THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

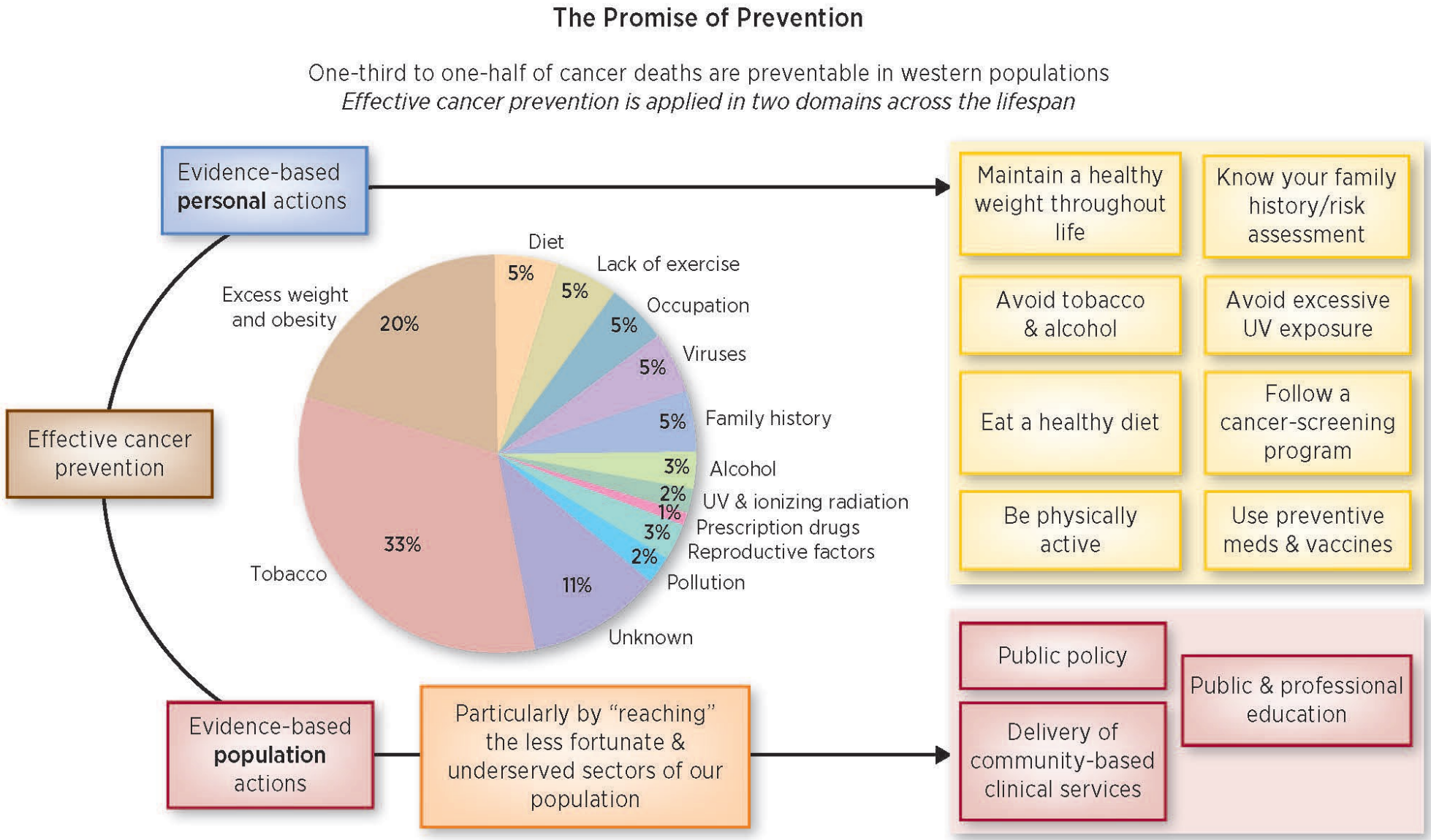
The NCI Cancer Prevention Steering Committee
Opportunities & Challenges to Accelerate Progress

November 7, 2018

Ernest Hawk, MD, MPH
Vice President & Head
Division of Cancer Prevention and Population Sciences

One-Third to One-Half of Cancer Deaths are Preventable in Western Populations

Effective Cancer Prevention is Applied in Two Domains Across the Lifespan



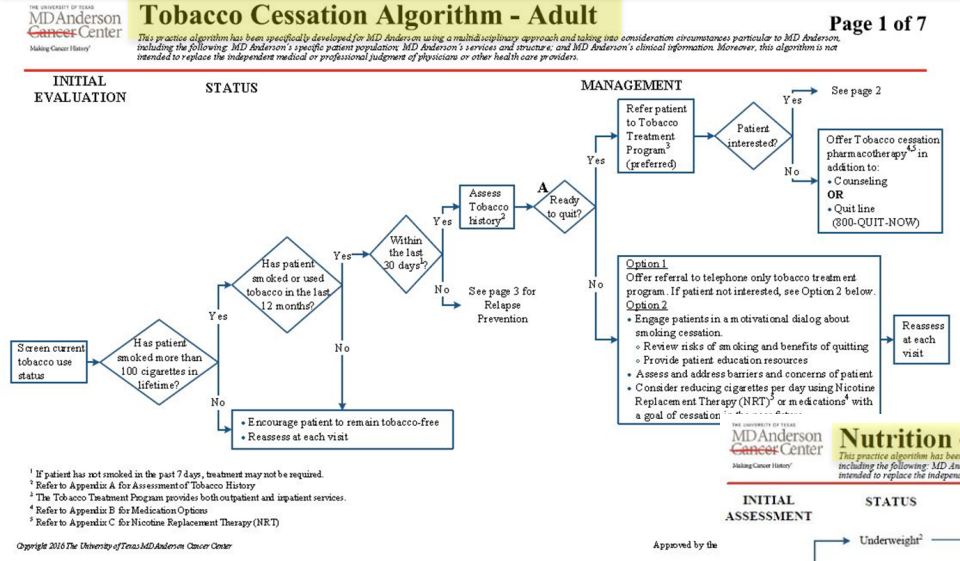
E. Hawk – unpublished work, based on data from Colditz, et al. Sci Trans Med., 2012 & Wolin, et al., Oncologist, 2010

