Major Trends in the Imaging Sciences: 2007 Eugene P. Pendergrass New Horizons Lecture¹

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Editor's Note: The video recording of Dr Zerhouni's 2007 Eugene P. Pendergrass New Horizons Lecture, complete with audio, images, and movies, is available for viewing at <http://www.rsna.org/GeneralSessions/Zerhouni/index.html>. This article is a slightly abridged version of the lecture.

It was a real pleasure and privilege to be asked to share my thoughts about the likely place of imaging sciences over the next few decades. And that pleasure is amplified by the feeling that this is, for me, a kind of homecoming. I remember the 25 years when, without fail, I came to the Radiological Society of North America (RSNA) Scientific Assembly and Annual Meeting, and I remember the 25 times when, without fail, my children would say, "Well, that means we are going to have a shorter Thanksgiving than everybody else." When I became director of the National Institutes of Health (NIH) back in 2002, my younger son said, "Finally, we're going to have a real Thanksgiving."

When you run a large agency with an annual budget of \$29 billion, you make a lot of new friends very fast. But this is why the friends I have made here over these 25 years, coming up through the ranks, are so precious to me: I know you are true friends.

And so, my friends, I now turn to the task you have given me: sketching the horizons I see for imaging sciences. These horizons will extend even beyond radiology and touch on the whole of 21st century biologic sciences. To that end, I will begin by describing what I see as the major trends in health and in science. Then, I will discuss what drives the need for further advances in the imaging sciences. From there, I will move to the real frontiers, or horizons, of imaging innovation. Finally, I will conclude by proposing a unifying vision, and a unifying redefinition, of how we might evaluate our progress over the next decades.

First, I will give a bit of historical perspective about the development of the NIH. It is a particularly interesting history, because, as you will see, whenever NIH was transformed, reformed, or in some substantial way augmented, it was as the result of two forces: public health need and scientific advance. These historical forces have most recently come together in the creation of our newest institute, the National Institute of Biomedical Imaging and Bioengineering (NIBIB).

The NIH started as a small bacteriologic laboratory in the U.S. Marine Hospital on Staten Island, NY, back in 1887 (1). Soon dubbed—rather generically—the "Hygienic Laboratory," it was led by its founder, Joseph J. Kinyoun. It was created because the germ theory of disease had recently been demonstrated by Robert Koch and Louis Pasteur, and it had quickly become the dominant theory of biomedical research. This was the scientific development. The late 19th century public health need for a way to understand and control infectious disease is so evident that I will not belabor it here. As bacteriology proved its usefulness, the laboratory was moved to Washington, DC, and its divisions and services were expanded.

The next big transformation came in 1930, when the Ransdell Act was signed into law. The act transformed the Hygienic Laboratory into the National Institute—singular—of Health. The driving force behind this change was the American Chemical Society (2), largely because after World War I certain influential American chemists were eager to apply their science to improving American health. Also, just before the war began, the German chemist Paul Ehrlich had shown how this might be done. Ehrlich believed that one could study the chemical structure of drugs and use that knowledge to fight diseases more effectively. Some described his work as looking for

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“magic bullets”; he coined the phrase “chemotherapy.” His most notable breakthrough came with his 1909 demonstration that an arsenical substance, Salvarsan (arsphenamine), could be used to treat syphilis. His discovery was put to good—and frequent!—use during the upcoming war. Moreover, it sparked medical imaginations the world over. It was becoming clear that progress in medicine was going to be related to our mastery of biochemistry. The National Institute of Health would help blaze the trail.

Continuing this pattern of development where science and public health needs converged, the National Cancer Institute (NCI) was created in 1937 (3). In the 20th century, cancer was an escalating public health concern. At the same time, cancer treatment with radium was raising hopes that the disease might be cured. It was also encouraging researchers to ask new experimental questions. The new NCI was tasked with distributing extramural grants to support further research. Then, near the close of World War II, President Franklin D. Roosevelt signed the Public Health Service Act into law. Subsequently, the National Institute of Health, like NCI, was charged with conferring extramural grants. It was also set on a path that had begun with the formal attachment of NCI in 1944. Soon, more institutes were added, their focus dictated by the convergence of scientific and public health needs. By 1948, the parent institute’s name was changed to the plural. Today, NIH boasts 27 institutes and centers. The last of these, officially established in 2000, was none other than the NIBIB. Why, then, did NIH and the radiology community create this institute?

