NCI's Division of Cancer Prevention: *Vision*
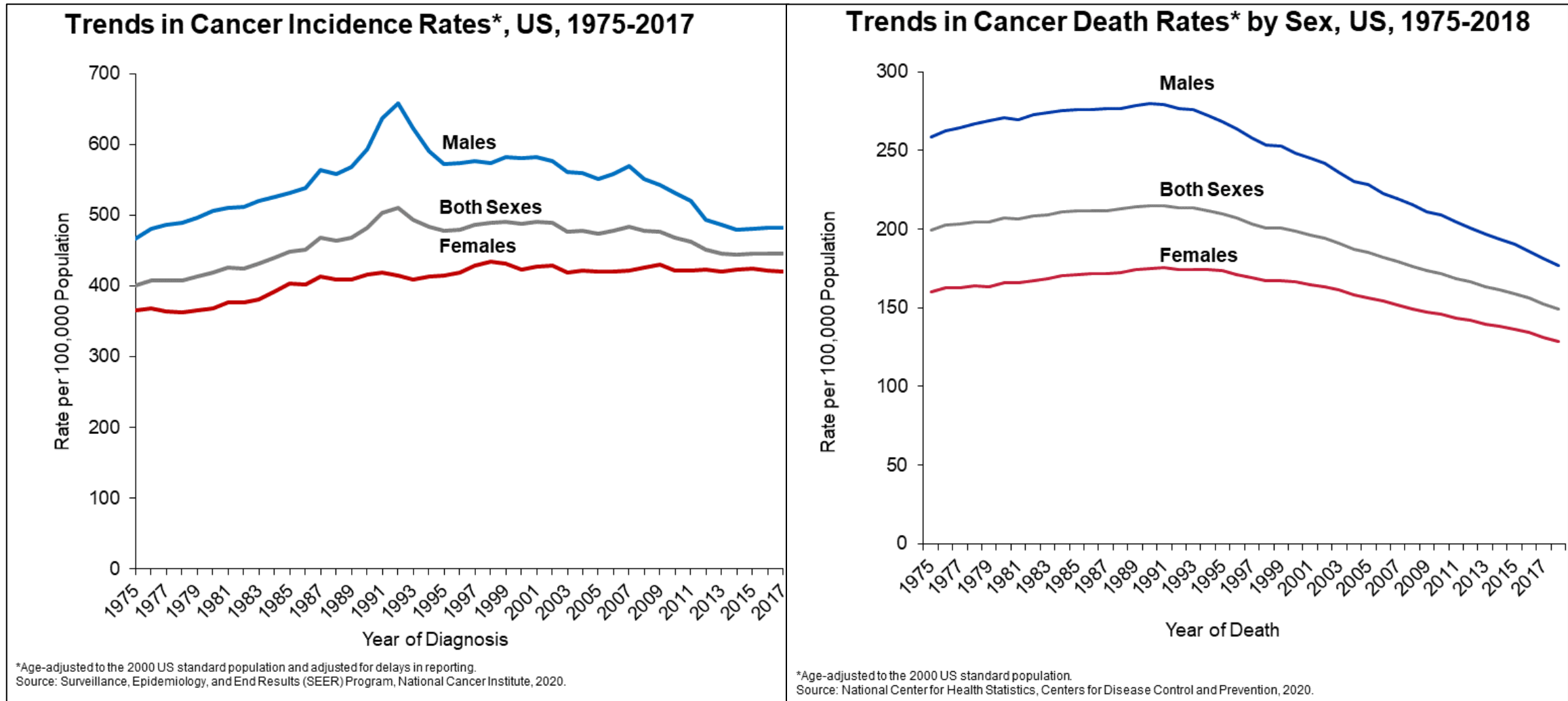
Philip E. Castle, PhD, MPH

On behalf of the Division of Cancer Prevention, NCI/NIH/DHHS

NIH ▶ NATIONAL CANCER INSTITUTE

December 9, 2021

Cancer Burden

Trends in Cancer Incidence Rates*, US, 1975-2017

*Age-adjusted to the 2000 US standard population and adjusted for delays in reporting.
Source: Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute, 2020.

Trends in Cancer Death Rates* by Sex, US, 1975-2018

*Age-adjusted to the 2000 US standard population.
Source: National Center for Health Statistics, Centers for Disease Control and Prevention, 2020.

The Mission of the Division of Cancer Prevention (DCP)

"The NCI Division of Cancer Prevention leads, supports, and promotes rigorous, innovative research and training to reduce risks, burdens, and consequences of cancer to improve the health of all people."

Organizational Structure

Office of the Director
Phil Castle, Ph.D., M.P.H.

Cancer Prevention Fellowship Program
Lisa Signorello, Ph.D.

Deputy Director
Lori Minasian, M.D.

Associate Director for Clinical Research
Leslie Ford, M.D.

Protocol Information Office
Troy Budd

Biometry Research Group
Victor Kipnis, Ph.D.

Cancer Biomarkers Research Group
Sudhir Srivastava, Ph.D., M.P.H.

Early Detection Research Group
Paul Pinsky, Ph.D.

Nutritional Science Research Group
Harold Seifried, Ph.D., D.A.B.T.

Chemopreventive Agent Development Research Group
Robert Shoemaker, Ph.D.

Community Oncology and Prevention Research Group
Worta McCaskill-Stevens, M.D., M.S.

Breast and Gynecologic Cancer Research Group
Brandy Heckman-Stoddard, Ph.D., M.P.H.

Gastrointestinal and Other Cancer Research Group
Asad Umar, D.V.M., Ph.D.

Lung and Upper Aerodigestive Cancer Research Group
Eva Szabo, M.D.

Prostate and Urologic Cancer Research Group
Howard Parnes, M.D.

Extramural/Stakeholder Engagement (Examples)

- **Multi-Cancer Early Detection Study Design Workshop** (Dr. Lori Minasian & the MCED "Tiger Team")

- **Cancer Screening Workshop** (Drs. Paul Pinsky and Brandy Heckman-Stoddard)

- **Translational Advances in Cancer Prevention Agent Development Virtual Workshop on Immunomodulatory Agents** (Drs. Mark Miller & Altaf Mohammed)

- **Cannabis Workshop** (Dr. Alexis Bakos, DCCPS, DCTD, FDA, NIDA)

- **FNIH Cancer Prevention Workshop** (Drs. Lori Minasian & Leslie Ford)

- **FDA-NCI Mini-Symposium on Cancer Prevention and Risk Reduction** (Dr. Brandy Heckman-Stoddard)
  - Initiated new FDA-NCI working group on cancer prevention (CDER, CBER, and CDRH)

- **IPAs** with KOLs/Experts (in progress)

- **New engagements with industry partners!!!**

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Cancer Prevention: Avoidance, Vaccination (1° Prevention), & Screening & Treatment/Interception (2° Prevention)

Normal | Initiated | Mild dysplasia | Moderate dysplasia | Severe dysplasia | Carcinoma *in situ* | Invasive cancer

