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Inorganic Nitrite Delivery to Improve Exercise Capacity in HFpEF

INDIE-HFpEF

A Randomized Clinical Trial

Barry A. Borlaug
On behalf of the
NHLBI Heart Failure Clinical Research Network

U.S. Department of Health and Human Services
National Institutes of Health

NIH National Heart, Lung, and Blood Institute

Heart Failure Clinical Research Network

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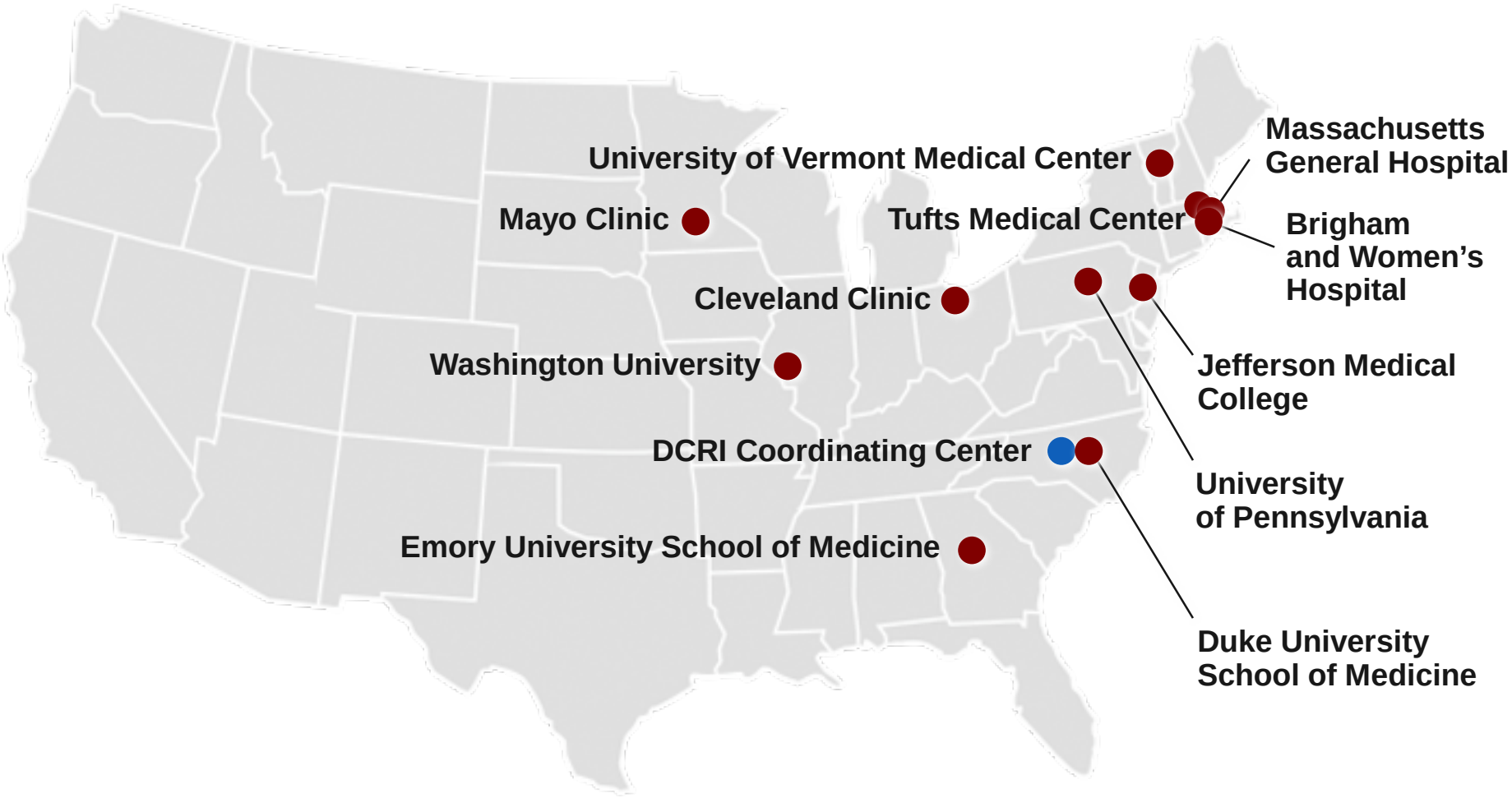

