Special Report

Transforming Cancer Prevention through Precision Medicine and Immune-oncology

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ABSTRACT

We have entered a transformative period in cancer prevention (including early detection). Remarkable progress in precision medicine and immune-oncology, driven by extraordinary recent advances in genome-wide sequencing, big-data analytics, blood-based technologies, and deep understanding of the tumor immune microenvironment (TME), has provided unprecedented possibilities to study the biology of premalignancy. The pace of research and discovery in precision medicine and immunoprevention has been astonishing and includes the following clinical firsts reported in 2015: driver mutations detected in circulating cell-free DNA in patients with premalignant lesions (lung): clonal hematopoiesis shown to be a premalignant state; molecular selection in chemoprevention randomized controlled trial (RCT; oral); striking efficacy in RCT of combination chemoprevention targeting signaling pathway alterations mechanistically linked to germline mutation (duodenum); molecular markers for early detection validated for lung cancer and showing promise for pancreatic, liver, and ovarian cancer. Identification of HPV as the essential cause of a major global cancer burden, including HPV16 as the single driver of an epidemic of oropharyngeal cancer in men, provides unique opportunities for the dissemination and implementation of public health interventions. Important to immunoprevention beyond viral vaccines, genetic drivers of premalignant progression were associated with increasing immunosuppressive TME; and Kras vaccine efficacy in pancreas genetically engineered mouse (GEM) model required an inhibitory adjuvant (Treg depletion). In addition to developing new (e.g., epigenetic) TME regulators, recent mechanistic studies of repurposed drugs (aspirin, metformin, and tamoxifen) have identified potent immune activity. Just as precision medicine and immune-oncology are revolutionizing cancer therapy, these approaches are transforming cancer prevention. Here, we set out a brief agenda for the immediate future of cancer prevention research (including a "Pre-Cancer Genome Atlas" or "PCGA"), which will involve the inter-related fields of precision medicine and immunoprevention – pivotal elements of a broader domain of personalized public health. Cancer Prev Res; 9(1); 2–10.

A Time of Transformation

Immense breakthroughs in understanding the progression of genomic events and inflammatory microenvironment that drive premalignancy provide unprecedented possibilities to transform cancer prevention. Although opinions about the current state of cancer prevention science are still wide-ranging (1–5), as is characteristic of emerging fields, we stand on the cusp of opportunity. Just as precision therapy and immunotherapy are transforming cancer treatment, precision medicine and immunoprevention are now moving to the clinic with great promise. Additional gains, such as identification of tractable molecular targets, more sophisticated risk stratification strategies and algorithms, better preclinical models, earlier detection of premalignant lesions and early-stage cancers, new agents, rational development of combinatorial chemopreventive interventions, current availability of 14 FDA-approved drugs and vaccines for application to cancer prevention (5) and advances in implementation science (defined as the application of what we already know), all point to a strong possibility to reduce cancer
incidence, morbidity, and mortality in the near future. Given that the global burden of cancer is enormous and increasing (the number of diagnosed cases is expected to grow worldwide from 13.3 million in 2010 to 20 million by 2030; ref. 6), cancer prevention (including early detection) is essential to our ability to lessen the burden of cancer in our lifetime. The optimism surrounding progress in cancer therapeutics is propelling investigation into applications of enabling technologies and extrapolation of effective interventions in established disease to the more difficult challenges of cancer prevention or interception (7).

Here, we set out a brief agenda for the near-term future of this exciting field through the inter-related disciplines of precision medicine and immunoprevention—elements of a broader domain of personalized public health.

