Comments

PROPOSED ACTION PLAN

The Nation needs better ways of encouraging innovation in diagnostic imaging. An ideal system would have three essential characteristics:

- It would route technology development preferentially toward the most important areas of biomedical opportunity and unmet clinical need;
- It would insure the support of critical technologies, or elements of a technology, even if the degree of business risk seems, in its early stages, too high to assure commercial interest;
- It would have a predictable, rational review process that rewards effective and innovative imaging products that meet an unmet clinical need with rapid regulatory approval and affirmative coverage decisions. Such processes would enable expeditious market introduction, widespread adoption, and changes in the standard of care.

How to create such a system? To do so, we shall have to deal effectively with a few large issues

1. Aligning technology development decisions with clinical and biomedical need and opportunity

This was the original premise on which the National Forum was based: technology developers will make better decisions the more information they have about what the biomedical and clinical needs really are. Public meetings, large or small, that include both formal presentations and information discussions and interactions involving biomedical scientists, clinicians and technology developers would seem the best way to achieve this. These meetings can be scientifically focused in any way the participating communities think are useful. They should include representatives of large and small companies that encompass the full range of technologies critical to imaging development in the years ahead.

The major driver of the agendas ought to be unmet clinical and biomedical need and scientific opportunity. How can diagnostic imaging tests change the clinical outcome of patients? How can we detect tumors earlier in their natural history? How can we achieve better sensitivity without loss of specificity? How can we characterize the physiology and behavior of cancers non-invasively? How can we read the molecular signatures of cancer in the radiology suite, thus allowing us eventually to predict by non-invasive means the most efficacious choice of therapy for individuals? What types of scientific opportunities are created by new technologies in search of a use?

Spin-offs of the Forum might include international conferences that establish standards for various aspects of the effort, such as, for example, consensus criteria for metabolic responses and their validation. As our first meeting nicely illustrated, the Forum's discussions would also highlight unresolved problems in the system that would benefit from additional attention.

In addition to meetings of the usual kind, we should also consider possible uses of the Web as a medium for information exchange, and as a way of directing public queries to one or more of the communities involved in our effort. As a hypothetical example, a research physician might wish to ask the community of imaging technology developers whether anyone is working on approaches to the non-invasive detection of specific mRNA transcripts in tumor masses. Asking the question publicly on an open Website could lead to either public responses on the same Website or, if there are confidentiality issues, private responses directly to the source of the query.

2. Clarifying the Pathways

Those who support or regulate technology development or who pay for its utilization must clearly define the pathways and expectations for all key elements in the process. Attendees at the Forum asked the three participating federal agencies (NCI, HCFA, FDA) to define explicitly the steps needed to insure success, and to eliminate the "guess what I'm thinking" aspect of the process. Clear pathways and clear rules of procedure would permit a much better calculation of business risk by industry.

We know that NCI's current repertoire of funding mechanisms does not meet all the needs of imaging. The NCI's processes and procedures were hardly discussed, but there is ample reason to think that knowledge about available granting mechanisms, new initiatives relevant to imaging, what to do if your first grant application does not score well, etc. is not optimal in the imaging research community.

Criteria for regulatory approval for new technologies will clearly be the subject of extensive further consideration. Clearly criteria need to be data-based, scientifically appropriate, and practicable for the two major regulatory landmarks: approval for initial experimentation in human subjects and market approval. The evidence may be greater or more difficult to obtain for the initial approval of novel or innovative products than for the secondary indication of a product that is already in use. The statutory requirements for evidence are different if the new product is an imaging drug or an imaging device. At least for familiar technologies the FDA has published clear guidance on the regulatory pathways. This includes clear guidance on the standards for clinical studies and data to demonstrate the effectiveness for drugs and biologic products for a broad spectrum of indications in medical imaging and well-defined regulatory pathways for investigation and approval of drugs, biologics, and devices.

HCFA 's reimbursement decisions historically have not been as open a process as FDA market approval decisions. However, the new coverageadvisory committee on reimbursement will help. Future discussions should focus on how to foster effective development of innovative products that address unmet medical need, even while all health-care payers (governmental and non-governmental) strive to contain costs. For example, how do new product developers plan for a technology that is most likely to be indirectly reimbursed through diagnostic related groups (DRG's) or systems with capitated coverage?

The establishment of broad and very general criteria, a "one-size-fits-all" approach to the development of approval criteria and pathways for success is not likely to work. Specific development pathways

leading to regulatory approval and coverage reimbursement might well vary depending on the characteristics of particular technologies, the medical settings in which they are used, and the claims made for them.

In the discussion that will follow, several kinds of questions will need particular attention:

- Under what circumstances are valid unbiased measures of patient benefit not the most reasonable and appropriate criterion?
- If it seems unrealistic to demand measures of clinical benefit as criteria for regulatory approval, should "efficacy" sometimes be interpreted to refer to the performance or operational characteristics of a device or probe?
- If patient benefit is demanded, are there appropriate measures other than survival or quality of life (e.g., avoidance of morbid procedures, shorter hospitalization, and reduction in cost of care)?
- How much needs to be known about the biological and clinical relevance of a new type of claim? For example, if someone proposes to market an imaging probe that can detect apoptosis non-invasively, should validation of the claim of accurate "apoptosis detection" suffice to warrant marketing approval?
- Is it reasonable to ask the research community and sponsors to address the question of what insurers should no longer pay for, when coverage is requested for a new technology? In other words, do new technologies ever definitively replace old ones in the medical marketplace?

