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Integration of Molecular Pathology, Epidemiology, and Social Science for Global Precision Medicine

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Summary

The precision medicine concept and the unique disease principle imply that each patient has unique pathogenic processes resulting from heterogeneous cellular genetic and epigenetic alterations, and interactions between cells (including immune cells) and exposures, including dietary, environmental, microbial, and lifestyle factors. As a core method field in population health science and medicine, epidemiology is a growing scientific discipline that can analyze disease risk factors, and develop statistical methodologies to maximize utilization of big data on populations and disease pathology. The evolving transdisciplinary field of molecular pathological epidemiology (MPE) can advance biomedical and health research by linking exposures to molecular pathologic signatures, enhancing causal inference, and identifying potential biomarkers for clinical impact. The MPE approach can be applied to any diseases, although it has been most commonly used in neoplastic diseases (including breast, lung and colorectal cancers) because of availability of various molecular diagnostic tests. However, use of state-of-the-art genomic,

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Use of standardized official symbols: We use HUGO (Human Genome Organisation)-approved official symbols for genes and gene products, including BRAF, EGFR, KRAS, and PIK3CA; all of which are described at www.genenames.org. Gene symbols are italicized, and gene product symbols are non-italicized.

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epigenomic and other omic technologies and expensive drugs in modern healthcare systems increases racial, ethnic and socioeconomic disparities. To address this, we propose to integrate molecular pathology, epidemiology, and social science. Social epidemiology integrates the latter two fields. The integrative social MPE model can embrace sociology, economics and precision medicine, address global health disparities and inequalities, and elucidate biological effects of social environments, behaviors, and networks. We foresee advancements of molecular medicine, including molecular diagnostics, biomedical imaging, and targeted therapeutics, which should benefit individuals in a global population, by means of an interdisciplinary approach of integrative MPE and social health science.

Keywords

clinical outcome; disparity; epigenetics; interdisciplinary; molecular pathologic epidemiology; network analysis; personalized medicine; social medicine

Introduction and Purpose

The field of molecular pathology has advanced our understanding of disease pathogenesis. The disease classification system increasingly incorporates new knowledge on pathogenesis, to better predict the natural history and response to therapy or intervention. Thus, molecular pathology and diagnostics are playing a pivotal role in personalized treatment and management of patients. Along this trend, the concept of precision medicine has emerged and become very popular in the medical community.[1,2]

It should be of note that the field of “epidemiology” has been transforming for recent decades. It is unfortunate that “epidemiology” has been commonly regarded as a field of study to merely describe incidence, distribution and risk factors of diseases. Thus, one can still see a book chapter (written by a non-epidemiologist) on “epidemiology of breast cancer” which only describes incidence of colon cancer in different parts of the world, and its known risk factors. However, the field of “epidemiology” has become a much more influential core methodologic science to study how and what we can do research on big data of health and diseases in human populations. Big data of health and diseases can encompass all data on health and diseases in people which have been and will be accumulated in health-related research studies as well as hospitals around the world. In particular, the evolving field of “causal inference” in epidemiology enables us to mathematically simulate a purely observational data into a trial dataset regarding risk factors under question, and gain new insights on causal associations.[3–7] For instance, Mendelian randomization approach (one of causal inference methods)[8–13] can help us infer causality of the relationship of a common risk factor (such as obesity) with a specific type of cancer. Hence, the common notion of epidemiology (as science of mere description of disease incidence, distribution and risk factors) has become obsolete.

Since epidemiology is the field of study of human health and diseases, the emerging molecular disease classification system needs to be incorporated into epidemiology, which also necessitates the development of new research framework and analytic methodologies.

Along with this trend, integration of molecular pathology and epidemiology has led to the formation and development of “molecular pathological epidemiology (MPE)”.[14–16]

In parallel with the development of molecular pathology and epidemiology, social science disciplines such as sociology, economics, and psychology have also advanced. In addition, interdisciplinary areas such as health economics, health psychology, medical sociology, and medical anthropology have been developing. Social science aims to understand the human society, social relationship of humans, and their behavioral patterns. Since biological processes in humans follow the nature's law, the interdisciplinary approach between natural and social sciences can advance our understanding of the humans.

In this general trend, social epidemiology, which was first described in 1950,[17] has developed as a special discipline that studies social distribution and determinants of health with various concepts and theories.[18] One of major goals of social epidemiology is to address social inequalities in health and diseases.[19–23] For example, social epidemiologists have identified that social contexts such as lower socioeconomic status, larger income inequality and poor social support are major risk factors for population health and various diseases.[24–29] On the other hand, social scientists such as economists and sociologists have investigated socioeconomic status, income inequality, and social support themselves.[30,31]

Since social epidemiology concerns health and diseases of individuals in populations, molecular pathology and pathogenesis need to be fully incorporated into social epidemiology in the future. Despite progresses of both molecular medicine and public health science, we are facing expanding knowledge gaps,[32] as scientific fields are, in general, increasingly compartmentalized into narrower disciplines.[16] In this article, we propose a trans-multidisciplinary integration of molecular pathology, epidemiology, and social science (Figure 1), and discuss advantages and new opportunities, as well as challenges.

Major advancements of science have commonly occurred with an integration of multiple fields, which may seem dissimilar. Such interdisciplinary integrations include biomedical engineering (biomedicine and engineering), biophysics (biology and physics), computational biology (computer science and biology), health economics (health science and economics), pharmacogenetics (pharmacology and genetics), to name just several. In addition, it has often happened that a certain scientific field can be advanced and transformed by experts from other fields, which can attest to benefits of gaining paradigm-shifting viewpoints from experts in other disciplines. The main purpose of this article is to explain why integration of MPE and social epidemiology can be beneficial to global populations.

Molecular pathological epidemiology (MPE)

Use of molecular pathology techniques in epidemiology research became common in 1990s and 2000s, typically under the umbrella term of molecular epidemiology.[33–37] Molecular pathological characterization of disease such as cancer is crucial to link risk factors to plausible pathogenic mechanisms, to estimate the natural history of an individual tumor, and to better predict the response/resistance to treatment or lifestyle intervention to maximize its benefit to each individual. Although the “molecular epidemiology” term had been

convenient in including molecular pathology analyses, most molecular epidemiology studies have used molecular analyses of exposures (including germline genetics) and relied on disease data without detailed molecular pathological assessment. This situation led to an underestimation of unique features of molecular pathology analysis in epidemiology, and limited the development of concepts and methods.[16] In fact, use of molecular pathology provided not only unprecedented opportunities to link exposures to molecular pathologic signatures but also various challenges including underdeveloped statistical methods and a need for standardizations of laboratory methods and procedures. Because epidemiology is based on the premise that individuals with the same diagnosis have similar causes and disease evolution, it is essential that epidemiologic research rely on modern molecular classification of disease. Thus, it is increasingly necessary to consider disease heterogeneity more explicitly in modern epidemiology.

In this general trend, since 2010, MPE has emerged as an integrative field of molecular pathology and epidemiology,[14,15] which requires new research frameworks, methodological development, and standardized research guideline.[16] MPE integrates analyses of exposures, host factors (including immunity) and dysfunction of cells or organ unit.[38] MPE is conceptually based on the unique disease principle,[38] and the disease continuum theory.[39] The former posits that each disease process is unique given a diversity of exposures (exposome) and host response,[38] while the latter attests to not only complex cause and consequence effects of various disease processes on each other within one individual, but also a continuum of disease phenotypes (of a certain disease) across individuals.[39] The emerging field of MPE provides not only conceptual advancements but also new framework for the development of epidemiologic methods. To address complex hypothesis testing regarding etiologic heterogeneity, efforts have been ongoing to develop efficient and practical statistical methods that can be applied to various research settings. [40–48] General strengths and caveats of the MPE approach have been discussed in detail elsewhere.[15,16] As strengths, MPE enables us to link putative etiologic exposures to disease molecular signatures, to refine effect estimates for specific exposure-subtype associations,[15] and hence, to enhance causal inference. In fact, the MPE approach can decipher what appear to be paradoxical findings,[49] which represent vexing problems in not only clinical medicine but also the causal inference area of epidemiology.[50–52] As caveats, MPE research is prone to multiple hypothesis testing by subgroup analyses, and there are paucities of interdisciplinary experts, training programs and international forums dedicated to the MPE field, which results in lack of international research guideline.[16,53] Although MPE has been most commonly applied in cancer research, because of a wide variety of available molecular pathology tests for cancer, MPE can be applied to virtually all disease areas,[39] including non-neoplastic diseases,[54–56] as both pathology and epidemiology are method-based disciplines not limited by disease or organ system.[16] A further integration of microbiology, immunology and MPE has also been explored to study cancer etiologies.[57–65] Microbial subtypes can be linked to exposures and host factors by the MPE approach.[66] The idea and concept of MPE have been accepted and applied by a large number of scholars in the medical and public health science literature.[42,64,67–134] Its importance has been discussed in well-established international meetings,[135–137] as well as the International MPE Meeting Series that has a focus on MPE.[138]

Fundamentally, pathology and epidemiology share the same goal of elucidating disease etiologies to better understand diseases, while pathology and epidemiology use different approaches to achieve goals.[16] The presence of the field of MPE proves that integration of the two fields can create a large intersection (between the two fields) where the two fields synergistically function.[16]

Primarily, MPE focuses on the inherent heterogeneity of disease processes and pathogenesis in individuals. As disease evolution process in each individual is influenced by a unique combination of endogenous and exogenous exposures (i.e., the exposome) and their interactions with both normal and dysfunctioning cells, a disease itself is unique to each individual.[38,139] Nonetheless, persons who share similar molecular signatures of disease likely share similar etiologies and pathogenic mechanisms. Thus, in the framework of MPE, subgrouping of disease patients who share similar pathologic signatures enables us to link putative risk factors to specific pathogenic mechanisms, which also encompasses microbial contribution,[59,140,141] and response of the immune system to the disease.[58] Integration of MPE into genome-wide association studies (GWAS) has been termed the GWAS-MPE approach,[15,116] which can refine associations for specific subtypes and uncover hidden associations when heterogeneous subtypes are not separated. As the MPE approach can be applied to various population research settings, a variety of subfields of epidemiology can incorporate molecular pathology to represent new disciplines; such examples include social MPE (discussed in this article), lifecourse-MPE,[142] causal inference-MPE,[49] pharmaco-MPE, and environmental-MPE.

