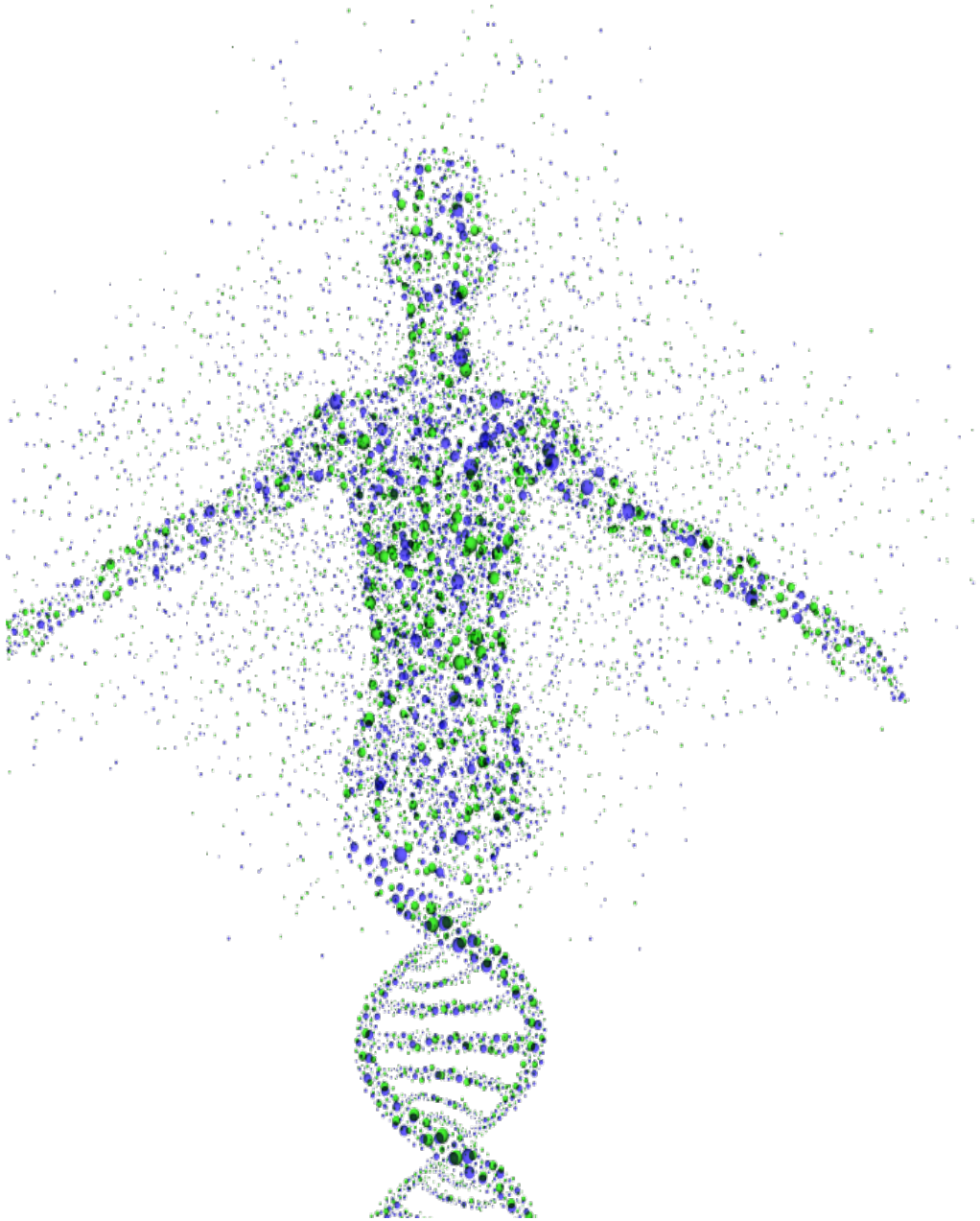


# Identification of Symptoms Associated with irAEs in the I-SPY Trial


## Presented by: Amrita Basu, PhD

[1]Basu A, [1]Umashankar S, [1]Melisko M, [2]Lu R, [2]Yu H, [1]Musthafa M, [1]Jones T, [1]Yau, C, [2]Asare S, [2]Pitsouni M, [3]Shatsky R, [4]Isaacs C, [5]DeMichele A, [6]Nanda R, [1]Kim M, [1]Wolf D, [7]Hershman D, [1]Esserman L, [1]Rugo HS

