Post-marketing studies of modalities for screening and diagnosis: the evaluation of effectiveness

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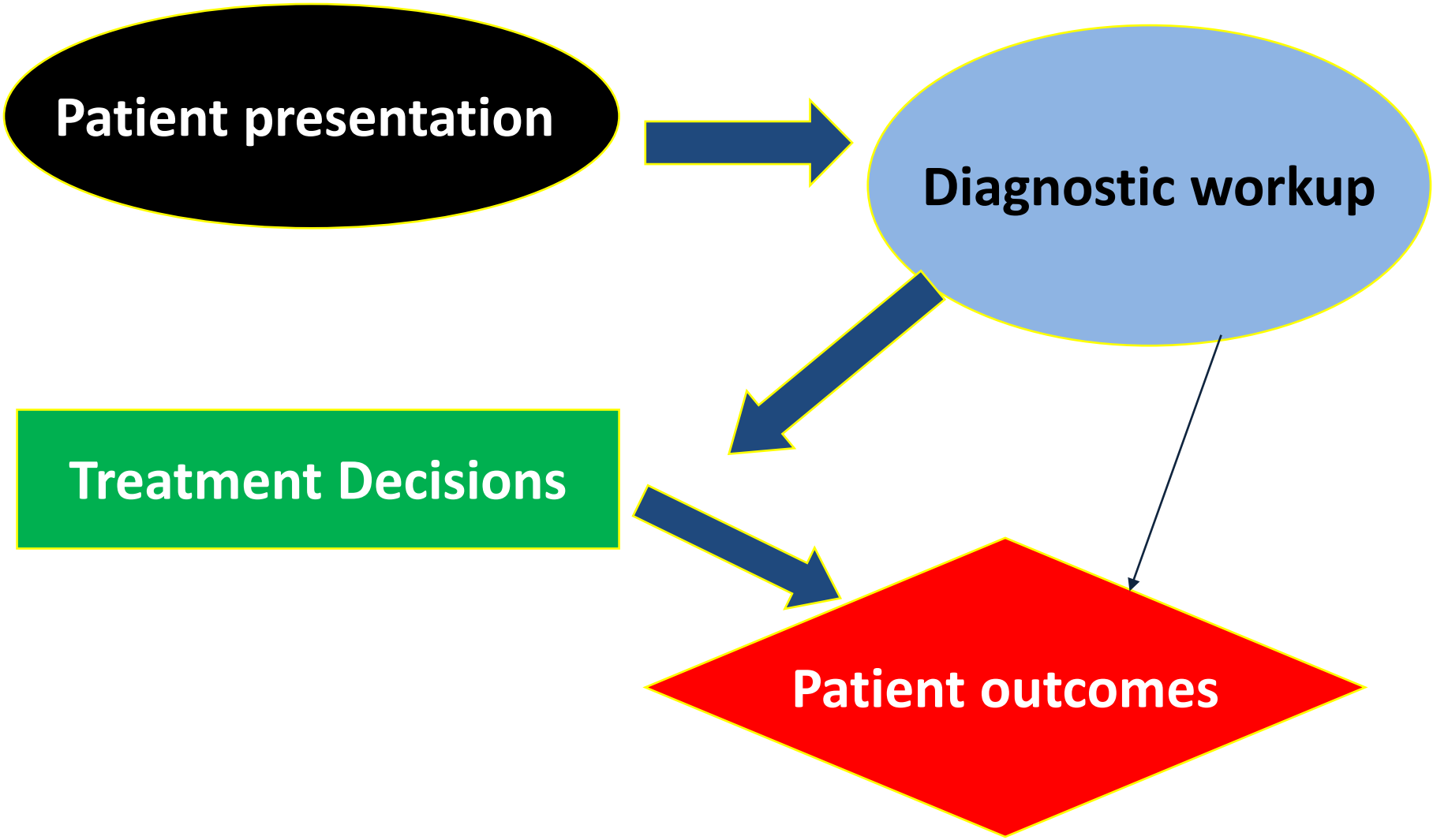
Outline

1. **The evaluation of modalities for diagnosis and prediction: Conceptual Framework**
2. **The assessment of effectiveness via observational studies:**
   - **Large databases: EMR, Health Insurance Claims**
   - **Large registries: The National Oncology PET Registry studies**
   - **Combining registries with administrative and insurance databases**
3. **Closing remarks**

The study of modalities for diagnosis and Prediction: Conceptual Framework

- **Fundamentally tests provide *information* for use in selecting course of care.**
- **Both long- and short-term effects of tests materialize in context of available health care options, including therapeutic interventions.**
- **Not possible to define and measure test effects outside the particular health care context in which the test will be used.**
- **However, oftentimes diagnosis may be *ahead* of therapy: Diagnosis of DCIS; Amyloid plaque imaging for Alzheimer's.**


Patient presentation
Diagnostic workup
Treatment Decisions
Patient outcomes

Main questions in test evaluation

Accurate?

- **Diagnostic performance:**
  - **measures of accuracy in detection**
  - **measures of predictive value**

Affects care??

- **Intermediate process of care:**
  - **Diagnostic thinking/decision making**
  - **Therapeutic thinking/decision making**

Affects Outcomes?

- **Patient outcomes:**
- **Quality of life, satisfaction, cost, mortality, morbidity**

Use of large databases (e.g. EMR, Claims)

- General approach:
  - Construct longitudinal record including test and outcome information.
  - Use methods for observational data to make comparisons.
- Recent examples:
  - Coronary calcium study using Medicare claims.
  - Testing of ER patients with chest pain study using EMR data.

