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CONTRACTING ORGANIZATION: Georgia Institute of Technology, Atlanta, GA

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14. ABSTRACT

Intervertebral disc degeneration (IDD) is a common condition characterized by the deterioration of the discs separating the spine. Magnetic resonance elastography has shown potential in earlier diagnosis and investigation of DDD, but has been limited by available actuation techniques. This project aims to solve these actuation challenges by developing tunable resonance MRE actuators, establishing control methods for automated tuning and dual actuation, and combining these developments to characterize IVD stiffness in healthy human subjects. The project has been proceeding towards completion of each of the three aims, with development of tunable actuators, theoretical and practical advancements in self tuning capabilities and technology for IVD characterization *in-vivo.* The developed actuators demonstrated a nearly 500Hz resonance range, while positioning experiments validated the need for active tuning of actuator parameters.

15. SUBJECT TERMS
None listed.

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1. INTRODUCTION:

Intervertebral disc degeneration (IDD) is a common condition characterized by the deterioration of the discs separating the spine. The onset of IDD is caused by several factors including genetics, injury, or aging, and is diagnosed using current magnetic resonance procedures. However, these existing MR procedures lack in providing information related to the mechanical state of the discs. With magnetic resonance elastography (MRE), which is a non-invasive in vivo imaging technique based on phase-contrast MRI, the clinical diagnosis of the disc's mechanical condition could now be possible. MRE contains three main steps: 1) Generating shear waves along the imaging target, 2) Using motion encoding gradients to measure the accumulated phase offset among the spins, 3) applying inversion algorithms to acquire elastograms depicting tissue stiffness. MRE allows for the measurement of shear moduli of soft tissues through external excitation, and could therefore be helpful in differentiating pathological changes inside biological tissues. Existing actuator technologies for MRE are not suitable for the high stiffness and small region of interest target that the discs present. Particularly, variable actuation frequency, and the ability to focus excitation to smaller regions of interest are critical features in future characterization of IDD via MRE. This project aims to solve these actuation challenges by developing tunable resonance MRE actuators, establishing control methods for automated tuning and dual actuation, and combining these developments to characterize IVD stiffness in healthy human subjects.

This Y2 annual report will elaborate on the development of a 5 DOF positioning system for image guided orientation of the MRE drivers, and preliminary experimental results. Additionally, finite element analysis of single actuator MRE was conducted to begin optimizing design features and eventually, multi-actuator placement.

2. KEYWORDS:

Magnetic Resonance Elastography, Intervertebral Disc Degeneration, Tissue Stiffness, Shear Waves

3. ACCOMPLISHMENTS:

- **What were the major goals of the project?**

Specific Aim 1 – Design and fabrication of frequency tunable actuators for MRE applications	**Timeline**	**Status**
Major Task 1	Months	
Subtask 1: Complete design of MRE compatible actuators	1-6	Completed
Milestone # 1 ***Complete 3D drawings and FEM analysis results***	6	Completed
Subtask 2: Fabrication and MRI compatibility test	4-9	Completed
Milestone # 2 Proof-of-concept prototype and functionality test in the lab	9	Completed
Subtask 3: Implementation and performance testing	6-9	70%
Milestone # 3 Demonstration of multi-source, varying resonant frequency actuation in MRI	12	30%
Specific Aim 2 – Establishment of automated self-calibration and on-site tuning algorithms for the frequency tunable actuators	**Timeline**	**Site 1**
Major Task 2		
Subtask 1: Formalization of piezoelectric self-sensing theory and hysteresis modeling	3-9	50%
Milestone # 2 Computer algorithms for self-sensing actuation and empirical hysteric parameter estimation	9	50%

