Population Sciences, Translational Research, and the Opportunities and Challenges for Genomics to Reduce the Burden of Cancer in the 21st Century

Muin J. Khoury1,2, Steven B. Clauser2, Andrew N. Freedman2, Elizabeth M. Gillanders2, Russ E. Glasgow2, William M.P. Klein2, and Sheri D. Schully2

Abstract

Advances in genomics and related fields are promising tools for risk assessment, early detection, and targeted therapies across the entire cancer care continuum. In this commentary, we submit that this promise cannot be fulfilled without an enhanced translational genomics research agenda firmly rooted in the population sciences. Population sciences include multiple disciplines that are needed throughout the translational research continuum. For example, epidemiologic studies are needed not only to accelerate genomic discoveries and new biological insights into cancer etiology and pathogenesis, but to characterize and critically evaluate these discoveries in well-defined populations for their potential for cancer prediction, prevention and response to treatment. Behavioral, social, and communication sciences are needed to explore genomic-modulated responses to old and new behavioral interventions, adherence to therapies, decision making across the continuum, and effective use in health care. Implementation science, health services, outcomes research, comparative effectiveness research, and regulatory science are needed for moving validated genomic applications into practice and for measuring their effectiveness, cost-effectiveness, and unintended consequences. Knowledge synthesis, evidence reviews, and economic modeling of the effects of promising genomic applications will facilitate policy decisions and evidence-based recommendations. Several independent and multidisciplinary panels have recently made specific recommendations for enhanced research and policy infrastructure to inform clinical and population research for moving genomic innovations into the cancer care continuum. An enhanced translational genomics and population sciences agenda is urgently needed to fulfill the promise of genomics in reducing the burden of cancer.

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The Widening Gap between Basic Genomic Discoveries and Their Impact on the Population Burden of Cancer

Advances in genomics and other "omics" fields are ushering in a new era of clinical practice in cancer care and prevention including better tumor classification, prognostic markers, predictive indicators of drug response, and the development of new drug therapies, and strategies for monitoring disease (1–4). For decades, many genes have been known to be related to cancer susceptibility, with a strong integration of medical genetics into oncology practice (5). However, the new tools of genomics (including large-scale genotyping, sequencing, as well as the study of gene expressions, proteomics, epigenomics) in both germ cell and cancer tissues are paving the way for a more personalized practice of cancer care involving the development of targeted therapies as well as the identification of diagnostic markers for early detection and prognosis (1, 2, 6). Numerous genetic variants have been discovered in relation to cancer etiology using population-based genome-wide association studies (GWAS; ref. 7). In addition, many genome-based tests, including personal genome profiles, are already available and some are marketed directly to consumers (8). In an online knowledge base of all new genome-based tests and applications that have either reached the commercial marketplace, or are under development in clinical trials, there are more than 250 new tests in the past year (as of May 1, 2011), most of which are related to cancer (9). Nevertheless, translation of these discoveries into clinical practice and health benefits has been slow (3). In contrast to the implementation of testing for high-penetrance alleles in those with a family history where benefit to individuals and families has been clear, implementation of testing for low-penetrance alleles and other...
complex biomarkers has unclear benefits and risks. Skepticism still abounds as to the near term value of this emerging technology to reduce the burden of cancer. This can be attributed to a number of factors, including incomplete information on biological pathways and functions, genotype-outcomes relationships, gene-environment and gene-drug interactions, clinical utility of genomic information in improving health outcomes, as well as behavioral and social factors affecting comprehension, uptake, and impact. There is also a lack of understanding of the validity and utility, effectiveness and cost-effectiveness of genomic applications in cancer care and prevention compared with existing standards of care and prevention that do not use genomic approaches (10). Finally, there has been very little information to inform best approaches to implement genomic applications in practice; ensure quality of testing and decision-making processes; educate providers, patients, and the general public; influence public policy; and measure impact on population health outcomes (11–14). In the setting of a U.S. healthcare system that does not provide even basic primary care to a substantial proportion of the population, a strong case needs to be made why, at this point, we should add genomic medicine to the mix. Hence, we see an important emerging role for population sciences not only in facilitating translation of genomic discoveries but also in providing an important scientific perspective for assessing the promise and potential unintended consequences of genomics in cancer control and prevention.

