Special Article

Interdisciplinary Education to Integrate Pathology and Epidemiology: Towards Molecular and Population-Level Health Science

Shuji Ogino*, Emily E. King, Andrew H. Beck, Mark E. Sherman, Danny A. Milner, and Edward Giovannucci

* Correspondence to Dr. Shuji Ogino, Cancer Epidemiology Program, Dana-Farber/Harvard Cancer Center, 450 Brookline Avenue, Room JF-215C, Boston, MA 02215 (e-mail: shuji_ogino@dfci.harvard.edu).

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In recent decades, epidemiology, public health, and medical sciences have been increasingly compartmentalized into narrower disciplines. The authors recognize the value of integration of divergent scientific fields in order to create new methods, concepts, paradigms, and knowledge. Herein they describe the recent emergence of molecular pathological epidemiology (MPE), which represents an integration of population and molecular biologic science to gain insights into the etiologies, pathogenesis, evolution, and outcomes of complex multifactorial diseases. Most human diseases, including common cancers (such as breast, lung, prostate, and colorectal cancers, leukemia, and lymphoma) and other chronic diseases (such as diabetes mellitus, cardiovascular diseases, hypertension, autoimmune diseases, psychiatric diseases, and some infectious diseases), are caused by alterations in the genome, epigenome, transcriptome, proteome, metabolome, microbiome, and interactome of all of the above components. In this era of personalized medicine and personalized prevention, we need integrated science (such as MPE) which can decipher diseases at the molecular, genetic, cellular, and population levels simultaneously. The authors believe that convergence and integration of multiple disciplines should be commonplace in research and education. We need to be open-minded and flexible in designing integrated education curricula and training programs for future students, clinicians, practitioners, and investigators.

education, public health professional; health care reform; individualized medicine; interdisciplinary communication; molecular epidemiology; pathology

Abbreviations: MPE, molecular pathological epidemiology; STROBE, Strengthening the Reporting of Observational Epidemiology.

Editor’s note: An invited commentary on this article appears on page 668, and the authors’ response appears on page 672.