ACS* Lifestyle Recommendations for Cancer Prevention

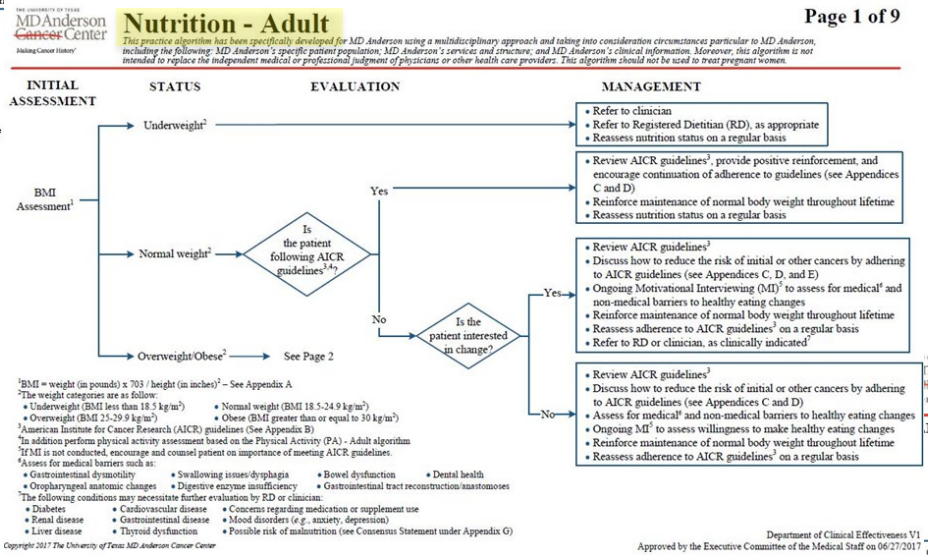
	ACS – 2018
Achieve & maintain a healthy weight throughout life	• Be as lean as possible throughout life without being underweight • Avoid excessive weight gain at all ages • Get regular physical activity & limit intake of high-calorie foods & drinks as keys to help maintain a healthy weight
Be physically active	• Adults: Engage in at least 150 minutes of moderate intensity PA or 75 minutes of vigorous intensity/week or combination • Children/adolescents: Engage in 60+ minutes/day of moderate to vigorous PA 5+ days/week, with vigorous activity on at least 3 days each week
Eat a healthy diet, with an emphasis on plant foods	• Consume at least 2.5 c of various fruits & vegetables/day • Choose whole grains rather than processed grains • Limit consumption of processed and red meats
If you drink alcohol, limit your intake	• Women: Drink no more than 1 drink/day • Men: Drink no more than 2 drinks/day
Stay away from tobacco	• Decide to quit, set a date, and prepare • Consider formal programs • Consider nicotine replacement therapy • Seek additional help, if needed

*American Cancer Society

Implementing Healthy Lifestyle Algorithms into MD Anderson's Clinical Care



[1] If patient has not smoked in the past 7 days, treatment may not be required.
[2] Refer to Appendix A for Assessment of Tobacco History
[3] The Tobacco Treatment Program provides both outpatient and inpatient services.
[4] Refer to Appendix B for Medication Options
[5] Refer to Appendix C for Nicotine Replacement Therapy (NRT)

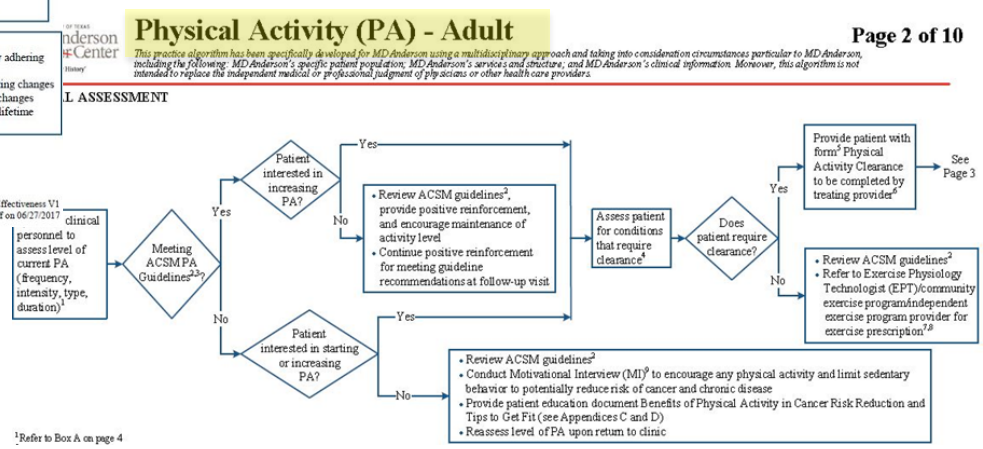


Approved by the

[1] BMI = weight (in pounds) x 703 / height (in inches)[2] – See Appendix A
[2] The weight categories are as follow:
• Underweight (BMI less than 18.5 kg/m²)
• Normal weight (BMI 18.5-24.9 kg/m²)
• Overweight (BMI 25-29.9 kg/m²)
• Obese (BMI greater than or equal to 30 kg/m²)
[3] American Institute for Cancer Research (AICR) guidelines (See Appendix B)
[4] In addition perform physical activity assessment based on the Physical Activity (PA) - Adult algorithm
[5] If MI is not conducted, encourage and counsel patient on importance of meeting AICR guidelines.
[6] Assess for medical barriers such as:
• Gastrointestinal dysmotility • Swallowing issues/dysphagia • Bowel dysfunction • Dental health
• Oropharyngeal anatomic changes • Digestive enzyme insufficiency • Gastrointestinal tract reconstruction/anastomoses
[7] The following conditions may necessitate further evaluation by RD or clinician:
• Diabetes • Cardiovascular disease • Concerns regarding medication or supplement use
• Renal disease • Gastrointestinal disease • Mood disorders (e.g., anxiety, depression)
• Liver disease • Thyroid dysfunction • Possible risk of malnutrition (see Consensus Statement under Appendix G)

Program Components:

- Systematic evaluation
- Defined trigger
- Motivational interviewing & monitoring
- Assessment



[1] Refer to Box A on page 4

https://www.mdanderson.org/for-physicians/clinical-tools-resources/clinical-practice-algorithms/cancer-screening-algorithms.html &
https://www.mdanderson.org/for-physicians/clinical-tools-resources/clinical-practice-algorithms/cancer-screening-algorithms.html