[1]University of California, San Francisco, San Francisco, CA
[2]Quantum Leap Healthcare Collaborative, San Francisco
[3]University of California, San Diego, San Diego, CA
[4]Georgetown University, Washington DC
[5]University of Pennsylvania School of Medicine, Philadelphia, PA
[6]University of Chicago, Chicago, IL
[7]Columbia University, New York, NY

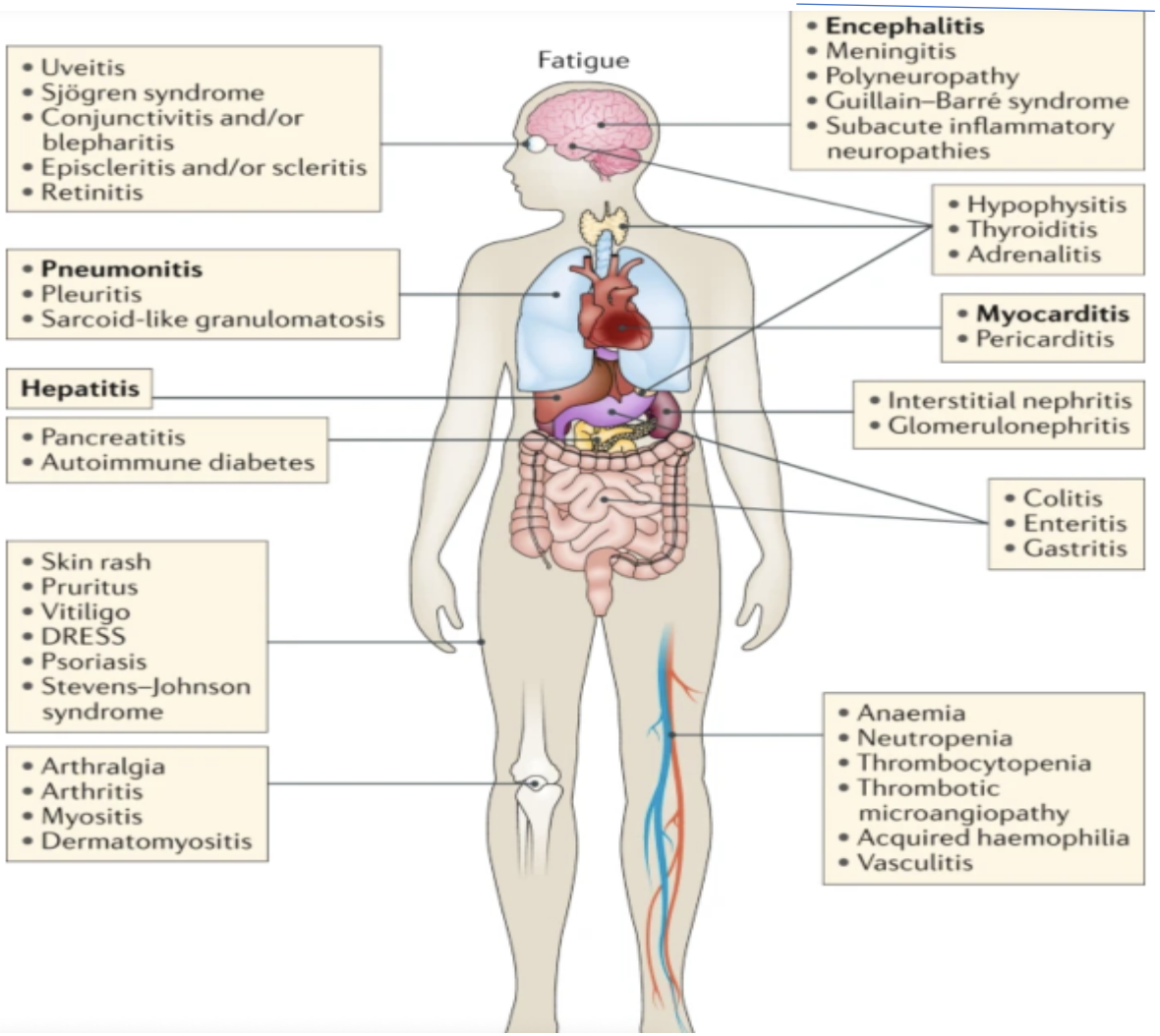
*On behalf of the I-SPY2 Investigators*

# Immune checkpoint inhibitors

- Introduced first in the metastatic breast cancer setting with improved outcome in PD-L1 positive disease
- The checkpoint inhibitor, pembrolizumab, is now approved as standard neoadjuvant therapy for high-risk early-stage triple negative breast cancer, with improvements in both response and event free survival