Here, we discuss colorectal cancer which represents one of the most commonly studied diseases in MPE, and numerous studies on colorectal cancer have shown the utility of molecular disease classification in clinical practice and epidemiologic research.[143–148] In fact, accumulating evidence from MPE studies indicates that different risk factors play roles in the development of different subtypes of colorectal cancer, and that response to treatment or other interventions depends on cancer subtypes reflecting inherent heterogeneity of the disease.[15] For example, *KRAS* mutation status in colorectal cancer cells can be used as a biomarker to select patients for targeted therapy with anti-EGFR antibody Cetuximab, as studies have shown that a subset of *KRAS*-wild-type cancer cases respond to Cetuximab in contrast to *KRAS*-mutated cancers that are virtually unresponsive to Cetuximab.[149–152] Therefore, the pretreatment examination of cancer subtype (i.e., *KRAS* genotyping) may enable not only better personalized precision medicine at the individual level, but also improved resource allocation at the population level. MPE research has also shown that regular aspirin use may be beneficial to not only certain individuals in general populations, [153–156] but also patients with particular subtypes of established diseases such as colorectal cancer.[157,158] As one example, aspirin use may be associated with a greater survival benefit in patients with *PIK3CA*-mutated colorectal cancer compared to those with *PIK3CA*-wild-type cancer,[158,159] suggesting that aspirin can be beneficial for a selected group of patients.[160–164] Hence, MPE research can help identify tumor *PIK3CA* mutation as a potentially useful biomarker.[39,53,165]

Future of medicine and epidemiology

In the future, as medical practice will increasingly utilize the precision medicine approach based on molecular pathology diagnostics, the term “medicine” will effectively indicate precision medicine. Likewise, as molecular pathologic diagnosis is increasingly prevalent in diagnosis and classification of virtually all diseases,[39] the concept of MPE will prevail in the field of epidemiology, likely to the point where epidemiology will mean MPE. This change in the mindset of epidemiologists may not readily occur but require a new education system to integrate pathology and epidemiology.[16] Nonetheless, this change will eventually happen, and must happen in order for epidemiology to keep up with advancements of biomedical sciences.

Molecular pathological epidemiology (MPE) can enhance global health science

Research in social epidemiology and global health sciences has been traditionally conducted, utilizing large databases of health and diseases typically without modern molecular characterization of diseases. There is a necessity of substantial accumulation of data on molecular disease subtyping before we utilize the MPE approach in large population settings. As integration of World Health Survey and the MPE paradigm has been discussed, [118] MPE research on global population databases will enable us to decipher etiologies of diseases and address health disparities in a global scale, together with the social science approach.

In addition, MPE has a substantial potential to change the way in which global disease control can be addressed. Predicting future trends of molecular pathological change of disease in different populations can be a practical application. For example, colonoscopy screening has been shown to reduce colorectal cancer risk.[166–168] However, its preventive effect may differ according to molecular subtypes of colorectal cancer, and may be less effective for colorectal cancer subtype with microsatellite instability (MSI) [167,169], which is associated with high-level CpG island methylator phenotype (CIMP-high).[143,170–175] Studies have consistently shown that smoking is a risk factor for MSI-high colorectal cancer.[176–182] Thus, colonoscopy screening may be less effective in smokers than in non-smokers, because smokers tend to develop MSI-high cancer subtype which is less effectively prevented by colonoscopy. Evidence also indicates that MSI-high and CIMP-high subtypes of colorectal cancer are associated with older age at diagnosis. [152,183–189] Considering both aging populations and increasing prevalence of colonoscopy screening practice, these results enable us to predict that the fraction of the MSI-high subtype in colorectal cancer will increase in the future. The predicted prevalence of molecular pathological subtypes will help in forecasting the long-term consequence of current procedures of colonoscopy for cancer screening. It is also indicated that it is necessary to develop more effective prevention strategies against MSI-high colorectal cancer. Hence, MPE research can give mechanistic rationale and evidence for tailored cancer screening strategy according to lifestyle risk factors, as well as global trend projection of molecular subtype frequency and distribution in the future.

Challenges of molecular pathological epidemiology (MPE) approach in context of global social diversities

Although the MPE approach can accelerate the more detailed and personalized approach in prevention of disease and mortality, MPE may face two major challenges when we aim to achieve global disease control. First, although molecular pathology tests will change routine clinical practice and enable the MPE approach as ubiquitous epidemiology framework in the near future,[16,53] it will likely augment socioeconomic inequalities and disparities. The molecular pathological tools are generally costly, which may pose a considerable challenge in resource-poor populations.[190–192] Inequalities in healthcare are increasing between developed and developing countries and between rich and poor populations in one country. [193,194] Molecular pathology and MPE approaches may enlarge already existing health disparities.[190] Although evidence from MPE research on resource-rich populations may be generalizable to resource-poor populations, there is a possibility of substantial effect modification by socioeconomic or health disparity status, which will make it impossible to directly translate findings from resource-rich populations into resource-poor populations.

Second, social, political, and cultural factors such as socioeconomic status, cigarette tax rate, and cultural acceptance of “Westernized” mass consumption have not been adequately integrated into the current conceptual or practical model of MPE. As a result, implementation of health policies and health promotion programs based on evidence from MPE research may not happen smoothly as it should be. Although MPE research can provide evidence for actionable recommendations such as aspirin use and physical activity, especially for specific populations,[154,158,195–197] lifestyle or behavioral recommendations may not be readily implemented without considering the social background of individuals and a population. Some lifestyle habits and chemopreventive behaviors (such as aspirin use) can spread through social networks.[198] The social capital of a local community can also influence lifestyle factors such as physical activity levels. [199]

To address these two issues, integration of MPE and social epidemiology may be theoretically and practically feasible, which we will discuss in the next section.

Integrative approach of social epidemiology and molecular pathological epidemiology (MPE)

The main goal of social epidemiology is to identify social determinants of health and diseases. Social factors can influence and determine lifestyle and other exposure status of individuals, and implementation of healthy behavior can be greatly enhanced with consideration of social factors. As MPE has emerged, integration of molecular analysis of disease pathogenesis into social epidemiology can lead to deeper insights on social influences on pathogenic processes. For example, to decipher racial cancer disparities, genetic, social, lifestyle and hormonal exposures can be examined in relation to molecular subtypes of cancer (such as breast cancer), and the associations can be compared between racial groups.[200–206] Differences in molecular signatures of diseases can also be

examined between racial and ethnic groups.[206–209] To decipher the relationships of complex social factors and other epidemiologic exposures with molecular signatures of disease, substantial development of new methodologies (including network analyses and causal inference analyses) is needed. Network analysis approaches can be useful in analyses of not only social interaction networks but also biological interaction networks among cells and within a cell.

In the integrative approach of social epidemiology and MPE (which can be called “social MPE”), we aim to incorporate social, economic, cultural, behavioral and other exposures into the MPE model, and to identify socioeconomic and cultural determinants of molecular pathological changes. Figure 2 illustrates how each of social epidemiology and MPE can address weaknesses of the other field, to augment strengths of the integrated approach. In this integrative model, social epidemiology can give insights on social determinants of health and diseases, broaden impact of MPE research to a global scale, and address challenges in health disparities, whereas MPE can provide useful biological insights into disease heterogeneity and pathogenesis, refine effect sizes of associations, and enhance causal explanation of the pathways from social factors toward disease development. In addition, social epidemiologists and social scientists can monitor (1) if new sciences (such as MPE) can increase or decrease health disparity, (2) if new sciences can fit with existing social norms and political climates, or change them, and (3) if prevention or treatment strategies based on new sciences can be more or less cost-effective than those based on established sciences. In this sense, their effort can make new sciences more appropriate politically and ethically.

