National Cancer Institute
Board of Scientific Advisors
Ad Hoc Working Group on Prevention

Strategies to Accelerate Progress in Cancer Prevention Research

Bethesda, Maryland
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NATIONAL INSTITUTES OF HEALTH
National Cancer Institute
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Table of Contents

Executive Summary

Dr. Douglas Lowy, Acting Director, National Cancer Institute (NCI), in October 2019 charged the Board of Scientific Advisors (BSA) Working Group on Prevention, comprised of experts across a range of disciplines from the intramural and extramural communities. Given the changing nature and opportunities related to cancer prevention, screening, and early detection, the working group was to consider how best to utilize the resources and personnel of NCI in accelerating progress across the range of activities comprising cancer prevention and early detection research. Dr. Lowy asked the working group to evaluate which areas of NCI-supported prevention and screening research are progressing well and which areas need more NCI emphasis. The purview of this working group consisted of primary and secondary prevention. To bring cross cutting themes together, the following headings were used by the working group: (1) Increasing lifestyle and environment research: prevention opportunities, challenges, and communication; (2) Enabling research that addresses prevention in disparate populations; (3) Optimizing opportunities using biomarkers in cancer prevention research; (4) Expanding data science opportunities in risk stratification and point of care precision prevention; (5) Promoting novel and innovative research designs; and (6) Considering infrastructure resources NCI could facilitate to enhance prevention research.

The working group recognizes that there are significant and special challenges inherent in cancer prevention and screening research that make it difficult to do well. These include the healthy population who should not be exposed to undue risk, the need for successful conduct of prevention research in all communities, the critical importance of work in exposures and lifestyle, where most people want to reduce cancer risk, and the ongoing difficulty with assessment of long-term endpoints within grant periods that are artificially brief. The research community must be incentivized to expand to prevention and screening research the application of the explosion of basic science, technologies, immunology and big data that have been rapidly and so successfully applied to therapeutics research. Finally, the experience of the COVID-19 pandemic has renewed recognition of the important effects of social determinants of health, which impact cancer prevention research as well.

Lifestyle and environmental exposures continue to offer the potential to modify cancer risk at the population and individual levels. Strategies should continue to improve precision in prevention through lifestyle interventions. The NIH Precision Nutrition Initiative is enthusiastically endorsed. In the areas of lifestyle and the environment, the NCI should leverage the investments of the Surveillance, Epidemiology, and End Results (SEER) Program, the NCI Community Oncology Research Program (NCORP) and the CDC funded networks (Cancer Prevention and Control Research Network, Prevention Research Centers), VA, etc., to speed research that meets needs of all populations. Researchers should target multiple behaviors simultaneously; use mobile apps and wearable technologies (mHealth approaches); use AI and ML in preventive technologies; implement early interventions in children/AYA before behavioral habits are engrained jointly with mHealth approaches; study the impact of behavior change on recurrence and mortality (tertiary prevention); study the impact of behavior/lifestyle on quality of life during survivorship; determine the mechanisms underlying successful behavior change and/or relapse; validate and measure intermediate biomarkers (immune, microbiome, etc.); use behavioral prevention strategies targeted to under-represented minorities and underserved populations; conduct cohort studies of specific ethnic/racial groups or rural populations; study interventions

that translate to the population (effectiveness, implementation, sustainment, and evaluation); and conduct communications research to support and sustain behavior changes.

Like COVID-19 which highlights the stark inequalities in health care, cancer health disparities highlight the role of social determinants of health and unequal access to resources (education, clean water, housing, healthy food choices, structural racism, technology, etc.) that drive incidence and mortality differentially across racial and ethnic groups within the United States. To enable research that addresses prevention in disparate populations, NCI should increase basic and translational science to focus on populations experiencing cancer disparities and identify new strategies to bring evidence-based cancer prevention interventions to reduce the burden of cancer for all populations. NCI must develop a deeper understanding of how racism drives cancer risk; increase eligibility for research studies and clinical treatment trials of populations with multiple comorbidities as experienced by populations with cancer disparities; and promote the development of patient engagement approaches tailored to minority and underserved populations.

To address opportunities involving biomarkers, the working group recognized the substantial investment NCI has made in the development of a range of biomarkers, and their important efforts to require rigor in their evaluation and standardization. However, given the exciting new opportunities in molecular, computational and imaging technologies, the working group recommends that, before the next wave of biomarker programs is begun, NCI leadership should convene an expert working group to provide critical and thoughtful assessment of the most important opportunities in the field, and make recommendations regarding not only the most promising areas for investment but also the best strategies to accelerate their development.

NIH has defined priorities in data science but bringing these tools to prevention is especially important. In particular, the areas of big data, imaging, -omics, multidimensional data and expanding opportunities in risk stratification and point of care measurement precision prevention are emphasized. NCI should accelerate adaptation of technologies for real time, point of care diagnostics, monitoring, and decision making; build rubrics and standards for machine learning (ML) and artificial intelligence (AI) models as a priority; and develop strategies for visualizing data. To visualize data, NCI should accelerate capabilities of data mining of existing population-based data sources through AI and ML; use change point detection for prevention intervention timing; utilize AI capabilities in imaging to successfully triage prevention trials; maximize populations engaging in the data sources to achieve population coverage to avoid disparities; identify efficient analytic approaches to multidimensional data for risk stratification; and expand communication research to bring these strategies to point of care delivery and decision making.

Novel and innovative research designs must be encouraged in order to expedite progress in precision prevention in particular. The working group endorses investment in basic science targeting molecular mechanisms underlying the relationships between obesity and cancer, and the cross talk with the tumor microenvironment, the carcinogenic process, and immunologic interactions across populations. There is interest in additional work on exposures, cancer vaccines that anticipate the most likely neoantigens in the highest risk populations, and applying AI and ML to improve prediction of aggressive versus indolent behavior of early stage solid tumors. Ongoing efforts in risk prediction and modeling, in viral carcinogenesis, biostatistics

and bioinformatics for screening and prevention should be continued and, if possible, expanded. The application of big data to these problems should also be supported. Several specific recommendations for chemoprevention research are proposed, including development of public education strategies that could improve uptake and investment in preclinical and clinical efforts that could expedite progress across tumor types and population groups.