The Emerging Role of Population Sciences in Closing the Genomics Translation Gap

The path from basic science discovery to improved population health outcomes involves several overlapping and nonlinear phases of translational research as described in detail elsewhere (15, 16). Translational research is guided by knowledge synthesis and evidence-based recommendations as shown in Figure 1. Traditionally, research investments are heavily concentrated in discovery (T0) and the first phase of translation (T1 or bench to bedside; ref. 16). The outcomes of discovery and early translational research are promising tests, drugs, and other interventions (e.g., policy or environmental) that need to be evaluated for their validity and utility in clinical and population settings. To fulfill the promise of these applications to improve health, a robust "post-bedside" translational research agenda is needed to evaluate the efficacy of the new applications leading up to evidence-based recommendations and policies for their use (T2), to conduct implementation and dissemination science to move discoveries into practice and control programs (T3), and to assess effectiveness, cost-effectiveness, and outcomes at the population level (T4; ref. 15, 16; summarized in Fig. 1). To achieve a post-bedside translational research agenda, population sciences are crucial. Population sciences encompass multiple disciplines, including among others, epidemiology (17, 18), behavioral, social and communication sciences (19, 20), implementation and dissemination research (21), health services and comparative effectiveness and outcomes research (22), and regulatory science (23). Population sciences are involved at each step of the translational research continuum and their role predominates in the latter phases of translation (T2 and beyond; ref. 16). Even though population sciences have traditionally made individual contributions to advancing cancer genomics, the influence of these disciplines is best realized when working together with basic and clinical sciences as part of "team" or transdisciplinary science (24). In the rapidly moving field of cancer genomics, randomized clinical trials (RCT) may not be always feasible or...
affordable to establish efficacy and effectiveness of new interventions. Although RCTs have been the primary source of information on the predictors of treatment efficacy, adverse outcomes and safety, such studies often are of limited size and duration making it difficult to study rare and long-term events such as cancer and effects of cancer treatment, and they also often under-represent patients with chronic or comorbid health conditions, advanced age, socioeconomic disparities, and diverse ethnicities. In many situations, data (such as on comorbid conditions and lifestyle factors) and specimens may not be available or collected in adequate numbers within existing clinical trials and preclude ancillary studies to answer important clinical questions relevant to cancer genomics. Therefore, well-conducted observational population-based studies, pragmatic and adaptive trials (25–27), carefully monitored natural experiments, simulation modeling (28), and studies based on electronic health records in health care systems (29) will become even more important research tools to complement RCTs in translational genomics in the years to come.

Table 1 illustrates how selected population sciences can address scientific questions that can help close the translation gap of how genomic discoveries contribute to the cancer care continuum, both in healthy and affected persons in community and cancer care settings. In primary care and population settings, knowledge of genes involved in cancer etiology can be used in risk assessment, targeted prevention, and early detection as well as reducing the burden of cancer risk factors based on genetic information relevant to behavioral, pharmacologic, and environmental interventions. In cancer care settings, molecular characterization of tumors, prognostic indicators, and pharmacogenomic testing can be used to enhance the safety and effectiveness of cancer therapeutics and improve health outcomes.

