Imaging as a Quantitative Science[1]

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Seismic change is occurring in medicine. Although the practice of medicine is both applied science and art, the scientific component underlying health care is rapidly maturing. Following the use of randomized clinical trials to test the effectiveness of antibiotics in the 1940s, data from controlled clinical experiments became preferred over collections of anecdotal observations as therapeutic evidence, and the pace of clinical experimentation has been accelerating ever since. The accompanying increased emphasis on evidence-based medicine—that is, medicine based on the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients (1)—requires the treating physician to gather data from clinical examination, laboratory tests, and imaging studies when constructing a treatment plan and to assess and alter the plan as necessary as treatment progresses. The growing emphasis on quality that accompanies the shift toward evidence-based medicine demands that outcomes, and the accuracy of information on which those outcomes depend, be measurable. Constructing a health care system in which diagnostic information from clinical examination and diagnostic tests leads to predictable and reproducible outcomes requires that diagnostic information be expressed in quantitative form. In addition to the scientific changes that underlie the trend toward evidence-based medicine, economic pressures leading to "pay-for-performance" plans also push for measurable outputs from diagnostic tests.

Another major contributor to the transformation of health care delivery, and another driver of the need for more quantitative data from diagnostic tests, is the molecular revolution in medicine. Advances in genomics, gene sequencing technology, molecular biology, biochemistry, computer sciences, and informatics are giving us a new understanding of illness, one that defines disease in terms of the cellular-level molecular alterations that result in the altered state of health. Progressively more diseases are being categorized by their molecular signatures—the collection of genetic and proteomic changes associated with a particular disorder—rather than the constellation of signs and symptoms with which patients present. Although some diseases, such as certain cancers, are caused by or related to mutated or abnormal genes and associated abnormal gene products, the majority of diseases are related to genes and metabolic pathways that are normal in chemical structure but are either overactive or underactive in various combinations.

Related evolution in the field of systems biology is providing us an increased appreciation of the enormous complexity of metabolic pathways within cells (both normal and abnormal) and of the heterogeneity of the molecular signatures for any given disease. As our knowledge of the extraordinarily complex biochemical and metabolic cellular pathways grows, and as technology gives us the capability to completely identify all of the molecules in a cell, we will eventually discern that each patient has a unique molecular signature (phenotype) for whatever disease is present. One consequence of this molecular understanding of disease is the need for clinical tests that give quantitative information about biochemical events in patients' normal and abnormal cells and tissues. Tests that simply indicate whether particular molecular events are present are insufficient. Since most disorders are likely related to abnormalities in quantity of molecules or rates of otherwise molecularly normal biochemical pathways, it is increasingly important to measure and monitor how much molecular activity of various kinds is

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present. Functional imaging methods that provide such quantitative biochemical information can and should be thought of as in vivo assays. An assay is a procedure that tests for the presence and amount of a chemical substance.

The search for "targeted therapies," that is, drugs that will interact only with the disease-associated molecular abnormalities, also challenges us to develop quantitative diagnostic tests. In theory, targeted drugs will selectively treat only diseased cells, leaving normal cells unaffected and thus reducing or eliminating toxicity. The quest for targeted drugs will result in an increasing number of targeted therapies available for a particular disorder and, perhaps more important, a rising number of combinations of those targeted therapies. This is already the case in gastrointestinal oncology, for example, where there are now about half a dozen targeted drugs approved by the U.S. Food and Drug Administration for treating colon cancer. Thus clinicians will be faced with the need to select from among multiple therapeutic options, and they will require tests and decision-support tools to help them choose the best treatments. It is unlikely that a result from a single test, whether laboratory, imaging, or clinical, will reflect the underlying molecular signature of a patient's disease with sufficient detail to allow an accurate choice of therapy. Information from multiple tests will have to be merged to give physicians reasonable assurance in their choice of therapies. Reproducible integration of results from disparate tests requires that the test results be expressed in objective or quantitative form.

The molecular heterogeneity underlying the molecular basis of disease has engendered the phrase "personalized medicine," sparking science fiction fantasies of targeted drugs developed for each unique, patient-specific, molecular signature of a disease. In reality, "personalized medicine" is not quite so specific but rather is the process of identifying the therapy, or combination of therapies, most likely to benefit a particular patient. In a general sense, physicians have always practiced personalized medicine. They use diagnostic tests to determine a patient's disease and try to optimize treatment. However, this traditional form of personalized medicine has been based on the observable manifestations of a disease or treatment. It is the new possibility of incorporating a patient's molecular information into the decision-making process that is at the heart of the current use of the term "personalized medicine." Two ongoing breast cancer trials are examples of this approach. Patients in the National Cancer Institute–sponsored "Tailor Rx" trial and in the Netherlands Mammaprint trial are randomized to different therapies on the basis of their genetic profile, rather than on the basis of traditional anatomic and clinical staging (2,3). Moreover, patients in these trials are not stratified simply by the pattern of genetic abnormalities present but by their quantitative score on the genetic profiling tests.

