Low-Dose Tamoxifen to Reduce High Background Parenchymal Uptake on Molecular Breast Imaging

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1 BACKGROUND AND RATIONALE

1.1 MBI as a Supplemental Screening Test

Approximately 40-50% of women presenting for screening mammography have mammographically dense breasts, a factor that severely limits sensitivity of the test. Molecular breast imaging (MBI) is one option offered for supplemental screening of dense breasts. As MBI is a functional imaging technique that relies on differences in preferential uptake of Tc-99m sestamibi in metabolically-active cells, it is able to reveal cancers hidden among dense fibroglandular tissue on a mammogram. Performing MBI after a negative mammogram in women with dense breasts detects an additional 7.7 to 8.8 breast cancers per 1000 women screened [1-3].

MBI is a nuclear medicine test that uses a high-resolution, semiconductor-based gamma camera to image the uptake of a radiotracer, typically Tc-99m sestamibi, in the breast. Mayo Clinic investigators have pioneered current MBI techniques and developed a low-radiation-dose MBI protocol for clinical use [4, 5]. Recently, MBI has been implemented across the multi-site Mayo Clinic practice.

1.2 Background Parenchymal Uptake (BPU) on MBI

In addition to detecting breast cancer, MBI also depicts the level of Tc-99m sestamibi uptake in non-cancerous fibroglandular tissue, termed background parenchymal uptake (BPU). BPU is subjectively assessed according to a validated lexicon as one of four categories (photopenic, minimal to mild, moderate, and marked) that describe the relative intensity of uptake in fibroglandular tissue[6]. A quantitative measure of BPU is also currently under development by Dr. Hruska's team (R21 CA197752). BPU varies among women with similar-levels of mammographic density and is associated with hormonal factors such as menopausal status and use of postmenopausal hormone therapy (Fig. 1) [7]. Importantly, we recently showed BPU associated with breast cancer risk; women with moderate or marked BPU have 3.4 to 4.8-fold increased risk compared to women with photopenic or minimal-mild BPU [8].

The exact mechanism of uptake of Tc-99m sestamibi in breast tissue is not entirely understood, but has been correlated with blood flow, tissue viability, mitochondrial activity, and mitotic activity in breast cancers. In an effort to understand histological characteristics that may account for variability in BPU, analysis has been performed on core biopsy specimens from 48 volunteers with mammographically dense breasts who have one of the extreme BPU categories of either photopenic BPU (N = 28) or marked BPU (N

