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Foreword

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In developing these supplemental issues on the Functional Imaging of Early Markers of Disease, we considered not only the various kinds of imaging, their capabilities, and their future prospects; but also the relationship between imaging, early detection, and disease markers. In defining the arrangement of the articles within this supplement, we asked ourselves a series of questions, including:

- What does early detection mean?
- What is an early marker of disease?
- What is normal?
- What are people dying with? What are people dying of? What can imaging tell us?
- Who can benefit from imaging?
- What does imaging mean for early detection?
- What are the new technologies that might mature?

Our efforts to answer these questions led us to select the authors and topics contained in this special issue. In exploring early detection, we consider the usual model to be one in which cancer develops after a series of invisible steps in a single cell or a series of cells in the same milieu, perhaps in a sensitive individual. The model developed from a series of experiments in cell cultures that showed that even cells that have been immortalized are not converted easily into neoplastic cells. Cancer cells must lack both the signal to die and the signal to avoid wild growth; or, to put it in the positive, cancer cells contain signals that promote immortalization and growth. Since these signals represent errors, the error may be different in every cell. To the extent that the errors may be caused by similar circumstances, such as exposure to tobacco smoke, the errors may be similar.

Experiments with cells in culture are not successful if the cells regress without treatment. The object of the experiment is to develop cells that can be used in further experiments. In life, however, it is probable that most cell changes – even those that would lead to neoplasia – in fact regress. Thus, we are presented with the conundrum that we want to detect disease early, but not too early. We lament that cancers have progressed from the one-cell stage to the stage of perhaps one centimeter in size through 30 doublings, which may take months to years, while we are unaware of their existence. On the other hand, lung and colon lesions that are large enough to see also have been known to disappear. Because of the great harm and cost that would be incurred, we do not want to expose such lesions to invasive treatment. Thus, we are looking for rather specific markers: those that signal not only the presence of disease, but also the potential for disease progression with a negative outcome.

One way to approach this problem is to look at the most severely affected patients. Another is to consider the population of all of the people who die – including those who die an unnatural death – and to consider not only what they died of, but what they died with. The difficulties that people die with either are those that would have afflicted them had they lived longer or those that would never have afflicted them. Autopsies and other samples of cadavers give us perspective on the spectrum of disease in the population. The current autopsy rate in the United States is so low that there basically is no flow of information about disease prevalence and severity. Of course, autopsy results also provide a grasp of what is normal – what people are "walking around with" – and a sense of how much of what they "walk around with" actually progresses to clinical disease.

Interestingly, the population has been engaging in another medical experiment; one that is not planned and in which data is being collected in an unsystematic way. This is the experiment in which individuals

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subject themselves to imaging by computed tomography (CT) and magnetic resonance imaging (MRI) in walk-in facilities across the country. There has been no systematic study of the ability of a whole-body image to detect clinically important disease in the population. The reality is that, without clinical symptoms, the meaning of the images is not clear. The medical system as a whole is not accustomed to having people with no symptoms ask for a diagnosis; the result is that many normal variants and clinically unimportant differences from normal are seen. Once seen, such variations are reported and then must be acted on. Acting on them may bring more harm than good to the patients collectively, although individual patients will be grateful that their disease was caught early. Systematically collecting data from these walk-in examinations of the "worried well" could yield a view of what the population is walking around with and could supplement autopsy data from those killed in the midst of life by accident and war.

A lesson that must be taken from this is that animal models in which lesions develop and regress are important, as are animal models in which lesions progress to full-blown, unchecked growth. As with cell culture, these models are not interesting to most developers, but they may be the models that are closest to the human situation. To the extent that certain genetic changes predispose for, or even ensure, the development of certain malignant lesions, these genetic changes are used as templates for the models. They represent a "sure thing", which is important in the milieu of creating and raising model animals for a particular experiment. Animal models that are "less successful" may be more suitable for experiments in which, for example, animals are subjected to massive tobacco smoke exposure, only some of the animals actually develop lesions, and only some of the lesions progress to unchecked growth. In this milieu, the molecular biology of the changes in the lungs exposed to smoke – as well as that of the small lesions with potential to regress – can be studied, and treatments to prevent the progression to frank disease can be perfected. This is not an easy experiment to promote. Tobacco smoke or other chemical exposure represents a good model because it can be regulated. Many substances to which we are exposed may be carcinogenic, but we have little knowledge of the amount of hazard that they represent.

Doubtless there are many early markers of disease, but the focus is on those that signal the possibility of disease progression as the most important areas for study. There may be a universality about these markers, or they may be very specific. Perhaps, for example, a test panel for blood samples that contains both specific and general markers might be developed as a screening tool. When these substances can be detected in the blood, it may be possible to image the sites of production. What is important for imaging at this stage in the detection of a lesion is signal intensity above noise; not resolution. An intense enough signal can penetrate much tissue depth. With regard to signal intensity, factors to be considered include what the background is and what the depth of tissue penetration of the signal might be, as well as the concentration capability of the contrast agent in the cells of interest. This assumes that it will be possible to attach contrast agents to collections of tumor cells of perhaps 10^{+6} cells or about 10 doubling times less than the 30 needed to perceive a tumor at the 1 cm size.

When considering how imaging can help with early detection, we need to think about risk stratification of the population. It is not possible to image the whole population routinely, no matter what the technique. In the future, it is expected that the combination of the constellation of familial risk factors, personal risk factors, and factors discovered in blood and urine will enable stratification of people according to risk for particular diseases. Then, individuals will be able to put themselves under surveillance for the disease or diseases for which they are at risk; not for all diseases. Every day, the news brings stories of a particular genetic mutation that has been found to be important in diseases, perhaps in a particular cancer or heart disease, for example; or of another particular mutation that puts someone at risk for heart disease and Alzheimer's disease at the same time, for example. We cannot expect that any single factor alone is important, any more than we can expect that one screening test will be adequate to "tell all".

Once the population is stratified according to specific diseases, then imaging – along with other specific diagnostic tests – can be applied for screening. Ideally, imaging is done after another test indicates that there is a problem; again because testing blood, urine, or cell scrapings from available surfaces is much less expensive than is imaging. What imaging can do better than other tests is to locate a lesion. Hence, if the other tests are specific, then the imaging test must be sensitive.

The imaging technologies considered in this volume cover a wide range of the electromagnetic spectrum and are used in a wide variety of settings. We editors asked each group of authors to consider what currently is being done in the milieu of using disease markers for early detection and also to ponder what the future might

hold for the techniques in this milieu. Our hope is that producing the chapters has been a thought-provoking exercise for the authors and that reading the chapters will prove likewise for the readers. In so far as the usual readers of this journal are not acquainted with medical imaging, we hope that the information will provide food for thought and new collaborations. This is based on the belief that the array result of today is the imaging test of the day after tomorrow.