- Associated with immune-related adverse events, some of which are irreversible
  - Hypothyroidism
  - Adrenal insufficiency (often late onset)
  - Diabetes (late onset)

D'Abreo and Adams,*Nat Rev Clin Oncol, 2019,*
Emens et al, *J. Immunotherapy Cancer, 2021*

# Immune-related Adverse Events and Associated Symptoms




| SYMPTOMS |
|---|
| Diarrhea |
| Fatigue |
| Dizziness |
| Shortness of breath |
| Rash |
| Vomiting |
| Neuropathy |
| Headache |
| Nausea |
| Palpitations |
| Decreased appetite |
| Acne |
| Itching |
| Insomnia |
| Muscle pain |
| Mouth/Throat sores |
| Joint pain |
| Abdominal pain |
| Cough |
| Constipation |
| Taste changes |
| Swelling |
| Blurry vision |
| Pain urination |
| Dry eyes |

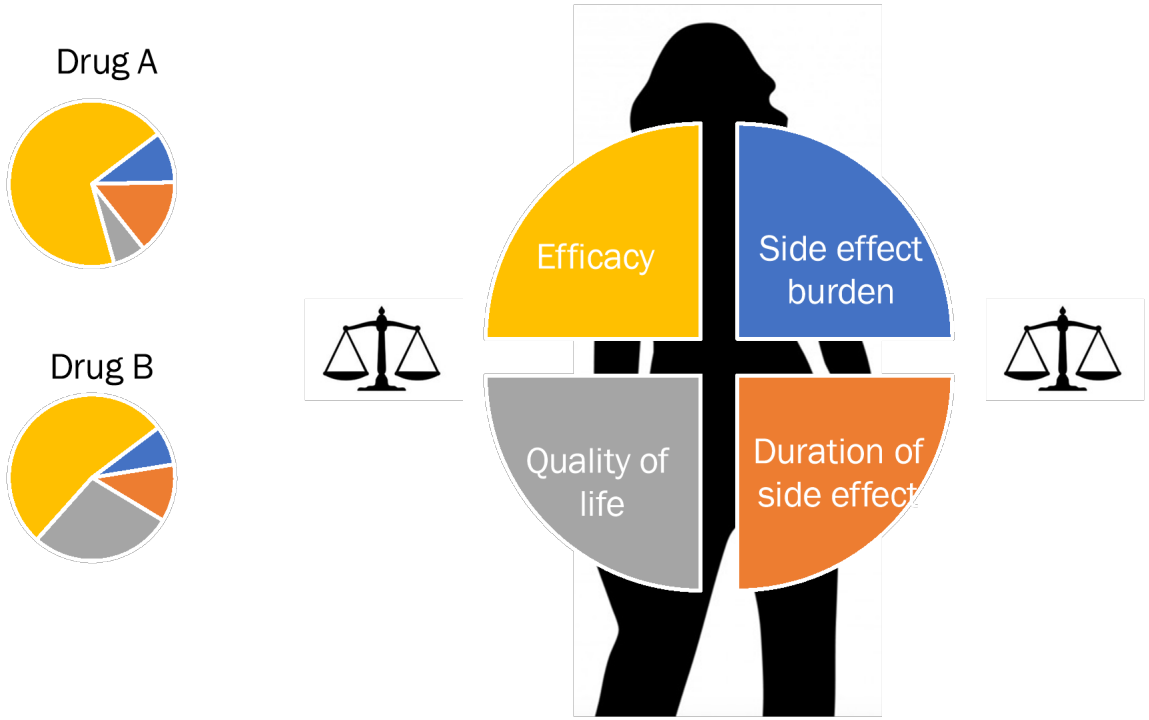
Martins et al, 2019, Nature Reviews Clinical Oncology