Education is a crucial mission of the academic community. Excellence in research and education requires the combined efforts of many different disciplines (1, 2). As fundamental disciplines of biomedical and public health sciences, both pathology and epidemiology are fields of study of the entire spectrum of human diseases—the former focused on disease mechanisms in individual cases, the latter on patterns of disease in populations. The importance of these fields is well exemplified by the universal presence of pathology in medical school curricula and that of epidemiology in public health school curricula. Because of advances in both laboratory technologies and epidemiologic methods, pathology and epidemiology have become compartmentalized in schools of medicine and public health, respectively. By virtue of our training in both pathology and epidemiology, we can appreciate that knowledge, skills, and concepts from both fields can be integrated and synergized to advance biomedical, public health, and population sciences. In this era of personalized medicine (3), we need integrated, convergent scientific disciplines, which will enable us to decipher the characteristics of diseases simultaneously at both the individual and population levels (4–6).
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<th>First Author, Year (Reference No.)</th>
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<th>Putative Etiologic Factor</th>
<th>Tumor Molecular Changes (Subtypes)</th>
<th>Direction of Association</th>
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<tr>
<td>Chen, 2007 (31)</td>
<td>Colorectal cancer</td>
<td>Case-case</td>
<td>383</td>
<td>MLH1 rs1800734 SNP</td>
<td>MLH1 methylation</td>
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<td>Chen, 2007 (31)</td>
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<td>766 cancer cases, 1,098 controls</td>
<td>MLH1 rs1800734 SNP</td>
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<td>Samowitz, 2008 (33)</td>
<td>Colon cancer</td>
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<td>795 cancer cases, 1,968 controls</td>
<td>MLH1 rs1800734 SNP</td>
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<td>Allan, 2008 (34)</td>
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<td>MLH1 loss of expression</td>
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<td>Campbell, 2009 (35)</td>
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<td>de Vogel, 2009 (39)</td>
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<td>373 cancer cases, 4,774 in subcohort</td>
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<td>Schernhammer, 2010 (40)</td>
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<td>Prospective cohort</td>
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<td>LINE-1 hypomethylation</td>
<td>Lack of folate and excess alcohol are associated with increased incidence of LINE-1 hypomethylated cancer but not that of LINE-1 methylation-high cancer.</td>
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<td>Curtin, 2011 (43)</td>
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<td>MTHFR rs1801131 SNP and folate intake interact to modify an association with CIMP-positive rectal cancer</td>
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<td>Ogino, 2007 (44)</td>
<td>Colorectal cancer</td>
<td>Case-case (in prospective cohort studies)</td>
<td>182</td>
<td>MGMT rs16906252 SNP</td>
<td>MGMT methylation</td>
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<td>Hawkins, 2009 (45)</td>
<td>Colorectal cancer and normal individuals (colon mucosa)</td>
<td>Case-case</td>
<td>1,039 cancer cases, 97 normal samples from cancer patients, 20 normal mucosa samples from persons without cancer</td>
<td>MGMT rs16906252 SNP</td>
<td>MGMT methylation in cancer and normal colon mucosa</td>
<td>Positive</td>
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<td>Candiloro, 2009 (46)</td>
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<td>89</td>
<td>MGMT rs16906252 SNP</td>
<td>MGMT methylation (in peripheral blood cells)</td>
<td>Positive</td>
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<td>Leng, 2011 (47)</td>
<td>Lung adenocarcinoma</td>
<td>Case-case</td>
<td>179</td>
<td>MGMT rs16906252 SNP</td>
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<td>Kristensen, 2011 (48)</td>
<td>Malignant pleural mesothelioma</td>
<td>Case-case</td>
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<td>MGMT rs16906252 SNP</td>
<td>MGMT methylation</td>
<td>Positive</td>
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<td>Pedroni, 1999 (49)</td>
<td>Colorectal cancer</td>
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<td>78 (all synchronous cancer patients and 0 solitary tumors)</td>
<td>Tumor synchronicity/metachronicity</td>
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<td>Concordant pattern of MSI status in synchronous/metachronous tumor pairs</td>
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<tr>
<td>Velayos, 2005 (50)</td>
<td>Colorectal cancer</td>
