Development of novel and targeted agents in precision cancer prevention and interception

The Cancer Drug Development Forum

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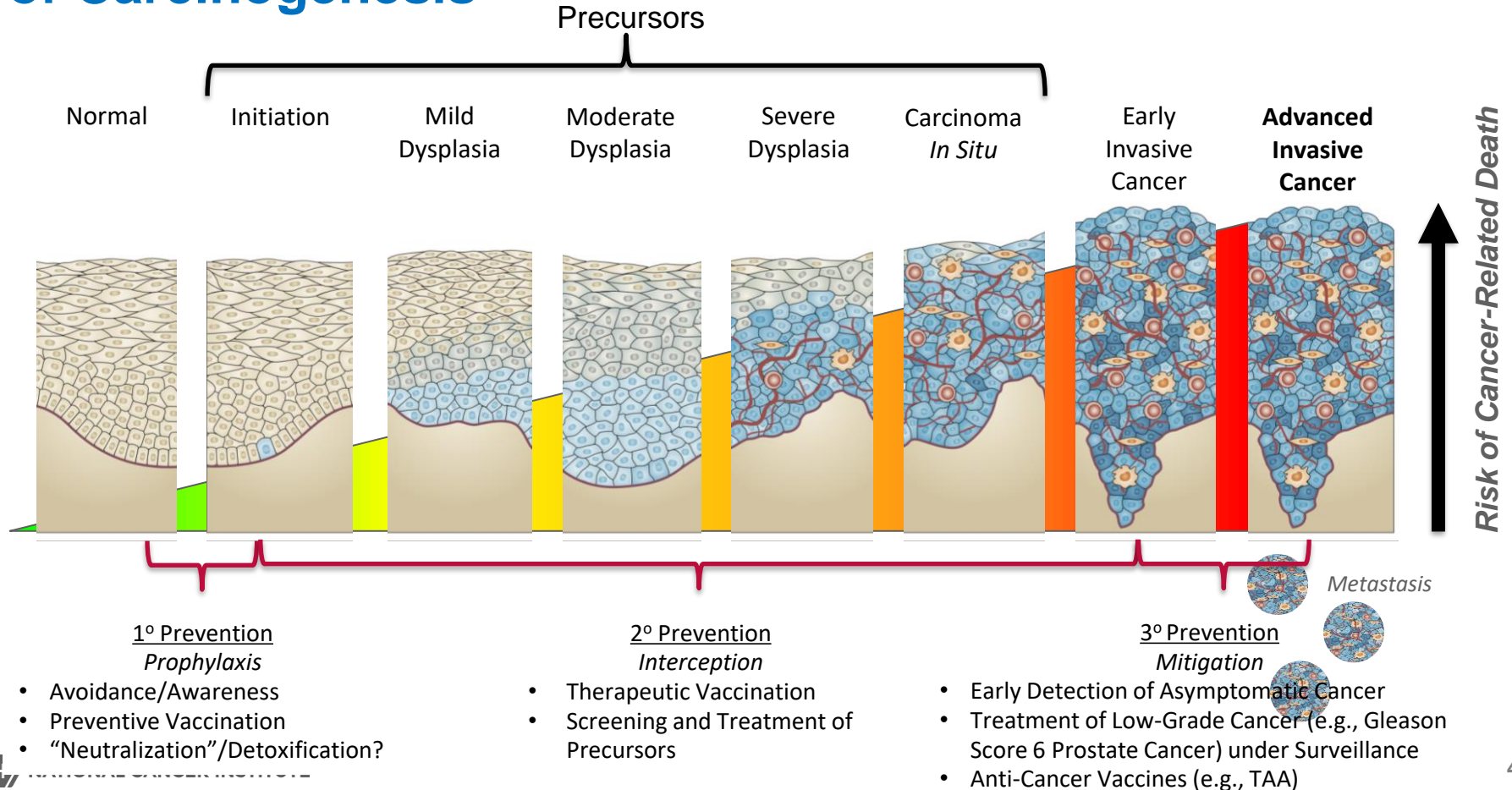
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Disclaimers

- I have no conflicts of interest to disclose.

- Opinions expressed by Dr. Cholewa are his own and do not reflect those or the National Cancer Institute.