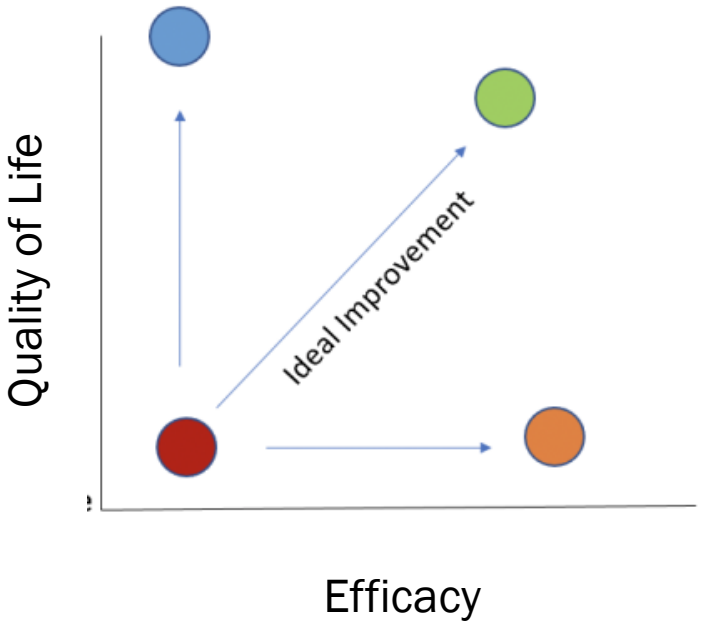
# Objectives

- Predict which patients are at risk for developing a serious irAE to enable early consideration of optimal treatment choices

