

SPARC

***S Study of Perfusion and Anatomy's Role in
CAD***

AHA Meeting Update: 4th November 2007

Meeting Agenda

- Welcome and Introductions
 - SPARC recruiting sites (summary, ‘standings’)
 - Review of original protocol
 - Current Enrollment
 - Rationale for & Summary of proposed changes to SPARC protocol
 - Revised sample size
 - Enrollment update and projections based on revised sample size
 - Demographics Update
 - Image Repository Status
 - Ancillary studies
 - Q&A
-

SPARC Recruiting Sites

Overall Enrollment as of 28 October 2007

| ID | Study Sites | Overall Totals [N (%)] | ----- Cardio-Diagnostic Procedures ----- | | | | |
|-----|---|------------------------------|--|----------------|-------------------|-----------------------|----------------|
| | | | SPECT-MPI [N (%)] | PET [N (%)] | PET-CT [N (%)] | PET-CT+CTA [N (%)] | CTA [N (%)] |
| 000 | All Institutions | 2749 (100%) | 919 (33.4%) | 467 (16.6%) | 485 (17.6%) | 19 (0.7%) | 869 (31.6%) |
| 101 | Brigham and Womens Hospital | 265 (9.3%) | 121 (4.4%) | | 118 (4.3%) | 16 (0.6%) | |
| 102 | Hartford Hospital | 79 (2.9%) | 40 (1.5%) | 29 (1.1%) | 7 (0.3%) | | 3 (0.1%) |
| 103 | Sinai Hospital of Baltimore | 35 (1.3%) | 9 (0.3%) | | 26 (0.9%) | | |
| 104 | Massachusetts General Hospital | 124 (4.5%) | 60 (2.2%) | | | | 64 (2.3%) |
| 105 | Washington Hospital Center | 163 (5.9%) | 52 (1.9%) | | | | 111 (4.0%) |
| 106 | NYU Medical Center | 115 (4.2%) | 76 (2.8%) | | | | 39 (1.4%) |
| 107 | Lahey Clinic | 46 (1.7%) | 32 (1.2%) | | | | 14 (0.5%) |
| 108 | Mount Sinai Medical Center | 26 (0.9%) | | | 26 (0.9%) | | |
| 109 | Yale-New Haven VA Hospital | 23 (0.8%) | 6 (0.2%) | 1 (0.0%) | 16 (0.6%) | | |
| 112 | Rhode Island Hospital | 9 (0.3%) | 5 (0.2%) | | | | 4 (0.1%) |
| 113 | St. Francis Hospital-The Heart Center | 32 (1.2%) | | | | | 32 (1.2%) |
| 114 | Holy Name Hospital | 34 (1.2%) | 3 (0.1%) | | 22 (0.8%) | | 9 (0.3%) |
| 115 | Columbia University Medical Center | 27 (1.0%) | 12 (0.4%) | 15 (0.5%) | | | |
| 118 | Cardiac Specialists (CT) | 41 (1.5%) | 1 (0.0%) | | 40 (1.5%) | | |
| 119 | Montefiore Medical Center | 4 (0.1%) | | | 4 (0.1%) | | |
| 126 | Medical Univ. of South Carolina | 46 (1.7%) | 29 (1.1%) | | | | 17 (0.6%) |
| 128 | Cardiovascular Associates (AL) | 133 (4.8%) | 7 (0.3%) | | 126 (4.6%) | | |
| 129 | Fuqua Heart Center-Piedmont Hospital | 133 (4.8%) | 69 (2.5%) | | | | 64 (2.3%) |
| 130 | Univ. of Florida - Jacksonville | 31 (1.1%) | 9 (0.3%) | | | | 22 (0.8%) |
| 131 | Vanderbilt Hospital | 64 (2.0%) | | 16 (0.6%) | 26 (0.9%) | | 12 (0.4%) |
| 132 | Duke University Medical Center | 15 (0.5%) | 3 (0.1%) | | | | 12 (0.4%) |
| 133 | University of Alabama-Birmingham | 35 (1.3%) | 22 (0.8%) | | | | 13 (0.5%) |
| 134 | Tennessee Heart and Vascular Institute | 39 (1.4%) | 4 (0.1%) | | | | 35 (1.3%) |
| 136 | The Heart Center (AL) | 301 (10.9%) | 65 (2.4%) | 130 (4.7%) | | | 106 (3.9%) |
| 151 | Cleveland Clinic Foundation | 61 (2.2%) | 35 (1.3%) | 17 (0.6%) | | | 9 (0.3%) |
| 152 | Oklahoma Foundation-Cardiovascular Research | 31 (1.1%) | 6 (0.2%) | 25 (0.9%) | | | |
| 154 | Wisconsin Heart Hospital | 32 (1.2%) | 15 (0.5%) | | | | 17 (0.6%) |
| 156 | Ohio State Univ. Medical Center | 83 (3.0%) | 33 (1.2%) | | | | 50 (1.8%) |
| 157 | Minneapolis Heart Inst. Foundation | 113 (4.1%) | 8 (0.3%) | | | | 105 (3.8%) |

Overall Enrollment at of 28 October 2007

| ID | Study Sites | Overall | ----- Cardio-Diagnostic Procedures ----- | | | | |
|-----|---|-------------------|--|----------------|-------------------|-----------------------|----------------|
| | | Totale [N (%)] | SPECT-MPI [N (%)] | PET [N (%)] | PET-CT [N (%)] | PET-CT+CTA [N (%)] | CTA [N (%)] |
| 158 | University of Michigan | 27 (1.0%) | 15 (0.6%) | | | | 12 (0.4%) |
| 159 | University of Chicago | 56 (2.0%) | 43 (1.6%) | 11 (0.4%) | | | 2 (0.1%) |
| 161 | Mayo Clinic | 162 (6.9%) | 61 (2.2%) | 99 (3.6%) | | | 2 (0.1%) |
| 162 | Meritcare Hoospital | 55 (2.0%) | 9 (0.3%) | 38 (1.4%) | 6 (0.3%) | | |
| 176 | Cedars-Sinai Medical Center | 109 (4.0%) | 40 (1.5%) | | | | 69 (2.5%) |
| 177 | Univ. of Washington | 9 (0.3%) | 6 (0.2%) | 2 (0.1%) | 1 (0.0%) | | |
| 178 | Los Angeles Biomedical Research Institute | | | | | | |
| 182 | Scottsdale Medical Imaging | 33 (1.2%) | | | 28 (1.0%) | | 5 (0.2%) |
| 199 | University of Ottawa Heart Institute | 178 (6.6%) | 23 (0.8%) | 74 (2.7%) | 37 (1.3%) | 3 (0.1%) | 41 (1.5%) |

31 sites
21 sites
26 sites

Review of Original Protocol

4. STUDY OBJECTIVES

SPARC will have two components consisting of a *Pilot* CT coronary angiographic study and a *Main* study. The Pilot study will be completed to optimize imaging protocols, quality, and interpretation of coronary CT angiographic studies across multiple study sites. Operational aspects for the pilot study are found in Appendix A (Section 13.1) at the end of the protocol.

The Main study will be completed to assess the following specific objectives:

4.1.1 *Primary Objective*

The primary objectives of the Main study are to:

1. Assess the impact of Myocardial Perfusion (stress SPECT and stress PET), CT Coronary Angiography (CTA), and combined Myocardial Perfusion-CTA Imaging (PET/CT) on post-test resource utilization.
2. Determine the incremental prognostic value of stress SPECT, stress PET, CTA, and PET/CT for predicting cardiac death and nonfatal myocardial infarction following a procedure

4.1.2 *Secondary Objectives*

Secondary objectives of the Main study are to:

1. Assess the diagnostic accuracy of these modalities for detection of obstructive epicardial coronary stenosis as assessed by cardiac catheterization.
2. Assess the risk-adjusted referral rate to revascularization within 90 days of cardiac catheterization after the index noninvasive imaging study.
3. Assess the use of and change in cardiac medications at 90 days and one year after the index noninvasive imaging study.
4. Determine the combined occurrence of (1) death from any cause, (2) nonfatal myocardial infarction, and (3) late (>6 month) referral to revascularization after the index noninvasive imaging study.
5. Determine the cost-effectiveness of strategies incorporating different noninvasive imaging modalities.

4.2 Study Endpoints

4.2.1 *Primary Endpoints*

1. Referral to cardiac catheterization within 90 days of index noninvasive testing.
2. Occurrence of cardiac death or nonfatal myocardial infarction at two years after index noninvasive testing.

4.2.2 *Secondary Endpoints*

1. Diagnostic accuracy of the stress SPECT, stress PET, CTA, and PET/CT for detection of epicardial coronary stenosis as assessed by cardiac catheterization.
2. Documented referral to cardiac revascularization within 90 days of cardiac catheterization after the index noninvasive imaging study.
3. Use of and change in cardiac medications at 90 days and 1 year following after the index noninvasive imaging study.
4. Combined occurrence of (1) death from any cause, (2) nonfatal myocardial infarction, and (3) late (>6 month) referral to revascularization after the index noninvasive imaging study.
5. Direct and indirect cost associated with a clinical endpoint event.

Figure 3. Population Required for Objective 1.

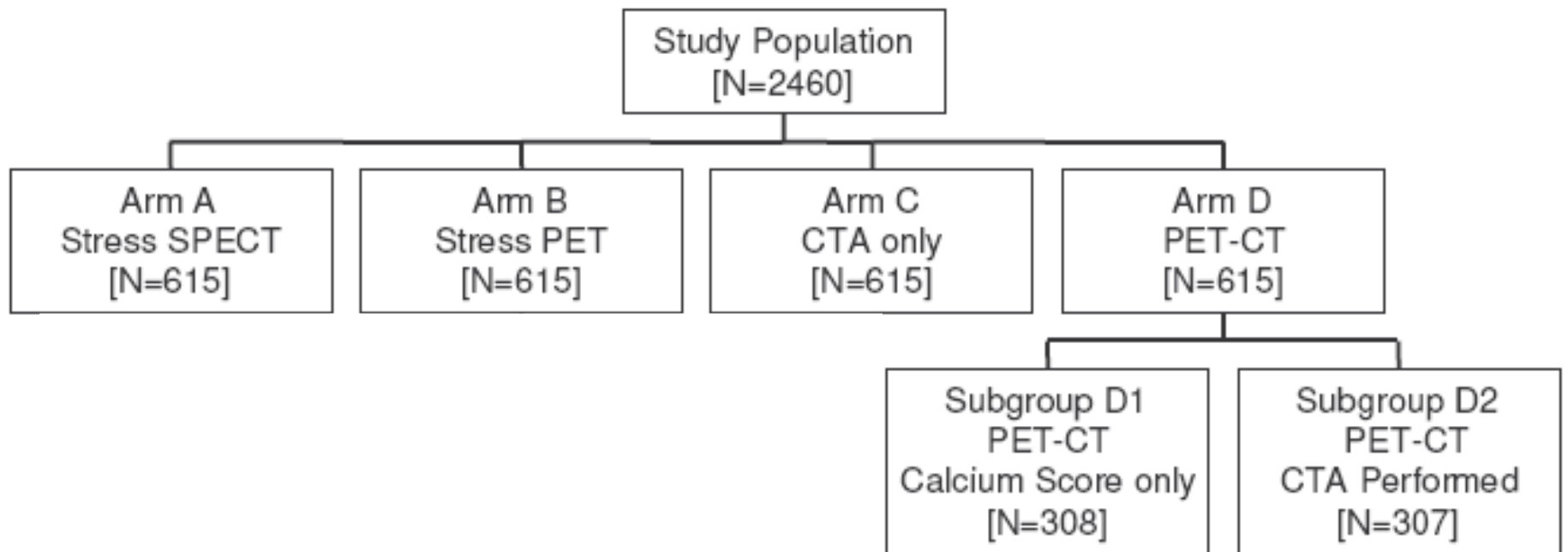
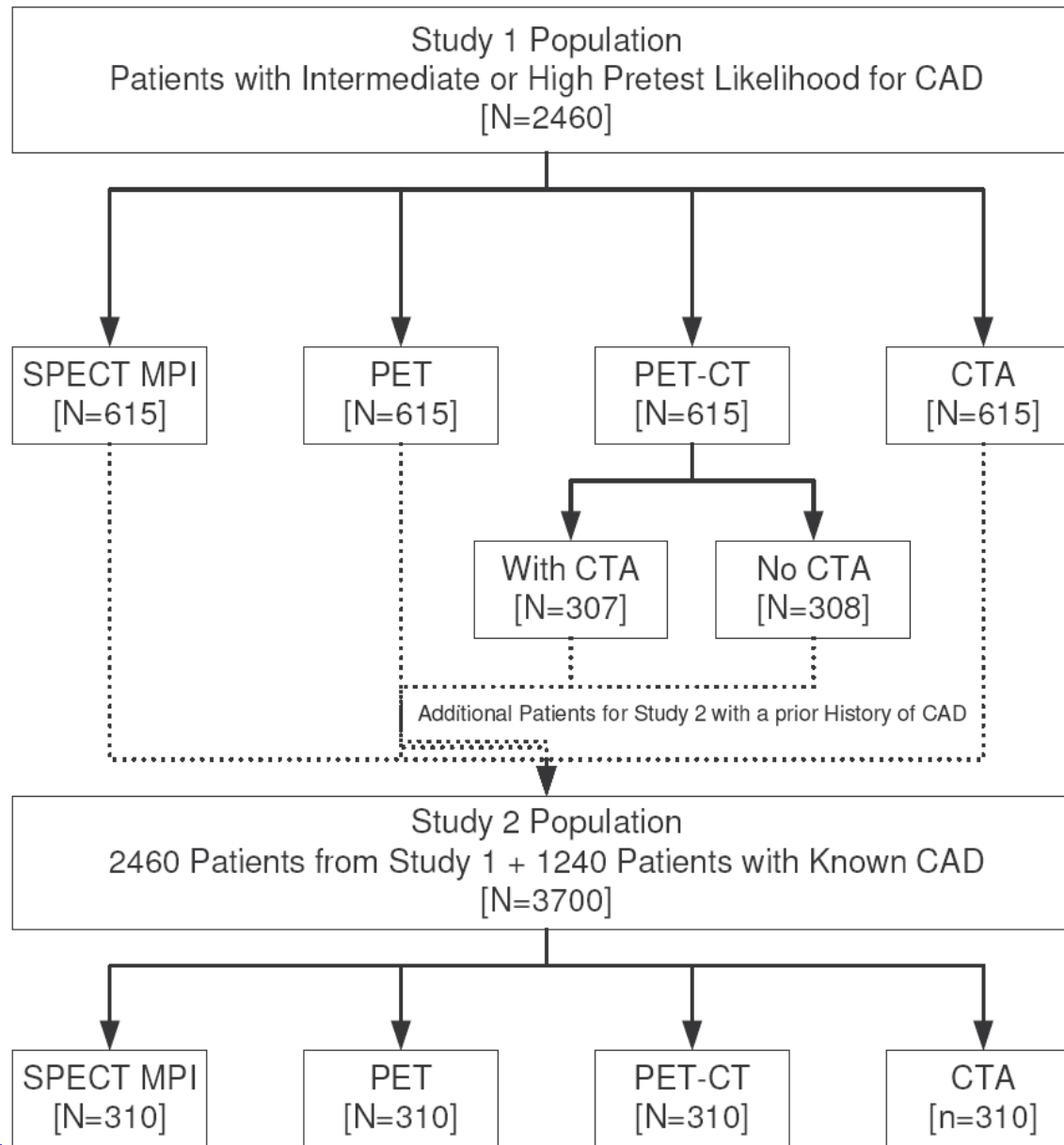
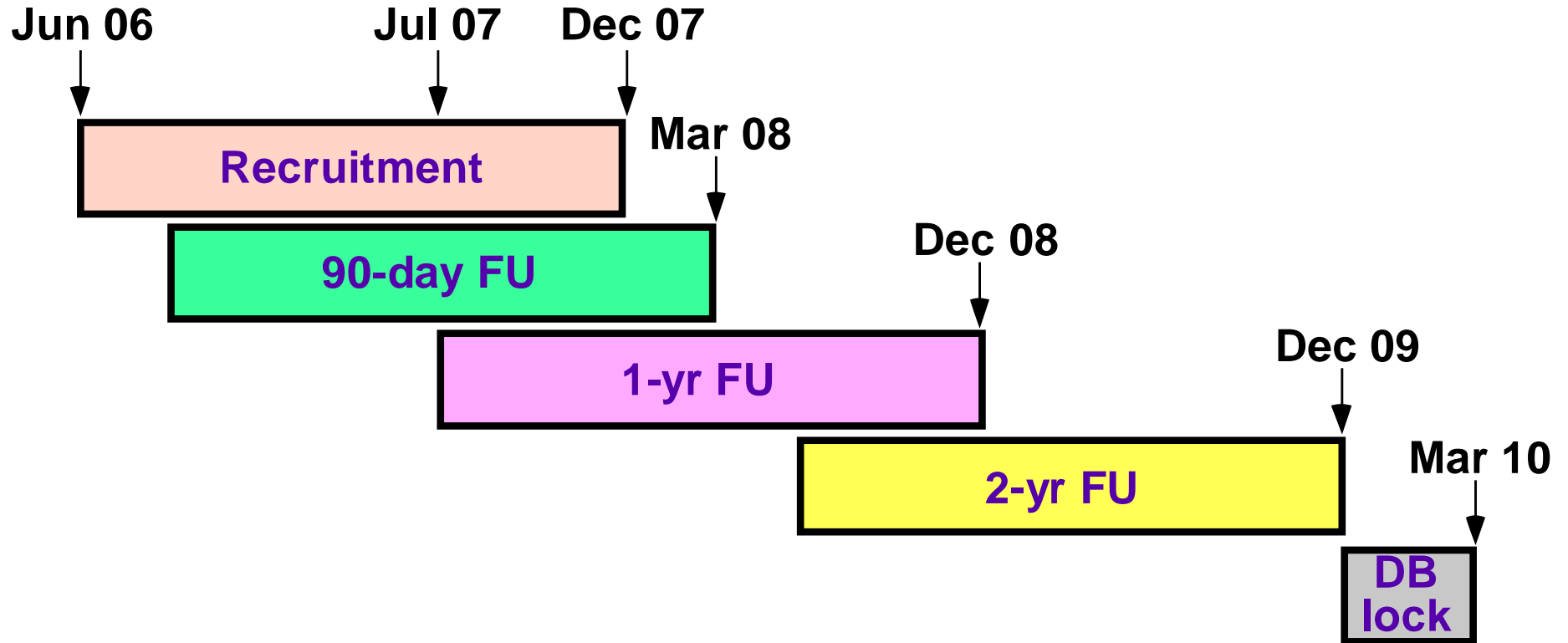


Figure 4. Population Required for Objective 2.