<td></td>
<td>110 (all synchronous/metachronous cancer patients and 0 solitary tumors)</td>
<td>Tumor synchronicity/metachronicity</td>
<td>MSI</td>
<td>Concordant pattern of MSI status in synchronous/metachronous tumor pairs</td>
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<td>Nosho, 2009 (51)</td>
<td>Colorectal cancer</td>
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<td>1,113 (29 synchronous cancer patients)</td>
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<td>Positive; concordant pattern of LINE-1 hypomethylation in synchronous tumor pairs</td>
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<td>Konishi, 2009 (52)</td>
<td>Colorectal cancer</td>
<td>Case-case</td>
<td>97 (28 synchronous cancer patients)</td>
<td>Tumor synchronicity</td>
<td>CIMP</td>
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<tr>
<td>Gonzalo, 2010 (53)</td>
<td>Colorectal cancer</td>
<td>Case-case</td>
<td>82 (37 synchronous cancer patients)</td>
<td>Tumor synchronicity/metachronicity</td>
<td>Methylation in MGMT, RASSF1</td>
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<td>Slattery, 2000 (54)</td>
<td>Colon cancer</td>
<td>Case-control</td>
<td>1,510 cancer cases, 2,410 controls</td>
<td>BMI</td>
<td>MSI</td>
<td>Obesity is associated with MSS cancer but not MSI-high cancer</td>
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<td>Satia, 2005 (55)</td>
<td>Colon cancer</td>
<td>Case-control</td>
<td>486 cancer cases, 1,048 controls</td>
<td>BMI</td>
<td>MSI</td>
<td>Obesity is associated with MSS cancer but not MSI-high cancer</td>
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<tr>
<td>Slattery, 2007 (56)</td>
<td>Colon cancer</td>
<td>Case-control</td>
<td>1,154 cancer cases, 2,401 controls</td>
<td>BMI</td>
<td>CIMP</td>
<td>Obesity is associated with CIMP-negative cancer but not CIMP-high cancer</td>
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<tr>
<td>Campbell, 2010 (57)</td>
<td>Colorectal cancer</td>
<td>Case-control</td>
<td>1,250 cancer cases, 1,880 controls</td>
<td>BMI</td>
<td>MSI</td>
<td>Obesity is associated with MSS cancer but not MSI-high cancer</td>
</tr>
<tr>
<td>Sinicrope, 2010 (58)</td>
<td>Colon cancer</td>
<td>Case-case</td>
<td>2,222</td>
<td>BMI</td>
<td>MSI</td>
<td>Negative (inverse)</td>
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<tr>
<td>Kuchiba, 2012 (59)</td>
<td>Colorectal cancer</td>
<td>Prospective cohort</td>
<td>536 cancer cases, 109,051 participants</td>
<td>BMI</td>
<td>FASN expression</td>
<td>Obesity is associated with FASN-negative cancer but not with FASN-positive cancer</td>
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<td>Slattery, 2000 (54)</td>
<td>Colon cancer</td>
<td>Case-control</td>
<td>1,510 cancer cases, 2,410 controls</td>
<td>Smoking</td>
<td>MSI</td>
<td>Smoking is associated with MSI-high cancer but not MSS cancer</td>
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<td>Wu, 2001 (60)</td>
<td>Colon cancer</td>
<td>Case-case</td>
<td>276</td>
<td>Smoking</td>
<td>MSI</td>
<td>Positive</td>
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<td>Lüchtenborg, 2005 (61)</td>
<td>Colorectal cancer</td>
<td>Case-cohort</td>
<td>650 cancer cases, 2,948 in subcohort</td>
<td>Smoking</td>
<td>APC mutation</td>
<td>Negative (inverse)</td>
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<td>Chia, 2006 (62)</td>
<td>Colorectal cancer</td>
<td>Case-control</td>
<td>1,792 cancer cases, 1,501 controls</td>
<td>Smoking</td>
<td>MSI</td>
<td>Smoking is associated with MSI-high cancer but not MSS cancer</td>
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<td>Samowitz, 2006 (63)</td>
<td>Colon cancer</td>
<td>Case-control</td>
<td>1,315 cancer cases, 2,392 controls</td>
<td>Smoking</td>
<td>CIMP, BRAF mutation</td>
<td>Smoking is associated with CIMP-high cancer and BRAF-mutated cancer but not CIMP-negative or BRAF-wild-type cancer</td>
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<td>Poynter, 2009 (64)</td>
<td>Colorectal cancer</td>
<td>Case-control</td>
<td>1,564 cancer cases, 4,486 controls</td>
<td>Smoking</td>
<td>MSI</td>
<td>Smoking is associated with MSI-high cancer but not MSS cancer</td>
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<td>Rozek, 2010 (65)</td>
<td>Colorectal cancer</td>
<td>Case-control</td>
<td>1,297 cancer cases, 2,019 controls</td>
<td>Smoking</td>
<td>BRAF mutation</td>
<td>Positive</td>
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<tr>
<td>Limsui, 2010 (66)</td>
<td>Colorectal cancer</td>
<td>Prospective cohort</td>
<td>540 cancer cases, 41,528 participants</td>
<td>Smoking</td>
<td>MSI, CIMP, BRAF mutation</td>
<td>Smoking is associated with CIMP-high cancer, MSI-high cancer, and BRAF-mutated cancer but not CIMP-negative, MSS, or BRAF-wild-type cancer</td>
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Abbreviations: BMI, body mass index; CIMP, CpG island methylator phenotype; MSI, microsatellite instability; MSS, microsatellite stability; SNP, single nucleotide polymorphism.

