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*Pitt Med* is published by the Office of the Dean and Senior Vice Chancellor for the Health Sciences in cooperation with the alumni and public affairs offices. It is produced quarterly for alumni, students, staff, faculty, and friends of the School of Medicine. PR 6713

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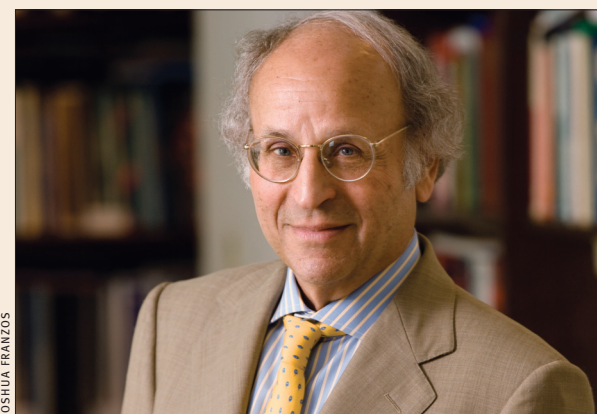
**S**cience, in the very act of solving problems, creates more of them.  
—Abraham Flexner

In 1950s Texas, Pitt alumnus Robert Egan (MD '50) spent countless hours perfecting a technique to detect masses in women's breasts by X-ray and sharing his knowledge with other physicians. Decades after Egan's noble efforts, we are in the middle of a confusing and very public debate regarding who should have routine mammograms.

I suggest that it is dyssynchrony between technology and biologic truth that drives this debate.

As we attempt to address profound questions in science, we often spur the development of new technologies. Some of these technologies, e.g., gene sequencing, seem to match, in time, the emergence of scientific insight and its application to diagnosis and/or treatment. This is scientific "zeitgeist." Other technologies may outpace our intellectual ability, at a point in time, to fully grasp their implications. This seems to be the case with mammography. Prescribing routine mammograms for women 40 and older made sense when we thought that all breast cancers behaved similarly and had to be eliminated at the earliest possible time to avoid metastases. Recently, however, we have come to realize that there is a broad spectrum of breast cancer behavior even if the cells look identical in the microscope. In fact, there seems to be a bell-shaped curve: At one end are tumors having early and aggressive metastatic capability; at the other end, little or no metastatic risk. The majority of breast cancers fall in between. In the highest-risk group, the tumor cells may metastasize even before they are detectable by mammography. Dr. Egan attempted to help doctors answer this question, *Who needs to be treated for breast cancer?* The more we learn, the more we realize we need to first determine, *Who is at risk?*

What has our 50-plus-year insight into the structure and function of DNA told us about who is at risk of disease? Now we understand that mutations in the *BRCA* genes will commonly eventuate in aggressive breast or ovarian tumors. But we can claim such genetic certainty with only a small fraction of most diseases. Even with the rapid advances and reduced cost of whole-genome sequencing, in the case of many diseases, including cancer, we are still years away from being able to identify who is truly at risk of morbidity and mortality and who is not. *BRCA* is the low-hanging fruit, but disease expressivity likely depends not only on mutations and single nucleotide polymorphisms (variations), but on the dynamics, compartmentalization, half-life et al. of messenger RNA and its micro-RNA inhibitors; protein-protein interactions; membrane dynamics; and other molecular risk factors. This understanding of personal risk will ultimately depend on further advances in technology and on ultrasophisticated computational and systems biology. At present, in the case of breast cancer, screening will likely benefit some women, but we do not yet have any way of identifying those women, other than in the case of *BRCA* mutations. Our efforts should be focused on further developing the technologies and computational methods that will tell us who should be screened frequently and who needn't be. Hopefully, technology and scientific insight will merge (another zeitgeist). Even so, if we had that knowledge today, there would still be women with the tiniest of tumors who nonetheless are at serious risk of metastases. Sadly, their cancers may not be curable (at least at present), no matter how early we identify them. The "mammography wars" may well offer a lesson for much, if not all, of human illness.



JOSHUA FRANZOS

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