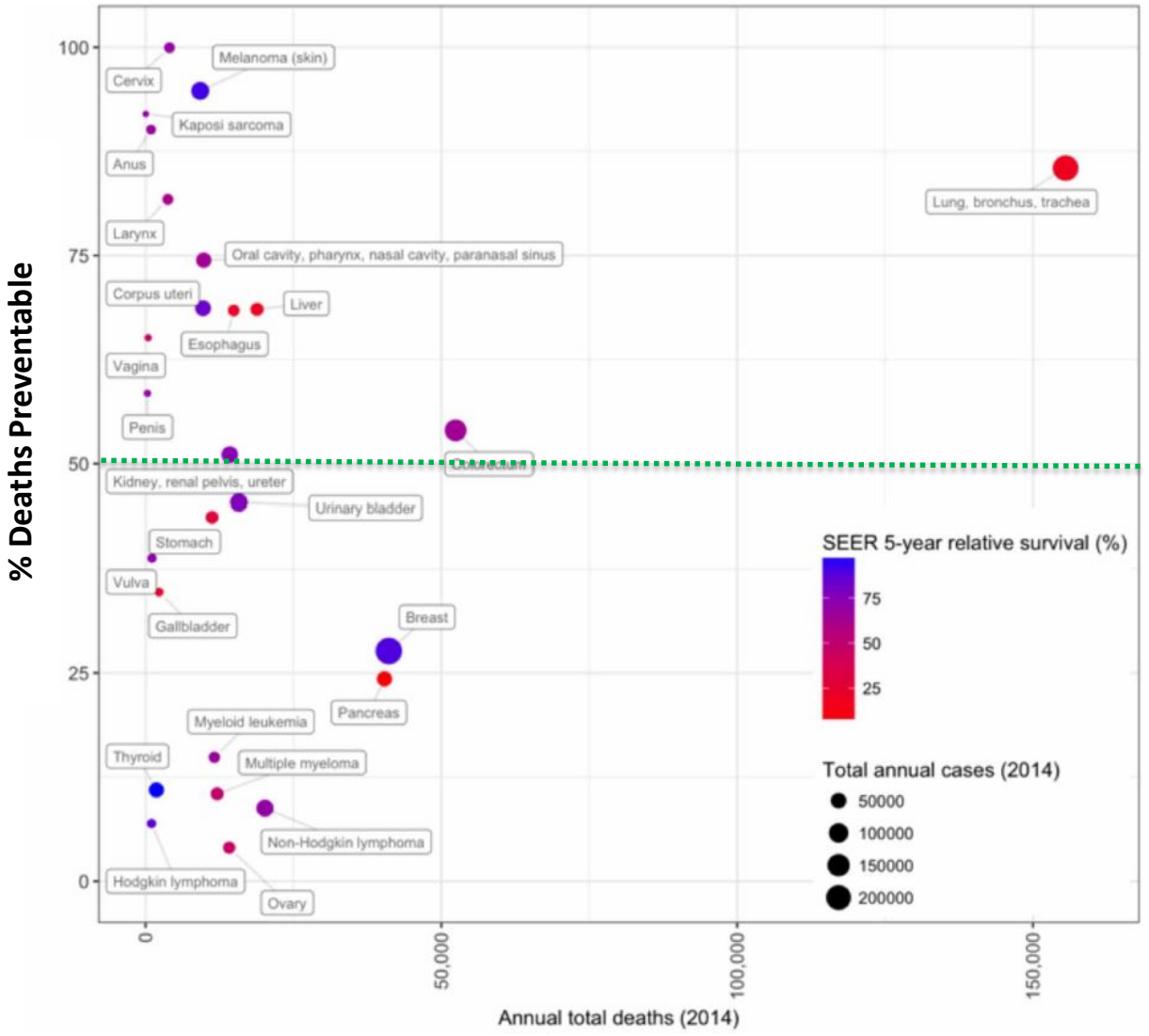
Adherence to Prevention Recommendations Reduces Cancer Incidence & Mortality *(as well as Cardiovascular & Overall Mortality)*

- Several prospective cohort studies & a systematic review demonstrate significant benefits for adherence to ACS cancer prevention guidelines, beyond tobacco avoidance
  - Each study computed scores to reflect adherence to ACS or AICR guidelines regarding: BMI, physical activity, diet, & alcohol intake

Study	Cohort	No. of Individuals	Follow-up Time	Reduction in All-Cancer Incidence	Reduction in All-Cancer Mortality	Reduction in CVD Mortality	Reduction in All-Cause Mortality
Cancer Prevention Study-II	50-74 y.o.	111,966	14 y	N/A	Women-24% Men-30%	Women-58% Men-48%	42% (Same in men & women)
NIH-AARP Diet & Health Study	50-71 y.o.	476,396	10.5 y – 13.6 y	10-19%	Women-24% Men-25%	N/A	Women-33% Men-26%
Systematic Review	8 studies in 7 cohorts	1,154,986	6 y – 14 y	4-45%	20-61%	N/A	N/A

Kabat, et al. Am J Clin Nutr, 2015
McCullough, et al. CEBP, 2011
Kohler, et al. CEBP, 2016

Estimates of the Preventable Fraction of Cancer Deaths vs. Total Annual Deaths in the U.S. *(2014)*



Golemis E., et al. Genes & Development; Published in Advance June 26, 2018, doi: 10.1101/gad.314849.118

Evidence-Based Cancer Screening & Estimated Mortality Reduction

Organ	Cohort	USPSTF Grade	% Mortality Reduction
Cervix	21-29 yo w cytology q 3 yrs 30-65 yo w cytology q 3 yrs *or* hrHPV testing q 5 yrs *or* co-testing q 5 yrs	A (2018)	80-90%
Breast	Biennial screening mammography for 50-74 yo	B (2016)	15%
	Individual decision prior to age 50	C (2016)	
Prostate	Individual decision for men 55-69 yo	C (2018)	21%
*Colon	Adults 50-75 yo	A	15-33% (FOBT) 28-50% (Flex Sig)
	Individual decision for adults 76-85 yo	C	
Lung	55-80 yo with a 30-PY smoking hx & currently smoke or have quit w/in past 15 yrs, annual LDCT	B	20%
Liver – Hep B & C	High-risk adults, incl those born btw 1945-1965 For Hep C (one-time screening)	B	43%

* ACS - adults aged 45+ years with average risk of CRC undergo regular screening

% Mortality Reduction data from USPSTF systematic reviews

Approved Agents for Treatment of Precancerous Lesions or Cancer Risk Reduction

2018

Agent	Targeted Cohort	Indication
Tamoxifen	Women with DCIS following breast surgery and radiation	Reduce the risk of invasive breast cancer
	Women at high risk for breast cancer	Reduce the incidence of breast cancer
Raloxifene	Postmenopausal women at high risk for invasive bc	Reduction in risk of invasive breast cancer
Cervarix	Females 9 through 25 years of age	Prevention of the following, caused by HPV types 16 and 18: • cervical cancer • cervical intraepithelial neoplasia (CIN) grade 2 or worse and adenocarcinoma in situ • cervical intraepithelial neoplasia (CIN) grade 1
Gardasil 9	Girls and women 9 through 26 years of age	Prevention of the following diseases caused by HPV types included in the vaccine: • Cervical, vulvar, vaginal, & anal cancer caused by types 16, 18, 31, 33, 45, 52, & 58 • Genital warts caused by HPV types 6 & 11 And the following precancerous or dysplastic lesions caused by types 6,11, 16, 18, 31, 33, 45, 52, & 58: • CIN grade 2/3 & cervical adenocarcinoma in situ (AIS) • Cervical intraepithelial neoplasia (CIN) grade 1 • Vulvar intraepithelial neoplasia (VIN) grades 2 & 3 • Vaginal intraepithelial neoplasia (VaIN) grades 2 & 3 • Anal intraepithelial neoplasia (AIN) grades, 1,2 & 3