We then use several examples from population sciences with a specific case approach focus on Lynch syndrome to illustrate the progression along the T1–T4 continuum. For T1 research, through National Cancer Institute (NCI) funded epidemiologic consortia, genome-wide association studies have led to the uncovering and risk characterization of numerous low penetrance genes for cancer etiology (30–37). These findings are giving important clues regarding mechanisms of cancer etiology and pathogenesis, with the potential for discovery and development of new intervention targets. For T2 research, a prominent example in cancer is the HER-2/neu oncogene; Slamon and colleagues show that the amplification of HER-2/neu oncogene correlates with a shorter time to relapse and lower survival rate in women with breast cancer in 2 independent observational study cohorts (38). These studies led to the development and approval of the target monoclonal antibody Herceptin for the treatment of breast cancer (39). Additional examples of T2 research include recent population-based studies that have evaluated and synthesized information on various prognostic, pharmacogenomic, and predictive genomic markers leading to evidence-based recommendations for use in practice. Another example is KRAS mutational analysis in the treatment of colorectal cancer. Two observational studies showed that mutations in the KRAS gene were associated with nonresponse in patients treated for metastatic colorectal cancer (CRC) with Cetuximab. This led to confirmatory studies conducted on specimens collected in completed RCTs (40, 41). In behavioral science, there is an evolving literature at the intersection of behavior, genes, and cancer. For example, there have been suggestions that dysregulation in the ras proto-oncogene might play a role in the observed association between depression and later onset of cancer (42). In T3 research, there is a rich literature on the psychosocial factors relevant to counseling for BRCA1 and treatment decisions (e.g., refs. 43–45). The impact of knowledge of low penetrance genes for colorectal cancer on screening behavior and quality of life was recently investigated by Ramsey and colleagues in a population-based study (46). More recently, Bloss and colleagues investigated the psychobehavioral impact of personal genome profile tests available directly to consumers on health individuals seeking these tests (8). In T4 research, multicenter follow-up studies have documented in “real world” settings how implementation of validated genomic applications can reduce the burden of cancer (e.g., showing drastic reduction of mortality with prophylactic surgery among BRCA1 patients in a multicenter observational cohort study; ref. 47).

A specific aspect of T3 research is assessing how consumers will process and make use of genomic information, particularly given its wide availability. Effective comprehension of this information requires a high level of health literacy and numeracy, yet significant portions of the population do not achieve this high level (48). Moreover, a host of psychologic processes can influence responses to the information. For example, some have cautioned that smokers who learn that they do not possess the CYP2A6 polymorphism (which has been linked to tobacco dependence) might be less inclined to quit (49), and smokers who believe that lung cancer is genetically predetermined might also be less interested in quitting (50). Genetic risk information could be interpreted differentially depending upon beliefs in fatalism, cultural beliefs, and mental models of disease.

