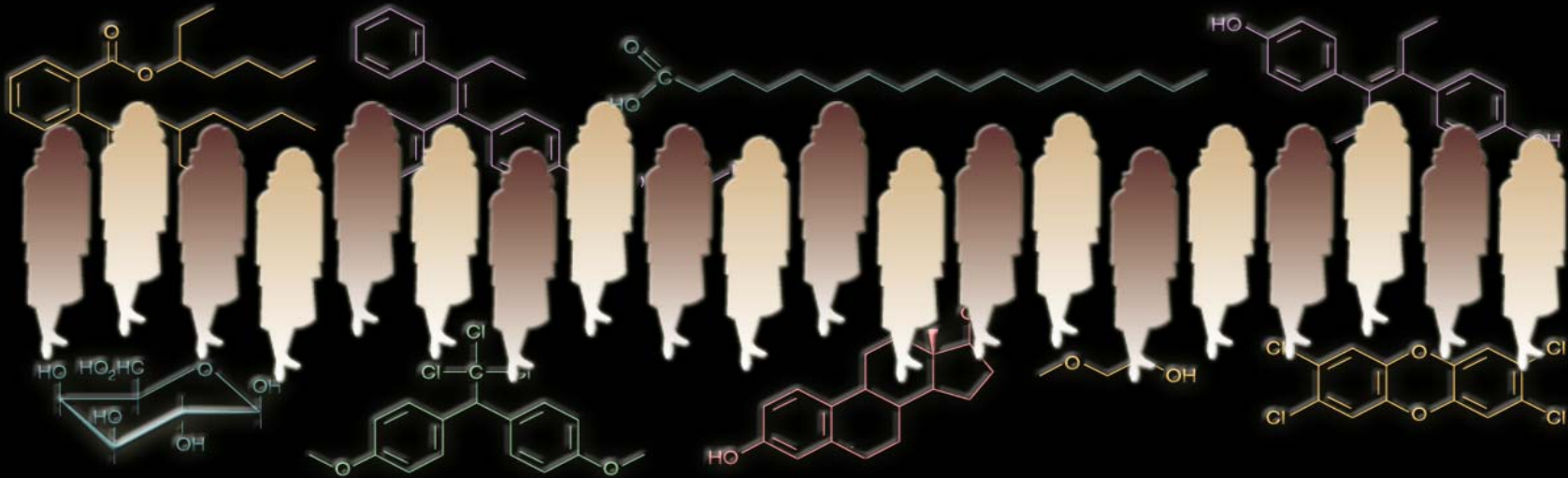


Uterine Leiomyoma Longitudinal Intervention Studies: The Fibroid Growth Study



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Funded by NIEHS and

National Center for Minority Health and Health Disparities



Uterine Leiomyoma

- Under-studied disease but a major public health problem
 - Hormonally dependent
 - Most common reproductive tumor in women
 - Leading cause of hysterectomy
- Fibroid-related bleeding leads to hospital emergency visits
 - Fertility and Pregnancy complications
 - Health Disparity

What causes fibroids to grow and become clinically symptomatic?

The Fibroid Growth Study Hypothesis

- Uterine leiomyomas are heterogeneous in growth and clinical symptoms.
- Growing tumors will have different molecular and cellular characteristics compared to non-growing tumors.

Fibroid Growth Study

Specific Aims

1. Compare leiomyoma growth as a function of multiplicity and location by magnetic resonance image (MRI) analysis in women with high risk for hysterectomy or myomectomy;
2. Examine the relationship between leiomyoma growth and clinical symptoms or outcome;
3. Identify molecular, cellular, and pathological characteristics of the leiomyomas with differing growth dynamics; and
4. Examine endocrinological parameters and environmental factors related to differential growth dynamics of uterine leiomyomas.