- Regional Clinical Centers
- Coordinating Center

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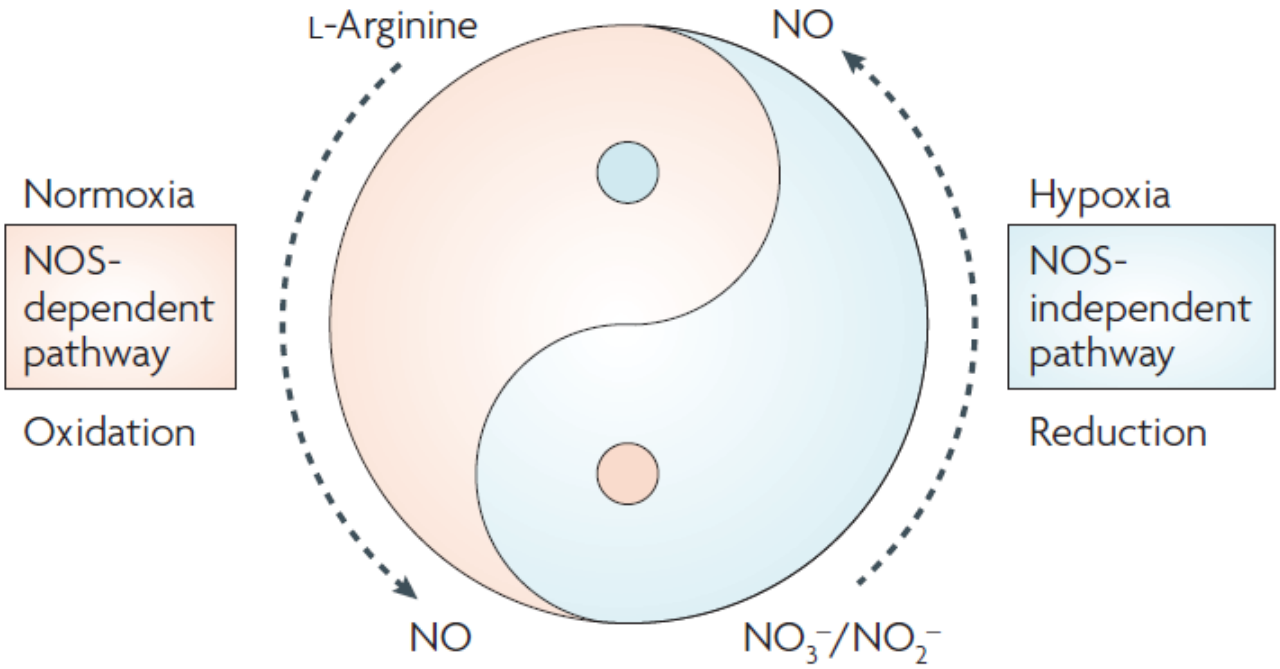
Background

- Exercise intolerance, manifest by dyspnea and fatigue, is a cardinal feature of HFpEF.
- Evidence suggests that impaired nitric oxide (NO) signalling plays key role in pathophysiology of HFpEF
- Prior efforts to improve NO with organic nitrates in HFpEF have failed
  - Poorly tolerated (ISDN)
  - Reduced activity levels (ISMN)

Background

Inorganic Nitrite: Novel NO providing therapy



Lundberg et al. *Nat Rev Drug Disc* 2008

Background

- Nitrite can be delivered by inhaled, nebulized administration
  - PK similar to intravenous route
- Small, single center studies have shown improvements in hemodynamics and exercise capacity with inorganic nitrite/nitrate in HFpEF
- No data available on longer term use in HFpEF