Current Enrollment: Update

Projected Timeline

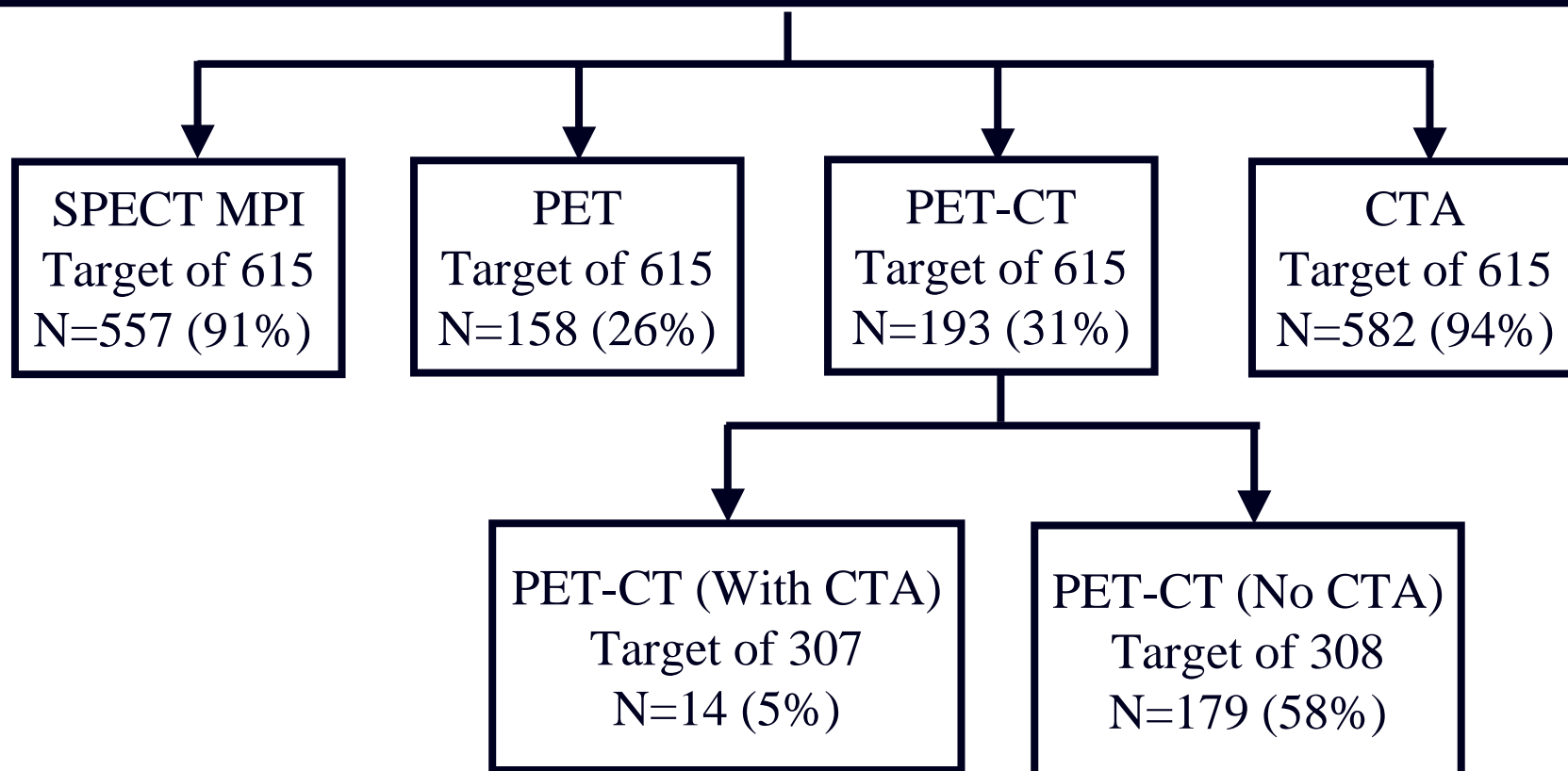


SPARC Participating Site Locations

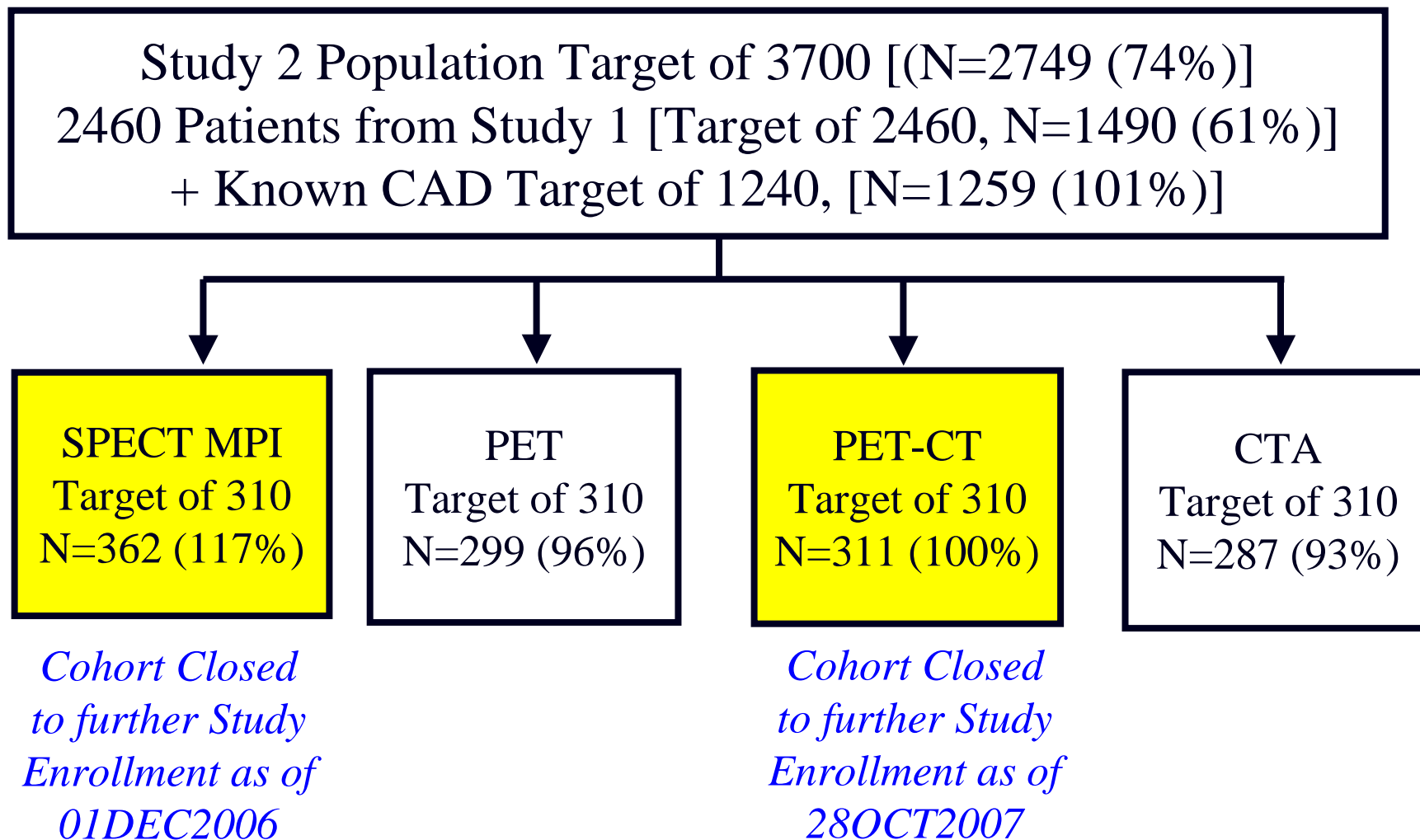


Current *SPARC* Enrollment as of 28Oct2008

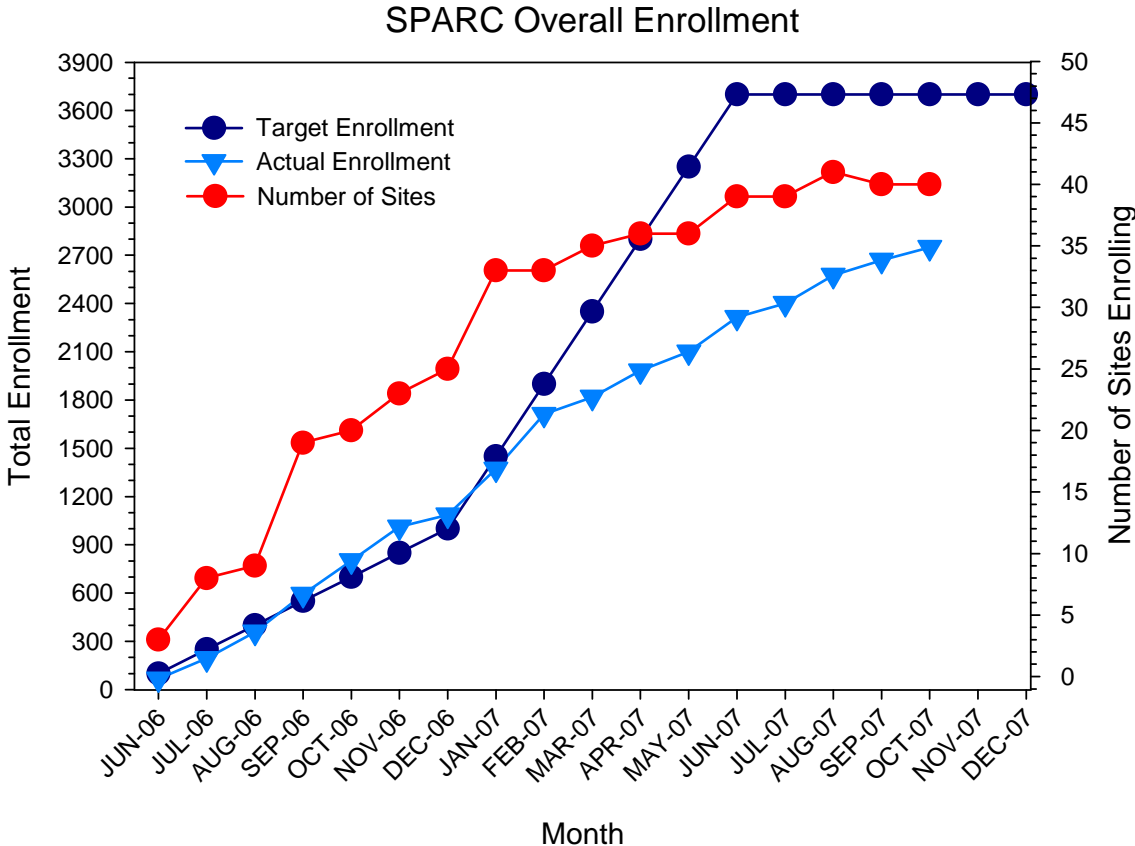
Study 1 Population: Intermediate/High Pretest Likelihood for CAD
Target N=2460, Current N=1490 (61%)



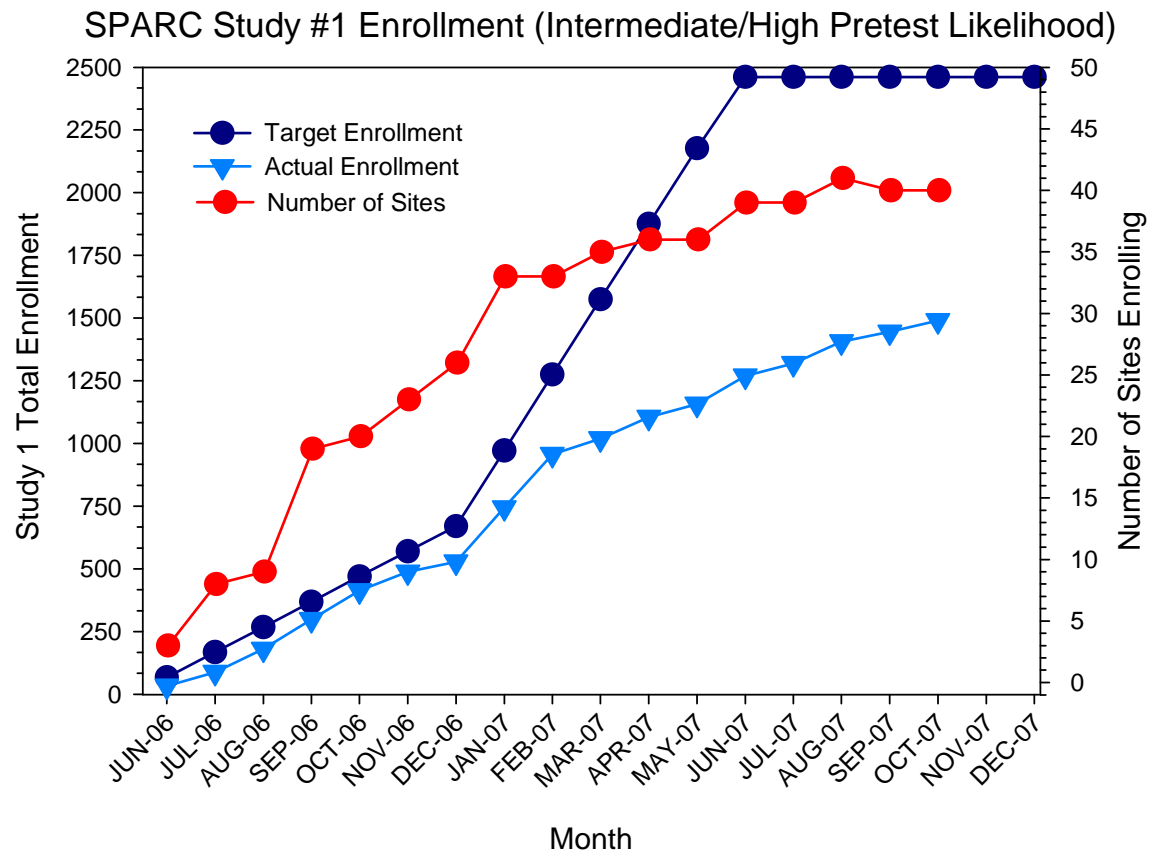
Current *SPARC* Enrollment as of 28Oct2008



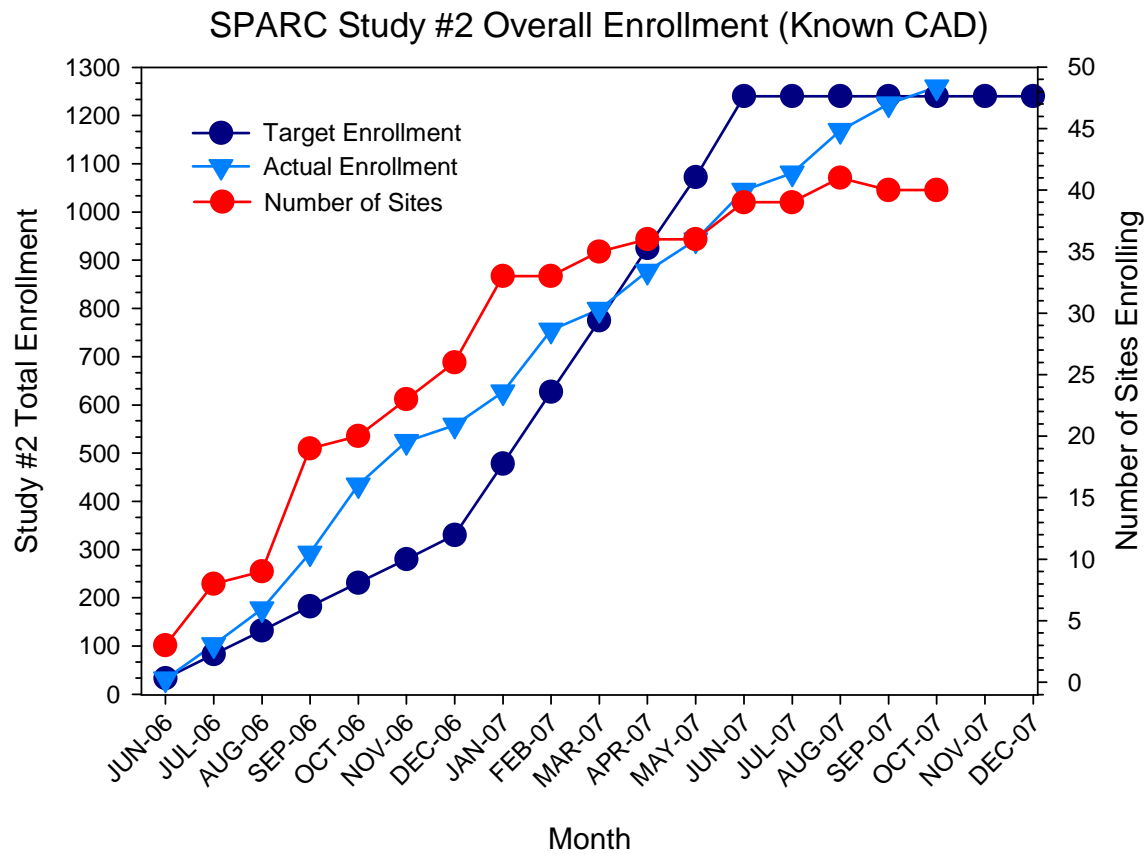
Overall *SPARC* Enrollment as of 28Oct2008



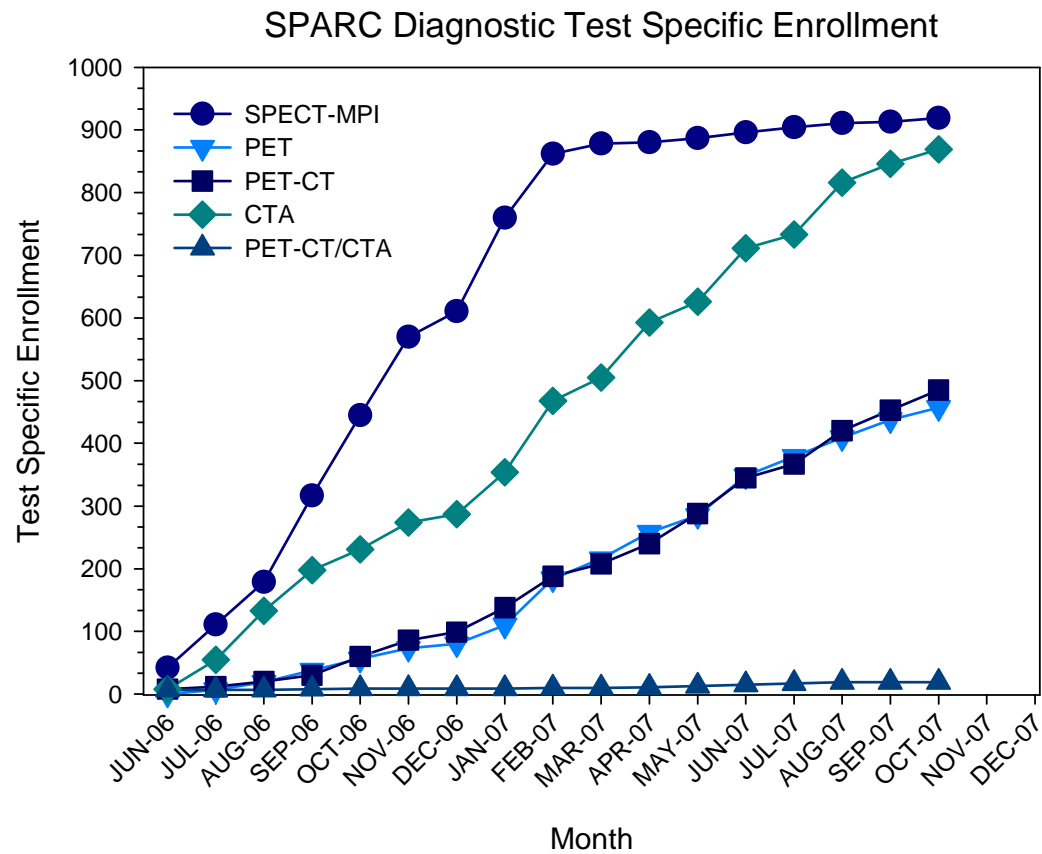
Overall *SPARC* Enrollment: Study #1 as of 28Oct2008



