safety studies—are required. This transition, although complex, can be accomplished quickly, and at Avid we required only 6 wk from the last patient out in the eIND studies until the IND submission.

Challenges Ahead

The eIND worked quite well for achieving the first step in clinical development of an amyloid imaging compound, and the transition to traditional IND was achieved efficiently. Our phase 2 development goals are relatively straightforward. What is needed now is a clear path toward commercialization. Among the specific challenges we face are:

- How do we demonstrate efficacy for imaging amyloid plaques when the gold standard requires biopsy or autopsy?
- How can clinical utility for an innovative imaging agent be proven without prohibitively long prospective trials based on clinical endpoints?
- What is the optimal path for working collaboratively with therapeutic drug developers to ensure approval of both a novel therapy and a novel imaging biomarker?

Questions for the Future

Amyloid imaging agents are not intended to supplant the fundamental criteria by which Alzheimer's disease is diagnosed. Instead, we recognize the importance of integrating knowledge about pathology (gained from imaging data) into the existing framework for clinical diagnosis. By focusing on the potential imaging to provide valuable pathology data in support of clinical data, we might find it easier to advance molecular imaging through the development pipeline. For example, a 2-step approval process has been proposed for novel molecular imaging agents. In the first step, approval is based on establishing safety and dosimetry in clinical trials, demonstrating efficacy in imaging a particular known target, and providing data that will support a reasonable expectation that imaging this target will be clinically useful in a defined patient population. Approval based on this first step could provide a label claim limited to imaging pathology. The second step would involve demonstration of utility in prospective clinical trials. Successful completion of this step could lead to a label claim that would be broadened to include diagnostic/prognostic uses.

Among the big questions that the molecular imaging community will need to address proactively in the near future are:

- Should a molecular imaging agent be eligible for approval if it is proven to be safe and effective for imaging a defined pathologic target?
- What criteria do we use to determine whether a particular target presents a potentially approvable indication for imaging agents? The literature may provide sufficient supporting documentation for some targets but not others.
- How do we prove that an agent is effective for imaging the pathologic target?

The future is bright for molecular imaging in general and, in our work, for amyloid imaging. The most significant challenge remains uncertainty, and continued open communication among industry, academia, and the FDA is the key to resolving this uncertainty and moving forward.

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Health Economics in Technology Development: Is It Worth It?

Health economics is a broad discipline that incorporates a wide range of tools and techniques. As a result, it is often misunderstood, and its role in health technology development can be difficult to comprehend. For example, a survey of the 22 largest payers in the United States yielded 22 very different definitions for health economics, ranging from the somewhat nebulous "the impact of the agent on the total costs to the health care system" to the more detailed "clinical and economic outcomes for our health plan members measured using internal drug, medical, and laboratory data (claims and other data) and analyzed to reflect alternative drug, medical education, and other health care interventions."

This brief review offers a primer on health economics and an insider's view of the ways in which tools in the health economist's toolkit can be used to assist in the development and commercialization of new medical technologies. Health economics is important in any health care product de-

velopment, but it is proving especially crucial in the bench-to-bedside pathway for new molecular tracers.

What is Health Economics?

Put simply, health economics is the science of value. The fundamental question that health economists address is: Are the clinical benefits derived from a new medical technology worth the additional costs?

Health economists perform 2 main categories of studies to assess value. "Descriptive" analyses measure the costs associated with a particular disease, diagnostic, or treatment from the perspective of the payer (e.g., Medicare or private payers), providers (e.g., physicians or hospitals), or society as a whole. In contrast, "economic evaluations" compare the costs and benefits of 2 or more competing health care interventions, including drugs, diagnostics, and medical procedures. The 4 types of economic evaluations include: (1) Cost minimization studies, in which the lowest cost intervention is identified after assuming equal efficacy; (2) Cost effectiveness studies, which compare the incremental costs between interventions to their incremental benefits. Here, benefits are measured using a single, usually clinical, endpoint such as deaths avoided or life years gained; (3) Cost utility studies, which are similar to cost effectiveness studies with the difference being that benefits are measured using multidimensional outcome metrics (e.g., a health utility measure); and (4) Cost benefit studies, which evaluate new medical interventions based on the willingness of patients, government, or third-party payers to pay for the innovation.

How Health Economic Assessments Work

Health economists develop sophisticated mathematical models to simulate the benefits and costs from technology over time. These models combine data from primary studies, epidemiologic studies, administrative sources, and clinical opinion to simulate the long-term health and cost consequences of alternative diagnostic and therapeutic strategies.

Simulation models invariably begin with a very specific patient cohort defined by age, disease, and even genetic characteristics, and then simulate the costs and benefits that would accrue if the patient were treated according to the current standard of care. The same mathematical model is then used to simulate the costs and benefits that would accrue if the new medical technology were available, and the difference in costs and benefits under the competing treatment scenarios are assessed in terms of an incremental cost effectiveness ratio (ICER), defined as the incremental cost per unit gain in benefit. To illustrate, a common ICER is the incremental cost per quality-adjusted life-year gained (QALY), or "cost per QALY." Although cost effectiveness thresholds vary by country, it is generally understood that new technologies with a cost per QALY less than $50,000 U.S. are deemed to be "cost effective." In other words, the payer is willing to pay at least $50,000 for 1 full-quality life year.