a The official symbols approved by the Human Genome Organization’s Gene Nomenclature Committee are used for genes and gene products (APC, BRAF, CDKN2A, FASN, MGMT, MLH1, and MTHFR).
The importance of integration of divergent disciplines has repeatedly been discussed (7–10). As an initial step toward such integrated scientific disciplines, our discussion is primarily focused on the integration of molecular pathology and epidemiology—that is, molecular pathological epidemiology (MPE) (4–6). This integrated field improves understanding of human diseases and may provide a model for future integrations of other subspecialties. Thus, this article will help foster an interdisciplinary integration of a wide variety of other fields in biomedical, public health, population, and social science and an establishment of hybrid disciplines.

**PATHOLOGY EDUCATION IN PUBLIC HEALTH SCHOOLS**

Epidemiology is a core component of public health school curricula, reflecting its pivotal role in the health sciences. However, in public health schools, most students get little, if any, opportunity to study pathology, resulting in limited understanding of disease pathogenesis. Recently, integration of pathology into epidemiologic studies has become increasingly common (4, 6, 11), because many diseases are being defined by molecular pathogenic mechanisms. As current disease classification schemes become more reflective of pathobiology (4, 6, 11), epidemiologists must appreciate the rationale behind disease classifications and subtyping in their study designs. Possibilities for pathology training include: lectures by pathologists, rotations at clinical pathology laboratories, and participation in MPE research.

**Epidemiology education in pathology and medical schools**

Pathology is a core component of medical school curricula, reflecting its central role in medical education. In addition, training in pathology as a medical specialty occurs as a part of postgraduate medical education. Unfortunately, most pathologists and other physicians have limited knowledge of epidemiology. Education in epidemiology can provide knowledge of proper study design, data interpretation, and statistical and causal inferences, which are necessary in correlative pathology research. However, neither epidemiology nor biostatistics is a common component of pathology training (12). Only a minority of pathologists and physicians have sufficient understanding of epidemiology to apply relevant principles to their investigations. Epidemiology can provide ideas about potential etiologic factors and can teach pathologists proper study design and conduct in terms of population selection, sample size determination, statistical methods, causal inference, assessment of generalizability, and validation of findings. In our opinion, pathology training and medical school programs should be encouraged to include formal epidemiology courses or lectures, preferably as a mandatory requirement.

Substantial concerns have been raised about the validity of much of published scientific research (13–17). Published studies are often called into question for inappropriate study design, biased sample selection, inadequate sample size, inappropriate statistical methods, etc. Studies conducted by pathologists and other clinical investigators are commonly biased, because cases typically come from tertiary referral medical centers. Those common problems in study design and analysis should be considered, and the best attempts to improve study design must be made.

**MPE as an interdisciplinary science**

MPE is a relatively new field of science, and no standard research guidelines have yet been established, as they have been for observational epidemiology (STROBE, which stands for Strengthening the Reporting of Observational Epidemiology) (16, 17, 75) and molecular epidemiology (STROBE-ME) (76). For MPE, there are specific caveats in addition to the typical limitations in observational epidemiology (6). We plan to develop international guidelines for MPE research (STROBE-MPE) as a logical extension of STROBE. To develop and implement guidelines, we need to produce more scientists with cross-disciplinary training and expertise in molecular pathology and epidemiology.

**Necessity for MPE guidelines and interdisciplinary scientists**

MPE is a relatively new field of science, and no standard research guidelines have yet been established, as they have been for observational epidemiology (STROBE, which stands for Strengthening the Reporting of Observational Epidemiology) (16, 17, 75) and molecular epidemiology (STROBE-ME) (76). For MPE, there are specific caveats in addition to the typical limitations in observational epidemiology (6). We plan to develop international guidelines for MPE research (STROBE-MPE) as a logical extension of STROBE. To develop and implement guidelines, we need to produce more scientists with cross-disciplinary training and expertise in molecular pathology and epidemiology.

**Integrated educational programs in public health and medical schools**

Pathology and epidemiology are inherently complementary disciplines. Both fields encompass the entire spectrum
Figure 1. Collaborative relation between pathology and epidemiology. Both pathology and epidemiology are method-based disciplines and fields of study covering the entire spectrum of human diseases. The methods of pathology and those of epidemiology can complement each other and can be synergized to create an integrated science: molecular pathological epidemiology. In the integrated interdisciplinary environment, pathologists and epidemiologists can help each other and benefit from educating each other as illustrated.