The proposed integrative approach (social epidemiology - MPE) aims to decipher which molecular subtype of disease (and to what degree) has the roots in social factors, and which disease subtype may be preventable by social and behavioral interventions. As it was not until 2010 that MPE emerged as a unique field,[14] studies which utilized the integrative social epidemiology - MPE approach remain rather uncommon. Nonetheless, it has been reported that *TP53*-mutated colorectal cancer, and *ESR1* (estrogen receptor 1; or ER)-negative breast cancer have been associated with lower socioeconomic status and social deprivation.[210–213] Moreover, “triple negative” type of breast cancer [*ESR1*-negative, *PGR* (progesterone receptor)-negative, *ERBB2* (HER2)-negative] has been associated with African American and Hispanic populations as well as the residence in socioeconomically deprived areas.[214–216] Hence, accumulating evidence suggests social etiologies of some of molecular pathologies. Nonetheless, since integration of social epidemiology and MPE has not been adequate to date, additional efforts are required to develop conceptual frameworks and practical guidelines. As one example, Khoury et al.[217] have proposed to integrate population sciences (epidemiology, behavioral, social, and communication sciences) into molecular pathology and precision medicine, which is a parallel trend with the social-MPE integration.

Successful transdisciplinary integration of MPE and social epidemiology requires collaborative efforts by experts in both fields who need to openly share and discuss their respective research viewpoints and insights. Certainly, a better understanding of the process of disease development caused by social and behavioral factors is their common goal. To

achieve seamless translation of the language and concepts across the disciplines, interdisciplinary education programs across pathology, epidemiology, social and behavioral sciences are needed.

Conclusions

We propose to integrate molecular pathology, epidemiology and social science (Figure 1). Currently, molecular pathological epidemiology (MPE) integrates molecular pathology and epidemiology, whereas social epidemiology integrates epidemiology and social science. MPE and social epidemiology can merge with the common core field of epidemiology. This integrative science, which may be called “social MPE”, can more adequately and more effectively address health disparities than any one field can. As the importance of the interdisciplinary approach has been recognized in various areas of science,[218–220] we have discussed the potential power and promise of integrating social epidemiology and MPE, based on the recent technological advancement and the development of molecular diagnostics and precision medicine. This trans-multidisciplinary integration of “social MPE” will enable us to better understand the biological consequences of socioeconomic and behavioral exposures at the molecular pathological level, and to identify more feasible, efficient and socially fair intervention plans to achieve a healthier and better world. As the field of molecular pathology will advance to study virtually all diseases, our improved knowledge of disease pathogenesis will be increasingly integrated into population health science. As a result, the MPE paradigm will become ubiquitous in epidemiology to the point where epidemiology and social epidemiology will essentially mean MPE and social MPE, respectively. We foresee advancements of molecular medicine, including molecular diagnostics, biomedical imaging, and targeted therapeutics in the future. These developments should and can benefit individuals in global populations, by means of an interdisciplinary approach of integrative MPE and social health science.

Expert commentary (the author's expert view on the current status of the field under discussion)

Use of molecular pathology and classification has been increasingly more common in medical and public health sciences. However, there have been increasing health disparities, as well as increasing knowledge gaps between molecular pathology, epidemiology, and social science. Because of recent success of integrative molecular pathological epidemiology (MPE), and integrative social epidemiology, integration of the three fields is feasible and can effectively address our knowledge gaps and global health disparities.

Five-year view (a speculative viewpoint on how the field will evolve in 5 years time)

In the next 5 years, important trends and directions in medical and health sciences are integrative holistic approaches, including molecular pathological epidemiology (MPE) and social epidemiology. To address globally increasing health disparities, integration of MPE and social epidemiology will become commonplace. There will be accumulations of data on molecular pathology of diseases in registries around the globe, which can be utilized for social MPE research in global settings. There will be more collaborations between molecular

pathologists, epidemiologists, biostatisticians, and social scientists, to address the disparities and achieve precision medicine and prevention in the global scale.

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References

- Collins FS, Varmus H. A New Initiative on Precision Medicine. *N Engl J Med*. 2015; 372(9):793–795. [PubMed: 25635347]
- Ashley EA. The precision medicine initiative: a new national effort. *JAMA*. 2015; 313(21):2119–2120. [PubMed: 25928209]
- Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology*. 2000; 11(5):550–560. [PubMed: 10955408]
- Rothman KJ, Greenland S. Causation and causal inference in epidemiology. *American journal of public health*. 2005; 95(Suppl 1):S144–150. [PubMed: 16030331]
- Vanderweele TJ, Hernan MA. From counterfactuals to sufficient component causes and vice versa. *European journal of epidemiology*. 2006; 21(12):855–858. [PubMed: 17225959]
- Hernan MA, Robins JM. Instruments for causal inference: an epidemiologist's dream? *Epidemiology*. 2006; 17(4):360–372. [PubMed: 16755261]
- Vanderweele TJ, Knol MJ. Interactions and complexity: goals and limitations. *Epidemiol Methods*. 2014; 3(1):79–81.
- Davey Smith G, Ebrahim S. 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol*. 2003; 32(1):1–22. [PubMed: 12689998]
- Schatzkin A, Abnet CC, Cross AJ, et al. Mendelian randomization: how it can--and cannot--help confirm causal relations between nutrition and cancer. *Cancer Prev Res (Phila)*. 2009; 2(2):104–113. [PubMed: 19174578]
- Sheehan NA, Didelez V, Burton PR, Tobin MD. Mendelian randomisation and causal inference in observational epidemiology. *PLoS Med*. 2008; 5(8):e177. [PubMed: 18752343]
- Taylor AE, Davies NM, Ware JJ, Vanderweele T, Davey Smith G, Munafo MR. Mendelian randomization in health research: using appropriate genetic variants and avoiding biased estimates. *Economics and human biology*. 2014; 13:99–106. [PubMed: 24388127]
- Vanderweele TJ, Tchetgen Tchetgen EJ, Cornelis M, Kraft P. Methodological challenges in mendelian randomization. *Epidemiology*. 2014; 25(3):427–435. [PubMed: 24681576]
- Thrift AP, Gong J, Peters U, et al. Mendelian randomization study of height and risk of colorectal cancer. *Int J Epidemiol*. 2015; 44(2):662–672. [PubMed: 25997436]
- Ogino S, Stampfer M. Lifestyle factors and microsatellite instability in colorectal cancer: The evolving field of molecular pathological epidemiology. *J Natl Cancer Inst*. 2010; 102(6):365–367. [PubMed: 20208016]
- Ogino S, Chan AT, Fuchs CS, Giovannucci E. Molecular pathological epidemiology of colorectal neoplasia: an emerging transdisciplinary and interdisciplinary field. *Gut*. 2011; 60(3):397–411. [PubMed: 21036793]
- Ogino S, King EE, Beck AH, Sherman ME, Milner DA, Giovannucci E. Interdisciplinary education to integrate pathology and epidemiology: towards molecular and population-level health science. *Am J Epidemiol*. 2012; 176(8):659–667. [PubMed: 22935517]
- Yankauer A. The relationship of fetal and infant mortality to residential segregation: an inquiry into social epidemiology. *Am Sociol Review*. 1950; 15:644–648.
- Berkman, LF.; Kawachi, I. *Social epidemiology*. Oxford University Press; New York, NY: 2000.

19. Krieger N. Theories for social epidemiology in the 21st century: an ecosocial perspective. *Int J Epidemiol*. 2001; 30(4):668–677. [PubMed: 11511581]
20. Oaks, JM.; Kaufman, JS. *Methods in Social Epidemiology*. Jossey-Bass; San Francisco: 2006.
21. Berkman LF. Social epidemiology: social determinants of health in the United States: are we losing ground? *Annual review of public health*. 2009; 30:27–41.
22. Galea, S. *Macrosocial determinants of population health*. Springer; New York: 2007.
23. Krieger, N. *Epidemiology and People's Health*. Oxford University Press; New York: 2011.
24. Wilkinson RG, Pickett KE. Income inequality and population health: a review and explanation of the evidence. *Social science & medicine*. 2006; 62(7):1768–1784. [PubMed: 16226363]
25. Kondo N, Sembajwe G, Kawachi I, Van Dam RM, Subramanian SV, Yamagata Z. Income inequality, mortality, and self rated health: meta-analysis of multilevel studies. *Bmj*. 2009; 339:b4471. [PubMed: 19903981]
26. Holt-Lunstad J, Smith TB, Layton JB. Social relationships and mortality risk: a meta-analytic review. *PLoS Med*. 2010; 7(7):e1000316. [PubMed: 20668659]
27. Uchino BN. Social support and health: a review of physiological processes potentially underlying links to disease outcomes. *Journal of behavioral medicine*. 2006; 29(4):377–387. [PubMed: 16758315]
28. Braveman PA, Cubbin C, Egerter S, et al. Socioeconomic status in health research: one size does not fit all. *JAMA*. 2005; 294(22):2879–2888. [PubMed: 16352796]
29. Nishi, A. *Social science & medicine*. 2016. Evolution and social epidemiology. in press/published online in 2015
30. Nishi, A.; Shirado, H.; Rand, DG.; Christakis, NA. *Nature*. 2015. Inequality and visibility of wealth in experimental social networks. in press (published online)
31. Breen R, Chung I. Income inequality and education. *Sociological Science*. 2015; 2:454–477. no issue number.
32. Bayer R, Galea S. Public Health in the Precision-Medicine Era. *N Engl J Med*. 2015; 373(6):499–501. [PubMed: 26244305]
33. Porta M, Malats N, Vioque J, et al. Incomplete overlapping of biological, clinical, and environmental information in molecular epidemiological studies: a variety of causes and a cascade of consequences. *Journal of epidemiology and community health*. 2002; 56(10):734–738. [PubMed: 12239196]
34. Sherman ME, Howatt W, Blows FM, Pharoah P, Hewitt SM, Garcia-Closas M. Molecular pathology in epidemiologic studies: a primer on key considerations. *Cancer Epidemiol Biomarkers Prev*. 2010; 19(4):966–972. [PubMed: 20332257]
35. Slattery ML. The science and art of molecular epidemiology. *Journal of epidemiology and community health*. 2002; 56(10):728–729. [PubMed: 12239192]
36. Bennett WP, Hussain SP, Vahakangas KH, Khan MA, Shields PG, Harris CC. Molecular epidemiology of human cancer risk: gene-environment interactions and p53 mutation spectrum in human lung cancer. *J Pathol*. 1999; 187(1):8–18. [PubMed: 10341702]
37. Renehan AG, Zwahlen M, Egger M. Adiposity and cancer risk: new mechanistic insights from epidemiology. *Nat Rev Cancer*. 2015; 15(8):484–498. [PubMed: 26205341]
38. Ogino S, Lochhead P, Chan AT, et al. Molecular pathological epidemiology of epigenetics: Emerging integrative science to analyze environment, host, and disease. *Mod Pathol*. 2013; 26(4): 465–484. [PubMed: 23307060]
39. Ogino S, Nishihara R, Vanderweele TJ, et al. Molecular pathological epidemiology is essential in studying neoplastic and non-neoplastic diseases in the era of precision medicine. *Epidemiology*. 2016 in press.
40. Chatterjee N, Sinha S, Diver WR, Feigelson HS. Analysis of cohort studies with multivariate and partially observed disease classification data. *Biometrika*. 2010; 97(3):683–698. [PubMed: 22822252]
41. Chatterjee N. A Two-Stage Regression Model for Epidemiological Studies With Multivariate Disease Classification Data. *Journal of the American Statistical Association*. 2004; 99:127–138.

