RIDER Database Resource:
Plans for a Public-Private Partnership

Executive Summary

7-13-06

1. Executive Summary: The Reference Image Database to Evaluate Response (RIDER) to therapy in lung cancer began as a highly leveraged and collaborative *pilot* project, initiated in September 2004, by the NCI's Cancer Imaging Program, NCI's Center for Bioinformatics, the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Cancer Prevention and Research Foundation, and with information technology support from the Radiological Society of North America (RSNA). The specific aims and proposed methods to develop this public resource include:

(a) Development and implementation of an NCI caBIG public resource with the following specific aims:

- Transfer and archiving of de-identified DICOM serial CT and, later, PET-CT image data and to include metadata and clinical outcome data where possible, from nationally and internationally distributed sites, acquired during the course of a range of different lung cancer drug and radiation therapy trials.
- Public access to the data by end users (researchers, academicians, the device and pharmaceutical industry) for the purpose of optimizing change analysis software tools and benchmarking their performance, and/or other software development and validation purposes; prior to their use in clinical therapy trials.
- Correlation of the results of change analysis tools that have the best benchmark performance with clinical outcome as a longer term goal, exercised in parallel with NCI or other privately funded drug trials, with knowledge that their clinical performance may be clinical protocol and drug specific.

(b) Development of a broad consensus for the design and implementation of this resource by the RIDER steering committee, comprising academic researchers, program staff at NCI, members of caBIG, NIBIB, FDA (CDRH, CDER) and NIST, and implementation of the this resource using the following approaches:

- Develop a validated database that will include methods of annotation and image markup and demonstrate its use for the assessment of change analysis software tools. The performance of software tools will be tested against this database during various stages of case accrual. One approach will include comparing the variance of a range of change-analysis software tools under development by the RIDER consortium members. This variance metric is expected to serve both as a reference estimate of change over time, and as a means to determine the size and case content of the database, i.e., as required to differentiate the performance of different software tools.
- Seek both national and international input into the design and implementation of the database that includes publications in peer-

reviewed scientific journals and presentations at national and international scientific meetings, including RSNA, ACR, SPIE, and AAPM, to ensure the public resource is broadly accepted.

- Develop validation and markup software, implemented in the caBIG Cancer Imaging Archive, consistent with NCI caBIG interoperability and open source requirements of the larger caBIG research community, which include metadata analysis as required for clinical decision making.

Building upon the success of this initial pilot phase, it is proposed that RIDER efforts be expanded from a *pilot* project to a *demonstration* project. As a demonstration project, the RIDER database would be expanded beyond a pilot project to include additional image and related metadata from modalities such as X-ray CT and extended to PET-CT as applied to lung cancer. This data will be collected from a wide range of therapy trials supported by NCI and by the pharmaceutical industry. One important goal of this effort would be to engage industry partners in the data collection, database design, and implementation to explore if the database could be useful in accelerating FDA approval and CMS reimbursement of therapeutic decisions made using software tools.

It is further proposed that this demonstration phase of the RIDER project include both continued support from the existing partners, as well as additional support for the private sector through a Public-Private Partnership (PPP). Because the RIDER project is not focused on a specific clinical treatment protocol, or a specific drug, there is little or no intellectual property associated with the generation of this public resource. This demonstration project may thus provide an especially good opportunity to develop a successful PPP of interest to and supported by a broad range of stakeholders in this field, including the imaging, information technologies (IT), software and pharmaceutical industries. The PPP would be coordinated by the Foundation for NIH, a non-profit organization chartered by Congress to raise funds and establish public-private partnerships that complement and enhance NIH priorities and activities.

A longer-term goal, which underlies the use of the term “demonstration project” for this next phase of RIDER, is to use the *organizational structure* of the RIDER PPP as a model for additional projects that would employ, and further evaluate, the most highly rated software tools, using data collected from future NCI clinical trials and, more broadly, trials conducted in other NIH institutes and centers. NIBIB is especially interested an effort to engage not only NCI but other NIH ICs where imaging is being used as a clinical measure for the pathology of disease or its progression and treatment effectiveness.