- The topics of discussion are informal and do not represent specific funding opportunities.
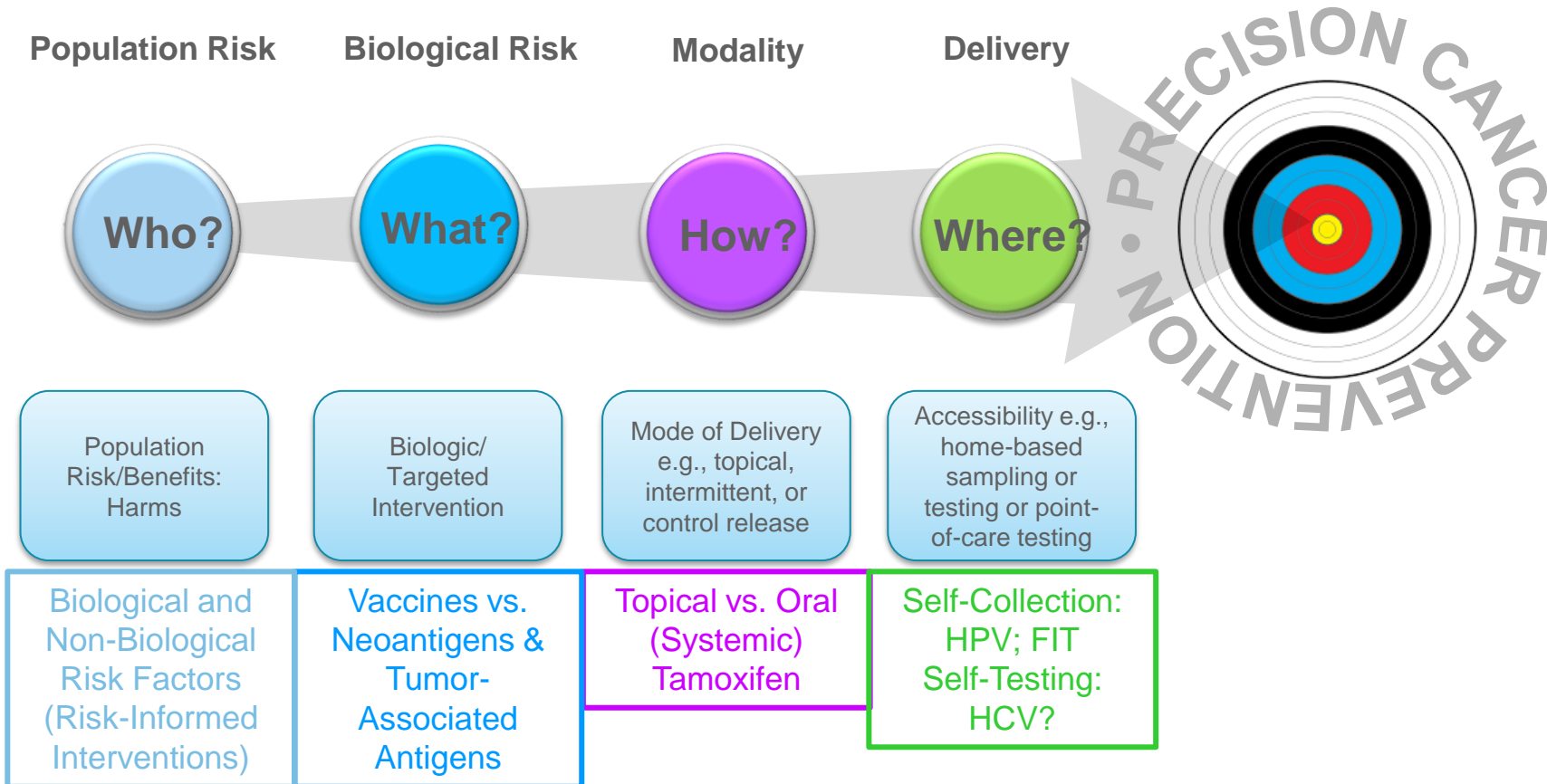
Overview

1. *Prevention and <u>Interception</u>*
2. *Clinical Challenges*
3. *Nonclinical Challenges*
4. *PREVENT and CP-CTNet*
5. *Open Discussion*

Underpinnings of Cancer Prevention: An Understanding of Carcinogenesis

Precursors

Normal · Initiation · Mild Dysplasia · Moderate Dysplasia · Severe Dysplasia · Carcinoma *In Situ* · Early Invasive Cancer · **Advanced Invasive Cancer**

Risk of Cancer-Related Death

Metastasis

1º Prevention
Prophylaxis
- Avoidance/Awareness
- Preventive Vaccination
- "Neutralization"/Detoxification?

2º Prevention
Interception
- Therapeutic Vaccination
- Screening and Treatment of Precursors

3º Prevention
Mitigation
- Early Detection of Asymptomatic Cancer
- Treatment of Low-Grade Cancer (e.g., Gleason Score 6 Prostate Cancer) under Surveillance
- Anti-Cancer Vaccines (e.g., TAA)

Precision Cancer Screening and Prevention Strategies

Population Risk — Who? — Population Risk/Benefits: Harms — Biological and Non-Biological Risk Factors (Risk-Informed Interventions)

Biological Risk — What? — Biologic/ Targeted Intervention — Vaccines vs. Neoantigens & Tumor-Associated Antigens

Modality — How? — Mode of Delivery e.g., topical, intermittent, or control release — Topical vs. Oral (Systemic) Tamoxifen

Delivery — Where? — Accessibility e.g., home-based sampling or testing or point-of-care testing — Self-Collection: HPV; FIT Self-Testing: HCV?