NCI should enhance prevention research through infrastructure support. This could include enhancing the development of initiatives like the Pre-Cancer Atlas that bridge technology development and improvement from work with established tumors to work in the premalignant space; requiring that data generated are made available to the research community; and supporting the development of inexpensive, point-of-care technologies to enhance implementation of early detection in healthy people for screening and prevention. NCI should consider supporting key longitudinal surveillance and monitoring systems with linkages to electronic medical record and claims data bases (e.g., NCI SEER Program), and leverage these resources for use in evaluation with AI/ML, in addition to the examination of imaging and pathology resources. Efforts should also be made to improve prediction of multi-level cancer risk for behavioral cancer prevention in multi-ethnic populations to reduce cancer disparities, and to develop capacity for synthesis and distribution of placebos for placebo-control chemoprevention trials for both NCI-supported and other investigator-initiated studies.

In conclusion, the working group reviewed strategies to accelerate progress in cancer prevention research and concluded that while the underlying issues in prevention research pose special considerations, advancing technology and data science offer many opportunities to bring new focus to prevention. Importantly, all prevention research must include a focus on reducing existing disparities in cancer across racial and ethnic groups, as well as other minorities and underserved populations. Identifying new approaches to bring evidence-based interventions to all population groups remains an urgent priority.

Introduction

Dr. Douglas Lowy, Acting Director, National Cancer Institute (NCI), in October 2019 charged the Board of Scientific Advisors (BSA) Working Group on Prevention, comprised of experts across a range of disciplines from the intramural and extramural communities. Given the changing nature and opportunities related to cancer prevention, screening, and early detection, the Working Group was to consider how best to utilize the resources and personnel of NCI in accelerating progress across the range of activities comprising cancer prevention and early detection research. Dr. Lowy asked the working group to evaluate which areas of NCI-supported prevention and screening research are progressing well and which areas need more NCI emphasis. The purview of this working group consisted of primary and secondary prevention. To bring cross-cutting themes together, the following headings were used by the working group:

- **Increasing lifestyle and environment research: prevention opportunities, challenges, and communication**
- **Enabling research that addresses prevention in disparate populations**
- **Optimizing opportunities using biomarkers in cancer prevention research**
- **Expanding data science opportunities in risk stratification and point of care precision prevention**
- **Promoting novel and innovative research designs**
- **Considering infrastructure resources NCI could facilitate to enhance prevention research**

The presentations and discussions are summarized below with a brief background, assessment, and recommendations and opportunities for enhancement for each of these categories.

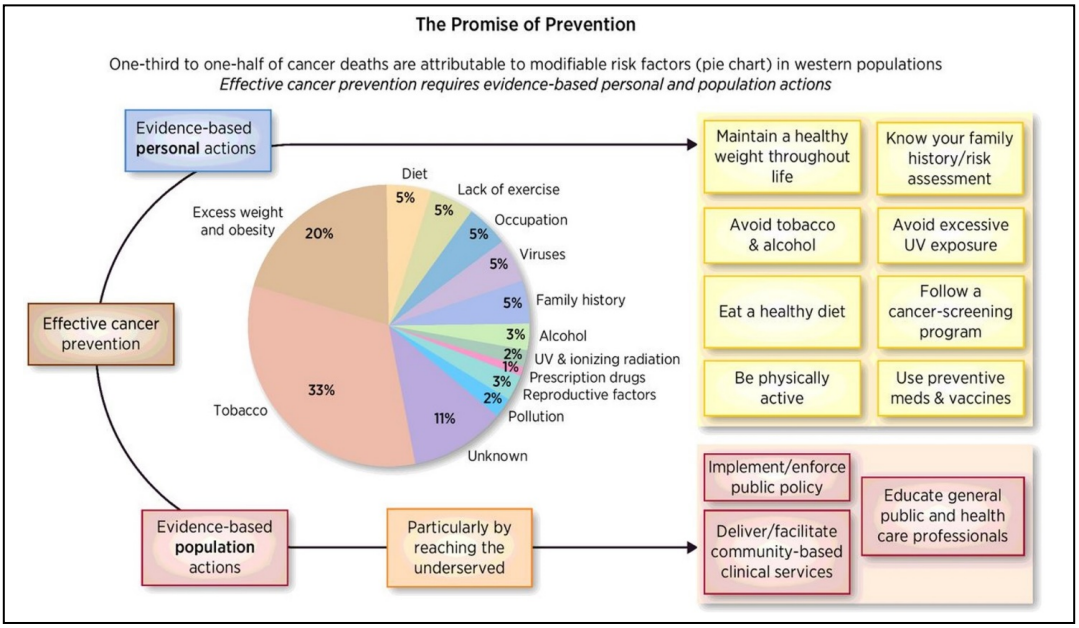
Increasing Lifestyle and Environment Research: Prevention Opportunities, Challenges, and Communication

Review of primary prevention indicates a comprehensive and well-established set of lifestyle and environmental exposures that offer opportunities for primary prevention of cancer [1-3]. (see figure 1) At the same time, some established causes of cancer are less modifiable though appropriately focused prevention and control strategies may still reduce risk in these populations (e.g., occupation, familial cancer risk, and viral infections, to name a few)[4]. Increased insight into the time frame from exposure to cancer development has sharpened the focus on age and risk-appropriate prevention strategies to reduce risk. Established strategies through avoiding smoking, reducing or eliminating alcohol, weight control to prevent obesity, improved diet, and avoiding excess radiation UV exposures that drive melanoma risk, can substantially reduce the population burden of cancer. Successes particularly in tobacco control translate to reductions in cancer incidence and mortality. However, the time frame for benefit to be observed challenges the funding structures.[5]

A plethora of emerging technologies (-omics, microbiome, virome, etc.) and increasing insight to their roles in cancer etiology, together with gene-environment interactions, drive an ever-increasing understanding of cancer causes and pathways / mechanisms for cancer development or prevention. These advances add complexity to focusing prevention strategies and challenges in communicating prevention science.