3. Reducing and Sharing Business Risk

Development of truly novel technology is an inherently risky business. Risk to an innovator is reduced when costs are reduced, time is shortened, and sometimes liability shared. Partnerships with NCI and use of its rapidly developing infrastructures for imaging (and other translational research) can make a major impact on the actual project-related costs in time and capital that a company assumes. A few examples of relevant NCI expertise, infrastructure, and research activities that may be available for participation by or collaboration with company scientists include:

- The Diagnostic Imaging Program, statistical staff, and clinical expertise - availability of staff for consultation with companies http://www.nci.nih.gov/dip
- A national clinical trials network for imaging (ACRIN) - a peer-reviewed, grant-supported clinical trials network available for collaboration with industry on clinical assessment and validation of emerging technologies http://acrin.org
- Phased Innovation Award (R21/R33 and its SBIR counterpart): a grant mechanism that supports exploratory studies of new modalities, followed by enhanced funding for development based on the achievement of milestone http://grants.nih.gov/grants/guide/pa-files/PAR-99-100.html
- Unconventional Innovations Program - a contracts program to support the development of integrated detection and delivery systems based on the molecular signatures of cancer http://grants.nih.gov/grants/guide/notice-files/not98-125.html
- Small-animal imaging centers - for the non-invasive imaging of cellular and molecular processes

in vivo http://www.nih.gov/grants/guide/rfa-files/RFA-CA-98-023.html

- In vivo Cellular and Molecular Imaging Centers - for the exploration of techniques to image the molecular processes within tumors and their microenvironment http://www.nih.gov/grants/guide/rfa-files/RFA-CA-99-002.html

In addition to these, the NCI is currently exploring expansion of its RAID (Rapid Access to Intervention Development, http://grants.nih.gov/grants/guide/notice-files/not99-110.html) program to include diagnostic imaging probes, as well as its commitment to clinical trials support for early, proof-of-principle studies of new diagnostic probes and devices. It is also considering ways to expand the partnership models it has used successfully in the past to include multiple industrial partnerships for large projects of great complexity. How might these be organized, funded, and managed? What kinds of projects might such novel consortia address?

4. Federal Agency Coordination

To achieve real alignment of priorities and decision-making processes by the major participants and players in imaging technology development, we shall have to achieve an unaccustomed degree of cooperation and coordination by NCI, FDA, and HCFA. This will require establishment of a steering group having representatives of the three agencies. The representatives should be high-level and be authorized to speak authoritatively for their respective agency in matters of policy. This group would work out a coordinated way by which the three agencies can interact productively with the industrial and academic sectors of the imaging community.

Achieving truly useful degrees of coordination will be a real challenge, since coordination cannot infringe on the essentially independent mandates of the three agencies. So how might this work? At the very least, FDA and HCFA would be made aware of pending NCI initiatives still in the formulation stages. This would give FDA and HCFA staff much more time to think through the implications for regulatory approval and coverage decisions well before the tangible products of these initiatives come forward for consideration. Also, explicit awareness of issues important to FDA and HCFA might well influence NCI's shaping of the initiatives themselves.

Another example might be creation of a new process that would provide technology developers with the opportunity to present projects to an expert group from the three agencies. This group could provide sponsors with coordinated feedback on prospects for the proposed product (the good, the problematic, points to consider, etc.). Such feedback might be very useful in guiding key decisions about commitment of resources. This group of experts from the federal agencies would clearly have to have fluid membership or, perhaps, actually be several groups to cover adequately the range of technologies and products that might be brought before it. It is anticipated that this forum could be a useful adjunct to the specific, detailed, and proprietary guidance provided by FDA to any sponsor (both academic and commercial) using an investigational drug, biologic or device with regard to pre-market development conducted under an investigational new drug/biologic application (IND) or an investigational device exemption (IDE).

Many Forum participants stressed the importance of HCFA as the government's own insurance company, as the payer for a large fraction of the imaging studies done in the United States, and as a bellwether of coverage decision-making by non-governmental health-care payers. All agreed that representatives of non-governmental payers and providers ought to be invited to participate in the Forum at an early stage.

5. Establishment of a Deliberative Process in the context of the Forum

We shall need some serious work to go on between public meetings of the Forum, if much is to be achieved. Specifically, we envisage the formation of Work Groups to take on the key complex issues identified by Forum participants. Each Work Group should have representatives of industry, academia, the NCI, the FDA, and HCFA, though not necessarily in equal proportion (individual groups may need to be weighted more with some kinds of participants than others).

The initial set of Working Groups might focus on the following general issues:

- Assuring a full range of support mechanisms for imaging science and technology
- A reevaluation of the FDA's current policy or approach to statutory requirements for assessment of risk: benefit at the point of clinical introduction of imaging probes, biomarkers, and other diagnostic procedures
- A clear description of the decision rules and criteria for affirmative coverage decisions by HCFA; subsequent to this description, outline the criteria for what would be reasonable and necessary for coverage of emerging imaging technologies

Each group might choose to work on these general issues by concentrating on some concrete examples. It would then become clear whether general solutions and criteria are possible, or whether we are dealing with a large number of special cases

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