Precursor States
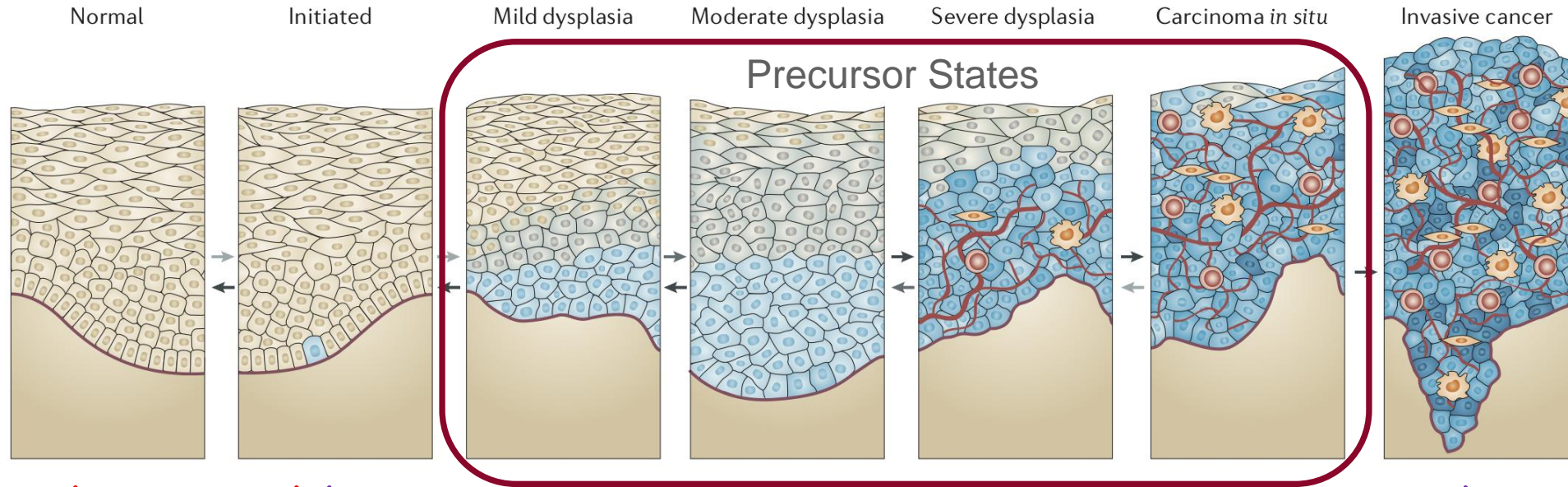
Carcinogen Avoidance/Early Treatment:
- Tobacco Prevention
- Human papillomavirus Vaccination
- Hepatitis B Vaccination
- Treatment of *H. pylori*

Tobacco Cessation

Screening, Diagnosis, & Removal (excision)/ Destruction (ablation) for Cancer Risk Reduction: polyps & intraepithelial neoplasia (IN), and prophylactic surgeries

Interception of Cancer

Molecular prevention and immunoprevention with targeted agents and immune modulators