Thus, communication is a cross-cutting priority issue. Many people have difficulty in understanding what risk means. Nevertheless, it remains important to communicate risks in a way that can be interpreted easily. A range of research issues persist despite longstanding commitment from NCI to advance the science of cancer risk communication that parallels the deeper understanding of causes of cancer and strategies to minimize their impact at the population level. [6, 7]

Figure 1: The Promise of Prevention



Recommendations and Opportunities for Enhancement in Interventions

There should be larger research networks and NCI should leverage the investments in SEER and in intramural and extramural etiologic research to inform behavioral interventions. In addition, NCI should leverage community research networks (NCORP), CDC funded networks (Cancer Prevention and Control Research Network, Prevention Research Centers), VA, etc., to speed research that meets the needs of all populations. Opportunities for enhancement include:

- Targeting multiple behaviors simultaneously
- Using mobile apps and wearable technologies (mHealth approaches)
- Using AI and ML in preventive technologies, jointly with mHealth approaches
- Implementing early interventions in children/AYA before behavioral habits are engrained
- Studying the impact of behavior change on recurrence and mortality (tertiary prevention)
- Studying the impact of behavior/lifestyle on quality of life during survivorship
- Determining the mechanisms underlying successful behavior change and/or relapse
- Validating and measure intermediate biomarkers (immune, microbiome, etc.)
- Using behavioral prevention strategies targeted to under-represented minorities and underserved populations
- Conducting cohort studies of specific ethnic/racial groups or rural populations
- Studying interventions that translate to the population (effectiveness, implementation, and evaluation)

Additional issues identified by the working group include the cost of cancer care, the burden of cancer care on families and social support networks, and the need for systems science modeling to inform monitoring and evaluation of implementation across the cancer care continuum. Research to develop and then implement financial support interventions across all cancer care patient populations and settings is needed.

Recommendations and Opportunities for Enhancement in Communication

Participants discussed the terminology preferences between cancer prevention and cancer risk reduction, as well as relative risk versus absolute risk.

Accurate and understandable cancer risk communication is an ongoing challenge in cancer prevention. This consistent issue emerged in discussion of primary prevention through lifestyle changes as well as in more risk-focused settings of secondary and tertiary prevention. Thus, communication of risk, time frames for benefits (and possible risks), and the challenge that risk factors operate across not just cancer but other chronic diseases, opens research opportunities to improve understanding of approaches to communication that fits with the level of scientific and health literacy in the target populations. Effective cancer prevention communication can take

place in a variety of settings, including directly or with families, engaging schools, partnering with state leaders, religious leaders, and other community organizations and leaders.

Emerging media strategies also offer opportunities for prevention messages and information research.[8] Social media, and hostile environments, including overlaps with vaccine truth are one example. How these messages and information integrate with provider record systems for cancer survivors to tailor strategies and messages to age and other characteristics of survivors remain research priorities.

These issues may be further refined for application in precision prevention (nutrition; chemoprevention, etc.) that may require integration of -omics into risk stratification and must be available in real time in clinical and other delivery settings.

How can we understand more comprehensively the role of cancer caregivers and how to support them (e.g., patient-provider-caregiver communication, psychoeducational support programs, screening and referral to resources)? Managing cancer risk and survivorship in the context of multiple comorbidities opens research in communication beyond the generation of evidence for best management practices. Research is needed to address the challenges and opportunities that arise after etiologic understanding has increased, challenges regarding data integration and -omics methods, and public communication.

Enabling Research that Addresses Disparities in Prevention

Like COVID-19 which highlights the stark inequalities in health care, cancer health disparities highlight the role of social determinants of health and unequal access to resources (education, clean water, housing, healthy food choices, structural racism, technology, etc.) that drive incidence and mortality differentially across racial and ethnic groups within the United States. Disparities in cancer incidence and mortality are well documented (Tables 1-4).[9-12] The working group acknowledges that race/ethnicity constructs are social and biologic.[13] In general, research has focused on behaviors and access to preventive and diagnostic/therapeutic services to describe disparities and attribute explanations.[14] The role of racism has been largely ignored. Furthermore, ongoing research aimed at reducing disparities typically focuses on translating evidence-based interventions for dissemination and implementation in all populations regardless of social class and race/ethnicity[15]. Much less focus has addressed biologic pathways that are potentially modifiable as drivers of cancer disparities. Gaps in tying the environment to genetic and epigenetic factors that may drive disparities needs further study.

AACR has published their Cancer Disparities Progress Report, 2020, that largely focuses on the state of disparities in the USA for African Americans and Hispanics, and reviews gaps and opportunities across preventable risk factors, cancer screening, treatment, and survivorship. The report also emphasizes capacity building for disparities research and expanding the workforce of under-represented minorities in research. We do not duplicate their detailed report but focus on initiatives the NCI can lead now.

Table 1: Disparities in Incidence by Cancer Type for Males

Incidence rates per 100,000, male, from SEER 2009-2015

	All	White	Black	Rate Ratio Black/White	Asian/Pacific Islander	Rate Ratio API/White	American Indian/Alaska Native	Rate Ratio AIAN/White	Latinx	Rate Ratio Latinx/White
Prostate	109.5	101.9	176.7	1.73	55.6	0.5	55.4	0.5	93.4	0.9
Lung & bronchus	63	63.5	73.5	1.16	46.3	0.7	43.3	0.7	35.2	0.6
Colon & rectum	44.2	43.4	52.4	1.21	37.9	0.9	42.1	1.0	40	0.9
Urinary bladder	35.2	38.5	19.7	0.51	15.5	0.4	14.9	0.4	19.5	0.5
Melanoma of the skin	28.8	33.9	1.1	0.03	1.6	0.0	5.8	0.2	5	0.1
Kidney & renal pelvis	22.1	22.8	24.3	1.07	12	0.5	21.2	0.9	20.8	0.9
Non-Hodgkin lymphoma	23.9	25	17.7	0.71	16.4	0.7	12	0.5	20.7	0.8
Leukemia	18.1	19.1	13.9	0.73	9.7	0.5	11	0.6	13	0.7
Oral cavity & pharynx	17	17.9	13.4	0.75	11.8	0.7	11.8	0.7	10.1	0.6
Pancreas	14.6	14.8	16.7	1.13	10.8	0.7	11.4	0.8	12	0.8
Liver & intrahepatic bile duct	13.6	12.2	17.8	1.46	19.9	1.6	19.3	1.6	20.3	1.7
Stomach	10	8.9	14.1	1.58	14.3	1.6	11.5	1.3	13	1.5
Multiple myeloma	8.7	8.1	16.3	2.01	4.9	0.6	6	0.7	8.2	1.0
Thyroid	8	8.6	4	0.47	7.7	0.9	4.1	0.5	5.7	0.7