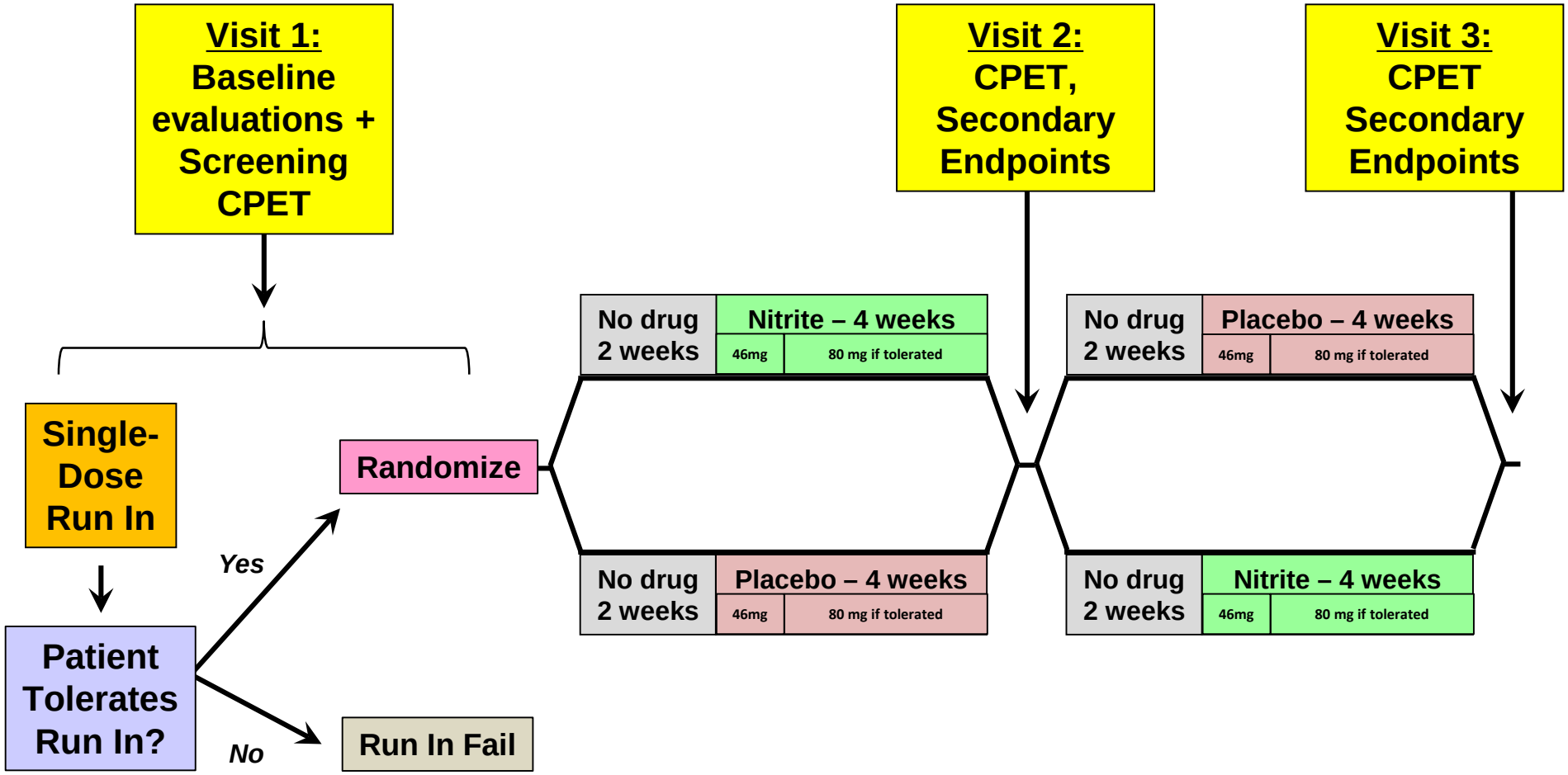
Hypothesis

- As compared to placebo, 4 weeks treatment with inhaled, nebulized inorganic nitrite will improve peak exercise capacity in HFpEF patients as assessed by cardiopulmonary exercise testing (CPET).

