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TITLE:

Quantitative Measures by Dedicated Breast PET and MRI for Early Prediction of Response to Neoadjuvant Chemotherapy

PRINCIPAL INVESTIGATOR:

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CONTRACTING ORGANIZATION:

Regents of The University of California
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13. SUPPLEMENTARY NOTES

14. ABSTRACT

The objective of this project is to combine imaging metrics from dedicated breast positron emission tomography (dbPET) and magnetic resonance imaging (MRI) with machine learning to produce diagnostic models to inform early redirection of treatment for non-responding patients, and to forego additional treatment for responding patients, sparing them from unnecessary toxic therapy.

15. SUBJECT TERMS
None listed.

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INTRODUCTION

In the neoadjuvant chemotherapy setting, imaging plays a critical role in non-invasively assessing the response of the intact primary tumor to systemic therapies. Changes in the primary tumor can serve as a surrogate marker for the therapeutic effect, and imaging evaluation of the primary tumor during treatment can provide important prognostic and predictive information. The objective of this project is to combine imaging metrics from dedicated breast positron emission tomography (dbPET) and magnetic resonance imaging (MRI) with machine learning to produce diagnostic models to inform early redirection of treatment for non-responding patients, and to forego additional treatment for responding patients, sparing them from unnecessary toxic therapy.

KEYWORDS

Breast cancer, dedicated breast PET, fluorodeoxyglucose (FDG), fluoroestradiol (FES), machine learning, molecular imaging, MRI

ACCOMPLISHMENTS

What were the major goals of the project?

The major goal of this project is to combine dedicated breast positron emission tomography (dbPET) and magnetic resonance imaging (MRI) with machine learning to develop a non-invasive imaging method to inform whether patients are responding to chemotherapy early in the course of treatment. This method can be used to guide treatment redirection for poor responders to a potentially more effective regimen and to guide treatment dose reduction for excellent responders, sparing them from unnecessary chemo-toxicities.

Specific Aim 1: Evaluate FDG-dbPET in comparison to MRI for prediction of response in I-SPY 2 patients
Milestone: Introduce diagnostic tool for treatment re-direction in I-SPY 2 (36 mos)

Specific Aim 2: Conduct radiomic analysis and apply machine learning algorithms to develop predictive models for treatment re-direction

Milestone: Identify a set of radiomic features from dbPET and MRI as prognosticators (36 mos)

Specific Aim 3: Exploratory study of FES-dbPET radiomics to identify an aggressive ER+ subtype

Milestone: Identify a set of FES-dbPET radiomic features in association with aggressive ER+ phenotype (36 mos)

What was accomplished under these goals?

Major activities from September, 2019 – September, 2020 include:

1) to accrue patients and continue to collect data for analyses
2) to compare PET data obtained from whole-body PET (wbPET) vs. dbPET
3) to assess the reproducibility of radiomic features calculation from dbPET patient data
4) to examine the relationship between FDG-dbPET and MRI features in a cohort of breast cancer patients receiving neoadjuvant chemotherapy
5) to develop standardized protocols to include HIPAA-complaint telehealth-based methods for patient accrual
6) to reopen the study in August 2020 after a temporary shut down due to the COVID-19 pandemic

Specific objectives

1) evaluate FDG-dbPET in comparison to MRI for prediction of response in a subset of I-SPY 2 breast cancer patients
2) conduct radiomic analysis and apply machine learning algorithms to develop predictive models for treatment re-direction
3) perform exploratory studies using ^{18}F-FES dPET and DCE-MRI to characterize primary ER+ breast cancer