Effectiveness of CAC and hs-CRP testing

Outcomes after coronary artery calcium and other cardiovascular biomarker testing among asymptomatic medicare beneficiaries
Shreibati JB, Baker LC, McConnell MV, Hlatky MA.

***Circ Cardiovasc Imaging*. 2014;7:655-662.)**

- **20% random sample of Medicare beneficiaries**
- **without CVD claims in previous 6 mos.**
- **Propensity score matching of patients receiving CAC and high sensitivity C-reactive protein testing**
- **Compared utilization and outcomes**

Findings

Higher health care utilization and expenditure, fewer CVD related events for patients undergoing CAC testing.

Testing of ER patients with chest pain

Comparative effectiveness of diagnostic testing strategies in emergency department patients with chest pain: an analysis of downstream testing, interventions, and outcomes.
Foy AJ, Liu G Davidson WR Jr, Sciamanna C, Leslie DL.

JAMA Intern Med. 2015;175(3):428-436.

- **>420K ER patients.**
- **Records from 2011 Marketscan**
- **Patients classified into 5 testing strategies**
- **Outcomes compared using regression analysis**

Findings:

More cardiac catheterization and revascularization, no difference in AMI when comparing strategies involving testing to the strategy involving no testing.

Limitations of Claims and EMR data

EMR and claims data often deficient in information about

- **Context of the test (indication, filtering)**
- **Test interpretation and findings**
- **Clinical characteristics of patient**
- **Subsequent diagnostic and therapeutic decisions .**

National Oncologic PET Registry:

A Nationwide Collaborative Program

http://www.cancerpetregistry.org

Sponsored by AMI ACADEMY OF MOLECULAR IMAGING

Advisor CMS CENTERS for MEDICARE & MEDICAID SERVICES

Managed by ACR AMERICAN COLLEGE OF RADIOLOGY ACRIN AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK

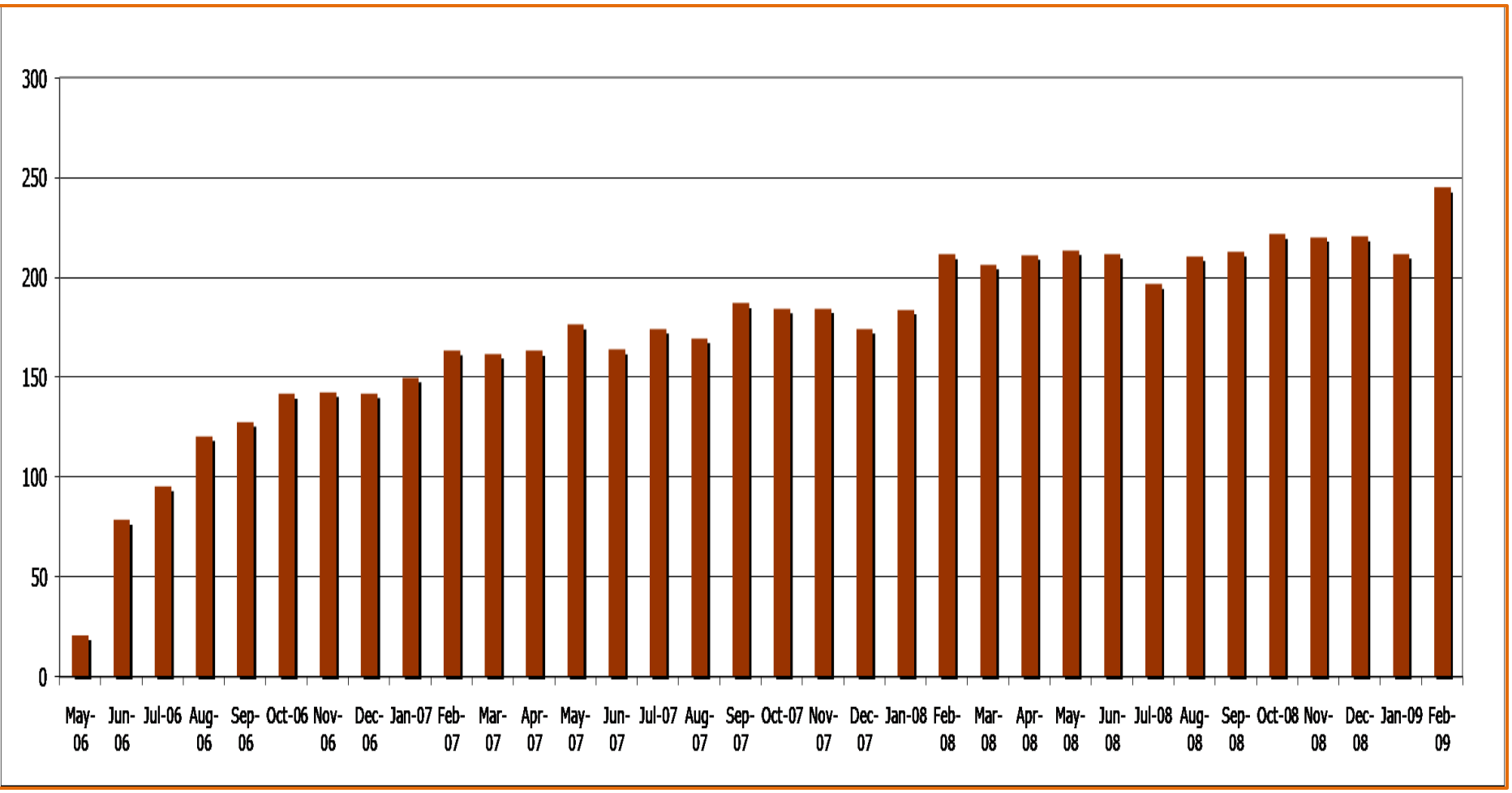
Biostatistics Center at Brown University

Goal:

Assess the effect of PET on referring physicians' plans of intended patient management.