Subtask 2: Self-sensing of resonance excitation	6-14	50%
Milestone # 2 Demonstration of resonant detection from self-sensing piezoelectric actuators	14	15%
Subtask 3: Combined with FEM and implement numerical search algorithm	10-18	70%
Milestone #3 Demonstration of self-tuning of resonant frequency for optimal tissue excitation	18	25%
Specific Aim 3 – Characterization of IVD based on stiffness to evaluate the level of disc degeneration	**Timeline**	**Site 1**
Major Task 3		
Subtask 1: Establish theory of multi-source elastography imaging	1-9	50%
Milestone # 1 FEM simulation of the wave fields during multi-source actuation	9-10	50%
Milestone # 2 Ex-vivo validation test of multi-source MRE	9-12	25%
Subtask 2: Submit protocol to IRB/HRPO	4-9	100%
Milestone # 3 IRB/HRPO protocol approval	9	95%
Subtask 3: Install actuators into MRI scanner	9-11	Completed
Milestone #4 Functionality test of the actuators in MRI	11	90%
Milestone #5 MRE data collection with a phantom model	12	90%
Milestone #6 MRE data collection with healthy volunteers	13-24	10%

- **What was accomplished under these goals?**

Major progress was made towards the realization of each of the goals of this project. For major task 1, the development of tunable resonance actuators, design, simulation, evaluation, and proof of concept testing done in Y1 was extended and refined. The continuously adjustable resonance actuator was designed and fabricated, with finite element analysis ongoing. The resonant frequency is adjusted by sliding the two masses on either side, changing both the inertial and stiffness characteristics of the actuator. A positioning system was designed and evaluated for the automated placement of MRE actuators within the scanner bore, the 5-DOF planar frame is morphologically similar to the one reported in the first annual report, but the actuators were changed to hydraulic cylinders for robustness and working range. This necessitated design changes to most of the robot components, as well as updates to the controller. The positioning experiments shown in Figure 2 and the MRE results in Figure 3 demonstrate that this 5-DOF system is capable of accurate configuration of MRE actuators. This is particularly necessary for the use of high frequency low strain piezoelectric actuators, due to attenuation. MRE experiments were performed at 3 different configurations on an intervertebral disc shaped phantom. The results shown in Figure 3 demonstrated a statistically significant difference in estimated stiffness depending on MRE driver configuration. This is critical for the future implementation of high frequency MRE, as it means that driver configuration is a necessary consideration.

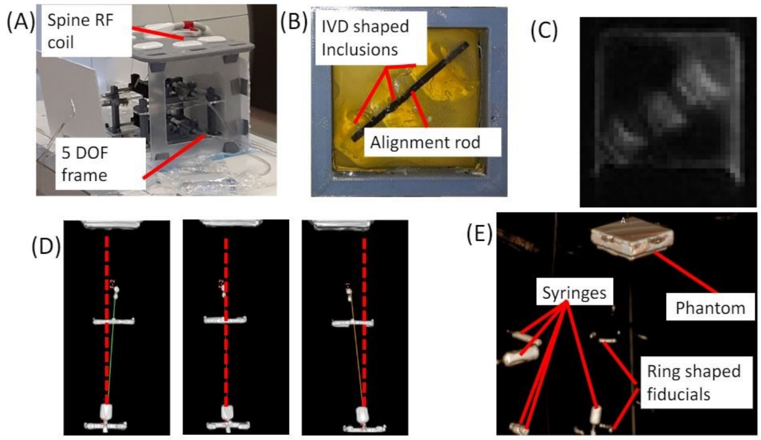

Figure 1 : (a) 5 DOF frame in the scanner (b) IVD shaped phantom (c) magnitude image of the phantom (d) the three evaluated orientations of the MRE actuator (e) fiducial markers

Towards major task 2, as part of the self-tuning work, the mechanism for image guided positioning was evaluated, as shown below in Figure 2 and 3. The positioning accuracy of the image guidance scheme was tested in the laboratory. The control configuration of a 4 DOF planar positioning step, with advancement of the 5^{th} DOF actuator as the final step was evaluated. Planar positions were measured via an RGB-D camera (Intel Realsense). In this case, a 4 DOF image Jacobian relating the planar position of each ball joint to the motion of the linear piezo actuators was used. After each ball joint reached the desired location, a stand-in 5^{th} DOF DC linear actuator was extended to place the endpoint at the target location. Location and orientation accuracy were measured via the visual fiducial shown in Figure 3. Mean error was below 1.8mm and 0.78 degrees.

