Quantitative Imaging Biomarkers Alliance RSNA

Application for QIBA Round-2 Project Funding

Title of Proposal: **Test-Retest Evaluation of Repeatability of DCE-MRI and DWI in Human Subjects**		
QIBA Committee/Subgroup: DCE-MRI		
NIBIB Task Number(s) which this project addresses: 1a and 1b		
Project Coordinator or Lead Investigator Information:		
Last Name: ROSEN	First Name: Mark	Degree(s): MD, PhD
e-mail:	Tel #:	
Institution/Company: University of Pennsylvania		
Amount Requested:		

Please check the primary category for this proposal from among the following:

- ☐ 1. Identification of Technical Characteristics and Standards
  - ☐ a. Creation and refinement of protocols for image acquisition, analysis, quality control, etc., for specific clinical utility
  - ☐ b. Phantom development and testing
  - ☐ c. Identification and assessment of intra-reader bias (1) and variance across scanners and centers
  - ☐ d. Identification and assessment of inter-reader bias and variance across scanners and centers
  - ☐ e. Other
- ☐ 2. Clinical Performance Groundwork
  - ☐ a. Assessment of intra-reader sensitivity and specificity
  - ☐ b. Assessment of inter-reader sensitivity and specificity
  - ☐ c. Other
- ☐ 3. Clinical Efficacy Groundwork
  - ☐ a. Assessment of correlation between new biomarker and 'accepted-as-standard' method
  - ☐ b. Characterization of value in clinical trials
  - ☐ c. Characterization of value in clinical practice
  - ☐ d. Development/merger of databases from trials in support of qualification
  - ☐ e. Other
- ☐ 4. Resources (money and/or people) committeed from other sources.

Requested funding is expected to represent 50% of the clinical trial budget. Remaining fund to be derived from ACRIN internal funding.

Please provide a one-page summary that includes the following information:

Project Description

In order to evaluate the profile claims for the repeatability of tumor DCE-MRI metrics, it is ultimately necessary to evaluate the performance of the QIBA DCE-MRI protocol in human subjects with tumors. This process would include not only implementing the imaging protocol, but also introducing site imaging personnel to proper procedures for magnet qualification, the selection of tumor-bearing human subjects, and the implementation of the proper DCE-MRI imaging exam to these subjects. Through discussions within the DCE-MRI subcommittee, it has been decided to seek a partnership with the American College of Radiology Imaging Network (ACRIN) to facilitate the development and ultimately the implementation of the test-retest DCE-MRI human study. The overall project, including the completion of the protocol, selection of participating sites, central and site regulatory approval, and implementation is expected to last two years.

Update since previous proposal for funding.

The PI appreciates the NIBIB board consideration of the previous proposal in December, 2010, for the initial phases of the human test-retest proposal. The critiques of the board have been considered in the formulation of this new proposal. The current proposal represents progress since the last proposal. Specifically, via discussion within the QIBA DCE-MRI committee, as well as with experts outside the committee, the PI has selected prostate cancer patients presenting for MRI evaluation as the appropriate target group for the DCE-MRI test-retest trial. The proposal seeks to recruit 30 such subjects across six imaging centers (representing two sites each with MRI scanners from each of the three major MRI scanner vendors). The protocol will build on existing QIBA DCE-MRI accomplishments, including the ongoing development and testing of the new DCE-MRI phantom (Ed Jackson, PI), and the development of portable analytic software at VirtualScopics, Inc. for DCE-MRI evaluation (Ed Ashton, PI) At the time of this proposal, a complete protocol, representing a redrafting of the prior ACRIN-FNIH prostate DCE-MRI/DWI protocol, is being completed for committee review within the ACRIN. The goals and objectives of the current proposal reflect this progress.

Primary goals and objectives

1) Determine the test-retest performance, as assessed by the coefficient of variation (CV), of the median pixel values of K^{trans} and $IAUGC^{bn}$, using the whole prostate as the target "tumor".
2) Determine the test-retest performance, as assessed by the coefficient of variation (CV) of the median pixel value of AUC^{fast}, and ADC^{slow}, using the whole prostate as the target "tumor".