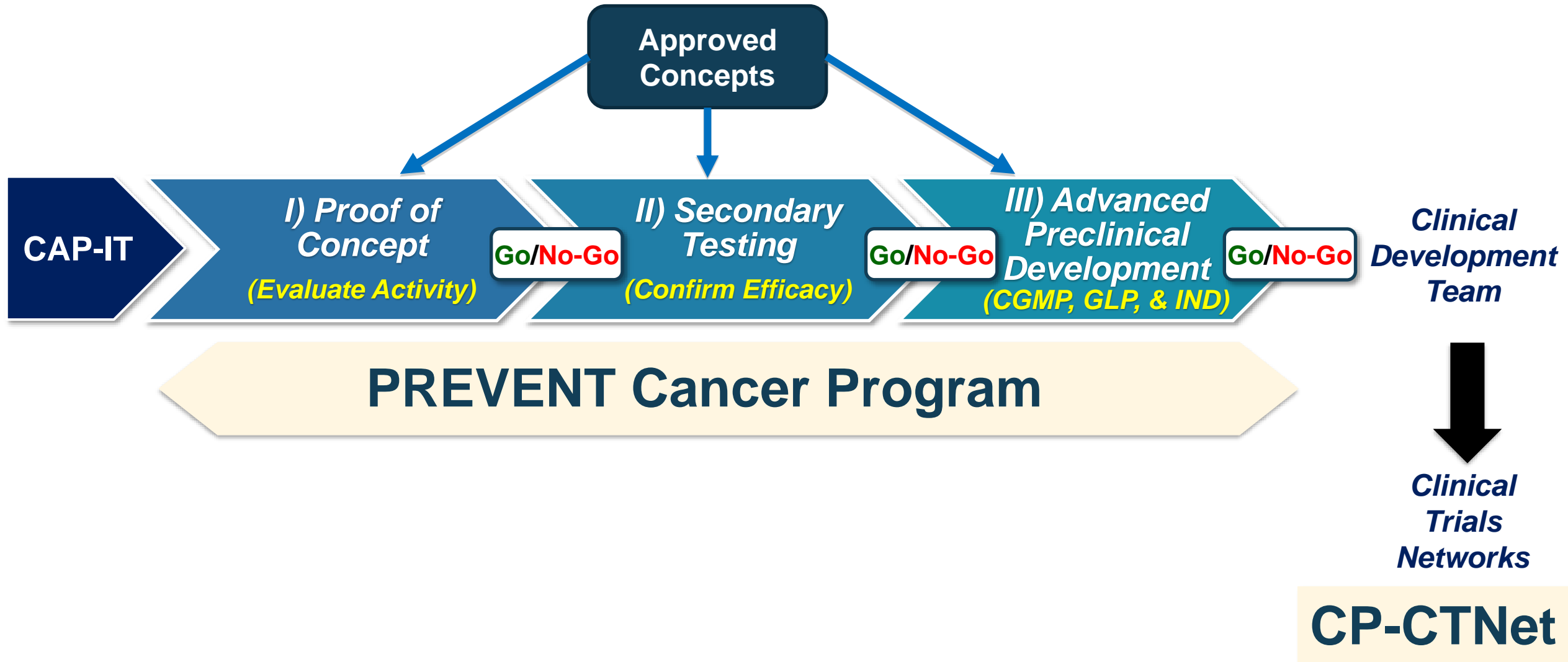(Adapted from Nat Rev Cancer 2012, 12:835)
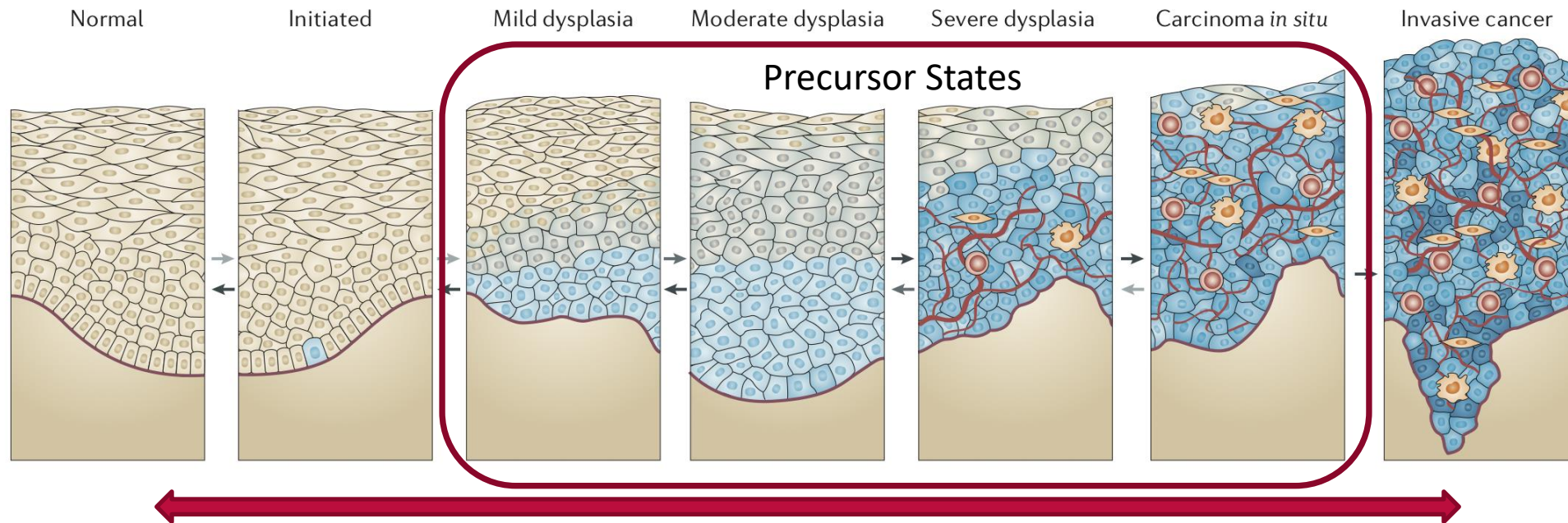
Agents targeting specific pathways:
- Tamoxifen and its derivatives for breast cancer
- NSAIDS for colon cancer
- Immune modulators such as STAT-3 inhibitors
- Drugs targeting oncogenic drivers (*e.g.,* mTOR inhibitor, EGFR inhibitors, and PARP Inhibitors)
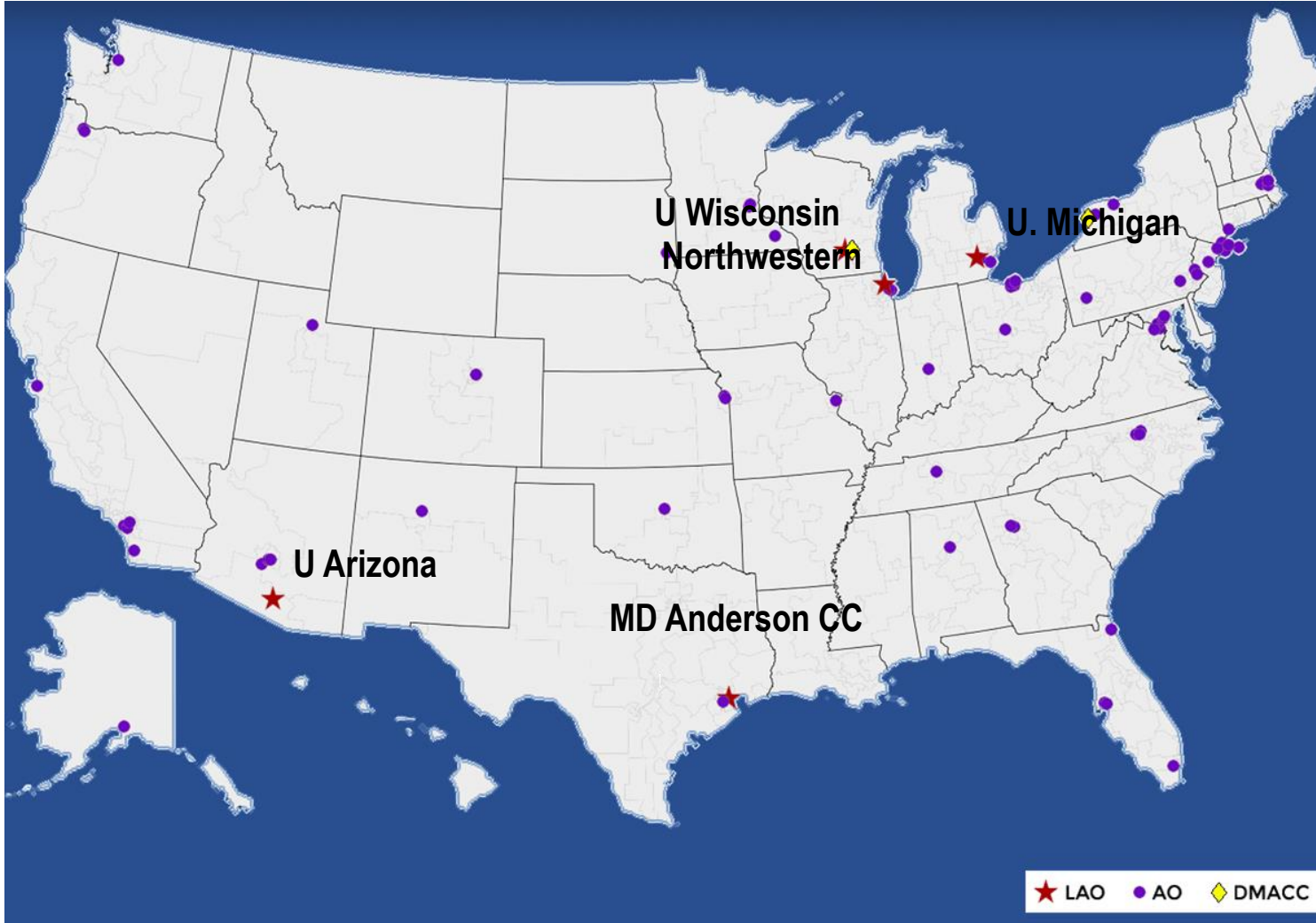- Reactivators of tumor suppressor genes (ONC-201)
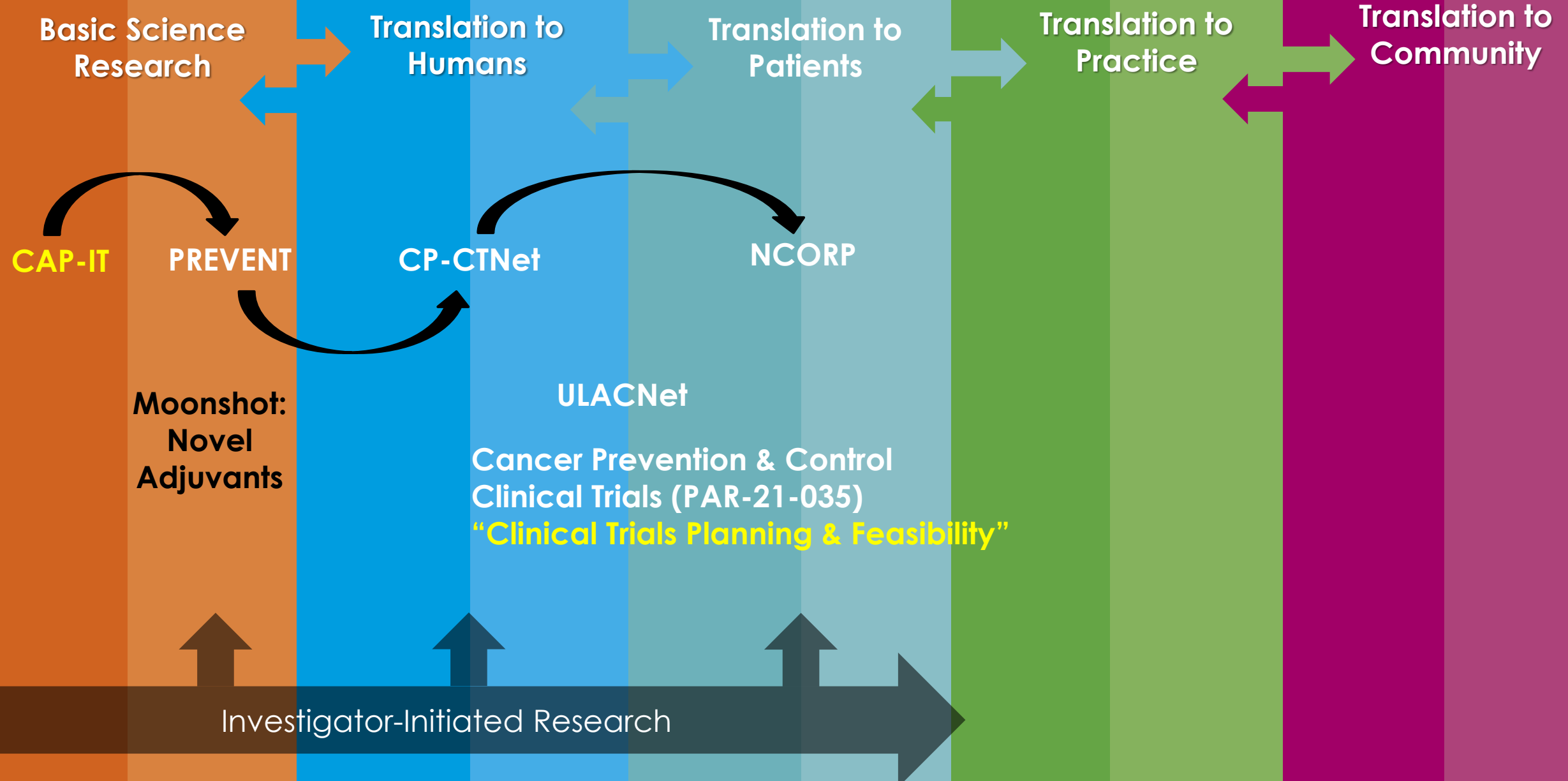
DCP Cancer Preventive Agent Pipeline (Drs. Sei and Shoemaker