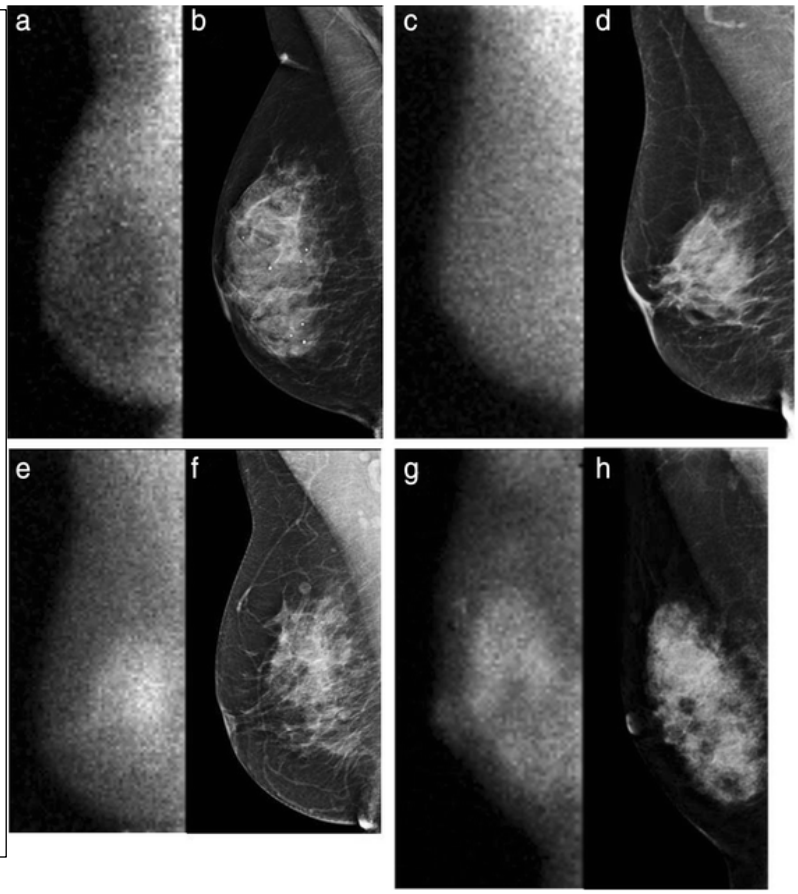

Fig. 1
Examples of background parenchymal uptake categories. Molecular breast imaging (MBI) examinations and corresponding full-field digital mammograms from four different women are shown. All images were acquired in the mediolateral oblique projection. MBI with photopenic background parenchymal uptake (BPU) (**a**) and corresponding mammogram (**b**). MBI with minimal to mild BPU (**c**) and corresponding mammogram (**d**). MBI with moderate BPU (**e**) and corresponding mammogram (**f**). MBI with marked BPU (**g**) and corresponding mammogram (**h**)

= 20) on MBI (unpublished data). BPU was associated with differences in tissue composition: specimens with marked BPU comprised a higher proportion of epithelial cells (22% vs. 2.8%, $p<0.0001$) and a lower proportion of stroma (47% vs. 75%, $p = 0.005$).

BPU was inversely correlated with lobular involution status and associated with Ki-67 positivity (8.6% positive in marked BPU vs. 2.6% positive in photopenic BPU, $p = 0.006$). These associations with histologic features further support a relationship between BPU and breast cancer risk.

We hypothesize that BPU is positioned to serve as a functional imaging biomarker to identify the subset of women with dense breasts who are at greatest breast cancer risk and most likely to benefit from tailored screening or preventive options. However, more study is needed to understand BPU as a marker of risk. It is yet unclear how BPU changes over the course of a woman's lifetime and whether these changes are related to changes in breast cancer risk. Further, it is unknown whether chemopreventive options such as tamoxifen would decrease BPU and whether these changes could serve as a surrogate marker for decrease in risk.

1.3 Low-dose Tamoxifen

Tamoxifen is a selective estrogen receptor modulator (SERM) that blocks the effects of estrogen on breast tissue. Tamoxifen is FDA-approved as a chemopreventive option for both premenopausal and postmenopausal women. Studies have shown that preventive tamoxifen, when taken daily for five years, can reduce risk of developing breast cancer by at least one-third. Results from the National Surgical Adjuvant Breast and Bowel Project showed that in women considered at increased risk for breast cancer, preventive tamoxifen reduced breast cancer risk by approximately one-half [9]. However, at the standard clinical dose of 20 mg per day, tamoxifen can produce side effects such as menopausal symptoms, and also carries a small risk (<1% of participants) of serious adverse events, including uterine cancer and blood clots in legs or lungs. Concerns about the risk of these adverse events accounts for overall low utilization of tamoxifen for chemoprevention. In patients who do start tamoxifen, side effects of the drug can lead to non-compliance with long-term use.

Because of these concerns, multiple investigations have been done to determine efficacy of tamoxifen at lower doses. Tamoxifen taken at 5 mg per day has been proposed as an optimal dosage that is associated with decreasing biomarkers of breast disease (including mammographic density), and reduced breast cancer risk while potentially mitigating the adverse events and side effects seen at the 20 mg/day dose [10-12]. Other studies have evaluated efficacy of tamoxifen at 10 mg/day [13-15]. In one study conducted among women being treated for breast cancer, tamoxifen at 10 mg per day over a short period of 14 days resulted in clinically and statistically meaningful declines in molecular markers of estrogen receptor positivity, progesterone receptor positivity and Ki-67 (a marker of cellular proliferation) [15].

1.4 Study Purpose

In this study, we aim to determine whether short-term intervention with low-dose tamoxifen can induce a decline in BPU. Results from this study will provide critical knowledge on factors that influence changes in BPU and inform future study of BPU as a modifiable risk factor.

2 STUDY OBJECTIVE

To assess changes in background parenchymal uptake (BPU) on MBI before and after low-dose tamoxifen intervention (5 mg per day for 30 days or 10 mg per day for 30 days), among women with a history of high BPU. *It is hypothesized that both subjective categorical and quantitative measures of BPU will decline with low-dose tamoxifen intervention.*

3 STUDY DESIGN

We propose a prospective clinical trial to be conducted within our cohort of women who have previously had an MBI test performed at Mayo Clinic. In this study, women with high

BPU on MBI will be invited to participate in a short-term intervention of low-dose tamoxifen (5 mg per day for 30 days or 10 mg per day for 30 days). MBI will be repeated at the end of the intervention. Change in BPU before and after the intervention will be assessed with both subjective and quantitative measures.