Table 2: Disparities in Mortality by Cancer Type for Males

Mortality rates per 100,000, male, from SEER 2009-2015

	All	White	Black	Rate Ratio Black/White	Asian/Pacific Islander	Rate Ratio API/White	American Indian/Alaska Native	Rate Ratio AIAN/White	Hispanic	Rate Ratio Latinx/White
Lung & bronchus	51.6	51.7	62.1	1.20	30.2	0.58	42	0.81	25.3	0.49
Prostate	19.2	18	38.9	2.16	8.6	0.48	19.2	1.07	15.8	0.88
Colon & rectum	16.9	16.5	23.8	1.44	11.6	0.70	19.1	1.16	14.4	0.87
Pancreas	12.6	12.6	14.8	1.17	8.2	0.65	9.9	0.79	9.4	0.75
Liver & extrahepatic bile duct	9.6	8.9	13.2	1.48	13.8	1.55	14.4	1.62	13.3	1.49
Leukemia	8.8	9.1	7.2	0.79	4.7	0.52	5.4	0.59	6	0.66
Esophagus	7.1	7.5	5.6	0.75	2.7	0.36	6.2	0.83	3.7	0.49
Urinary bladder	7.6	8	5.4	0.68	2.9	0.36	3.9	0.49	3.8	0.48
Non-Hodgkin lymphoma	7.3	7.6	5.2	0.68	4.9	0.64	5.8	0.76	6.4	0.84
Brain & other nervous system	5.4	5.8	3.2	0.55	2.6	0.45	2.8	0.48	3.5	0.60
Multiple myeloma	4.2	4	7.4	1.85	2	0.50	3.4	0.85	3.4	0.85
Stomach	4.3	3.7	8.2	2.22	6.8	1.84	6.9	1.86	6.5	1.76
Thyroid	0.5	0.5	0.4	0.80	0.5	1.00	0.5	1.00	0.6	1.20
Kidney & renal pelvis	22.1	22.8	24.3	1.07	12	0.53	21.2	0.93	20.8	0.91

Table 3: Disparities in Incidence by Cancer Type in Females

Incidence rates per 100,000, female, from SEER 2009-2015

	All	White	Black	Rate Ratio Black/White	Asian/Pacific Islander	Rate Ratio API/White	American Indian/Alaska Native	Rate Ratio AIAN/White	Hispanic	Rate Ratio Latinx/White
Breast	127.5	130.5	124	0.95	100.1	0.77	79.5	0.61	97.2	0.74
Lung & bronchus	48.9	51.8	44.6	0.86	28.2	0.54	33.9	0.65	24.8	0.48
Colon & rectum	33.9	33.6	39.1	1.16	26.9	0.80	37.9	1.13	28.8	0.86
Uterine corpus	27.5	28.1	57.4	2.04	20.8	0.74	19.7	0.70	24.1	0.86
Thyroid	23.3	24.5	14.3	0.58	22.6	0.92	14.2	0.58	21.9	0.89
Thyroid	23.3	24.5	14.3	0.58	22.6	0.92	14.2	0.58	21.9	0.89
Melanoma of the skin	17.5	21.3	0.9	0.04	1.2	0.06	5.3	0.25	4.7	0.22
Non-Hodgkin lymphoma	16.2	17	12.4	0.73	11	0.65	10.6	0.62	15.7	0.92
Pancreas	11.5	11.4	14	1.23	9.1	0.80	8	0.70	10.7	0.94
Kidney & renal pelvis	10.9	11.3	12.1	1.07	5.5	0.49	13.1	1.16	11.6	1.03
Leukemia	10.9	11.5	8.9	0.77	6.3	0.55	6.6	0.57	9.1	0.79
Cervical	7.3	7.2	8.7	1.21	6.4	0.89	7.9	1.10	9.3	1.29
Multiple myeloma	5.6	4.9	11.9	2.43	3	0.61	5	1.02	5.5	1.12
Stomach	5.3	4.6	7.7	1.67	8.2	1.78	6.4	1.39	8.5	1.85
Liver & intrahepatic bile duct	4.7	4.3	5.4	1.26	7.4	1.72	8.5	1.98	7.9	1.84

Table 4: Disparities in Mortality by Cancer Type in Females

Mortality rates per 100,000, female, from SEER 2009-2015

	All	White	Black	Rate Ratio Black/White	Asian/Pacific Islander	Rate Ratio API/White	American Indian/Alaska Native	Rate Ratio AIAN/White	Hispanic	Rate Ratio Latinx/White
Lung & bronchus	34.4	35.6	32.4	0.91	17.3	0.49	29.4	0.83	13.1	0.37
Breast	20.6	20.1	28.1	1.40	11.2	0.56	14.3	0.71	14.2	0.71
Colon & rectum	11.9	11.7	15.5	1.32	8.4	0.72	13	1.11	8.8	0.75
Pancreas	9.6	9.4	12.2	1.30	7.1	0.76	8	0.85	7.7	0.82
Ovary	7	7.3	6.1	0.84	4.4	0.60	6.3	0.86	5.2	0.71
Leukemia	4.9	5.1	4.4	0.86	2.8	0.55	3	0.59	3.8	0.75
Uterine corpus	4.7	4.4	8.5	1.93	3.1	0.70	3.5	0.80	3.9	0.89
Non-Hodgkin lymphoma	4.4	4.5	3.3	0.73	3.1	0.69	3.3	0.73	3.8	0.84
Liver & extrahepatic bile duct	3.9	3.7	4.7	1.27	5.8	1.57	7.4	2.00	6	1.62
Brain & other nervous system	3.6	3.9	2.1	0.54	1.9	0.49	2.1	0.54	2.6	0.67
Multiple myeloma	2.7	2.4	5.4	2.25	1.2	0.50	2.8	1.17	2.3	0.96
Stomach	2.3	2	3.8	1.90	4.2	2.10	3.6	1.80	4	2.00
Thyroid	2.2	0.5	0.6	1.20	0.6	1.20	0.4	0.80	0.7	1.40
Cervical	2.3	2.2	3.5	1.59	1.7	0.77	2.8	1.27	2.6	1.18
Kidney & renal pelvis	10.9	11.3	12.1	1.07	5.5	0.49	13.1	1.16	11.6	1.03

Also, of note, there is a well-documented disparity in utilization and/or access to screening (Table 5).

Table 5: Cancer Screening Among U.S. Racial and Ethnic Groups, 2015

	Whites	African Americans	Latinx	American Indian/Alaska Natives	Asians
Breast cancer screening rate	71.8	74.3	72.1	56.7	66.1
Cervical cancer screening rate	83.2	85.3	78.6	76.9	75.8
Colorectal cancer screening rate	63.7	59.3	47.4	48.4	52.1
Prostate cancer screening rate	37.1	30.7	25.5	N/A	17.4

From: White et al[16]

While NCI has recently placed greater emphasis on the intersection of biologic pathways and disparities through the Provocative Questions and the SPORE programs, much remains to be done.