Biology of Premalignancy

There has been increasing focus on the molecular origins of cancer over the last several years (8). In contrast to studies in malignancy, however, genome-wide analyses of premalignancy have been rare. Remarkable technological advances in next-generation sequencing (NGS; requiring only nanograms of starting DNA/RNA from minute biopsies down to single cells), computational biology, and high-throughput functional screening have now provided us with very real possibilities to deeply probe the biology of premalignancy. Recent studies in lung squamous premalignancy of single nucleotide polymorphism arrays identified losses of tumor suppressors RNF20 and SSBP2 and amplification of the RASGRF3 oncogene (9) and RNA-seq analyses identifying 3q26.33–3q29 (including SOX2) amplification/overexpression (10). Surprisingly, circulating DNA containing cancer driver mutations has been detected in circulating cell-free DNA in patients with atypical adenomatous hyperplasia, preinvasive (premalignant) lesions of the lung, which could be used for early detection and to follow the effects of preventive interventions (11). Studies of the airway field of injury have detected EGFR mutations in adjacent histologically normal epithelium of EGFR-mutant lung adenocarcinoma (12), and whole-genome expression profiling has identified other activated oncogenic signaling pathways (e.g., PI3K/AKT) in the airway of smokers with premalignant lesions and/or lung cancer (13) and in the cytologically normal bronchial airway of smokers with premalignant lesions, potentially enabling genomic approaches to monitoring the preventive effects of PI3K inhibitors (14). This precision genomics approach is currently being tested in a phase IIb prevention trial of myo-inositol among high-risk smokers with premalignant lesions.

Recent studies support the model that a specific sequence of acquired genomic events over many years characterize the transition from normal epithelium to invasive carcinoma and that
specific “driver” events, acquired in a particular order, enable cells to progress from benign growth to an invasive phenotype. A study sequenced 293 cancer-relevant genes in primary melanomas and their adjacent precursor lesions to study the succession of genetic alterations during melanoma progression (15). Whereas benign nevi harbored BRAF V600E mutations exclusively, this study identified an intermediate (premalignant) category of melanocytic neoplasia characterized by additional mutations, including TERT promoter mutations and NRAS mutations, and found a mutational signature implicating ultraviolet radiation as a major driver of melanocytic neoplasia progression. Ultra-deep sequencing of 74 signature genes in 234 biopsies of sun-exposed eyelid epidermis revealed mutations similar to those seen in many malignancies, including NOTCH1/2 and FAT1 genes (16). NOTCH1 driver mutations have also been detected in oral premalignancy (17). Studies in breast lobular carcinoma in situ, pancreatic mucinous cysts, and Barrett esophagus have identified genomic patterns of premalignant progression to cancer, which have important implications for risk prevention and early detection (18–20). Some data suggest that driver mutations in early neoplasia can differ from those in the corresponding cancer. A critical next step for this field will be developing systematic approaches for whole-genome profiling of premalignant lesions followed longitudinally as they progress toward cancer—the proposed initiative “Pre-Cancer Genome Atlas” or “PCGA” (21). This initiative will provide critical insights into the molecular events (and possible sequence) in premalignant cells and their microenvironment that drive progression to invasive cancer (Fig. 1), enabling precision approaches to cancer prevention and early detection.

As described above, the proposed PCGA focuses on solid tumors of epithelial origin; however, it also applies to hematological neoplasia. The Cancer Genome Atlas (TCGA) did include one blood cancer [acute myelogenous leukemia (AML)]. Recent genomic studies suggest that clonal hematopoiesis is a pre-malignant state. Somatic mutations observed mostly in three genes (DNMT3A, TET2, and ASXL1), known drivers of hematologic malignancies, have been identified in the blood of people without a known hematologic disorder. The prevalence of these mutations, termed clonal hematopoiesis of indeterminate potential, increases with age (22) and is associated with increased risk of progression to a blood cancer (23). Somatic mutations typical of myelodysplastic syndrome (MDS) and AML have been found in up to 40% of patients with idiopathic cytopenias of undetermined significance (24) who may be at greatest cancer risk. Clonal hematopoiesis detected by deep sequencing was identified in aplastic anemia (25) and associated with risk of developing therapy-related MDS or AML (26). Several prospective studies of ICU and CCS have been initiated to identify patients with preclinical MDS (27) most likely to progress and therefore potential candidates for early treatment or prevention. Related hematologic neoplasia work is studying the monoclonal gammopathy of undetermined significance (MGUS)–multiple myeloma sequence, including smoldering myeloma, which has an overall risk of progression to malignancy (multiple myeloma) of 10% per year (compared with 1% per year for MGUS). Recent genomic and immune studies of MGUS progression are providing novel targets for precision and immune prevention (28).