Fibroid Growth Study Enrollment Criteria

- Premenopausal
- Uterine size-”12 week pregnancy”
- 2-5 cm diameter leiomyoma confirmed by ultrasound

Compare leiomyoma growth over time by MRI analysis

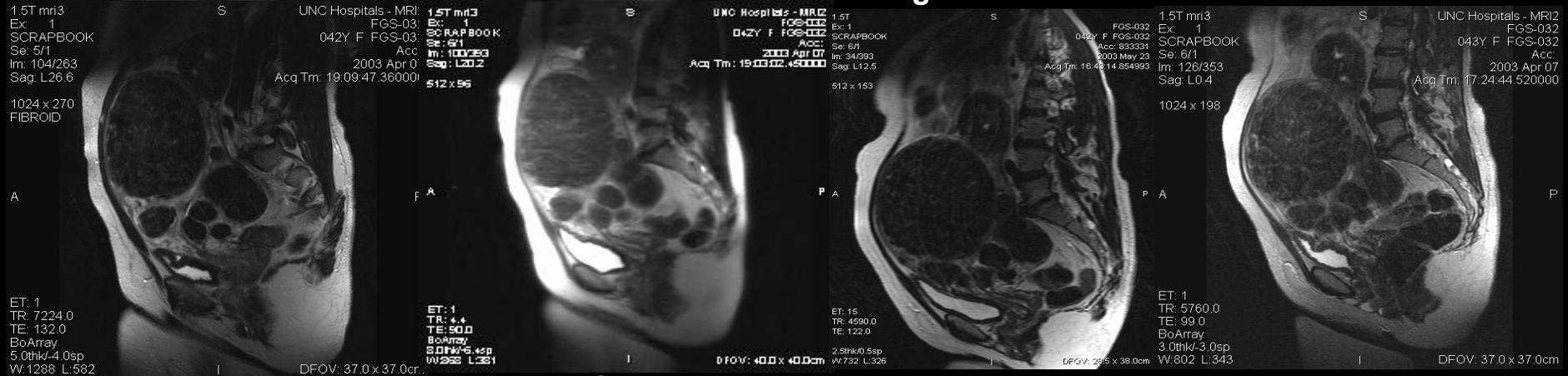
MRI 1
Time-point 0

MRI 2
Time-point 2
3 months

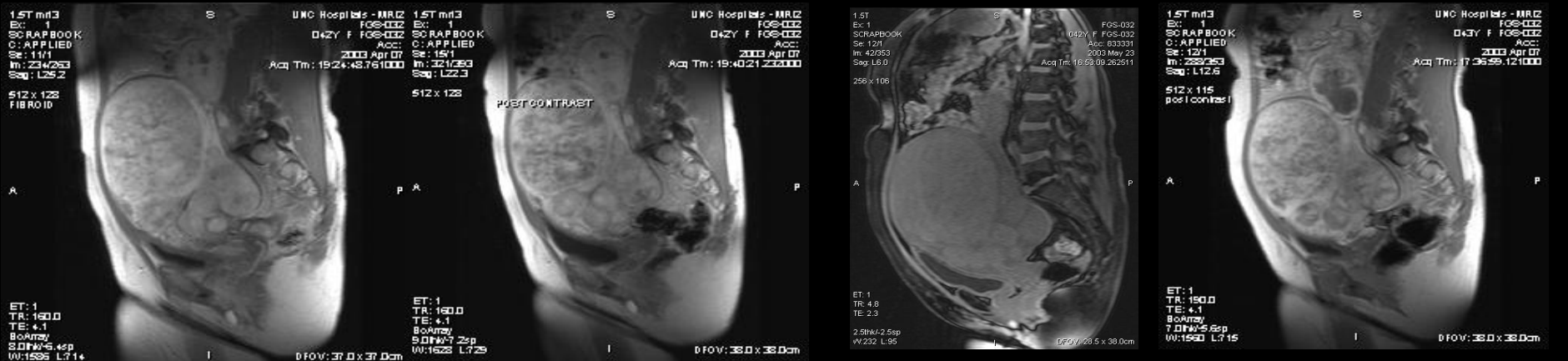
MRI 3
Time-point 3
6 months

MRI 4
Time-point 4
12 months

T2 -weighted images



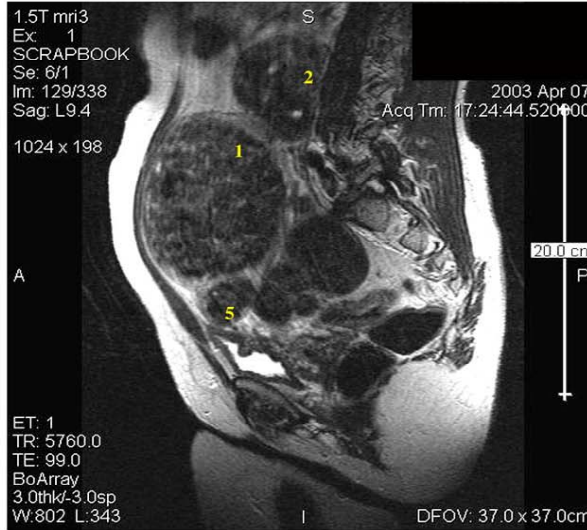