Lynch syndrome illustrates how multiple population sciences have converged to address epidemiologic, knowledge synthesis, and implementation issues influencing both affected patients and their asymptomatic relatives along the T1–T4 continuum. Lynch syndrome is a relatively common group of autosomal dominant conditions, accounting for approximately 3% of all CRC cases in the United States (51). In 2009, the independent multidisciplinary Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group recommended screening for Lynch syndrome in all newly diagnosed CRC cases to reduce morbidity and mortality in family members (52). This is based on systematic knowledge synthesis of epidemiologic information of
<table>
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<th>Scientific disciplines</th>
<th>General population/primary care</th>
<th>Cancer care</th>
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<tr>
<td>I. Epidemiologic and clinical research (T1–T2)</td>
<td>Cohort and case–control population studies can identify and characterize genetic risks, interactions with modifiable risk factors, and evaluate performance and added value of genomics as cancer risk predictors; these studies can also lead to biological insight on causes and pathways in cancer development; as well as inform population surveillance</td>
<td>Follow-up observational studies in cancer care settings assess how tumor and germ line genomic factors can predict treatment response, side effects, prognosis, recurrence, mortality, and quality of life indicators; evaluate how these factors interact with nongenomic factors in predicting various outcome; these studies can also lead to biological insight into pathways of cancer progression and response to various interventions</td>
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<td>Examples</td>
<td>Numerous recent findings from GWA studies of various cancers (30–37)</td>
<td>Mutations in the KRAS gene is associated with nonresponse in patients treated for metastatic CRC with Cetuximab (38, 39) HER2 discovery and correlation with outcomes led to the development of a targeted monoclonal antibody, Herceptin, which is now part of breast cancer treatment (40, 41)</td>
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<td>II. Behavioral, social and communication sciences</td>
<td>Studies that assess public and provider understanding of genomic information, evaluate how genomics can improve risk communication and health behavior change, and use genomics to identify behavioral and environmental intervention targets</td>
<td>Studies that assess patients’ understanding and use of genomic information to improve decision making regarding treatment options, assess how behavioral, communication and social factors can modulate impact of targeted genomic-based interventions to motivate health behavior and environmental changes</td>
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<td>Examples</td>
<td>Assessing the psychobehavioral impact of personal genomic profile tests on healthy individuals (8)</td>
<td>Assessing psychologic predictors of BRCA counseling and testing decisions among African-American women (44)</td>
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<td>III. Knowledge synthesis and evidence-based recommendations</td>
<td>Systematic reviews, meta-analysis and modeling of basic, clinical, and population data to guide evidence recommendations on use of genomic information in reducing cancer occurrence as well as inform additional research and stakeholder decision making</td>
<td>Systematic reviews, meta-analysis and modeling of basic, clinical, and population data to guide evidence recommendations on use of genomic information in improving cancer care and outcomes, as well as informing additional research and stakeholder decision making</td>
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<tr>
<td>Examples</td>
<td>EGAPP knowledge synthesis and recommendation that all new cases of CRC be tested for Lynch syndrome to reduce CRC morbidity and mortality in relatives (52)</td>
<td>EGAPP knowledge synthesis and recommendation that all breast cancer gene expression profiles have insufficient evidence to drive treatment of breast cancer in women called for RCTs to be done (63)</td>
</tr>
<tr>
<td>IV. Health services, comparative effectiveness and outcomes research and implementation science</td>
<td>Studies that assess multilevel determinants of implementation, dissemination, and outcomes of genomic information in reducing the population burden of cancer; these include provider and consumer education, policies, coverage, access to services, and cost-effectiveness analyses. Understanding ways to of evidence recommendations (personal, familial, community, and health systems)</td>
<td>Studies that assess multilevel factors for implementation and outcomes of using genomic information in cancer care settings. These include patient and provider factors, health care organization factors, policies, coverage and access, and cost-effectiveness analyses. Understanding ways to increase uptake of evidence recommendations (evidence on rapidly learning healthcare systems)</td>
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<tr>
<td>Examples</td>
<td>Cancer prevention and screening practices among women at risk for hereditary breast and ovarian cancer in community settings (43)</td>
<td>Multicenter follow-up study documenting drastic decline in on cancer screening and early mortality in BRCA1 carriers following prophylactic surgery (47)</td>
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the prevalence, penetrance, morbidity and mortality in these cases, and findings from intervention studies coupled with early detection in relatives (53, 54). Cost-effectiveness analyses have provided additional information on the value of screening for Lynch syndrome in the population (55). There are multiple challenges for exploring how to implement such a recommendation that will require additional data from pilot studies. To that end, the Centers for Disease Control and Prevention (CDC) in collaboration with NCI convened a multidisciplinary working meeting surrounding the issues in implementation of Lynch syndrome screening (Bellcross and colleagues, submitted). Challenges at individual, family, system, and policy levels were identified at the meeting leading to clinical and population research strategies. Challenges include lack of provider knowledge of Lynch syndrome and testing issue, ethical issues related to informed consent among probands, use of genetic services, responsibility and psychologic impact of cascading from probands to relatives (recently documented by Hadley and colleagues; ref. 56); patient, provider and relatives' compliance, public health and policy infrastructure needs, as well as cost-effectiveness for implementation. Thus, population sciences will inform the evolving knowledge for implementation and evaluation of Lynch syndrome cascade screening.