42. Begg CB, Orlow I, Zabor EC, et al. Identifying Etiologically Distinct Sub-Types of Cancer: A Demonstration Project Involving Breast Cancer. *Cancer medicine*. 2015; 4(9):1432–1439. [PubMed: 25974664]
43. Begg CB, Seshan VE, Zabor EC, et al. Genomic investigation of etiologic heterogeneity: methodologic challenges. *BMC medical research methodology*. 2014; 14:138. [PubMed: 25532962]
44. Begg CB, Zabor EC. Detecting and Exploiting Etiologic Heterogeneity in Epidemiologic Studies. *Am J Epidemiol*. 2012; 176(6):512–518. [PubMed: 22922440]
45. Begg CB, Zabor EC, Bernstein JL, Bernstein L, Press MF, Seshan VE. A conceptual and methodological framework for investigating etiologic heterogeneity. *Statistics in medicine*. 2013; 32(29):5039–5052. [PubMed: 23857589]
46. Begg CB. A strategy for distinguishing optimal cancer subtypes. *Int J Cancer*. 2011; 129(4):931–937. [PubMed: 20949563]
47. Wang M, Kuchiba A, Ogino S. A meta-regression method for studying etiologic heterogeneity across disease subtypes classified by multiple biomarkers. *Am J Epidemiol*. 2015; 182(3):263–270. [PubMed: 26116215]
48. Rosner B, Glynn RJ, Tamimi RM, et al. Breast cancer risk prediction with heterogeneous risk profiles according to breast cancer tumor markers. *Am J Epidemiol*. 2013; 178(2):296–308. [PubMed: 23645624]
49. Nishihara R, Vanderweele TJ, Shibuya K, et al. Molecular pathological epidemiology gives clues to paradoxical findings. *European journal of epidemiology*. 2016 in press.
50. Lajous M, Bijon A, Fagherazzi G, et al. Body mass index, diabetes, and mortality in French women: explaining away a “paradox”. *Epidemiology*. 2014; 25(1):10–14. [PubMed: 24270963]
51. Banack HR, Kaufman JS. The obesity paradox: understanding the effect of obesity on mortality among individuals with cardiovascular disease. *Preventive medicine*. 2014; 62:96–102. [PubMed: 24525165]
52. Vanderweele TJ. Commentary: Resolutions of the birthweight paradox: competing explanations and analytical insights. *Int J Epidemiol*. 2014; 43(5):1368–1373. [PubMed: 25301862]
53. Ogino S, Lochhead P, Giovannucci E, Meyerhardt JA, Fuchs CS, Chan AT. Discovery of colorectal cancer PIK3CA mutation as potential predictive biomarker: power and promise of molecular pathological epidemiology. *Oncogene*. 2014; 33(23):2949–2955. [PubMed: 23792451]
54. Field AE, Camargo CA, Ogino S. The merits of subtyping obesity: one size does not fit all. *JAMA*. 2013; 310(20):2147–2148. [PubMed: 24189835]
55. Ikramuddin S, Livingston EH. New Insights on Bariatric Surgery Outcomes. *JAMA*. 2013; 310(22):2401–2402. [PubMed: 24189645]
56. Van Winkel R. Aetiological stratification as a conceptual framework for gene-by-environment interaction research in psychiatry. *Epidemiology and Psychiatric Sciences*. 2015; 24(1):6–11. [PubMed: 25693861]
57. Ogino S, Galon J, Fuchs CS, Dranoff G. Cancer immunology-analysis of host and tumor factors for personalized medicine. *Nature reviews. Clinical oncology*. 2011; 8(12):711–719.
58. Song M, Nishihara R, Wang M, et al. Plasma 25-hydroxyvitamin D and colorectal cancer risk according to tumour immunity status. *Gut*. 2015 in press (published online) (doi:10.1136/gutjnl-2014-308852).
59. Mima K, Sukawa Y, Nishihara R, et al. *Fusobacterium nucleatum* and T-cells in colorectal carcinoma. *JAMA Oncol*. 2015; 1(5):653–661. [PubMed: 26181352]
60. Song M, Nishihara R, Wu K, et al. Marine omega-3 Polyunsaturated Fatty Acids and Risk of Colorectal Cancer According to Microsatellite Instability. *J Natl Cancer Inst*. 2015; 107(4):djv007. [PubMed: 25810492]
61. Mima K, Nishihara R, Qian ZR, et al. *Fusobacterium nucleatum* in colorectal carcinoma tissue and patient prognosis. *Gut*. 2016 in press (published online in 2015).
62. Mima, K.; Nishihara, R.; Nowak, J., et al. Cancer immunology research. 2015. MicroRNA MIR21 and T-cells in Colorectal Cancer. in press (published online)
63. Ito M, Kanno S, Noshio K, et al. Association of *Fusobacterium nucleatum* with clinical and molecular features in colorectal serrated pathway. *Int J Cancer*. 2015

64. Galon J, Franck P, Marincola FM, et al. Cancer classification using the Immunoscore: a worldwide task force. *Journal of translational medicine*. 2012; 10(1):205. [PubMed: 23034130]
65. Galon J, Mlecnik B, Bindea G, et al. Towards the introduction of the Immunoscore in the classification of malignant tumors. *J Pathol*. 2014; 232(2):199–209. [PubMed: 24122236]
66. Ramadhan AA, Alrefaei YN. Analytical study of the current trends of antibiotic resistance pattern among bacterial pathogens isolates in Kuwait hospital. *J Pathol Epidemiol*. 2015 in press.
67. Curtin K, Slattery ML, Samowitz WS. CpG island methylation in colorectal cancer: past, present and future. *Pathology Research International*. 2011; 2011:902674. no issue number. [PubMed: 21559209]
68. Hughes LA, Simons CC, Van Den Brandt PA, et al. Body size, physical activity and risk of colorectal cancer with or without the CpG island methylator phenotype (CIMP). *PLoS One*. 2011; 6(4):e18571. [PubMed: 21483668]
69. Jacobs R, Voorneveld P, Kodach L, Hardwick J. Cholesterol metabolism and colorectal cancers. *Current opinion in pharmacology*. 2012; 12(6):690–695. [PubMed: 22884562]
70. Hughes LA, Khalid-De Bakker CA, Smits KM, et al. The CpG island methylator phenotype in colorectal cancer: Progress and problems. *Biochimica et biophysica acta*. 2012; 1825(1):77–85. [PubMed: 22056543]
71. Iwagami S, Baba Y, Watanabe M, et al. Pyrosequencing Assay to Measure LINE-1 Methylation Level in Esophageal Squamous Cell Carcinoma. *Ann Surg Oncol*. 2012; 19(8):2726–2732. [PubMed: 22187122]
72. Limburg PJ, Limsui D, Vierkant RA, et al. Postmenopausal Hormone Therapy and Colorectal Cancer Risk in Relation to Somatic KRAS Mutation Status among Older Women. *Cancer Epidemiol Biomarkers Prev*. 2012; 21(4):681–684. [PubMed: 22337533]
73. Hughes LA, Williamson EJ, Van Engeland M, et al. Body size and risk for colorectal cancers showing BRAF mutation or microsatellite instability: a pooled analysis. *Int J Epidemiol*. 2012; 41(4):1060–1072. [PubMed: 22531127]
74. Ku CS, Cooper DN, Wu M, et al. Gene discovery in familial cancer syndromes by exome sequencing: prospects for the elucidation of familial colorectal cancer type X. *Mod Pathol*. 2012; 25(8):1055–1068. [PubMed: 22522846]
75. Rex DK, Ahnen DJ, Baron JA, et al. Serrated lesions of the colorectum: review and recommendations from an expert panel. *Am J Gastroenterol*. 2012; 107(9):1315–1329. [PubMed: 22710576]
76. Koshiol J, Lin SW. Can Tissue-Based Immune Markers be Used for Studying the Natural History of Cancer? *Ann Epidemiol*. 2012; 22(7):520–530. [PubMed: 22481034]
77. Fini L, Grizzi F, Laghi L. Adaptive and Innate Immunity, Non Clonal Players in Colorectal Cancer Progression. *Adaptive and Innate Immunity, Non Clonal Players in Colorectal Cancer Progression*. 2012; (15):323–340.
78. Gay LJ, Mitrou PN, Keen J, et al. Dietary, lifestyle and clinico-pathological factors associated with APC mutations and promoter methylation in colorectal cancers from the EPIC-Norfolk Study. *J Pathol*. 2012; 228(3):405–415. [PubMed: 22864938]
79. Chia WK, Ali R, Toh HC. Aspirin as adjuvant therapy for colorectal cancer-reinterpreting paradigms. *Nature reviews. Clinical oncology*. 2012; 9(10):561–570.
80. Dogan S, Shen R, Ang DC, et al. Molecular Epidemiology of EGFR and KRAS Mutations in 3026 Lung Adenocarcinomas: Higher Susceptibility of Women to Smoking-related KRAS-mutant Cancers. *Clin Cancer Res*. 2012; 18(22):6169–6177. [PubMed: 23014527]
81. Spitz MR, Caporaso NE, Sellers TA. Integrative cancer epidemiology--the next generation. *Cancer discovery*. 2012; 2(12):1087–1090. [PubMed: 23230187]
82. Shanmuganathan R, Nazeema Banu B, Amirthalingam L, Muthukumar H, Kaliaperumal R, Shanmugam K. Conventional and Nanotechniques for DNA Methylation Profiling. *J Mol Diagn*. 2013; 15(1):17–26. [PubMed: 23127612]
83. Rosty C, Young JP, Walsh MD, et al. Colorectal carcinomas with KRAS mutation are associated with distinctive morphological and molecular features. *Mod Pathol*. 2013; 26(6):825–834. [PubMed: 23348904]