Contrast enhanced images



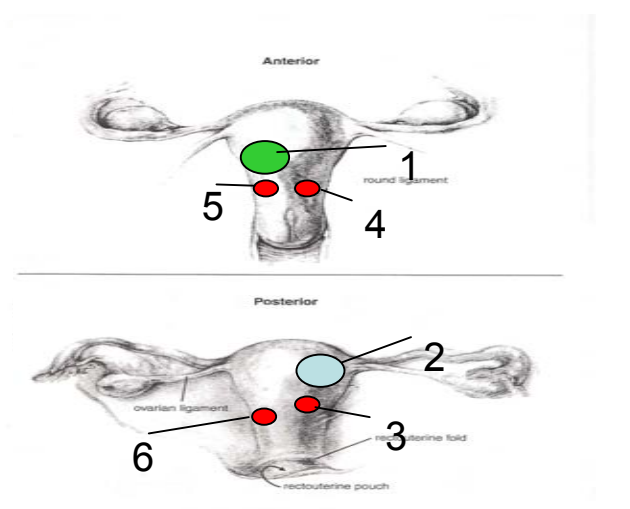
Participant Evaluation

- Physical (ultrasound)
- Initial Extensive Medical History
- Blood, urine collection at each visit
- Monthly questionnaires (by phone)
 - Medication
 - Quality of Life
 - Physical activity
 - Stress
 - Pain, Discomfort, Bleeding, Urinary incontinence

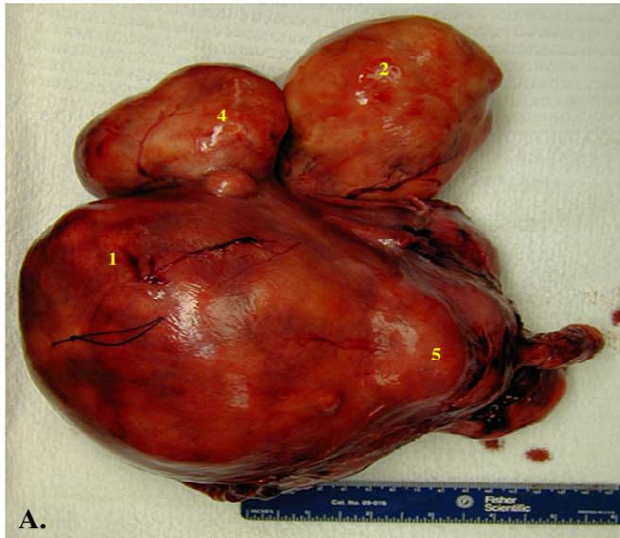
Map molecular and cellular pathways of growth and regression



