Educational outreach to referring physicians and patients, as others at this summit have emphasized, is crucially important to advancing molecular imaging utilization. At the same time that new technologies increase the interpreting physician's productivity and confidence, these same technologies can be applied to higher quality and faster reporting that can help to keep the referring physician satisfied. Industry, healthcare providers, and professional societies must partner to address these challenges.

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Individualizing Cancer Therapies Using "Anatomolecular" Imaging

Many of us remember the 1989 film *Field of Dreams*, starring Kevin Costner. In brief, the main character becomes convinced that a baseball field must be built on his failing farmland. Another character assures him that if he builds it, "they" will come. And come they did, not only within the storyline of the movie but, as a result of the movie's popularity, to the real field in Dyersville, IA. After some contention between the 2 adjacent landowners, the field created for the film was restored, attracting up to 50,000 visitors each year. Some came to hit a few balls, run the bases, and peer into the surrounding cornfields for the ghosts of past players. One question that guides the following discussion of our increasing ability to individualize cancer therapies using functional and anatomical imaging is: Is this the "field of dreams" for nuclear medicine?

Anatomolecular Imaging and Guided Therapy

Our field has been exponentially expanded by the ability to view molecular imaging results in an anatomic context, a capability that can be applied in PET, SPECT, MR imaging, MR spectroscopy, and a growing range of optical and fluorescent technologies. In fact, anatomic context is now requisite for most molecular imaging agents.

As we explore the possibilities of this expanded field, the number of stakeholders grows. These stakeholders include: patients and their families, payers (including the Centers for Medicare and Medicaid Services [CMS] and insurance companies), companies and shareholders (for pharmaceuticals, devices, molecular imaging agents, and molecular therapy agents), molecular imaging physicians and their staffs, referring physicians and their staffs, federal agencies (such as the National Institutes of Health [NIH], the Department of Energy, and the Food and Drug Administration [FDA]), professional organizations, and society in general.

Despite all these interested groups, a number of barriers stand in the way of rapid adoption and growing utilization. Among the areas in which these obstructions are most formidable are: securing FDA approval, ensuring ^{18}F-FDG availability, dealing with regulatory complexity and uncertainty, securing CMS acceptance and appropriate reimbursement, and reaching out for referring physician acceptance and routine utilization. Even when we meet these challenges, 2 critical questions are especially important for molecular imaging: (1) Are the economic models we are using viable? (2) How do we deal with the fairly rigid approval and reimbursement system when many of our new technologies are "disruptive" of the older models still in place?

As an example, we can look at ^{18}F-FDG and its uses as a tracer in glucose metabolism. Although some individuals talk about FDG as if it is not really a molecular imaging agent, it is a remarkably powerful tracer and a potent downstream marker of a variety of important upstream processes. It is extraordinarily useful as a response indicator for a variety of tumors and, therefore, useful in staging cancer. It provides extracellular and intracellular information about glucose metabolism, making it a truly molecular agent.

A number of oncology-specific PET indications for ^{18}F-FDG have been approved or partially approved by CMS. These include applications in solitary pulmonary nodules (SPNs), non–small cell lung cancer, colon cancer, Hodgkin's and non-Hodgkin's lymphomas (NHL), melanoma, head and neck cancer, esophageal cancer, thyroid cancer, and breast cancer.

Approval is only the first step in convincing our referring physician colleagues to accept and utilize these PET applications. Among the tools to increase physician acceptance that have been highlighted by others at this summit are: ensuring the regular publication of evidence-based literature supporting efficacy, attending tumor boards and conferences of other specialties, presenting high-quality images to these groups, making ourselves available to discuss cases with referring physicians, and providing prompt scheduling, consistent reads, and conscientious reporting and follow-up. I should add that outreach to referring physicians should also begin with making sure that medical students, as they

pass through the training process, have an opportunity to be introduced to the benefits that molecular imaging can leverage across the spectrum of clinical and research disciplines.