By leveraging database resources across NIH in this way, in concert with other efforts such as the Biomarkers Consortium now being established with the Foundation for NIH, the development of more standardized methods for image data collection and validation of change analysis software tools can be accelerated.

These goals are consistent with a recent trans-NIH BECON BISTI report (June 2004) submitted to the NIH roadmap committee; the potential for additional roadmap support for these resources could thus be explored (http://www.becon.nih.gov/symposium2004.htm). The goals are also consistent with a planned NIST workshop on standards for biomedical imaging scheduled to take place on September 14-15, 2006 (http://usms.nist.gov/workshops/bioimaging.htm).

2. Progress report and planned project time lines: The following is an estimated budget and is dependent on the level of private sector (industry) interest in populating the database with CT and/or PET-CT data, case accrual requirements (and thus the number of data collection sites needed), the scope of annotation requirements for CT and/or PET-CT data for lung cancer, and the level of private sector (industry) interest in creating standardized methods for software assessment. The project scope and budget will be reviewed with potential private sector (industry) stakeholders and, based upon those discussions, a detailed project budget, plan, and timeline will be established.

Deliverables Completed - May 2006:

- Accrual of image data into the RIDER database with advanced lung CA patients; currently over a 150 serial CT exams acquired, over 60 cases on the web.
- Initial annotation of 20 cases using the full implementation of the RECIST criteria, with two independent observers.
- Initial implementation of the RSNA MIRC software for image data collection that meets all de-identification and patient confidentiality requirements and permits a user friendly means to collect and archive image data through firewalls and from multiple sites both nationally and internationally (http://mirc.rsna.org/mirc/query).
- Integration of the open source MIRC software as part of the NCI caBIG infrastructure. Initial development of the web accessible public resource and query system, with second release implanted April 2006; version 3 due in September 2006 (http://imaging.nci.nih.gov/i3/).
- White paper on database design and requirements for imaging protocols, data annotation, markup, image registration and methods to demonstrate the functionality of this database as a means to measure the relative performance of change analysis software tools.
- Leveraged experience of NCI's LIDC-IDRI Public-Private Partnership, initiated in September 2005 (supported by eight imaging and PACS companies) to ensure industry requirements are met: for this resource (http://www.fnih.org/partners/research_environment/IDRI.shtml).
- Engagement of the FDA CDRH: implemented two fellowship positions at CDRH to address to change analysis problem from a statistical framework, funded by NCI and NIBIB, consistent with NCI-FDA Interagency Oncology Task Force (http://iotftraining.nci.nih.gov/).
- NIST support for imaging standards requested for FY07 and beyond (http://www.nist.gov/public_affairs/factsheet/bioimaging.htm).
- RIDER Initiative, which complements the recent DHHS Announcement "New Federal Health Initiative to Improve Cancer Therapy" (http://www.fda.gov/oc/mous/domestic/FDA-NCI-CMS.html).

Proposed Deliverables - Fall 2006:

- Completion of Version 2 of this document to cover PET-CT database design for lung cancer.
- Complete accrual of over 200 serial CT cases, for a range of lung cancer stages.
- Completion of initial annotation using the RECIST criteria for 100 serial cases.
- Extend the MIRC and caBIG IT infrastructure to include the transfer of annotated, marked up data, and meta-data from multiple sites, to populate the RIDER database.
- Develop a consensus on what constitutes acceptable lung cancer outcomes, for the purposes of correlation with change analysis results.
- Develop an initial consensus with industry on the scope of the RIDER project based on the RIDER white paper. It is anticipated that the RIDER project will be expanded to include about 1,000 CT annotated cases over two years (2006-2008), depending on the level of interest by the private sector (industry).
- Develop initial agreements with industry to explore development of standardized methods for benchmarking software tools, in partnership with NIST, to be exercised in 2007-2008 (http://usms.nist.gov/workshops/bioimaging.htm).
- Initiate a RIDER pilot PET-CT image database resource for lung cancer with data collection from NCI and pharmaceutical drug trials. See the planned NCI Society of Nuclear Medicine workshop (http://interactive.snm.org/index.cfm?PageID=4901&RPID=4912).

