Special Edition

Duncan C. Thomas, Ph.D.
Professor and Director, Biostatistics Division
University of Southern California

163rd Cutter Lecture on Preventive Medicine
### *What Does Precision Medicine Have to Say About Prevention*
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163ʳᵈ Cutter Lecture
Lecturer: Duncan C. Thomas, Ph.D.

Cutter Lecture on Preventative Medicine

Since 1912, the Cutter Lecture on Preventive Medicine has been one of the most respected presentations, especially in the field of epidemiology. The lectures are administered by the Department of Epidemiology at the Harvard T.H. Chan School of Public Health according to the bequest from John Clarence Cutter, MD (1851 - 1909), a graduate of the Harvard Medical School. He specified that the lectures be delivered in Boston, free of charge to medical professionals and the press. Covering a range of public health topics, the lectures remain dedicated to enhancing the physical and social welfare of the world's population.
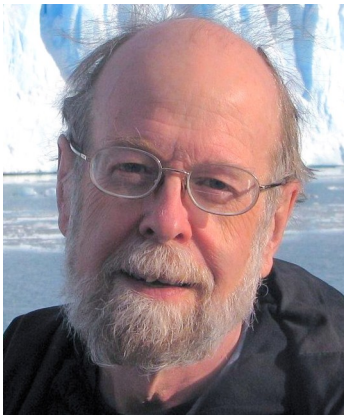
Duncan C. Thomas, Ph.D.

Dr. Thomas is Professor of Biostatistics in the Department of Preventive Medicine, and Verna R. Richter Chair in Cancer Research at the University of Southern California Keck School of Medicine. He received his Ph.D. from McGill University in 1976. His primary research interest has been in the development of statistical methods for environmental and genetic epidemiology, with numerous collaborations in both areas. On the environmental side, he has been particularly active in radiation carcinogenesis and air pollution health effects research, notably as one of the senior investigators on the Southern California Children's Health Study and as a member of President Clinton's Advisory Committee on Human Radiation Experiments. On the genetic side, he is a coinvestigator in the NCI's Colon Cancer Family Registry, the Genetic Analysis Workshop, the ENDGAME consortium to develop methods for genome-wide association studies, and past President of the International Genetic Epidemiology Society. Dr. Thomas has numerous publications, including the textbooks Statistical Methods in Genetic Epidemiology (Oxford University Press, 2004) and Statistical Methods in Environmental Epidemiology (Oxford University Press, 2009). These three broad areas of interest make him uniquely qualified to address methodological challenges in studying gene-environment interactions.

What Does Precision Medicine Have to Say About Prevention

There's a lot of buzz these days about "personalized medicine," which accounts for individual differences in genetics, environmental exposure, and lifestyle in treating and preventing disease. Much of the related activity currently focuses on developing genetically targeted treatments for cancer, but the concept may also have potential relevance for disease prevention. However, the central question we must consider when weighing the merits of a personalized approach, suggested Duncan Thomas, presenter of the 163ʳᵈ Cutter Lecture at the Harvard T.H. Chan School of Public Health on May 6, is whether or not genetically targeted prevention is worth the effort and expense. While personalization may indeed be a revolutionary approach to cancer *treatment*, the more precisely patients are targeted, the more expensive the drug development process becomes. Targeted *prevention*, which is more complex, may present even greater economic cost-benefit challenges.

Epidemiologists strive to discover both the underlying causes of individual cases of disease and the determinants of incidence rate across populations. They explore *associations* between exposure and disease, as well as *causation*—when changing exposures alters outcomes. So, in the ongoing quest to prevent various types of cancer, does it make sense to identify and target high-risk individuals in order to protect those who are most susceptible versus pursue a population-wide intervention strategy to control the catalysts of incidence? Essentially, as Thomas went on to explain, the dilemma comes down to weighing the benefits of genetically targeted prevention efforts against reducing the overall burden of disease.

Is Cancer Just a Matter of Bad Luck?

Many scientists believe that a better understanding of the interactions between human genes and environmental exposures will lead to novel prevention strategies based on modifiable risk factors. However, it is important to remember that some people are completely immune to disease while others are susceptible, regardless of exposure. Many experts contend that individual variability in susceptibility to disease and sensitivity to environmental exposures accounts for the phenomenon that allows some heavy smokers to live cancer free to a ripe old age while younger nonsmokers die of lung cancer. Other scientists argue that cancer is an inherently random process, and all of us face the same underlying risk.