Those of you who know the history cannot fail to conclude that there was, in fact, a convergence between imaging sciences and health needs. This theory of convergence and creation underlies much of what I will convey.

Let us start with the recent impact of medical imaging. Among the medical innovations of the past 3 decades, as ranked by physicians, three of the top five are directly related to imaging advances: (a) magnetic resonance (MR) imaging

and computed tomography (CT), (b) balloon angioplasty, and (c) mammography (4). Many other imaging-related advances occupy positions in the top 15 innovations. Indeed, as crucial as new ideas are to the advancement of science, technologic innovation is the engine of scientific progress. The two work in tandem to move science forward.

In that same 30-year span, radiology has become a fundamentally interdisciplinary science. No other field of science has integrated physics and computer sciences into itself as rapidly and successfully as our field has done. We—our generation of radiologists—succeeded because we realized that the progress of our discipline was going to be determined precisely by our ability to break barriers between disciplines—to bring together scientists from different walks of life, so that they could achieve what they have achieved. In a very real sense, my personal training through the RSNA and my career in radiology have been essential to my ability to assess the major trends in the broader biomedical enterprise that I currently oversee. And I see quite clearly that the combination of technologic innovation and biologic understanding is the fundamental driver of scientific change.

Today, the imaging sciences have found a home at NIH within NIBIB. I am delighted to see how this institute, in the 5 short years since it began functioning, has changed not only what is done in imaging, but also the thought process guiding it. Its successes have strengthened our belief that we can lead the development—and accelerate the emergence—of completely novel technologies, not only for imaging but for understanding biology as a whole. As the director of NIBIB, Roderic I. Pettigrew, PhD, MD, likes to say, “We are the NIH engine for integration of the physical and biological sciences.” The interdisciplinary integration of different walks of scientific life will continue to determine the success or failure of the scientific imaging world.

I have mentioned current trends in applying imaging to medical needs. But what are the broader trends in health and science? It is a crucial question,

because these trends give particular urgency to our efforts to improve imaging sciences. I see five essential public health trends before us. First, it has been remarkable to see the success we have had in controlling late-stage and acute forms of diseases. This is why we now have a fundamental shift in the epidemiology of disease, from acute to chronic conditions. Eighty percent of our health care expenditures are related to chronic diseases. A second challenge is demographics. The aging of the population will drive not only the type of diseases that will confront us but also the distribution of our efforts. Third, health disparities remain a serious challenge, both within countries and between countries on a global level.

Problems at once national and global bring up our fourth challenge: emerging and reemerging infectious diseases. We have seen this in the past few months with drug-resistant staphylococcal infections. Finally, we will see the emergence or escalation of noncommunicable diseases. The obesity epidemic is a prototype of this challenge.

I believe that these public health challenges will force a transformation of medicine and health. Let me be explicit. If we practice medicine in 20 years the way we practice it today, we will have failed. We will have failed the challenge of this century, as physicians and as health care providers. Why? We will have failed because of the socioeconomics, the demographics, and the landscape of disease—but also because of new scientific challenges and opportunities before us. A transformation is in the air, regardless of what we do. What we do, however, will help shape that transformation. These eventualities raise important questions: what are the broad contours of this transformation,

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and where might imaging sciences fit in directing it?

My sense that we are in a transformative period of history drove me to engage NIH in a process that gave rise to the Roadmap for Medical Research (5). Shortly after I arrived at NIH, I oversaw an extensive analysis that engaged hundreds of people, from stakeholders and health care providers to individual citizens and diverse scientists, to address this issue. We concluded that three trends were going to be very important in science. The first, we have called "New Pathways to Discovery." It is dedicated to developing new methods, technologies, and concepts to understand the complexity of biologic systems. The second, "Research Teams of the Future," is founded on the premise that today's science cannot be conducted without breaking barriers between its disciplines. In other words, the disciplines of science are not an end in themselves, they are a means—and we need to facilitate collaboration across scientific fields to encourage true interdisciplinary exchange. Last but not least is "Re-engineering the Clinical Research Enterprise." Such reengineering will provide a wholly different conceptual approach to how we train the next generation of clinician-scientists. This new approach will be essential to the effective translation of complex science into clinical practice. These, then, are the three legs, or pillars, of the NIH roadmap.