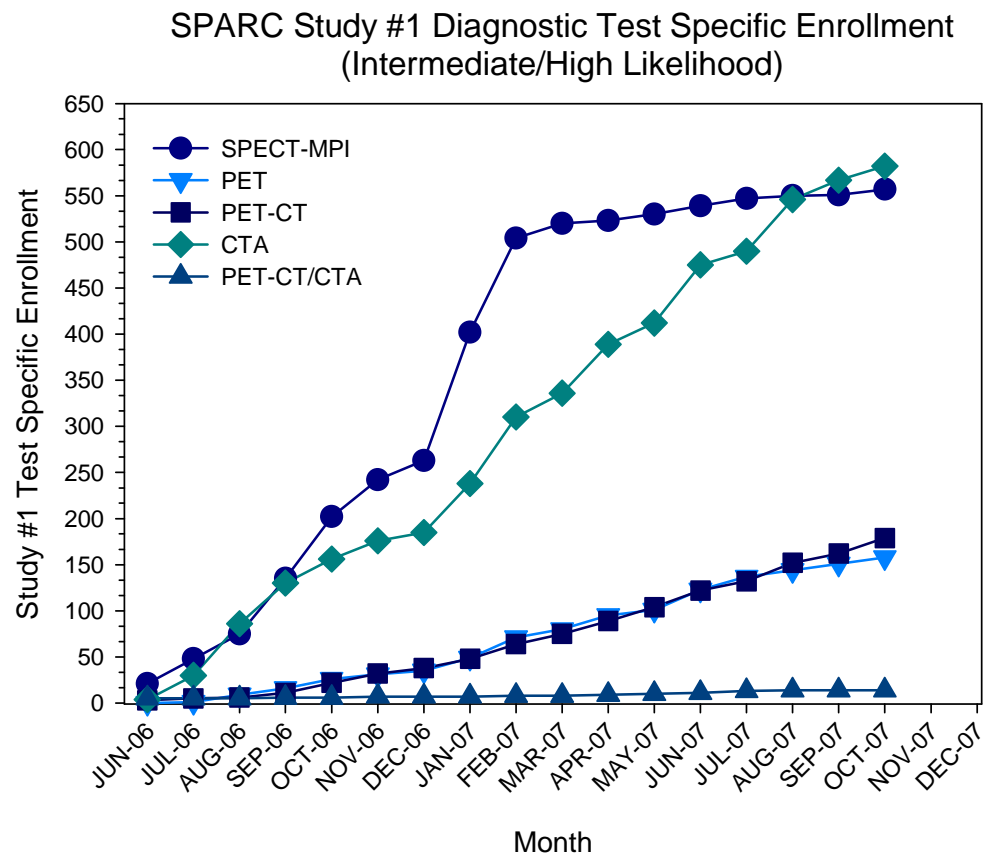
Overall *SPARC* Enrollment: Study #2 as of 28Oct2008



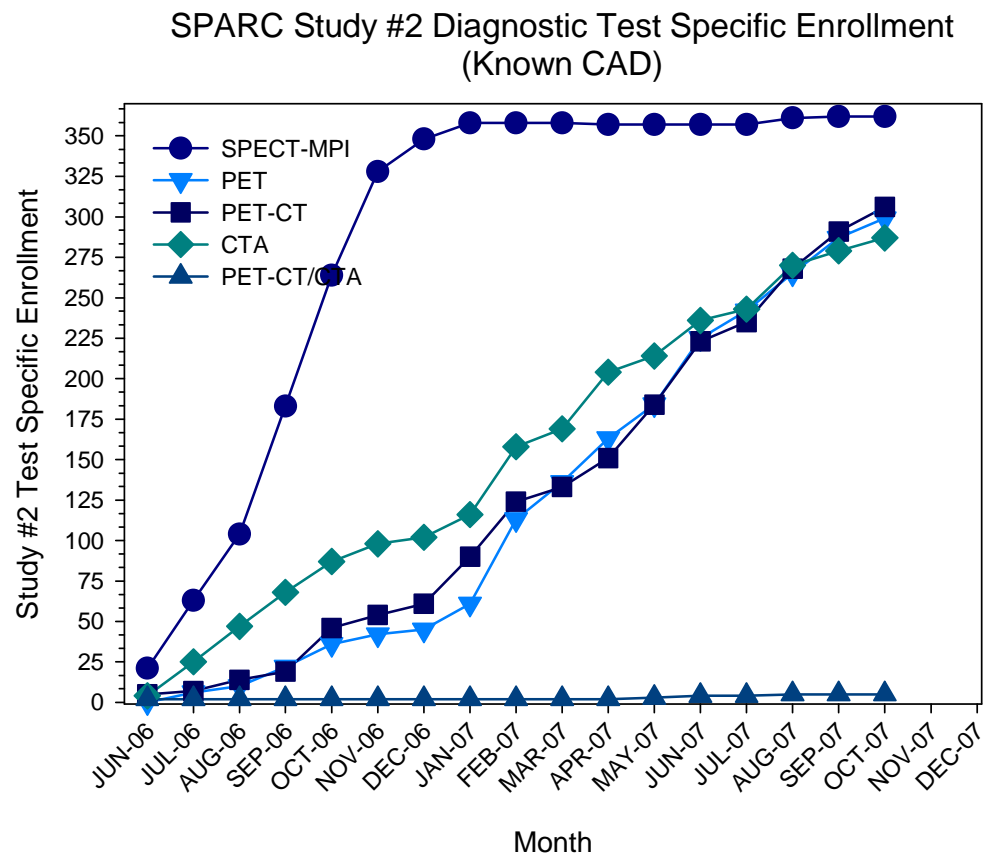
Overall *SPARC* Enrollment by Modality as of 28Oct2008



SPARC Enrollment by Modality: Study #1 as of 28Oct2008



SPARC Enrollment by Modality: Study #2 as of 28Oct2008



Rationale for Proposed Changes to SPARC Groups

Rationale

- Need to address recruitment challenges in the PET-CT and PET-CT/CTA arms in order to maintain the robustness of the study.
- SPARC study arms are being reduced from four arms [(a) SPECT-MPI, (b) PET, (c) PET-CT, and (d) CTA] to three arms [(a) SPECT-MPI, (b) Combined PET, and (c) CTA].
- The combination of all of the stress PET studies into a single arm (including stress PET/CT where CT is only used for attenuation correction, stress PET + calcium score and/or stress PET + CTA) allow for reducing the number of multiple comparisons with the control (SPECT-MPI) from three comparisons to two comparisons, thereby allowing for a reduction in the total sample size from 3700 to 2538 subjects in both study 1 and study 2.

Summary of Proposed Changes

4. STUDY OBJECTIVES

SPARC will have two components consisting of a *Pilot* CT coronary angiographic study and a *Main* study. The Pilot study will be completed to optimize imaging protocols, quality, and interpretation of coronary CT angiographic studies across multiple study sites. Operational aspects for the pilot study are found in Appendix A (Section 13.1) at the end of the protocol.

The Main study will be completed to assess the following specific objectives:

4.1.1 *Primary Objective*

The primary objectives of the Main study are to:

1. Assess the impact of SPECT-MPI, Combined PET (PET, PET-CT, PET-CT/CTA) and CT Coronary Angiography (CTA) on post-test resource utilization.
2. Determine the incremental prognostic value of SPECT-MPI, Combined PET (PET, PET-CT, PET-CT/CTA) and CT Coronary Angiography (CTA) for predicting cardiac death and nonfatal myocardial infarction following a procedure

4.1.2 *Secondary Objectives*

Secondary objectives of the Main study are to:

1. Assess the diagnostic accuracy of these modalities for detection of obstructive epicardial coronary stenosis as assessed by cardiac catheterization.
2. Assess the risk-adjusted referral rate to revascularization within 90 days of cardiac catheterization after the index noninvasive imaging study.
3. Assess the use of and change in cardiac medications at 90 days and one year after the index noninvasive imaging study.
4. Determine the combined occurrence of (1) death from any cause, (2) nonfatal myocardial infarction, and (3) late (>6 month) referral to revascularization after the index noninvasive imaging study.
5. Determine the cost-effectiveness of strategies incorporating different noninvasive imaging modalities.

4.2 Study Endpoints

4.2.1 *Primary Endpoints*

1. Referral to cardiac catheterization within 90 days of index noninvasive testing.
2. Occurrence of cardiac death or nonfatal myocardial infarction at two years after index noninvasive testing.

4.2.2 *Secondary Endpoints*

1. Diagnostic accuracy of the SPECT-MPI, Combined PET (PET, PET-CT, PET-CT/CTA) and CT Coronary Angiography (CTA) for detection of epicardial coronary stenosis as assessed by cardiac catheterization.
2. Documented referral to cardiac revascularization within 90 days of cardiac catheterization after the index noninvasive imaging study.
3. Use of and change in cardiac medications at 90 days and 1 year following after the index noninvasive imaging study.
4. Combined occurrence of (1) death from any cause, (2) nonfatal myocardial infarction, and (3) late (>6 month) referral to revascularization after the index noninvasive imaging study.
5. Direct and indirect cost associated with a clinical endpoint event.

Revised Sample Size Estimates

Revised Sample Size for Study # 1

A sample size of 1668 (556 patients in each of 3 arms) will have **power >90%**, for a two-sided test at $\alpha=0.01$ to detect a **2% difference in the diagnostic catheterization rates at 90 days between the 3 diagnostic arms** when the estimated referral rate to **catheterization is estimated to be between 25% and 40% for intermediate and high pretest likelihood patients.** These sample size simulations also account for a Bonferonni-Holm correction for multiple comparisons between each of the diagnostic tests combinations, and allows for a lost to follow-up rate of 5%.

Revised Sample Size for Study # 2

A population sample size of 2538 (1668 diagnostic patients from objective 1 + 870 patients with known CAD: [846=556 + 290 patients in each of 3 groups]) will have **power >90%**, for a two-sided test at $\alpha=0.01$ to detect a **2% difference in the primary endpoints (occurrence of cardiac death or nonfatal MI)** within 2 years of the index noninvasive test, when the estimated endpoint rate is between 3% and 12%. These sample size simulations also account for a Bonferonni-Holm correction for multiple comparisons between each of the three diagnostic tests combinations, and **allows for a complete follow-up rate of 90%**.

Figure 3. Population Required for Objective 1.

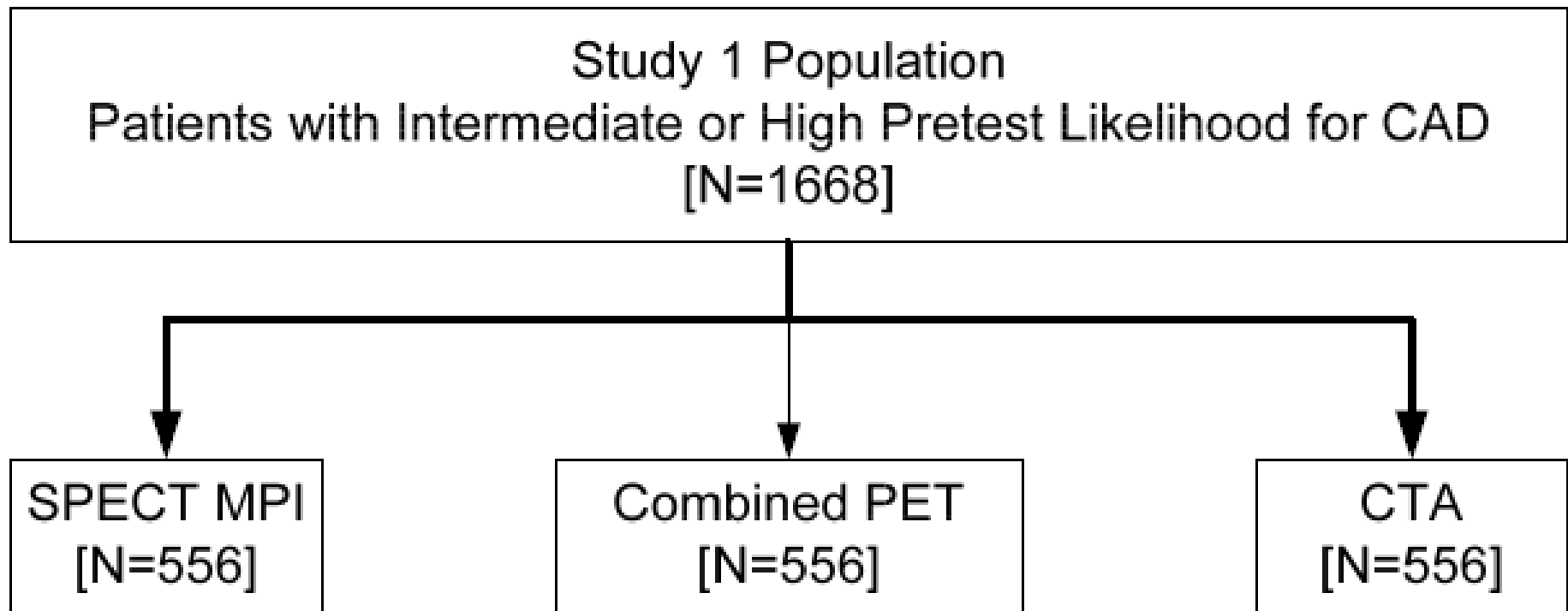
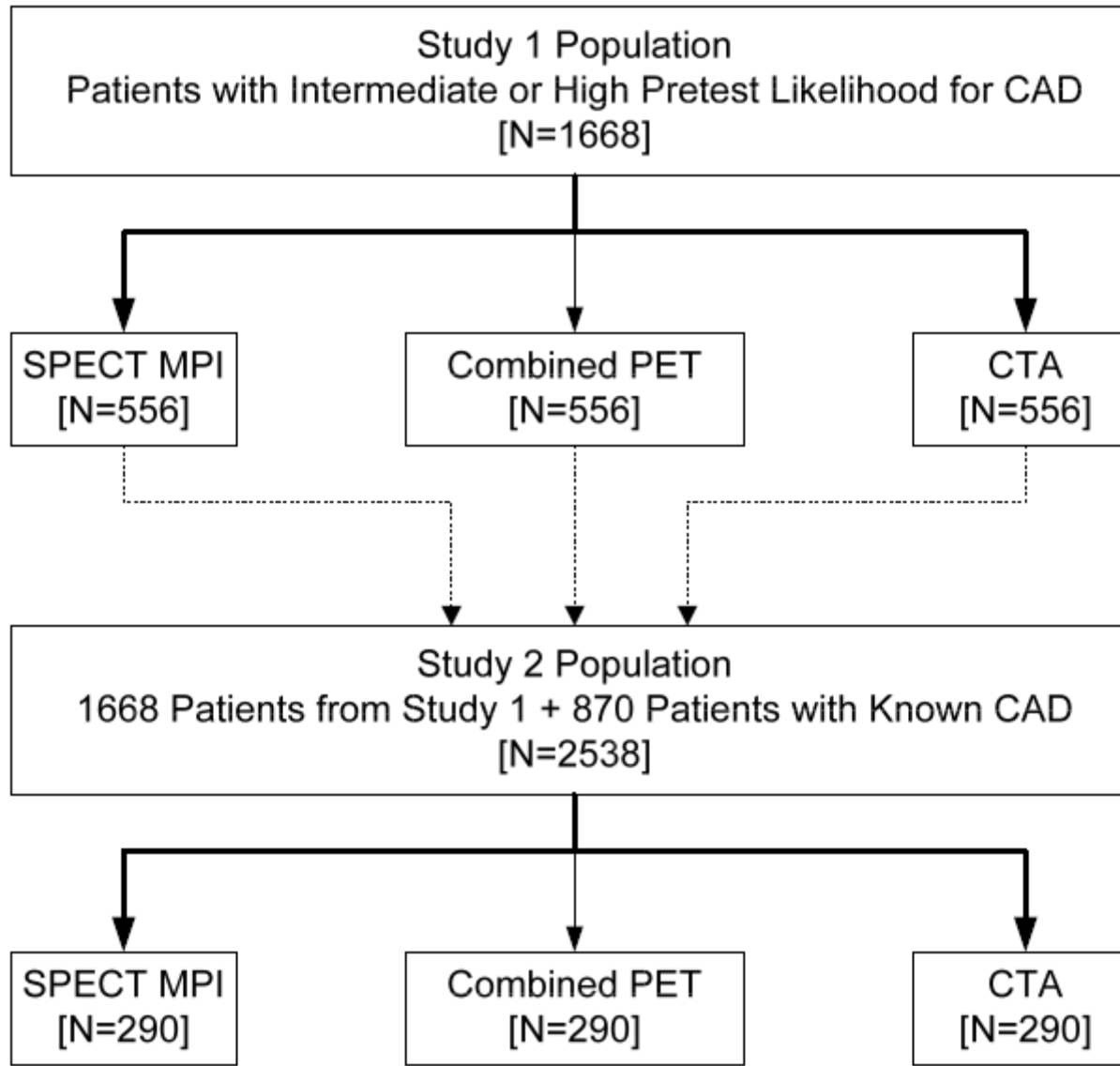
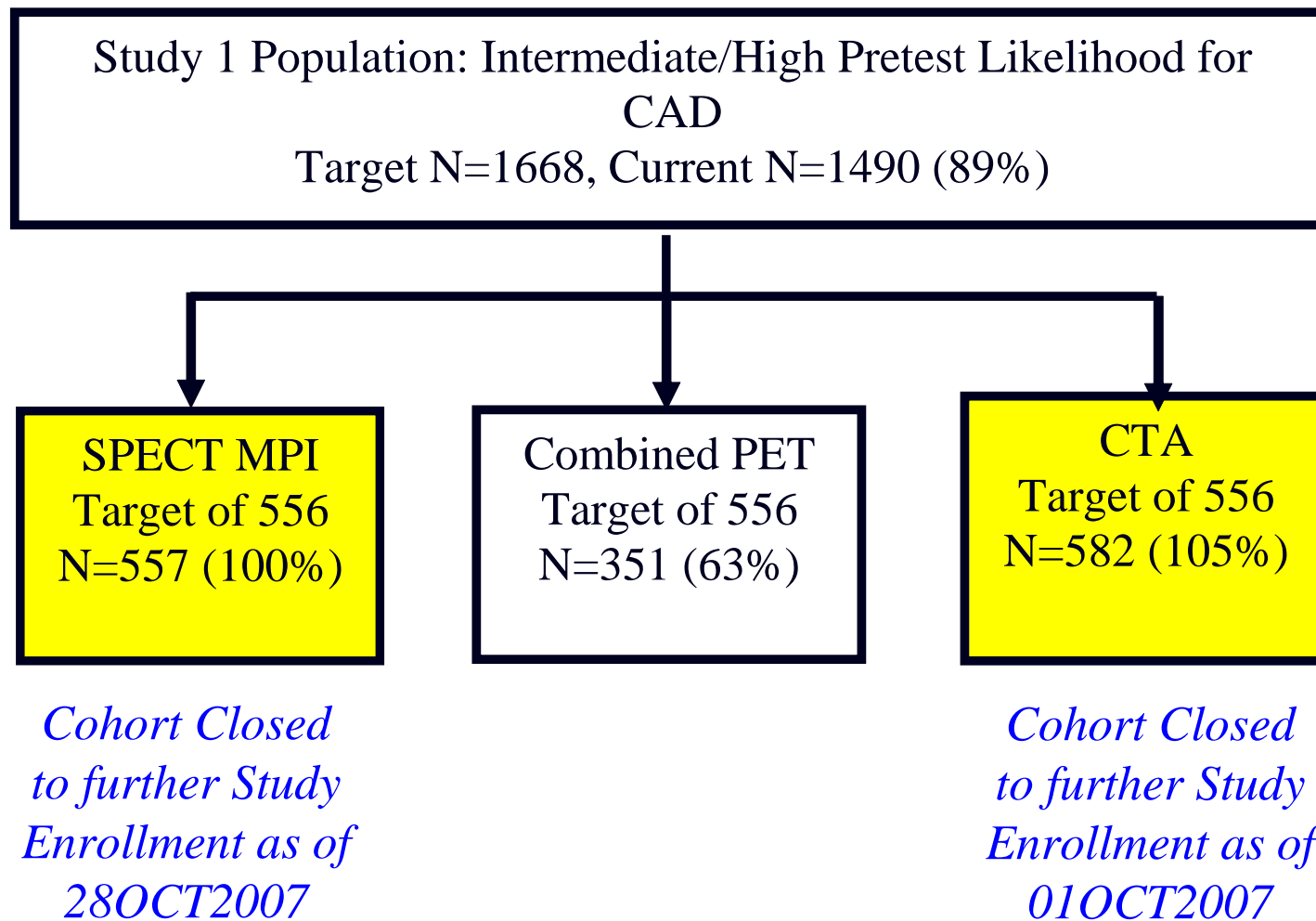


Figure 4. Population Required for Objective 2.