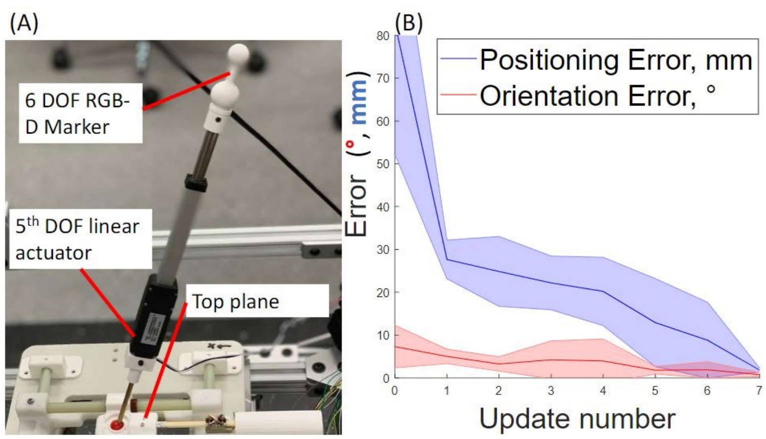

Figure 2: Positioning accuracy experiments. (a) Laboratory testing setup, and (b) Positioning and orientation results.

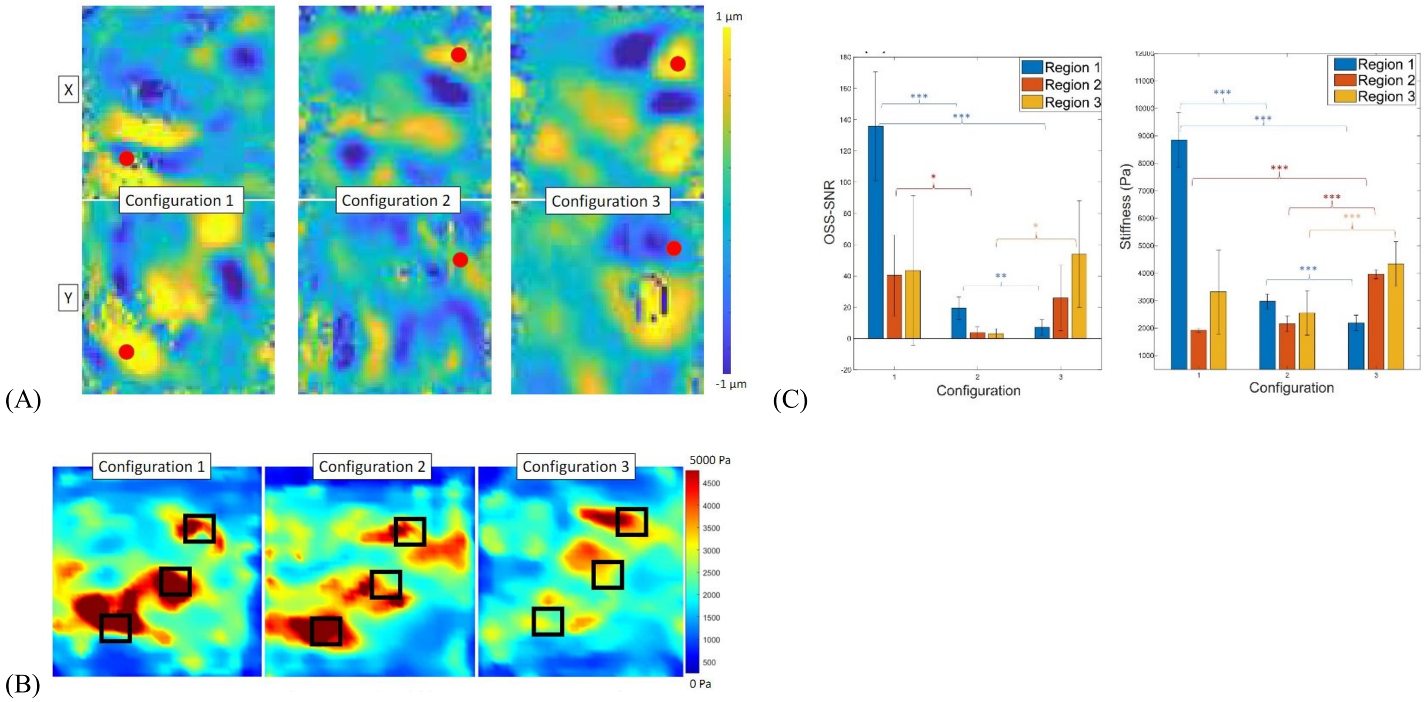

Figure 3: (a) Displacement fields (b) Computed shear stiffness (c) Mean octahedral shear stress SNR and stiffness estimation results