Significant results

Objective 1: We examined the relationship between FDG-dbPET and MRI features in a cohort of breast cancer patients receiving neoadjuvant chemotherapy. Of the 16 patients enrolled in this study, 13 patients (N = 15 unique tumors) with pre- and early post-treatment MRI and dbPET were included in the analysis. 46% (6/13) of the patients in this cohort had TNBC. Our initial findings indicated that ΔPE_{Max} and ΔSUV_{Max} had the highest correlation ($\rho = 0.59$, $p = 0.022$). ΔPE_{Max} and TLG at T1 were also correlated ($\rho = 0.56$, $p = 0.032$). Among all imaging features, ΔMTV had the largest post-treatment reduction difference (-54.5 vs. -6.06%) between the TNBC vs. non-TNBC groups. Among MRI features, ΔFTV exhibited the largest reduction difference (-70.4%, IQR: -79.0 to -62.1%) in TNBC vs. non-TNBC patients (-43.1%, IQR: -72.5 to 2.95%). ΔSUV_{Max} (-47.3% vs. -23.1%) and ΔTLG (-75.2 vs. -47.9%) were additional dbPET features with large early post-treatment reduction differences between TNBC and non-TNBC patients (**Figure 1**).

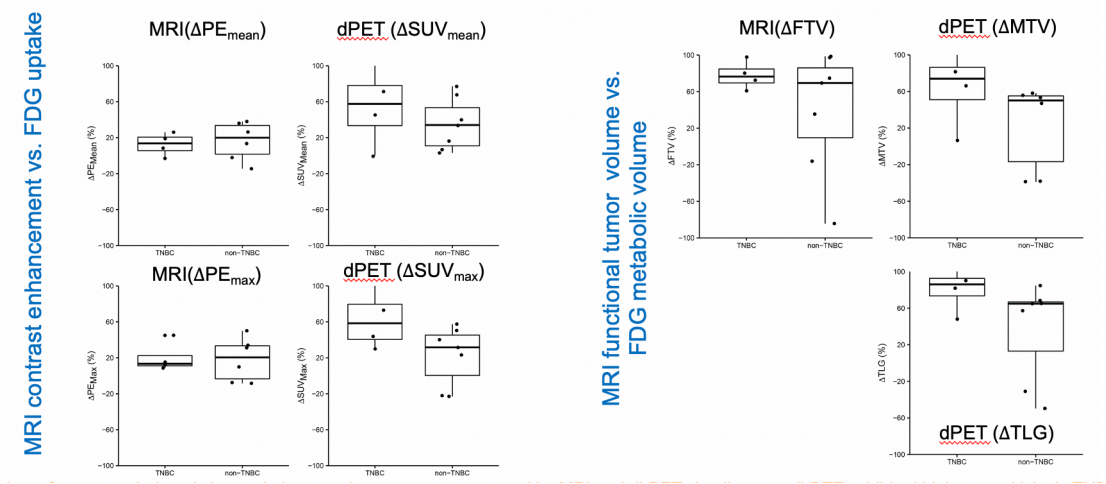

Figure 1. Box plots of treatment-induced change in breast primary tumors measured by MRI and dbPET. In all cases, dbPET exhibited higher sensitivity in TNBC vs. non-TNBC

In addition, we evaluated the similarities and differences in the uptake of [^{18}F]FDG in dbPET compared to whole-body PET (wbPET) in a cohort of 10 patients with biopsy-confirmed, locally advanced breast cancer at the pre-treatment timepoint. [^{18}F]FDG uptake measurements and 20 radiomic features based on morphology, tumor intensity, and texture were calculated and compared. There was a 5-fold increase in SUL_{peak} for dbPET (median difference (95% CI): 4.0 mL^{-1} (1.8 - 6.4 mL^{-1}), $p = 0.006$). Spatial heterogeneity features also showed statistically significant differences between dbPET and wbPET. The higher [^{18}F]FDG uptake in dbPET highlighted the dynamic range of this breast-specific imaging modality (**Figure 2**)