4 SELECTION AND ENROLLMENT OF PARTICIPANTS

The study population will include women who have no history of breast cancer and have previously had an MBI showing high BPU.

4.1 Inclusion Criteria

The following are requirements for entry into the study:

1) Female, age 40 or older at the time of enrollment
2) Most recent MBI examination, performed within 3 years of enrollment, showed moderate or marked background parenchymal uptake
3) Mammogram performed within 24 months prior to enrollment that is available for comparison
4) Willing and able to return for MBI following 30 days of low-dose tamoxifen
5) If able to become pregnant
    a. Negative pregnancy test within 48 hours prior to study MBI exam(s)
    b. Agrees to avoid pregnancy during the study and for at least 2 months after study participation ends, by abstinence, barrier method, or nonhormonal contraception.
6) Understands and signs the consent form

4.2 Exclusion Criteria

Subjects will be excluded if any of the following characteristics are present:

1) Evidence of suspected breast disease as defined by positive findings or recommendation for short-interval follow-up on most recent breast imaging (including mammography, MBI, MRI, ultrasound, etc.) not yet resolved prior to enrollment
2) Breast biopsy or breast surgery performed within 6 months prior to enrollment
3) Bilateral breast implants or status post-bilateral prophylactic mastectomy
4) Pregnant or lactating
5) Current or recent use (within 6 months prior to enrollment) of any of the following drugs:
    a. Systemic hormonal therapy (oral or transdermal patch formulations)
    b. Hormonal contraception (oral, transdermal, implanted, or injected formulations not allowed, however hormonal IUDs are acceptable)
    c. Selective estrogen receptor modulators (tamoxifen, raloxifene, or toremifene)
    d. Aromatase inhibitors (anastrazole, letrozole, or exemestane)
    e. GnRH analogs
    f. Prolactin inhibitors
    g. Androgens or antiandrogens

h. Anticoagulants or "blood thinners" (warfarin, heparin, rivaroxaban and other novel anticoagulants)
i. Drugs known to be strong inhibitors of CYP2D6, the major P450 enzyme that metabolizes tamoxifen, including:
    - bupropion (Wellbutrin)
    - fluoxetine (Prozac)
    - paroxetine (Paxil)
    - quinidine (Quinidex)

6) Personal history of any type of malignancy, with the exclusion of non-melanoma skin cancer, diagnosed prior to enrollment
7) Personal history or strong family history of blood clots in legs or lungs (also known as deep vein thrombosis or pulmonary embolism)
8) Personal history of transient ischemic attack (TIA) or cerebrovascular accident (CVA)
9) Active proliferative disorders of the endometrium such as atypical hyperplasia, history of active endometriosis, unresected polyps
10) Any type of retinal disorders or severe cataract
11) Current smoker
12) Known carrier of BRCA1 or BRCA2 genetic mutation or known DNA repair defect.
13) Blood pressure above 140/90

4.3 Enrollment Procedures

Our Mayo Clinic MBI databases will be reviewed to identify potential candidates for this study. Women who have had high (moderate or marked BPU) on a prior MBI study, performed within 3 years of enrollment in the current study, with no apparent conflict with inclusion and exclusion criteria will be contacted by invitation letter. This letter informs patients of our new research findings showing the association between high BPU and breast cancer risk and offers study participation. Patients may contact the study team by phone or email. The study coordinator will assess patient eligibility, discuss study procedures with the patient, and schedule an in-person enrollment visit at which informed written consent will be obtained. The physician co-principal investigator of the study will be available for consultation during the consent process.

5 STUDY PROCEDURES

5.1 Schedule of Evaluations

Potential participants will be screened for eligibility and undergo informed written consent with the study coordinator at the time of enrollment. At Study Visit 1, the participant will be asked to complete a study questionnaire and undergo MBI (after a negative pregnancy test as necessary). Participants will then undergo 30 days of low-dose tamoxifen medication followed by Study Visit 2, at which time a repeat MBI test will be performed.