- across a wide spectrum of cancer indications for PET, not covered currently by the Medicare program,
- in relation to cancer-type, indication, performance status, physician's role in management, and scan type

NOPR Accrual (Cases Completed/Business Day)



More than 200,000 patients registered

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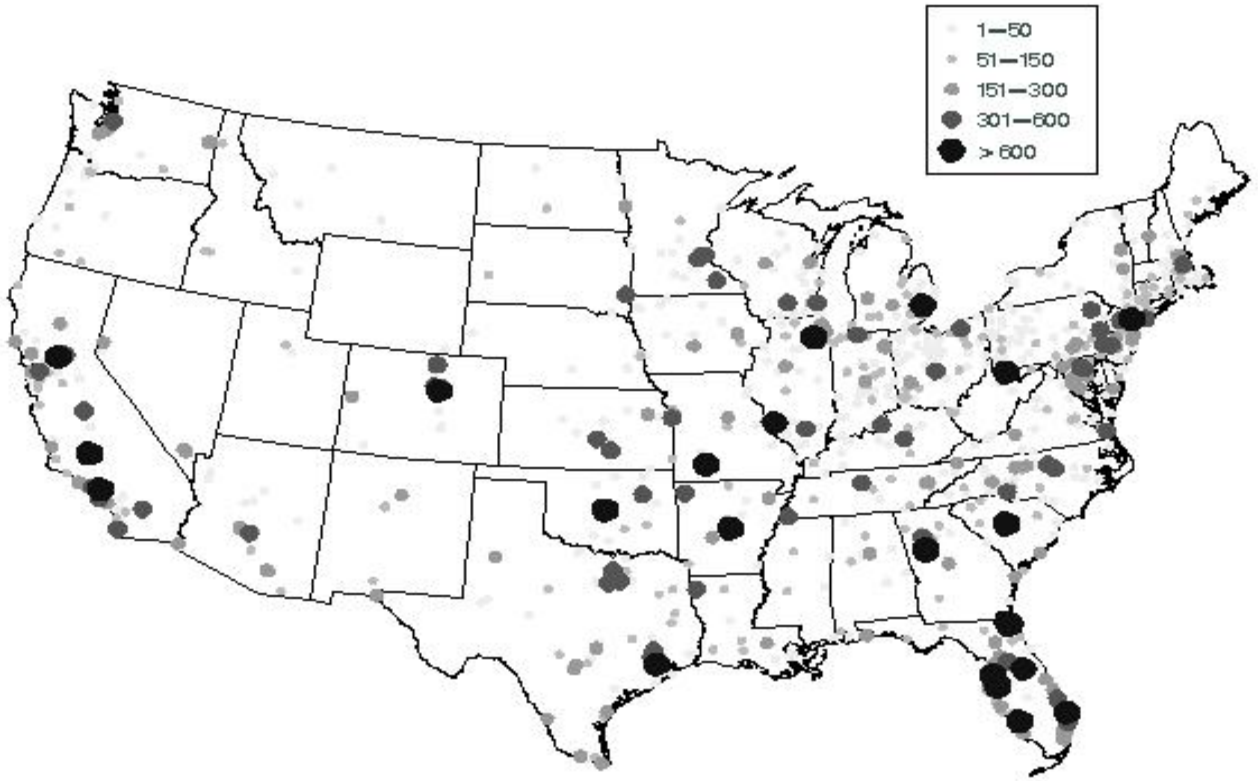
National coverage of NOPR registry (2006-2009)



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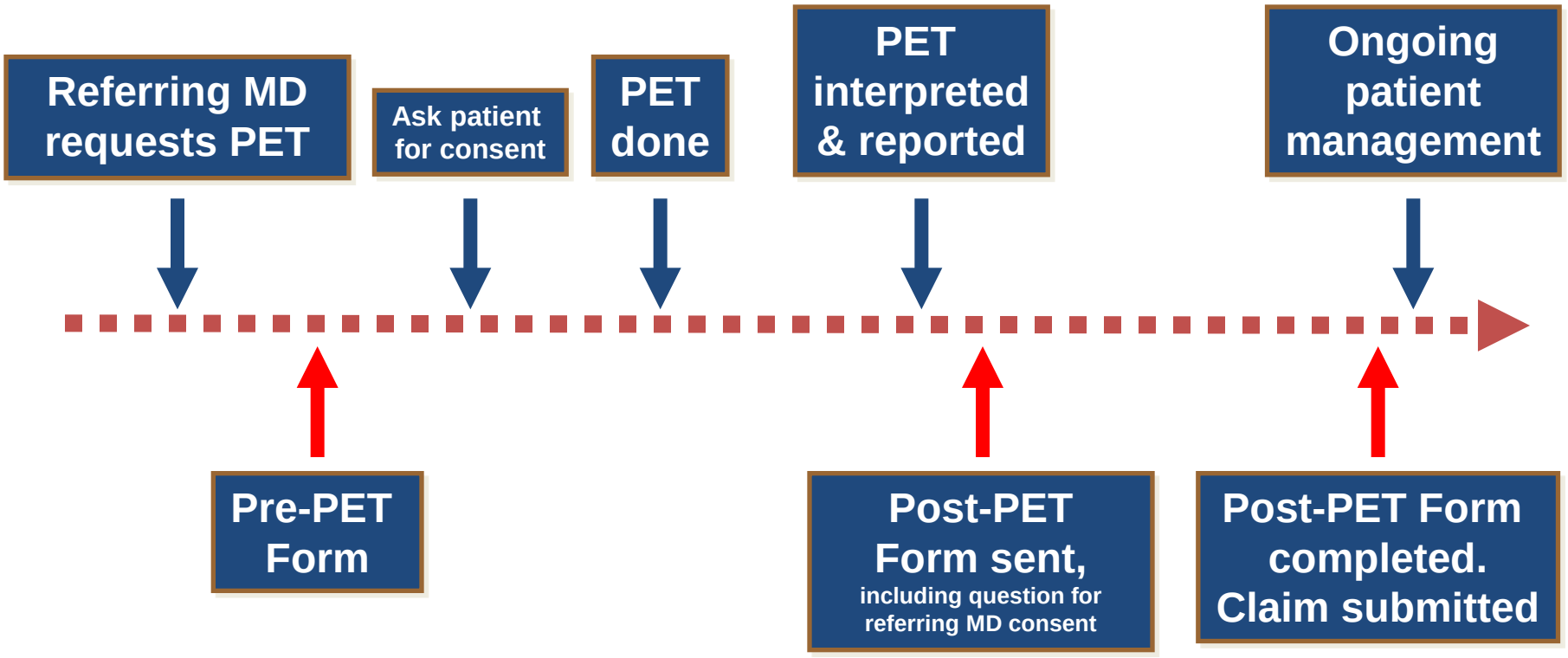
NOPR Workflow