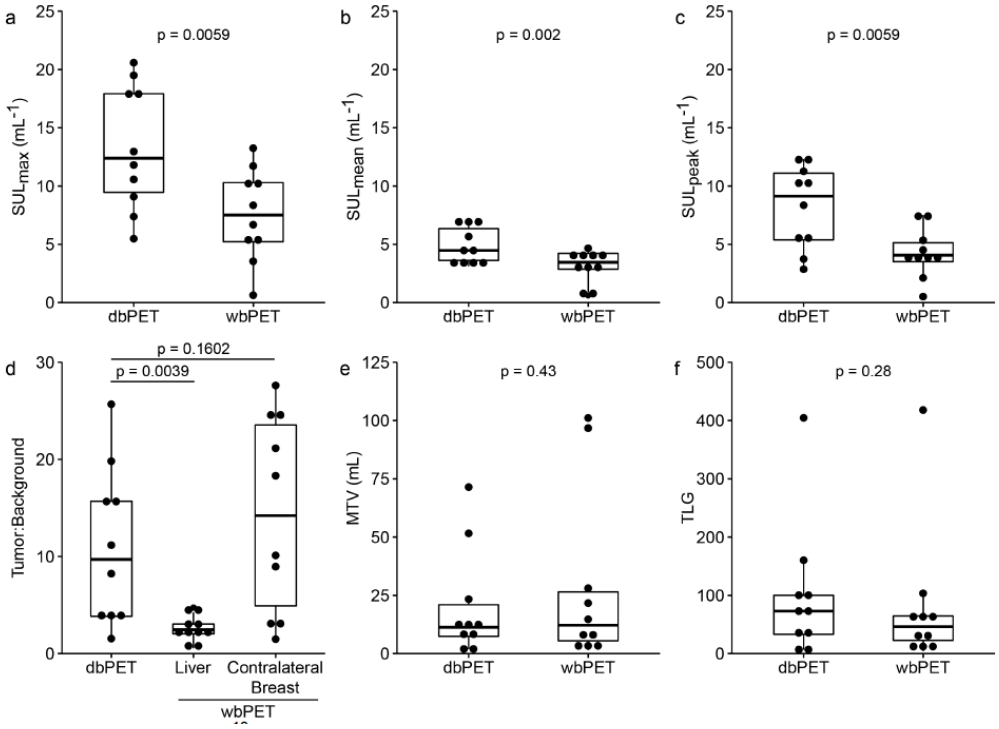

Figure 2. Comparison of [^{18}F]FDG uptake in lesions with dbPET and wbPET. (a) SUL_{max}; (b) SUL_{mean}; (c) SUL_{peak}; (d) Ratio of SUL_{peak} in tumor to SUL_{mean} in the background. For wbPET, the background VOIs were defined separately on the liver and the contralateral breast. Background VOI was defined in the contralateral breast for dbPET. (e) Metabolic tumor volume (MTV); and (f) Total lesion glycolysis (TLG).

Objective 2: 63 radiomic features (16 morphology, 18 intensity, 29 texture) were extracted from 14 breast tumors in 12 patients. 32 features (mostly intensity) were highly reproducible between readers (ICC3 >0.90) for both manual and semi-automated tumor segmentation methods. 57 features were highly repeatable by an individual reader (ICC3 >0.90) when using the same window width/level and threshold, but only for semi-automated segmentation. Some features had excellent ICCs only in manual segmentation. The difference may be related to difficulty separating adjacent tumors in multifocal disease using the semi-automated method. Most of the less reproducible features were from the morphology class (**Figure 3**).