84. Weijenberg MP, Hughes LA, Bours MJ, Simons CC, Van Engeland M, Van Den Brandt PA. The mTOR Pathway and the Role of Energy Balance Throughout Life in Colorectal Cancer Etiology and Prognosis: Unravelling Mechanisms Through a Multidimensional Molecular Epidemiologic Approach. *Current nutrition reports*. 2013; 2(1):19–26. [PubMed: 23396869]
85. Buchanan DD, Win AK, Walsh MD, et al. Family History of Colorectal Cancer in BRAF p.V600E mutated Colorectal Cancer Cases. *Cancer Epidemiol Biomarkers Prev*. 2013; 22(5):917–926. [PubMed: 23462926]
86. Burnett-Hartman AN, Newcomb PA, Potter JD, et al. Genomic aberrations occurring in subsets of serrated colorectal lesions but not conventional adenomas. *Cancer Res*. 2013; 73(9):2863–2872. [PubMed: 23539450]
87. Alvarez MC, Santos JC, Maniezzo N, et al. MGMT and MLH1 methylation in *Helicobacter pylori*-infected children and adults. *World journal of gastroenterology : WJG*. 2013; 19(20):3043–3051. [PubMed: 23716983]
88. Hagland HR, Berg M, Jolma IW, Carlsen A, Soreide K. Molecular Pathways and Cellular Metabolism in Colorectal Cancer. *Digestive surgery*. 2013; 30(1):12–25. [PubMed: 23595116]
89. Zaidi N, Lupien L, Kuemmerle NB, Kinlaw WB, Swinnen JV, Smans K. Lipogenesis and lipolysis: The pathways exploited by the cancer cells to acquire fatty acids. *Progress in lipid research*. 2013; 52(4):585–589. [PubMed: 24001676]
90. Abbenhardt C, Poole EM, Kulmacz RJ, et al. Phospholipase A2G1B polymorphisms and risk of colorectal neoplasia. *International journal of molecular epidemiology and genetics*. 2013; 4(3): 140–149. [PubMed: 24046806]
91. Hughes LA, Melotte V, De Schrijver J, et al. The CpG island methylator phenotype: what's in a name? *Cancer Res*. 2013; 73(19):5858–5868. [PubMed: 23801749]
92. Bae JM, Kim JH, Cho NY, Kim TY, Kang GH. Prognostic implication of the CpG island methylator phenotype in colorectal cancers depends on tumour location. *Br J Cancer*. 2013; 109(4):1004–1012. [PubMed: 23900220]
93. Amirian ES, Petrosino JF, Ajami NJ, Liu Y, Mims MP, Scheurer ME. Potential role of gastrointestinal microbiota composition in prostate cancer risk. *Infectious agents and cancer*. 2013; 8(1):42. [PubMed: 24180596]
94. Hoffmeister M, Blaker H, Kloor M, et al. Body mass index and microsatellite instability in colorectal cancer: a population-based study. *Cancer Epidemiol Biomarkers Prev*. 2013; 22(12): 2303–2311. [PubMed: 24127414]
95. Araujo RF Jr, Lira GA, Guedes HG, et al. Lifestyle and family history influence cancer prognosis in Brazilian individuals. *Pathology, research and practice*. 2013; 209(12):753–757.
96. Esterhuyse MM, Kaufmann SH. Diagnostic biomarkers are hidden in the infected host's epigenome. *Expert Rev Mol Diagn*. 2013; 13(6):625–637. [PubMed: 23895131]
97. Zhu Y, Yang SR, Wang PP, et al. Influence of pre-diagnostic cigarette smoking on colorectal cancer survival: overall and by tumour molecular phenotype. *Br J Cancer*. 2014; 110(5):1359–1366. [PubMed: 24448365]
98. Hagland HR, Soreide K. Cellular metabolism in colorectal carcinogenesis: Influence of lifestyle, gut microbiome and metabolic pathways. *Cancer letters*. 2015; 356:273–280. [PubMed: 24614287]
99. Shaheen NJ. Editorial: what is behind the remarkable increase in esophageal adenocarcinoma? *Am J Gastroenterol*. 2014; 109(3):345–347. [PubMed: 24594951]
100. Brandstedt J, Wangefjord S, Nodin B, Eberhard J, Jirstrom K, Manjer J. Associations of hormone replacement therapy and oral contraceptives with risk of colorectal cancer defined by clinicopathological factors, beta-catenin alterations, expression of cyclin D1, p53, and microsatellite-instability. *BMC cancer*. 2014; 14:371. no issue number. [PubMed: 24885829]
101. Coppede F. The role of epigenetics in colorectal cancer. *Expert review of gastroenterology & hepatology*. 2014; 8(8):935–948. [PubMed: 24871610]
102. Bishehsari F, Mahdavinia M, Vacca M, Malekzadeh R, Mariani-Costantini R. Epidemiological transition of colorectal cancer in developing countries: Environmental factors, molecular pathways, and opportunities for prevention. *World journal of gastroenterology : WJG*. 2014; 20(20):6055–6072. [PubMed: 24876728]