Figure 1. Collaborative relation between pathology and epidemiology. Both pathology and epidemiology are method-based disciplines and fields of study covering the entire spectrum of human diseases. The methods of pathology and those of epidemiology can complement each other and can be synergized to create an integrated science: molecular pathological epidemiology. In the integrated interdisciplinary environment, pathologists and epidemiologists can help each other and benefit from educating each other as illustrated.

of human diseases, generate hypotheses from observations, and attempt to elucidate disease etiologies. This shared scientific framework is the foundation of the field of MPE (4, 6) and should serve as the underpinning for integrated pathology and epidemiology educational programs.

Eventually, there will be a universal collaborative relation between pathology and epidemiology (Figure 1), which will facilitate high-quality health science at the molecular, cellular, and population levels. Pathology is capable of providing detailed insights into pathogenic mechanisms and improving understanding of disease processes. In comparison, epidemiology can identify novel potential etiologic factors for pathologic processes. Pathologists also often contribute to early recognition of new exposure-disease associations, such as those among microbiota, inflammation, and cancers (77–86). Another crucial component of the discipline of epidemiology is expertise in study designs, statistical methods, and causal inference, all of which are of utmost importance in correlative clinicopathologic and translational research.

As an integrated discipline, MPE will draw on the knowledge base of pathology and epidemiology. A scientist with integrated MPE training would have the skills to consider pathogenic hypotheses, design and conduct studies, analyze data, make inferences, and validate/generalize findings in populations. This type of researcher can work well with other investigators in diverse disciplines and can “translate” between collaborators who do not share this scientific background.

For these reasons, it is desirable to establish integrated educational programs of pathology and epidemiology. In the current system, such educational opportunities will require the merger of resources held by medical schools, public health schools, and hospitals with pathology training programs. We acknowledge that dual-degree Doctor of Medicine/Master of Public Health programs exist, but they are not standardized and do not systematically offer training in epidemiology and biostatistics. We hope that institutions will adopt integrated educational programs across medical and public health schools and hospitals to meet these interdisciplinary research and educational needs.

SUBSTANTIAL ROLE OF FUNDING AGENCIES

Most biomedical and public health research projects are funded by governments or nongovernment organizations. Currently, relatively few funded projects integrate molecular pathology and epidemiology or population health science. There exists a significant knowledge gap between various etiologic factors and cellular and molecular changes that occur during disease evolution, and interdisciplinary investigations in these areas are needed. Funding agencies need to increase career development grants in order to nurture the next generation of scientists who can fully integrate the fields of molecular pathology and epidemiology.

CONCLUSIONS AND FUTURE DIRECTIONS

Over the last century, biomedical and public health sciences have been practiced in a highly compartmentalized way, typically missing the value of the perspectives gained through integration of divergent scientific fields. MPE (4–6) is an example of the integration of molecular biologic and population health science in order to gain insights into disease etiology and pathogenesis. MPE research stands to benefit both individuals and the population at large. To advance integrated MPE research, appropriate interdisciplinary educational programs are needed. This will require reforms in medical and public health education as well as postgraduate pathology training. We need to be open-minded and flexible in designing optimal education and training programs at various levels. We believe that convergence and integration of scientific disciplines should become more commonplace in the future, as MPE will prove to be a successful field.

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Author affiliations: Cancer Epidemiology Program, Dana-Farber/Harvard Cancer Center, Boston, Massachusetts (Shuji Ogino, Andrew H. Beck, Edward Giovannucci); Department of Pathology, Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts (Shuji Ogino, Emily E. King, Danny A. Milner); Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts (Shuji Ogino, Edward Giovannucci); Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts (Shuji Ogino); Department of Pathology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts (Andrew H. Beck); Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland (Mark E. Sherman); Department of Immunology and Infectious Diseases, Harvard School of Public Health, Boston, Massachusetts (Andrew H. Beck), Dana-Farber/Harvard Cancer Center, Boston, Massachusetts (Shuji Ogino, Edward Giovannucci); Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts (Shuji Ogino); Department of Pathology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts (Andrew H. Beck); Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland (Mark E. Sherman); Department of Immunology and Infectious Diseases, Harvard School of Public Health, Boston, Massachusetts (Andrew H. Beck), Dana-Farber/Harvard Cancer Center, Boston, Massachusetts (Shuji Ogino)
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REFERENCES