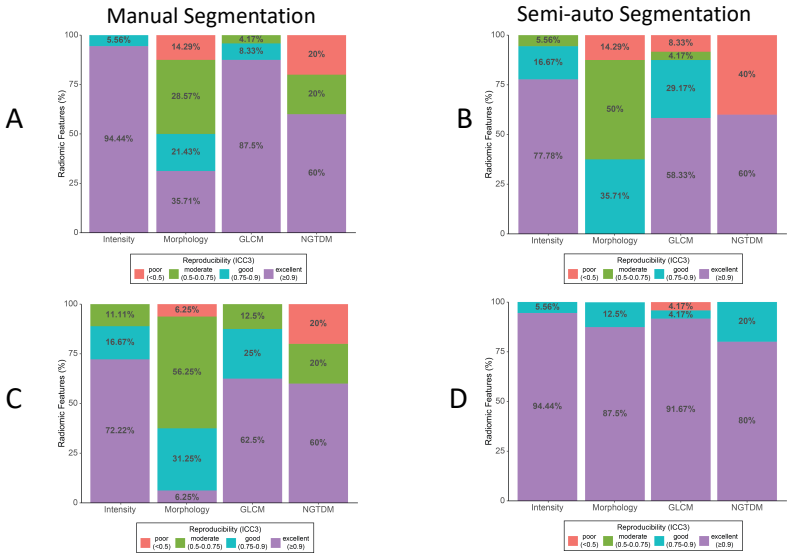

Figure 3. Inter-reader (A-B) and intra-reader (C-D) reproducibility of radiomic features on dbPET quantified by the intraclass correlation coefficient (ICC3) for the morphology, intensity, and texture [gray-level co-occurrence matrix (GLCM) and neighborhood gray-tone distance matrix (NGTDM)] classes. Reproducibility category cutoffs were applied on the lower 95% confidence limit of the ICC3 value.

Objective 3: To date, we had imaged 14 ER+ breast cancer patients using [^{18}F]FES-dbPET. Patient age ranged from 23 to 76, with a range of Ki67 from 1 to 30%. All of them were ER+ >90% and HER2−. Two underwent a mastectomy, six received endocrine therapy alone, and two received endocrine treatment followed by chemotherapy, four were treated with chemotherapy. In this small cohort, we observed a different [^{18}F]FES uptake pattern in these patients (**Figure 4A**). While all patients had ER+ >90%, not all patients had functional ER, with some showing low [^{18}F]FES uptake (**Figure 4B**). [^{18}F]FES-dbPET was also used to monitor treatment response in Patient #1 and #2. Patient #1 was imaged after two months of neoadjuvant endocrine treatment (NET). Her FES uptake measured by SUV_{max} decreased from 15.83 to 6.11 and the [^{18}F]FES uptake volume was reduced from 15.72 to 0.37 cm^3. Follow-up DCE-MRI showed tumor reduction in the extent of non-mass enhancement with significant background enhancement (**Figure 5 A to C**). Patient #2 had a 12.6 cm ER+ (>95%) invasive lobular cancer by MRI with high recurrence risk by MammaPrint®(**Figure 5 D to F**). After receiving NET followed by neoadjuvant chemotherapy (NAC), [^{18}F]FES-dbPET showed a significant reduction of SUV_{max} from 35.24 to 6.35. The total [^{18}F]FES uptake volume decreased from 227.97 to 8.29 cm^3, and MRI showed an overall improvement with the dominate mass reduced to a conglomerate of small masses. For this second patient, it is unknown whether NET or NAC impacted findings on [^{18}F]FES-dbPET, and whether SUV thresholds will differ by molecular signature status such as MammaPrint®.

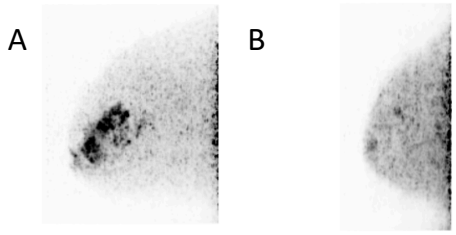

Figure 4. Examples of [^{18}F]FES-dbPET from two patients with biopsy-proven >95% ER+ HER2- ILC using the same window width and level setting. **A**: Patient #1 – a 61-year- old female patient with grade 2 ILC in her right breast. [^{18}F]FES-dbPET showed a maximum standardized uptake value (SUV_{max}) of 15.83. **B**: Patient #4 – a 50-year-old female patient with grade 2 ILC in her right breast. [^{18}F]FES-dbPET showed a SUV_{max} at 5.02.