Towards the completion of major task 3, Simulation and finite element analysis work was performed to tune the design and placement of the resonant actuators the theoretical and numerical methods from that work will be adapted and leveraged to complete task 2. Single actuator MRE seeks to induce a sinusoidal displacement at a given region of interest, where the displacement is directly correlated with elastogram stability and reliability. Wave propagation to the region of interest is limited by wave attenuation and the shadow effect, where waves are unable to reach tissues behind stiffer regions. Multi-actuator MRE has been studied to overcome these limitations by generating shear waves from multiple sources. It has been shown that constructive interference of the shear waves from multiple actuators will increase the overall displacement at the region of interest. Optimization of the displacement within the region of interest is then affected by the number of actuators, their location and orientation, and their individual wave parameters. Our work seeks to devise a simulation procedure for optimizing these model-specific parameters to induce the greatest displacement at the region of interest.

Ongoing work is focused on the development of FEA simulations to model single actuator MRE and develop a numerical parameter optimization procedure. This entails identifying the required options and creating the simulation using the Abaqus GUI to then begin automating the procedure. The procedure will be expanded to multi-actuator MRE and then to models of various geometries and stiffnesses. Figure 4 shows the displacement in a tissue-like phantom induced by a single actuator mimicking MRE shear wave generation.

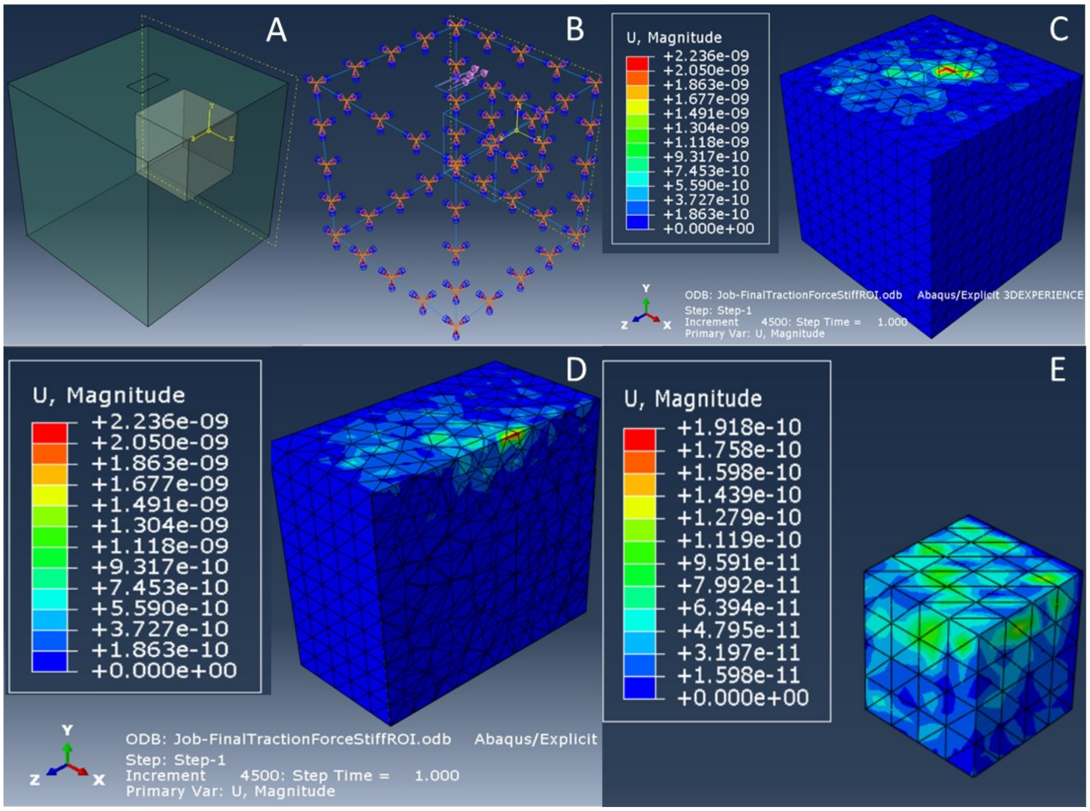

Figure 4. (A) Tissue-like phantom with softer surrounding tissue (green) with a stiff inclusion (white). (B) Fixed boundaries (orange and blue points) and applied harmonic load (purple arrows) on the model. (C) Strain magnitude during harmonic loading of the model. (D) Cross-section of the model showing strain magnitude during harmonic loading. E) Strain magnitude of the stiff inclusion during harmonic loading.

Challenges with IRB protocol review and approval due to a change of institutions and the COVID-19 pandemic limited progress towards the human subject portion of the project. However, IRB approval has now been granted at both institutions, and all the necessary materials have been submitted to HRPO for review.

- **What opportunities for training and professional development has the project provided?**