Even with this kind of concerted effort to increase utilization, referring physician acceptance may be slow. Reluctance to embrace molecular imaging may be the result of many factors. Some physicians may have very fixed practice patterns or simply may not believe the data on PET and PET/CT capabilities. Others demand 100% certainty from imaging studies and are discouraged at the first false-negative or -positive finding. Still others may, in fact, suffer economically from incorporating molecular imaging results into their practices. For example, on the basis of CT alone, a surgeon may, as his or her usual practice, resect esophageal and lung cancers in a relatively large percentage of patients whom PET/CT would classify as unresectable on the basis of metastases. The result for such a surgeon after adopting PET/CT would be a decrease in surgical volumes. This is what we mean by a disruptive technology—and the education process aims at identifying those referring physicians who have open minds and can adapt to change. Another example of the barriers to adoption can be found in PET in lung cancer staging. As far back as 1994, the literature indicated that PET was more accurate than CT. However, because PET was not available to all patients and because many surgeons were accustomed to performing mediastinoscopy, the routine adoption of PET in this setting was delayed long past the time when evidence of its value was clear.

Toward Individualized Medicine: The Example of ^{18}F-FDG PET

One of the most important paradigm shifts in contemporary medicine is the trend toward individualized or personalized medicine. Molecular imaging and therapy are and will remain in the forefront of this trend, especially in the area of cancer treatment. Current cancer therapies are, for the most part, based on an "average patient" and not on individual-specific metrics. The number of potential variables is high, including variations in pharmacokinetics in whole body, organs, and tumors; varying receptor statuses in tumors; varying proliferative/apoptotic rates in tumors; and many others. The goal is to be able to accurately assess these variables and to individualize treatments to optimize response and minimize toxicity. Molecular imaging is the only approach that shows the phenotype in the physiologic milieu.

In chemotherapy, PET can provide monitoring that differentiates responders from nonresponders, facilitating changes in management for those not responding. In an early study at the University of Michigan, we looked at the use of PET to monitor chemohormonotherapy for breast cancer (*J Clin Oncol*. 1993;11:2101–2111). The study included 11 women with newly diagnosed breast cancer who underwent PET at baseline and serially until 63 d after initiation of therapy. By d 63, we saw a 48% decline in ^{18}F-FDG uptake in the 8 patients who were responders, and no significant declines in the 3 nonresponders.

We know today that molecular imaging techniques have value in assessing response after a full course of treatment is completed as well as early after treatment begins. At the same time, these data can be used to predict response at various time points, including the potential for predicting treatment response even before therapy is initiated. These capabilities are now being incorporated into guidelines and response criteria.

One example is in the National Cancer Institute–sponsored International Working Group's revised response criteria for malignant lymphoma (*J Clin Oncol*. 2007;25:579–586). The new guidelines incorporate PET, immunohistochemistry, and flow cytometry into definitions of response in NHL and Hodgkin's lymphoma, along with standardized definitions of endpoints. Whereas the original criteria defined a complete response solely in terms of tumor size, a complete response is now defined by absence of uptake on PET in a previously FDG-avid tumor. Partial response, once defined as a $\geq$50% decrease in tumor size, is now defined by size, tracer avidity, and the presence of at least 1 PET-positive lesion.

PET imaging early in the course of treatment is the focus of numerous studies today. But an interesting question is whether, because of the nature of PET imaging and apoptosis, midtreatment PET might be superior to posttreatment imaging. This is certainly an area in which personalization of treatment might provide benefits. It is quite possible that some patients are being undertreated and some overtreated in cancer therapy. It is highly unlikely, for example, that everyone needs exactly 6 cycles of chemotherapy. This variation depends on how quickly the tumors are killed by the therapy. To be effective, 6-cycle therapy in lymphoma requires at least 1.5 logs of cell kill per cycle. PET likely can measure only the first 2–3 logs of cell kill (therefore negative PET does not indicate absence of tumor). But this also implies that a true-negative PET finding after 2 cycles indicates an adequate rate of tumor kill, whereas a true-negative PET finding at the end of therapy might be less predictive of a positive outcome. A true-positive PET finding after 2 cycles suggests that a cure is unlikely. If PET can predict sooner whether therapy will fail, then we have the possibility of using this information on cell kill rate to determine earlier whether therapies should be changed. The prognosis, then, depends not only on whether PET becomes negative but on how quickly this occurs.