Approved Agents for Treatment of Precancerous Lesions or Cancer Risk Reduction

2018

Agent	Targeted Cohort	Indication
Gardasil 9	Boys and men 9 through 15 years of age	Prevention of following diseases caused by HPV types included in vaccine: • Anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, & 58 • Genital warts caused by HPV types 6 & 11 And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, & 58: • Anal intraepithelial neoplasia (AIN) grades 1, 2, & 3
Photodynamic Therapy (PDT) with Photofrin	Males and females with high-grade dysplasia in Barrett's esophagus.	Ablation of high-grade dysplasia (HGD) in Barret's esophagus (BE) patients who do not undergo esophagectomy
Celecoxib*	Males and females ≥18 years old with familial adenomatous polyposis (FAP)	Reduction in the number of adenomatous colorectal polyps in FAP, as an adjunct to usual care (e.g., endoscopic surveillance, surgery)
Bacillus-Calmette-Guerin(BCG)	Males and females with carcinoma in situ (CIS) of the urinary bladder	Intravesical use in the treatment and prophylaxis of carcinoma in situ (CIS) of the urinary bladder and for the prophylaxis of primary or recurrent stage Ta and /or T1 papillary tumors following transurethral resection (TUR)
Valrubicin	Males and females with Bacillus-Calmette-Guerin(BCG)-refractory carcinoma in situ (CIS)	Intravesical therapy of BCG-refractory carcinoma in situ (CIS) of the urinary bladder in patients for whom immediate cystectomy would be associated with unacceptable morbidity or mortality.
Fluorouracil	Males and females with multiple actinic or solar keratoses	Topical treatment of multiple actinic or solar keratoses

**FDA labeling voluntarily withdrawn by Pfizer, February 2011*

Approved Agents for Treatment of Precancerous Lesions or Cancer Risk Reduction

2018

Agent	Targeted Cohort	Indication
Diclofenac sodium	Males and females with actinic keratoses	Topical treatment of actinic keratoses
Photodynamic Therapy (PDT) with 5-aminolevulinic acid	Males and females with actinic keratoses of the face or scalp	Topical treatment of minimally to moderately thick actinic keratoses of the face or scalp.
Masoprocol**	Males and females with actinic (solar) keratoses	Topical treatment of actinic keratoses
Imiquimod	Immunocompetent adults	Topical treatment of clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses on the face or scalp
Ingenol mebutate	Those with actinic keratoses on the face, scalp, trunk and extremities	Topical treatment of actinic keratoses

***Withdrawn from US Market, June 1996*

Cancer Prevention Steering Committee Members

2018

Chairs: Gary Goodman M.D., M.S. and Ernest Hawk, M.D. MPH

Isabelle Bedrosian, M.D., FACS	Alliance
Marie Wood, M.D.	Alliance
Tara Henderson, M.D, MPH	COG
Kevin Oeffinger, M.D.	COG
Raymond Bergan, M.D.	ECOG-ACRIN
Etta Pisano, M.D.	ECOG-ACRIN
Julie Bauman, M.D., MPH	NRG
Douglas Levine, M.D.	NRG
Banu Arun, M.D.	SWOG
Katherine Crew, M.D., M.S.	SWOG
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Kathleen Yost, M.D.	Community Oncology
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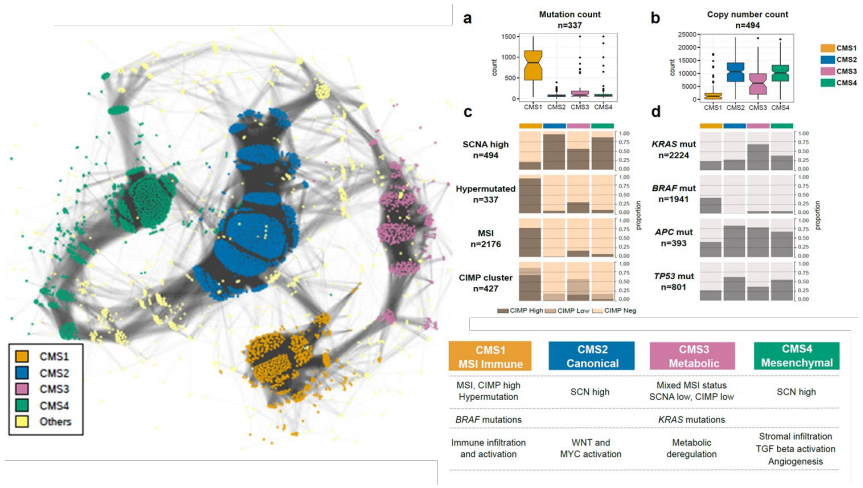
Arlene Stevens	Patient Advocate
KyungMann Kim, Ph.D.	Statistics
Cathy Tangen, DrPH	Statistics
Worta McCaskill-Stevens, M.D., M.S.	NCI DCP
Sandra Russo, M.D., Ph.D., MPH	NCI Medical Officer - DCP
Laronna Colbert, M.D.	FDA Observer