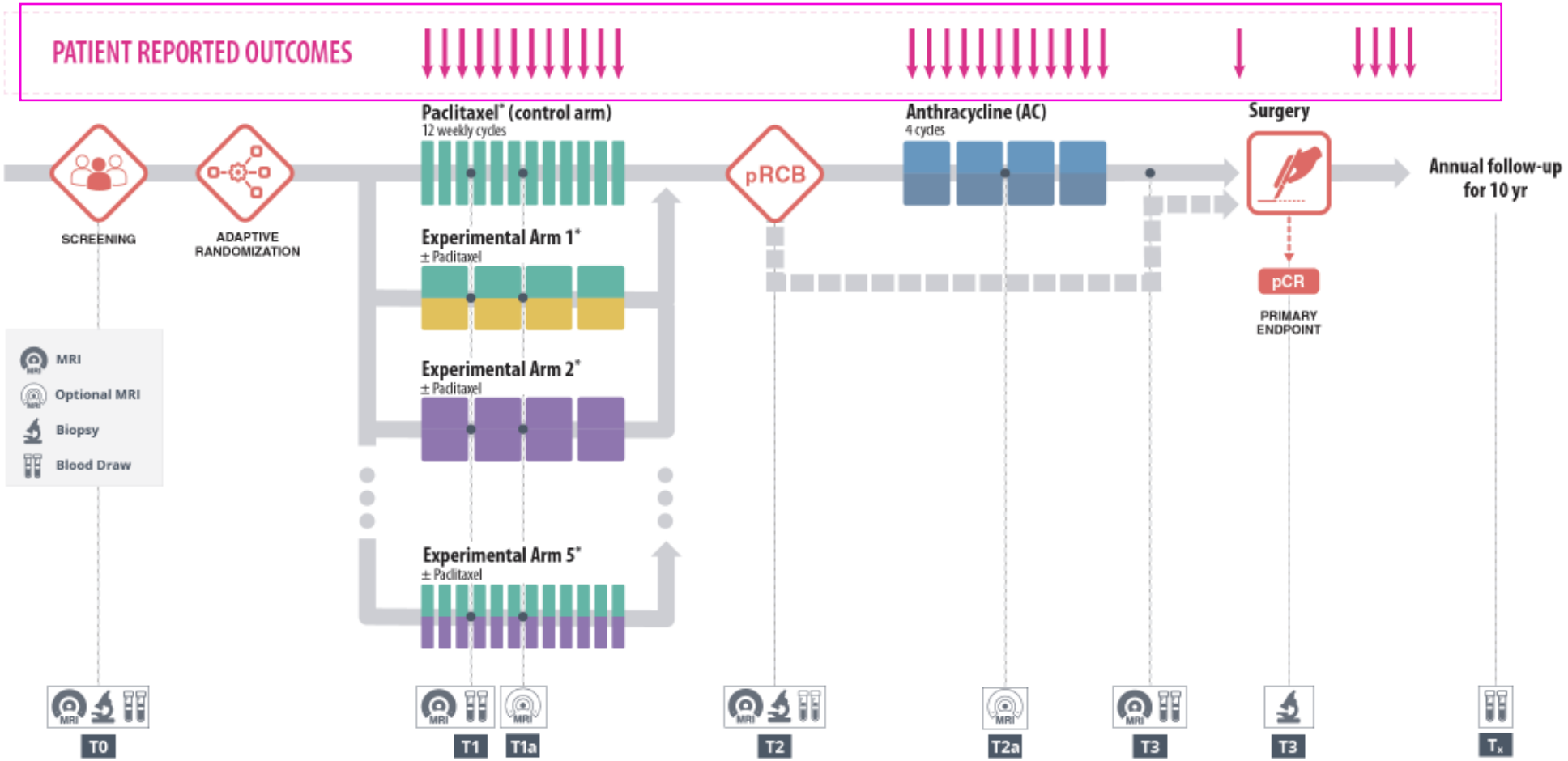
- Understand which symptoms during treatment most contribute to impairment in overall quality of life

# Balancing Toxicity and Efficacy: Developing a Standardized Method to Predict Immunotherapy Toxicities



# The I-SPY 2 Trial Schema



# Dataset Composition

## ASSESSMENTS

### *Clinician-assessed adverse events (CTCAE v 5.0)*

- Included all grade 1-4 AEs
- Collected weekly to every 2-3 weeks depending on chemotherapy schedule
- Follow-up: up to 1 year

### *Patient-reported Outcomes (PRO-CTCAE/PROMIS)*

- Patients filled in in at least 2 timepoints including baseline
- Surveys were collected weekly for symptoms, and monthly for QOL
- Surveys collected through 24 months
- Reported using the Likert scale 1-5 (from none/mild to severe)

## STUDY POPULATION

- 482 patients prescribed at least 4 doses of immunotherapy in combination with chemotherapy (CTCAE)
- 346 patients (PRO-CTCAE/PROMIS), 72% completion rates, 20% overlap with CTCAE