Approved Concepts

CAP-IT

I) Proof of Concept *(Evaluate Activity)*

Go/No-Go

II) Secondary Testing *(Confirm Efficacy)*

Go/No-Go

III) Advanced Preclinical Development *(CGMP, GLP, & IND)*

Go/No-Go

Clinical Development Team

PREVENT Cancer Program

Clinical Trials Networks

CP-CTNet

Cancer Prevention Clinical Trials Network (CP-CTNet)
(Eva Szabo, MD)

- Design/conduct early phase clinical trials to assess the safety, tolerability, and cancer preventive potential
- Additional goals:
  - Optimize clinical trial designs
  - Develop surrogate and intermediate endpoint biomarkers
  - Test novel imaging technologies
  - Develop further insights into mechanisms of cancer prevention by agents

Examples of Recent Protocols in the CP-CTNet

- Lisinopril to Prevent Progression of Non-Alcoholic Fatty Liver Disease (

- Nonavalent Prophylactic HPV Vaccine to Assess Immunogenicity of A Prime and Deferred-Booster Dosing Schedule among 9-11 Year-old Girls and Boys (Delayed Booster Trial- An Extended Follow-up Study)

- Clinical Study of Bioactivity of Low-Dose Apalutamide in Prostate Cancer Patients Scheduled for Prostatectomy

- Surgical Window of Opportunity Study of Megestrol Acetate Compared with Megestrol Acetate and Metformin for Endometrial Intraepithelial Neoplasia

- Targeting Dominant-Negative Missense Mutant p53 by Atorvastatin for Reducing the Risk of Longstanding Ulcerative Colitis-Associated Cancer: Two-Arm, Randomized and Placebo-Controlled Phase II Trial

Screening and Early Detection

Risk-informed screening: higher risk = more screening and/or different management, and potential for intervention with targeted preventive agents

Normal | Initiated | Mild dysplasia | Moderate dysplasia | Severe dysplasia | Carcinoma *in situ* | Invasive cancer

Precursor States
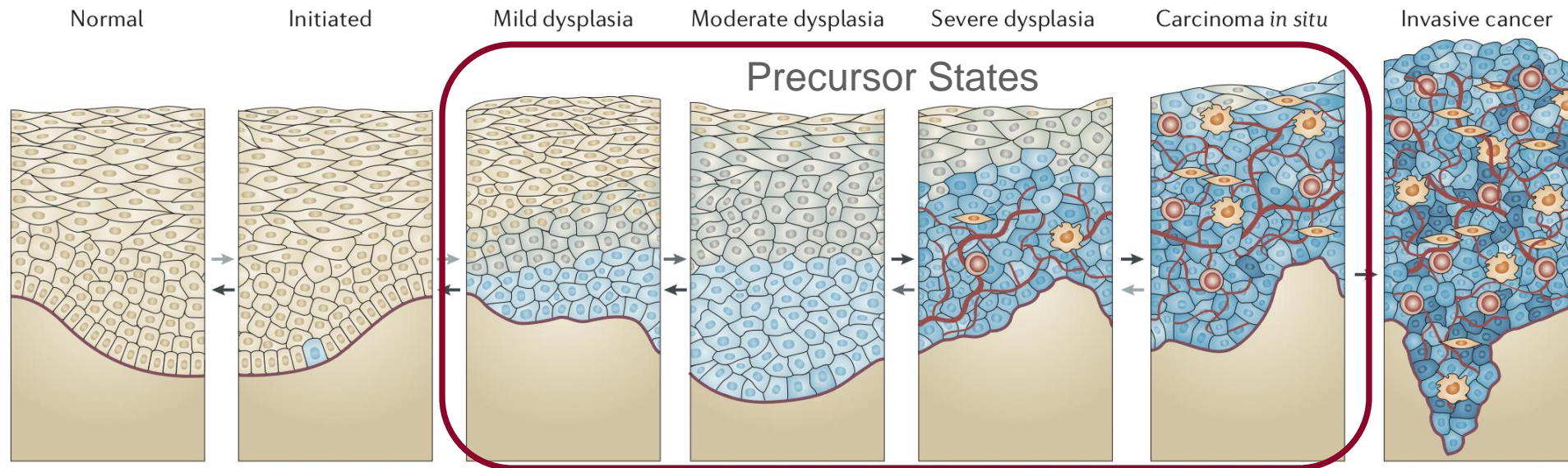
Screening for the prevention and control of breast, cervical, colorectal, lung, HCV (for liver), and prostate cancer in asymptomatic adults; targeted screening of higher-risk individuals for the prevention of less common but still important cancers

Screening and Early Detection R&D Pipeline

Basic Science Research

Translation to Humans

Translation to Patients

Translation to Practice

Translation to Community

TBEL
HTAN
PCA
Alliance of GBs
SCLC

EDRN

NCORP

PCDC
TLC
LBC
CIB

LDCT
Interpretation

ULACNet

Cascade

Last Mile
PLCO
NLST

Cancer Prevention & Control
Clinical Trials (PAR-21-035)
"Clinical Trials Planning & Feasibility"

Investigator-Initiated Research

EDRN Organizational & Operational Structure (Dr. Sudhir Srivastava)

Network Consulting Team ↔ **Steering & Executive Committees**
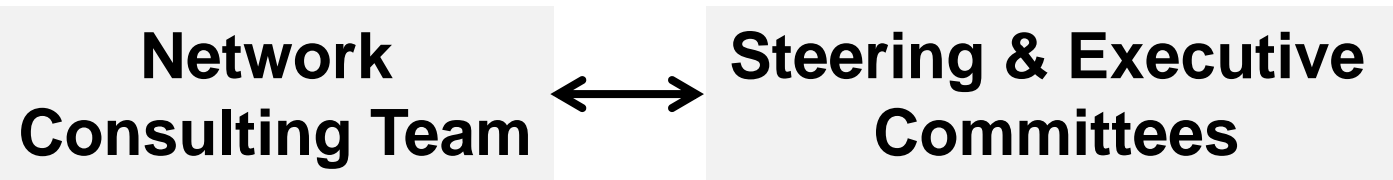
Research Groups

- ➤ Prostate & Other Urologic
- ➤ Breast and Other Gynecologic
- ➤ Lung & Upper Aerodigestive
- ➤ Colon & Other GI