**Precision Medicine**

**Chemoprevention**

The status of this field, including RCTs, has been recently reviewed (4, 5) and includes notable successes (e.g., with selective estrogen receptor modulators and aromatase inhibitors in breast cancer) and failures (vitamin E and selenium in prostate cancer). Two important new RCTs (29, 30) include a positive trial of oral nicotinamide (which enhances DNA repair) in nonmelanoma skin cancer, typically caused by UV-induced DNA damage (29); this provocative result is consistent with an earlier report of topical DNA repair enzymes in xerodermia pigmentosum, a germline DNA repair disorder (31). The first precision medicine RCT in chemoprevention (EPOC) was reported just two months ago (32), beginning a new era of molecular selection in this field (33). Perhaps the most promising current precision medicine approach to change standard of care in cancer prevention involves molecular selection (based on prostaglandin pathway studies) for the repurposed (and now established) chemopreventive drug aspirin in colorectal neoplasia. In September 2015, the US Preventive Services Task Force (USPSTF) recommended low-dose aspirin for colorectal cancer (CRC) prevention based on age and risk (34), a major milestone for the field of cancer prevention. The USPSTF’s recommendation for aspirin use in this setting acknowledges the substantial body of data that now exists supporting aspirin’s efficacy for the prevention of CRC. Given aspirin’s potential adverse effects (e.g., bleeding), further tailoring aspirin use is a high priority. A series of recent reports based on studies of colorectal neoplasia, prostaglandins, and aspirin mechanism support a precision medicine approach in this setting: (i) high urinary PGE-M levels were prognostic (associated with advanced adenomas risk) and predictive for aspirin and/or NSAID preventive activity (35); (ii) aspirin reduced colorectal cancer risk in patients with high 15-hydroxyprostaglandin dehydrogenase mRNA expression in the normal mucosa adjacent to cancer (36); and (iii) aspirin, NSAIDs, or both were associated with reduced colorectal cancer risk and the association of these agents with risk differed based on an SNP at chromosome 12 that could potentially affect prostaglandin synthesis (37). A related study reported that SLCO2A1 mutation carriers develop early-onset colon neoplasia and are NSAID resistant, suggesting for the first time that disordered prostaglandin catabolism can mediate inherited susceptibility to colorectal neoplasia in humans, mimicking the phenotype of the related HPGD-null mouse (38). SLCO2A1 encodes the prostaglandin transporter, shown to play a critical role in colorectal neoplasia (39). Related NSAID/CRC clinical trial data include: PIK3CA mutation in CRC (genetic driver also detected in adenomas) may predict aspirin efficacy (40), 5-aminosalicylates (related to NSAIDs but poorly absorbed) were associated with reduced colorectal neoplasia risk in the inflammatory bowel disease ulcerative colitis (41), and recent standard-of-care-changing RCTs in hereditary CRC (see Germline mutations below).

**Early detection**

Developing and validating precision medicine approaches for early cancer detection remains a critical challenge in the prevention field. Standard, conventional screening includes mammography (and MRI) for high-risk women, e.g., with BRCA mutation carriers or Li-Fraumeni syndrome), colonoscopy and fecal occult blood tests, PAP and HPV tests, and low-dose computed tomography for breast, colon, cervical, and lung tumors, respectively. Newer screening approaches in clinical development to detect premalignant disease include the following hepatic studies: MRI and magnetic resonance elastography (42), 3D molecular MRI collagen imaging (43), and plasma eicosanoid lipidomic...
validated as a screening tool for CRC (48). Gene-expression detection have overcome this important hurdle and successfully would be used. Two recent genomic biomarkers for early cancer challenge in designing and implementing prospective studies to struggle to translate into the clinic due, in large part, to the vaccines. 

...mRNA isoforms encode proteins with unique primary structure, which could be targeted by peptide or T cell-based therapies for more precise personalized risk estimates (60). Loss of this tumor tissue screening approach.

A clinical breakthrough for this field is the very recent RCT reporting striking efficacy of combination chemoprevention in familial adenomatous polyposis (FAP). Targeting the convergence between Wnt and EGFR signaling pathways and COX-2 activity (alterations mechanically linked to the germline adenomatous polyposis coli [APC] mutation causing this disease) with sulindac and erlotinib produces a highly significant reduction in duodenal adenoma burden (56), far more active than single agent sulindac or aspirin (57). This finding has major implications on standards of care for this devastating disease, which can be associated with thousands of colorectal adenomas and a near 100% cancer risk. After prophylactic colectomy (standard of care), duodenal adenocarcinoma is the leading cause of cancer death for these patients.

