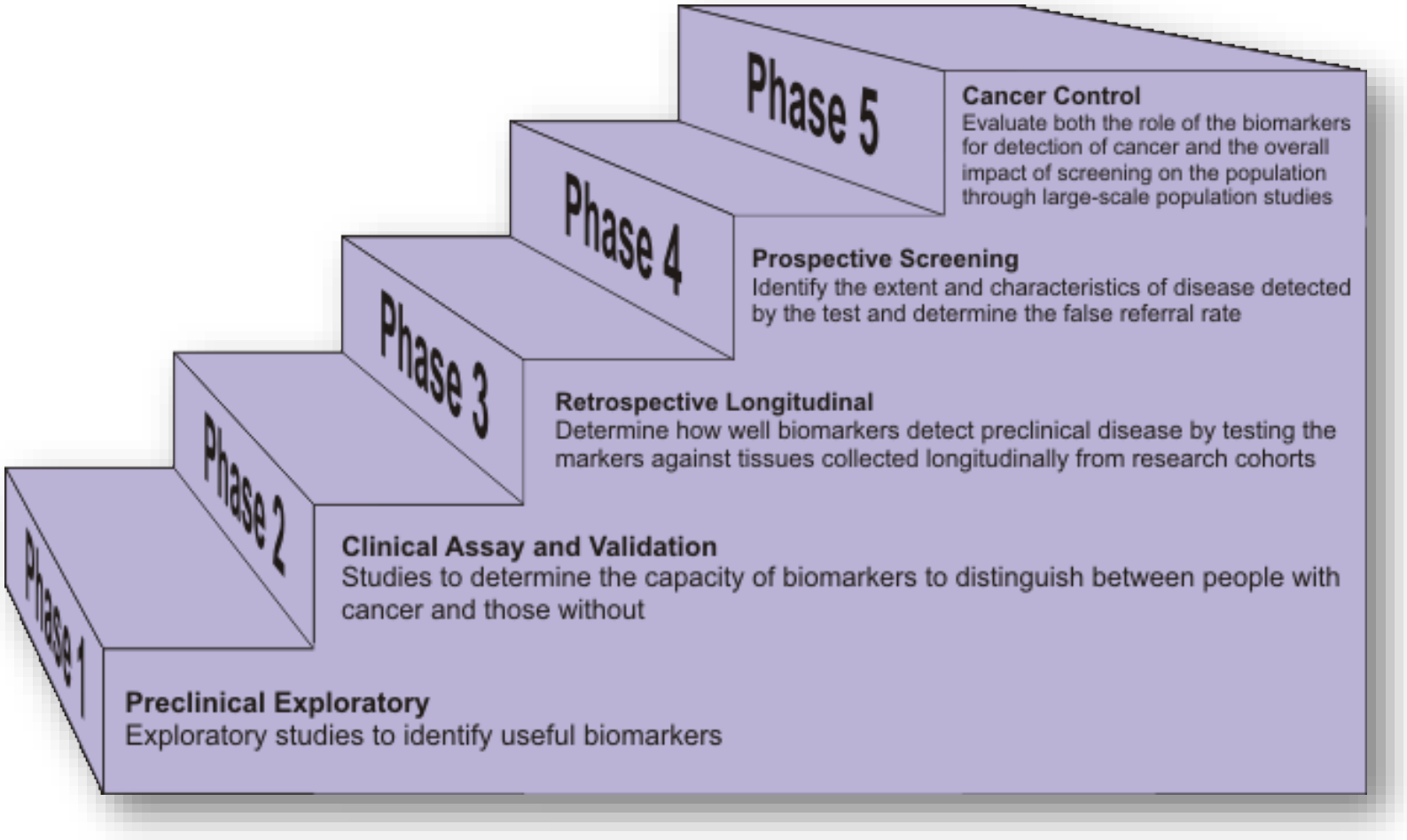




“Housekeeping” circRNAs are detectable in human plasma samples using qPCR



Phases of Biomarker Development



PRoBE Study Design:
Prospective-
Specimen-
Collection,
Retr**o**spective-
Blinded-
Evaluation

Pivotal Evaluation of the Accuracy of a Biomarker Used for Classification or Prediction: Standards for Study Design
Margaret Sullivan Pepe et al.,
J Natl Cancer Inst. 2008 Oct 15; 100(20): 1432-1438.

Citations: >400

Source: Pepe et al, *J. Natl. Cancer Inst.* 93, 1054-1061, 2001 >1300 citations