PRECISION CANCER PREVENTION

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Early Detection Research Network

BCCs and CVCs are highly integrated components and dependent on each other's expertise and resources
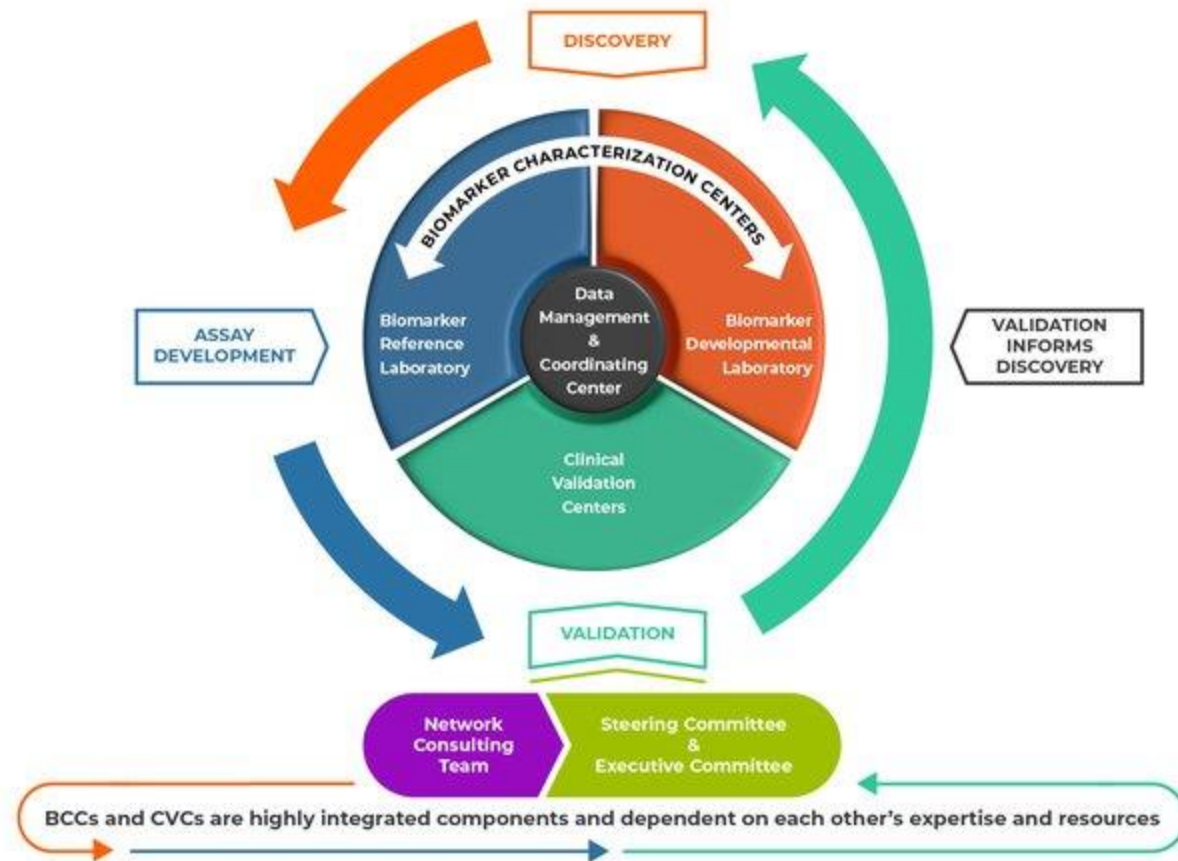
FDA-Approved Tests

- **EsoCheck™** Allows patients to undergo a non-invasive five-minute office-based procedure to detect Barrett's Esophagus. *2019 FDA-cleared tool*. Sanford Markowitz, M.D., PAVmed.

- **CancerSEEK** Detection of genetic mutations associated with pancreatic and ovarian cancer. *2019 FDA break through device*. Ken Kinzler, Ph.D., Robert Schoen, M.D., Randall Brand, M.D., Peter Allen, M.D., and Samir Hanash, M.D., Thrive Detection Corp.

- **Overa**(5 analytes: CA 125, apolipoprotein A-1, transferrin, follicle-stimulating hormone, human epididymis protein 4). Prediction of ovarian cancer risk in women with adnexal mass. *Approved 2016*. Zhen Zhang, Ph.D. and Daniel Chan, Ph.D., Vermillion.

- **%[-2]proPSA** Reduce the number of unnecessary initial biopsies during prostate cancer screening. *Approved 2012*. Daniel Chan, Ph.D., Beckman Coulter.