103. Cross AJ, Moore SC, Boca S, et al. A prospective study of serum metabolites and colorectal cancer risk. *Cancer*. 2014; 120(19):3049–3057. [PubMed: 24894841]
104. Simons CC, Van Den Brandt PA, Stehouwer C, Van Engeland M, Weijenberg MP. Body size, physical activity, early life energy restriction, and associations with methylated insulin-like growth factor binding protein genes in colorectal cancer. *Cancer Epidemiol Biomarkers Prev*. 2014; 23(9):1852–1862. [PubMed: 24972776]
105. Haque TR, Bradshaw PT, Crockett SD. Risk Factors for Serrated Polyps of the Colorectum. *Digestive diseases and sciences*. 2014; 59(12):2874–2889. [PubMed: 25030942]
106. Ryan BM, Wolff RK, Valeri N, et al. An analysis of genetic factors related to risk of inflammatory bowel disease and colon cancer. *Cancer epidemiology*. 2014; 38(5):583–590. [PubMed: 25132422]
107. Bragazzi, NL. Ramadan fasting and biological biomarkers: the new opportunities of systems biology and omics sciences. 2014. Ramadan fasting and biological biomarkers: the new opportunities of systems biology and omics sciences.
108. Hussain, N. Epigenetics in childhood health and disease. In: Maulik, N.; Karagiannis, T., editors. *Molecular mechanisms and physiology of disease: Implications for Epigenetics and Health*. Springer; 2014. p. 1-62.
109. Li P, Wu H, Zhang H, et al. Aspirin use after diagnosis but not prediagnosis improves established colorectal cancer survival: a meta-analysis. *Gut*. 2015; 64(9):1419–1425. [PubMed: 25239119]
110. Huser V, Sincan M, Cimino JJ. Developing genomic knowledge bases and databases to support clinical management: current perspectives. *Pharmacogenomics and personalized medicine*. 2014; 7:275–283. [PubMed: 25276091]
111. Wennersten C, Andersson G, Boman K, Nodin B, Gaber A, Jirstrom K. Incident urothelial cancer in the Malmo Diet and Cancer Study: cohort characteristics and further validation of ezrin as a prognostic biomarker. *Diagnostic pathology*. 2014; 9(1):189. [PubMed: 25278252]
112. Mikeska T, Craig JM. DNA methylation biomarkers: cancer and beyond. *Genes*. 2014; 5:821–864. no issue number. [PubMed: 25229548]
113. Campbell PT, Deka A, Briggs P, et al. Establishment of the Cancer Prevention Study II Nutrition Cohort Colorectal Tissue Repository. *Cancer Epidemiol Biomarkers Prev*. 2014; 23(12):2694–2702. [PubMed: 25472679]
114. Wild CP, Bucher JR, De Jong BW, et al. Translational cancer research: balancing prevention and treatment to combat cancer globally. *J Natl Cancer Inst*. 2015; 107(1):353. [PubMed: 25515230]
115. Caiazza F, Ryan EJ, Doherty G, Winter DC, Sheahan K. Estrogen receptors and their implications in colorectal carcinogenesis. *Front Oncol*. 2015; 5 no issue number. Article 19.
116. Ng JM, Yu J. Promoter hypermethylation of tumour suppressor genes as potential biomarkers in colorectal cancer. *Int J Mol Sci*. 2015; 16:2472–2496. no issue number. [PubMed: 25622259]
117. Tillmans LS, Vierkant RA, Wang AH, et al. Associations between Environmental Exposures and Incident Colorectal Cancer by ESR2 Protein Expression Level in a Population-Based Cohort of Older Women. *Cancer Epidemiol Biomarkers Prev*. 2015; 24(4):713–719. [PubMed: 25650184]
118. Witvliet MI. World health survey: a useful yet underutilized global health data source. *Austin J Public Health Epidemiol*. 2014; 1(3):id1012.
119. Potter, S. Body mass index 112 Success Secrets - 112 Most Asked Questions On Body mass index - What You Need To Know. Emeroe Publishing; 2014.
120. Ciszyk AL, Penner-Goeke S, Lichtensztejn Z, et al. Characterizing the prevalence of chromosome instability in interval colorectal cancer. *Neoplasia*. 2015; 17(3):306–316. [PubMed: 25810015]
121. Weisenberger DJ, Levine AJ, Long TI, et al. Association of the Colorectal CpG Island Methylator Phenotype with Molecular Features, Risk Factors and Family History. *Cancer Epidemiol Biomarkers Prev*. 2015; 24(3):512–519. [PubMed: 25587051]
122. Gao C. Molecular pathological epidemiology: an interdisciplinary field for study of hepatocellular carcinoma. *Austin J Gastroenterol*. 2015; 2(3):1040.
123. Szyllberg L, Janiczek M, Popiel A, Marszałek A. Serrated polyps and their alternative pathway to the colorectal cancer: a systematic review. *Gastroenterol Res Pract*. 2015; 2015 no issue number. ID 573814.

124. Wong EY, Chua C, Beh SY, Koh D, Chong D, Tan IB. Addressing the needs of colorectal cancer survivors: current strategies and future directions. *Expert review of anticancer therapy*. 2015; 15(6):639–648. [PubMed: 25927672]
125. Campbell PT, Newton CC, Newcomb PA, et al. Association between body mass index and mortality for colorectal cancer survivors: overall and by tumor molecular phenotype. *Cancer Epidemiol Biomarkers Prev*. 2015; 24(8):1229–1238. [PubMed: 26038390]
126. Mehta AM, Osse M, Kolkman-Uljee S, Fleuren GJ, Jordanova ES. Molecular background of ERAP1 downregulation in cervical carcinoma. *Analytical Cellular Pathology*. 2015; 2015 no issue number. article ID 367837.
127. Miller, KD.; Simon, M. Global Perspectives on Cancer: Incidence, Care, and Experience. 2015. ABC-CLIO, Online 761
128. De Ruijter TC, De Hoon JP, Slaats J, et al. Formalin-fixed, paraffin-embedded (FFPE) tissue epigenomics using Infinium HumanMethylation450 BeadChip assays. *Laboratory investigation; a journal of technical methods and pathology*. 2015; 95(7):833–842.
129. Zakhari, S.; Hoek, JB. Alcohol and Breast Cancer: Reconciling Epidemiological and Molecular Data. In: Vasilidou, V., editor. *Biological Basis of Alcohol-Induced Cancer*. Springer International Publishing; Switzerland: 2015.
130. Kyriazis M. Translating laboratory anti-aging biotechnology into applied clinical practice: problems and obstacles. *World J Transl Med*. 2015 no issue number. manuscript ID 17795.
131. Cebola I, Custodio J, Munoz M, et al. Epigenetics override pro-inflammatory PTGS transcriptomic signature towards selective hyperactivation of PGE2 in colorectal cancer. *Clinical epigenetics*. 2015; 7(1):74. [PubMed: 26207152]
132. Valdespino V, Valdespino PM. Potential of epigenetic therapies in the management of solid tumors. *Cancer management and research*. 2015; 7:241–251. [PubMed: 26346546]
133. Van Harten-Gerritsen AS, Balvers MG, Witkamp RF, Kampman E, Van Duynhoven FJ. Vitamin D, inflammation and colorectal cancer progression: A review of mechanistic studies and future directions for epidemiological studies. *Cancer Epidemiol Biomarkers Prev*. 2015 in press (published online).
134. Sylvestsky AC, Nandagopal R, Nguyen T, et al. Randomized clinical trial Buddy Study: partners for better health in adolescents with type 2 diabetes. *World J Diabetes*. 2015 in press (published online).
135. Ogino, S. Molecular pathological epidemiology (MPE): Overview of its paradigm and wide applicability even without tumor tissue [abstract]. *Proceedings of the Twelfth Annual AACR International Conference on Frontiers in Cancer Prevention Research*; 2013 Oct 27–30; National Harbor, MD: Cancer Prev Res (Phila)CN06-01 (2013)
136. Kuller LH, Bracken MB, Ogino S, Prentice RL, Tracy RP. The role of epidemiology in the era of molecular epidemiology and genomics: Summary of the 2013 AJE-sponsored Society of Epidemiologic Research Symposium. *Am J Epidemiol*. 2013; 178(9):1350–1354. [PubMed: 24105654]
137. Epplein M, Bostick RM, Mu L, Ogino S, Braithwaite D, Kanetsky PA. Challenges and Opportunities in International Molecular Cancer Prevention Research: An ASPO Molecular Epidemiology and the Environment and International Cancer Prevention Interest Groups Report. *Cancer Epidemiol Biomarkers Prev*. 2014; 23(11):2613–2617. [PubMed: 25277796]
138. Ogino S, Campbell PT, Nishihara R, et al. Proceedings of The Second International Molecular Pathological Epidemiology (MPE) Meeting. *Cancer Causes Control*. 2015; 26(7):959–972. [PubMed: 25956270]
139. Ogino S, Fuchs CS, Giovannucci E. How many molecular subtypes? Implications of the unique tumor principle in personalized medicine. *Expert Rev Mol Diagn*. 2012; 12(6):621–628. [PubMed: 22845482]
140. Kostic AD, Gevers D, Pedamallu CS, et al. Genomic analysis identifies association of *Fusobacterium* with colorectal carcinoma. *Genome research*. 2012; 22(2):292–298. [PubMed: 22009990]
141. Tahara T, Yamamoto E, Suzuki H, et al. *Fusobacterium* in colonic flora and molecular features of colorectal carcinoma. *Cancer Res*. 2014; 74(5):1311–1318. [PubMed: 24385213]