Pre-PET Form: Intended Patient Management

If PET were not available, your current management strategy would be (select one)?

- ❑ **Observation (with close follow-up)**
- ❑ **Additional imaging (CT, MRI) or other non-invasive diagnostic tests**
- ❑ **Tissue biopsy (surgical, percutaneous, or endoscopic).**
- ❑ **Treatment (if treatment is selected, then also complete the following)**

  Treatment Goal: *(check one)* ❑ **Curative** ❑ **Palliative**

  Type(s): *(check all that apply)*

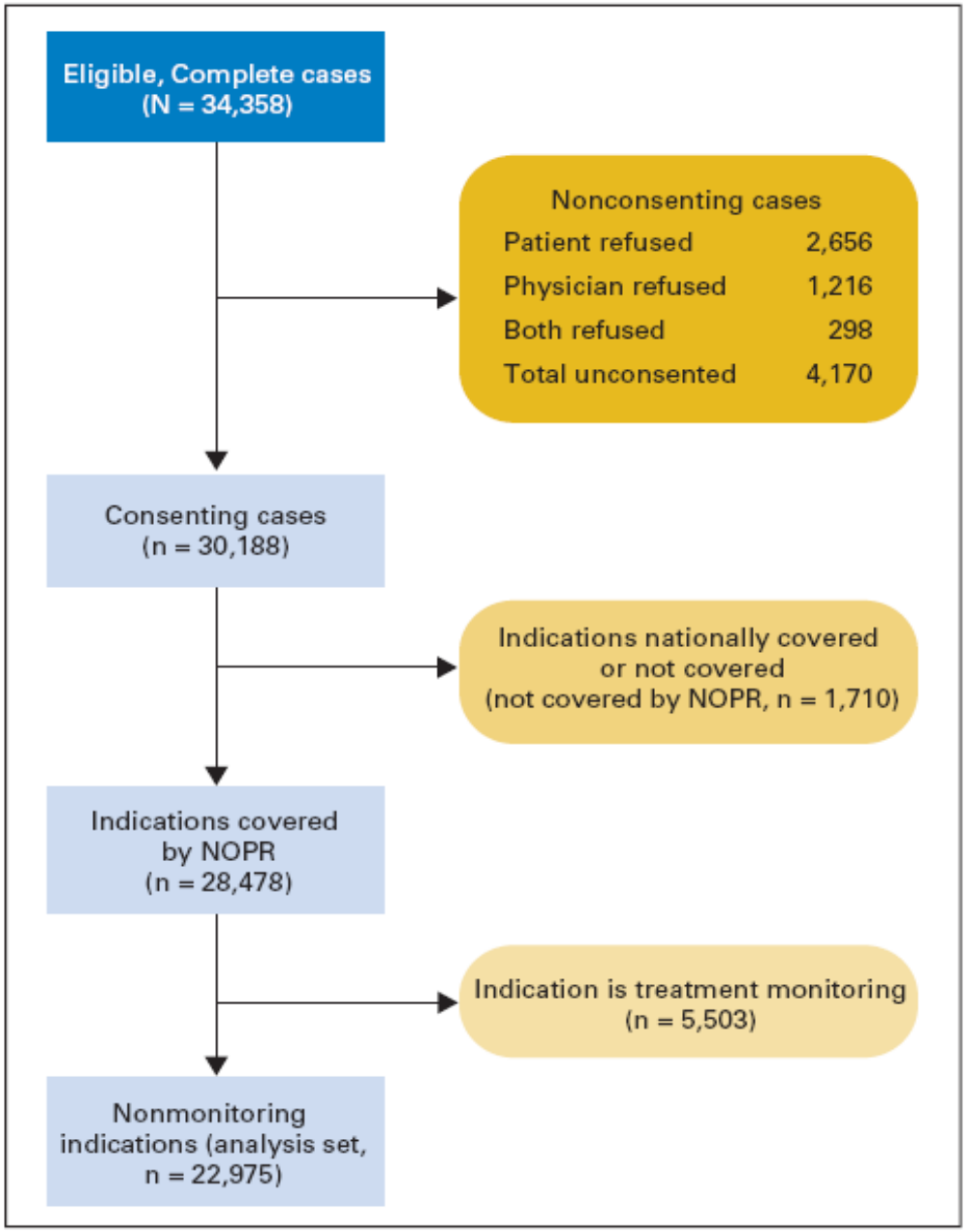
  – ❑ **Surgical** ❑ **Chemotherapy (including biologic modifiers)**