As medical care shifts toward this evidence-based model of care and molecular interpretation of disease, what are the implications for radiology? The changing information requirements of treating physicians indicate they will increasingly need *(a)* tests to identify and quantify the biochemical phenotype of a patient's disease so that it can be matched to the appropriate targeted therapy, *(b)* tests to indicate whether a selected dose of drug is maximally effective for the given patient (ie, sufficient to affect the molecular target), and *(c)* tests to measure response to therapy so that therapy can be changed if the initial choice is not working as expected. Thus this new era of health care carries with it three imperatives for radiology: Clinical imaging must increasingly provide *(a)* biochemical information that is *(b)* as quantitative as reasonably achievable and information that is *(c)* relevant to the therapeutic options available to the treating physicians.

With regard to the first and third imperatives—that is, methods for providing biochemical information and methods that are relevant to therapeutic decision-making—much has been written in the past few years about the emerging field of molecular imaging and the maturation of imaging as a biomarker, and I will not elaborate here about their increasing importance in future health care. However, there is less recognition and emphasis on the second imperative, the evolving need for practicing radiologists to provide more objective, quantitative results to referring physicians (4). As imaging becomes more sophisticated and more central to clinical decision-making, any observed change or variation on a clinical imaging study should reliably reflect biology, and not a random difference due to instrumentation or subjective difference due to interpreting physician variability.

While efforts have been made in decades past to extract quantitative information from medical images, these have met with limited success and limited acceptance among radiologists or clinicians. There are technical and parochial reasons for this, but conditions are ripe for rapid change.

Clinical images are intrinsically quantitative. The process itself of administering energy of known quantity and distribution to a living organism, and measuring with spatial and/or temporal localization the energy that is emitted, transmitted, or reflected, would seem to lend itself inherently to quantitative interpretation. The difference between the energy administered and the energy detected tells us something about the properties of matter with which the energy has interacted. Most current methods of medical imaging involve the solution of inverse problems. That is, computer algorithms provide an estimate or hypothesis as to the nature of matter that the energy encountered, and this estimate is displayed as the image we view. Many of our conventional imaging methods process and/or display the difference between administered and detected energy in a way that tells us primarily about the structural properties of the living subject, but increasingly we are developing more ways to infer information about the chemical properties of matter with which the energy has interacted (ie, molecular imaging). But because of the clinical imperatives described above, we also need to focus on

methods to extract quantitative data about whatever anatomic or biochemical properties our imaging systems signify are present.

The general concept of clinical imaging described here (ie, recording energy signals with temporal and/or spatial localization) means that all clinical images are inherently *n*-dimensional (*n*-D) data sets. In other words, every clinical image is a set of numbers and is therefore fundamentally quantitative. Every pixel or voxel has a number associated with it. Even standard film images can be considered two-dimensional data sets. The density of each grain of emulsion is proportional to the number of photons that struck that area of film. But today, virtually all clinical images are digital. Many standard clinical images are two-dimensional data sets; volumetric computed tomography, magnetic resonance imaging, positron emission tomography (PET), and tomosynthesis images are three-dimensional data sets; and dynamic volumetric studies are four-dimensional data sets. All medical images are ordered sets of numbers.

The practice of radiologic interpretation of these images by human observers is a complex mental process, not completely understood. It is sometimes described as a two-step procedure of perception and cognition. In the perception stage, the radiologist examines an image and identifies one or more regions of interest (ROIs). These ROIs usually include one or more areas judged to be abnormal and, for comparison purposes, one or more areas judged to be normal. In the cognition stage, the radiologist performs a comparison of the chosen ROIs, assessing whether they are different in size, structure, or intensity of signal from expected norms, and makes judgments about the potential clinical importance of the presence or absence of such differences. Although this two-step model has been a useful paradigm for studying the interpretive method, it probably oversimplifies a much more complex set of cognitive processes.