	Enrollment	Study Visit 1	30 days between visits	Study Visit 2
Eligibility Checklist	X			
Informed Consent	X			
Questionnaire: Breast Health and History		X		
Blood pressure measurement		X		
Urine pregnancy test (if necessary)		X		X
MBI		X		X
Tamoxifen (5 mg/day for 30 days or 10 mg/day for 30 days)			X	
Check-in phone calls at day 5 and 20			X	
Study close-out				X

5.2 Pregnancy test

All participants who can become pregnant will be required to have a urine pregnancy test performed with negative results within 48 hours prior to each MBI injection. The study coordinator will administer this test.

5.3 Blood pressure test

Participants will undergo a blood pressure test prior to starting low-dose tamoxifen. The study coordinator will administer this test with an automated machine. If a participant has blood pressure over 140/90, she will not proceed with the study.

5.4 Molecular breast imaging (MBI)

MBI testing will be performed at Mayo Clinic Rochester within the Division of Breast Imaging and Intervention. MBI procedures will be done as per clinical standard of care (described below).

5.4.1 *Equipment* – MBI examinations will be performed on an FDA-approved dual-head gamma camera system comprised of cadmium zinc telluride detectors and collimation optimized for low-dose breast imaging (LumaGem, Gamma Medica, Salem, NH).

5.4.2 *Technologists* – Radiotracer injection and MBI image acquisition shall be performed by female nuclear medicine technologists who have received training in mammographic positioning techniques.

5.4.3 *Patient preparation* - Patients will be asked to fast for a minimum of 3 hours prior to the MBI examination, when possible, as prior studies have shown fasting to improve uptake of Tc-99m sestamibi in breast tissue by reducing splanchnic and hepatic blood flow.[16] Patients may take fluids, including black coffee, tea, diet soda and water.

Patients will remove all clothing and jewelry above the waist and put on a patient gown. Patients may be given a warm blanket to wrap around their shoulders and chest prior to

the MBI examination, in order to increase peripheral blood flow to breast tissue and thus improve Tc-99m sestamibi uptake.

5.4.4 *Tc-99m sestamibi injection* - The technologist should verify that the patient is not pregnant or breast feeding prior to injection of Tc-99m sestamibi.

MBI examinations will be performed with a dispensed dose of 8 mCi (300 MBq) Tc-99m sestamibi (range 7.2 – 8.8 mCi). A nuclear medicine technologist will deliver an intravenous injection of the Tc-99m sestamibi dose in an antecubital vein of either arm. Flushing of the syringe with saline and use of syringes that provide low sestamibi adhesion is recommended to minimize residual activity.

Infiltration, or extravasation of the injected dose into the soft tissue rarely occurs (~1-2% of studies). If infiltration is suspected, the technologist will observe the count rate obtained on a persistence view prior to beginning imaging. If the count rate is lower than typical (defined as less than 0.2 kcts/minute in the craniocaudal [CC] view and less than 0.3 kCts/minute in the mediolateral oblique [MLO] view for an average-sized breast) the technologist will image the injection site to evaluate.

If there is no evidence of infiltration on imaging of the injection site, the technologist will proceed with the breast images. If infiltration is confirmed by both low count rates and high uptake at the injection site, the technologist will ask for the patient's consent to proceed with a second injection of 8 mCi Tc-99m sestamibi. The patient will be given the option to refuse a second dose and continue with the study, although poor image quality may be obtained, or to discontinue MBI imaging and thus end study participation.

5.4.5 *Image acquisition* - MBI imaging will commence immediately after injection. Two views of each breast will be acquired in the CC and MLO projections. Acquisition duration will be 10 minutes per view. Images will be acquired in static mode using an energy acceptance window of 110-154 keV.

For each view, patients will be seated with the breast positioned between the two detectors. The persistence-scope should be used to validate correct breast positioning. If available, the recent mammogram can be viewed to replicate positioning on the MBI. Light compression is applied to stabilize the breast and to limit motion artifact. Placement of pillows behind the patient's back is recommended to reduce motion and increase comfort. Verification of the patient's comfort level and ability to complete 10 minutes of imaging in the position should be done before acquisition begins. Compression thickness for each MBI view will be recorded. At Study visit 2, the compression thickness for each view will be adjusted to match that recorded from the Study visit 1.

In participants with breasts larger than the detector field of view, the technologist may opt to acquire two 10-minute tiled MLO views of each breast, in place of a CC and MLO view, in order to ensure that the entire breast is included in the image set.