- **PCA3 (Prostate Cancer Antigen 3) RNA in urine.** Determination of need for biopsy or repeat-biopsy in patients at risk for prostate cancer. *Approved 2012.* John Wei, M.D., Gen-Probe.

- **Risk of Ovarian Malignancy (ROMA) algorithm.** Prediction of ovarian cancer risk in women with pelvic mass. *Approved 2011*. Steve Skates, Ph.D., Fujirebio Diagnostics.

- **DCP and AFP-L3; a combined panel of biomarkers.** Risk assessment for development of hepatocellular carcinoma. *Approved 2011*. Jorge Marrero, M.D. Wako Diagnostics.

- **OVA1™** (5 analytes: CA 125, prealbumin, apolipoprotein A-1, beta2 microglobulin, transferrin). Prediction of ovarian cancer risk in women with adnexal mass. *Approved 2009*. Daniel Chan, Ph.D. and Zhen Zhang, Ph.D., Vermillion.

Clinical Challenges

Who and how of precision cancer prevention

Identifying high risk cohorts

- Barrett's esophagus, HPV, Lynch Syndrome
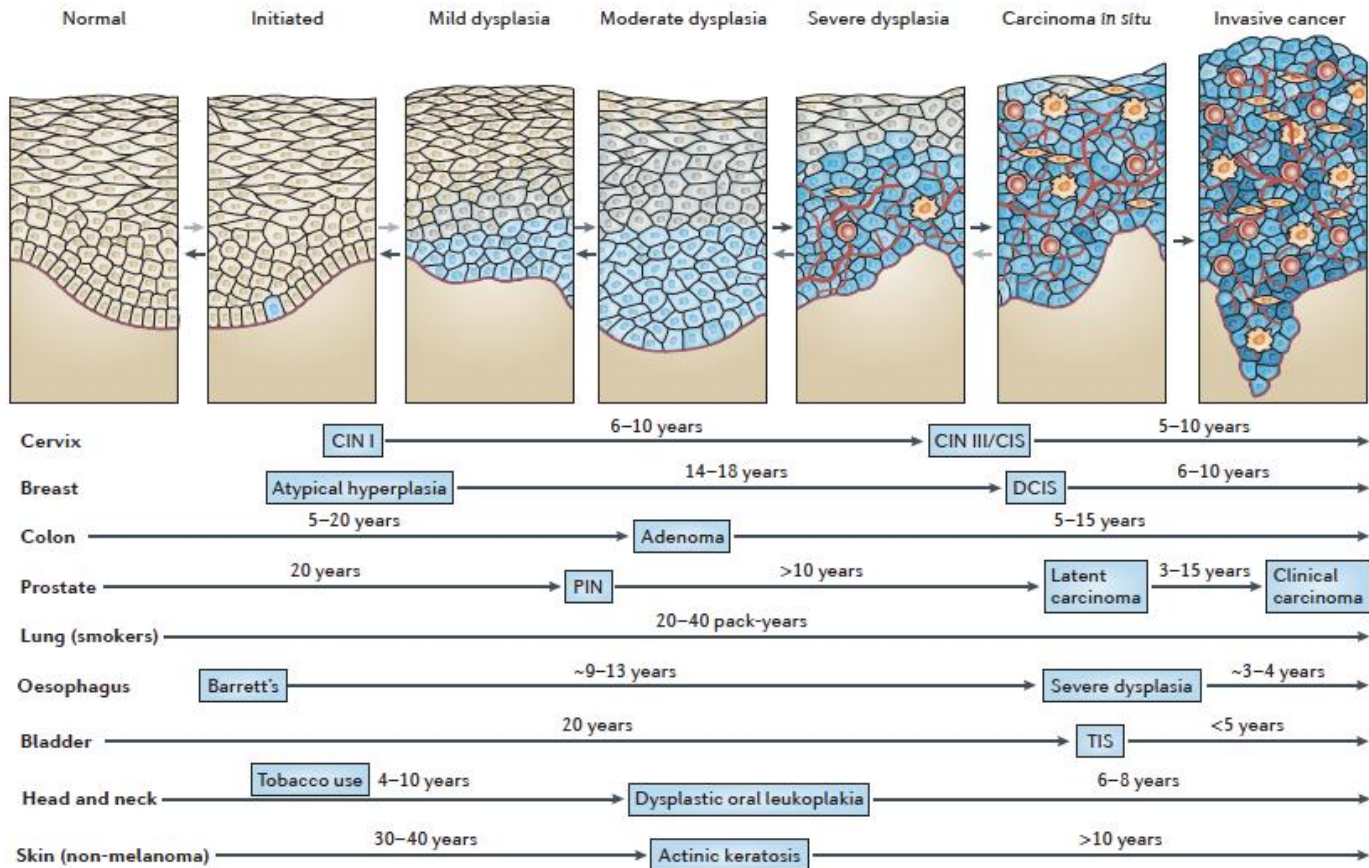- Molecular signatures