In the second year of the project, Dr. Ueda and Dr. Kurt have each continued to mentor 2 PhD students working on the research project. (Waiman Meinhold and Heriberto Nieves; Efe Ozkaya and Emily Triolo respectively) (Waiman Meinhold became a postdoc with Dr. Ueda 3 months into the reporting period, and Efe graduated and started a postdoc in a different group 9 months into the reporting period). All 4 of the graduate students/Postdocs each had regular meetings with their advisors to discuss research progress and dissemination. The graduate students have also met regularly with each other in order to keep up with their respective progress. The weekly meetings have included a range of interdisciplinary collaborators, MRI imaging experts, and undergraduate mentees. Although the COVID 19 pandemic limited physical travel during the report period, graduate students held virtual meetings with a variety of collaborators, gaining valuable skills in interdisciplinary scientific collaboration. The nature of the project lead to discussions with various potential collaborators, giving the students opportunity to learn how scientific collaborations can begin.

- **How were the results disseminated to communities of interest?**

A manuscript was submitted and accepted to IEEE transactions on Biomedical Engineering, detailing the development and pilot testing of a system for positioning of high frequency MRE drivers with image-based feedback in MRI. (DOI: 10.1109/TBME.2022.3168494)

- **What do you plan to do during the next reporting period to accomplish the goals?**

The results from the FEA studies will be used to fine tune the mechanical design parameters and placement of the actuators. Phantom and human subject studies will then be completed at University of Washington.

4. **IMPACT:**
- **What was the impact on the development of the principal discipline(s) of the project?**

The first repositionable image guided MRE system was developed. A clear case for its necessity was published, likely impacting future use of not only piezoelectric but other MRE actuators.
- **What was the impact on other disciplines?**

In addition to the Pfirrman score, tissue stiffness could potentially be used as a biomarker to monitor the condition of the IVD. In other words, noninvasive tissue stiffness measurement can be accomplished.
- **What was the impact on technology transfer?**

The project lead directly to the filing of a joint PCT patent application, Georgia Institute of Technology took the unusual step of filing for the full patent without a commercial partner, indicating their belief in the commercial viability of the IP.
- **What was the impact on society beyond science and technology?**

With the proposed MRE actuator system, the researchers aim to make this diagnostic technique became available at every hospital. And since the components are 3D printable, compared to the current FDA approved MRE actuator system, the proposed design will be more affordable. Finally, with the early diagnosis of disc degeneration, it is aimed avoid more serious health conditions such as bulging disc with proper physical therapy and medication.