Biomarker Reference Laboratories (BRL) — **Assay Development**

Clinical Validation Centers (CVC) — **Validation**

Data Management & Coordinating Center (DMCC)

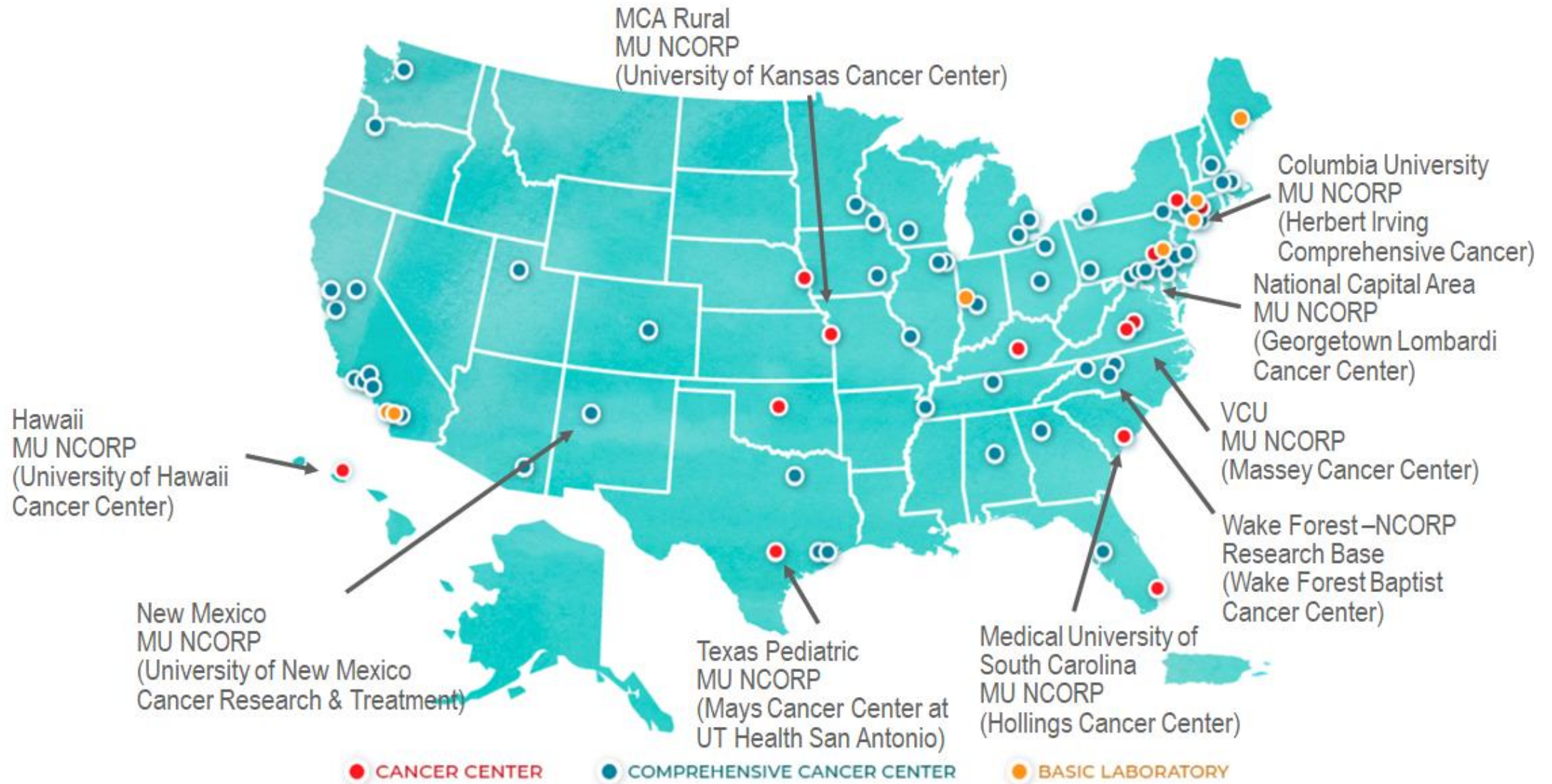**Biomarker Developmental Laboratories (BDL)** — **Discovery**
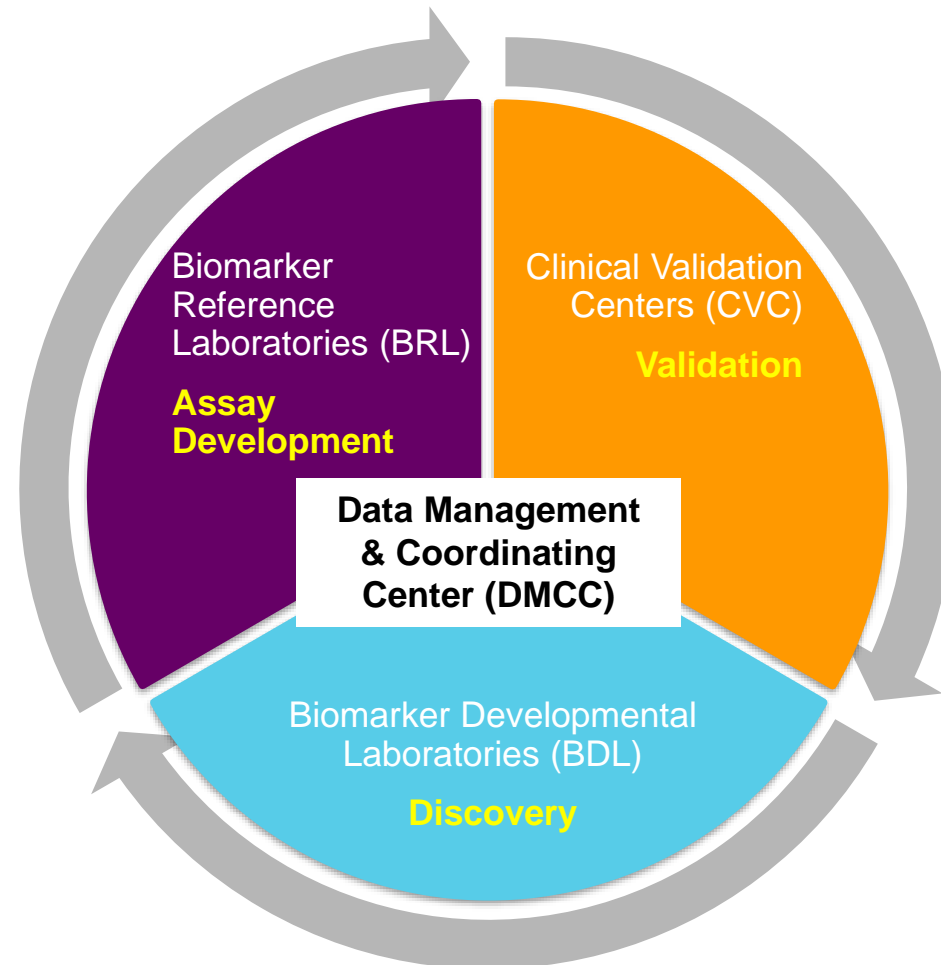
EDRN Collaborations & Partners

- ▪ Parallel, EDRN-Advised Initiatives:
- ▪ **Co-funding** e.g., PanCAN, Canary Foundation, & Cancer Research UK
- ▪ **Independent, collaborative groups** e.g., Pancreatic Cancer Detection Consortium, Consortium for Imaging and Biomarkers, Human Tumor Atlas Network (Pre-Cancer Atlas), & Center for Global Health (NCI)
- ▪ **Associate Members (>350)**
- ▪ **Federal Partners** e.g., NIST, FDA, & Jet Propulsion Lab (JPL)
- ▪ **Pharma/Biotech Industry** (15 active)