Evaluable interim endpoints

- Molecular surrogates

Toxicity

- "Healthy" populations

Cancer Progression

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

Cervix: CIN I — 6–10 years → CIN III/CIS — 5–10 years →

Breast: Atypical hyperplasia — 14–18 years → DCIS — 6–10 years →

Colon: 5–20 years → Adenoma — 5–15 years →

Prostate: 20 years → PIN → >10 years → Latent carcinoma — 3–15 years → Clinical carcinoma →

Lung (smokers): 20–40 pack-years →

Oesophagus: Barrett's — ~9–13 years → Severe dysplasia — ~3–4 years →

Bladder: 20 years → TIS — <5 years →

Head and neck: Tobacco use — 4–10 years → Dysplastic oral leukoplakia — 6–8 years →

Skin (non-melanoma): 30–40 years → Actinic keratosis — >10 years →

Umar, Dunn, Greenwald Nat Rev Cancer. 2012

Current Approaches

	Window of Opportunity studies	Pre-surgery/resection/biopsy

	Surveillance	Imaging

	Risk mitigation	Routes of administration Dose reduction/modification

Nonclinical Challenges

What toxicities cannot be identified in clinical trials?

- Teratogenicity: don't want to deliberately expose pregnant women

- Carcinogenicity: long latency period and insensitivity of epidemiological studies preclude identification of this adverse effect