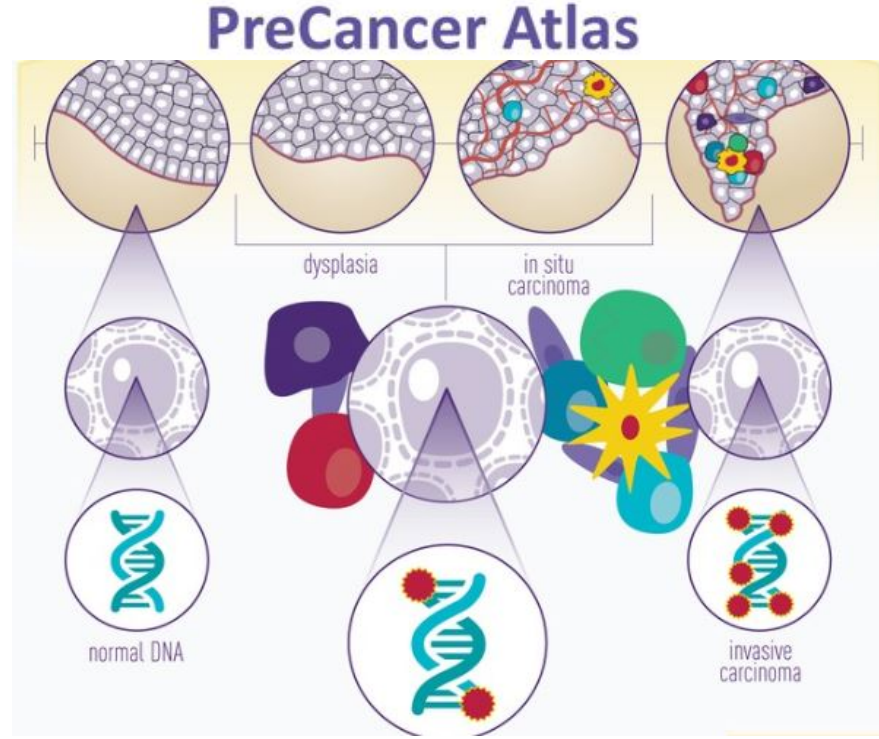
Challenges & Opportunities in the Field

Biology / Biomarkers

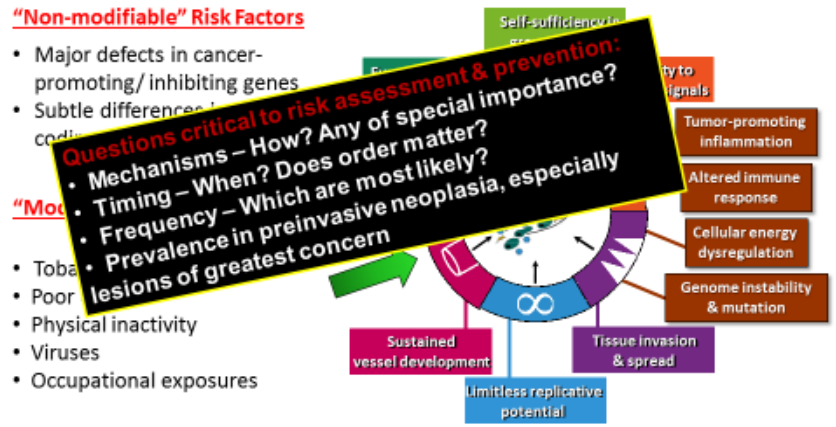
Need to Better Understand the Early Determinants & Drivers of Dysplasia



Consensus Molecular Subtypes Guide Treatment in CRC



Principle #2 - Cancer Results From A Chronic Interplay of Inherited Factors & Exposures That Progressively Alter Cellular Identity, Relationships & Growth Control



Modified from Hanahan & Weinberg, Cell 100:57, 2000 & 144:646-674, 2011; Science 2006

CANCER MOONSHOT

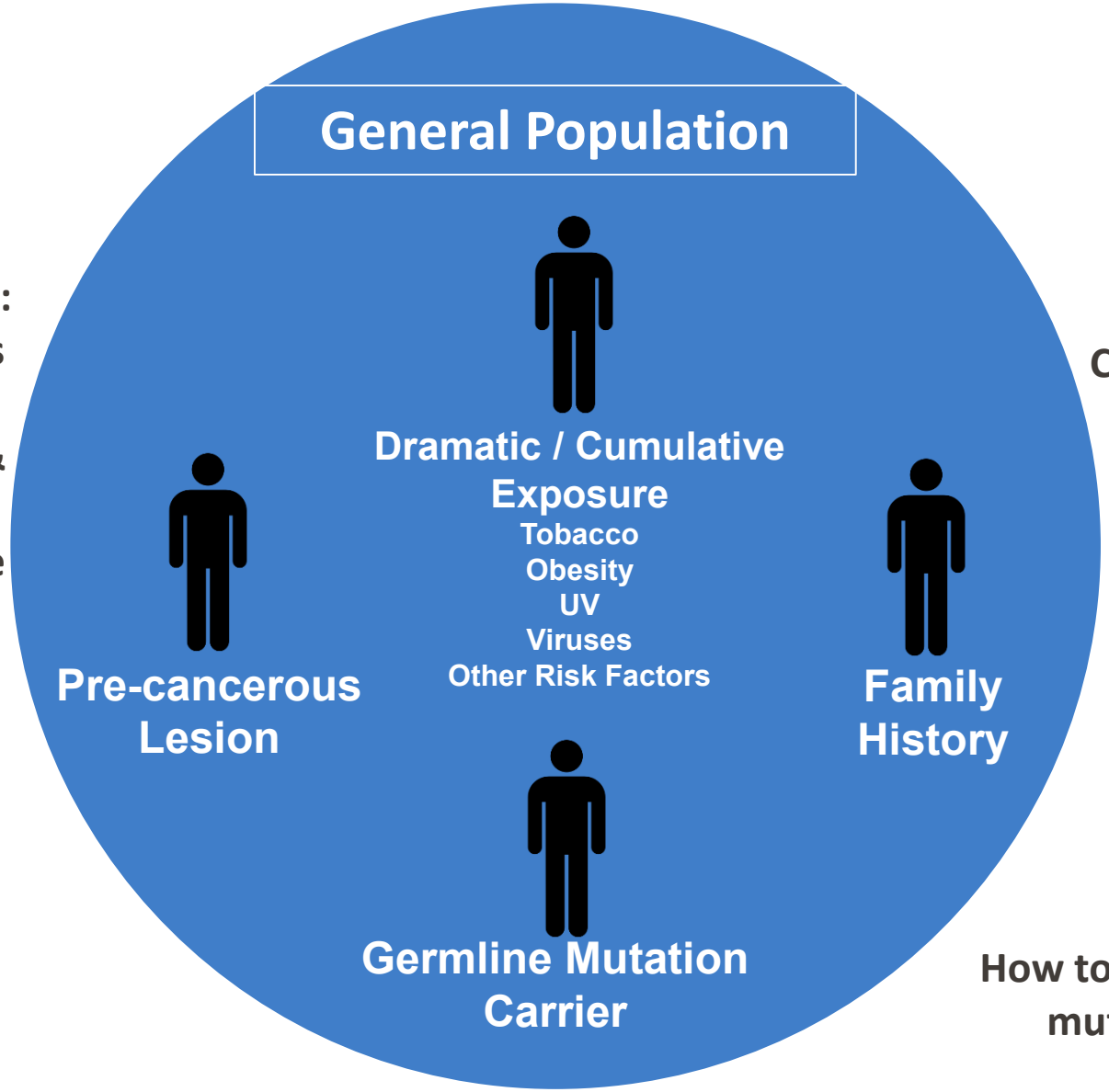
Challenges & Opportunities in the Field

Cohorts

How to Optimally Identify Those at Increased Risk?

Additional science needed to:
1) Develop new technologies to detect silent lesions;
2) Refine current screening & surveillance programs to improve risk/benefit balance

Which will progress? Which will regress/remain stable?



Collect data on SDH & SES factors that are strongly correlated with cancer outcomes

Standardize & improve collection of behavioral & family hx data as it evolves in clinical settings across time

How to systematically screen for germline mutations? (e.g., Lynch syndrome)