In the end, our collaborative effort to define the roadmap also helped us define its ultimate destination. This involves a paradigm shift. Ever since the days of Hippocrates, western medicine has rested on a curative paradigm. We have waited for symptoms to appear before intervening in a disease process, and we have done this because we lacked the ability to identify patients ahead of time. Today, however, molecular or cellular signatures are increasingly telling us how to intervene and in whom. This knowledge will ultimately give us the power to transform our traditional curative paradigm into a preemptive one. We must intervene in disease processes before symptoms ap-

pear and function is lost. Already today, we can do this to a greater extent than ever before, because we understand better than ever before the preclinical molecular events of disease. We are better able to detect which patients are at risk. Progress in imaging has been central to this medical progress. It will be essential if we are to transform the way we practice medicine and enter a preemptive medical era.

This is my dream. And if you look to the horizon that is our best destination, you will see where our fields need to go. If medicine is to become preemptive, it must be based on what I call the four Ps. First, we need to be more *predictive*, by having better disease signatures and better disease classification. Actually, I predict that in the next 50 years we will completely reclassify our understanding of the diseases we suffer from today. Even now, when reclassified on the basis of molecular behavior, "cancer" is some 200 different conditions. The same is true for diabetes and for heart disease.

The second P is for *personalized*. We are aware that human variation plays an enormous role in our ability to control disease in individual patients. Further individual targeting of treatment will be necessary. We can no longer apply one-size-fits-all procedures to the entire population. We must personalize those procedures. Once we understand the early events that lead to disease processes, such as those for Alzheimer disease or diabetes, we will be able to intervene early in that process and *preempt* the disease—the third P. The best example I can give that is already in place is the vaccine against cervical cancer. The vaccine preempts this cancer. Ultimately, preemptive medicine will require a fundamental change in the philosophy and culture of how we deliver health care. No longer will patients come to doctors and have doctors tell them what to do. Instead, there will be a cooperative network linking patients, their communities, and their health care providing institutions. This brings up the fourth P: a *participatory* approach to medical care. Finally, if the four Ps are to be realized, they will have to rest on the latest advances in science.

The scientific advances that we have witnessed over the past 10 years have been nothing less than radically different from what we have seen in the past 50 years. It is evident that these changes are occurring at an increasing pace.

The start of the Human Genome Project in 1990 got this process officially underway. The NIH and the Department of Energy led this international consortium, which had as its goal the sequencing of all 3 billion base pairs of the human genome. All data generated by participants were made available online, freely and rapidly. We celebrated the completion of the human genome sequence in April 2003, just as we were celebrating the 50th anniversary of Watson and Crick's seminal description of the DNA double helix. And, 6 months previously to that, NIH's National Human Genome Research Institute had launched the International HapMap Project. The HapMap project sought to catalogue haplotypes in the human genome. NIH supported this effort because we knew it would help speed the translation of the Human Genome Project's accomplishments into improved understanding of disease processes. HapMap achieved its goal in 3 short years.

Still, I was not convinced that we were exploiting the human genome at the pace necessary and, with planning, possible. NIH therefore invested heavily in understanding not only variation across humans, but between populations of patients who had specific diseases and their controls (people of the same age and background who did not have the disease). This is what we call *genomewide association studies*, or GWAS. Though these studies were already being conducted, we at NIH were convinced that they could be conducted, and reported, more efficiently. We have taken active steps to ensure this progress.

My office has given me a front-row seat from which to watch the eventual parade of results. For example, we were aware that complex diseases like diabetes would require more than one gene, and I eagerly anticipated more discoveries would follow after I became director. Over the next few years, however, I

witnessed only an occasional positive result. Then, in 2005, NIH researchers using a GWAS approach reported the remarkable finding that genetic polymorphism can explain why some patients develop age-related macular degeneration (AMD) (6–8). The AMD discovery turned out to be the herald of a virtual cascade of discoveries that have followed. Studies have demonstrated the identification of definitive disease risk alleles for a variety of conditions including prostate cancer (9,10), Crohn disease (11), breast cancer (12–14), Alzheimer disease (15), asthma (16), atrial fibrillation (17), human immunodeficiency virus and acquired immunodeficiency syndrome (18), and multiple sclerosis (19). Recently, it sometimes seems that news of GWAS findings cross my desk on a weekly basis. And we are not done yet.