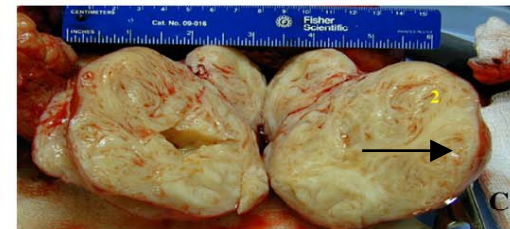
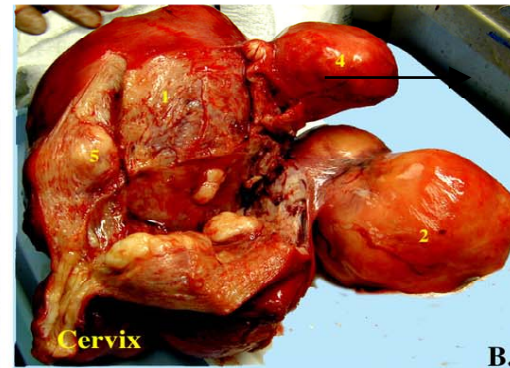
**T-2 weighted sagittal view MRI,
3 mm thickness, 1.6 mm gap.**



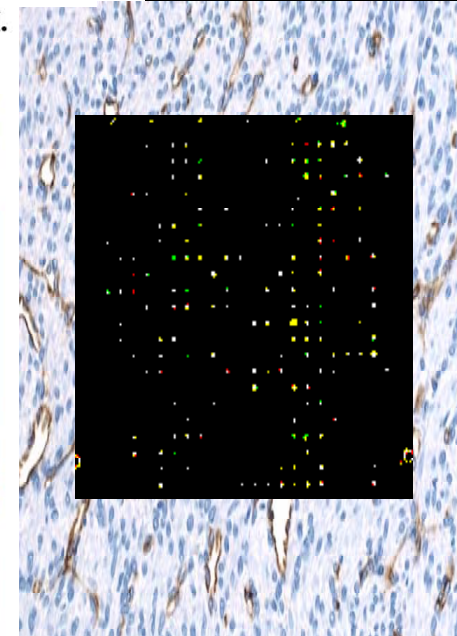
Mapping of uterine leiomyomas from MRI.



**Uterus post-hysterectomy. (A) Anterior view.
(B) Opened through cervix and uterine lumen.**



(C) Cross-section through fibroid.



Study Statistics

- 123 women enrolled in the study.
- 120 participated.
- 3 enrollees did not meet eligibility requirements.
- Study ended December 2004.

Race and Ethnicity

- **Black 48%**
 - **White 41%**
 - **American Indian/Alaskan Native 1%**
 - **Asian or Pacific Islander 1%**
 - **Other 8%**
-
- **Hispanic 4%**
 - **Not Hispanic 95%**
 - **Not Reported 1%**

Race/Ethnicity	Non-Surgery	Surgery
American Indian/Alaskan Native	1	0
Not of Hispanic Origin	1	0
Asian or Pacific Islander	1	0
Not of Hispanic Origin	1	0
Black	40	18
Hispanic Origin	0	1
Not of Hispanic Origin	39	17
Unknown	1	
White	40	10
Hispanic Origin	0	1
Not of Hispanic Origin	40	9
Other	7	3
Hispanic Origin	2	1
Not of Hispanic Origin	4	2
Refused	1	0
TOTAL	89	31