Challenges & Opportunities in the Field

Agents

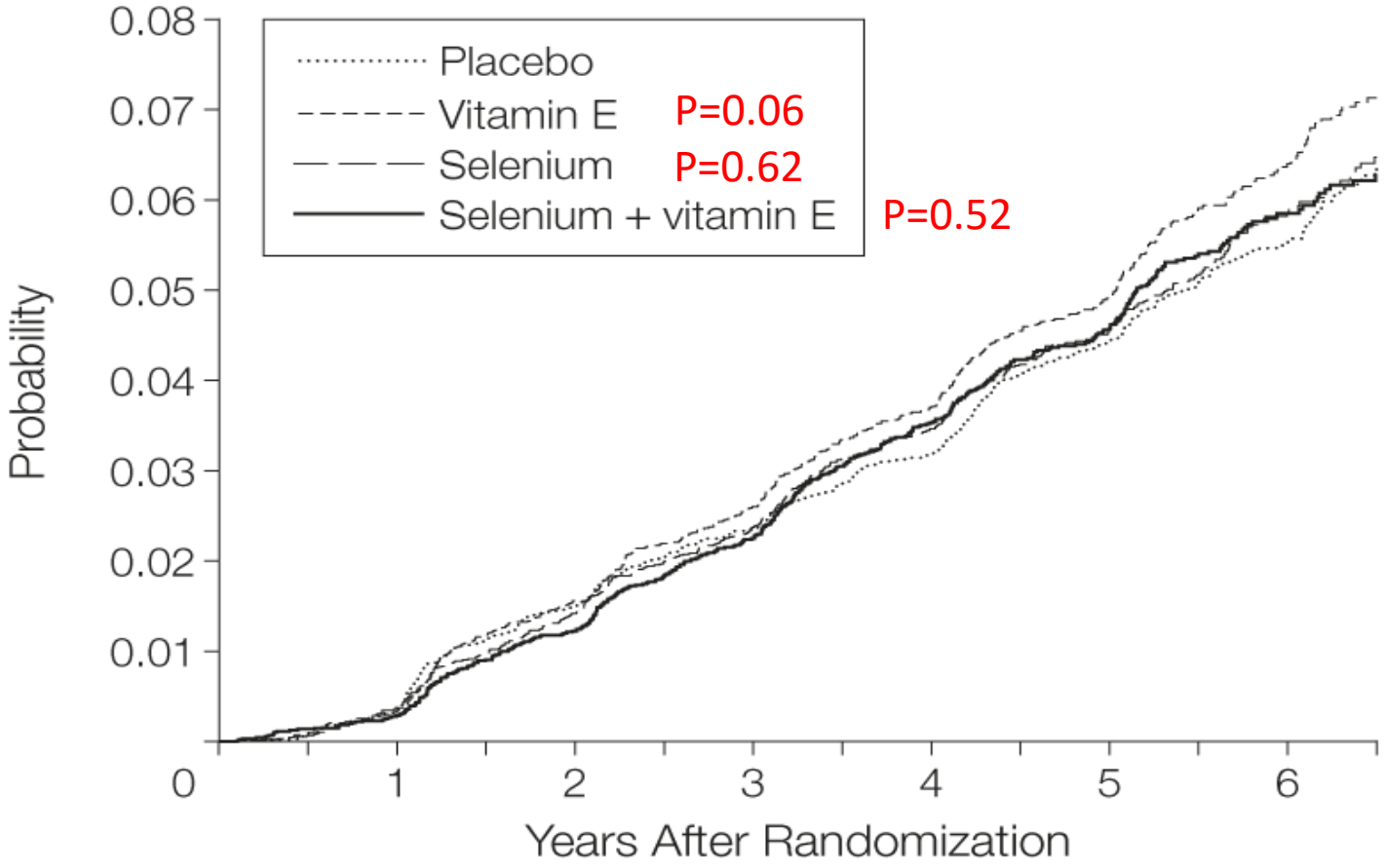
Selenium & Vitamin E for Prostate Cancer Prevention

False Leads

Cumulative Incidence of Prostate Cancer Detected Each Year by Intervention Group in the SELECT Trial

35,533 men (mean age =62) with a serum PSA ≤ 4 ng/mL & a DRE not suspicious for prostate cancer randomized to 1 of 4 groups (vitamin E + placebo, selenium + placebo, vitamin E + selenium, placebo + placebo). Median f/u of 5.5 yrs.

Lippman, et al., JAMA, 2009



No. at risk							
Placebo	8689	8553	8328	8039	7389	4892	2516
Vitamin E	8732	8610	8373	8098	7401	4867	2537
Selenium	8750	8597	8341	8083	7393	4848	2558
Selenium + vitamin E	8700	8585	8371	8097	7428	4894	2580

Lack of Private Investment in Cancer Prevention Drug Development

Table 71–2. Characteristics of Clinical Chemoprevention Agent Development Trials

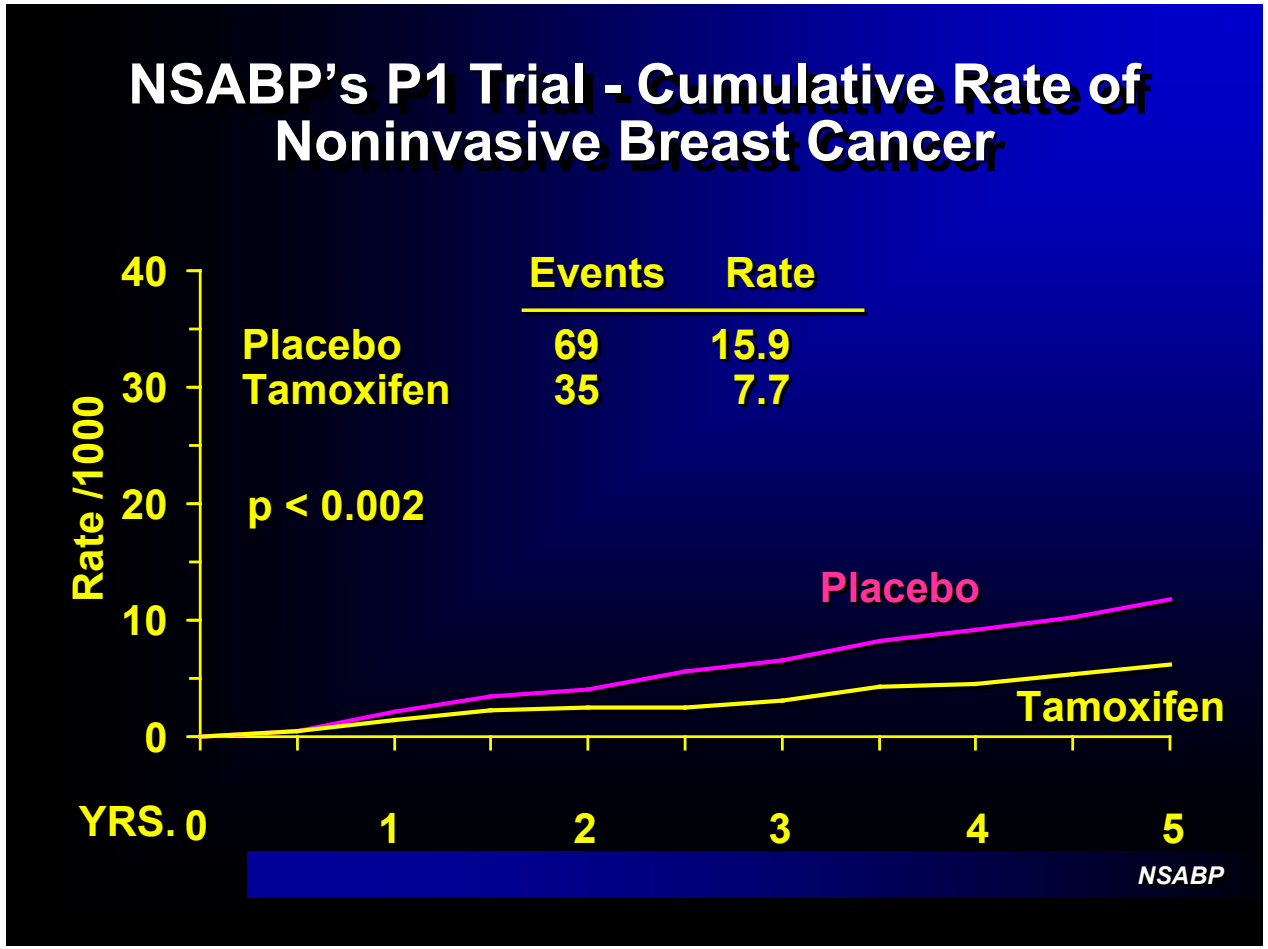
Phase	Agent Dosing	Duration	Sample Size and Allocation	Control Group	Goals
I	Escalation	Weeks–months	<25; nonrandomized or randomized	Occasionally	Pharmacokinetics; dose finding based upon short-term, mild to moderate toxicity
IIa	De-escalation	Months	<50; nonrandomized	Never	Dose finding based on reliable biomarker modulation
IIb	Stable	Months–year	<100–200; randomized	Standard care*	Biomarker modulation (e.g., dysplasia regression) *vs.* standard care*
III	Stable	Years	100–≥1,000; randomized	Standard care*	Definitive efficacy to complement or replace standard care (e.g., reduce dysplasia/cancer incidence)
IV	Stable	Unspecified	General post-marketing population	N/A	Long-term safety in target population