The activity of choosing one or more ROIs is referred to as segmentation. The segmented area is a subset of the entire *n*-D data set we call the image. In other words, segmented regions consist of matrices of numbers from the parent set of numbers we call the "image." In clinical practice, the radiologist is performing segmentation in his or her head and classifying the segments according to some mental schema. The classification process probably involves applying some quasi-arithmetic operations to the segmented areas to determine whether they differ in size, character, or signal intensity. Studies performed since the 1940s, combined with years of clinical experience, tell us that this subjective process of identifying subsets of data and mentally applying arithmetic manipulations to them leads to significant intra- and interreader variability (5,6). When clinical images are on hardcopy, emulsion-based film, there is little alternative to the subjective interpretation approach. But now that almost all clinical images are digital, it is feasible to bring advances in computer-assisted image assessment and interpretation to bear. This will inevitably lead to improved consistency and objectivity in image interpretation, which are among the major advantages of quantitative interpretations for patients.

However, there are still technical obstacles hindering our ability to extract information from clinical images in objective, quantitative ways. The infinite variations in normal and abnormal biologic systems, and additional inconsistencies from the imaging devices themselves, make it very difficult to develop fully automatic (ie, with no human intervention) segmentation or analysis algorithms. Nevertheless, some fully automated and an increasing number of semiautomated segmentation algorithms are improving in sophistication. After normal and abnormal ROIs are identified and characterized, whether by computer or human observer, comparisons based on a variety of features have to be made (classification). Artificial intelligence techniques, such as neural networks, have been designed to try to replicate the results of the human cognitive process but, although developments in artificial intelligence in many applications are impressive, it has proved very difficult to develop computer algorithms that accurately mimic the analytical process that a trained radiologist uses in interpreting clinical images. The only system that can currently reliably cope with the real-world variability in clinical images is the human observer. Although the power of the human mind will need to be a component of the medical image interpretive process for some time to come, advances in computer-assisted segmentation and artificial intelligence techniques are rapidly maturing and increasingly provide reliable quantitative data to aid the radiologist's analysis of findings on clinical images.

To effectively extract quantitative information from a given image, we must answer a key question: What portion of the energy represented in a given pixel or voxel is the biologic signal of interest and what portion is noise? Each data point within the ROI (ie, each pixel or voxel) has a large component of noise relative to the signal of interest. Some of this noise comes from normal, random variations in the physical, engineering, and manufacturing aspects of the imaging device, and some of the noise comes from biologic and physiologic variation in the subject being imaged. With regard to biologic noise, consider that even with submillimeter spatial resolution, a single pixel or voxel in a clinical image represents hundreds of thousands or millions of cells and orders of magnitude larger numbers of individual molecules. For example, if the biologic signal we are studying is glucose utilization from a fluorodeoxyglucose PET scan, each single pixel or voxel in the PET image represents signals from hundreds or thousands of fluorine 18 (^{18}F) atoms combined into a single number. Most of those ^{18}F atoms will be attached to fluorodeoxyglucose (and therefore convey the glucose utilization information we are interested in), but not all. Furthermore, during the time we acquire the PET scan (ie, several minutes) the ^{18}F-labeled molecules will be moving in and out of the cells included within each voxel in response to stimuli and with time scales that we do not completely understand. Therefore, because of all these physical and biologic sources

of uncertainty, obtaining absolute quantification in dynamic biologic systems is extremely difficult.

In addition to these technical hurdles, another factor limiting the incorporation of quantitative results into routine radiologic interpretation has been the assumption by many radiologists and clinicians that quantitative results are not essential to clinical management. This is changing, and may be changing more rapidly than radiologists appreciate. One of the simplest quantitative indexes to extract from medical images is a linear measurement of some anatomic or disease structure. Interestingly, however, radiologists have often been reluctant to actually measure structures on images and record those measurements in the radiologic report. The reluctance seems to stem from two sources. One is that radiologists understand that what appears to be an edge on a medical image is actually an estimate of the location of that edge by the imaging system, and that there is some uncertainty about the accuracy of the displayed location. They therefore are hesitant to state that a distance between two points is "x" when they believe it really is "$x \pm y$." Second, radiologists think it is unlikely that substituting a measurement of some structure for a qualitative statement about its size would actually lead to clinical benefit. One example of this is tumor size measurement. In oncology, although tumor measurements are typically mandatory in clinical trials, it is unusual for radiologists to measure and record tumor measurements in their routine radiologic reports. They believe it is sufficient to state qualitatively that the tumor is getting larger or smaller or staying the same. Oncologists, however, faced with an increasing array of therapeutic options and responding to pressure to practice evidence-based medicine, do use linear tumor measurements in their decision-making. At a workshop a couple of years ago I heard one oncologist express frustration in this way: "Just because radiologists are not measuring tumors does not mean the tumors are not being measured. The oncologists are doing it in their offices." There are similar examples of differences of opinion between radiologists and clinicians about the accuracy of and clinical value of anatomic measurements in cardiology, neurology, orthopedics, and a variety of other specialties.