Limited Investment in Translational Genomics and Population Sciences

We recently published a portfolio analysis of cancer genomic research funded by NCI showing that less than 2% of funded research is post "bench to bedside" (Fig. 2; ref. 16). Moreover, less than 1% of published cancer genomic research is post-bedside (16). Although epidemiologic studies are well represented in discovery and early translation through the numerous consortia that NCI has funded, they, along with other population disciplines are severely underrepresented in T2 and beyond. Using funding provided through the American Recovery and Reconstruction Act, NCI has tried to fill part of the translation gap through investment in comparative effectiveness research (CER). In 2009, NCI funded a network of 7 research groups to carry out knowledge generation and synthesis projects in CER in genomic medicine (57). Examples of these projects include: (i) enabling efficient and accurate collection and integration into electronic medical records of personal, family, and genomic information for risk assessment and delivery of decision support to providers and patients; (ii) conducting CER on the genomics of CRC including evaluating the cost-effectiveness for genetic testing of Lynch syndrome and KRAS testing in CRC treatment management; (iii) developing biospecimen and data registries to support evidence generation and clinical effectiveness research for evaluating pharmacogenomic markers in lung and breast cancer; (iv) developing an information infrastructure for CER; (v) CDKN2A/p16 testing and adherence to melanoma prevention behaviors; (vi) collaboration with external stakeholders, decision modeling, database linkage, ethics, policy, and clinical trial design to leverage the Southwest Oncology Group clinical trials network; and (vii) clinical validity and utility of genomic testing for targeted chemoprevention for prostate cancer. Although
Table 2. Synopsis of recommendations from recent selected independent and NIH sponsored multi-disciplinary panels and working groups for enhancing the population sciences agenda in cancer translational genomics

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<th>Workshop/panel</th>
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<th>Recommendations</th>
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<tr>
<td>President’s Council of Advisors on Science and Technology (66)</td>
<td>Identify scientific priorities for personalized medicine</td>
<td>Integrated nationwide network of standardized biospecimen repositories, research for validating clinical utility, large U.S. population cohort study investigating genetic and environmental health impacts (selected recommendations)</td>
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<td>Institute of medicine report on cancer biomarkers (67)</td>
<td>Review cancer biomarker research, development and implementation</td>
<td>Develop high quality biorepositories in prospectively collected samples, create well-defined consensus standards and guidelines for biomarker development validation and use, establish high quality population-based assessments of efficacy and cost-effectiveness of biomarker tests (selected recommendations)</td>
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<tr>
<td>Institute of medicine report on CER (68)</td>
<td>Establish a definition of CER and a national top 100 priority list</td>
<td>Compare the effectiveness of adding new biomarkers (including genetic information) with standard care in motivating behavior change and improving clinical outcomes; compare the effectiveness of genetic and biomarker testing and usual care in preventing and treating breast, colorectal, prostate, lung, and ovarian cancer (selected recommendations)</td>
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<td>NIH-CDC (69)</td>
<td>Enhancing the scientific foundation for using genetic risk profiles in risk assessment and disease prevention</td>
<td>Develop scientific standards for personal genomic tests; enhance multidisciplinary population research; enhance credible knowledge synthesis and dissemination to providers, consumers and policy makers; explore the value of personal utility of genetic information</td>
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<td>NCI pharmacoepidemiology and pharmacogenomics working group (70)</td>
<td>Setting a research agenda in pharmacoepidemiology and pharmacogenomics to accelerate translation</td>
<td>Develop and support a knowledge synthesis study group; support observational studies that assess genomic and nongenomic factors affecting treatment response and adverse effects; support research on the utility of promising pharmacogenomic applications in practice; support efforts that integrate basic, clinical and population research</td>
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<td>NHGRI multidisciplinary panel (71)</td>
<td>Priorities for behavioral, social and communications research</td>
<td>Research to improve the public’s genetic literacy to enhance consumer skills, assess if genomic information improves risk communication and adoption of healthy behaviors more than current approaches, explore if genomics can lead to new behavioral intervention targets, consider multiple levels of influence that contribute to public health problems</td>
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#### Table 2. Synopsis of recommendations from recent selected independent and NIH sponsored multidisciplinary panels and working groups for enhancing the population sciences agenda in cancer translational genomics (Cont’d)