During the acquisition of each view, the technologist will briefly place the appropriate Co-57 laterality markers (R for right and L for left) in the field of view until well seen on the persistence screen.

The patient will be visually monitored by the nuclear medicine technologist from the time of injection of the radionuclide until image acquisition is completed.

5.4.6 *Post-acquisition processing* - Following completion of the acquisition, the technologist will format the acquired images in the standard format used for MBI display and interpretation.

5.5 MBI Interpretation

MBI interpretation will be performed by study radiologists. The radiologists will subjectively assess BPU on a 5-category scale as 1 – photopenic, 2 – minimal, 3 – mild, 4 – moderate, or 5 – marked. Changes in BPU between pre-tamoxifen and post-tamoxifen MBI will be assessed, with blinding to the order of the studies.

The interpreting study radiologist will issue a report in the patient's medical record to state that the MBI was performed for research purposes under IRB #16-008736. The report will either state that no suspicious findings were noted, or will describe any incidental findings seen on MBI for which diagnostic workup is recommended. Any necessary diagnostic workup of MBI findings will be performed according to the established standard of care [17].

5.6 Low-dose tamoxifen intervention

Subjects will be enrolled to one of two arms of the study. The study arms will be identical, except for the dose of tamoxifen. For Arm 1, the dose of tamoxifen will be 5 mg per day for 30 days. For Arm 2, the dose of tamoxifen will be 10 mg per day for 30 days.

Participants will receive a prescription for tamoxifen. A physician co-principal investigator will order participant prescriptions, which will be filled through the Mayo Clinic Outpatient Research Pharmacy. For subjects in Arm 1, the research pharmacy will perform splitting of the standard tamoxifen tablets (available in either 10 mg or 20 mg doses) and over-encapsulation to arrive at 5 mg tablets.

Participant instructions for the tamoxifen medication will be as follows:

- Take one capsule per day for 30 days
- Take each dose at approximately the same time each day
- Capsules should be taken with water or a non-alcoholic beverage. Capsules can be taken with or without food.
- If you miss a dose, take the missed dose as soon as you remember it. However, if it is almost time for the next dose, skip the missed dose and continue your regular dosing schedule. Do not take a double dose to make up for a missed one.

Participants will also be given a "Drug Diary" log and asked to make notes of when each dose is taken and to record any symptoms experienced. Participants will be asked to return

Drug Diary logs and pill bottles at the Study Visit 2. Any remaining pills will be returned to the Outpatient Research Pharmacy for disposal.

Participants will be advised that they may elect to stop the tamoxifen medication at any time, should they experience unwanted side effects. Patients will be asked to contact study staff if they do choose to stop. Patients who start tamoxifen but choose to stop earlier than 30 days will be asked to return for their post-tamoxifen MBI test (Study Visit 2) at that time.

5.7 Image Analysis

Quantitative assessments of BPU on all MBI studies will be performed by study staff using region of interest analysis. Counts within breast fibroglandular tissue and areas of fat in the breast will be obtained to calculate the ratio of counts per pixel in fibroglandular tissue vs. fat. Change in this ratio across MBI studies performed within patients will be determined.

6 STUDY RISKS

6.1 Discomfort during MBI

An MBI exam involves an intravenous injection in the arm, which may cause minor discomfort. Following each injection, the subject is required to sit on a chair for ~40 minutes for the MBI with either breast placed in light compression during the image acquisitions. This procedure should cause little to no discomfort to the subject.

6.2 Tc-99m sestamibi

Tc-99m sestamibi is an FDA-approved drug with an excellent safety profile. This drug has been safely used in clinical practice for over 30 years. Very rarely, patients receiving sestamibi experience mild symptoms such as flushing, a rash, or a brief metallic taste after injection.

6.3 Radiation

The radiation dose from a total administered dose of 8 mCi Tc-99m sestamibi has an effective (whole-body) dose of ~2.1 mSv. Subjects will undergo two MBI examinations for a total effective dose of about 4.2 mSv. This radiation dose has a very low risk of harmful effects. Pregnant women and women who are nursing will not be permitted to participate in this study.