  – ❑ **Radiation** ❑ **Other** ❑ **Supportive care**

Intended management, given PET findings, asked on post-PET form

Cohort Profile

- First year of NOPR (5/8/06 to 5/7/07)
- 22,975 “consented” cases from 1,519 facilities
- Technology profile
  - 84% PET/CT
  - 71% non-hospital
  - 76% fixed sites



Hillner et al., J Clin Oncol 2008

PET Changed Intended Management in 36.5% of Cases

		Clinical Indication for PET Study (Percent)				
Pre-Pet Plan	**Post-PET Plan**	**Dx** n=5,616	**Staging** n=6,464	**Restaging** n=5,607	**Recurrence** n=5,388	**All** n=22,975
Treat	Same	**16.0**	**46.5**	**15.8**	**20.4**	**25.5**
Non-Treat	Same	**52.9**	**14.0**	**48.0**	**40.7**	**37.9**
Non-Treat	**Treat**	**23.2**	**31.6**	**28.6**	**29.2**	**28.3**
Treat	**Non-Treat**	**7.9**	**7.9**	**7.5**	**9.7**	**8.2**
Patients with change post-PET (%)		**31.1**	**39.5**	**36.1**	**39.0**	**36.5**

Hillner et al J Clin Onc 2008

Summary of NOPR Results (*Before 2009 NCD)*

Overall Impact on Patient Management

- Diagnosis, Staging, Restaging, Recurrence
- Data on 22,975 scans from May 8, 2006 – May 7, 2007
- *J Clin Oncol* 2008; 26:2155-61

Impact on Patient Management by Cancer Type

- Confirmed Cancers
- Staging, Restaging, Recurrence
- Data on 40,863 scans from May 8, 2006 – May 7, 2008
- *J Nucl Med* 2008; 49:1928-35

Treatment Monitoring

- Data on 10,447 scans from May 8, 2006 – Dec 31, 2007
- *Cancer* 2009:115:410-18

Do NOPR findings agree with those from

- other studies or
- other sources of information on the same participants

Australian Prospective Studies of Impact of PET Agreement in Post-PET Plan and Actual Care (2003-2006)

Cancer	Pts	Centers	Indication	Change in Plan	F/U (mo.)	Agree-ment
Ovarian	90	3	SR	58.9	6	67.8
Esophagus	129	5	IS	38.0	12	53.2
Lymphoma	74	6	IS	34.0	6	74.3
Colorectal	93	4	SR	65.6	6	62.0
Colorectal	98	4	Resect Hepatic	49.0	6	70.1
Head/Neck	71	3	IS	33.8	3	74.7

SR: Suspected Recurrence. IS: Initial Staging

Combining registries with administrative and insurance databases

- Linking NOPR and CMS claims data

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NOPR linked to CMS claims data

Approach

- **Construct health care utilization history using CMS claims data**
- **Cohort of 8640 consenting registry participants, age 65+, enrolled in 2007-2008 undergoing PET for cancer restaging.**
- **Extensive database work involved to identify patterns of care and classify into post-PET treatment categories.**

(Med Care 2013; 51: 361–367)

Intended Versus Inferred Management After PET For Cancer Restaging

Analysis of Medicare Claims Linked to a Coverage With Evidence Development Registry

Bruce E. Hillner, MD, Tor D. Tosteson, ScD,† Anna N. A. Tosteson, ScD,† Qianfei Wang, MS,† Yunjie Song, PhD,† Tracy Onega, PhD,† Lucy G. Hanna, MA,‡ and Barry A. Siegel, MD§*

Agreement of Post-PET Plan and Claims-inferred Actions at 30 Days

Med Care 2013;51: 361–367

	Bladder	Ovary	Stomach
Patients (total), n	1127	2075	632
Systemic tx only planned, n	261	811	134
PPV (%)	66.7	65.0	51.5
Raw agreement (%)	71.2	71.1	65.7
k	0.33	0.40	0.17
Radiation only planned, n	71	46	34
PPV (%)	74.6	67.4	35.3
Raw agreement (%)	89.4	96.9	95.3
k	0.42	0.48	0.23
Surgery only planned, n	50	87	37
PPV (%)	44.0	57.5	35.3
Raw agreement (%)	84.5	89.5	86.7
K	0.14	0.27	0.16
Biopsy planned, n	150	176	85
PPV (%)	64.7	55.1	48.2
Raw agreement (%)	74.4	80.5	75.2
K	0.27	0.23	0.21
Watching, n	473	804	320
PPV (%)	70.8	74.1	66.3
Raw agreement (%)	71.0	69.1	60.8
k	0.41	0.38	0.21

Conclusion: **Moderate concordance**

Intended vs Inferred Care after PET for initial staging

Cohort of 4661 consenting registry participants, age 65+, enrolled in 2007-2008. PET for initial cancer restaging.