- Long term toxicities

Nonclinical Challenges

Investigational agents

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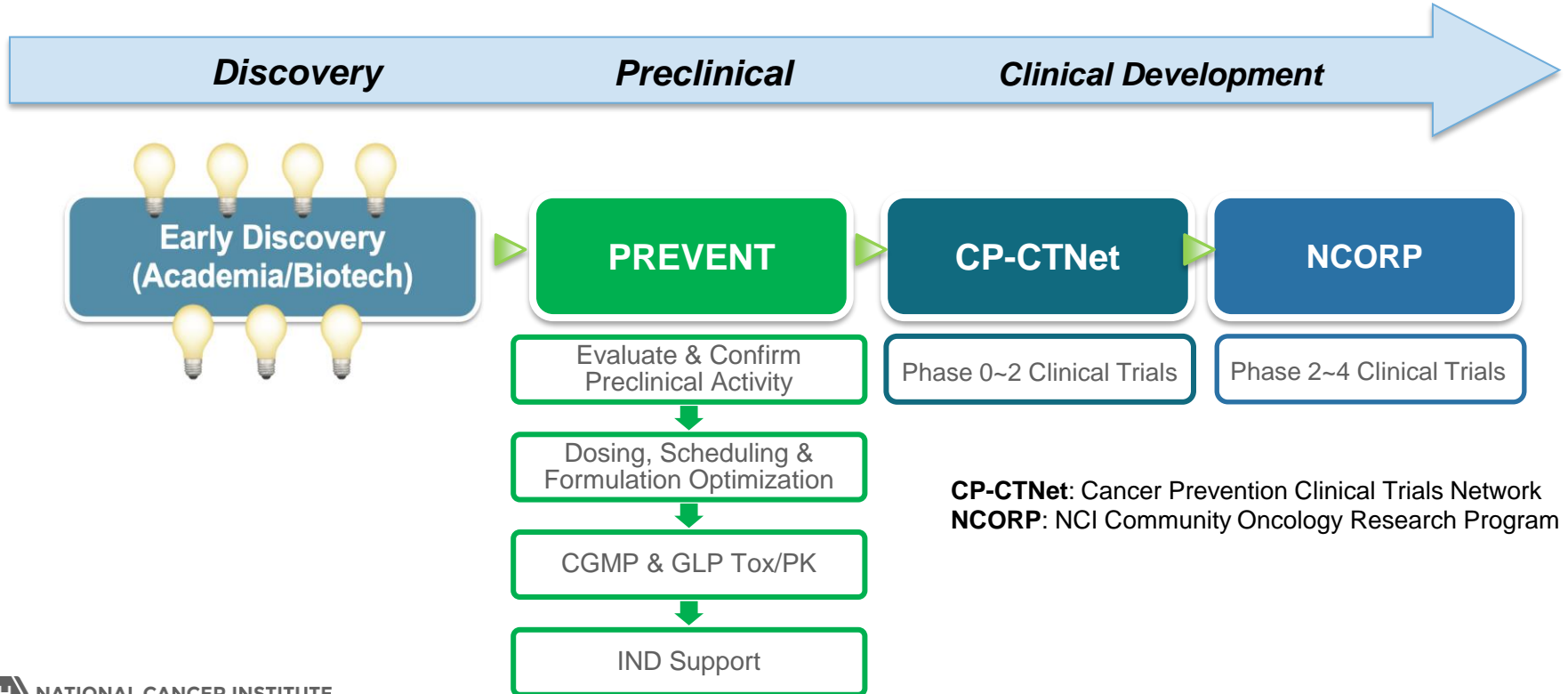
High cost with high risk
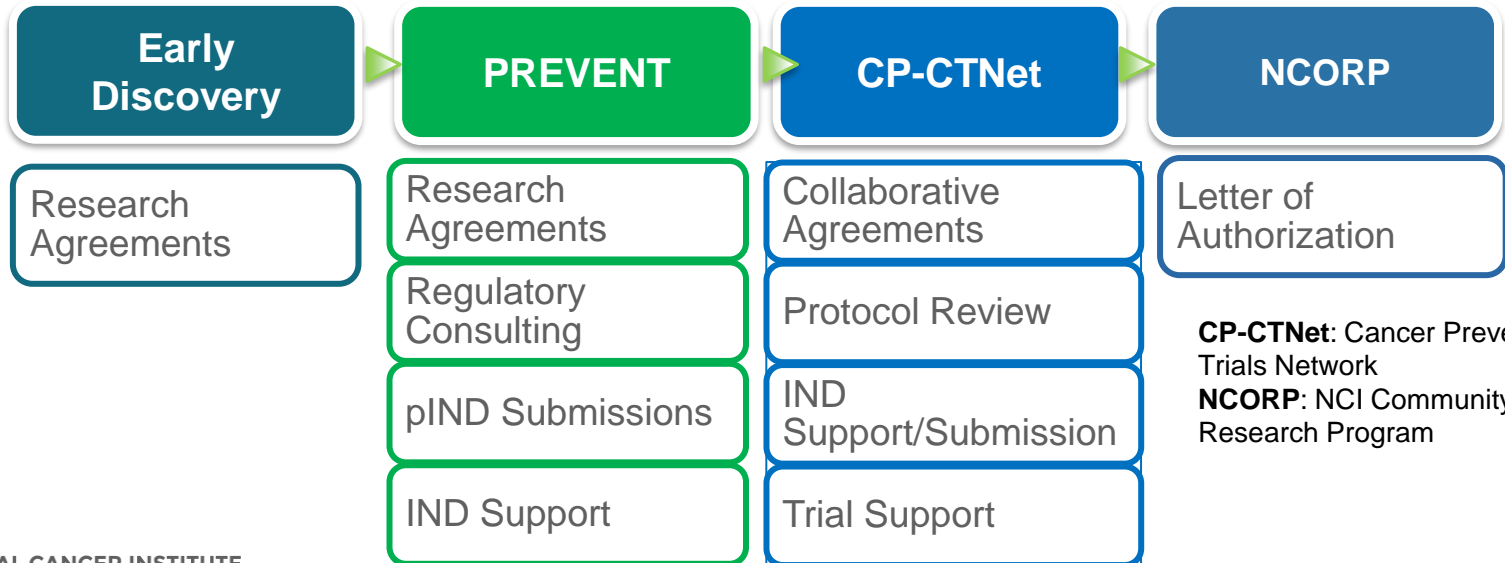
NOAEL v MTD

Long-term clinical trials

Funding opportunities

Grant mechanisms often don't reward general toxicology

DCP Agent Discovery and Development Pipeline

Discovery **Preclinical** **Clinical Development**

Early Discovery (Academia/Biotech) → **PREVENT** → **CP-CTNet** → **NCORP**

Evaluate & Confirm Preclinical Activity

↓

Dosing, Scheduling & Formulation Optimization

↓

CGMP & GLP Tox/PK

↓

IND Support

Phase 0~2 Clinical Trials

Phase 2~4 Clinical Trials

CP-CTNet: Cancer Prevention Clinical Trials Network
NCORP: NCI Community Oncology Research Program