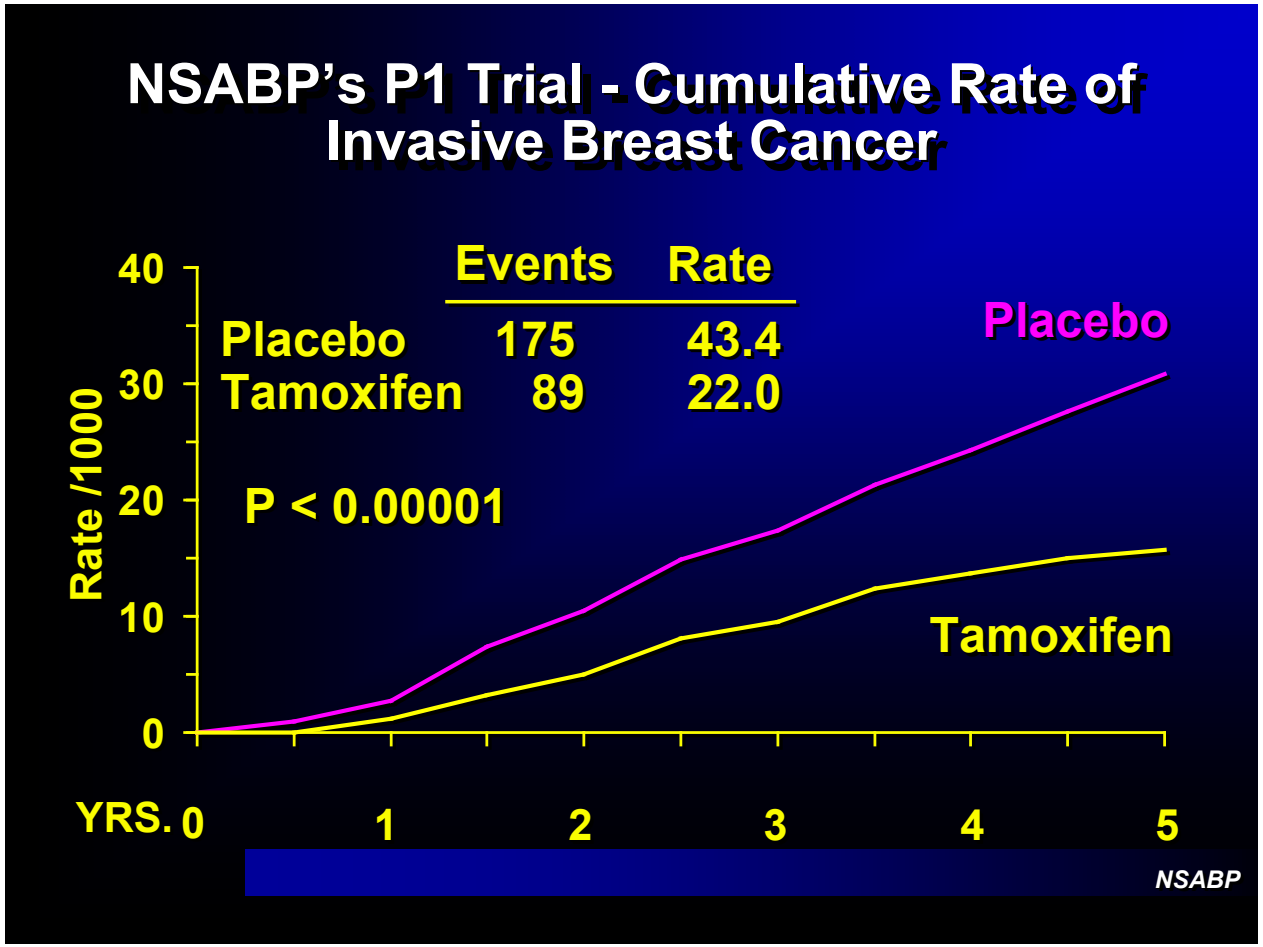
Source: Adapted from Viner et al. 2002.
*In cancer chemoprevention, placebo may represent the standard of care.

Viner JL, Hawk ET, Lippman SM: Cancer Chemoprevention, in *Cancer Epidemiology & Prevention*, third ed., Eds: Schottenfeld D & Fraumeni, Jr. JF. Oxford Univ Press, 2006

Re-Purposing Established Therapeutic Agents for Cancer Prevention, Risk Reduction, or Treatment of Pre-Cancers

Tamoxifen in the Adjuvant Setting: First Suggested Results for Tamoxifen for Prevention





Fisher B, et al., JNCI, 1998

Fisher B, et al., NEJM, 1989

Rutqvist LE, et al., JNCI, 1991

Agent Combinations - *Prevention of Colorectal Cancer in APC Polyposis*

Sulindac + Erlotinib = 69.4% reduction in polyp burden from baseline compared to placebo (intact colon)

Table. Change in Colorectal Polyp Number From Baseline for Intention-to-Treat Analysis