Explanation

- The choice of prostate cancer patients undergoing MRI represents a consensus agreement of the PI and members of the QIBA DCE-MRI committee as the most viable target population for the test-retest study. This population provides an appropriate target in the "torso" region of the body while limiting issues of motion, provides for similar anatomic prescription among all patients, and presents a patient population that includes individuals easily accessible to participating sites based on current clinical practices.
- For **Primary Aim 1**, the use of K^{trans} and $IAUGC^{bn}$ represent the two best studied DCE-MRI metrics and are therefore outlined in the QIBA profile claim. While other metrics, such as v_e and k_{ep}, may also be evaluated, the primary aim will focus on those metrics felt most representative of the tissue vascular status and most applicable to drug therapy trials.
- As tumor visualization in localized prostate cancer is variable, the use of whole prostate as a target tumor represents a compromise that insures adequate region-of-interest (ROI) size for DCE-MRI analysis. The prostate generally comprises a range of tissue types, from highly

vascularized glandular BPH nodules, intermediately vascularized tumor and non-tumorous peripheral zone tissue, to poorly vascularized stromal and fibrotic regions, thus representing a reasonable surrogate of the range of vascularity encountered in tumors. In the subset of patients in whom a dominant tumor nodule is clearly visualized on T2-weighted imaging, secondary analyses of the CV of the DCE-MRI metrics of these ROIs will be performed.

- The inclusion of diffusion weighted imaging (DWI) for **Primary Aim 2**, while not directly in the purview of the QIBA DCE-MRI subcommittee, represents the recognition by the PI and committee members that DWI is an additional viable function tumor metric in both prostate MRI and tumor MR imaging in general. As is reflected in the original FNIH proposal, the isolation of DCE-MRI as the sole functional tumor metric of interest in a multi-site test-retest trial fails to recognize the potential importance of ADC in oncologic MRI research. The acquisition of DWI is concurrent with that of DCE-MRI. Furthermore, the analysis of DWI metrics ADC relies on the same reader input (ROI definition) as does DCE-MRI analysis, with a less complex analytic algorithms. As such, the inclusion of DWI in this protocol can be accomplished essentially no additional cost, but with potential high benefit. The combined investigation of perfusion and diffusion is in alignment with newer developments of investigating angiogenesis and reflects the strategic thoughts of the QIBA DCE-MRI committee.

Secondary goals and objectives

1) Determine the test-retest performance, as assessed by the coefficient of variation (CV), of the median pixel values of K^{trans} and $IAUGC^{bn}$, using the dominant tumor nodule as the target.
2) Determine the test-retest performance, as assessed by the coefficient of variation (CV) of the median pixel value of ADC^{fast}, and ADC^{slow}, using the dominant tumor nodule as the target.
3) Determine whether T1-dependent or T1-independent methods for gadolinium quantification produce differing values for the CV for DCE-MRI metrics K^{trans} and $IAUGC^{bn}$.
4) Determine the effect of reader on the CV of DCE-MRI and DWI metrics for whole prostate and tumor nodule target lesions.
5) Explore the degree to which vendor selection affects the co-efficient of variation of DCE-MRI and DWI metrics.
6) Explore the correlation between DCE-MRI and DWI metrics for both whole prostate and dominant tumor nodule as target lesions.

Explanation

- The primary objectives for repeatability assessment are tailored for evaluation of the whole prostate, in order to assure that an adequate number of evaluable cases are available to produce a robust CV estimate. While specific subject entry criteria (minimum number of positive cores and Gleason grade) will be set to increase the proportion of prostate cancer patients who have visible dominant tumor nodules, it is expected that a proportion of subjects will not be evaluable for the **Secondary Aims 1 and 2**. It is further anticipated that a proportion of subject scans may have technically deficiencies (i.e. failure of site to adhere to injection protocol), such that DCE-MRI quantification will not be accurate. Therefore, of the 30 subjects we anticipate enrolling, it is possible that 20 or fewer will be evaluable for the secondary endpoints 1 or 2. We therefore intend to use the dominant tumor nodule, when evaluable, as a secondary endpoint, while using the highly vascularized prostate as a whole as the target for the primary endpoints.
- One factor that has emerged as a prominent potential source of variation in DCE-MRI is the choice of modeling, specifically the use of T1-dependnent (e.g. Bloch equation-based) vs. T1-independnent (a.k.a the "linear" assumption) methods for conversion of signal intensity versus time curves to estimated gadolinium concentration. While the study is not powered to determine whether one method is truly superior to the other, **Secondary Aim 3** will assess whether trends regarding the improvement in DCE-MRI metric CV will become evident. The image acquisition protocol will allow for both methods of modeling, using the coil correction algorithm of derived by Ed Ashton (VirtualScopics, Inc.) to standardize the use of change in

signal intensity of the target tumor as a surrogate for gadolinium concentration when normalized to that of the arterial input function.