NCI Community Oncology Research Program (NCORP)
(Worta McCaskill-Stevens, MD, MS)

MCA Rural
MU NCORP
(University of Kansas Cancer Center)

Columbia University
MU NCORP
(Herbert Irving Comprehensive Cancer)

National Capital Area
MU NCORP
(Georgetown Lombardi Cancer Center)

VCU
MU NCORP
(Massey Cancer Center)

Wake Forest –NCORP
Research Base
(Wake Forest Baptist Cancer Center)

Hawaii
MU NCORP
(University of Hawaii Cancer Center)

New Mexico
MU NCORP
(University of New Mexico Cancer Research & Treatment)

Texas Pediatric
MU NCORP
(Mays Cancer Center at UT Health San Antonio)

Medical University of South Carolina
MU NCORP
(Hollings Cancer Center)

● CANCER CENTER   ◉ COMPREHENSIVE CANCER CENTER   ● BASIC LABORATORY

1,000+ Clinical Sites (46 Centers & Affiliates), 4,000+ Investigators

TMIST (NCORP) Design Modifications

- Primary endpoint remains as occurrence of advanced cancer. However, assessment approach was modified:

  - Original design: occurrence of advanced cancer within a fixed time period of 4.5 years from randomization (binary endpoint, binomial comparison). Screening schedule of participants does not change.

  - Revised design: occurrence of advanced cancer at any time up to 7 years from randomization (time-to-event endpoint, comparison via logrank test).

- Power lowered to 85% from original 90% (Reduced sample size of 36K). Derivation of sample size continues to assume 20% relative reduction in advanced cancer at 4.5 years from randomization.

- Study duration: 10 years (7-year accrual, 3-year follow-up). Projected completion date: Aug 30, 2027

TMIST (NCORP) Accrual (12/1/2021): 60,422
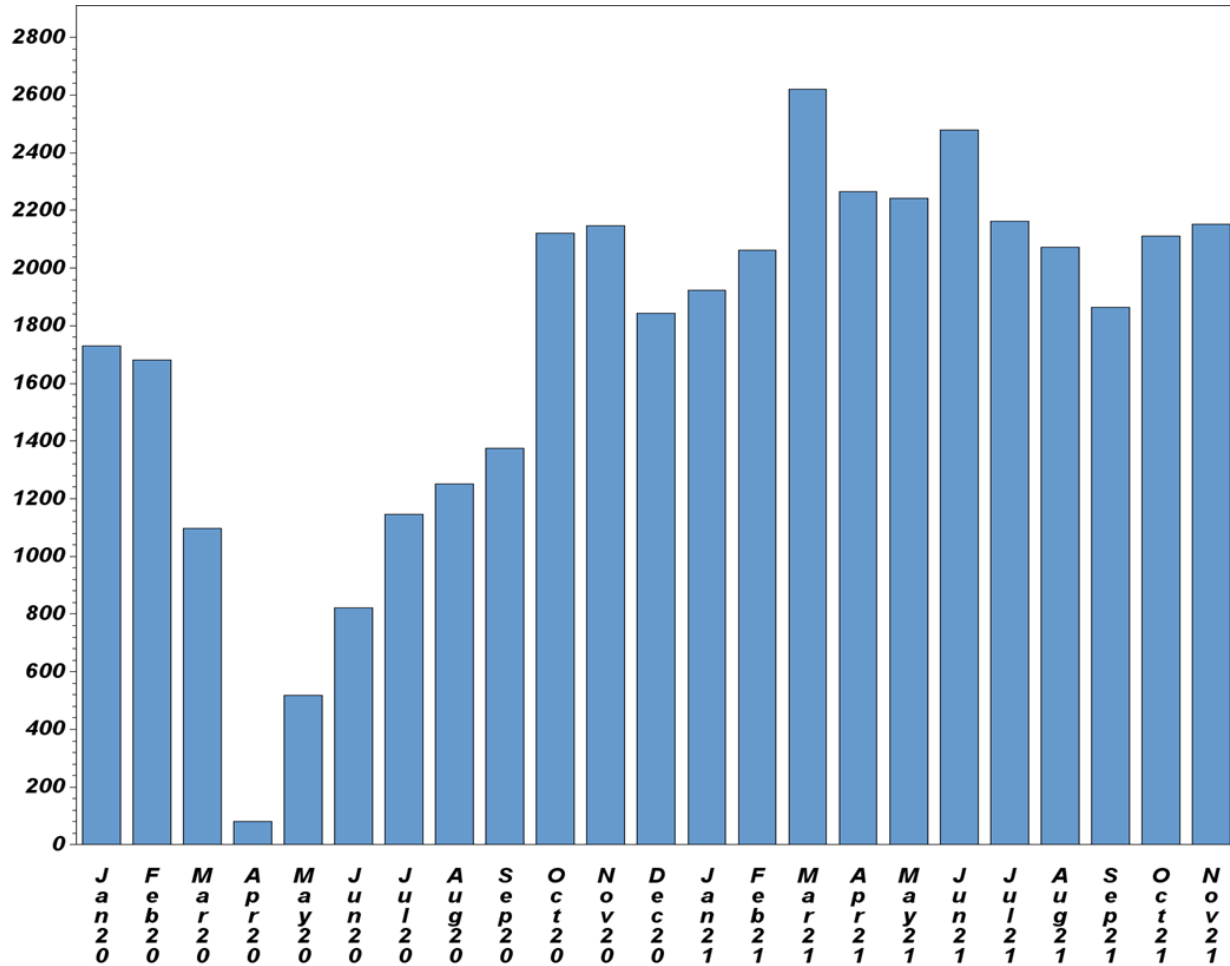
New accrual target: 129,000

Minority Accrual=28%

- 20% Black/African American Women

- 6% Hispanic Women

- 2% Women of Other Racial/Ethnic Groups

Examples of Research Under Way or Recently Approved by the NCORP Steering Committee

Large Screening/ Management Trials

- FORTE: Five- or ten-year colonoscopy for 1-2 non-advanced adenomatous polyps

- TMIST: Randomized to 2D digital mammography versus 3D tomosynthesis mammography for 4 years; primary endpoint is reduction in advanced cancers

Symptom Management & Quality-of-Life Trials

- Immune Checkpoint Inhibitor Toxicity (I-CHECKIT): A Prospective Observational Study

- Optimizing Functional Outcomes of Older Cancer Survivors After Chemotherapy

Other Studies

- Comparing the clinical impact on pancreatic cyst low versus high intensity surveillance

- Comparing the non-inferiority of salpingectomy to salpingo-oophorectomy to reduce the risk of ovarian cancer among BRCA1 carriers

MCED Study Design Workshop (Dr. Lori Minasian)

- **Current knowledge on MCED assays focuses on diagnostic performance**
  - ➢ Sensitivity is modest for early stage, greater for advanced stage
  - ➢ Specificity appears to be high (97% or higher)

- **Clinical utility of widespread implementation of MCED testing is unknown**
  - ➢ Favorable diagnostic performance does not always translate to satisfactory outcome
  - ➢ Risks and harms associated with using MCED for cancer screening are not known

- **MCED tests present novel implementation challenges**
  - ➢ How to quickly and reliably confirm cancer status and site after a positive test
 - ➢ How best to screen for multiple cancers with different latency periods

Themes that Emerged from the Workshop

- **NCI needs to support a trial to evaluate MCED assays**

  ➢ Rigorously assess risk and benefits from the screening process

  ➢ Comparison for a trial would be MCED assay + standard of care screening versus standard of care screening alone

- **Several unknowns for the screening process**

  ➢ Variability in diagnostic workup

    o Different assays may or may not point to a "tissue of origin " for the workup

    o Even with a tissue "locator," the follow up testing to reach a diagnostic resolution varies with providers and patients' access to further diagnostic studies and willingness to complete those diagnostic studies (time away from work, etc.)