	N	PPV	Agreement	Kappa
Any systemic tx				
All	3,030	79.3	74.1	0.40
Bladder	676	79.0	73.0	0.42
Ovarian	223	86.1	82.5	0.52
Stomach	648	67.6	67.6	0.34
Any radiation				
All	1,293	64.7	80.8	0.53
Bladder	337	68.8	83.3	0.60
Ovarian	23	30.4	91.6	0.32
Stomach	250	48.8	79.0	0.39
Any surgery				
All	1,031	63.6	77.9	0.43
Bladder	248	56.9	75.8	0.36
Ovarian	57	52.6	75.9	0.31
Stomach	458	71.4	75.7	0.50

J Nucl Med 2013 54:2024–2031

Conclusion

Better concordance than in restaging PET

Intended Versus Inferred Care After PET Performed for Initial Staging in the National Oncologic PET Registry

Bruce E. Hillner[1], Anna N. Tosteson[2], Tor D. Tosteson[2], Qianfei Wang[2], Yunjie Song[2], Lucy G. Hanna[3], and Barry A. Siegel[4]

NOPR strengths

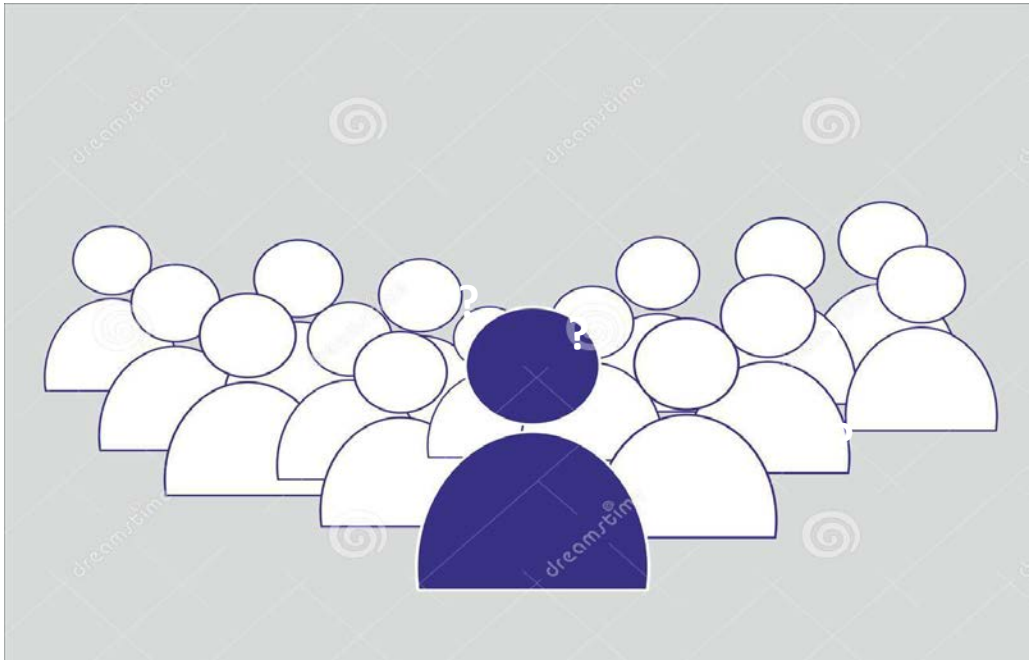
- **Provided extensive, timely, "real world" data, that are very difficult and expensive to collect in clinical trials.**
- **Prospectively organized and controlled data collection**
- **Registry data can be effectively linked to data from other information sources**
- **Results consonant with more tightly controlled studies (later in presentation)**
- **Supports the Coverage with Evidence Decisions approach of CMS**

NOPR weaknesses (long list!)

- Evidence documents change in ***intended*** management, not *actual* management
- No evaluation of whether management changes were **appropriate.**
- No information on whether the use of PET improved **long-term outcomes**
- How should PET should be used in the flow of patient care.
- Plus the concerns about generalizability and bias in data obtained from registries

Combining registries with administrative and insurance databases

- **Amyloid plaque imaging:** Comparison of
  - Registry of participants undergoing Dx, and
  - Matched Controls identified from CMS claims data



A harder case: Diagnosis ahead of therapy
Imaging Amyloid Plaques (PIB-PET)

Amyloid vs.FDG-PET in Differential Diagnosis of AD vs. FTD

AD (N=62, age 65, MMSE 22)

FTD (N=45, age 65, MMSE 22)

Rabinovici et al. Neurology 2011
Rabinovici et al. AAN 2014

Amyloid (PIB) PET visual reads

- 90% sensitivity, 83% specificity
- Inter-rater agreement κ=0.96

FDG-PET visual reads

- 78% sensitivity*, 84% specificity
- Inter-rater agreement κ=0.72*

47 autopsy-proven cases

- PIB: Sensitivity 100%, Specificity 90%
- FDG: Sensitivity 87%, Specificity 78%

Klunk et al., Ann Neurol 2004

Amyloid vs. FDG-PET in Differential Diagnosis of AD vs. FTD

AD (N=62, age 65, MMSE 22)

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PET Amyloid Imaging

- **Imaging biomarkers for amyloid deposits have been approved by FDA:**
  - **^{18}F-florbetapir in April 2012,**
  - **^{18}F-flutemetamol in October 2013**
  - **^{18}F-florbetaben in March 2014**
- **CMS National Coverage Decision in September 2013**
- **Coverage for one study per patient, *but only under CED* to:**
  - **Develop better treatments or prevention strategies for AD, or, as a strategy to identify subpopulations at risk for developing AD**
  - **Resolve clinically difficult differential diagnoses (e.g., FTD vs. AD) with goal of improving health outcomes (including short term outcomes related to changes in management as well as longer term dementia outcomes).**

Key challenges

- **Best target population (age range?; MCI vs. atypical dementia?)**
- **No established clinical management algorithms based on scan results (unlike situation for FDG-PET in cancer)**
- **No good historical control data**
- **Some patient-centered outcomes will take quite long to be detectable (slowing of functional decline vs. avoiding futile Rx)**

IDEAS (Imaging Dementia—Evidence for Amyloid Scanning)

Two main goals:

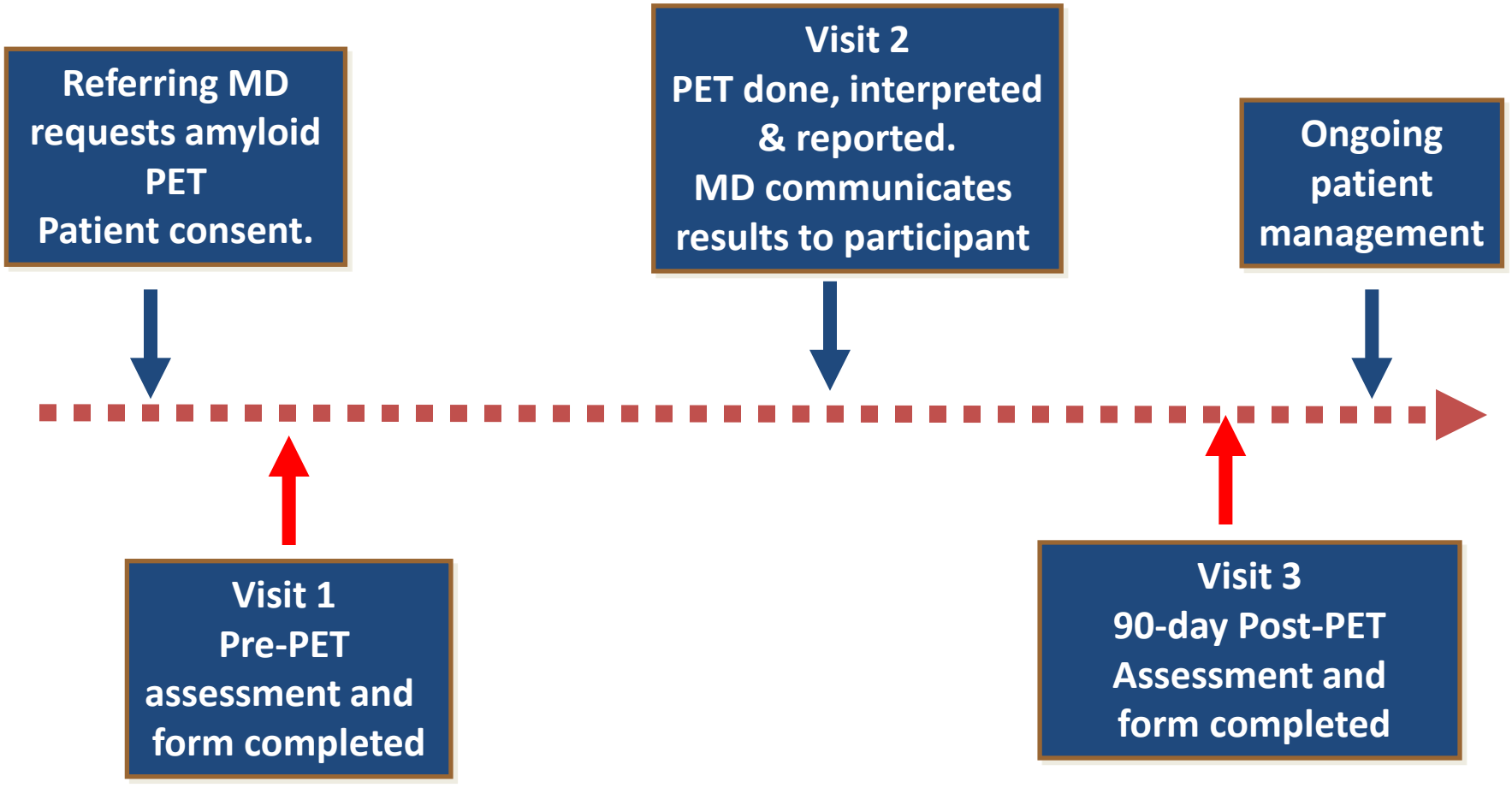
- **Aim 1: To assess the impact of amyloid PET on the management of patients meeting Appropriateness Use Criteria .**
  - **This aim will be addressed using a registry of participants undergoing amyloid PET.**
- **Aim 2: To compare hospital admissions and emergency room visits within 12 months in patients enrolled in the registry to matched controls (no amyloid PET), to be identified from CMS claims data.**
  - **This aim will be addressed using registry and CMS claims data.**
- **https://clinicaltrials.gov/ct2/show/NCT02420756?term=IDEAS&rank=1**

IDEAS study (under development)