Study population

- NYHA class II-IV HF symptoms + EF ≥ 50%
- Objective evidence of HF (at least one)
  - *HF hospitalization*
  - *Elevated NT-proBNP or BNP*
  - *Elevated rest or exercise PAWP at RHC*
  - *Echo Doppler DD + Loop diuretic*
- Reduced exercise capacity (peak VO_2≤75%)
- Identify HF symptoms as the primary factor limiting ability to be active on questionnaire
  - *Versus neurologic, orthopedic or life-style factors*

Study Design: *Randomized, double-blind, placebo-controlled crossover study*



INDIE Primary End-point

- Peak oxygen consumption (Peak VO_2) during cardiopulmonary exercise testing

Secondary End-points

- Daily activity by patient-worn accelerometer
  - *Arbitrary activity Units (AAU)*
- Other standard HF endpoints
  - *HF specific quality of life (KCCQ)*
  - *NT-proBNP levels*
  - *NYHA functional class*
  - *Echocardiographic indicators of congestion*
  - *Other Exercise Endpoints*
- Safety and tolerability

Crossover Analysis

- Intention to treat
- Mixed Model: Treatment Effect (Nitrite-Placebo)
  - *Sequence effect*
  - *Period effect*
  - *Random effect of each patient*
- 105 patients powered to detect:
  - *0.6 ml/min*kg difference in peak VO_2 (>80%)*
  - *2.5% change relative to baseline in AAU (>90%)*
  - *5 pts difference in KCCQ (>80%)*

Baseline Features

Characteristic	Placebo 1st (n=52)	Nitrite 1st (N = 53)
Age (years)	68	68
Female	44%	68%
White race	87%	89%
BMI (kg/m^2)	35.0	35.6
HF hsp in past year	19%	25%
Hx hypertension	81%	81%
Ischemic etiology	71%	68%
Diabetes	33%	38%
Hx of atrial fibrillation	45%	45%