  ➢ Need to assess the full process for the workup and when to stop the workup
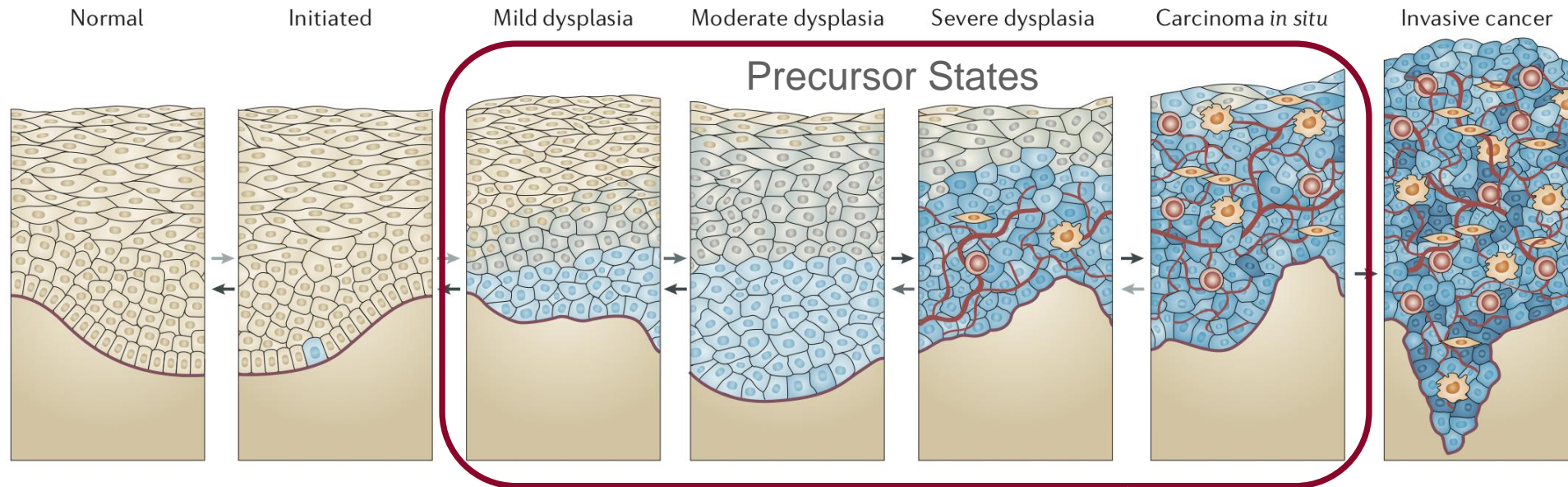
Additional Themes Discussed

- **Assure enrollment of various populations**
  - ➤ Underserved populations
  - ➤ Diverse populations
  - ➤ Vulnerable (socio-economically disadvantaged, others)
  - ➤ High-risk individuals

- **Need concrete process for the recruitment:**
  - ➤ Communication strategy to include a combination of remote and in-person recruitment approaches

- **Need to assure means for adequate follow up to occur and not inadvertently or disproportionally expose vulnerable people to the harms**

My Holy Grail: Precision Cancer Prevention
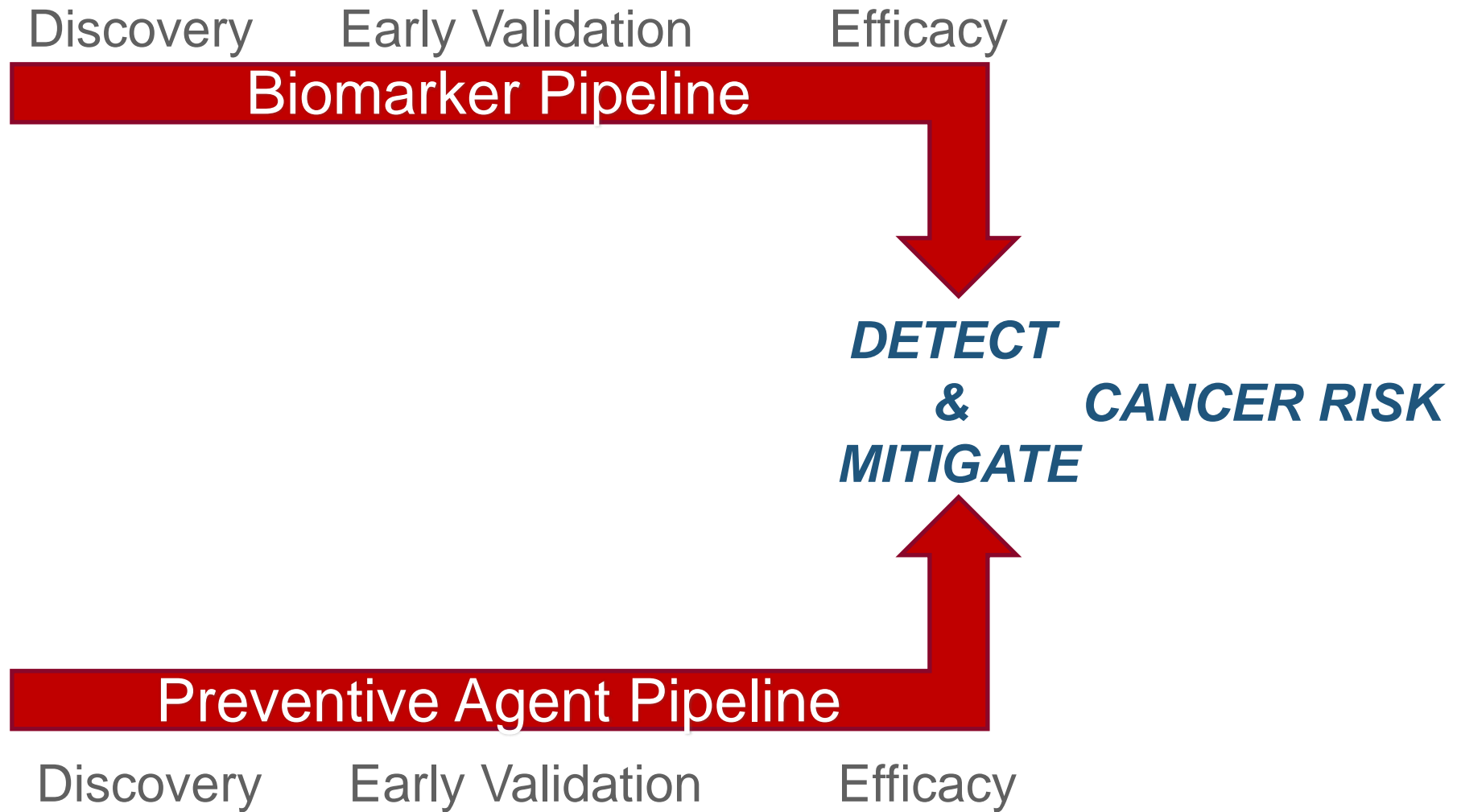
Symptom Science and Management

Basic research to uncover mechanisms and markers of risk for adverse events

Normal | Initiated | Mild dysplasia | Moderate dysplasia | Severe dysplasia | Carcinoma *in situ* | Invasive cancer

Precursor States

3° prevention with chemotherapy, immunotherapy, surgery, radiation therapy, and hormonal therapy