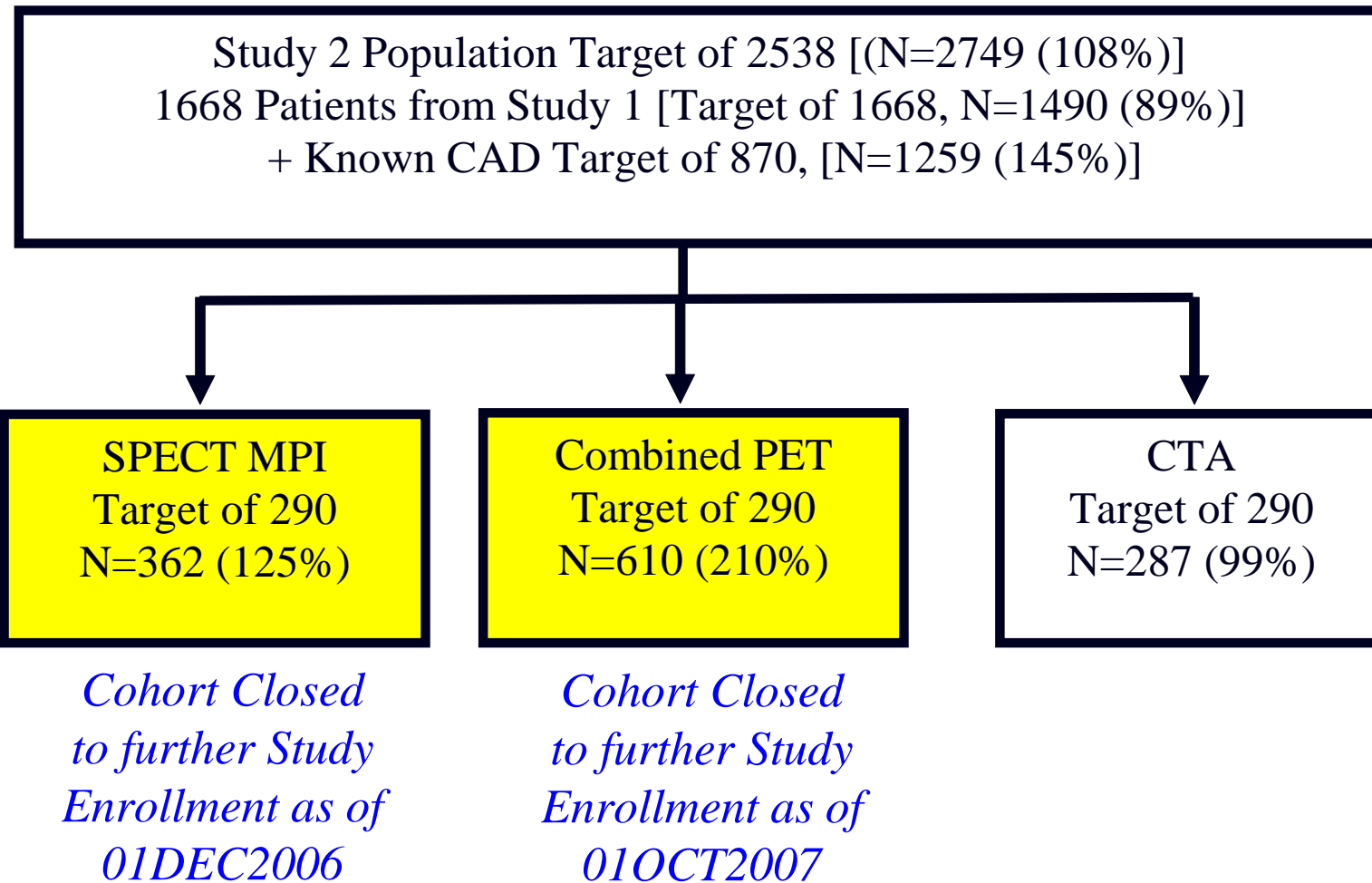


Current enrollment projections based on revised sample size

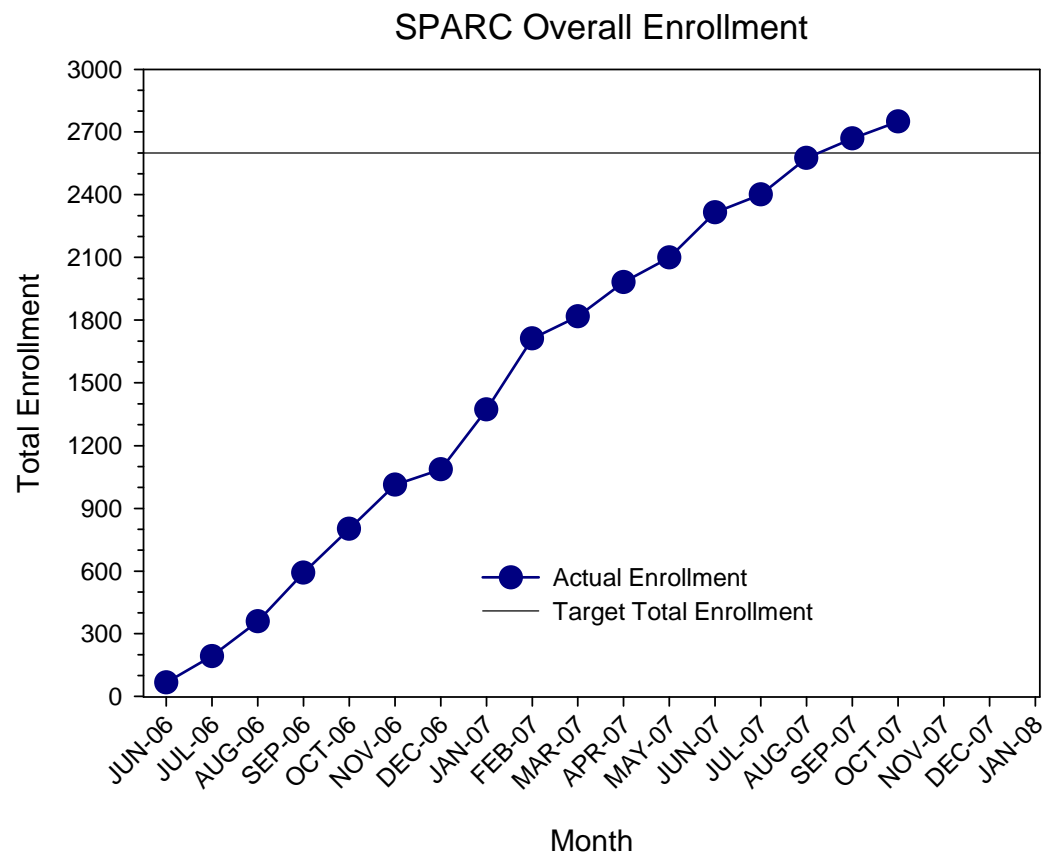
SPARC Enrollment: Study #1 as of 28Oct2008 (Adjusted Sample Size, Combined PET Arms)



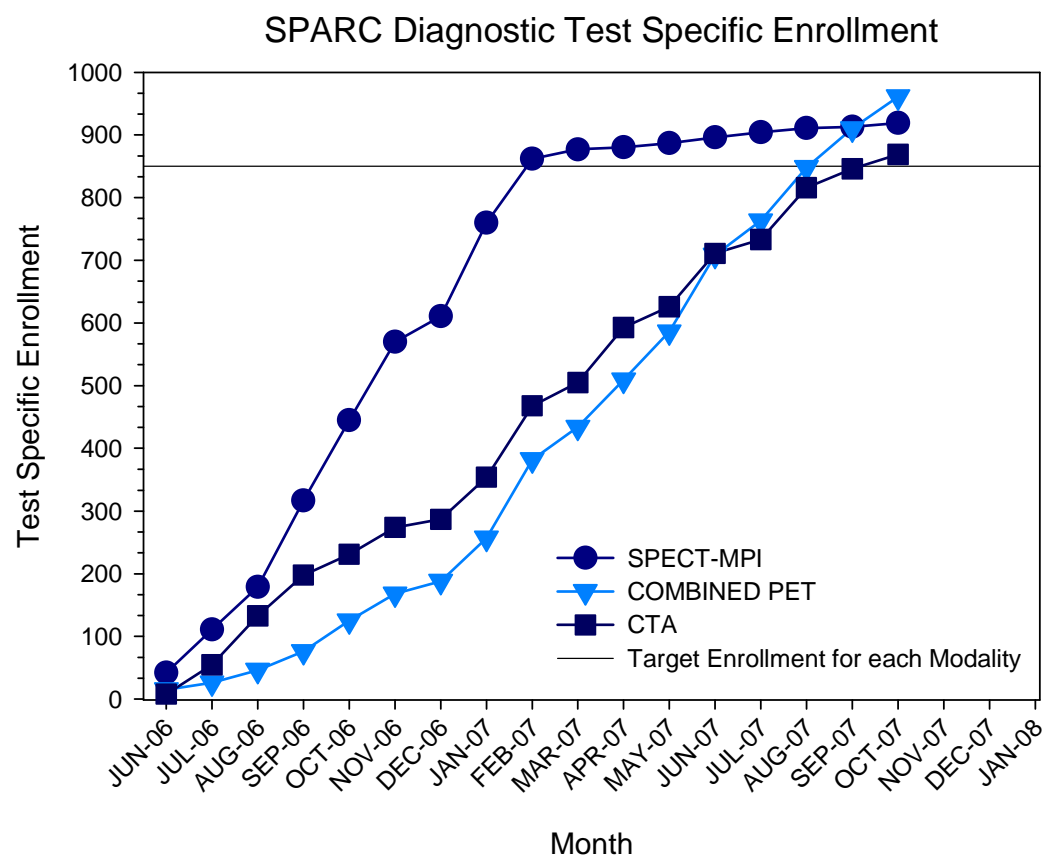
SPARC Enrollment: Study #2 as of 28Oct2008 (Adjusted Sample Size, Combined PET Arms)



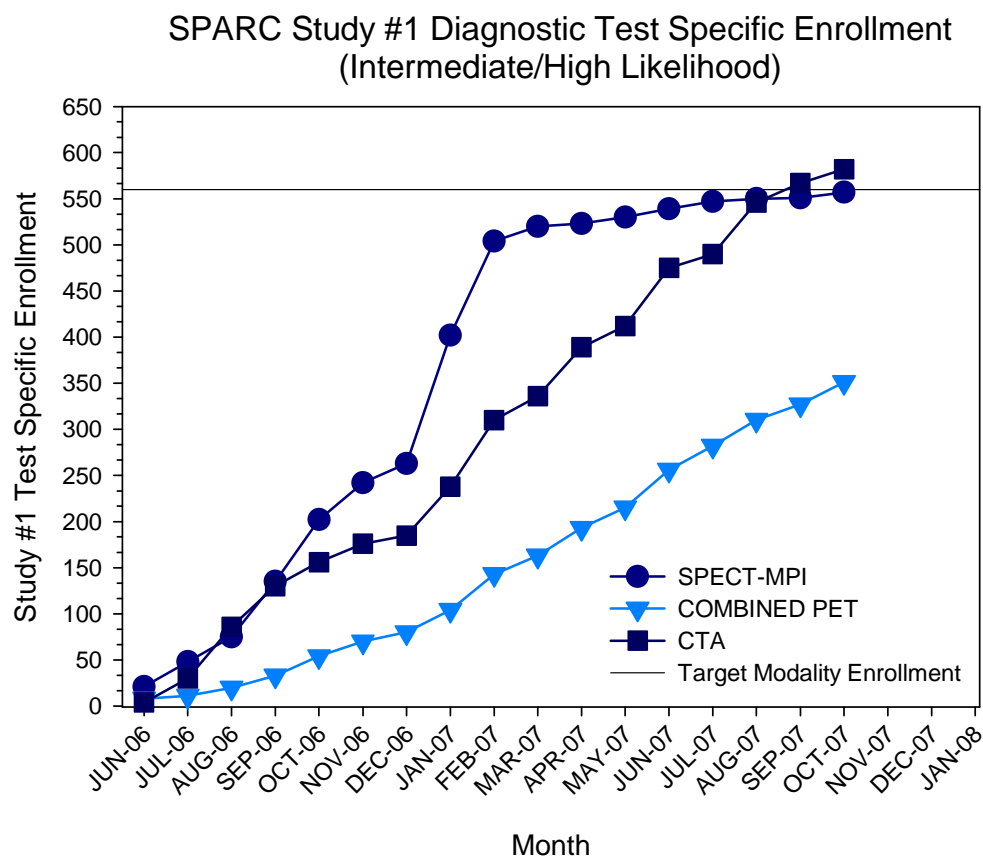
Overall *SPARC* Enrollment as of 28Oct2008 (Adjusted Sample Size, Combined PET Arms)



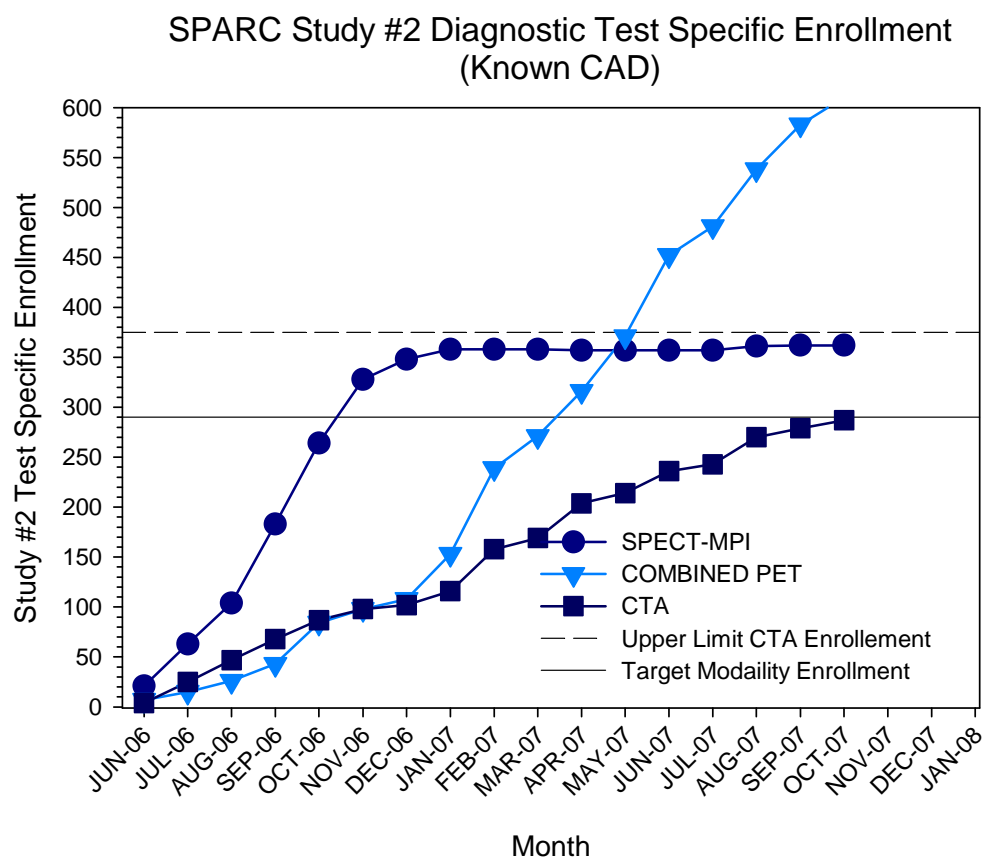
Overall *SPARC* Enrollment as of 28Oct2008 (Adjusted Sample Size, Combined PET Arms, By Modality)



SPARC Modality Enrollment: Study #1 as of 28Oct2008 (Adjusted Sample Size, Combined PET Arms, By Modality)



SPARC Modality Enrollment: Study #2 as of 28Oct2008 (Adjusted Sample Size, Combined PET Arms, By Modality)