# irAEs Included in the Data Analysis

**OUTCOMES VARIABLES** – CTCAE Defined

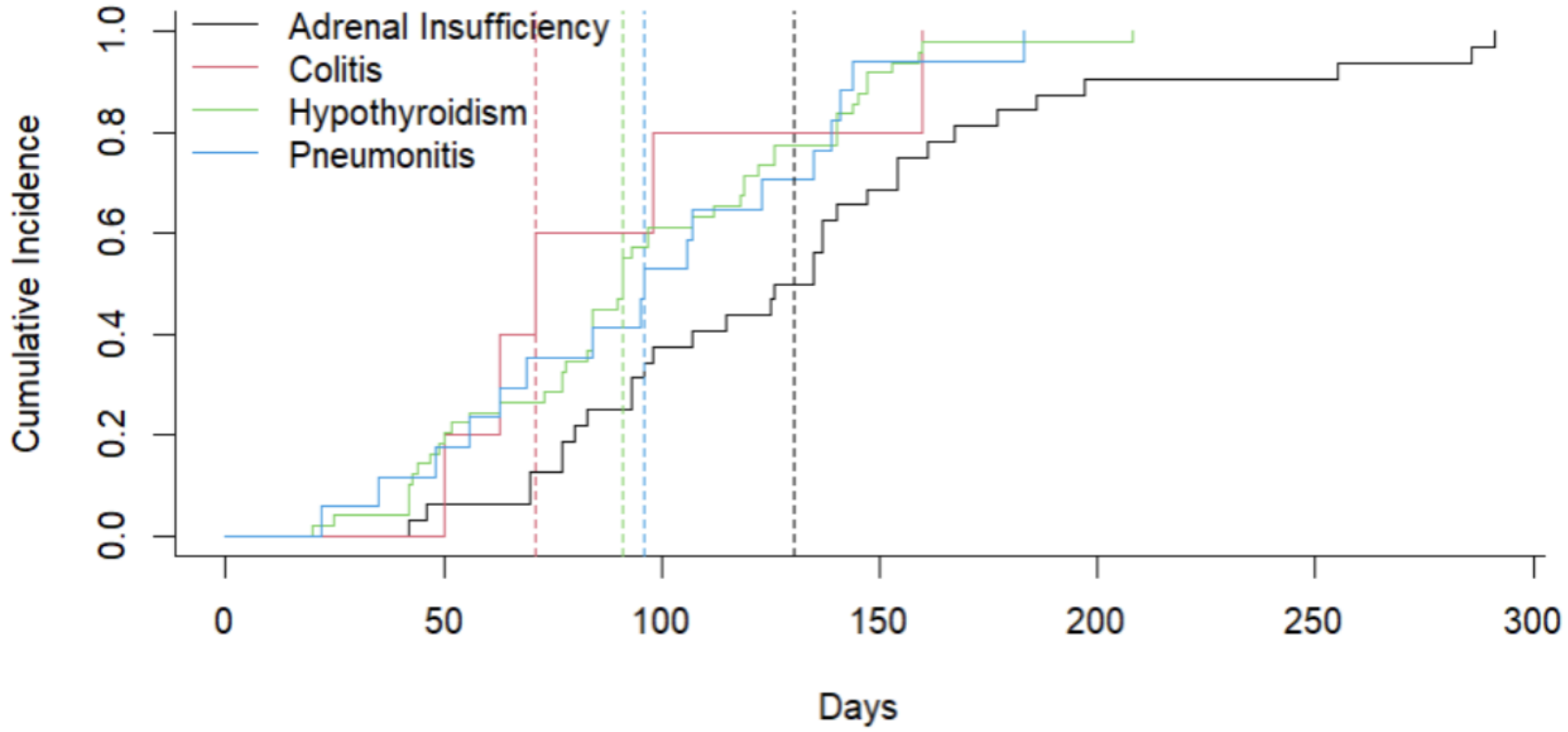
- Hypothyroidism (12%)
- Adrenal insufficiency (AI) (8%)
- Pneumonitis (4%)
- Colitis (1%)