Working Group Assessment

Despite advances in understanding lifestyle and access to preventive services, substantial cancer disparities persist. Emphasis on equity and disparities cuts across all recommendations and

priorities in prevention research. Risk factor research/epidemiology to date do not identify exposures across the life course that can explain the substantial disparities in cancer incidence and has largely ignored socioeconomic position and related social determinants of health. Further, cancer risk prediction models and clinical applications often model race as an indicator without any understanding of biology of race.[17] Approaches to model patient level social risk of disease have also been suggested, but they need refinement and validation in applicable settings.[18] Moreover, there is still a great need for more epidemiological resources to evaluate risk factors among minorities. A number of priority areas stand out where variation in incidence or mortality by race has not been fully explored: triple negative breast cancer in African-American women; prostate cancer in African American men; multiple myeloma in African-American men and women; and liver cancer in LatinX, to name a few.

Laboratory approaches in animal models have largely not addressed disparities. The working group noted the challenge of precision prevention in the setting of genetic and race/ethnic diversity. This gap must be addressed. Greater engagement of minority populations in research is essential to advance understanding of pathways to prevention and reduce disparities.

Many clinical trials and related studies are underpopulated with minority participants. This is due, in part, to eligibility criteria, and lack of engagement strategies tailored to minorities. Evidence shows that concerted efforts to modify eligibility to include broader populations of patients, and use of culturally tailored materials and processes, result in increased research and trial accruals of minorities. These strategies should be higher priority.

Recommendations and Opportunities for Enhancement

- Identify new strategies to bring evidence-based cancer prevention interventions to reduce the burden of cancer for all populations
- Increase basic and translational science to focus on populations experiencing cancer disparities
- Develop a deeper understanding of how racism drives cancer risk
- Increase eligibility for research studies and clinical treatment trials of populations with multiple comorbidities as experienced by populations with cancer disparities and promote the development of patient engagement approaches tailored to minority and underserved populations

Optimizing Opportunities Using Biomarkers in Cancer Prevention Research

In 1998, a biomarker was defined by the National Institutes of Health Biomarkers Definitions Working Group as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention".[19] The NCI has been heavily invested in biomarker development, validation and evaluation across a number of malignancies for the past two decades. Much of the activity in this space is coordinated through the Cancer Biomarkers Research Group (CBRG) which is charged with promoting research to identify, develop, and validate biological markers for early cancer detection and cancer risk assessment. Additional activities include the construction of collaborative databases and informatics systems to improve access to them, as well as new technologies or the refinement of existing technologies. The main programs within the CBRG are collaborative research programs. An example is the

- **Early Detection Research Network (EDRN),** a collaborative program that has developed a repository of reference sets stored the Frederick National Laboratory for Cancer Research for the triaging and rapid pre-validation of candidate biomarkers across a range of cancer diagnoses, including bladder, breast, colon, liver, ovary, pancreas and prostate cancers. The data and specimens are available to non-EDRN investigators.

There are also four Trans – NCI collaborative initiatives:

- **The Consortium for Molecular Characterization of Screen-Detected Lesions (MCL**) is focused on the need to characterize molecular and cellular features of screening-detected pre-cancers and early cancers, including within the tumor microenvironment, to distinguish between indolent and aggressive lesions using minimally invasive methods.
- **The Consortium of Imaging and Biomarkers** seeks to reduce overdiagnosis and false positive screening tests and improve the earliest possible diagnosis of aggressive cancers by integrating imaging strategies with biomarkers.
- **The Collaborative Research Networks** are currently supporting 2 programs in pancreatic cancer, one in liver cancer and the Liquid Biopsy Consortium which is actively examining the technology across multiple cancers.
- **The Pre-Cancer Genome Atlas (PCGA) – Human Tumor Atlas Network** may be the program with the potential to most directly expand opportunities for the NCI to support efforts in cancer prevention research. PCGA was created to establish a research initiative to better understand the molecular underpinnings and fate of the earliest stages of neoplastic development in high-risk individuals. The project has been broadened to enable examination of a range of tissues, premalignant lesions and the range of indications of increased cancer risk. The data is designed to be widely utilized by a range of investigators in the manner of The Cancer Genome Atlas (TCGA).
- **The Cancer Biomarker Aggregator (CBAG)** was established to test the feasibility of an artificial intelligence (AI)-empowered platform for the development of image-based AI algorithms for risk assessment and early detection of cancer. Expanded

efforts in AI-based algorithms and models should improve existing practices through (i) more accurate identification of benign, indolent, and aggressive lesions in at risk-individuals; and (ii) provide more precise recommendations for their follow-up care.

This impressive network of activities is focused to a large extent on the development and improvement of biomarkers of early detection and cancer risk assessment. Some of the more recent efforts, the PCGA and MCL, for example, have refined the scope of biomarker applications under study to focus other aspects of early detection and target generation. However, the research community has also begun to explore biomarkers that predict the responsiveness of tumors and premalignant lesions to various interventions. The explosion in technologies and the application of those technologies to an expanding array of biological specimens ensures that biomarker development will remain an active and likely expanding focus of the NCI, particularly in the prevention program. The challenges, however, remain at least as daunting.

Opportunities/Challenges in Biomarkers

The nature of cancer prevention/interception requires a very long timeline for assessment of effectiveness. Rational validated biomarkers to improve risk assessment, to characterize premalignancy, and to predict tumor aggressiveness remain active areas for support. The need for biomarkers to predict responsiveness to various interventions, to serve as surrogate endpoints for intervention trials and to predict toxicities of prevention interventions also remain essential for progress in cancer prevention. All continue to present challenges across the array of diseases encompassed by cancer.

The NCI should retain its priorities in the active funding of efforts to improve biomarkers that provide insights into the biology of both precancers and cancers and increase effective options for screening and early detection. In addition, the NCI should expand its efforts in biomarkers that enable the development and assessment of interventions targeting prevention/ interception/ risk-reduction. These efforts must increasingly integrate novel technologies, but also biostatistics and bioinformatics, epidemiology, data science, and artificial intelligence. The NCI will have special responsibility to ensure that candidate biomarkers are appropriately validated before their introduction into care. Novel screening approaches should be adequately examined to reduce overdiagnosis and improve accuracy, and the predictive value compared to established markers should also be examined. The expansion of biomarker programs to take on additional roles, such as prediction of improved outcomes and reduced treatment toxicities, and the role of modifiable biomarkers that may enable better prediction of outcomes of a range of interventions, should also be supported.