Although absolute quantification of many image features remains elusive, and subjective integration by a human observer of many image features continues to be an essential aspect of clinical image analysis, it is possible and increasingly necessary to develop interpretive criteria that categorize qualitative interpretations into groups to which probabilistic estimates can be assigned. The Breast Imaging Reporting and Data System schema for interpreting mammograms is an example. Ascribing a probability, or range of probabilities, to each category creates a semiquantitative result that can be incorporated into statistical models or algorithms for clinical decision-making. Such multi-parametric approaches will more realistically reflect the unique phenotype of a patient's disease than would the result of a single test, whether it is an imaging, laboratory, or clinical assessment. One recent example of this approach is a nomogram that combines laboratory, clinical, and imaging data to give a probability of a patient having insignificant prostate cancer (7).

For the past 2 decades leaders in radiology have worked hard to promote radiologic imaging as a science deserving of equal status with other fields of scientific endeavor in medical schools. The formation of the National Institute of Biomedical Imaging and Bioengineering at the National Institutes of Health provides some validation and recognition of progress from those efforts. But we have ground to cover to fully establish imaging as a quantitative science. Though the definition of "science" varies depending on your source, a recurring concept is that of a systematized body of knowledge acquired through use of the scientific method. The scientific method is a system that uses observation and experimentation to describe and explain natural phenomena, and it requires that the observations be reproducible and preferably quantitative.

Imaging seems ideally suited to flourish as a quantitative science. A clinical image is inherently quantitative—it is a matrix of numbers. The key questions for our field to answer are these: What is the biologic significance of each number in the image? Which subsets of numbers on a given image are important (most clinically relevant)? What arithmetic operations should we apply to those subsets? What can we infer from the arithmetic results?

From the standpoint of imaging physics and engineering, we need to better understand which components of each data point are signal and which are noise. That is, physicists and engineers need to better understand the inherent sources of variability in the response characteristics of the imaging detectors we use and develop methods to diminish the background noise in the imaging device. As our knowledge of the biologic and chemical events occurring at the subcellular level increases, we need corresponding improvements in spatial, contrast, and temporal resolution in our clinical imaging devices to make the signal in each pixel more closely reflect the underlying biologic process of interest. For reasons described above, it is probably not realistic to think we will see clinical imaging devices in the near future that can quantitatively display the amount of any given molecular entity in each cell, but continued improvements in spatial, contrast, and temporal resolution are essential to increase the quantitative robustness of the biochemical measures we do extract. We need image analysis techniques that can automatically identify regions that are distinct from one another, both normal and abnormal, and then produce numerical characterizations of their differences. We need artificial intelligence algorithms that ascribe conclusions to these numeric differences, at least in probabilistic if not absolute terms. In other words, we need algorithms that would identify a group of pixels or voxels in an image and tell us, "These pixels have an x probability of being tumor (or, e.g., infection, amyloid plaque)." These im-

age analysis and artificial intelligence techniques must work within a given imaging study and across serial imaging studies to identify improvement or progression of disease.

What do we need to do as a profession to exploit the quantitative nature of our field? Our professional organizations should foster communication with other professional organizations to understand what quantitative measures clinicians need or believe would be medically useful. Academicians must perform outcome studies to determine the added clinical value of the requested or proposed quantitative methods and establish probability values to ascribe to various findings. Training programs should include more focus on quantitative methods. Basic scientists need to improve methods to extract robust quantitative data from medical images. Manufacturers should incorporate technical advances and adhere to standards such that quantitative results will be consistent and accurate across vendors and platforms. If our profession ignores these issues, we invite competitors who will respond.

The practice of radiology is both applied science and art. Just as the applied science component of clinical practice is maturing, so too is the applied science component of clinical radiology. For many years radiologists have adhered to the aphorism, "as low as reasonably achievable" (or ALARA), signifying the goal of using the lowest amount of ionizing radiation possible for a given indication. As we move into the next few decades of increasingly scientific medical practice it may be prudent to add a parallel aphorism, "as quantitative as reasonably achievable" (or AQARA), in order for radiology to remain relevant in the evolving world of quantifiable evidence-based and molecular medicine.

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