AGE CHARACTERISTICS

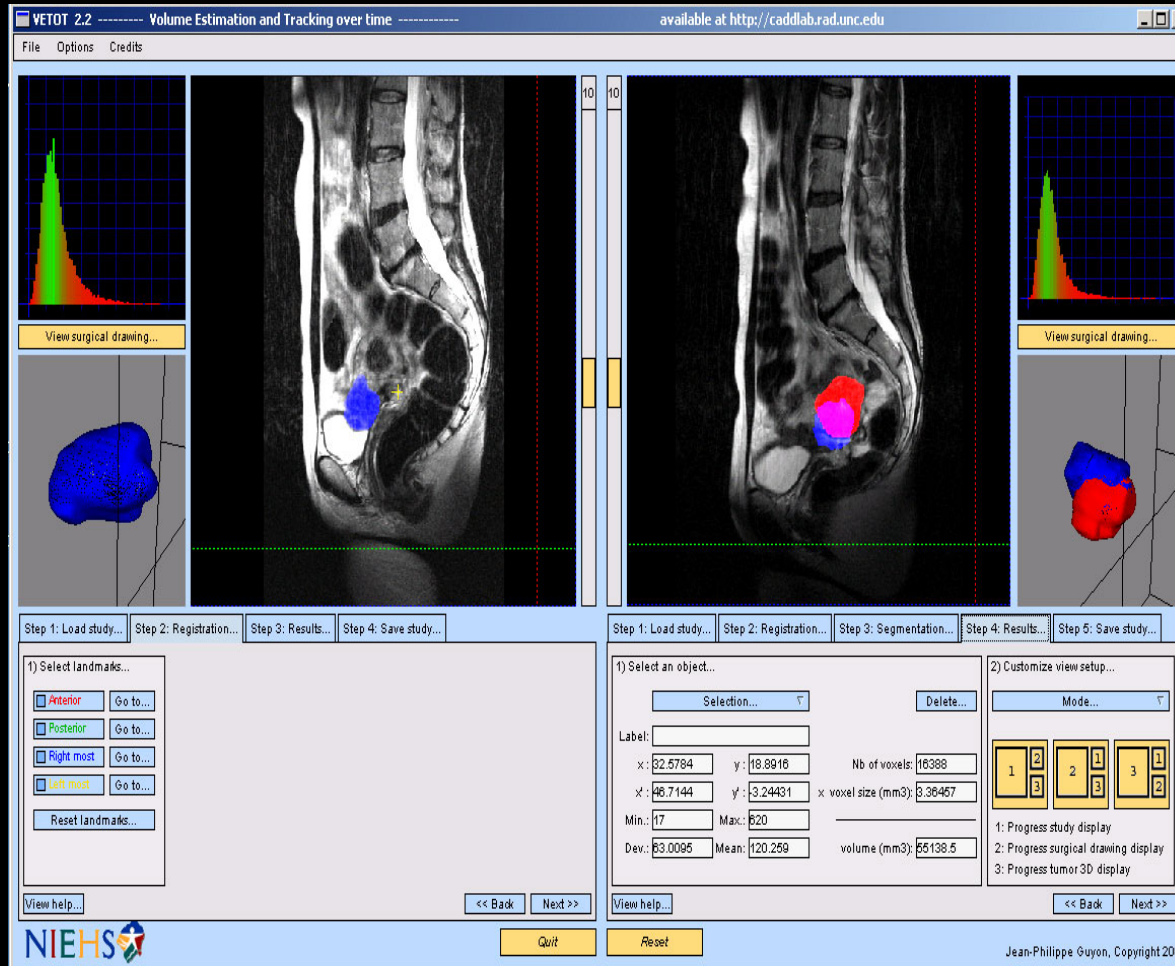
- All participants : **39.1** (24-54)
- Non- surgery : **40.0** (24-54)
- Surgery patients: **37.8** (26-49)

MRI Time Points Completed

	0 MRIs	1 MRI	2 MRIs	3 MRIs	4 MRIs	Total	Percent
Myomectomy	0	6	5	4	12	27	22%
Hysterectomy	0	9	3	1	4	17	14%
Embolization	0	0	2	0	0	2	2%
No Treatment	2	8	13	15	36	74	62%
Total	2	23	23	20	52	120	
Percent	2%	19%	19%	17%	43%		



Volume Estimation and Tracking Over Time (VETOT) software used to measure fibroids



- The volumetric analysis was done on 98 women.
- The number of fibroids ranged from 1 to 11.
- A total of 1076 volumes over at most 4 times points were calculated using VETOT.