A study by Spaepen et al. (*Ann Oncol*. 2002;13:1356–1363) assessed the value of a midtreatment ^{18}F-FDG PET scan to predict clinical outcomes in 70 patients newly diagnosed with aggressive NHL. They found that midtreatment PET strongly predicted progression-free survival and was a more accurate predictor than use of the International Prognostic Index (IPI) in these same patients. Median time to treatment failure in PET-positive patients was 1.5 mo, whereas median time to treatment failure in PET-negative patients was 1 y.

PET, then can be useful in early risk stratification. In an example from our institution, CT showed a dramatic

response in a patient after 3 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) for defuse large B-cell lymphoma. Persistent FDG uptake was noted, however, indicating early disease progression prior to bone marrow transplant. This is the kind of finding that could be used to deliver "response-adapted therapy," with a goal of characterizing those who will benefit from specific aggressive therapies and distinguishing them from those who will not benefit. PET would be the basis for deciding which patients should be treated aggressively and which should be treated differently or less aggressively.

As an example of work being done in individualized molecular imaging, at Hopkins we are currently conducting a phase 2 pilot study (J0348) of ^{18}F-FDG PET in determining the risk of relapse in patients with NHL undergoing combination chemotherapy with or without autologous peripheral blood stem cell or bone marrow transplantation. The rationales for the study are that: (1) early ^{18}F-FDG PET (after 2–4 cycles) is highly predictive and more individualized than the IPI, with event rates of 78%–100% when PET is positive at midtreatment compared with only 8%–16% when PET is negative at that point; and (2) that the benefit of early bone marrow transplantation is most pronounced in poor-risk patients. Our hypothesis is that early PET imaging can identify those patients who are most likely to benefit from early treatment intensification. The primary endpoint of the study is 25% absolute improvement in 2-y event-free survival (from 20% to 45%) for patients who are PET positive, compared with historical outcomes, through early bone marrow transplant. The goal for the study is to enroll 55 patients, of whom we expect approximately 50% will be PET positive, with about 19 transplants. At this point in the study, immediate treatment intensification for patients with persistently positive PET scans is feasible and appears promising. We have seen few treatment failures in this group on short-term follow-up. We also believe that analysis of gradations of ^{18}F-FDG uptake may be of additional use in selecting patients for early treatment intensification.

Risk-adaptive, patient-individualized therapy is not a guaranteed success. A number of limitations must be addressed. First, although trials like the one we are doing at Hopkins illustrate the promise of molecular imaging in supporting risk adaptive therapy, in practice it is not sufficiently predictive of outcomes in individual patients. Current interpretations of images may also be too variable across centers and physicians to conduct effective and definitive multicenter trials. Variability within patients and specific diseases may also be a factor, because alternate therapies such as this in high-risk groups may not be effective because of underlying biology. We also have questions about the threshold at which the possibility of response is deemed acceptable. Matters of choice in cancer treatment are extremely important when considering risk-stratified treatment and will play a big role in acceptance by practitioners. Physicians want to treat their patients, and patients want every chance of successful therapy. It is difficult for both physicians and patients to give up hope when no promising alternative is available, regardless of what imaging may tell them.

How might this risk-adaptive, personalized therapy be integrated into cancer care in the future? In a patient with cancer, PET/CT would be performed at baseline and after 1 cycle of therapy. If the result of the second study indicates response, therapy would be continued. Nonresponders would begin alternative therapies that could be dose intensive or part of clinical trials. This is not, of course, a scenario that could become commonplace without surmounting a number of barriers to adoption and use, among them: FDA approval, tracer availability, regulatory complexity and uncertainty, CMS acceptance and reimbursement, and physician acceptance and utilization. As noted, we must also meet the challenges that are inherent in introducing disruptive technologies and in creating viable economic models.