Seminal work showing that BRCA1/2 mutations induce defects in DNA repair, which confer sensitivity to PARP inhibitors across associated tumor types, including breast, ovary, prostate, and pancreas, establishes a new paradigm of targeted therapeutics in the cancer predisposition setting (58). The possibility of specific therapies for BRCA mutation carriers has led to incorporation of BRCA germline characterization for all ovarian and triple-negative breast cancers into the National Comprehensive Cancer Network (NCCN) guidelines. Opportunities for medical risk reduction for BRCA mutation carriers may target DNA-repair defects and/or capitalize on other site-specific data, such as tamoxifen in breast cancer prevention (59). The application of genome-wide association study data as modifiers of high-penetrance genes or more complex risk models of common less-penetrance genes offers promise for more precise personalized risk estimates (60). Loss of heterozygosity screening of oral brushings may help stratify head and neck cancer risk in Fanconi anemia, a rare DNA repair disorder associated with an extremely high risk of oral cancer (61). Novel vaccine prevention strategies in Lynch syndrome and BRCA1/2 carriers are discussed in the next section.

**Immunoprevention**

**Viral vaccines**

A successful example of immunoprevention is the nationwide hepatitis B virus (HBV) vaccination program in Taiwan...
that began in 1984 and produced an 80% reduction in the incidence of hepatocellular carcinoma (62). Expanding worldwide access to HBV vaccination is a harbinger of benefits to come. Global perspectives on the patterns of human papillomavirus (HPV)-related cancers (e.g., oropharyngeal) and preventing virally related cancers with vaccines, including efforts to make these vaccines available to countries experiencing financial hardships, highlight the burden and challenges of these viral diseases (63, 64). EBV vaccine development has been challenging due in part to complex viral antigen expression patterns.

The standard three-dose schedule of prophylactic HPV vaccine given before infection has 90–100% efficacy in preventing HPV infection and associated anogenital neoplasia (vulva, vagina, cervix, anus and penis), and limited data from secondary analysis of RCT in women reported vaccine protection for oral HPV infection implicated in oropharyngeal cancer. High antibody concentrations have been reported in HPV-vaccinated younger populations receiving two doses, which is now the schedule recommended by the WHO for girls under 15 years (65). RCTs in Costa Rica and India suggest that even a single HPV16/18 vaccine dose could induce a sustained antibody response (66, 67). Of great public health significance, planning is now under way for an RCT specifically designed to evaluate the protection of one versus two doses in Costa Rica and a US immunobridging study (including males) done in parallel. Another preventive vaccine approach is to eradicate existing premalignant lesions where the pathway to transformation is known. The first vaccine tested clinically in premalignant HPV disease (vulvar intraepithelial neoplasia) was composed of long peptides derived from HPV16 E6 and E7 oncoproteins and produced major activity and strong T-cell responses (68). This therapeutic vaccine approach has produced histopathologic regression and viral clearance in a phase II RCT in cervical intraepithelial neoplasia (69).

A number of prevention studies have focused on the growing public health epidemic of HPV-associated oropharyngeal cancer (70), including two early-detection research studies: oropharyngeal "PAP" smears (71) and influence of childhood tonsillectomy effect on subsequent oropharyngeal cancer (72). The dramatic cancer disparity of blacks versus whites in HPV-positive oropharyngeal cancer (73) is well established; updated data suggest that these patterns are changing over time (74). No premalignant lesions have been identified in this setting, but current prevention work is focusing on oral HPV16 infection, which tracks closely to oropharyngeal cancer, e.g., both are 4-fold higher and increasing in men compared to women (70). A recent report on the long-term persistence of oral HPV16 infection in men (75) adds important new data to the scarce natural history information currently available. Genomic and imaging studies to identify high-risk groups and early neoplasia in the setting of persistent oral HPV16 infection are ongoing.