Prevention and management of symptoms of cancer and cancer treatment

Symptom Mgt/Supportive Care R&D Pipeline

Basic Science Research

Translation to Humans

Translation to Patients

Translation to Practice

Translation to Community

- **RFAs CA-15-008, 16-010, 18-019 (Provocative Questions)**
- **PAR-19-325**
- **RFA-17-052**

NCORP

Moonshot: Tolerability Consortium

Investigator-Initiated Research

# Symptom Management and Toxicity Mitigation

- **Understand mechanisms of action for the chronic adverse effects**
  - Investigator community interested in exploring mechanisms of adverse effects of cancer treatment to normal tissue
  - Provocative question RFA had significant response

- **Rigorously characterize the clinical syndrome for the toxicity or symptom**
  - Need appropriate and robust measures for symptomatic toxicities
    - Examples: chemotherapy induced peripheral neuropathy and cancer-related fatigue
  - Need longitudinal studies to evaluate the natural history of the toxicity
  - Current approach is to capture most severe event using CTCAE at single point in time

- **Capture how the patient functions & feels through patient reported outcomes**
  - Symptom management and toxicity mitigation trials frequently have PROs as the primary endpoint
  - Need systematic approach to collection, analysis and reporting of PRO data

Trans-NCI Research Opportunities

- **Provocative Question:**
  - ➤ PQ9 or 12: *What are the molecular and/or cellular mechanisms that underlie the development of cancer therapy-induced severe adverse sequelae?*
  - ➤ RFAs CA-15-008, 16-010, 18-019

- **Clinical Characterization of Cancer Therapy-Induced Adverse Sequelae and Mechanism-Based Interventional Strategies**
  - ➤ PAR-19-325
  - ➤ Specifically, identified the need for longitudinal phenotyping projects

- **Analyzing and Interpreting Clinician and Patient Adverse Event Data to Better Understand Tolerability**
  - ➤ RFA-17-052

Cannabis, Cannabinoids, and Cancer (Dr. Alexis Bakos)

- Virtual Workshop December 2020

- Members from multiple NCI divisions, FDA, and NIDA

- Monograph published last week (Volume 2021 Issue 58 | JNCI Monographs | Oxford Academic (oup.com))
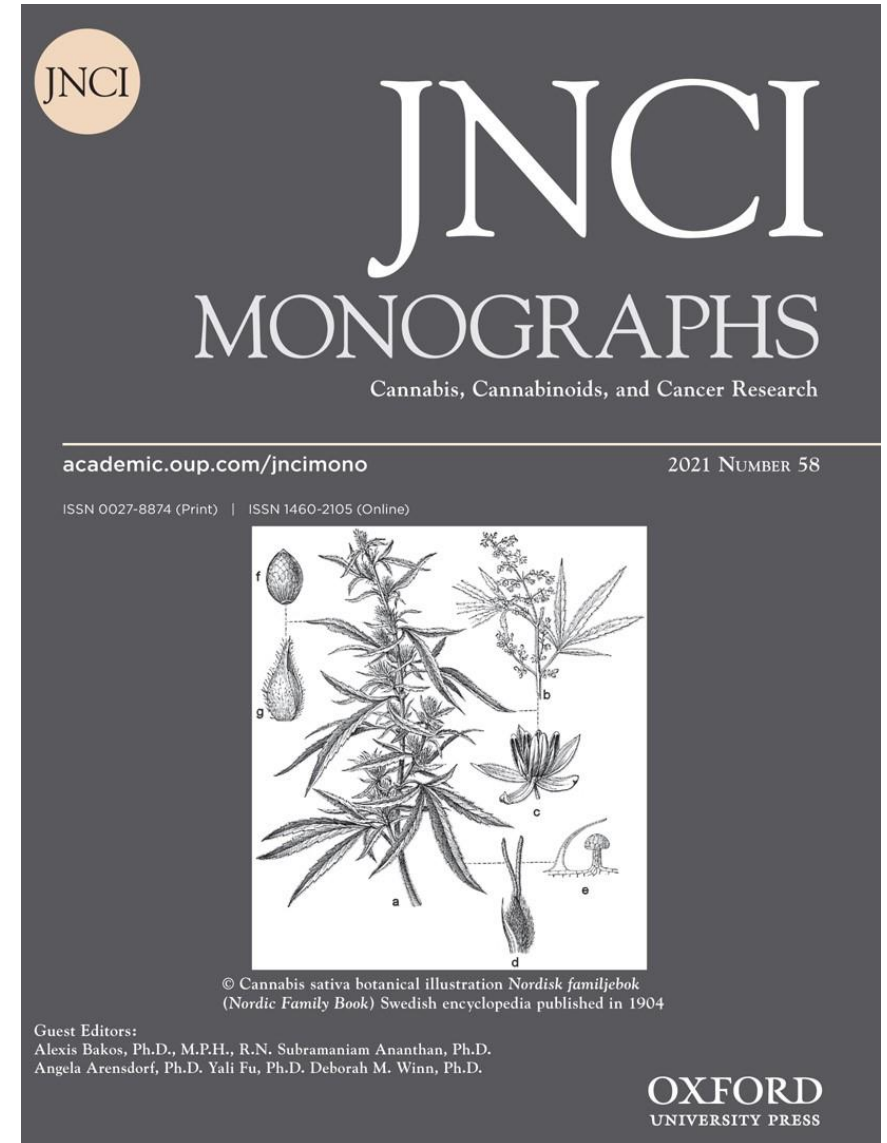
Final Comments: Some Proposed DCP Priorities

- **Biological & Population Risk-Informed Interventions:**

  ➢ Biological Risk --- Targeted interventions (agents or biomarkers) based on the biology/pathways of carcinogenesis, i.e., "precision cancer prevention"

  ➢ Population Risk --- Using risk to decide who gets screened and how, how screen+ are managed, and harmonizing care i.e., "equal care for equal risk"

- **Obesity**: ≥20% of cancers are attributable to obesity but we do not really understand how obesity contributes to carcinogenesis. If we did, we could mitigate its effects.

- **Symptom Science/Precision Symptom Prevention & Management**: How can we use biology, genetics, and epidemiology to:

  ➢ Understand the "etiology" of symptoms (symptom science)

  ➢ Explain adverse responses to treatments

  ➢ Move symptom management from trial-and-error to precision medicine

Final Comments: Some Proposed DCP Priorities

- **Health Disparities**: Innovations in technologies (e.g., self-collection, POC testing, etc.) to bring standard-of-care (or better) to underserved populations who are typically at *higher* risk of cancer.

- **New Technologies**: AI, multi-cancer early detection, synthetic biomarkers, etc., etc. We need to get out front and figure out what is good and what is not.

- **Immunology and Preventive Vaccination:** What constitutes an effective immune response to a carcinogenic insult; neoantigen discovery and validation

Final Comments: Redefining Precision Cancer Prevention to Promote Health Equity*

- Maximizing Benefits to Harms for the Entire Population (B:H)

- Understanding all causes of differences---not just biological---informs how we can be more "precise"

Who: use population risk to decide needs the intervention

What: use biological risk for a targeted approach

Where: increasing access by alternative healthcare delivery strategies

How: B:H can be increased by alternative routes of administration to increase bioavailability at the target site and limit exposure at non-target sites

Acknowledgements

- Staff of DCP
- Deborah Winn
- NCI Leadership:
  - Ned Sharpless
  - Doug Lowy
  - Jim Doroshow
  - Dinah Singer
  - Bob Croyle
  - Dan Gallahan
  - Stephen Chanock
  - Tom Misteli
  - Satish Ghopal
  - Michelle Bennett

THANK YOU!

www.cancer.gov   www.cancer.gov/espanol