Mean values or % shown

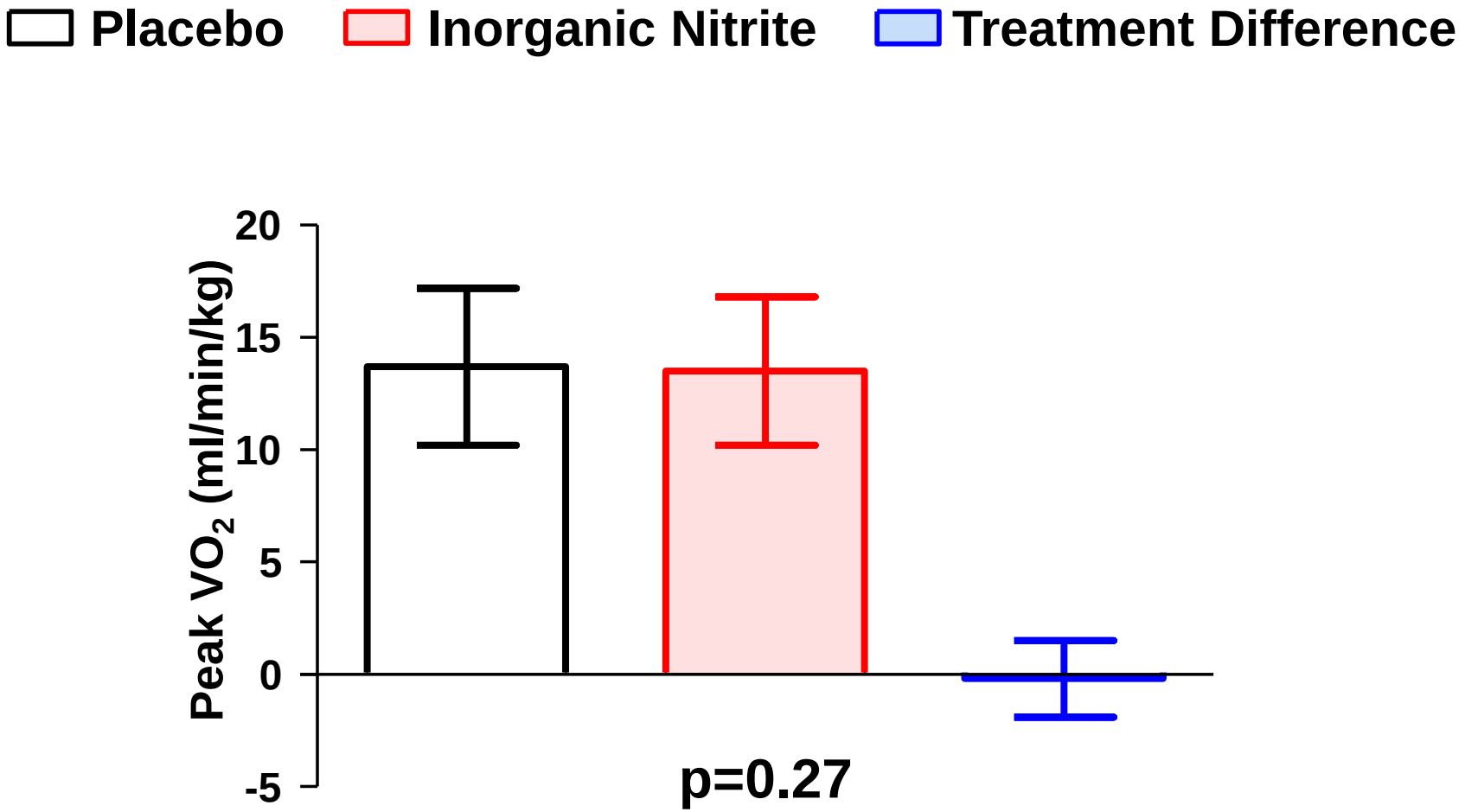
All p > 0.05 except sex

Baseline Features

Characteristic	Placebo 1st (n=52)	Nitrite 1st (N = 53)
Systolic BP	131	130
NYHA class II/III	38% / 62%	47% / 51%
Peak VO_2 (ml/kg/min)	13.8	13.9
KCCQ (higher better)	52	59
Ejection fraction (%)	61	61
NT-proBNP (pg/ml)	528	471

Mean values or % shown

Primary Endpoint



Secondary Endpoints

	Placebo	Nitrite	P value
Accelerometry			
Arbitrary units	5503	5497	0.91
Relative to BL (%)	97%	100%	0.60
KCCQ (Lower worse)	60.8	61.8	0.32
NT-proBNP (pg/ml)	533	520	0.74
NYHA class	2.5	2.5	0.43

Data are the model derived estimates of the mean treatment value

Secondary Endpoints

	Placebo	Nitrite	P value
Systolic BP (mmHg)	124	121	0.10
E/e' ratio (trough)	16.6	16.4	0.93
LA volume index (ml/m^2)	39	38	0.82
PASP (mmHg)	37	38	0.47
Ventilatory efficiency	33.0	32.7	0.11
Exercise Duration (min)	11.0	10.8	0.30

Data are the model derived estimates of the mean treatment value

Safety / Tolerability Endpoints

Characteristic	Placebo (n=105)	Nitrite (n=105)
Discontinued study drug	5	8
Any Event of Interest	11	6
Arrhythmia	2	1
Worsening HF	8	3
Stroke	0	0
Syncope	1	0
SAE - Death	0	1
SAE - Any	4	5

All p > 0.05

Summary

- As compared to placebo, inhaled, nebulized inorganic nitrite did not improve peak exercise capacity, daily activity levels, quality-of-life scores, NT-proBNP levels, or other indicators of clinical status in patients with HFpEF.

Conclusions

- These data do not support use of inhaled, nebulized inorganic nitrite for symptom relief in patients with HFpEF.
- Further study is urgently needed to identify effective, alternative interventions to restore NO-related signaling deficiencies and improve clinical status in HFpEF.