Non-viral vaccines

Recent clinical success of HPV (including therapeutic) vaccines for prevention and checkpoint inhibition (proving that immunity can inhibit cancer growth) for therapy has generated tremendous enthusiasm for non-viral vaccine immunoprevention. The immune-checkpoint inhibitors (e.g., targeting CTLA-4 or PD-1), which act on previously induced T cells, are producing durable remissions in some patients with metastatic, previously treated cancers. Their utility in prevention, however, is limited by their serious autoimmune toxicities. Furthermore, it is not clear that these checkpoint signals are important in early TME. Vaccines are an immune approach that is broadly available, specific, cost-effective, and work best in immunocompetent individuals. Vaccines targeting cancer-associated antigens have been studied extensively over the last 30 years in thousands of patients and have been shown to have a very favorable safety profile setting the stage for prevention vaccines, and limited dosing should improve implementation and adherence. Tumor-specific antigens (TSAs), such as KRAS and p53 mutations exclusively on tumor/premalignant cells, have safety advantages as vaccine targets compared with tumor-associated antigens (TAAs) present on tumor and normal cells because of potential for less autoimmunity toxicity.

Although more complex and recent than the development of vaccines against foreign pathogen-associated viral targets (e.g., hepatitis B), vaccines against the less-immunogenic neoantigens (genetic drivers and other tumor antigens) are showing promise in preclinical prevention models (e.g., Kras in pancreas models; activating EGFR mutations in lung adenocarcinoma; refs. 76–78) and have now entered early-phase clinical trials (e.g., HER2 and MUC1). This focus is very timely, as evidenced by a major new initiative by Cancer Research UK, which just issued a £20M Grand Challenge that includes a charge to develop vaccines to prevent non-viral cancers (79). The first clinical trial of a preventive vaccine based on a tumor antigen was in patients with advanced colorectal adenomas (80). The vaccine consisted of the 100-mer peptide derived from the tandem repeat region in the TAA MUC1 extracellular domain and adjuvant, toll-like receptor (TLR)-3 agonist Poly-LCIC. It elicited a strong humoral and cellular MUC1-specific immunity and increased IgG levels after a booster injection at one year, demonstrating induction of immune memory. Patients who did not respond (i.e., no increase in MUC1 IgG antibody) had high levels of circulating myeloid-derived suppressor cells (MDSCs) before vaccination, providing the first clinical evidence suggesting that non-infectious/viral vaccines will require adjuvants/immune modulators that decrease immunosuppression (e.g., reduce suppressive immune cell populations like MDSCs and Tregs at the time of vaccination). The vaccine was well tolerated or without any toxicity or evidence of autoimmunity. Currently, this vaccine is being tested for efficacy (prevention of adenoma recurrence) in a multicenter RCT (NCT02134925).

Classic adjuvants are stimulants such as non-specific bacterial extracts and newer subtype-specific TLR stimulants. More recently, GEM model studies indicate that the first genetic alterations can initiate a cascade of genetic, epigenetic, and inflammatory changes that lead to an immunosuppressive TME (consistent with the clinical data discussed above; ref. 80), suggesting need for inhibitory adjuvants for vaccine preventive efficacy. This hypothesis was supported when Kras vaccine efficacy (reduced pancreatic intraepithelial neoplasia progression) in the Kras-p53-Cre mouse model required Treg depletion. Recent studies in pancreatic models found that metformin and aspirin can modulate inflammatory pathways within the early TME that promote tumorigenesis, suggesting their potential as adjuvants to enhance vaccine efficacy (81, 82). Current work in this context is developing more specific adjuvants (e.g., miRNA or other epigenetic regulators) to reverse the functional (tumor...
promoting/immunosuppressive) immune cell polarity to inhibit the immunosuppressive TME.

Genomic technologies and large data sets are helping identify vaccine targets for cancer prevention, including early genetic drivers in premalignancy. Preclinical studies demonstrate that multi-antigen vaccines are more effective than single-antigen vaccines by inducing immunity to more antigens, generating more activated T cells homing to the premalignant lesion (83). A multi-antigen vaccine for colon cancer, targeting several immunogenic proteins that are upregulated in adenomas and conserved through carcinoma (84), is moving toward the clinic. Preliminary studies of single-antigen vaccines are encouraging in reducing the risk of developing malignant disease, is in development.

A renewed focus on and funding of implementation science in cancer prevention; ref. 90) is due to the growing recognition of the potential to prevent the majority of cancer and reduce disparities. Medical interventions across all sectors of society adds to the complexity of study designs beyond RCTs. The importance of implementation science also applies to precision medicine and immunoprevention as briefly discussed below. For example, uptake of CRC universal tumor screening for Lynch syndrome is limited despite data showing clear public health benefits (discussed in detail above in Germline mutations section) and recommendations of several professional organizations, including NCCN. Tamoxifen (and related FDA-approved agents) produces durable reduction of breast cancer risk by 75% (91) in atypical hyperplasia (10% of patients with a biopsy for benign breast disease; invasive cancer risk of 30% at 25 years [92], similar to BRCA mutation carriers). Appalling under-use in this high-risk subset suggests that providers and patients are not fully aware of the clinical risks and benefit in this setting.