However, the scale and scope of a thoughtful biomarker program is potentially enormous. It is not clear that all previous investment by the NCI in biomarker programs has yielded the kind of results that advance the field despite substantial effort. Therefore, before the next wave of biomarker programs is begun, the panel recommends that the leadership convene a working group to provide critical and thoughtful assessment of the most important opportunities in the

field, and recommendations regarding not only the optimal areas for investment but also the best strategies to accelerate their development.

Recommendations and Opportunities for Enhancement

The NCI has overseen remarkable work in biomarker development using the range of available technologies and has made consistent efforts to maintain rigorous standards to guide their implementation. Technologies continue to expand, including opportunities in molecular, data science and imaging approaches with AI and ML, among others. NCI should continue to invest significantly in biomarker development, which remains critical to efforts in precision prevention.

In addition, before the next wave of biomarker programs has begun, the panel recommends that the leadership convene a working group to provide critical and thoughtful assessment of the most important opportunities in the field, and recommendations regarding not only the optimal areas for investment but also the best strategies to accelerate their development.

Expanding Data Science Opportunities in Risk Stratification and Point of Care Precision Prevention

Artificial intelligence, analytics and applied statistics, engineering and data science bring opportunities to speed precision medicine and precision prevention. A recent report from the National Academy of Medicine (NAM) reviews and highlights opportunities, promise and perils in application of AI in health care [20].

An increasing array of technologies allows non-invasive imaging with increasing precision. Opportunities for impact on prevention range from primary prevention to early detection and applications in cancer care and survivorship. Imaging is spatially defined, adaptable to a variety of instruments, minimally invasive, and sensitive to capturing detailed information, and it supports the use of contrast agents. For primary prevention—including prevention trials—imaging provides information on organ health, such as sun damage to skin, liver fat or fibrosis, and breast density. For secondary prevention, imaging identifies early disease in high-risk populations through such screenings as mammography, colonoscopy, colposcopy, lung computed tomography (CT), dermoscopy, and in prostate cancer, where better stratification of patients who may be able to forego biopsy if MRI shows evidence of indolent disease. For tertiary prevention, imaging is used to monitor a primary tumor or metastasis. Advanced imaging techniques enable digital pathomics analyses of cell shape, nucleus texture, stroma patterns, and tissue architecture arrangement.

Much of this is coupled with AI and ML to speed discovery and translation of applications. The ultimate goal is often delivery of results at point of care, with immediate decision making and action. Importantly, point of care can increasingly be used in under-resourced settings to potentially bridge access gaps and reduce cancer health disparities. AI/ML methods are good if the data set is sufficiently large, often requiring huge data sets for training (100,000+ individual image data, etc.) in order for them to perform optimally.

Interfaces with data science and machine learning in -omics and other applications beyond imaging are rapidly expanding. Opportunities for application in precision prevention include development of conventional analysis as well as AI/ML to handle disparate data types from imaging, omics, demographic, lifestyle, environmental exposure and generate actionable information.

Multidimensional data typically combines several lines of evidence, such as whole-genome sequencing, gene expression, copy number variation, and methylation, to produce plots that can predict patient outcomes. Multidimensional data can be separated into two categories: 1) high dimensional fixed baseline covariates (e.g., -omic, baseline images), and 2) longitudinal covariates are usually infinite dimensional, since they theoretically have values at every possible time points (e.g., time-varying factors, markers, and images). This approach with high dimensional baseline covariates is being used in the ongoing NCI Precancer Atlas (PCA) and other advances in applications require novel analytic strategies and methods to verify the robust AI and ML approaches. To complement the exploding data sources, the working group identified the need for more computational biologists and additional strategies to visualize data and methods for data integration across different levels (imaging, biological, lifestyle, etc.).

The Common Fund of NIH has already approved AI for Biomedical Excellence, an initiative to harness the emerging power of AI for the NIH mission. This NIH initiative aims to generate new biomedically relevant data sets amenable to ML analysis at scale. It should convert ML-friendliness attributes into rubrics and standards that allow planning and evaluation. The project will support the creation of software and hardware to speed annotation and structuring of data. It will immediately initiate collaboration with existing projects to maximize return on investment and generate large multimodal, metadata-complete, available data that exemplify ML-friendliness.

Work Group Assessment

There is great promise in the integration of multidimensional data into cancer risk prediction. Risk stratification algorithms will be required. This work will build on the record of methods development and application in cancer prevention for risk models (both classic statistical models and Bayesian approaches).[21] Strategies to bring multidimensional data to point of care for risk stratification and precision prevention decision making will need integrated studies of communication of these approaches and their interpretation.[7] At the same time coverage of populations regardless of socioeconomic status and race/ethnicity is essential to eliminate disparities and provide complete population application for the multidimensional data studies. The underlying importance of cohort data for model development and validation is well established and remains a priority for precision prevention. [22, 23]

Recommendations and Opportunities for Enhancement

Accelerate adaptation of technologies for real time, point of care diagnostics, monitoring, and decision making. These technologies then translate into multidimensional time-varying measurements (or images) requiring statistical/analytic methods for dynamic diagnostic and prediction methods.

Build rubrics and standards for ML and AI models as a priority. This includes assessment and reporting of uncertainty, along with model comparison and validation. Refined approaches to external validation for broader application of these algorithms in real world settings should be considered.

Develop strategies for visualizing data. Support quantitative methods development for multidimensional/-omic data and application in risk stratification/prediction models, either fixed or dynamic over time. With explosion of real-time data being recorded, and updated, analytical procedures applied for prevention, stratification and prediction, efforts can be divided into two categories: 1) a first-line of prevention/ stratification/ prediction which is solely based on high dimensional fixed data (baseline only), and 2) dynamic prevention/ stratification/ prediction which is on a real-time basis based on longitudinal data with infinite dimensionality. This second category more typically applies in the big data era, as electronic records, etc., are updated every

now and then. Thus, full utilization would be good data visualization for investigators, and it should also be adapted to improve methods for data/risk visualization for patients and physicians as an aid in decision-making. Adapting data displays in a culturally-appropriate manner is an integral component of these display and communication priorities. Finally, incorporating individual patient priorities (e.g., cancer risk versus side effect/complication risk of diagnosis and treatment) are also important. Strategies for visualizing data are highlighted below.

- **NCI should accelerate capabilities of data mining of existing population-based data sources through AI and ML**. Electronic health records and population-based registries and databases present a treasure trove of data for discovery research, prevention research, and health services research, with a clear pipeline to translational application.