This explosion of scientific knowledge requires us to rethink how we might best advance our understanding of health and disease. Today, however, a fundamental obstacle to devising an effective strategy is our limited ability to study complex and dynamic biologic systems. I have sought answers in different applications and in different fields of science, to no avail. We simply lack the tools we need to understand these complexities.

Think of a pathway map of a cell's response to damage. There is a tremendous amount of crossover and cross talk between the proteins that are implicated in different organelles in the cell. We do not yet understand the quantitative relationships between the various elements of this system. We do not yet understand the complexities of this system. One could liken the situation to that of an alien coming to Earth from another galaxy. Hoping to understand this strange new planet, the alien begins studying the planet's native materials—and comes across a laptop computer. What was human civilization doing with this device? Looking for answers, the alien pulls out the chip to examine it more closely. Being a logical creature, the alien looks at the elements of that chip: the transistors, the resistors, all its component parts. This is what we

have been doing in science for the past 50 years. We have identified the elements of the system: DNA, RNA, proteins, organelles. We have even made enormous progress in understanding how these complex circuits are connected. But what we do not understand is the same thing our alien is unable to understand from analyzing an integrated circuit chip. How do these parts come together to run Word or PowerPoint or query the Internet? How do we get from the hardware to the software of life?

This is the fundamental transition we are beginning to see in science. We are moving from what I call the “hardware” phase of life science discoveries, where we are trying to understand the specific elements, to the “software” phase, where we seek to understand how these elements work together, how they interact with each other in both normal and abnormal “programs.” And this—the understanding of molecular pathways in the regulation of health and disease—is our fundamental challenge. This is where the race for science is going right now, worldwide.

Some of you may be wondering what all this has to do with imaging sciences. It has everything to do with imaging sciences. To do what we need to do, to understand the software of all these proteins and genes and interactions, we will need a way to examine these objects. That method must be underpinned by a revolutionary change in the characteristics of biologic data. Imaging must lead this revolution.

Today, we generally try to understand biologic systems by destroying them. We separate tissues, grind them up, dissolve them. We tend to be qualitative, and the data we usually generate are unidimensional. Obviously, this is not the way life is organized. If we wish to study a complex system and its varied responses, these methods are inadequate. Instead, we must improve our ability to collect data in a nondestructive manner. Our methods must allow us to obtain quantitative, multidimensional data. We cannot simply interrogate one protein at a time; we must study many proteins at a time across multiple pa-

rameters. Our data must have high temporal resolution. They must be spatially resolved. We will require high data density that will allow us to understand biologic events. Moreover, our data must have common standards.

We will find the methods and technologies to nondestructively acquire quantitative, multidimensional, and time- and spatially resolved data right here, in the work of radiologists. Imaging already offers these approaches. Therefore, imaging will be central to generating the kinds of biologic data we will need to make sense of biologic complexity.

This is the basis of my conviction that imaging will be relevant to the scientific adventure over the next 100 years, at all physical scales—from angstroms to meters. At the molecular level, we are using imaging to better understand molecular pathways. We also need to understand how multiple molecules come together in micromolecular assemblies that affect cellular function in both normal cells and cancer cells. At the cellular level, we need to understand trafficking within the cell or trafficking within tissues; we need to understand cell-to-cell interactions. At the level of organs, we must understand dynamic changes over time. There is no way we can study Alzheimer disease with only one test at any one time. Longitudinal information will be key.

In the body, early disease detection is going to be a major activity of imaging. Imaging-guided delivery and retrieval for novel therapies is an obvious implication. More important, imaging has to evolve as a sort of objective biomarker for comparing genotype information with phenotype information. It will also help advance systems biology research.

How can we understand complex systems? To answer such a question, we must understand what is happening on a fundamental level between molecules, for example. To do that, we need in vivo imaging. What molecule does a macrophage sense in a bacterium? We need to specifically target it to answer the question. What is it within a macrophage that is activated during its chase of its target? You need to track the answer in vivo. Are we making progress?

Let me describe some of the breakthroughs that have happened just over the past year.