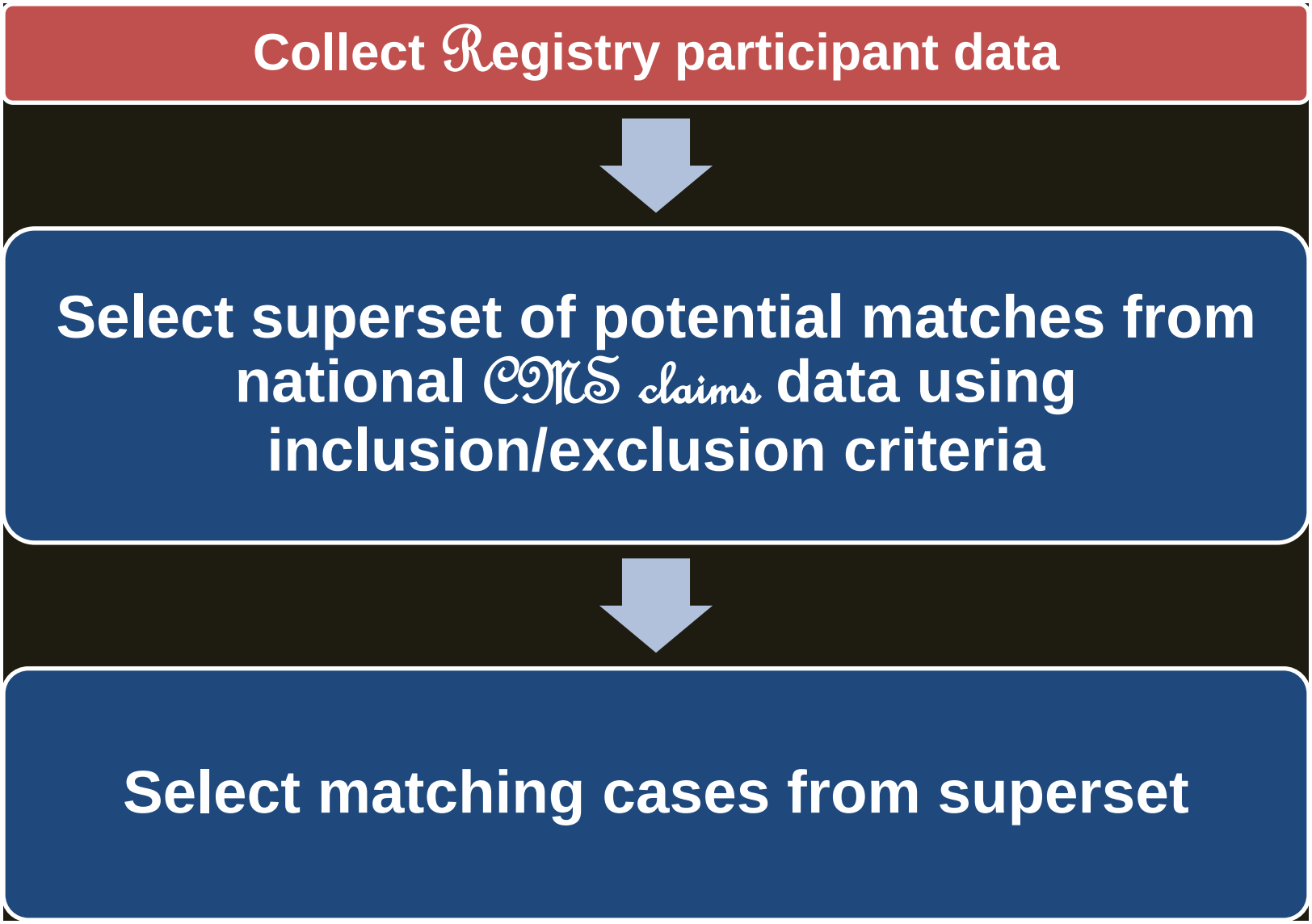
Organization:

- **Working collaboration of researchers from NOPR Working Group, Alzheimer's Association, SNMMI, American College of Radiology Imaging Network, and Brown Biostatistics.**
- **Stakeholders from industry and professional organizations.**
- **Support from industry and from CMS (coverage of scans)**

IDEAS Registry Workflow (main steps)



Streamlined process flow of selection of controls



Control group construction: Selection of superset

	Criterion	Factors/Examples	Time
1	New Diagnosis of MCI or Dementia*	CMS claims related to dementia and MCI in the 24 mo. prior to IDEAS Study initiation	≥24 mo.
1A	MCI CODE	331.83 Mild cognitive impairment -other codes to be selected in sensitivity analysis	
1B	DEMENTIA CODE: Prior to structural imaging Inconsistent claims patterns*	≥2 different categories of dementia codes or >2 claims with exclusively limited to non-specific dementia codes) occurring within a two year (24 month) time interval	
2	Minimal Structural Brain Tests Minimal Blood Laboratory w/u	Head MRI or CT (+/-) CBC, standard blood chemistry profile, TSH, vitamin B12	<12 mo.
3	Exclude cases with unanticipated brain pathology on intake MRI/CT	Such as primary or metastatic cancers at time of match and at baseline for contemporaneous cohort	
4	Exclude cases with: - All Non-Skin Cancers, Lymphomas, Hematologic Malignancies - Hip/Pelvic Fracture		<12 mo.

Control group construction: Matching criteria

	Criterion	Factors/Examples	Time
1	Age	Minimal age of 66 to 67 years	+/-24mo.
2	Gender		N.A.
3	Marital status		N.A.
4	Ethnicity		N.A.
5	Location/Service Area	Hospital Referral Region (n=306)	N.A.
6	Match Chronic Condition Warehouse per table below: Focus is on conditions related to hospitalizations	Match on number or specifics of associated CMS Codes. Non-CHF heart disease is an aggregate of Acute MI, A fib,, HTN, and CAD/IHD), CKD, COPD, diabetes	<24 mo.
7	Match for Chronic Neurological Conditions, not included in Warehouse	Prior stroke, TIA, PD, MS, epilepsy, TBI	<24 mo.
8	Hospitalization/Emergency Room Visits	Dementia or delirium	<12 mo.
9	Medicare/Medicaid Eligibility	Single or dual eligibility	N.A.

Sample size considerations

***Aim 1 Hypothesis*: Determine whether amyloid PET imaging will lead to a ≥ 30% change between intended and actual patient management within 90 days in a composite measure consisting of the following:**

a) AD drug therapy; b) Other drug therapy; or

c) Counseling about safety and future planning

N=11,050 for 80% power (separate analyses for dementia and MCI subgroups)

***Aim 2 Hypothesis:* Determine whether amyloid PET is associated with a ≥ 10% *relative* reduction in registry patients in comparison to matched controls in the following endpoints: a) Inpatient hospital admissions over 12 months. b) Emergency room visits over 12 months**

N= 18,500 for 90% power (separate analyses for each endpoint)

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In closing

- **Linking tests to downstream outcomes is a challenging undertaking.**
- **Large secondary databases can be used, but may lack necessary information.**
- **Registries offer flexibility but typically have narrow focus.**
- **Combination of information from several sources holds promise.**

Thank you!