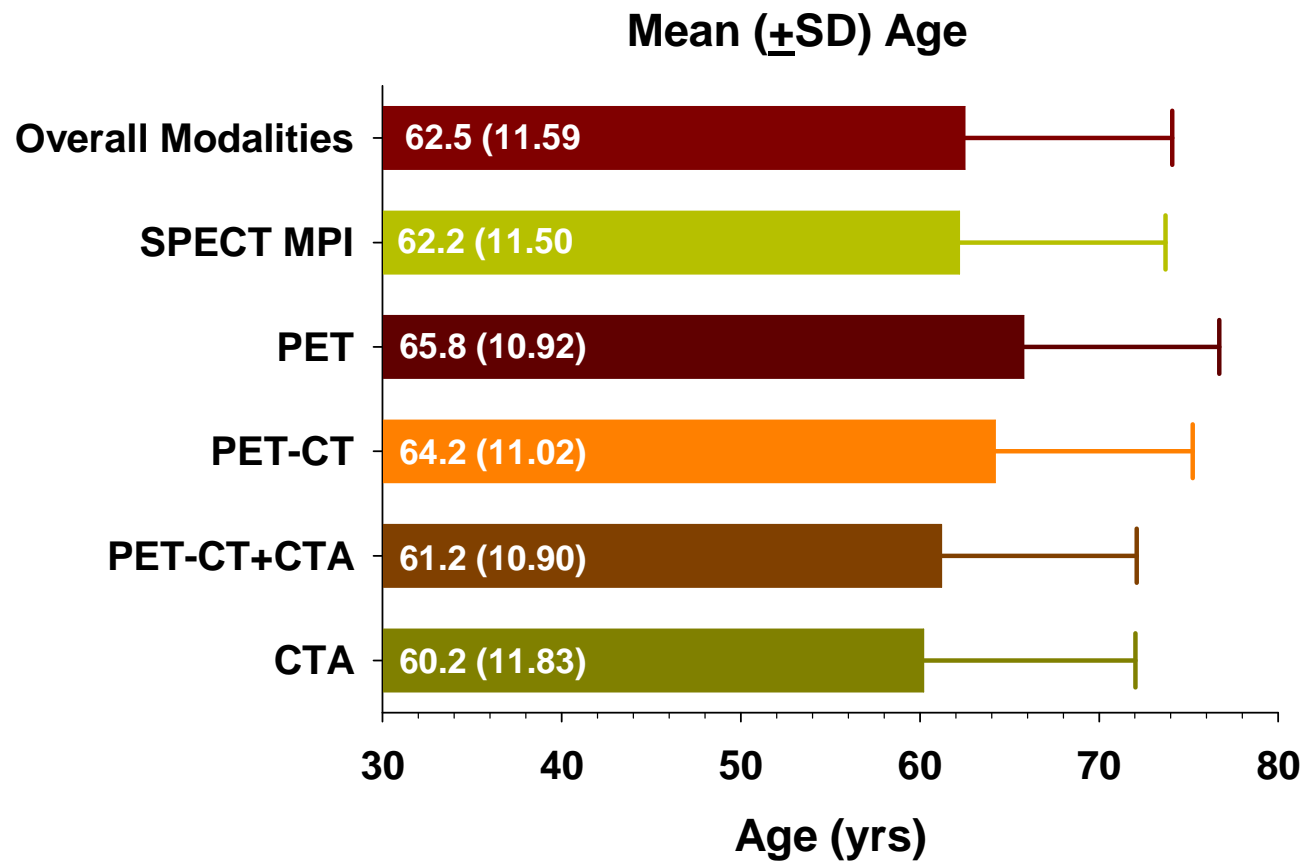


Demographic Update Summary

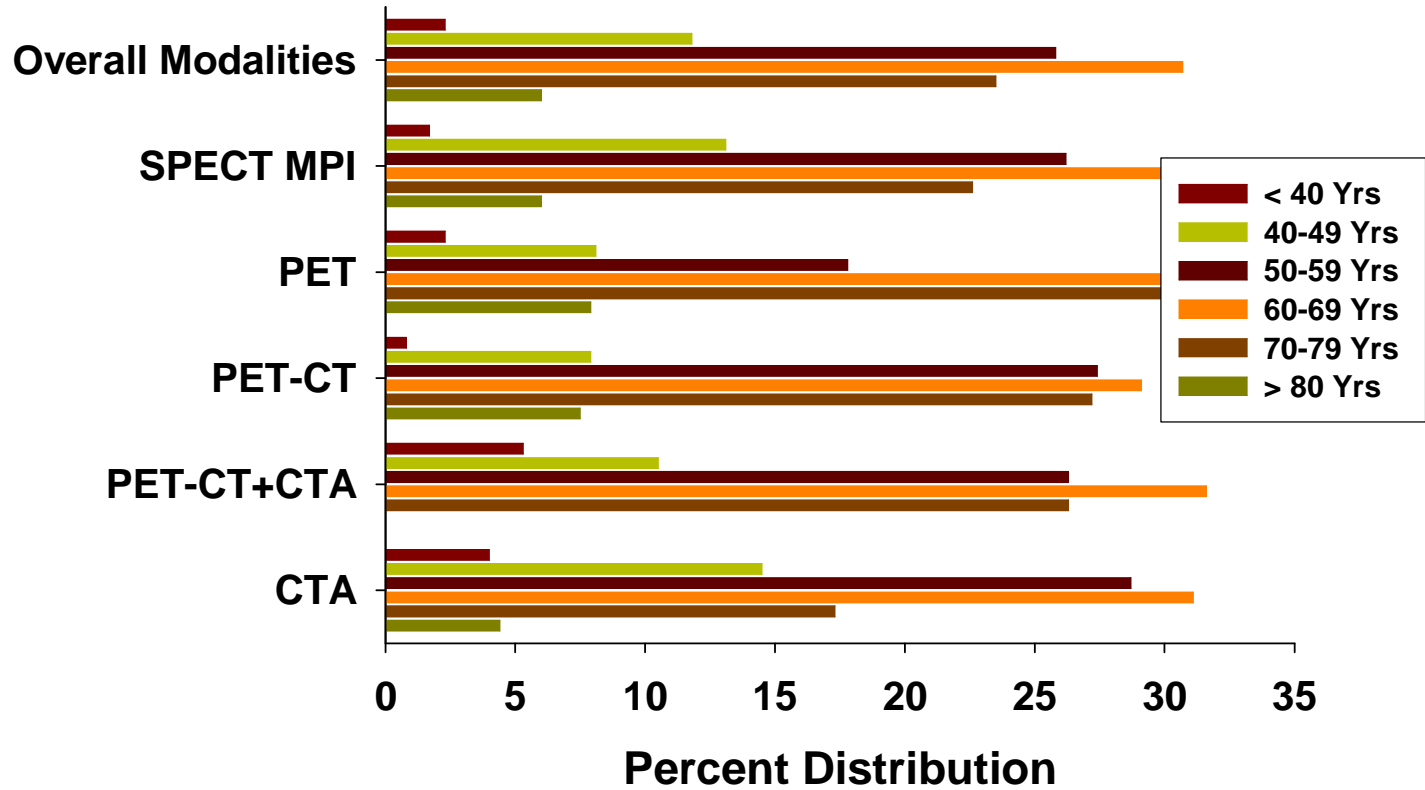
Demographics Analyses as of 28 October 2007

- **Age**
- **Gender**
- **BMI**
- **Presenting sx**
- **Hx**
- **Medications**
- **Prior modalities (30 day)**

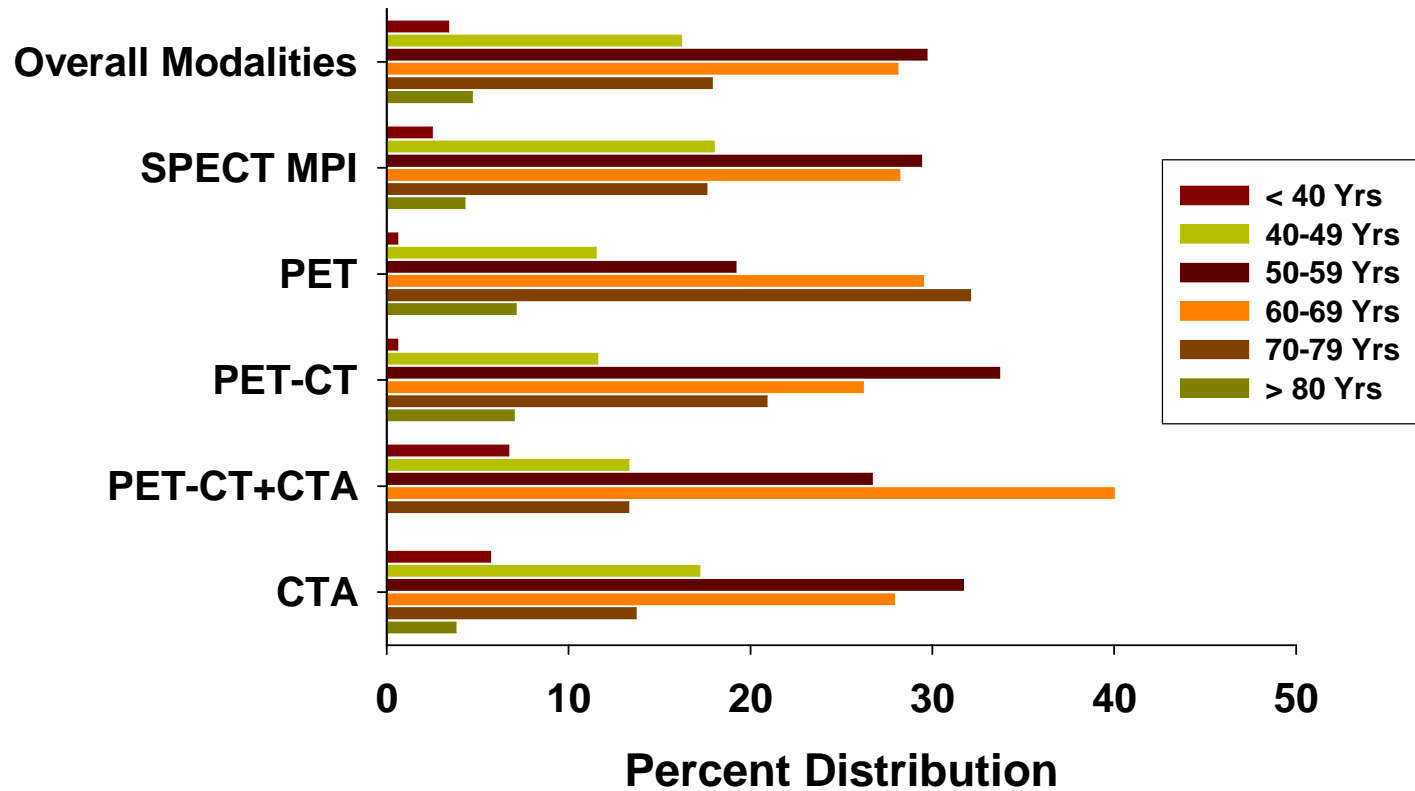
Overall Age (Mean \pm SD)