142. Nishi A, Kawachi I, Koenen KC, Wu K, Nishihara R, Ogino S. Lifecourse Epidemiology and Molecular Pathological Epidemiology. *Am J Prev Med.* 2015; 48(1):116–119. [PubMed: 25528613]
143. Ijspeert JE, Vermeulen L, Meijer GA, Dekker E. Serrated neoplasia-role in colorectal carcinogenesis and clinical implications. *Nature reviews. Gastroenterology & hepatology.* 2015
144. Reimers MS, Zeestraten EC, Kuppen PJ, Liefers GJ, Van De Velde JH. Biomarkers in precision therapy in colorectal cancer. *Gastroenterology Report.* 2013; 1:166–183. [PubMed: 24759962]
145. Zoratto F, Rossi L, Verrico M, et al. Focus on genetic and epigenetic events of colorectal cancer pathogenesis: implications for molecular diagnosis. *Tumour Biol.* 2014; 35(7):6195–6206. [PubMed: 25051912]
146. Song M, Garrett WS, Chan AT. Nutrients, Foods, and Colorectal Cancer Prevention. *Gastroenterology.* 2015; 148(6):1244–1260. e1216. [PubMed: 25575572]
147. Okugawa Y, Grady WM, Goel A. Epigenetic Alterations in Colorectal Cancer: Emerging Biomarkers. *Gastroenterology.* 2016 in press (published online 2015).
148. Aleman JO, Eusebi LH, Ricciardiello L, Patidar K, Sanyal AJ, Holt PR. Mechanisms of obesity-induced gastrointestinal neoplasia. *Gastroenterology.* 2014; 146(2):357–373. [PubMed: 24315827]
149. Lievre A, Blons H, Laurent-Puig P. Oncogenic mutations as predictive factors in colorectal cancer. *Oncogene.* 2010; 29(21):3033–3043. [PubMed: 20383189]
150. Bokemeyer C, Bondarenko I, Makhson A, et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. *J Clin Oncol.* 2009; 27(5):663–671. [PubMed: 19114683]
151. De Roock W, Claes B, Bernasconi D, et al. Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. *Lancet Oncol.* 2010; 11(8):753–762. [PubMed: 20619739]
152. Dienstmann R, Salazar R, Tabernero J. Personalizing Colon Cancer Adjuvant Therapy: Selecting Optimal Treatments for Individual Patients. *J Clin Oncol.* 2015; 33(16):1787–1796. [PubMed: 25918287]
153. Chan AT, Ogino S, Fuchs CS. Aspirin and the Risk of Colorectal Cancer in Relation to the Expression of COX-2. *N Engl J Med.* 2007; 356(21):2131–2142. [PubMed: 17522398]
154. Nishihara R, Lochhead P, Kuchiba A, et al. Aspirin use and risk of colorectal cancer according to BRAF mutation status. *JAMA.* 2013; 309(24):2563–2571. [PubMed: 23800934]
155. Nan H, Morikawa T, Suuriniemi M, et al. Aspirin use, 8q24 single nucleotide polymorphism rs6983267, and colorectal cancer according to CTNNB1 alterations. *J Natl Cancer Inst.* 2013; 105(24):1852–1861. [PubMed: 24317174]
156. Fink SP, Yamauchi M, Nishihara R, et al. Aspirin and the Risk of Colorectal Cancer in Relation to the Expression of 15-Hydroxyprostaglandin Dehydrogenase (HPGD). *Sci Transl Med.* 2014; 6(233):233re232.
157. Chan AT, Ogino S, Fuchs CS. Aspirin use and survival after diagnosis of colorectal cancer. *JAMA.* 2009; 302(6):649–658. [PubMed: 19671906]
158. Liao X, Lochhead P, Nishihara R, et al. Aspirin use, tumor PIK3CA mutation status, and colorectal cancer survival. *N Engl J Med.* 2012; 367(17):1596–1606. [PubMed: 23094721]
159. Domingo E, Church DN, Sieber O, et al. Evaluation of PIK3CA mutation as a predictor of benefit from NSAID therapy in colorectal cancer. *J Clin Oncol.* 2013; 31(34):4297–4305. [PubMed: 24062397]
160. Cathomas G. PIK3CA in Colorectal Cancer. *Front Oncol.* 2014; 4:35. [PubMed: 24624362]
161. Amatu A, Bencardino K, Sartore-Bianchi A, Siena S. Aspirin for colorectal cancer with PIK3CA mutations: the rising of the oldest targeted therapy? *Annals of translational medicine.* 2013; 1(2): 12. [PubMed: 25332957]
162. Kothari N, Kim R, Jorissen RN, et al. Impact of regular aspirin use on overall and cancer-specific survival in patients with colorectal cancer harboring a PIK3CA mutation. *Acta oncologica.* 2015; 54(4):487–492. [PubMed: 25549537]

163. Tougeron D, Sha D, Manthravadi S, Sinicrope FA. Aspirin and colorectal cancer: Back to the Future. *Clin Cancer Res*. 2014; 20(5):1087–1094. [PubMed: 24327271]
164. Guilgen G. Reviewing the Role of Aspirin in Chemoprevention of Colorectal Cancer. *Curr Colorectal Cancer Rep*. 2015 in press (published online).
165. Fuchs CS, Ogino S. Aspirin therapy for colorectal cancer with PIK3CA mutation: simply complex! *J Clin Oncol*. 2013; 31(34):4358–4361. [PubMed: 24166520]
166. Doubeni CA, Weinmann S, Adams K, et al. Screening colonoscopy and risk for incident late-stage colorectal cancer diagnosis in average-risk adults: a nested case-control study. *Ann Intern Med*. 2013; 158(5 Pt 1):312–320. [PubMed: 23460054]
167. Nishihara R, Wu K, Lochhead P, et al. Long-term Colorectal Cancer Incidence and Mortality after Lower Endoscopy. *N Engl J Med*. 2013; 369(12):1095–1105. [PubMed: 24047059]
168. Brenner H, Chang-Claude J, Jansen L, Knebel P, Stock C, Hoffmeister M. Reduced risk of colorectal cancer up to 10 years after screening, surveillance, or diagnostic colonoscopy. *Gastroenterology*. 2014; 146(3):709–717. [PubMed: 24012982]
169. Arain MA, Sawhney M, Sheikh S, et al. CIMP Status of Interval Colon Cancers: Another Piece to the Puzzle. *Am J Gastroenterol*. 2010; 105:1189–1195. [PubMed: 20010923]
170. Barrow TM, Michels KB. Epigenetic epidemiology of cancer. *Biochem Biophys Res Commun*. 2014; 455(1–2):70–83. [PubMed: 25124661]
171. Suzuki H, Yamamoto E, Maruyama R, Niinuma T, Kai M. Biological significance of the CpG island methylator phenotype. *Biochem Biophys Res Commun*. 2014; 455(1–2):35–42. [PubMed: 25016183]
172. Sepulveda AR, Jones D, Ogino S, et al. CpG methylation analysis—current status of clinical assays and potential applications in molecular diagnostics: a report of the Association for Molecular Pathology. *J Mol Diagn*. 2009; 11(4):266–278. [PubMed: 19541921]
173. Kim JH, Kang GH. Molecular and prognostic heterogeneity of microsatellite-unstable colorectal cancer. *World journal of gastroenterology : WJG*. 2014; 20(15):4230–4243. [PubMed: 24764661]
174. Teodoridis JM, Hardie C, Brown R. CpG island methylator phenotype (CIMP) in cancer: Causes and implications. *Cancer letters*. 2008; 268(2):177–186. [PubMed: 18471961]
175. Li X, Hu F, Wang Y, et al. CpG Island Methylator Phenotype and Prognosis of Colorectal Cancer in Northeast China. *Biomed Res Int*. 2014; 2014:236361. [PubMed: 25243122]
176. Samowitz WS, Albertsen H, Sweeney C, et al. Association of smoking, CpG island methylator phenotype, and V600E BRAF mutations in colon cancer. *J Natl Cancer Inst*. 2006; 98(23):1731–1738. [PubMed: 17148775]
177. Limsui D, Vierkant RA, Tillmans LS, et al. Cigarette Smoking and Colorectal Cancer Risk by Molecularly Defined Subtypes. *J Natl Cancer Inst*. 2010; 102(14):1012–1022. [PubMed: 20587792]
178. Nishihara R, Morikawa T, Kuchiba A, et al. A prospective study of duration of smoking cessation and colorectal cancer risk by epigenetics-related tumor classification. *Am J Epidemiol*. 2013; 178(1):84–100. [PubMed: 23788674]
179. Curtin K, Samowitz WS, Wolff RK, Herrick J, Caan BJ, Slattery ML. Somatic alterations, metabolizing genes and smoking in rectal cancer. *Int J Cancer*. 2009; 125(1):158–164. [PubMed: 19358278]
180. Poynter JN, Haile RW, Siegmund KD, et al. Associations between smoking, alcohol consumption, and colorectal cancer, overall and by tumor microsatellite instability status. *Cancer Epidemiol Biomarkers Prev*. 2009; 18(10):2745–2750. [PubMed: 19755657]
181. Lindor NM, Yang P, Evans I, et al. Alpha-1-antitrypsin deficiency and smoking as risk factors for mismatch repair deficient colorectal cancer: A study from the colon cancer family registry. *Molecular genetics and metabolism*. 2010; 99(2):157–159. [PubMed: 19853488]
182. Chia VM, Newcomb PA, Bigler J, Morimoto LM, Thibodeau SN, Potter JD. Risk of microsatellite-unstable colorectal cancer is associated jointly with smoking and nonsteroidal anti-inflammatory drug use. *Cancer Res*. 2006; 66(13):6877–6883. [PubMed: 16818666]
183. Carethers JM, Jung BH. Genetics and Genetic Biomarkers in Sporadic Colorectal Cancer. *Gastroenterology*. 2015; 149(5):1177–1190. e1173. [PubMed: 26216840]

