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EXPERT REVIEWS

Integration of molecular pathology, epidemiology and social science for global precision medicine

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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, 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

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 nonepidemiologist) on 'epidemiology of colon cancer' that 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 methodological 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

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diseases can encompass all data on health and diseases in people that 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 data set 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.

As 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 the 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, the authors 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 a few. 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.

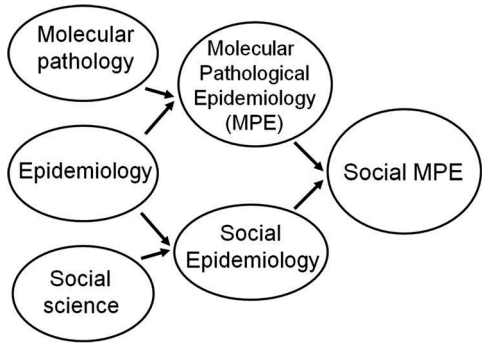

Figure 1. Trans-multidisciplinary integrations of molecular pathology, epidemiology and social science.
The integration of molecular pathology and epidemiology has given risen to MPE, while the integration of social science and epidemiology has given risen to social epidemiology. We propose that the 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. MPE: Molecular pathological epidemiology.

Molecular pathological epidemiology

Use of molecular pathology techniques in epidemiology research became common in the 1990s and the 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 epidemiological 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 epidemiological 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 etiological 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 pathological 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 in typical GWAS. 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), life course-MPE,[142] causal inference-MPE,[49] pharmaco-MPE and environmental-MPE.

Here, the authors 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 epidemiological 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 with 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 pathological 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.

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 nonsmokers 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 or CIMP-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 MPE approach in context of global social diversities

Although the MPE approach can accelerate the more detailed and personalized approach in the 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 the authors will discuss in the next section.

Integrative approach of social epidemiology and 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 epidemiological 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'), the authors 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 towards disease development. In addition, social epidemiologists and social scientists can monitor whether new sciences (such as MPE) can increase or decrease health disparity, whether new sciences can fit with existing social norms and political climates, or change them and whether 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.

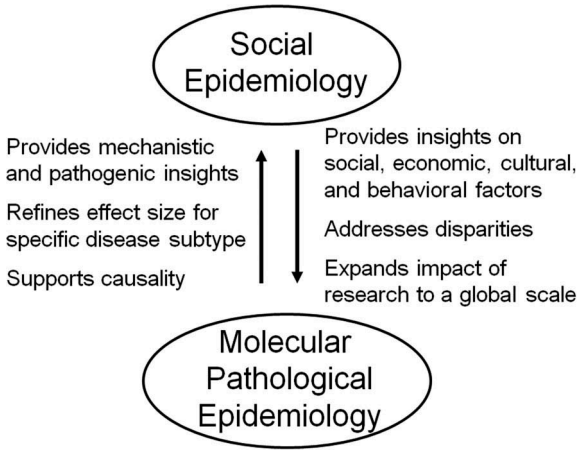

Figure 2. Collaborative relationship between social epidemiology and molecular pathological epidemiology. Both fields are method-based subspecialty disciplines in epidemiology and cover the entire spectrum of human diseases. The methodological strengths of each field can complement those of the other field. Both fields can be synergized to create an integrative field of social molecular pathological epidemiology, which can further enhance research and education in both fields.

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 that utilized the integrative social epidemiology – MPE approach remain rather uncommon. Nonetheless, it has been reported that *TP53*-mutated colorectal cancer and ESR1 (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-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 the 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, 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

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 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

In the next 5 years, important trends and directions in medical and health sciences are integrative holistic approaches, including 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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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 can advance biomedical and health research by linking exposures to molecular pathological 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 molecular pathological epidemiology.

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