Zevalin as a Disruptive Technology

We can look at some of the ways that these challenges have been addressed and some of the unexpected responses to a disruptive technology in the case of ^{90}Y-labeled ibritumomab tiuxetan radioimmunotherapy (Zevalin). In a 2002 report from Witzig et al. (*J Clin Oncol*. 2002;20:2453-2463), Zevalin was compared with a control immunotherapy, rituximab, in a phase 3 randomized trial of response rates in 143 patients with relapsed or refractory low-grade, follicular, or CD20+ transformed NHL. The researchers found that Zevalin was well tolerated and produced statistically and clinically significant higher overall and complete response rates than rituximab alone. A follow-up study (*J Clin Oncol*. 2002; 20:1262–1269) confirmed that Zevalin was effective, with only minor hematologic toxicity.

These results were confirmed in other studies and, in late 2007, by presentation of results when the multinational, randomized phase 3 First-Line Indolent Trial (FIT) with Zevalin met its primary endpoint (*Blood*. 2007:110;[abstract 643]). The study investigated whether a single infusion of Zevalin would prolong progression-free survival in patients with (minimal) residual disease. More than 400 patients were enrolled at 77 study centers in 12 European countries and Canada. After completing induction therapy, patients were randomized to receive either Zevalin or no further treatment. With a median follow-up of 2.9 y, the median progression-free survival increased from 13.5 (controls) to 37 mo (Zevalin). Median progression-free survival was 6.3 mo without and 29.7 mo with Zevalin for patient subgroups in partial remission and 29.9 mo without and 54.6 mo with Zevalin, for those in complete remission. The authors concluded that Zevalin consolidation of first remission in advanced-stage follicular lymphoma is highly effective, resulting in a total response rate of 87% and prolongation of progression-free survival by 2 y, with a favorable toxicity profile.

So it is clear that Zevalin is beneficial. Yet as others at the Molecular Imaging Summit pointed out, it is incredibly

disruptive. Its use affects the revenue stream for both hospitals and oncologists, with a paradigm-shifting approach to which current reimbursement models cannot effectively respond. Zevalin, in fact, has many of the key characteristics of a disruptive technology: it is good for patients and good for society but shifts the revenue stream, resulting (at least at this point) in losses for hospitals, losses for some drug companies, and a reduction in the revenue stream for oncologists.

Reimbursement for nuclear medicine physicians is also low for the time involved. CMS reimbursement for the Zevalin regimen has shrunk from $24,000 in 2002 to $15,000 in 2008. Zevalin sales in 2007 remained below $20 million. Rituximab sales for the same period were more than $200 million. We have seen outrage in the media about the lack of referrals for radioimmunotherapy and the cut in payments. It is perhaps time that patients, patient advocates, companies, and professional societies take on CMS directly in an effort to correct this situation, which is clearly working to the detriment of thousands of patients in the United States.

Summary

If molecular imaging and molecular imaging–guided therapies are to be successful: they must perform well in humans in controlled, multicenter trials; they must address an important medical need for which an effective therapy is available; and a suitable economic model must sustain their use. If they are disruptive (as they are likely to be), the molecular imaging community must be prepared to face difficulties in acceptance. Conventional pathways for acceptance may not be in place to handle the multiple levels of complexity and opportunities for failure along the way. For this reason, we should be prepared to use all available methods, including legislative influence, to ensure that these promising diagnostics can be made available.

Finally, a concluding word about the *Field of Dreams* ballpark in Iowa mentioned at the beginning. They built it, and people came. But in recent years, declining attendance and revenues, coupled with rising prices of corn and soybeans and increased production of ethanol, have led the landowners to decide to plow the field back under and return it to farmland. If there is a moral for us in molecular imaging, it may be that although we have found our field of dreams, a watchful eye will be needed to make sure that "they" (including patients, referring physicians, regulators, and others) will continue to come.

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