DCP Regulatory Pipeline

Discovery — Preclinical — Clinical Development

Early Discovery → **PREVENT** → **CP-CTNet** → **NCORP**

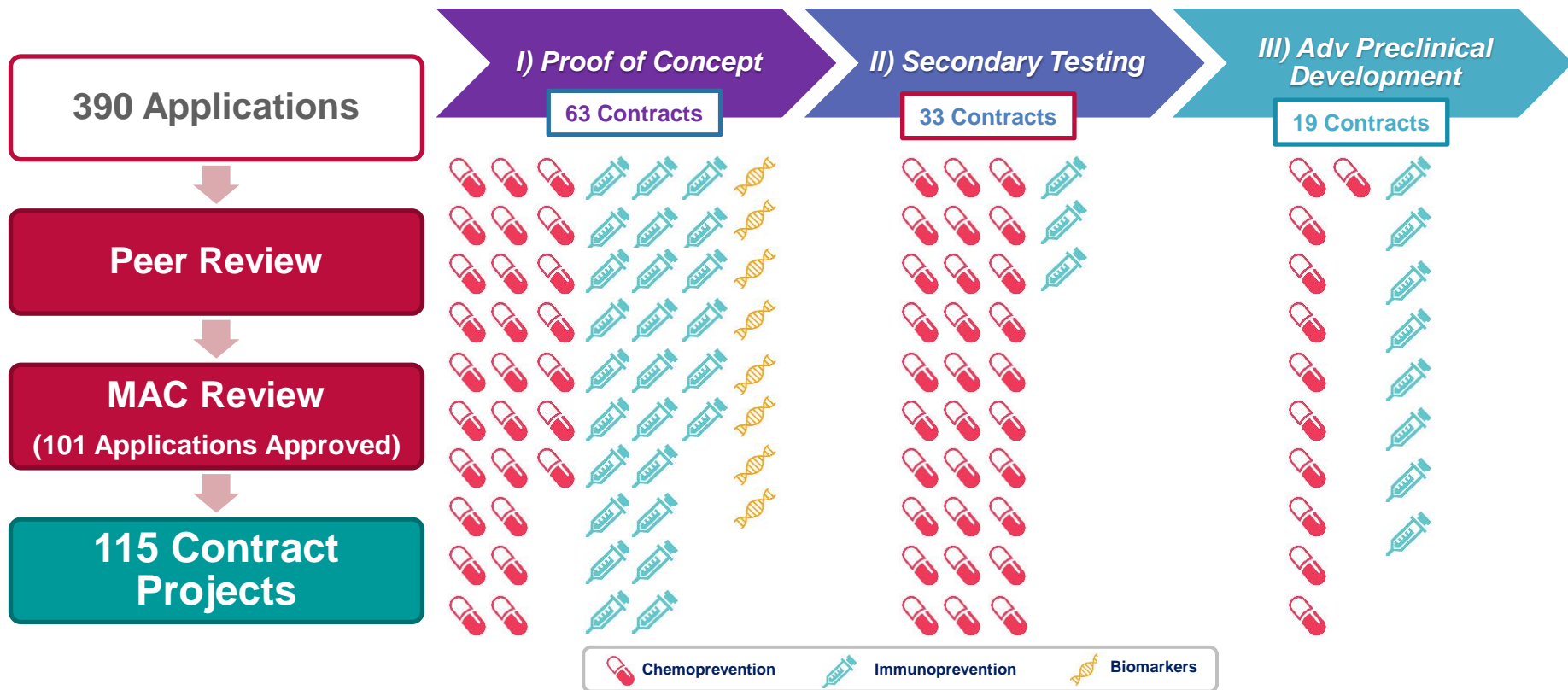| Early Discovery	PREVENT	CP-CTNet	NCORP
Research Agreements	Research Agreements	Collaborative Agreements	Letter of Authorization
	Regulatory Consulting	Protocol Review	
	pIND Submissions	IND Support/Submission	
	IND Support	Trial Support	

CP-CTNet: Cancer Prevention Clinical Trials Network
NCORP: NCI Community Oncology Research Program