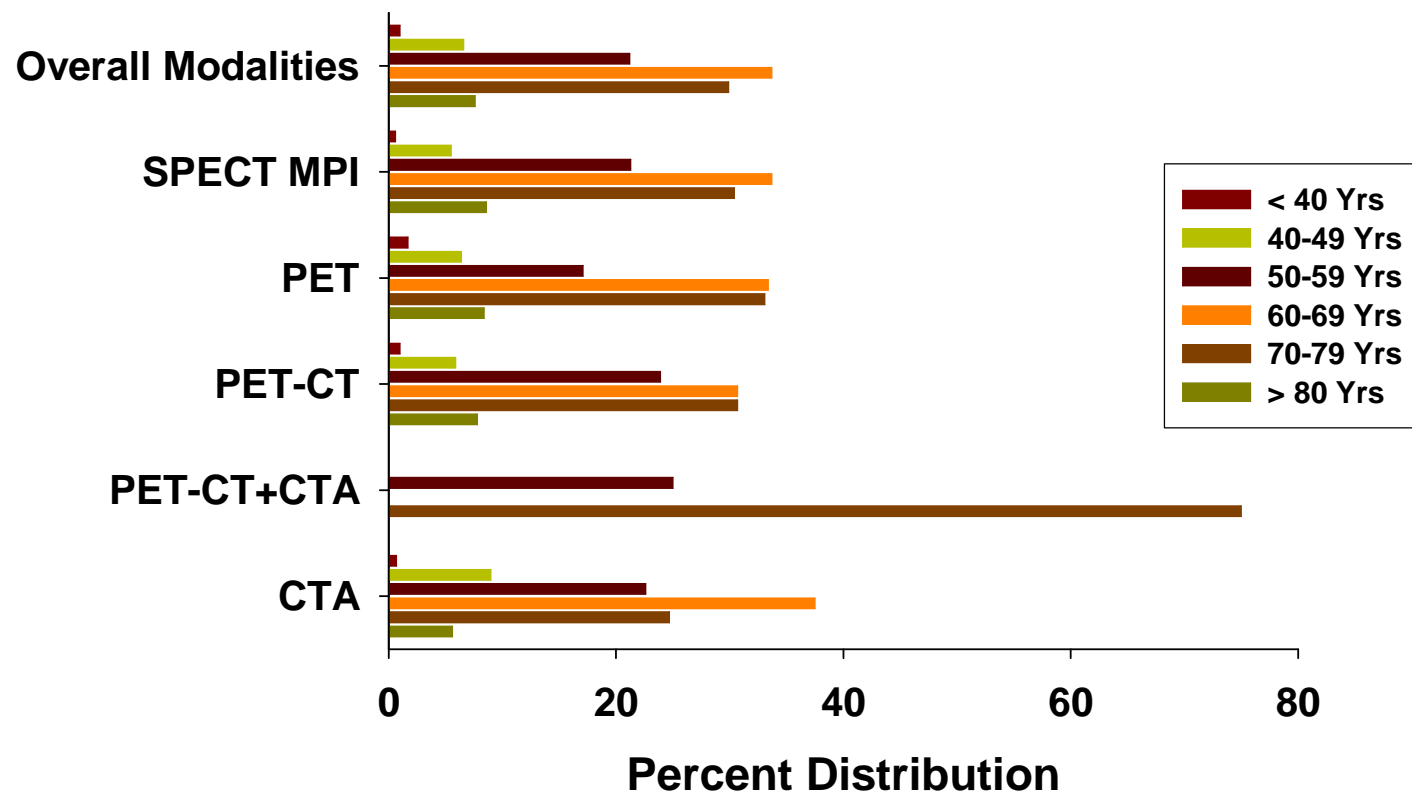
Overall Age Distribution



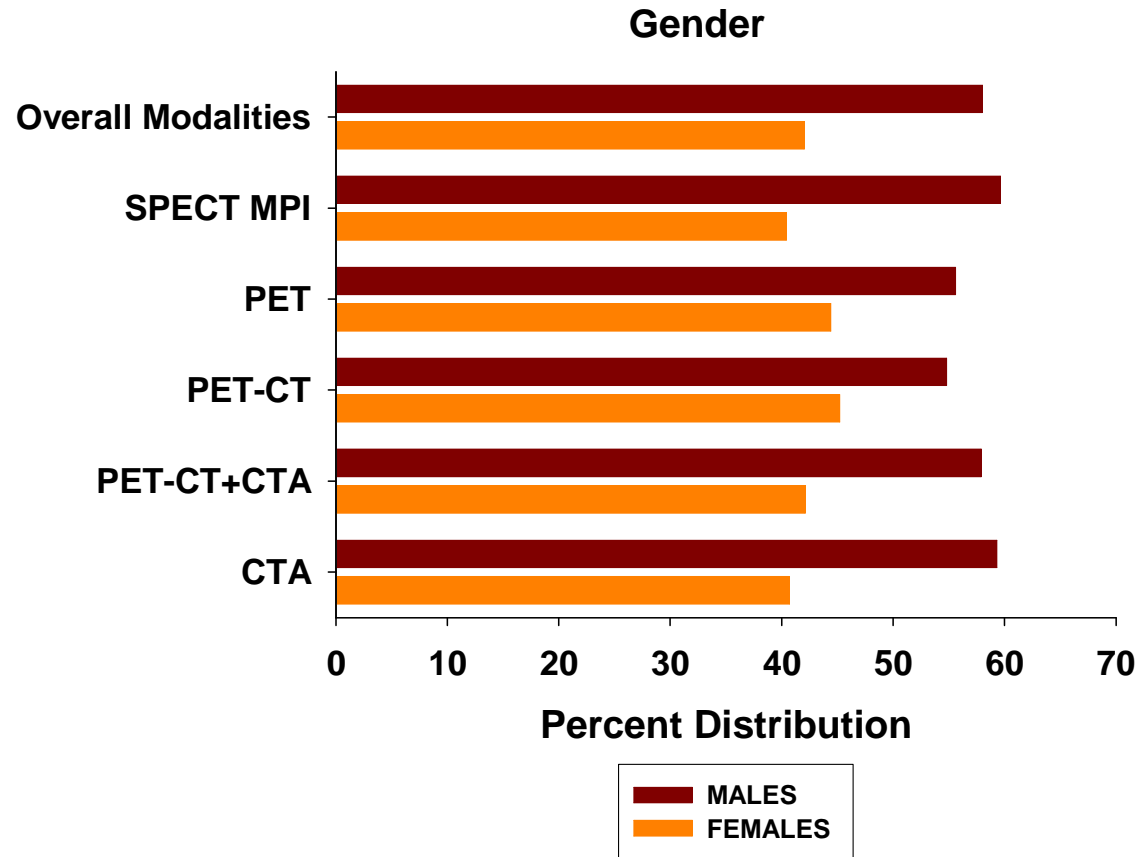
Study 1 Age Distribution



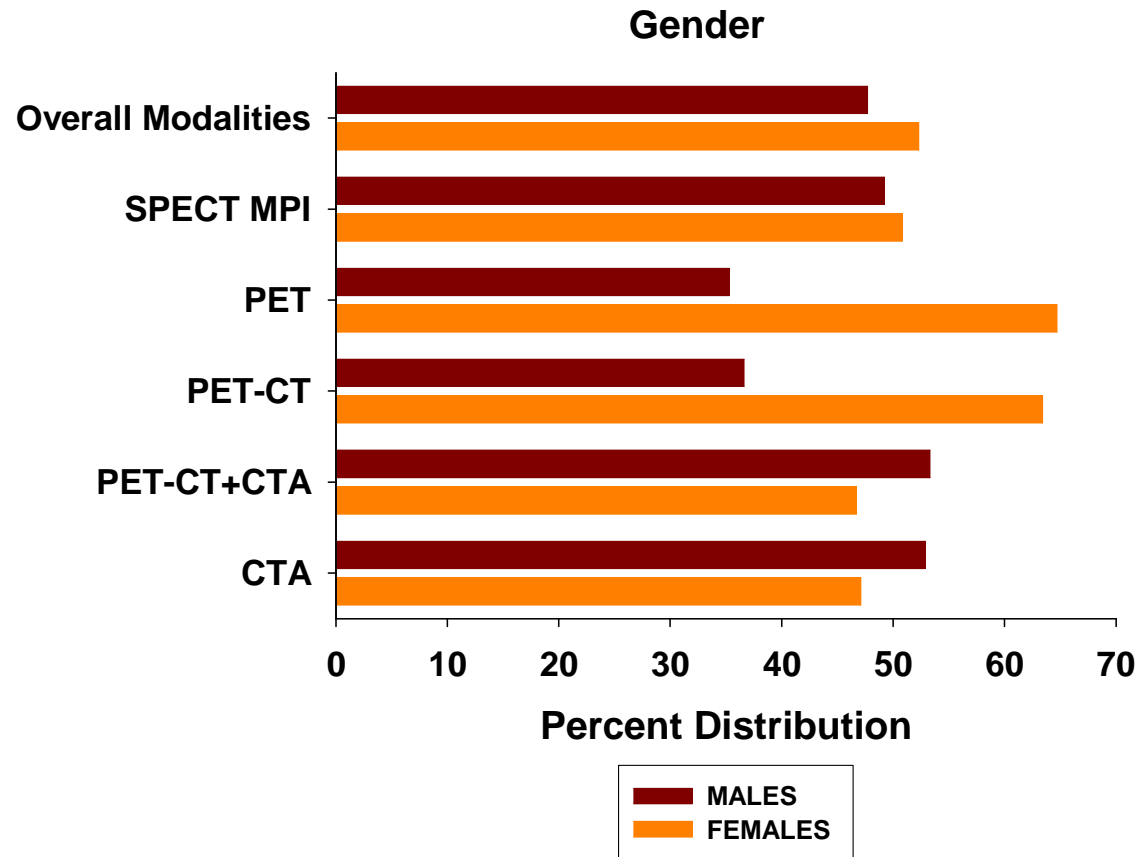
Study 2 Age Distribution



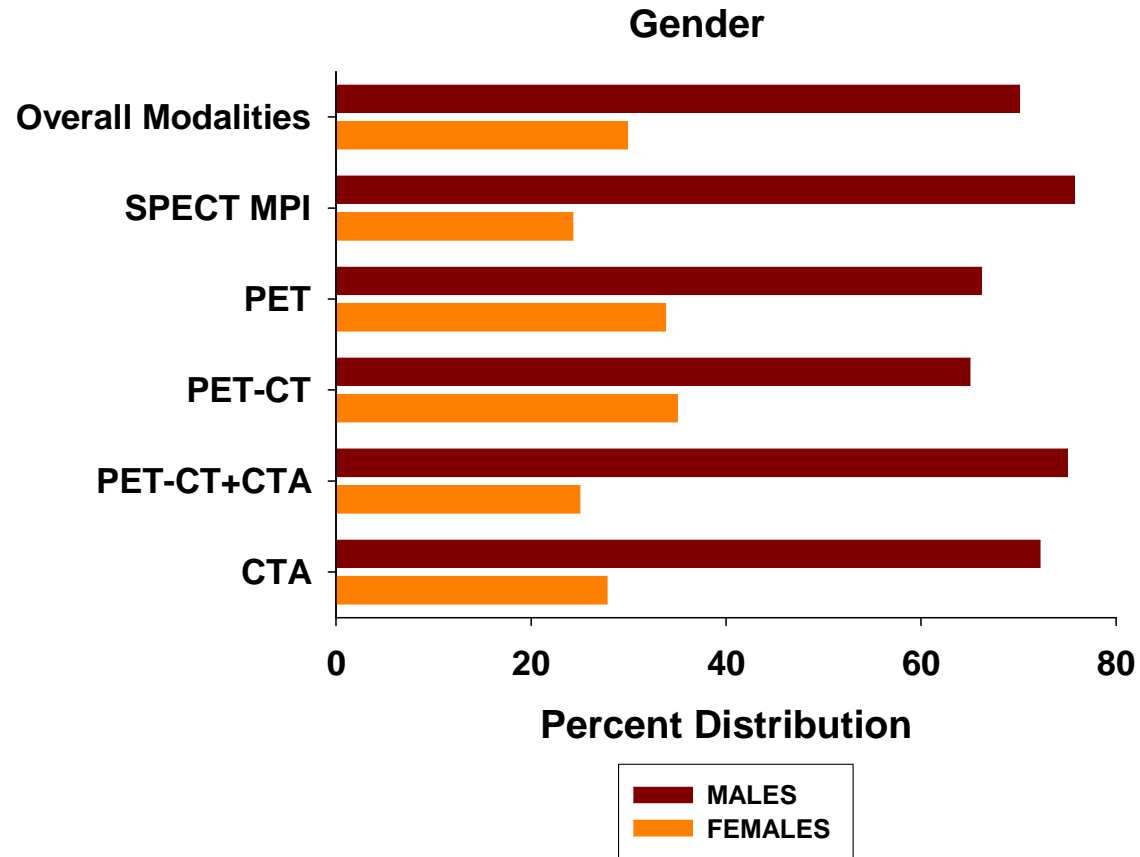
Overall Gender Distribution



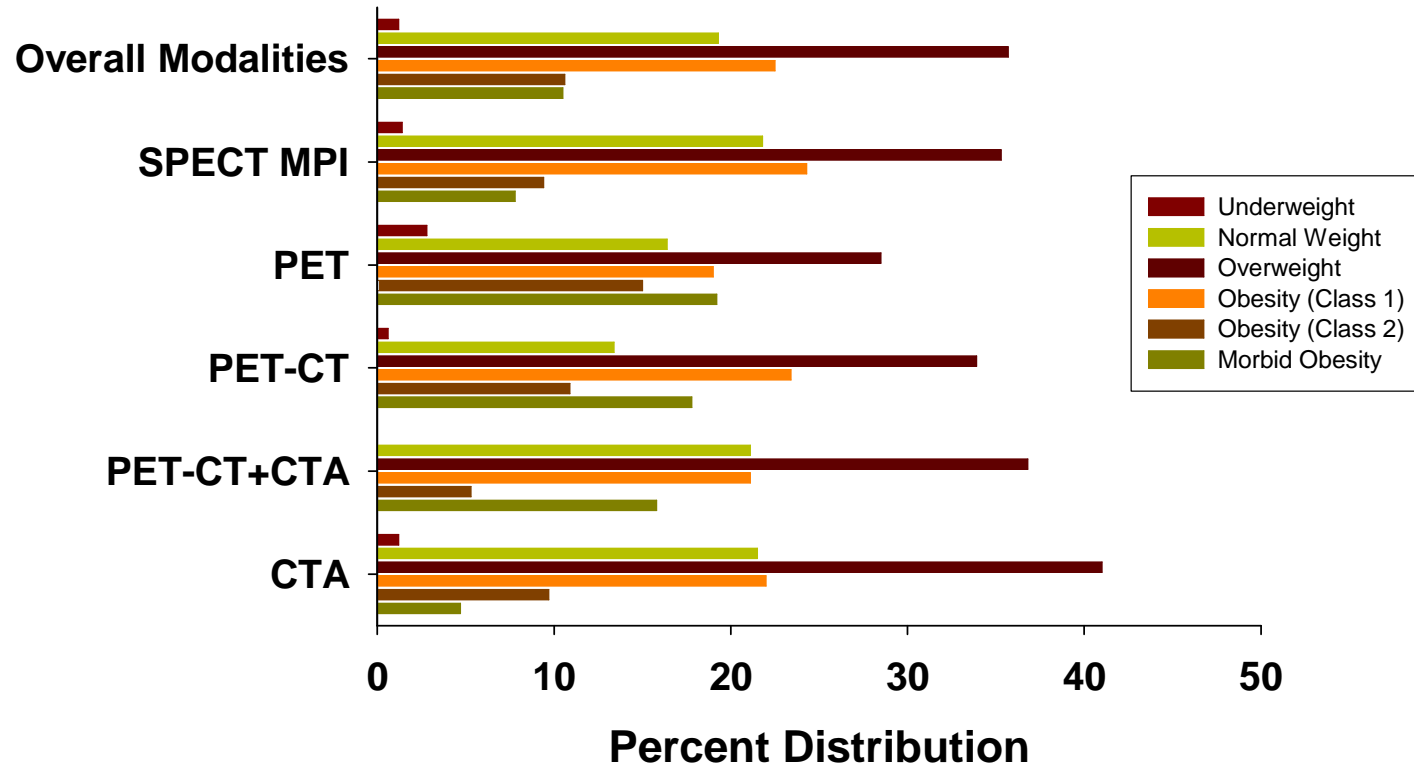
Study 1 Gender Distribution



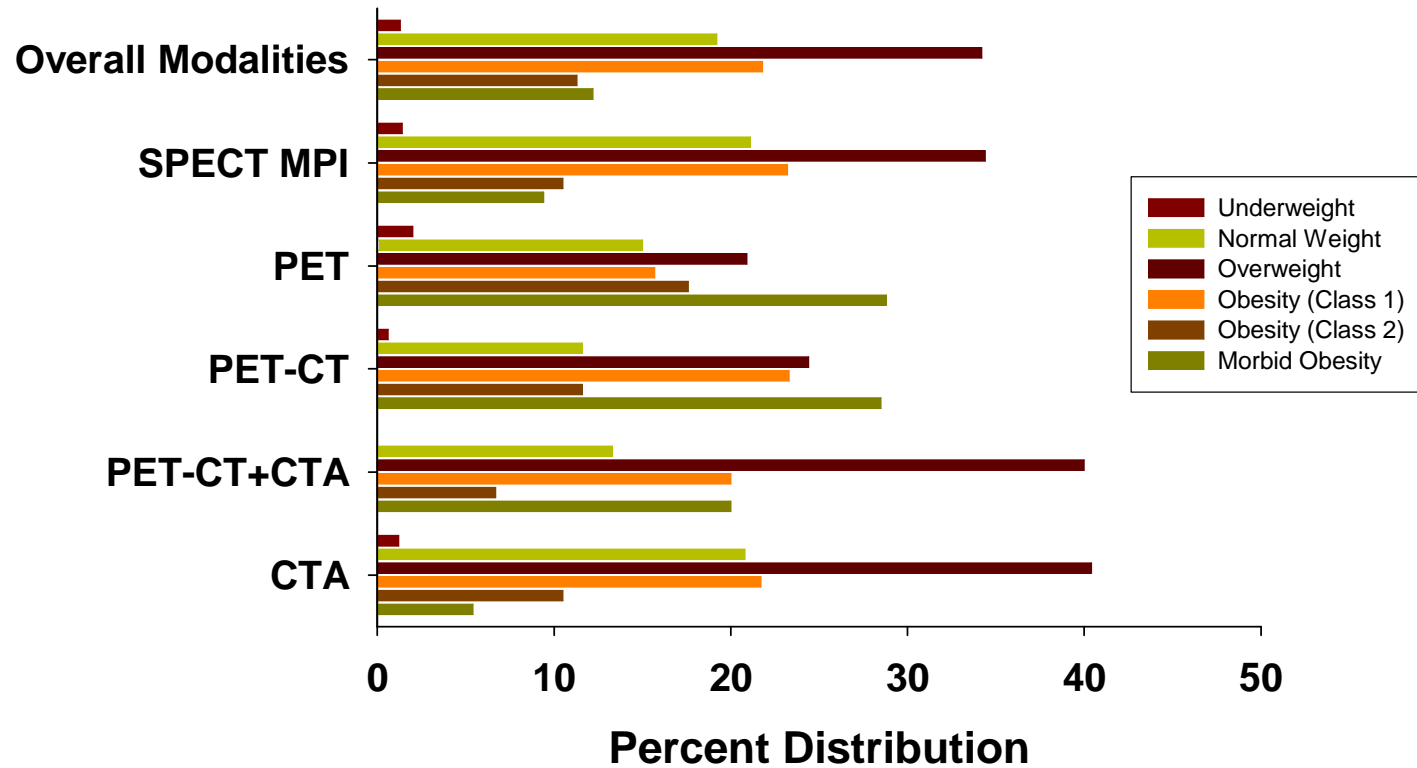
Study 2 Gender Distribution



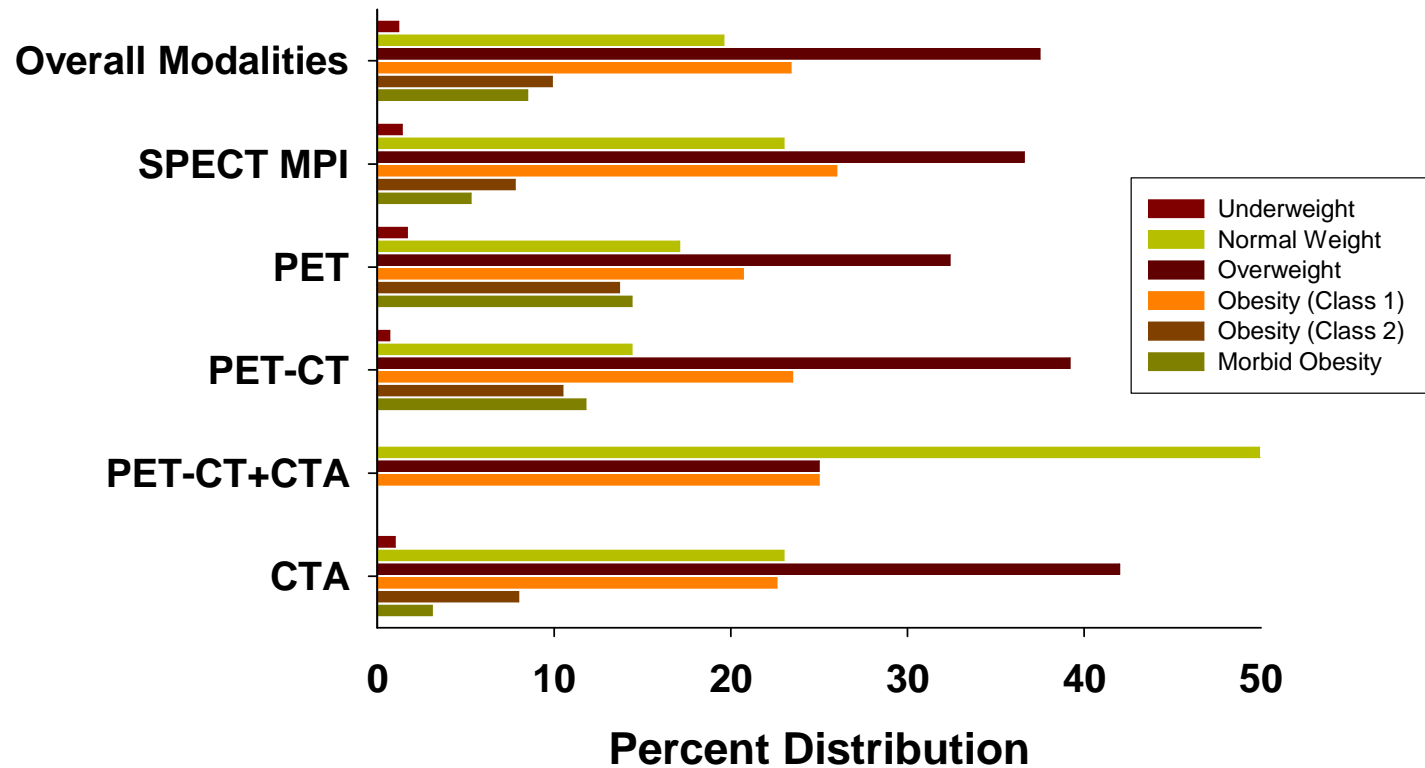
Overall BMI Distribution



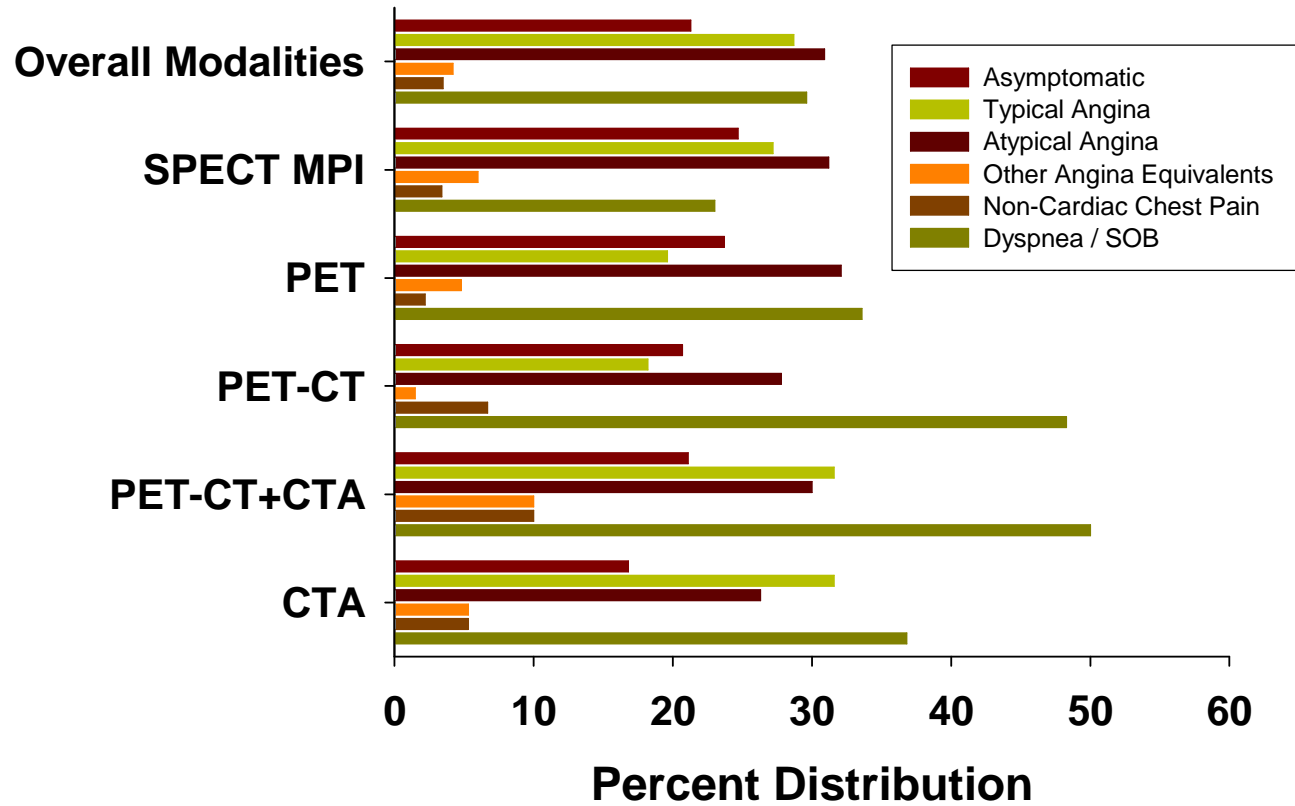
Study 1 BMI Distribution



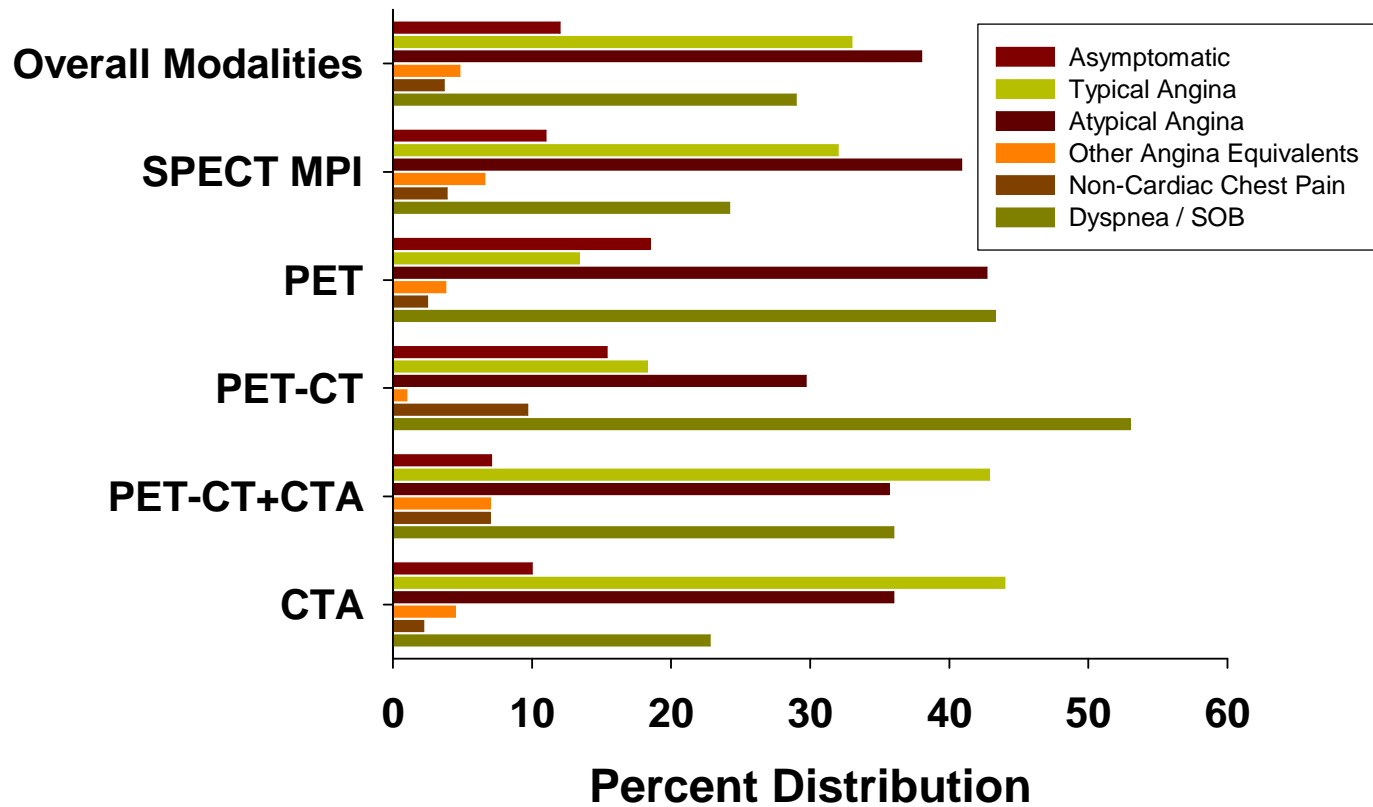
Study 2 BMI Distribution



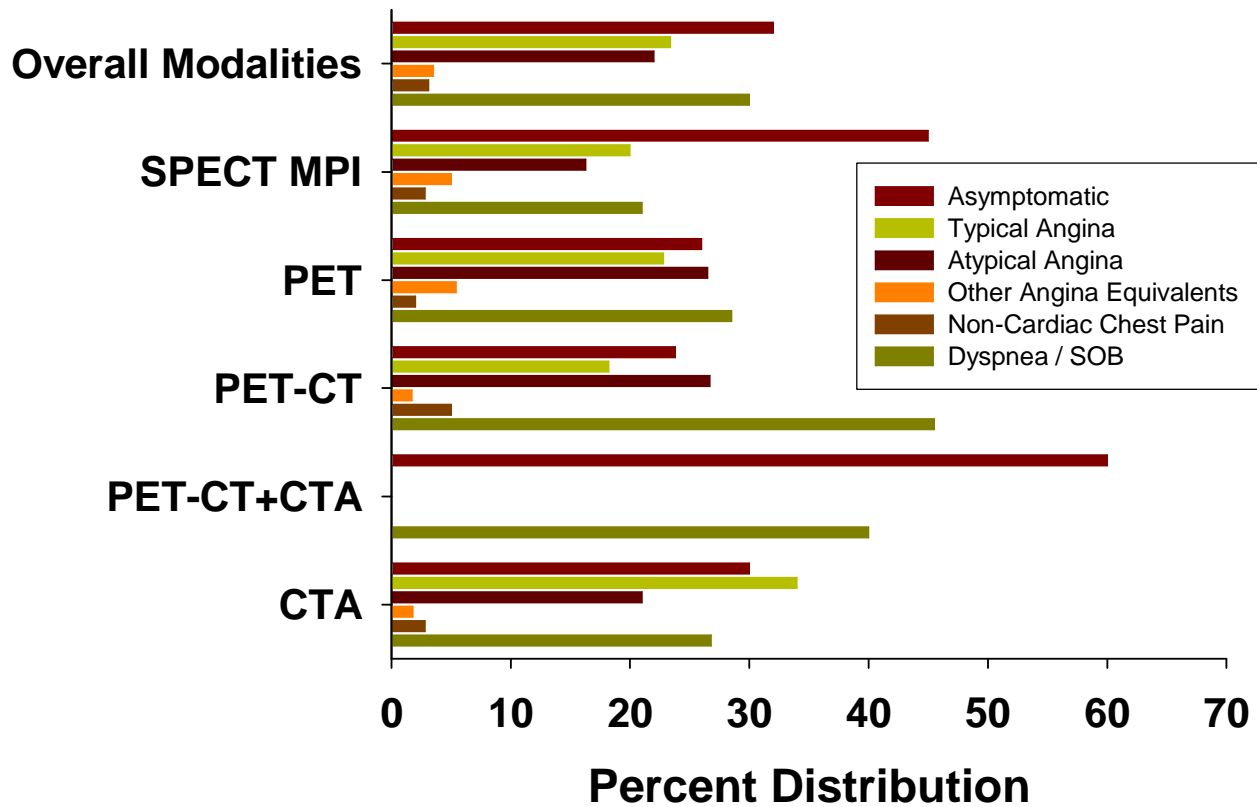
Overall Presenting Symptoms



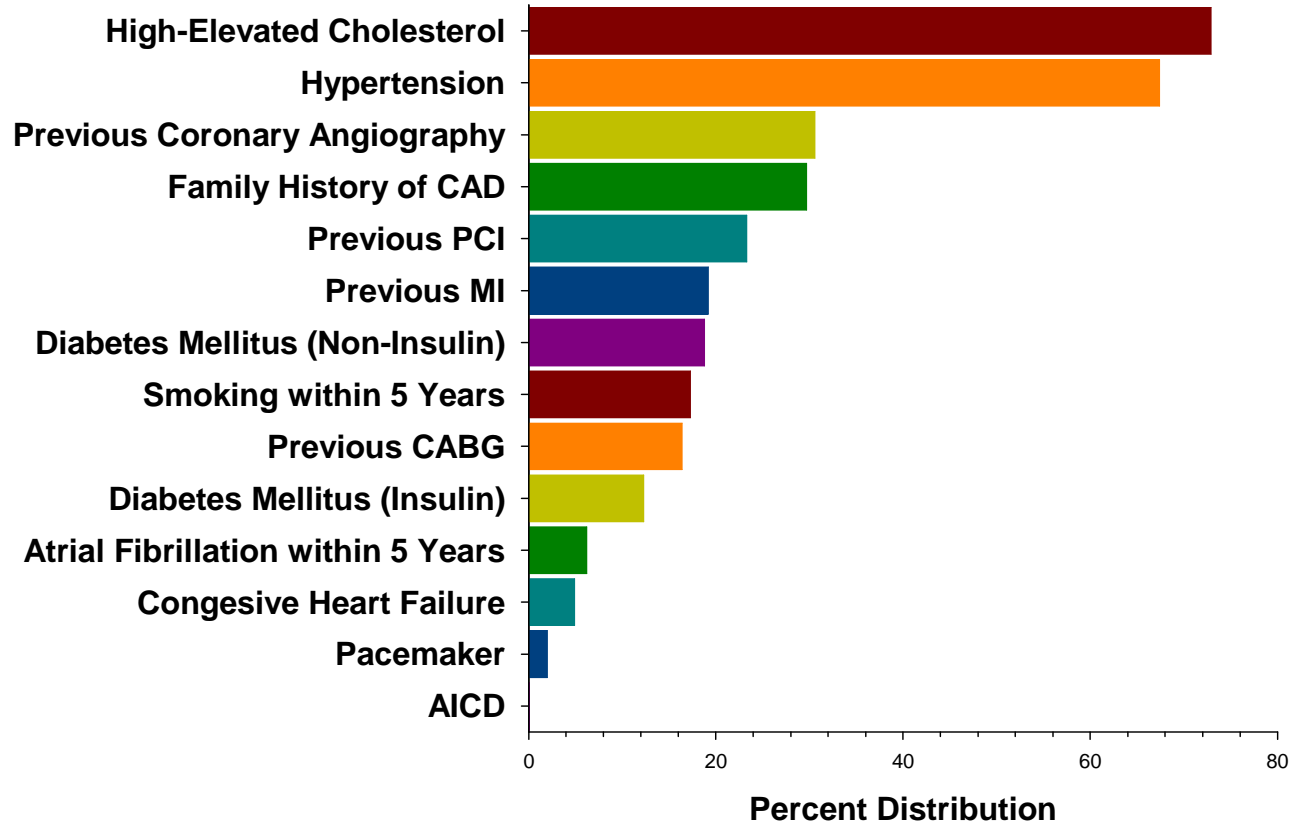
Study 1 Presenting Symptoms



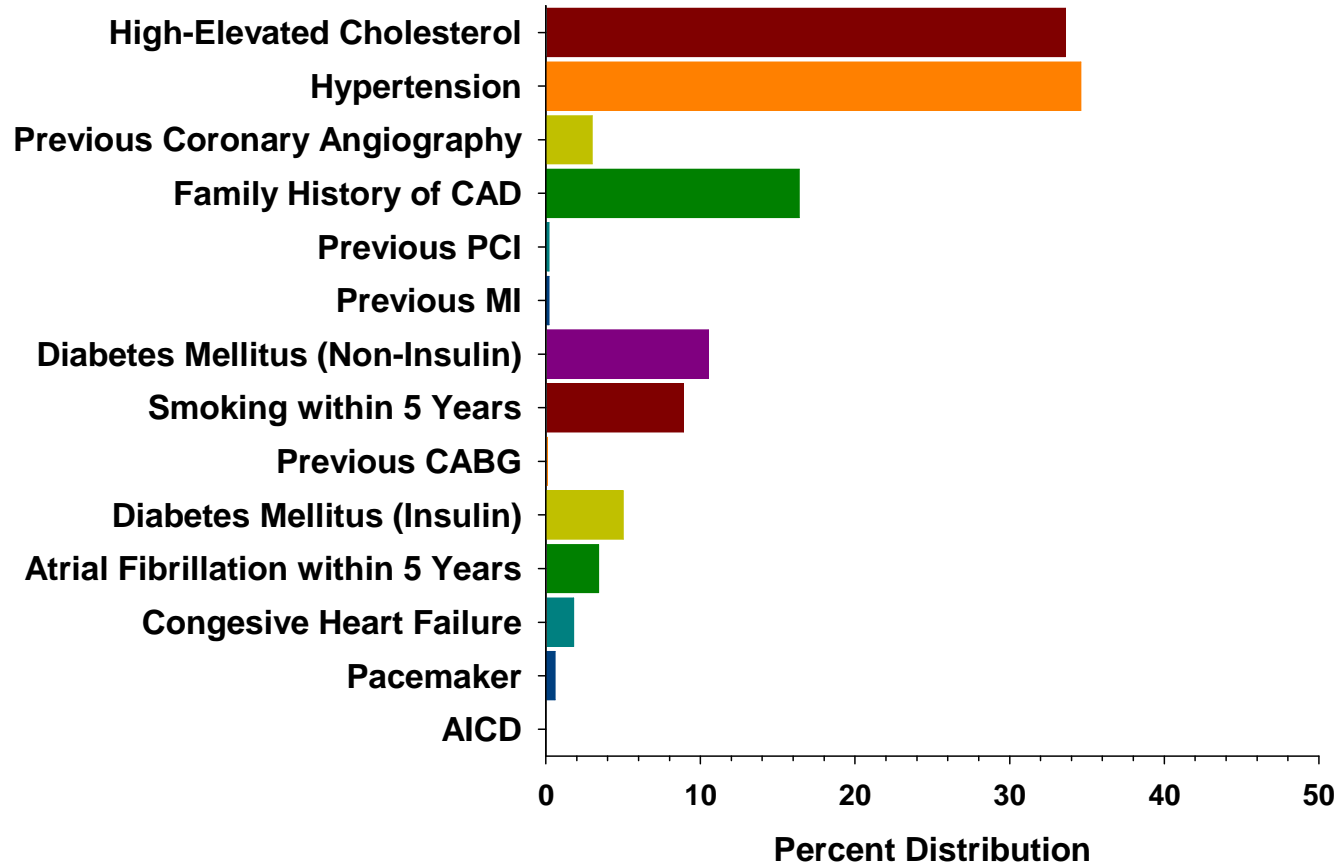