A few basic truths are essential in understanding heath economics. The first is that health economic analyses simply translate changes in patient outcomes into economic terms. Therefore, economic analyses cannot be performed without clinical data. The second is that even if a new technology improves patient care, there are no guarantees that it will be considered cost effective. Finally, the role of incidental findings is unique to the evaluation of diagnostic imaging technologies and has the potential to greatly influence the cost effectiveness of a new technology. For example, an imaging intervention may be quite effective if incidental findings are excluded but not so promising when such findings are included and vice versa. The net impact depends on the cost of working up incidental findings and the net costs and benefits of the detected disease.

Why Use Health Economics?

Health economics informs payers about whether a new technology is a good value for money and has slowly become a "fourth hurdle" to achieving market access behind quality, safety, and efficacy. Payers increasingly want reassurance that they are spending their health care dollars wisely, and health economic analysis is the vehicle for providing this reassurance.

A Changing Paradigm

This process of questioning value for money is happening globally. I must note that this is a particularly difficult hurdle for imaging, where the general perception is that much of advanced imaging itself does not create significant value for patients. This is a challenge that the molecular imaging field will need to address in the near future and is the direct result of a changing paradigm in decision making on new technologies and agents. Payers are becoming more powerful and more sophisticated in their demands for technologies that definitively demonstrate clinical and economic value. New imaging innovations are increasingly characterized as adding only modest value for very high additional costs. Under the old paradigm, technical feasibility, patient safety, high-quality images, impressive technology, and validated accuracy of procedures was sufficient to propel new imaging modalities and techniques into the marketplace. Today, effects on patient management and health have been added to change the paradigm so that new technologies are now asked to demonstrate improvements in health outcomes, a decrease in adverse reactions, improvements in quality of life, and decreases in health care costs.

This paradigm is exerting a growing influence on global decision making about the pace and acceptance of health care innovations. A few examples are the Canadian Coordinating Office for Health Technology Assessment, which uses cost effectiveness criteria to evaluate both contrast agents and devices; the U.S. Medicare Payment Advisory Commission, which is pushing for cost effectiveness to be incorporated into future coverage decisions; the United Kingdom's National Institute for Health and Clinical

Excellence, which requires economic evaluations (100% of the United Kingdom's general practitioners indicated that economic information has previously influenced them and should be incorporated into medical decision making); Germany's Institute for Quality and Efficiency in Health Care, which is introducing cost effectiveness and evidence-based health care measures; and France's newly established High Authority for Health, which is likely to include cost effectiveness in future technology assessments. Budget effects are also a cornerstone of the French Transparency Commission's decision making processes.

Health Economics Without Apology

Although imperfect, health economics is the only practical solution to rational decision making in an environment of uncertainty. The field is not without its critics. One source of criticism is the use of models instead of clinical trials to evaluate new technologies. Although clinical trials are clearly superior in terms of the evidence generated, they are impractical because of the long-term evaluation required for assessments and because the sample sizes required for clinical trials can be cost prohibitive. The field is also criticized for its reliance on assumptions that are frequently embedded in models and the quality of data that are incorporated. Health economists respond that transparency in analyses makes any assumptions clear and that the impact of these assumptions is measurable using sensitivity analyses. Such analyses can also be applied to the data used in any given model, and decisions on which data to use are based on the best available evidence.

Parting Advice from a Practicing Health Economist

From the health economics perspective, the most important thing that clinical developers of new technologies such as radiotracers can do is to be specific. By that I mean that developers should focus on a single application in a specific population at a specific point in the patient care pathway, because that is how payers evaluate technological advances. This advice, of course, runs counter to the idea of a broad-based label indication, but as we have heard from other presenters in this session, a development strategy aimed at getting broad U.S. Food and Drug Administration marketing approval is inconsistent with securing payment/coverage.

It is also important that clinical development of new radiotracers go beyond demonstrating diagnostic accuracy to include studies on the ability to change treatment decisions and, ultimately, affect patient outcomes. This type of information is essential for conducting health economic assessments and is also what payers are looking for as they make coverage decisions. Do not underestimate the need for health economics analyses. Just because official requirements do not stipulate the need for such studies, it does not mean that the agencies and payers will not want to see them.

I like to say that the world needs only 1 disease model and requires only 1 health economic model. My advice to developers of new technologies or agents is to pick a disease, pick a specific place within that disease, pick a single model, and stick with this through the pipeline. The more credibility that rests in a single model, the more likely that payers will accept it and it can then be expanded to other indications and used to develop other products.

Finally, clinical researchers should take advantage of health economic models to guide their decisions about which new technologies to develop. Because health economic models simulate patient care, they can be used to play "what if" games related to new diagnostics that can provide direction on optimal combinations of cost, sensitivity, and specificity. For example, these models can tell us whether the health economic payoff is better by improving sensitivity or specificity, and researchers can use this information to design new diagnostic technologies accordingly.

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