Intention-to-Treat	Colorectal Polyp Number							
				Change (6-mo Follow-up-Baseline) Median (IQR)				
	Participants, No.	Baseline Median (IQR)	6-mo Follow-up, Median (IQR)	Median Change	Median Change, %	Net Between-Group Differences (95% CI)	*P* Value	Net % Change (95% CI)
Intact colon (colorectal)								
Sulindac and erlotinib	11	39 (19 to 81)	2 (1 to 2)	−27 (−34 to −26)	−96.3 (−96.3 to −85)	−27.5 (−106.5 to −9.6)	.009	−69.4 (−109.2 to −28.8)
Placebo	11	16 (4 to 26)	14 (9 to 17)	−2 (−3 to −0.8)	−11.1 (−20.5 to −2.8)			
IPAA								
Sulindac and erlotinib	21	5 (2 to 17)	0 (0 to 1)	−4 (−5.1 to −3)	−83 (−100 to −71.8)	−14.5 (−28.1 to −3.5)	.003	−121.7 (−280 to −71.6)
Placebo	23	6 (0 to 22)	22 (8 to 28)	1 (0 to 3)	21.7 (0 to 120)			
Rectum (IRA)								
Sulindac and erlotinib	9	7 (4 to 15)	6 (2 to 15)	−1 (−5 to 5.9)	−60 (−71.4 to 93.9)	−13 (−30.5 to 3.9)	.24	−175.5 (−1087.3 to 52.5)
Placebo	7	3 (2 to 12)	18.3 (17 to 30)	11.4 (8 to 16)	119.3 (114.3 to 133.3)			

Abbreviations: IPAA, ileal pouch anal anastomosis; IQR, interquartile range; IRA, ileo-rectum.

Samadder, et al., JAMA Oncology 2018; 4(5):671-677

Explore De-implementation Science

Needed to determine an optimal approach to de-implement less effective or less safe interventions when updated devices, drugs, or schedules are in place, or harms are more fully demonstrated

- Cervical cancer screening
- Prostate cancer screening

Cancer Prevention Research

Accelerating the Pace of Cancer Prevention- Right Now

Graham A. Colditz and Karen M. Emmons

"De-implementation will likely not be the inverse of implementation and dissemination uptakes."

JAMA Internal Medicine

Invited Commentary | Less Is More

May 2015

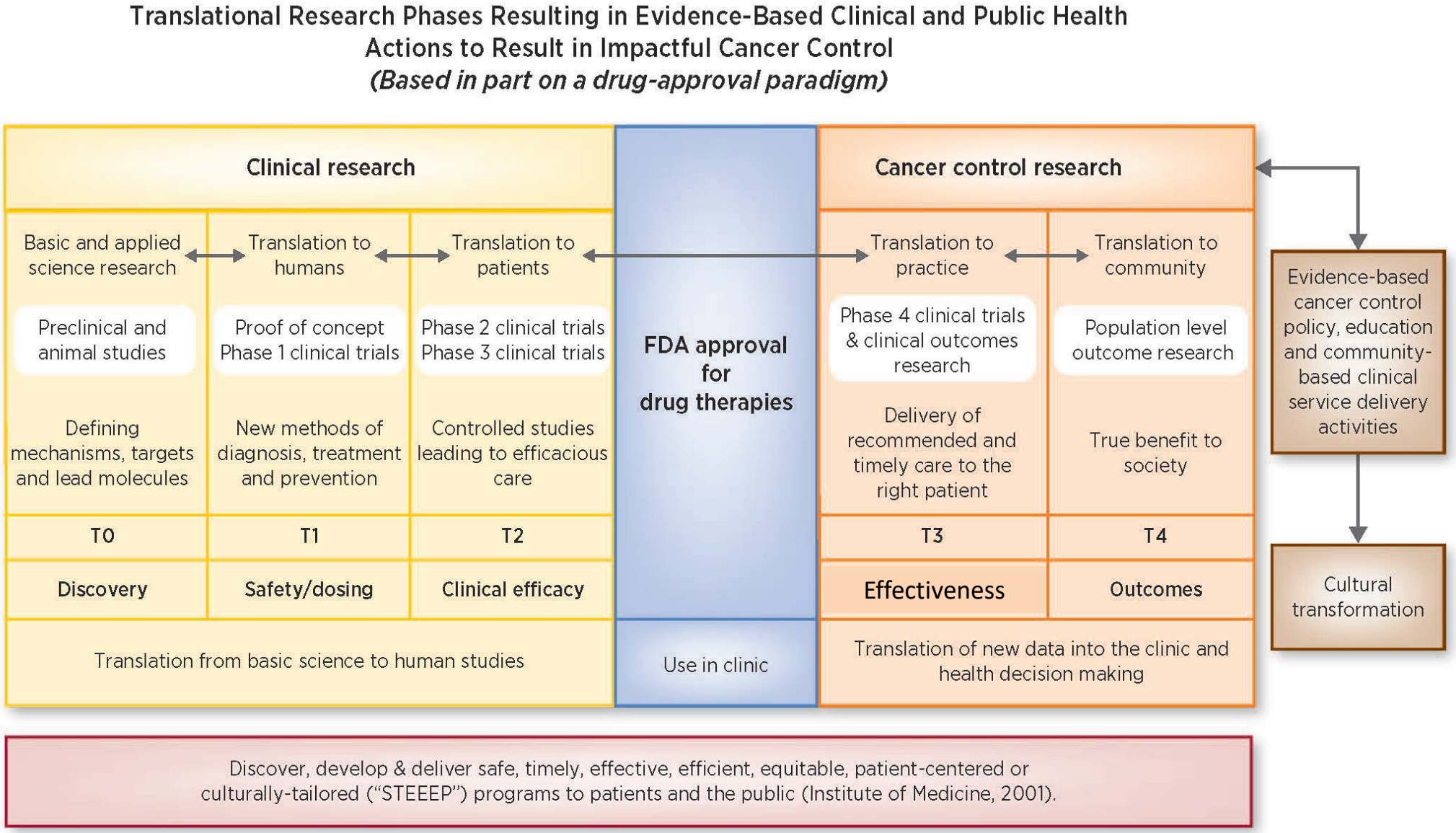
On the Undiffusion of Established Practices

Frank Davidoff, MD, MACP[1]

NCORP Opportunities

1. Need for more interaction & coordination across groups – more regular portfolio updates
    - Make use of CPSC monthly meetings
2. Improve template for concept submissions to bolster success
3. Create & disseminate threshold standards for prelim data re: efficacy, safety, feasibility
4. Collaborate more closely with other relevant professionals (e.g., PCPs - family med & general internists, gastroenterologists, pulmonologists, dermatologists, radiologists)
5. Identify germline risk cohorts across groups

The T0 - T4 Translational Research to Evidence-based Cancer Control Paradigm



E. Hawk, unpublished work
Graphic modified from Blum

Responsible Parties In Implementation & Dissemination of Evidence-based Cancer Prevention and Control

Evidence-based cancer control policy, education, and community-based clinical service delivery activities

Responsible Parties

Primary Care Providers
Health Care Systems
Insurers
Employers
Government Agencies
(CDC, state/county/city health depts.)
NGOs
Schools
NCI-designated Cancer Centers

Cultural Transformation

Funding?

Thank You

Questions?