Thank you for your attention

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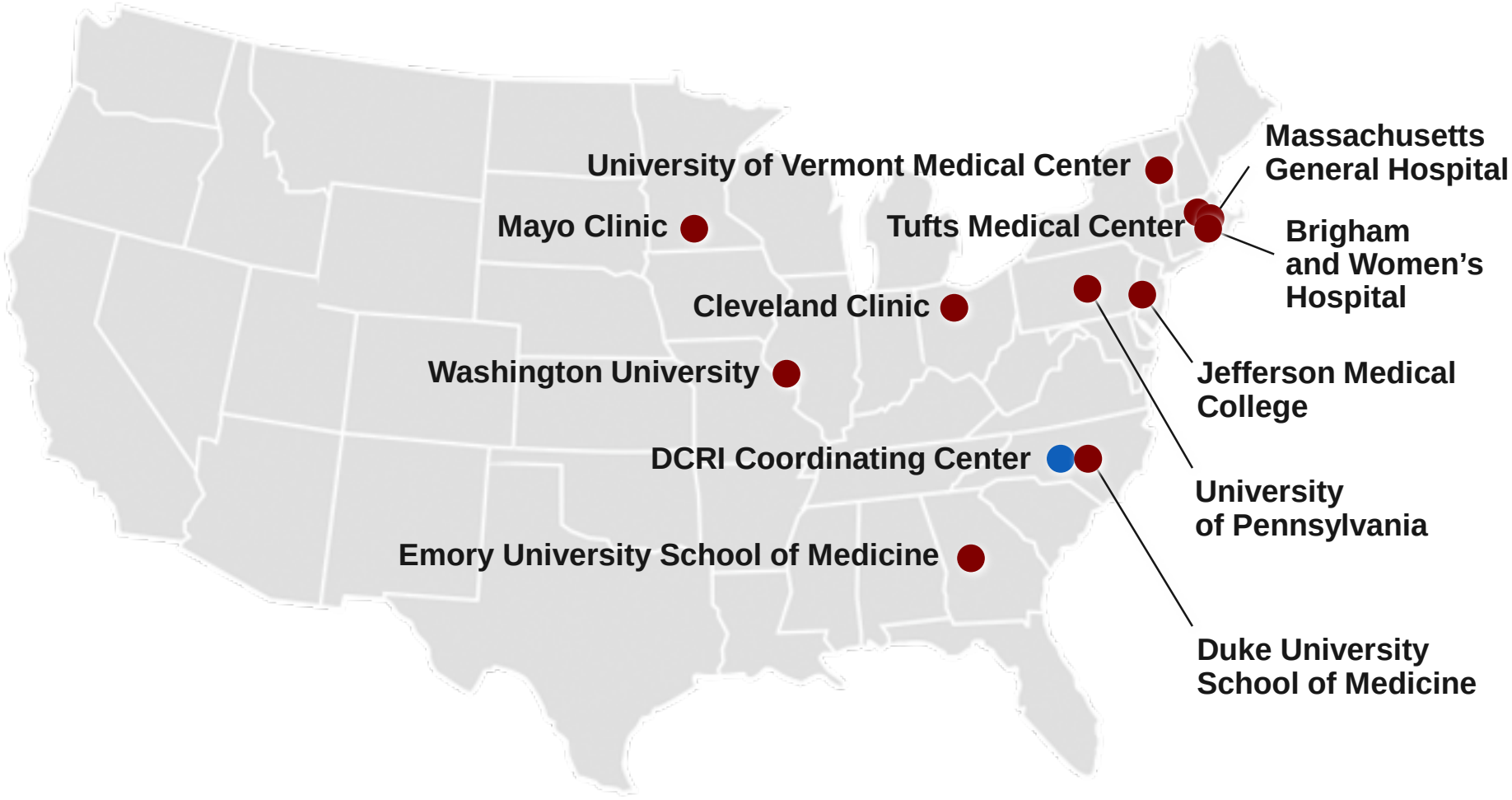

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