5. **CHANGES/PROBLEMS:**
- **Changes in approach and reasons for change**

Nothing to report.
- **Actual or anticipated problems or delays and actions or plans to resolve them**

A no cost extension request was submitted and approved during the report period, due to the time to add subawardee. Adding Sinai took place, but after IRB was reviewed and approved by Sinai, Co-PI Mehmet Kurt moved to University of Washington from Stevens, and after some administrative challenges, Sinai (the original imaging facility) decided not to continue on the project. This necessitated resubmission of a new IRB and new facility approvals for the MRI experiments and University of Washington. These are now completed, but caused significant delays.
- **Changes that had a significant impact on expenditures**

Nothing to report.
- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

The IRB review process was restarted at University of Washington (Dr. Kurt's new institution), with approval for all planned human subject experiments at both UW and Georgia Institute of technology.
- **Significant changes in use or care of human subjects.**

Nothing to report.
- **Significant changes in use or care of vertebrate animals.**

Nothing to report.
- **Significant changes in use of biohazards and/or select agents**

Nothing to report.

6. **PRODUCTS:**
- **Publications, conference papers, and presentations**

W. Meinhold, E.Ozkaya, D.Petti, V. Rice, E. Triolo, F. Rezayaraghi, P. Kennedy, L. Fleysher, A. Hu, J. Ueda, M. Kurt, Towards Image Guided Magnetic Resonance Elastography via Active Driver Positioning Robot, *IEEE Transactions of Biomedical Engineering*, *accepted*.

Report only the major publication(s) resulting from the work under this award.
- **Other publications, conference papers, and presentations.**

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.
- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. In addition to a description of the technologies or techniques, describe how they will be shared.
- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. State whether an application is provisional or non-provisional and indicate the application number. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

International Application PCT/US2021/025131 directed to METHOD AND SYSTEM FOR MRI-GUIDED VISUAL SERVOING was published October 7, 2021

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment, and/or rehabilitation of a disease, injury or condition, or to improve the quality of life.

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?**

Name:	Jun Ueda
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	0000-0001-7807-6863
Nearest person month worked:	1 Months
Contribution to Project:	Conceptualization, mentoring
Funding Support:	Academic Instruction and NSF
Name:	Mehmet Kurt
Project Role:	Co-PI
Researcher Identifier (e.g. ORCID ID):	0000-0002-5618-0296
Nearest person month worked:	1 Months
Contribution to Project:	Conceptualization, mentoring
Funding Support:	NSF/NIH
Name:	Waiman Meinhold
Project Role:	Postdoctoral Fellow/Graduate Student
Researcher Identifier (e.g. ORCID ID):	0000-0002-7215-6958
Nearest person month worked:	12 months
Contribution to Project:	Design, testing, conceptualization
Funding Support:	NSF and this project
Name:	Efe Ozkaya
Project Role:	Graduate Student
Researcher Identifier (e.g. ORCID ID):	0000-0003-0583-7507
Nearest person month worked:	6 months
Contribution to Project:	Design, testing, conceptualization

Funding Support:	NSF CMMI 1826270
Name:	Heriberto Nieves
Project Role:	Graduate Student
Researcher Identifier (e.g. ORCID ID):	0000-0001-8193-3811
Nearest person month worked:	6 months
Contribution to Project:	Computer simulation and evaluation
Funding Support:	NSF GRFP
Name:	Emily Triolo
Project Role:	Graduate Student
Researcher Identifier (e.g. ORCID ID):	0000-0002-3003-1110
Nearest person month worked:	4.5 months
Contribution to Project:	Computer simulation
Funding Support:	NA

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

Nothing to report.

- **What other organizations were involved as partners?**
    - **Organization Name:** Biomedical Engineering and Imaging Institute (BMEII)
    - **Location of Organization:** 1470 Madison Ave, New York, NY 10029
    - **Partner's contribution to the projec**t providing access to 3Tesla Siemens Scanner and 7Tesla Bruker Scanner
        - **Financial support;** do not exist
        - **In-kind support** computers, MRI sequence protocol design software, MRI coils
        - **Facilities** MRI scanners;
        - **Collaboration** Lazar Fleysher, Paul Kennedy, Kamil Banibaker, Dewey Chu;
        - **Personnel exchanges** Graduate students went to BMEII to perform the MRE experiments;
        - **Other** Dr. Priti Balchandani served as Co-PI for a portion of the Y2 time period, but Mount Sinai elected to not continue on the project after Dr. Kurt moved to University of Washington.

8. SPECIAL REPORTING REQUIREMENTS

NA

9. **APPENDICES:** NA