NCI PREVENT Program

- **Focus Areas:**
  - **Immunoprevention (e.g. vaccines for cancers associated with/without infectious agents; immunomodulatory agents)**
  - **Chemoprevention**
    - ✓ **Novel agents**
    - ✓ **Novel mechanisms**
    - ✓ **Anti-inflammatory approaches**
    - ✓ **Drug repurposing**
    - ✓ **Reducing toxicity (e.g. dosing, alternative delivery route, scheduling, and combinations)**
  - **Clinically translatable biomarkers of tumor progression and/or preventive efficacy**
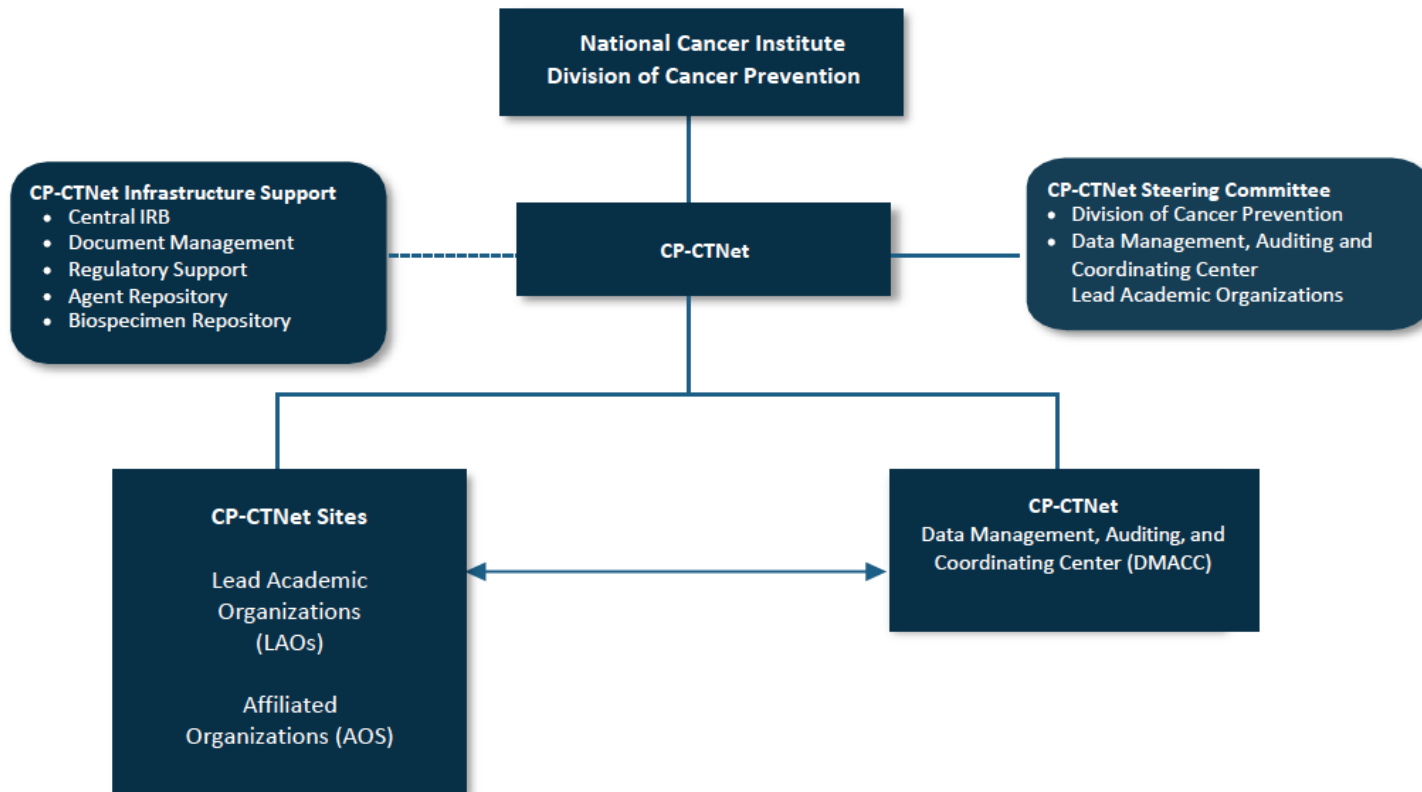
PREVENT Projects Implemented to Date

390 Applications

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Peer Review

↓

MAC Review
(101 Applications Approved)

↓

115 Contract Projects

I) Proof of Concept
63 Contracts

II) Secondary Testing
33 Contracts

III) Adv Preclinical Development
19 Contracts

Chemoprevention   Immunoprevention   Biomarkers

Who Can Apply & How to Apply

- **Everyone is eligible to apply:**
  - ✓ **Researchers in academia, government, industry**
  - ✓ **Nationally or internationally**

- **Submission deadlines twice per year: 2nd Mondays in January & July**

- **Application in PDF format electronically (Email) transmitted to:**

    PREVENT@mail.nih.gov

- **Submission details on the PREVENT website:**

  https://prevention.cancer.gov/major-programs/prevent-cancer-preclinical-drug-development-program

CP-CTNet

National Cancer Institute
Division of Cancer Prevention

CP-CTNet

CP-CTNet Infrastructure Support
- Central IRB
- Document Management
- Regulatory Support
- Agent Repository
- Biospecimen Repository

CP-CTNet Steering Committee
- Division of Cancer Prevention
- Data Management, Auditing and Coordinating Center
  Lead Academic Organizations

CP-CTNet Sites

Lead Academic
Organizations
(LAOs)

Affiliated
Organizations (AOS)

CP-CTNet
Data Management, Auditing, and
Coordinating Center (DMACC)

Working with CP-CTNet (non-affiliated)

- An investigator interested in conducting a clinical trial with an agent ready for clinical testing can join a Lead Academic Organization to become an Affiliated Organization

  - Northwestern, University of Arizona, MD Anderson, University of Michigan, University of Wisconsin

- An investigator who wishes to provide an agent for clinical study (but not to perform the clinical trial) can discuss with NCI/DCP if the agent is appropriate for study in CP-CTNet and then enter into a formal agreement with NCI/DCP to allow CP-CTNet to perform the trial

Open Discussion

"So I guess this probably counts as an adverse event."

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