184. Lao VV, Grady WM. Epigenetics and colorectal cancer. *Nature reviews. Gastroenterology & hepatology*. 2011; 8(12):686–700. [PubMed: 22009203]
185. Colussi D, Brandi G, Bazzoli F, Ricciardiello L. Molecular Pathways Involved in Colorectal Cancer: Implications for Disease Behavior and Prevention. *Int J Mol Sci*. 2013; 14:16365–16385. no issue number. [PubMed: 23965959]
186. Lin JH, Giovannucci E. Environmental exposure and tumor heterogeneity in colorectal cancer risk and outcomes. *Curr Colorectal Cancer Rep*. 2014; 10:94–104.
187. Bardhan K, Liu K. Epigenetics and colorectal cancer pathogenesis. *Cancers*. 2013; 5:676–713. no issue number. [PubMed: 24216997]
188. Dahlin AM, Palmqvist R, Henriksson ML, et al. The Role of the CpG Island Methylator Phenotype in Colorectal Cancer Prognosis Depends on Microsatellite Instability Screening Status. *Clin Cancer Res*. 2010; 16(6):1845–1855. [PubMed: 20197478]
189. O'Brien MJ, Zhao Q, Yang S. Colorectal serrated pathway cancers and precursors. *Histopathology*. 2015; 66(1):49–65. [PubMed: 25263173]
190. Carlson JW, Lyon E, Walton D, et al. Partners in pathology: a collaborative model to bring pathology to resource poor settings. *The American journal of surgical pathology*. 2010; 34(1): 118–123. [PubMed: 19898229]
191. Rubin EH, Allen JD, Nowak JA, Bates SE. Developing precision medicine in a global world. *Clin Cancer Res*. 2014; 20(6):1419–1427. [PubMed: 24634465]
192. African Strategies for Advancing Pathology Group M. Quality pathology and laboratory diagnostic services are key to improving global health outcomes: improving global health outcomes is not possible without accurate disease diagnosis. *Am J Clin Pathol*. 2015; 143(3): 325–328. [PubMed: 25696789]
193. Clegg LX, Reichman ME, Miller BA, et al. Impact of socioeconomic status on cancer incidence and stage at diagnosis: selected findings from the surveillance, epidemiology, and end results: National Longitudinal Mortality Study. *Cancer Causes Control*. 2009; 20(4):417–435. [PubMed: 19002764]
194. Ayanian JZ, Carethers JM. Bridging behavior and biology to reduce socioeconomic disparities in colorectal cancer risk. *J Natl Cancer Inst*. 2012; 104(18):1343–1344. [PubMed: 22952312]
195. Morikawa T, Kuchiba A, Yamauchi M, et al. Association of CTNNB1 (beta-catenin) alterations, body mass index, and physical activity with survival in patients with colorectal cancer. *JAMA*. 2011; 305(16):1685–1694. [PubMed: 21521850]
196. Morikawa T, Kuchiba A, Lochhead P, et al. Prospective analysis of body mass index, physical activity, and colorectal cancer risk associated with beta-catenin (CTNNB1) status. *Cancer Res*. 2013; 73(5):1600–1610. [PubMed: 23442321]
197. Lee J, Jeon JY, Meyerhardt JA. Diet and Lifestyle in Survivors of Colorectal Cancer. *Hematology/oncology clinics of North America*. 2015; 29(1):1–27. [PubMed: 25475570]
198. Strully KW, Fowler JH, Murabito JM, Benjamin EJ, Levy D, Christakis NA. Aspirin use and cardiovascular events in social networks. *Social science & medicine*. 2012; 74(7):1125–1129. [PubMed: 22361089]
199. Davison KK, Nishi A, Kranz S, et al. Associations among social capital, parenting for active lifestyles, and youth physical activity in rural families living in upstate New York. *Social science & medicine*. 2012; 75(8):1488–1496. [PubMed: 22818486]
200. Ademuyiwa FO, Edge SB, Erwin DO, Orom H, Ambrosone CB, Underwood W 3rd. Breast cancer racial disparities: unanswered questions. *Cancer Res*. 2011; 71(3):640–644. [PubMed: 21135114]
201. Ambrosone CB, Zirpoli GR, Bovbjerg DH, et al. Associations between estrogen receptor-negative breast cancer and timing of reproductive events differ between African American and European American women. *Cancer Epidemiol Biomarkers Prev*. 2014; 23(6):1115–1120. [PubMed: 24718280]
202. Chandran U, Zirpoli G, Ciupak G, et al. Racial disparities in red meat and poultry intake and breast cancer risk. *Cancer Causes Control*. 2013; 24(12):2217–2229. [PubMed: 24091794]

203. Quan L, Gong Z, Yao S, et al. Cytokine and cytokine receptor genes of the adaptive immune response are differentially associated with breast cancer risk in American women of African and European ancestry. *Int J Cancer*. 2014; 134(6):1408–1421. [PubMed: 23996684]
204. Phipps AI, Ahnen DJ, Cheng I, Newcomb PA, Win AK, Burnett T. PIK3CA Somatic Mutation Status in Relation to Patient and Tumor Factors in Racial / Ethnic Minorities with Colorectal Cancer. *Cancer Epidemiol Biomarkers Prev*. 2015; 24(7):1046–1051. [PubMed: 25994739]
205. Palmer JR, Viscidi E, Troester MA, et al. Parity, lactation, and breast cancer subtypes in African American women: results from the AMBER Consortium. *J Natl Cancer Inst*. 2014; 106(10):dju237. [PubMed: 25224496]
206. Ambrosone CB, Young AC, Sucheston LE, et al. Genome-wide methylation patterns provide insight into differences in breast tumor biology between American women of African and European ancestry. *Oncotarget*. 2014; 5(1):237–248. [PubMed: 24368439]
207. Mokarram P, Kumar K, Brim H, et al. Distinct high-profile methylated genes in colorectal cancer. *PLoS One*. 2009; 4(9):e7012. [PubMed: 19750230]
208. Ashktorab H, Daremipouran M, Goel A, et al. DNA methylome profiling identifies novel methylated genes in African American patients with colorectal neoplasia. *Epigenetics: official journal of the DNA Methylation Society*. 2014; 9(4):503–512.
209. Xia YY, Ding YB, Liu XQ, et al. Racial/ethnic disparities in human DNA methylation. *Biochimica et biophysica acta*. 2014; 1846(1):258–262. [PubMed: 25016140]
210. Vogtmann E, Shanmugam C, Katkoori VR, Waterbor J, Manne U. Socioeconomic status, p53 abnormalities, and colorectal cancer. *Journal of gastrointestinal oncology*. 2013; 4(1):40–44. [PubMed: 23450636]
211. Baker L, Quinlan PR, Patten N, et al. p53 mutation, deprivation and poor prognosis in primary breast cancer. *Br J Cancer*. 2010; 102(4):719–726. [PubMed: 20104224]
212. Gordon NH. Association of education and income with estrogen receptor status in primary breast cancer. *Am J Epidemiol*. 1995; 142(8):796–803. [PubMed: 7572955]
213. Taylor A, Cheng KK. Social deprivation and breast cancer. *Journal of public health medicine*. 2003; 25(3):228–233. [PubMed: 14575198]
214. Brown M, Tsodikov A, Bauer KR, Parise CA, Caggiano V. The role of human epidermal growth factor receptor 2 in the survival of women with estrogen and progesterone receptor-negative, invasive breast cancer: the California Cancer Registry, 1999–2004. *Cancer*. 2008; 112(4):737–747. [PubMed: 18189290]
215. Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer Registry. *Cancer*. 2007; 109(9):1721–1728. [PubMed: 17387718]
216. Parise CA, Bauer KR, Brown MM, Caggiano V. Breast cancer subtypes as defined by the estrogen receptor (ER), progesterone receptor (PR), and the human epidermal growth factor receptor 2 (HER2) among women with invasive breast cancer in California, 1999–2004. *The breast journal*. 2009; 15(6):593–602. [PubMed: 19764994]
217. Khoury MJ, Gwinn ML, Glasgow RE, Kramer BS. A population approach to precision medicine. *Am J Prev Med*. 2012; 42(6):639–645. [PubMed: 22608383]
218. Wuchty S, Jones BF, Uzzi B. The increasing dominance of teams in production of knowledge. *Science*. 2007; 316(5827):1036–1039. [PubMed: 17431139]
219. Sharp PA, Langer R. Research agenda. Promoting convergence in biomedical science. *Science*. 2011; 333(6042):527. [PubMed: 21798916]
220. Spitz MR, Lam TK, Schully SD, Khoury MJ. The Next Generation of Large-Scale Epidemiologic Research: Implications for Training Cancer Epidemiologists. *Am J Epidemiol*. 2014; 180(10):964–967. [PubMed: 25234430]

Key Issues

Use of molecular pathology tools and diagnostics has been advancing biomedical science, but it is also increasing health disparities and inequalities around the world.

As a core method field in population health science and medicine, epidemiology is a growing scientific discipline that can develop novel statistical methodologies to maximize utilization of big data on populations and disease pathology.

Integrating molecular pathology and epidemiology, molecular pathological epidemiology (MPE) can advance biomedical and health research by linking exposures to molecular pathologic signatures, enhancing causal inference, and identifying potential biomarkers for clinical impact.

Integrating social science and epidemiology, social epidemiology can examine social determinants of health and diseases.

Integrating molecular pathology, epidemiology, and social science, social MPE can embrace precision medicine, address increasing health disparities in global health settings, and elucidate biological effects of social environments.

We foresee advancements of molecular medicine, including molecular diagnostics, biomedical imaging, and targeted therapeutics, which should benefit individuals in global populations, by means of integrative social MPE.

Figure 1.

Trans-multidisciplinary integrations of molecular pathology, epidemiology and social science. The integration of molecular pathology and epidemiology has given rise to molecular pathological epidemiology (MPE), while the integration of social science and epidemiology has given rise to social epidemiology. We propose that the integration of MPE and social epidemiology gives rise to social MPE. Note that epidemiology plays a pivotal role as a core field of population health science in these transdisciplinary integrations.

Figure 2.

Collaborative relationship between social epidemiology and molecular pathological epidemiology (MPE). Both fields are method-based subspecialty disciplines in epidemiology, and cover the entire spectrum of human diseases. The methodologic strengths of each field can complement those of the other field. Both fields can be synergized to create an integrative field of social MPE, which can further enhance research and education in both fields.