Collaborations in the Development and Validation of Imaging Biomarkers

Specific physical and physiologic characteristics must be standardized and controlled in the process of evaluating and validating imaging biomarkers. Expertise is therefore needed from physicists, physicians, "customers" (academic and commercial clinical trial specialists), regulators, and payers. Collaborations among academic, commercial, federal, and professional society groups are essential, but defining these collaborations and forming successful and purposeful coalitions in developing biomarkers can be challenging.

Because many of us already have an idea of what academics look for in collaboration, I approached this issue by looking first at the commercial/industry point of view and asking, "Why collaborate?" The business management literature includes several definitions, from fairly specific ("Collaboration occurs when people from different organizations or units within 1 organization produce something [or formulate policy; resolve an issue] together through joint effort, resources, and decision making and share ownership of the final product or service") to broader perspectives ("The purpose or goal of collaboration is to work across boundaries to deliver better service, value, and outcomes for customers, stakeholders, and communities"). These definitions share a focus on final outcomes—an important element to remember in collaborating with companies.

The industry sees a number of potential advantages in collaboration, including better use of scarce resources, cost savings, the ability to create something that might not be possible otherwise, a higher-quality and better-integrated product or service, potential for organizational and individual learning from collaborative resources, and, most important, an enhanced ability to achieve targeted outcomes.

Collaboration is only worthwhile for a company, however, if it passes a critical test: Does it help the organization better achieve the outcomes (not simply outputs) that it intends to achieve? Most good business leaders would ask, "If you can do it on your own, why collaborate?" A willingness to collaborate requires a significant impetus. One of the most important factors driving collaboration in drug and pharmaceutical development today is the complexity of knowledge, expertise, techniques, and instrumentation required. The development of biomarkers, including imaging biomarkers, is an area in which the challenge of complexity drives collaboration.

Defining the Stakeholders

Initiating an effective collaboration involves accurately identifying the stakeholders. The term *stakeholders* is used loosely and broadly, with many definitions in the literature. On the broadest level, stakeholders are those individuals and organizations who may affect, be affected by, or perceive themselves to be affected by a decision or activity. The convening organization does not define eligible participants in this "town hall" approach, and anyone who for any reason believes he or she is a stakeholder is included. Although this is an inclusive and nonjudgmental definition that encourages self-identification, it is somewhat unwieldy when used to identify collaborators who can work together to accomplish specific goals. A narrower definition states that stakeholders are persons or entities with a financial or other specific interest in a matter. Those who meet this definition are often referred to as primary stakeholders: those who have something to lose if the collaboration is not successful. The narrower definition is more operationally practical, because the most motivated individuals drive the collaboration.

Collaborating in Biomarker Validation

Several givens characterize the current environment in which imaging biomarker collaborations will form. First is the fact that a biomarker must be validated specifically for its intended purpose. It is also certain that the future of molecular medicine will see increased demands for quantitative imaging methods. Imaging biomarkers represent a fertile domain for refining quantitative techniques in drug trials. Molecular imaging, like molecular medicine, is fundamentally interdisciplinary. Collaborations among academic, commercial, federal, and professional society groups are therefore essential to bring quantitative imaging methods to patient care. The accuracy of quantitative imaging biomarker data is influenced by both physical and physiologic parameters and requires broad contributions and collaborations from physicists, image processing scientists, manufacturers, engineers, regulators, biologists/chemists, physicians, biostatisticians, methodologists, and patient advocates.

If we use PET as an example and look at the range and complexity of the physical variables alone, the need for collaboration becomes clear. Among the hardware issues that must be resolved are count rate accuracy, reproducibility, spatial resolution, the question of 2D versus 3D, and workstation/display parameters. Software issues include scatter and attenuation correction, reconstruction/filtering/smoothing algorithms, region of interest algorithms (e.g., for partial volume correction, segmentation), motion correction, standardized uptake value algorithms, and Digital Imaging and Communication in Medicine (DICOM standard) implementation.

Various academic, federal, and professional organization collaborations are already underway to identify challenges

inherent in these physical variables and to propose strategies for resolution. Examples include the work that SNM has done with the American Association of Physicists in Medicine (AAPM) and the National Cancer Institute (NCI), a similar effort by the International Society for Magnetic Resonance in Medicine with the AAPM and NCI, and the AAPM/Radiological Society of North America (RSNA) committee looking at phantom development. Federal agencies and institutions, such as the National Institute of Standards and Technology, the Food and Drug Administration (FDA), and the National Institute of Biomedical Imaging and Bioengineering, convene numerous workshops and information meetings each year during which potential collaborators can meet and exchange ideas. Another example is the RSNA-facilitated alliance to address scanner issues. Modeled on the Integrating the Healthcare Enterprise experience, the group held a planning session in November 2007 and an initial meeting in May 2008.

To continue with the example of PET, the physiologic variables that must be addressed in biomarker validation are also daunting. These include but are not limited to: body mass, blood glucose, metabolic milieu, scan time after injection, magnitude of changes from baseline, and heterogeneity (e.g., SUV_{max} versus SUV_{mean}). Adequately addressing these variables requires collaboration from a broad spectrum of contributors. Even from the perspective of a manufacturer, collaboration begins to look quite attractive.

Examples of potential collaborative solutions include cosponsored workshops to identify issues and make recommendations, the resources of the National Institutes of Health (NIH) Biomarkers Consortium, and the RSNA/industry–sponsored Imaging Biomarkers Roundtable.

Educational collaborations are also important and productive. At the 2008 RSNA Annual Meeting the RSNA/AAPM quantitative imaging initiative will offer educational sessions on the theme "Toward Quantitative Imaging." Another example of successful collaborative education is the RSNA/NIH partnership to provide imaging research education, core resources, informatics support, quantification resources, and protocol services to institutional recipients of NIH Clinical and Translational Science Awards.

A number of avenues are open to encourage collaboration with makers of pharmaceuticals. One example is in the NCI Industry–Academic Partnership grants in biomedical imaging. Another is a meeting planned for the summer of 2008 and organized by SNM and RSNA at which representatives from the pharmaceutical industry and FDA will come together to discuss the availability and distribution of research radiopharmaceuticals.

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