> **"To ask why a particular individual failed to get cancer is probably as meaningless as asking why a particular uranium atom failed to decay."**
> -Julian Peto, "Genetic Predisposition to Cancer," *Banbury Report*

Despite these different perspectives, researchers concur that genetics and exposure, which can be quantified, influence the rate of cancer development. Therefore, potentially modifiable risk factors are likely worthy targets for primary prevention strate-

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gies to limit mortality. Yet, again, there is a caveat. Genetic risk scores provide only modest predictive value for most cancers.

> **"Only a third of the variation in cancer risk… is attributable to environmental factors or inherited predispositions. The majority is due to 'bad luck'… random mutations in normal stem cells."**
> -Christian Tomasetti and Bert Vogelstein, "Variation in Cancer Risk…,"*Science* (2015)

Would Targeted Screening Reduce the Incidence of Colon Cancer?

Despite the existence of fourteen established and mostly modifiable risk factors associated with colorectal cancer (i.e., body mass index, alcohol consumption, and sedentary lifestyle), comprehensive genetic risk score analyses have revealed no significant gene-environment interactions associated with the disease.

According to a recent perspective in the *New England Journal of Medicine*, there has been a nearly 50 percent decline in incidence and mortality related to colorectal cancer since 1975. But while evidence documents the effectiveness of various screening methods, other factors, including early detection, improvements in treatment, and changes in risk factors, are likely responsible for the decreases in incidence and mortality. Uniform screening regimens (i.e., baseline colonoscopy at age 50) are a relatively recent reality.

So is a baseline colonoscopy for all at age 50 best practice prevention, or would targeted screening programs based on risk factors and genetics yield better outcomes?

The NEJM study did not address the potential advantages of personalized prevention or screening programs. However, Thomas and colleagues compared current population-based screening recommendations with a genetically targeted approach based on risk and family history, and found that in the latter model, men at high risk should first be screened at age 42 and men at low risk at age 52. The findings were similar for women, but initial screens would be recommended five years later (i.e., age 47 for high risk, age 57 for low risk).

Since scientists are unable to observe disease development in real time and accurately estimate the effects of various screening programs, they create simulations to mimic the disease process. Thomas relied on a simulation cohort study to examine factors that influence colon cancer development and screening behavior. He simulated times to polyp development, growth, malignancy, and cancer diagnosis, as well as screening patterns based on individual and family history.

Thomas warned that standard analysis of some simulations like this one can yield incorrect conclusions. For example, risk of colon cancer should be associated with the number of polyps discovered, not number of screens, because those with a personal or family history of polyps and/or colon cancer tend to opt for more frequent screenings. A more sophisticated analysis that employs propensity score weighting—accounting for the number of previous screens, family history, and other risk factors—enhances the ability to accurately estimate screening effectiveness. Thomas's research revealed fewer clinically diagnosed cancers and a slight increase in screen-detected cancers using targeted approaches.

Does Screening Save Lives?

The unfortunate reality is most people don't benefit from colonoscopies in terms of cancer detection or prevention. The preparation and procedure are unpleasant, especially for older people and those in poor health. And, the emphasis on screening may distract from focusing on primary prevention. So it seems sensible to target those who face the greatest risk… but it still might not be the best approach.

In one study, researchers concluded that without any screening, nearly 5,000 per 100,000 people would develop colon cancer. A population-wide screening program, adhering to current age and results-based recommendations, would reduce that number to less than 2,000 cases. If screening programs were stratified by family history and other risk factors, the number of cancer cases per 100,000 would drop to approximately 600. Also important to note is the fact that significantly fewer screens are required for a program that tests on the basis of both family history and other risk factors. However, it is not clear that the targeted approach results in a significant enough impact to justify the complexity involved, including obtaining information on individual risk factors, family history, and genetics. Do the potential benefits warrant the effort and expense? Also critical to consider is that while targeted screening may reduce cancer incidence, the impact on mortality remains unknown.

The Jury Is Still Out on Precision Medicine

"Precision medicine can potentially transform the treatment and prevention of disease, but we have a long way to go in terms of more effectively identifying who should be targeted," said Thomas. More importantly, not all targeted programs will be practical or cost efficient.

> **"The biggest bang for the buck will be in identifying those who have unusually high genetic sensitivity to avoidable exposures or modifiable behavioral factors. But simply predicting genetic risk is not sufficient; we need evidence of gene-environment interaction."**

Thomas concluded by saying that scientists should not let the enthusiasm for personalized medicine and emphasis on genetics distract them from pursuing opportunities for classical population-wide public health approaches to prevention. "Translating science into public policy is something many scientists are uncomfortable doing," observed Thomas. "But I feel we have an obligation to speak out about prevention within our area of expertise. I think [John Clarence] Cutter would want us to do so."

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