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<td>NCI workshop (72)</td>
<td>Examine the state of health services research in cancer cellular, molecular and genomic technologies; identify priorities for expanding knowledge base</td>
<td>Development of a comprehensive research agenda on health and safety endpoints, utilization patterns, patient and provider preferences, quality of care and access, disparities, economics and quality of life</td>
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<tr>
<td>NCI genomics and personalized medicine CER methods working group (Goddard, in preparation)</td>
<td>Identify CER approaches that can be employed to answer questions about cancer genomic applications faced by various stakeholders</td>
<td>Several CER approaches can be applied to cancer genomics including evidence generation and synthesis, stakeholder engagement, in trials and observational studies; decision modeling and economic analyses</td>
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Knowledge Synthesis to Drive Genomics Research, Policy and Practice

Even though many genomic applications are being developed, most currently do not have sufficient evidence to evaluate their clinical validity and utility in practice. The rapid emergence of information on genomic applications requires studies in well-defined population groups to evaluate their significance and utility for reducing the burden of cancer as well as advanced methods of systematic reviews using biological, clinical, and population data. Additional types of reviews can address concerns of clinicians, health policy makers, health plan administrators, citizen advocates, and other stakeholders, and answer specific questions on what works for what subgroups under what conditions to move genomics into large-scale applications (59–61).

To drive research, policy and practice, CDC, in collaboration with NCI and other partners, sponsors an independent multidisciplinary, nonfederal working group (EGAPP; ref. 62). The EGAPP working group systematically reviews, synthesizes, and updates evidence of validity and utility of genomic applications and makes recommendations for appropriate use. Several recommendations have been issued to date and more are under way (a total of 10, 6 of which are relevant to cancer, including “insufficient evidence” on gene expression profiling in the management of breast cancer; ref. 63). In the process of knowledge synthesis, stakeholder engagement is crucial to understanding various perspectives on how much evidence is needed to cross an evidentiary threshold from research to clinical practice (64). An enhanced collaboration is needed among basic scientists, industry, consumers, clinicians, regulators, payers, and policy decision makers using a population perspective (65). This is currently being undertaken by the NCI funded comparative effectiveness research network in cancer genomic medicine (Deverka and colleagues, in preparation).

Recommendations from Recent Multidisciplinary Panels for an Enhanced Population Science Agenda in Translational Genomics

Table 2 summarizes the recommendations for enhancing the population sciences agenda in genomic medicine from several independent panels such as the President’s Council of Advisors on Science and Technology (66), the Institute of Medicine (reports on cancer biomarkers; ref. 67), and CER (68), as well as multidisciplinary workshops sponsored and cosponsored by the NCI. The workshops covered a wide variety of topics such as the scientific foundation for the use of genetic risk profiles in risk assessment and disease prevention (69); accelerating discovery and translation of pharmacogenomic applications in the cancer care continuum (70); the role of behavioral, social and communication sciences in fulfilling the potential of genomic applications (71); the use of health services research in implementation and evaluation of genomic applications in cancer (72); and the use of CER methods in outcome evaluations of genomic applications as well as evidence synthesis and modeling of effects (Goddard in preparation). In addition, issues relevant to implementation in community settings need to be addressed early in the translational research cycle and not delayed until research has been completed to find out major flaws that
can interfere with the implementation of genomic applications into practice (73, 74). The emerging picture is that of a rich and nuanced translational genomics research agenda firmly rooted in population sciences. This research agenda can supplement and extend, now and in the future, cancer genomics research in basic sciences and clinical trials.

Concluding Remarks

To summarize, there is a large and widening gap between the promise of cancer genomics and the current reality of its impact on cancer care and prevention. We have highlighted the increasing role and need for multiple population sciences to close this translation gap. Population disciplines include, among others, epidemiology, behavioral, social and communication sciences, implementation sciences, health services and CER. Nevertheless, the current investment in cancer translational genomics research in these disciplines is severely limited. Several recent independent panels and NIH sponsored workshops have recommended increased emphasis and investment in these translational genomics and population sciences. Ideally, such investment should be part of transdisciplinary groups, involving basic, clinical, and population sciences. Such an enhanced research agenda in genomics and population sciences is crucial to fulfill the promise of genomics in reducing the global burden of cancer in the 21st century.

Disclosure of Potential Conflicts of Interest

The opinions in this article reflect those of the authors and do not necessarily reflect the official position of the CDC or NCI.

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