Identification of HPV as the cause of a major global cancer burden, including as a necessary driver of cervical cancer (the leading cause of cancer deaths in women in many developing countries) and a dramatically increasing subset of oropharyngeal cancer among men in the US and other developed countries, provides exceptional prospects for implementation of public health interventions (70). Three HPV vaccines – bivalent (HPV 16 and 18), quadrivalent and 9-valent – have been FDA-approved (first in 2006), but the uptake remains slow in parts of the US and world. In 2013, only 38% of girls and 14% of boys in the US were fully vaccinated despite recommendations from the CDC, American Academy of Pediatrics, and other groups. HPV vaccination in the US is lower in areas of high cervical cancer incidence and mortality and among non-Hispanic Blacks, helping direct public health implementation efforts (93). Major global efforts are now focusing on implementing HPV vaccination programs in countries where the burden of disease is highest, including through school-based programs in low-income countries (65, 94). Recent RCTs suggest that a single vaccine dose can provide durable protection against HPV infection (66, 67), which if confirmed by the planned definitive RCT, would dramatically improve vaccine implementation and uptake globally.

**Conclusion**

Remarkable advances in NGS (including single cell sequencing), liquid biopsy technology, computational biology methods and algorithms, and high-throughput functional screening are transforming cancer prevention through the inter-related fields of precision medicine and immune oncology. These extraordinary tools provide unprecedented opportunities to interrogate the biology of premalignancy, including site-specific genomic events that initiate a cascade of genetic and epigenetic changes and an inflammatory (increasingly immunosuppressive) TME, driving premalignant progression to cancer. These studies are identifying driver mutations in the blood of patients with epithelial premalignant lesions (11) and premalignant states for blood cancer (23, 24) and are providing molecular targets for prevention (including vaccines) and early detection, including a bronchial airway genomic classifier validated for lung cancer (49) and promising leads for pancreatic, liver, and ovarian cancer (43, 44, 46, 47). Prostaglandin pathway studies may help personalize standard aspirin CRC prevention (34–38) and possibly other agents targeting this pathway such as iloprost, the most promising lung cancer chemopreventive agent
based on positive phase II RCT (95). Study of the biology of tumors that develop in individuals carrying predisposition mutations has led to recent paradigm-changing therapy (e.g., PARP and immune checkpoint inhibitors in BRCA carriers and LS; refs. 55, 58, 96) and prevention (e.g., chemoprevention, screening, and vaccines in LS and FAP; refs. 53, 54, 56, 86, 87). Clinical success of HPV vaccines for cancer prevention (including encouraging RCT data supporting single-dose prophylactic vaccine [66, 67] and therapeutic vaccine for cervical premalignancy [69]) and checkpoint inhibitors for cancer therapy has generated tremendous enthusiasm for immunoprevention, including developing vaccines targeting premalignant genetic drivers (EGFR, Kras, and Hras mutations; refs. 76–78). Targeting the TME has shown promise in GEM models, including arresting progression of intraepithelial neoplasia (97) and as adjuvants for non-viral vaccines (98). Potential vaccine adjuvants include repurposed drugs (aspirin and metformin; refs. 81, 82, 85, 98) and new agents under development (e.g., epigenetic regulators). Even tamoxifen (FDA-approved for breast cancer prevention) was just shown to have striking off-target immune effects (99). Finally, studies of microbiome effects on inflammation and immune mechanisms influencing cancer development are also providing novel insights into and directions for cancer prevention (100, 101). Just as precision therapy and immunotherapy are transforming cancer treatment, precision medicine and immunoprevention approaches are being translated to the clinic and showing great promise. We stand at the edge of a new frontier that will include comprehensively characterizing the molecular and cellular events that drive premalignant progression (e.g., the PCGA). The technology and science are evolving rapidly and herald a new era of precision medicine and immunoprevention in cancer prevention that will require new paradigms for implementation into clinical practice.

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