- **For prevention intervention timing**, if we have access to a continuously updated database such as electronic health records that include markers of risk, then **change point detection is important.** Electronic health records can also be effectively used for tailored interventions, especially in conjunction with appropriate data mining.

- **AI capabilities in imaging can be used to successfully triage in prevention trials**, prior to human involvement, assessment, and intervention. This area deserves further exploration and support, as it will reduce costs and accelerate assessment to have a multi-tiered approach.

- **Maximizing populations engaging in the data sources for these applications and achieving population coverage is essential to avoid disparities**. In parallel with population coverage, we must advance ethical considerations in the context of precision prevention and multidimensional data.

- **Studies should identify efficient analytic approaches** to multidimensional data for risk stratification and eligibility determination for precision prevention studies and broader use of prevention pathways in clinical settings. With repeated measures of markers over time, there can be refined methods for change point detection in the setting of continuous trajectory of markers, etc., for prevention purposes and in survivorship settings.

- **Communication research** to parallel the exploding data sources and bring results to point of care decision making applications, with particular adaptation for audiences across the care continuum, including cultural adaptation, is needed.

Promoting Novel and Innovative Research Designs

Harnessing the explosive progress in cancer biology and biotechnology that has revolutionized cancer therapeutics into focus for cancer prevention is an enormous and multi-faceted challenge. The NCI has initiated the process of applying the highly successful genome sequencing approaches that created the TCGA to the development of the PCGA. The PCGA is intended to elucidate early steps in cancer initiation and evolution that may lead to the identification of new biomarkers or targets for risk reducing therapies. The PREVENT Cancer Preclinical Drug Development Program is designed to support preclinical development of innovative interventions and biomarkers for cancer interception (and ultimately prevention) for early phase clinical trials. Currently, this competitive contract program supports 61 chemoprevention and 32 immunoprevention projects as well as eight biomarker projects. However, there is no structured program for moving the discoveries in these projects to more definitive clinical trials in humans. The quality of the research encompassed in this program is exceptional, but still more investment will be needed to achieve the full return on this investment for prevention.

There are numerous opportunities to accelerate progress in cancer prevention by exploiting novel technologies in the analysis of carefully collected and annotated premalignant and malignant specimens or samples from very high-risk individuals. There are also likely to be important opportunities for progress in exploring novel interventions. Traditionally, preventive strategies have been chosen for assessment because they were relatively non-toxic and therefore more likely acceptable to the population at modest risk as something to be ingested daily for many years. Others, like tamoxifen, have been first shown to reduce the risk of second cancers in treatment trials, though toxicities have presented greater obstacles to uptake in the prevention setting.

The availability of new rationally designed effective therapies may require some revision of existing assessment systems before the agents could be considered for use for cancer interception, even in high-risk populations. For example, PARP inhibitors have therapeutic efficacy for breast, ovarian, pancreatic and prostate cancer in *BRCA1/2* mutation carriers and delay the development of mammary carcinoma in mouse models. They have some significant toxicities, however, even at lower doses, that may preclude their long-term use.[24] Perhaps the same drugs could be taken at even lower doses or on a far more intermittent dosing schedule, to enable them to remove premalignant cells and prevent the establishment of very early tumors while reducing potentially significant toxicities. Revisiting dosing schedules for prevention across all drug strategies is a priority. Testing of chemoprevention interventions on novel schedules might include less frequent regimens such as one to three months every one to two years.

There is also great interest in the adaptation of immunologic strategies for risk reduction that may have longstanding benefit. Immune modulation is a complex multifaceted process with very long duration of effect. With the introduction of therapeutic immune strategies, new approaches to measurement of duration of benefit had to be developed, because of the occurrence of long duration tumor control and modulatory effects on novel biomarkers. It seems likely that measurement of immune effects on biomarkers and more clinical outcomes may require redefinition of success. Further, as noted in other sections of this report, new measures of risk assessment and risk stratification will be needed to integrate multi-omic data, imaging,

lifestyle factors, and exposures. These will enable far more accurate determination of risk and permit refined eligibility criteria for prevention trials. Modifiable biomarkers might enable early identification of those not benefiting from a cancer prevention intervention, enabling them to be removed and reassigned to an alternative agent or established intervention. Also, as noted elsewhere in this report, there remains a critical need for novel informative biomarkers to serve as surrogate endpoints in clinical trials, since the time needed to truly assess risk reduction before prevention of invasive cancer remains far longer than the duration of a grant or a research program. Finally, the study of well-defined high-risk populations may necessitate examination of possible differences in the process of carcinogenesis or immune resistance to cancer between those identifiable high-risk individuals and the rest of the at-risk population who may experience exposures or interventions differently. Understanding the mechanisms of those potential differences will also require study and could open alterative prevention pathways.

Recommendations and Opportunities for Enhancement

The working group recommends consideration of the following areas for investment, which include modifications to current approaches in order to accelerate progress in cancer prevention.

- **Investment in basic science targeting molecular mechanisms underlying the relationships between obesity and cancer, cross talk with the tumor microenvironment, the carcinogenic process, immunologic interactions, influences of exposures and potential interventions remains a high priority.** It will also be important to examine the extent to which these mechanisms are modifiable and by which strategies.

- **It will be increasingly important to generate and evaluate vaccines that anticipate the most likely neoantigens in the highest risk populations – inherited cancer predisposition, cancer survivorship cohorts, etc.** Other vaccine targets must also be examined. Can vaccines be individualized based on the HLA types of the individual at risk and the ability of specific alleles to present specific neoantigens? Can vaccines be generalized to enable application to broader populations?

- **Investment in AI directed toward improvement in prediction of aggressive versus indolent behavior of early stage solid tumors is needed.** AI is already being applied to imaging and pathology for diagnosis, but applications could be extended to encompass new measurements of exposures, variants in cancer susceptibility genes, immune interactions, and evolution of tumor microenvironments, trajectories of markers over time and improved dynamic risk classification for precision prevention. AI could contribute to using -omics data in tumors to identify potential signatures of exposures that may give clues to etiological factors. This can support finding multi-level signatures (somatic alterations, epigenetics, proteomics) that may give clues as to the evolution of the tumor and potential initiation events and carcinogenic factors and promoters.