6.4 Incidental findings on MBI

Based on prior studies of screening MBI in women with dense breasts, we expect that about 5% of study participants will have an abnormality found on the MBI test. Finding an abnormality on the study testing can be emotionally distressing to participants. Participants with concerning findings on MBI will be recommended to return for additional diagnostic

workup, as per routine clinical standard of care. Participants will be informed that any additional testing beyond the MBI test is not part of this research study and financial costs will need to be covered by the patient and their insurance.

6.5 Risks of Tamoxifen

Tamoxifen has been used for over 40 years to treat hormone-receptor positive breast cancer. Side effects of tamoxifen taken at the standard 20 mg dose, ranging from mild to serious, have been reported. We expect side effects at the 5 mg or 10 mg dose to occur less frequently, if at all, especially over the short time frame of 30 days.

In patients taking standard 20 mg dose tamoxifen, vasomotor symptoms (hot flashes and night sweats) and vaginal discharge are the most likely side effects. However, in studies of women taking low-dose (5 mg or 10 mg) tamoxifen, hot flashes and vaginal discharge were not increased compared to women taking placebo.

Among women taking 20 mg tamoxifen for 5 years, there is a small increased risk of uterine cancer, abnormal blood clots, or vision changes. Other less serious side effects reported from 20 mg tamoxifen treatment include changes in menstrual cycle (among premenopausal women), weight gain, depression, insomnia, and urinary incontinence. These side effects are not expected to occur for short-term, low-dose tamoxifen used in this study.

Tamoxifen can cause birth defects. Participants who can become pregnant will undergo a pregnancy test prior to MBI, which must be negative. Participants will be instructed to avoid pregnancy during the study and for at least 2 months after study participation ends, by abstinence, barrier method, or nonhormonal contraception. If a participant should become pregnant, she will be instructed to stop using tamoxifen immediately.

7 ADVERSE EVENTS

Participants will be asked to report any adverse events or side effects, should they occur, by contacting study staff. At approximately days 5 and 20 of the tamoxifen intervention, the study coordinator will contact participants by phone to assess medication compliance and inquire about any adverse events. Adverse events will also be assessed at the study closeout during Study Visit 2. The duration and severity of adverse events will be recorded.

Although we do not expect serious side effects to occur with 5 mg tamoxifen over a 30-day period, patients will be advised to stop taking tamoxifen medication immediately if any of the following should occur:

- vision problems
- loss of appetite
- yellowing of skin or eyes
- unusual bruising or bleeding
- fever
- blisters

- rash
- swelling of eyes, face, lips, tongue, throat, hands, arms, feet, ankles, or lower legs
- thirst
- muscle weakness
- restlessness
- vaginal bleeding or spotting

8 REMUNERATION

Participants will receive a total of $200 to compensate for their time spent in the study. If participants start the study but do not finish, they will receive part of the money. The breakdown of remuneration payments will be as follows:

Study Visit 1: $50
Completion of 30 days tamoxifen: $100
Study Visit 2: $50

9 SAMPLE SIZE CONSIDERATIONS

There have yet to be any studies examining BPU response to tamoxifen. Thus, this study is a pilot design that will aim to enroll 30 patients who complete pre- and post-tamoxifen MBI. A sample size of 30 will have 80% power to detect a means change of 1 BPU quantitative unit (e.g. overall mean of 4.5 pre low-dose tamoxifen intervention, and post tamoxifen mean of 3.5), assuming a standard deviation of differences of 1.89 (effect size = 0.53), using a paired t-test with an α=0.05 two-sided significance level.

Allowing for potential study withdrawals, we will allow for a total of 50 patients to begin the low-dose tamoxifen intervention. In addition, women who are invited to participate may not have persistent BPU on their MBI performed at Study Visit 1. Prior pilot data showed that approximately half of women with prior high BPU had persistent high BPU on a current MBI. Therefore, up to 100 women will be screened with MBI to assess potential enrollment in the low-dose tamoxifen intervention. We will aim to balance enrollment of premenopausal and postmenopausal subjects.

10 CONFLICT OF INTEREST

Mayo Foundation and two of the co-investigators (M.K. O'Connor, C.B. Hruska) on this protocol have a conflict of interest, due to licensing arrangements between Mayo Foundation and the manufacturer of the CZT detectors, Gamma Medica – Ideas, for rights to the hardware and software technology developed for low dose MBI. This conflict is noted in all the consent forms. Neither Dr. O'Connor nor Dr. Hruska will be permitted to consent subjects for the study. None of the other investigators have a conflict of interest.

11 REFERENCES

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