- It is recognized that variability in MRI machine performance (inter-scanner and intra-scanner) is likely to be the primary source of variability in tumor DCE-MRI and/or DWI quantification. However, a secondary source of variability is likely be the manual segmentation step performed by the expert reader. Central image analysis will provide for standardization of the analytic algorithms is ensured via central image analysis using the algorithms developed in funding period 1. However, the use of two independent readers to segment ROI maps will allow for evaluation of the effects of reader segmentation on the quantitative analyses, as discussed in **Secondary Aim 4**. Ultimately, successful completion of this proposal will provide a data set that may be used by external readers using a variety of software platforms for quantitative analysis. As such, although such an analysis is beyond the scope of this project, this data may serve to complement the current DCE-MRI committee activities toward software evaluation from the synthetic data project (Dan Barboriak, PI).
- In the course of the testing of the DCE-MRI phantom during prior QIBA activities, the DCE-MRI committee has identified possible vendor-specific differences in excitation flip angle propagation that may contribute to vendor-specific differences in DCE-MRI quantification. Direct interaction with the vendor representatives in the QIBA DCE-MRI technical committee is included to provide sufficient information on how to best plan and perform clinical DCE-MRI studies across different scanner models. In version 1.0 of the QIBA DCE-MRI profile all major vendors provide guidance on how to comply with the profile claims using respective vendor's specific scanner models. This sequence information (Appendix G of the profile) will be used for the clinical test-retest scanning procedures. It is also understood that vendors provide different methods for the performance of DWI, specifically with regard to the application of diffusion gradients. Other vendor- or site-specific differences in DCE-MRI and/or DWI acquisition are likely to be present, which may affect the quantification. As such, the proposal will specifically tailor subject accrual such that a total of 10 test-retest image sets from each major vendor are available for analysis. While this number will not likely provide statistical power to determine whether significant variation in DCE-MRI and/or DWI metric CV's exist, this data analysis in **Secondary Aim 5** may propel vendor to investigate the robustness of their image acquisition schemes for quantitative MRI performance.
- There is currently much debate in the quantitative MRI community regard the relative value of DCE-MRI and DWI as a means of providing functional tumor evaluation. These competing quantitative methods have all been proposed to improve diagnostic accuracy, provide meaningful information regarding tumor grade, and to provide a metric of responsiveness of tumors to a variety of conventional and targeted anti-tumor therapies. Many potential advantages of DWI, specifically the ability to generate functional tumor maps without the use of contrast, and the potential of DWI as a true "whole-body" MR tumor imaging technique, have emerged. However, there is a larger repository of literature evidence supporting the use of DCE-MRI, despite its technical challenges, for evaluation of tumor response to anti-angiogenic therapy. **Secondary Aim 6** of this proposal will evaluate whether DCE-MRI metrics correlate with either ADC^{slow} (as a surrogate marker of tumor grade) and ADC^{fast} (as a surrogate marker of tumor vascularity).

Deliverables

This proposal provides that at the end of the twenty-four months following the initiation of funding, the human test-retest study will have been completed. During the initial twelve month funding period, the PI, in conjunction with the DCE-MRI subcommittee of QIBA, and in partnership with ACRIN, will produce a CTEP-approved protocol, will complete site selection and qualification, and will initiate patient accrual in the trial. Additional funding for the proposal is expected to be derived via ACRIN internal funds, possibly supplemented by NIBIB support if the contract extends beyond the current NIBIB funding cycle.

The second year of this proposal will be focused on completion of the trial and data analysis. Specific timelines for the proposal are listed below. Deliverables include:

1) Completed ACRIN-approved test-retest protocol
2) Completion of site-qualification via phantom testing and submission of human clinical prostate studies.
3) Completion of the test-retest analysis for the primary aims.

Timeline [must include intermediate measureable milestones.]

- Mo. 1-3: NCI/CTEP approved protocol (deliverable will be provided via the NCI approval letter issued to ACRIN)

- Mo. 4-6 : Completion of site-qualification using phantom testing at 3 of the 6 participating centers (deliverables will be summary report of qualification showing site approval)

- Mo. 7-12: Accrual of 25% of the sample size (7 patients) to the protocol (deliverable will be study summary report noting approved sites and accrual per center)