There is a new technique called photoactivated localization microscopy, or PALM (20). With it, you can label specific molecules by using a photoactivatable tag and then, after repeated photactivation pulses, go in and observe the molecules in a cell or tissue with 20-nm resolution. This allows counting of single molecules. The potential of this method for illuminating disease processes is tremendous. For example, today, we do not truly understand molecular-level energy metabolism in diseases such as diabetes and cardiomyopathy. Until we understand these processes, we will not be able to devise new diagnostic imaging tests to detect the disease or track it over time. PALM and other new imaging techniques will be essential to our ability to understand such processes and will thereby be central to the development of new therapies.

Similarly, when you look at its capabilities, imaging has the potential to show structure, function, and metabolism in vivo. This is the real frontier. For example, scientists are already using different labels to study multiple molecules of interest. In vivo fluorescence (21) can be used to generate images of the kidney in its physiologic place to study, for example, transplant rejection or nephrosis in a whole new way. Over time, such interrogation techniques will give us a much fuller picture of the complex system that interacts in health or disease. In short, physiology and cell biology will never be the same again.

Let us consider an in vivo example from immunology. It comes from Drs Ronald N. Germain and Jackson Egen, who work at the National Institute of Allergy and Infectious Diseases. They used two-photon imaging of the ear of a living mouse with a delayed type hypersensitivity (DTH) reaction in progress (R. N. Germain, personal communication). The dermal blood vessels were made red by an injected blood tracer, while the antigen-activated T lymphocytes involved in the DTH response appeared green due to expression of green

fluorescent protein. The activated T cells not only accumulate in the inflamed tissue, as they knew from static tissue sections, but now could be seen to move rapidly throughout the tissue in search of their antigens or other foreign bodies they can attack. When they find their antigen they will produce the molecules that cause local inflammation and mediate host protection or autoimmune responses. Germain and colleagues went on to study infections, using imaging to better understand immune responses.

Image processing and analysis technologies will be essential to our continued progress in understanding biologic complexity. We must continue to work interdisciplinarily and to sustain the development of smart analysis techniques. Simultaneous analysis of multiple parameters will occur. We are already seeing analyses of change over time in radiology. We are creating population image databases that can be used as standards for diagnosis.

We are also developing novel phenotyping strategies. At the National Institute of Mental Health, we are sponsoring an 8-year project that, for the first time, will create a database of normal brain development. Imaging is central to this effort. Researchers at several academic centers in the United States and Canada will correlate MR images of the brains of healthy children with the findings of cognitive and physical testing. They will then deposit their results in a common database. This database, and others like it, will help radiologists the world over diagnose the presence of disease with untold speed and accuracy. Consider the potential impact of access to such databases on your own practice. Imagine being able to query this database the way you currently query PubMed. You could compare the image of your patient's brain with the standard image from the database of a normal brain in a child your patient's age. The differences between the two would help you diagnose conditions in your patient far more effectively than ever before. Radiology must participate in the development of such reference databases.

Once you have these analysis methods and this imaging technology, you

can combine them with medical devices and novel therapeutics to create innovative, minimally invasive, image-guided therapies. We have seen progress. For instance, Dr James Duncan at Yale University and colleagues (22), with funding from NIBIB and the National Institute of Neurological Disorders and Stroke has demonstrated dramatic improvements in integrated characterization of neurologic networks as defined electrophysiologically, functionally, and metabolically by blood flow to allow improved intervention in localization-related epilepsy.

We are also seeing advances in high-field-strength MR imaging. Dr Jeff Duyn at NIH has generated one of the first images with a 7-T system in humans, showing the layers of neurons within the gray matter (23). I believe that by combining this sort of information with our growing understanding of the underlying biology, we will be able to determine new ways to intervene in disease processes.

Dr Helen Mayberg and colleagues' work on refractory depression (24) provides an excellent example of how this combination of imaging, scientific understanding, and therapeutics might work. It had long been thought that a particular part of the brain, area 25 of the cingulate gyrus, was important in this disease process. With this in mind, Mayberg and colleagues used deep brain stimulation on the area. When they applied electrodes and stimulated the brain, they observed something wholly unanticipated: Patients' depression lifted in a matter of hours—or even minutes. This therapeutic result further suggests that depression is not a long-term phenomenon but is instead a problem of balancing networks between different regions of the brain. Positron emission tomographic scans provided a possible explanation. The frontal regions, shown by scans to have low blood flow, were reactivated after deep brain stimulation, and the patients improved.