Aim 1: Preliminary analysis of rate of growth (change in volume over time) as a function of location and other factors

Race	0.5368
Age	0.0554
Pedunculated or not	0.1662
Location in Uterus	0.0606
Location on Uterus	0.1168
Time Point	0.9027
Size	0.0038 **

Effects of Size

- Classification of fibroids by size based on the observed volumes computed at surgery

Small: If volume is at most 7 cm^3

Medium: If volume is more than 7 cm^3 but at most 50 cm^3

Large: If volume is greater than 50 cm^3

Rate of growth different in different sized fibroids

Pairwise comparisons:

-----	P-value
• Large versus Medium	0.8218
• Large versus Small	0.0059 *
(Large is faster than small)	
• Medium versus Small	0.0022 **
(Medium is faster than small)	

Rate of growth different by location

- Intramural versus Subserosal $p = 0.0220$ *
(Intramural is slower in growth than Subserosal)
- Submucosal versus Subserosal $p = 0.1160$
- Intramural versus Submucosal $p = 0.6177$
(power?)

Aim 2: Relationship between growth and clinical outcome

Race 0.5368

Surgery status 0.4891

(No significant difference in growth rates between non-surgical and surgical participants)

Pedunculated or not 0.1662

Location in Uterus 0.0606

Location on Uterus 0.1168

Size 0.0038 **

Determinants of Surgical Outcome- Bleeding, Pain and Discomfort Scores

Perceived Bleeding

<u>Non-sx</u>	<u>Pre-Sx</u>	<u>Post-Sx</u>
21.6	45.1	14.8

Combined Bleeding

<u>Non-sx</u>	<u>Pre-Sx</u>	<u>Post-Sx</u>
23.1	41.1	16.7

Pain

<u>Non-sx</u>	<u>Pre-Sx</u>	<u>Post-Sx</u>
19	36	23

Discomfort

<u>Non-sx</u>	<u>Pre-Sx</u>	<u>Post-Sx</u>
26	44	25

Self-Report Reason for Surgical Intervention

Heavy Bleeding	8 (40%)
Attempting Pregnancy	4 (20%)
Pelvic Pain or Discomfort	2 (10%)
Sexual Pain or Discomfort	1 (5%)
Frequent Urination	1 (5%)
Other	5 (25%)
Total	20

Aim 3: Molecular, cellular, and pathological characteristics of the leiomyomas with differing growth dynamics

Preliminary data for amount of fibrous connective tissue (Trichrome staining)

Fibroid Size	N	Mean
Large	389	66.8741*
Medium	442	59.9334
Small	458	62.0198

Histological Analysis

COMPARISON OF NORMAL VERSUS TUMOR

Tissue type	N	Mean Number of Area Vessels	Mean of Vessels
Fibroid	1383	13.54	.002
Normal	428	19.90*	.004*

Histological Analysis

Preliminary data for vasculature (Factor VIII staining)

Size	N	Mean Area of Vessels
Large	390	0.00180*
Medium	450	0.00154
Small	468	0.00147

Size	N	Mean Number of Vessels
Large	390	9.46
Medium	450	12.48
Small	468	16.00*

Preliminary Conclusions

- Growth rates are similar between races/ethnic background
- Large fibroids have a greater growth rate than small fibroids
- Growth rates vary by location
- Growth rates are similar between non-sx and sx participants—bleeding, pain, discomfort different
- Large fibroids have significantly greater amounts of fibrous connective tissue than small fibroids
- Growth related to connective tissue (collagen deposition)
- Vessel components vary with size (and location)
- Need to examine multiplicity, age....



Tissue Collection from Surgery Patients

Surgery Type	Tissue Collected	No Tissue Collected	Total
Hysterectomy	12	5	17
Hysteroscopic Myomectomy	2	1	3
Myomectomy	17	7	24
Embolization	0	2	2
Total	31	15	46

**Reasons for exclusion/withdrawal included:

- Started taking Lupron
- Planning pregnancy
- Non-compliance
- Study-related concerns (claustrophobic, blood draws, reimbursement schedul)