Study 2 Presenting Symptoms



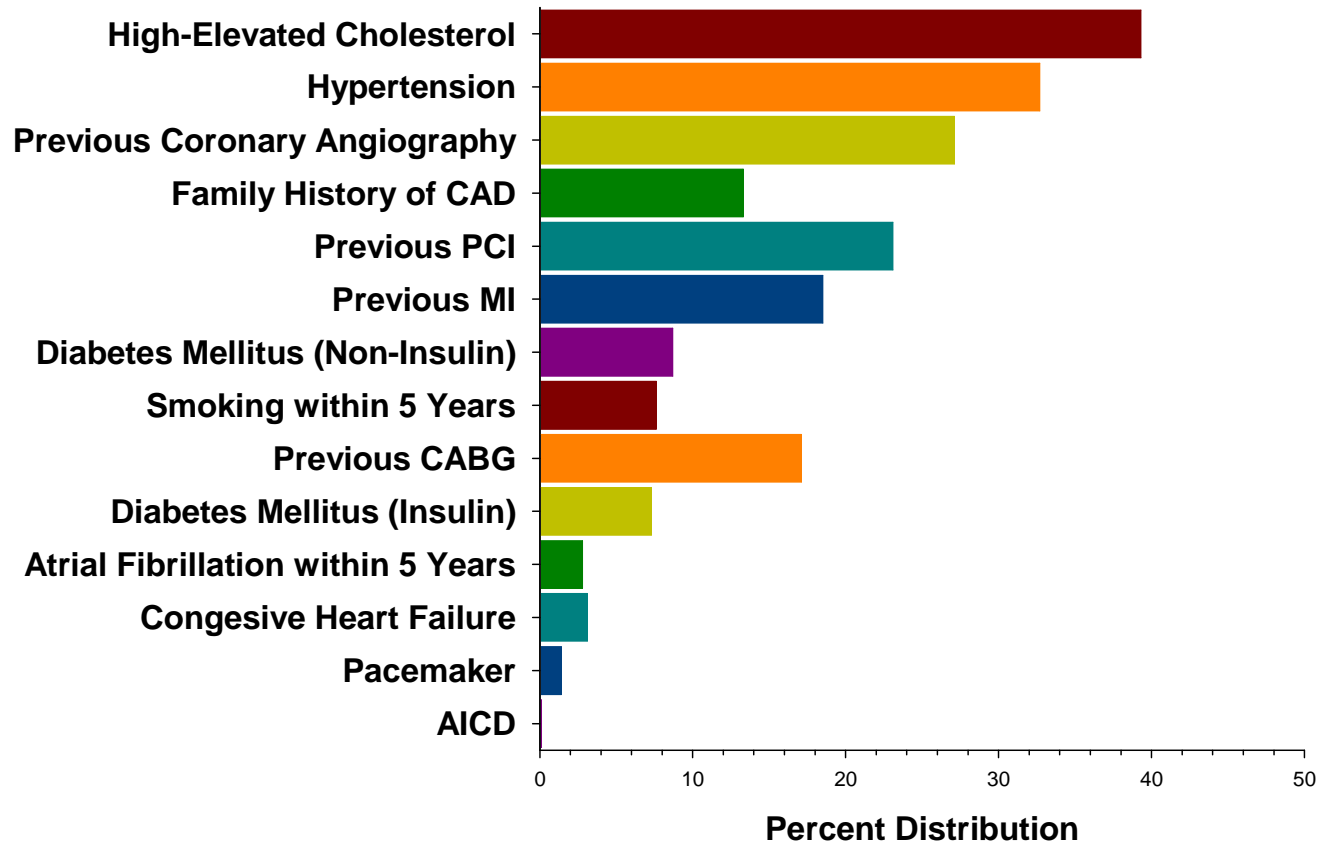
Overall Medical History



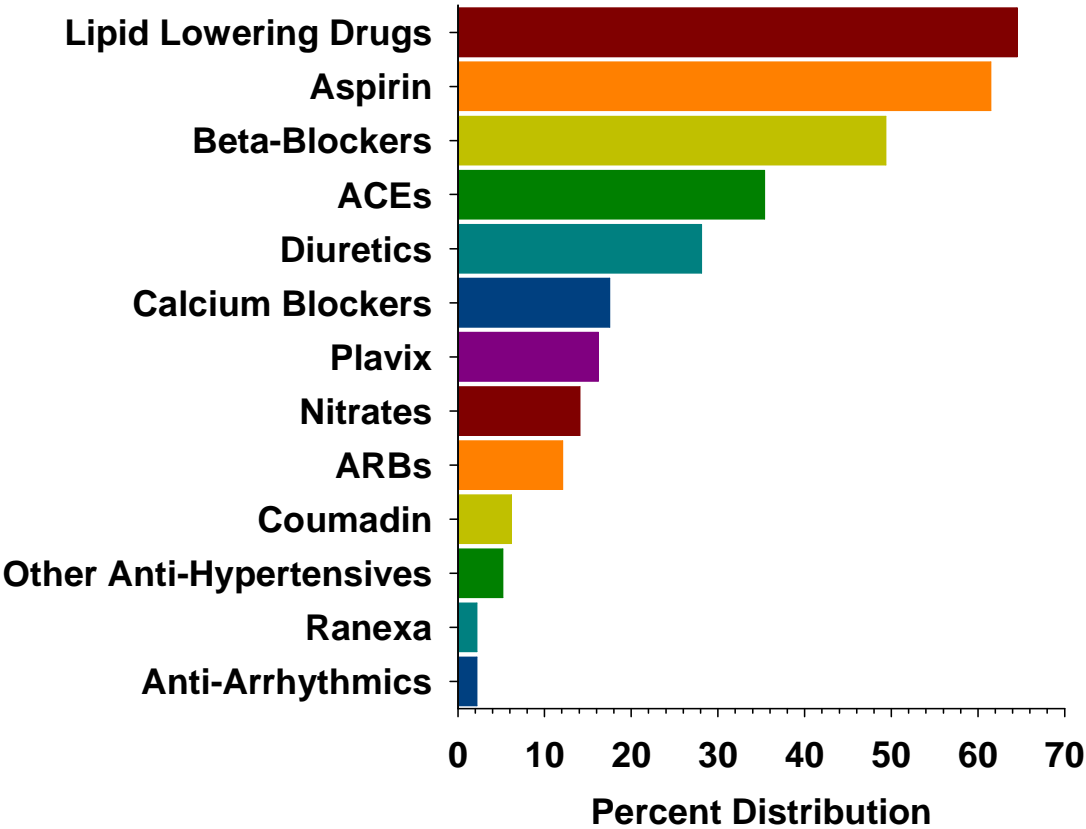
Study 1 Medical History



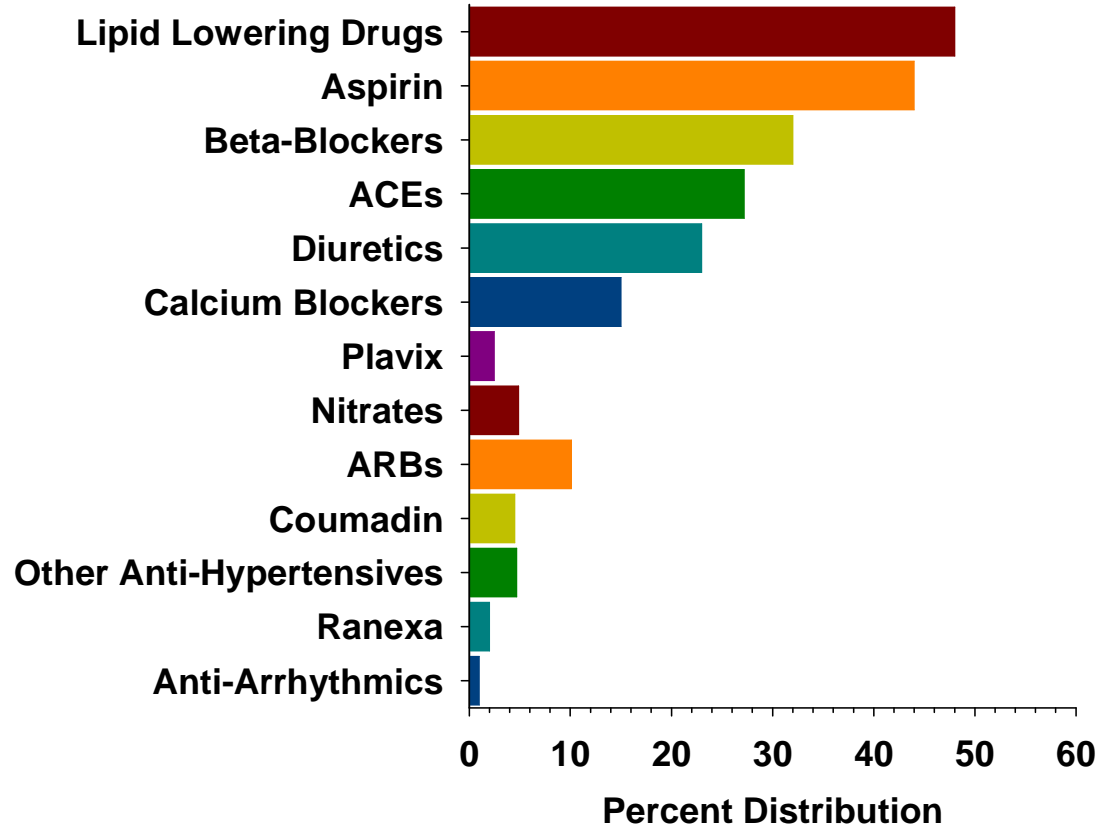
Study 2 Medical History



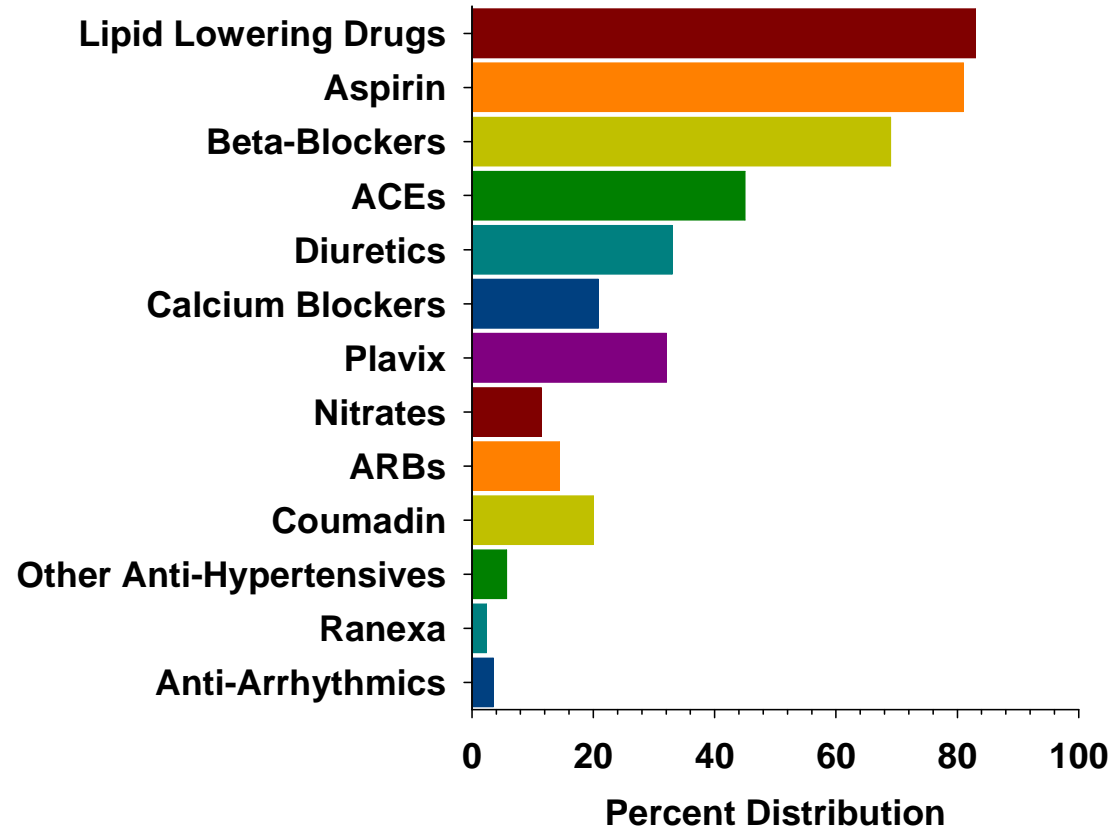
Overall Baseline Medications



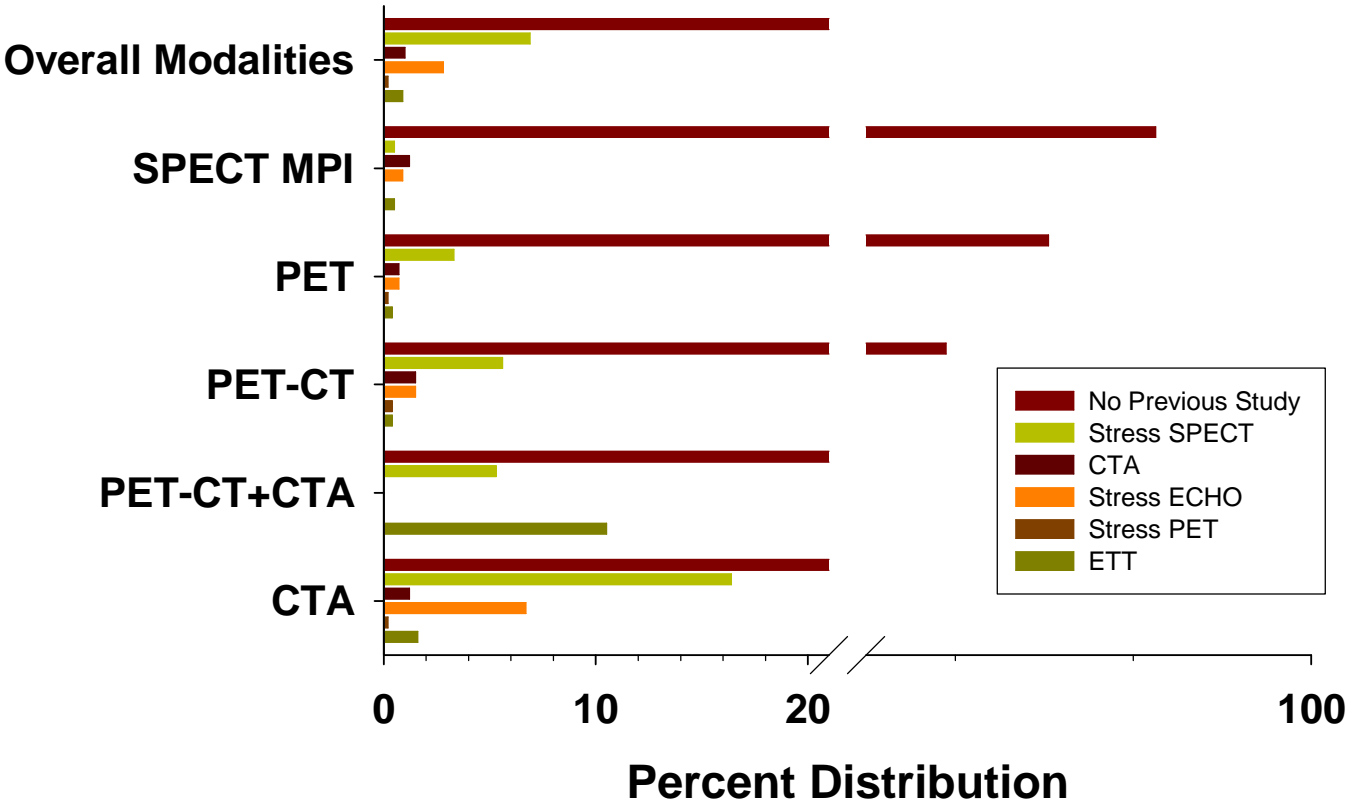
Study 1 Baseline Medications



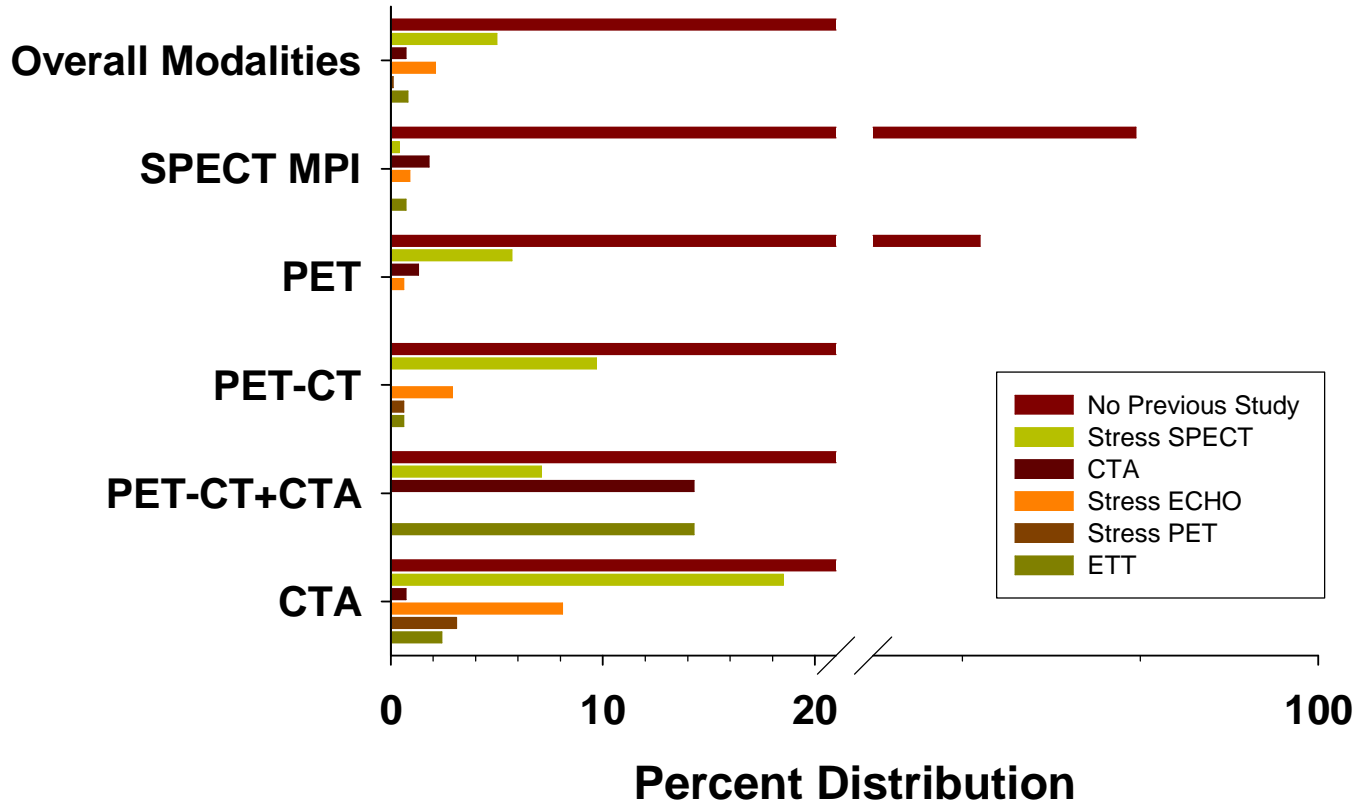
Study 2 Baseline Medications



Overall Previous Cardiac Studies at BL



Study 1 Previous Cardiac Studies at BL



Study 2 Previous Cardiac Studies at BL

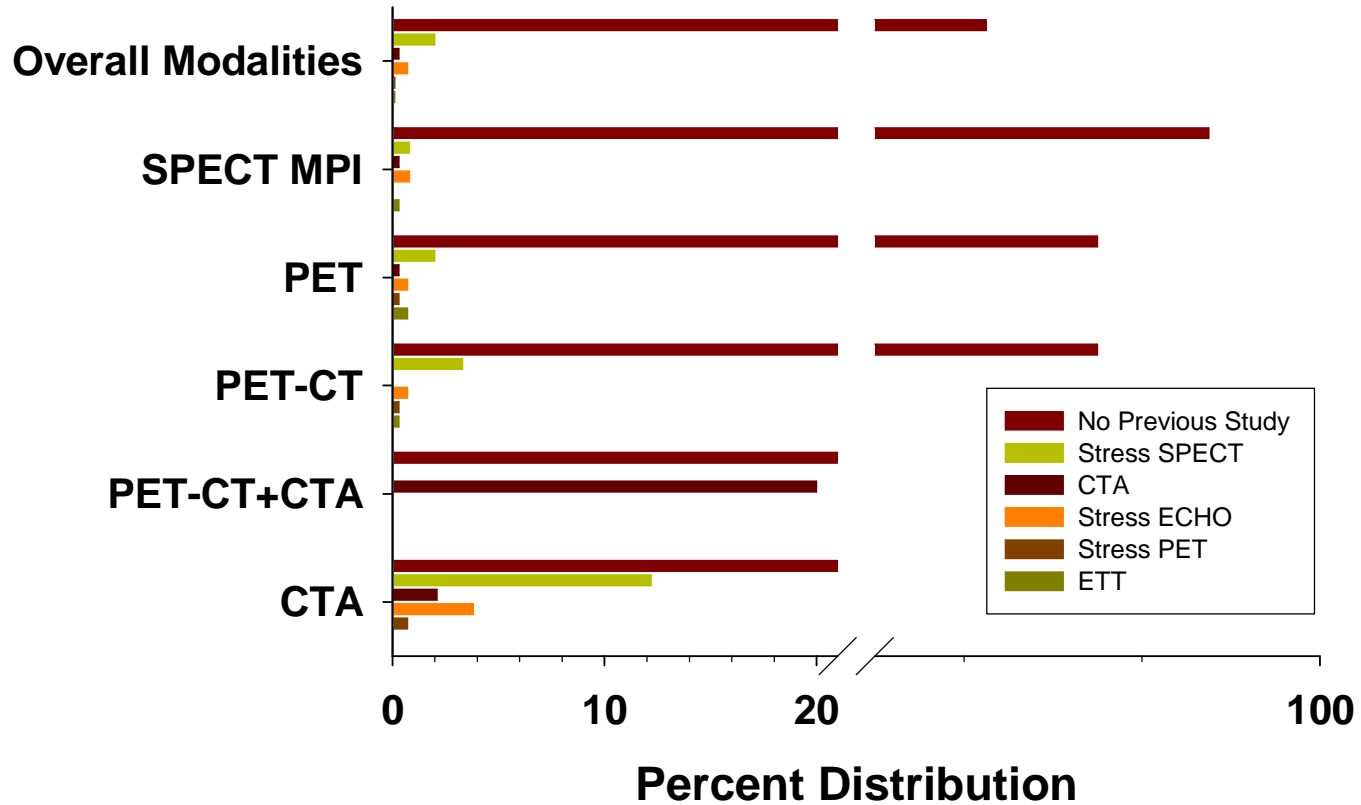
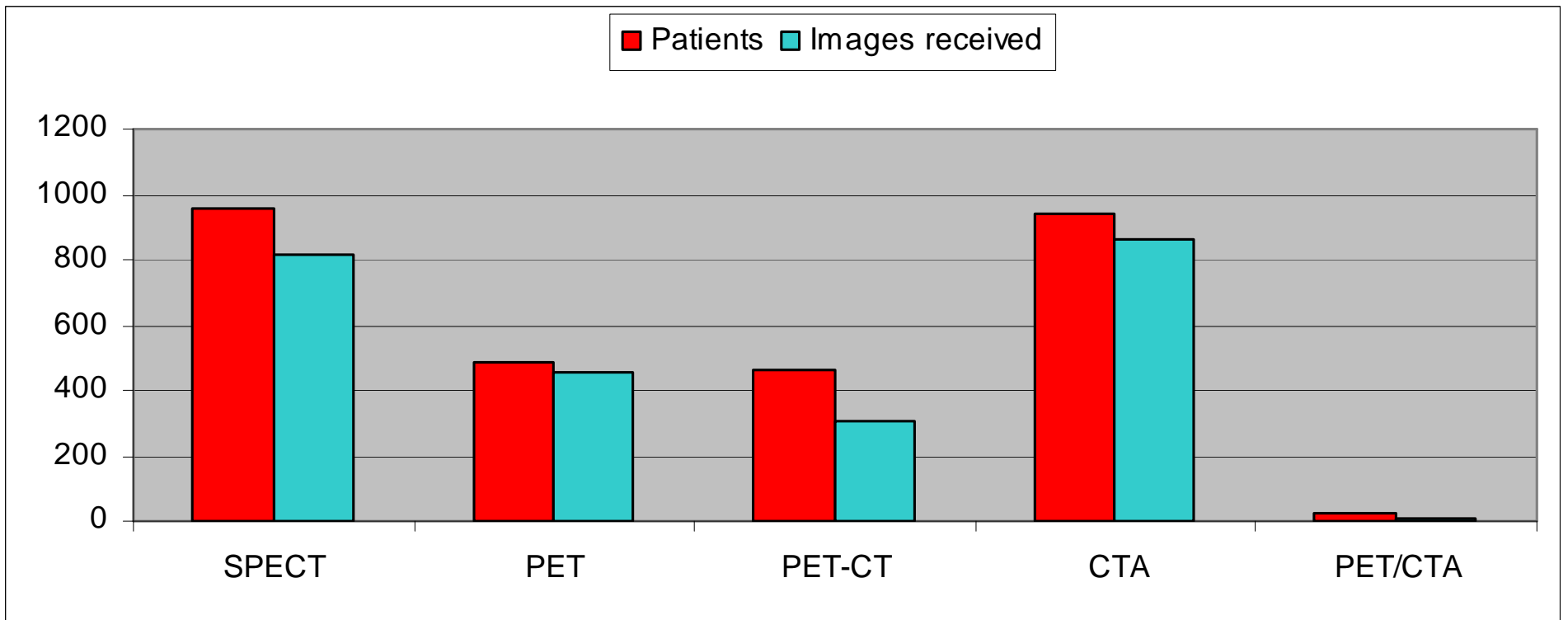


Image Repository Status

Imaging Repository



SPARC QA Imaging Program

SPARC QA Imaging Program

- The QA Test Cases aide in SPARC statistical calculations and are vital to the overall results of the study. It is imperative that site physicians turn in their completed QA Test Cases in a timely fashion.
- As of the April 1, 2007, pay period, recruitment payments will be withheld from site's that are delinquent in their QA Test Case submissions.

Ancillary Studies

Proposed Ancillary Studies

- **Initial invitation for submissions emailed April 17, 2007**
- **To date, 3 received.**
 - **2 acceptable**
 - **1 revisions requested**
- **Anticipate more over time**
- **Priority by date of submission and site enrollment**

Proposed Ancillary Studies

- 1. CTA plaque and outcomes in women**
- 2. Sex-related differences in test utilization and disease**
- 3. Obesity and resource utilization**
- 4. Obesity and adverse events**

Questions and Answers

Thank you for your
participation in SPARC