Proposed Deliverables for Year 1 - Fall 2007:

- Complete the annotation and markup of 500 serial CT cases.
- Finalize the web accessible public resource and query system.
- Publish all scientific criteria for CT database design and its functionality.
- Continue collection for 250 cases and initiate the annotation of PET-CT data.

Proposed Deliverables for Year 2 - Fall 2008:

- Complete the collection and annotation of all CT cases.
- Initial efforts to create standards for software tools assessment with NIST.
- Complete the collection and annotation of 500 PET CT data.
- Initiate efforts to create standards for software assessment for PET-CT, to be completed in early 2009 or later, in collaboration with NIST.

3. Clarification of the Goals of the Federal Trans-Agency Oncology Biomarker Qualification Initiative (OBQI) and the RIDER Project

OBQI Initiative:

Two important categories of biomarkers are biological indicators of disease and markers of therapeutic efficacy. They may involve assessment of genomic and proteomic alterations using laboratory methods or *in vivo* biomedical imaging methods. Recent work has shown that biomedical imaging methods, such as X-ray CT, and more recently FDG-PET, provide a means for early indication of drug response.

These research advances have recently resulted in a federal inter-agency announcement of a Memorandum of Understanding (MOU) among the FDA, NIH and CMS. These agencies have agreed to collaborate on improving the development of cancer therapies, in part through the use of biomarkers that correlate with clinical

outcomes (*DHHS "New Federal Health Initiative to Improve Cancer Therapy", http://www.fda.gov/oc/mous/domestic/FDA-NCI-CMS.html).*

The scope of this MOU covers both the development and clinical assessment of biomarkers in the area of oncology. One specific goal of NCI is to identify those biomarkers that provide a means to measure cancer therapy response. Such biomarkers could be considered "qualified" from an FDA perspective (i.e., they could potentially be adopted as clinical assessment tools in clinical trials intended to be submitted to the FDA for regulatory approval). CMS interests include the development of evidence to make informed reimbursement decisions for biomarkers being used in clinical care.

This trans-agency initiative is referred to as the "Oncology Biomarker Qualification Initiative" (OBQI) and complements the goals of the NCI FDA Interagency Oncology Task Force (IOTF); see http://iotftraining.nci.nih.gov/.

RIDER Project:

There are many sources of uncertainty in the use of imaging as a biomarker for the assessment of drug response. For example, biological variability is a factor that is drug, organ, tumor and patient dependent and thus best addressed through carefully designed clinical trials such as those proposed by the OBQI.

However, there is also measurement variability associated with two other interrelated factors namely: (a) image data collection across different commercial platforms, and (b) uncertainty in the performance of different image analysis software tools employed to measure therapy response. The latter software tools typically involve measurement of change in image-related computer extracted features over time. Both sources of uncertainty often result in an increase in the required number of subjects in and therefore cost of drug trials. The development of standardized methods to physically characterize these two sources of uncertainty would stimulate the development of improved imaging methods and software tools.

The approach proposed for RIDER is to evaluate the proposed software tools for change analysis by first testing their relative performance against a validated and standardized reference database. This approach will include standardized data collections across imaging platforms to populate the database, as this will be also a requirement for multi center drug trials.

The final selection of these well-characterized software tools could then be potentially employed in drug trials submitted to the FDA. The RIDER project therefore has a different technical goal and a different timeline than the OBQI but will be very complementary.

Related URLs:

http://imaging.nci.nih.gov/i3/

http://www.fnih.org/partners/research_environment/IDRI.shtml