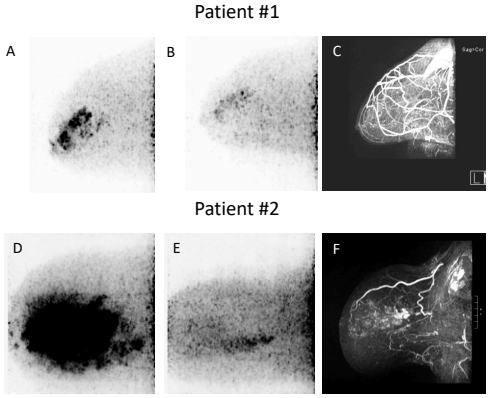

Figure 5. Examples of [^{18}F]FES-dbPET being used to monitor neoadjuvant treatment response. **Patient #1**: **A)** At baseline, [^{18}F]FES-dbPET showed a SUV_{max} of 15.83 and a [^{18}F]FES uptake volume of 15.72 cm^3. **B)** After two months of NET, her [^{18}F]FES-dbPET showed a reduction of SUV_{max} at 6.11 and the uptake volume of 0.37 cm^3. **C)** Her corresponding DCE-MRI showed tumor reduction in the extent of non-mass enhancement with significant background enhancement. **Patient #2**: **D)** At baseline, [^{18}F]FES-dbPET showed a SUV_{max} at 35.24 and the ^{18}F]FES uptake volume of 227.97 cm^3. **E)** After NET followed by NAC, her [^{18}F]FES-dbPET showed a favorable response with the SUV_{max} at 6.35 and the uptake volume reduced to 8.29 cm^3. **C)** Her corresponding DCE-MRI confirmed the overall improvement with the dominant mass reduced to a conglomerate of small masses.

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

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

Dr. Deep Hathi, a post-doctoral fellow, continues to work on this project. Dr. Hathi had the opportunity to attend several national scientific meetings including:

1) 2020 Society of Nuclear Medicine and Molecular Imaging (SNMMI) annual meeting, July 11 – 14, 2020
2) 2020 International Society for Magnetic Resonance in Medicine (ISMRM) annual meeting, August 08 – 14, 2020
3) 2020 San Antonio Breast Cancer Symposium annual meeting, December 8 – 11, 2020

Dr. Hathi's work titled "*Evaluation of primary breast cancers using dedicated breast PET and whole-body PET*" was selected as an oral presentation at the 2020 SNMMI annual meeting. He will also present our work titled "Relationship of dedicated breast PET and MRI features in breast cancer patients receiving neoadjuvant chemotherapy" at the 2020 SABCS annual meeting.

Dr. Hathi participated in the UCSF Breast Oncology Program (BOP) seminars, where he was able to acquire new knowledge of breast cancer biology. He also attended the annual UCSF Radiology Research Symposium, where he gave a poster presentation titled "*Evaluation of primary breast cancers using dedicated breast PET and whole-body PET*" and received a poster award.

We supported Julissa Melina-Vega, who is an intern responsible for patient accrual and coordination. We provided training on the clinical workflow and the basic calculations to quantify voxel intensities on dPET images. She also participated in the BOP seminar, where she was able to learn about breast cancer biology.

How were the results disseminated in communities of interest?

Findings from this work was presented at:

1) 2020 Society of Nuclear Medicine and Molecular Imaging (SNMMI) annual meeting, July 11 – 14, 2020
2) 2020 UCSF Radiology Imaging Research Symposium, October 14, 2020
3) 2020 San Antonio Breast Cancer Symposium annual meeting, December 8 – 11, 2020
4)

An original research paper entitled "*Evaluation of primary breast cancers using dedicated breast PET and whole-body PET*" was accepted for publication in NPJ Scientific Reports.