- **The study of multi-omics approaches must include opportunities to integrate diverse data including lifestyle and exposure measures from novel data sources and require rigorous standards for evaluation, validation and ultimately implementation.**

- **There must also be significant investment in what we can learn from the study of known carcinogens, including viral agents (e.g. HPV, HBV, HIV, HCC) and their effects on the immune system.**

- The improvement of existing models for risk assessment will require data that may enable better quantified models for approaches to measure modifiable risk factors and outcomes affected by an intervention. **Ongoing investment in biostatistics and bioinformatics will be essential across all areas.**

- **For chemoprevention research, there are particular challenges that NCI must / should address. These include:**
    - **Efforts to improve risk stratification of at-risk populations to permit better defined study populations are needed.**
    - **Continued efforts in the development of improved preclinical models to enable the identification of better targets for interventions are needed.**
    - **NCI should consider novel trial designs that may support different models of chemoprevention,** such as intermittent exposures to agents otherwise too toxic for long duration use (this could enable adoption of targeted agents that might remove early cancer cells, though issues of resistance from repeated exposure must be examined), or long term evaluation of interventions that modulate the immune systems for unanticipated effects.
    - **Strategies to improve communication of risks, benefits, and concepts of chemoprevention are essential to improve "uptake" of effective chemopreventive interventions by the public.** This includes both public and provider understanding and communication. Is it time to change the name?
    - **Recognition of the many biases that can mislead prevention and efforts to account for them in preliminary work and trials are critical. Adequate attention to these issues** should reduce the chance of error in the identification of appropriate populations and interventions for the long path to definitive intervention trials.
    - **Studies should develop biomarkers that are appropriately sensitive, specific, reproducible, accessible, acceptable, and potentially generalizable** since prevention intervention ultimately for the general population remains a critical goal.

Recommending Consideration of Infrastructure Resources NCI Could Facilitate to Enhance Prevention Research

The transformation of cancer research that has led to remarkable progress in cancer care has been fueled by both molecular and computational revolutions. Massively parallel sequencing, targeted therapies, the immunologic revolution, and artificial intelligence are among the technologic strategies that are transforming cancer investigation and care. Achievement of the goal of accelerating progress in cancer prevention research will include enabling the application of these technologies more broadly. The development of precision prevention will require adaptation of these technologies to the challenge of early detection that can be applicable to all populations within the US. In parallel, as noted in the Promoting Novel and Innovative Research Designs section of this report, new approaches are needed to study designs that takes advantage of -omics technologies. The molecular details of new malignancies must be anticipated, and biomarker modulation to permit early assessment of response and efficacy of risk reduction interventions are challenged by the outcome of interest being the absence of an event – the development of a malignancy.

In the AACR Cancer Prevention White Paper [1], the group specifically cited, as the rate-limiting step in cancer prevention, our limited in-depth understanding of cancer biology. The need for identification of molecular and cellular drivers of precancers, their transformation from normal cells to early premalignant lesions, the opportunity to intervene or intercept the transformation, and the complexities of disease heterogeneity across the cancer spectrum will require extensive study. Focus on these challenges is essential to progress in cancer interception.

Applications of innovative technologies for early cancer detection provide additional opportunities for government investment to enable more rapid access for investigational projects that might accelerate their wider adoption. Emerging technologies will provide entirely new ways to measure in real-time both exposures and individual reactions to them. Improvements to existing technologies that make them more accessible and acceptable for large scale use through modifications that reduce cost, time, and ease of use, for example, are likely to result in novel tools for measurement and subsequent harmonization across studies. Opportunities to invest in the evaluation of technologies to facilitate their rigorous evaluation for early cancer detection may prove useful, and the data they generate also be made more available for scientific review. NCI has experience in negotiation with industry to provide access to various tools for cancer research, as they did in the days of nanotechnology development, and will likely be well-positioned to pursue these goals again in the early detection setting. The approach may also be useful for some of the novel AI-enhanced approaches to interpretation of radiographic images and histopathology images that are already being evaluated for detection and diagnostics in clinical care.

A different area of infrastructure need involves the potential role of the NCI providing access to essential resources otherwise difficult for intramural and extramural investigators to obtain. A current example is the NCI Formulary, which provides accelerated access to investigators for investigator-initiated clinical trials in both therapeutic and prevention arenas. As industry support for prevention trials is not frequent because of liability concerns as well as the timing of transition of drugs from brand name to generic, this resource has provided access to agents for investigator-initiated trials. A new challenge has developed because of the recent regulation

around the production of placebos resulting from the meningitis outbreak from a contaminated product from a compounding pharmacy.[25] Trials including placebo comparisons will now be required to utilize a more tightly regulated – and safer – process for synthesis and distribution of placebos that will markedly increase the cost of these trials. There are no alternative sources for placebo except for the compounds rarely provided by industry.

Working Group Assessment

The group recognizes the importance of the opportunities for innovation throughout the spectrum of the challenges of early detection and prevention of diverse malignancies across the full spectrum of the US population. To enhance progress in these important areas, the NCI should consider opportunities that will empower the research community to accelerate progress in prevention, particularly when the tools and data have already been used in the evaluation of tumors for treatment or measurement. The NCI should also consider situations in which it may provide unique resources to facilitate important work in prevention and related areas.

Recommendations and Opportunities for Enhancement

- Enhance the development of initiatives like the Pre-Cancer Atlas that bridge technology development and improvement from work with established tumors to work in the premalignant space, and require that data generated are made available to the research community

- Support the development of inexpensive, point of care technologies to enhance implementation of early detection in healthy people for screening and prevention

- Support key longitudinal surveillance and monitoring with linkages to electronic medical records and claims data bases (e.g., NCI SEER Programs), and leverage these resources as well as expertise in spatial sciences/GIS mapping to monitor and assess progress in reducing cancer incidence and disparities

- Link translational and population scientists with existing tissue/clinical archives to monitor and study mechanisms of cancer evolution with time and treatment

- Consider support to create data repositories for AI- and ML-generated data from imaging and pathology that can be accessed for research in pre-cancer and risk reduction in addition to serving as a common validation data source

- Harness AI and ML to improve prediction of multi-level cancer risk for behavioral cancer prevention in multi-ethnic populations to reduce cancer disparities

- Develop capacity for synthesis and distribution of placebos for placebo-control chemoprevention trials, in both NCI-supported and other investigator-initiated studies

Conclusion

The work group reviewed strategies to accelerate progress in cancer prevention research and concluded that while the underlying issues in prevention research pose special considerations, advancing technology and data science offer many opportunities to bring new focus to prevention. Importantly, all prevention research must focus on reducing existing disparities in cancer across racial and ethnic groups, as well as other minorities and underserved populations. Identifying new approaches to bring evidence-based interventions to all population groups remains an urgent priority.

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