One cannot help but imagine the therapeutic possibilities for other severe refractory diseases of the brain. Might “smart” electric stimulation interfere, for example, with drug addiction?

Moreover, the power of combining new understandings of biologic complexity with tools for specific interventions is a formula that promises to work not only for brain diseases but also for cancer and countless other conditions.

Take, for example, the case of the molecular profiling of genes expressed in a particular cancer. We are finding that certain genes, when expressed, can predict the ability of breast cancer to recur. With this knowledge, we can adjust our approach to best fit the needs of individual patients and offer them far more personalized, targeted treatment.

A striking example of this possibility is provided by a study of gene expression patterns reported by Dave et al (25). They focused on Burkitt lymphoma and diffuse large B cell lymphoma. Histologically, the two lesions are indistinguishable. By looking at the expression arrays of the genes, however, the investigators were able to identify genes that are turned on in one condition or turned off in the other. Think about what imaging could do with such information! Imaging could help identify targets and enhance understanding of how these changes are occurring in patients being treated for cancer. In this context, imaging is no longer peripheral to clinical treatment. It is no longer *ex post facto* information, confirming a diagnosis and assessing therapeutic efficacy after the fact, but an online partner in the management of this disease. This is why I think imaging must actively develop techniques to participate in the treatment of these conditions online.

We are already in an era when investigation is driving the place of imaging, in both fundamental scientific discovery as a research tool as well as novel medical applications. Radiologists such as Dr Brad Wood and his team at NIH are at the forefront of innovations that combine device, image, and smart drugs (26–30). By using nanoparticle liposomal vectors or carriers, they are attempting to combine local activation with noninvasive image-guided energy and tumor targeting on the surface of the nanoparticle that can identify a specific protein that was expressed by the

tumor. Adding an imaging agent to the nanoparticle then allows “personalized dose painting,” according to the MR or CT image. The nanoparticle thus carries a drug and/or contrast agent. Essentially, Wood and colleagues are working to develop these nanoparticles further and to use them to target specific tissues with known molecular profiles. Once the drug is in the tissue, it can be activated in that location by using image-guided noninvasive (or minimally invasive) heat—or perhaps ultrasound, microwaves, radio waves or any of a number of techniques, including “medical GPS” smart needles that deposit energy.

When you look at the innovation cycle that has emerged from the past 40 years of interdisciplinary research in radiology, you see that innovation is ultimately based on the discovery of basic imaging physics, which is enhanced by computing speed and software to acquire and/or analyze the image, which then gives us information on biology. That is well understood. What is less well understood is that this is a continuous cycle in which biology also dictates that you create the image differently, and the image dictates that you control your physics differently, and your physics can then change the image you are obtaining.

It is therefore my prediction that we are going to see a much closer interaction between biologic discoveries and basic imaging physics, adapted with modern computing algorithms, that will allow us to form images and understand the information that is within these systems on a level no other science can provide. Biologic complexity will require us to have noninvasive, time-resolved, spatially resolved information. If you think about it in these terms, you raise a couple of urgent questions: Is it time to redefine who we are and what imaging sciences are? My answer is, perhaps.

I propose that for the 21st century, we start defining imaging not by the tools it uses but by its overall importance and purpose at the core of biologic exploration. For me, I have come to realize imaging as the core interdisciplinary science for generating, under-

standing, and using spatially and temporally resolved biologic information. At the end of the day, ours is an information science. As such, it must be operating at all physical scales, from angstroms to meters, in intact biologic systems.

Perhaps this sounds like a complicated conceptual shift in our identity. But, knowing what I know about public health challenges, about what is happening on the frontiers of science, and about our consequent and urgent need to understand biologic complexity, I can only conclude that somehow, somewhere, imaging must be at the core of any progress we hope to make. There will be no predictive, personalized, and preemptive medicine if imaging does not take a central role in effecting the crucial paradigm shift on which it will rest.

Our greatest risk is to lack imagination. I have said this before, and I will repeat it—emphatically—now: The greatest risk in science is to stop taking risks. Our community of radiologists has done an extraordinary job over the past 40 years. All the same, we are entering an era of transition and transformation that promises to be more exciting still—particularly if we embrace the challenge of risk taking and redefinition that I have proposed.

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