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

In the next report period, we will

1. continue to acquire patient dbPET data and perform additional correlation studies with MRI.
2. continue to examine the radiomics-based analysis in dbPET and MRI images to predict treatment response
3. continue to acquire [^{18}F]FES-dbPET data and examine the[^{18}F]FES uptake pattern in aggressive vs. less aggressive ER+ breast cancers.

Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

Nothing to report.

IMPACT

What was the impact on the development of the principal discipline(s) of the project?

This project seeks to use a breast positron emission tomography (PET) with magnetic resonance imaging (MRI) and computational methods to estimate the relationship linking imaging features and treatment outcome. Through computer programming, mathematical models will be built to learn from the imaging data and to make accurate predictions about early response outcome to enable treatment modifications for patients at the extreme ends of the response spectrum. Ultimately, this work may produce a breakthrough technology that enables digital assessment of the primary breast tumor early in the treatment to guide better clinical decisions to improve breast cancer patients' quality of life during chemotherapy and their overall survival.

disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

CHANGES/PROBLEMS

The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are *significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

Nothing to report.

Changes in approach and reasons for change

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them

Due to the COVID-pandemic and the state order of Shelter-in-place, this study was put on-hold from March 16 to August 01. The PI had developed standardized protocols to include HIPAA-complaint telehealth-based methods such as video-conferencing virtual study visits, electronic consent, and health screen by phone to minimize in-person interaction. As a result, the study was re-opened in August 2020.

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

Significant changes in use or care of human subjects

Nothing to report.

Significant changes in use or care of vertebrate animals

NA

Significant changes in use of biohazards and/or select agents

Nothing to report

PRODUCTS

- **Publications, conference papers, and presentations**

  Journal publications.

Nothing to report.

Books or other non-periodical, one-time publications.

Nothing to report.

Other publications, conference papers and presentations.

Nothing to report.

- **Website(s) or other Internet site(s)**

Nothing to report.

- **Technologies or techniques**

Nothing to report.

- **Inventions, patent applications, and/or licenses**

Nothing to report.

- **Other Products**

Nothing to report.

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Ella Jones
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	0000-0001-8700-2129
Nearest person month worked:	3.72 mos
Contribution to Project:	Dr. Jones provided oversight of the conduct of the overall research project. She was responsible for patient accrual, coordination, scan, image processing, analysis and interpretation. She provided training for the intern and post-doctoral fellow on the project and implement the hardware repair, upgrade and relocation to the new site within UCSF.
Funding Support:	

Name:	Nola M. Hylton
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	0.35 mos
Contribution to Project:	Dr. Hylton provided oversight of all the breast MR imaging of breast cancer patients. She also served as the primary liaison to the I-SPY 2 trial networks, including linkage to clinical, bioinformatics and statistical centers for I-SPY 2.
Funding Support:	

Name:	Robert Flavell
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	0.36 mos
Contribution to Project:	Dr. Flavell replaced Dr. Benjamin Franc to assume the responsibility to review and interpret breast dbPET images and co-read dbPET and MR images with Dr. Bonnie Joe.
Funding Support:	

Name:	Youngho Seo
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	0.6 mos
Contribution to Project:	Dr. Seo worked with Dr. Jones to provide input for dbPET data reconstruction and metric calculation.
Funding Support:	

Name:	Deep Hathi
Project Role:	Post-doctoral Fellow
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	0.48 mos
Contribution to Project:	Dr. Hathi received training on all aspect of the dbPET work as outlined in this project. He was also trained on radiomics feature extraction as well as analyses using R statistical software packages.
Funding Support:	

Name:	Julissa Melina-Vega
Project Role:	Intern
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	0.3 mos
Contribution to Project:	Julissa was responsible for patient accrual and imaging coordination
Funding Support:	

Name:	Margarita Watkins
Project Role:	Clinical research coordinator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	0.6 mos
Contribution to Project:	Margarita was responsible regulatory compliance, patient workflow and scheduling.
Funding Support:	

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

What other organizations were involved as partners?

Nothing to report.

Nothing to report.

SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

APPENDICES