# Demographic distribution of irAEs

| | Overall (n=482) | Pneumonitis (n=20) | No Pneumonitis (n=462) | Colitis (n=6) | No Colitis (n=476) | Adrenal Insufficiency (n=38) | No Adrenal Insufficiency (n=444) | Hypothyroidism (n=61) | No Hypothyroidism (n=421) |
|---|---|---|---|---|---|---|---|---|---|
| **Age** | | | | | | | | | |
| Mean (SD) | 47.6 (11.6) | 54.0 (9.2) | 47.4 (11.6) | 51.6 (12.2) | 47.6 (11.6) | 48.5 (11.7) | 47.6 (11.6) | 46.4 (10.3) | 48.5 (11.7) |
| Median (Min-Max) | 47.3 (20-79) | 55.3 (35-69) | 47 (20 – 79) | 54.5 (32 – 66.2) | 47(20 – 79) | 49.5 (31 – 79) | 47 (20 – 76) | 45.5 (28.8 – 71) | 47.9 (20 – 79) |
| **Race** | | | | | | | | | |
| American Indian Alaska Native | 3 (.6%) | 1 (5 %) | 2 (.4%) | 0 (0%) | 3 (0.63%) | 0 (0%) | 3 (0.7%) | 1 (1.6%) | 2 (0.5%) |
| Black | 60 (12.4%) | 2 (10%) | 58 (12.6%) | 1 (16.7%) | 31 (6.5%) | 5 (13.2%) | 55 (12.4%) | 2 (3.3%) | 58 (13.5%) |
| White | 382 (79.3%) | 16 (80%) | 366 (79.2%) | 4 (66.7%) | 378 (79.4%) | 32 (84.2%) | 350 (78.8%) | 53 (86.9%) | 329 (78.1%) |
| Asian | 32 (6.6%) | 0 (0%) | 32 (6.9%) | 1 (16.7%) | 31 (6.5%) | 1 (2.6%) | 31 (7.0%) | 2 (3.3%) | 30 (7.1%) |

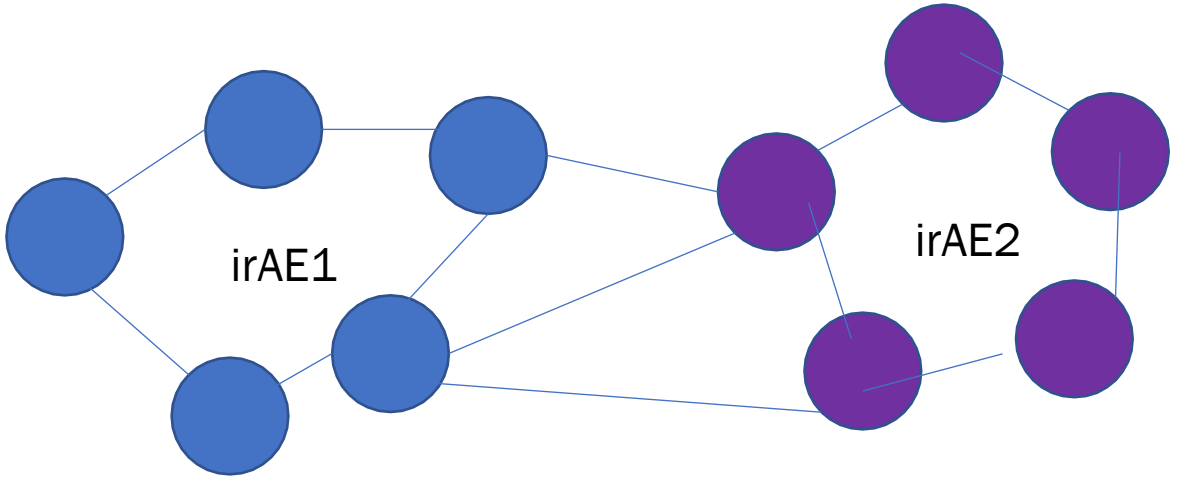
- Pneumonitis rates were higher in patients over 50 than under 50 (P<.01)
- No other significant associations were observed

# Cumulative incidence of irAEs over time



# Goal: Predict which patients were at risk for developing an irAE using symptom trajectory

- Symptoms leading up to an AE may be interconnected- “symptomics”
- Knowledge about which individual or constellation of symptoms (mild or severe) leading up to an AE are more predictive or sentinel
- Important implications for individualizing therapy to minimize toxicity



# Methods: Predicting who is at risk for developing an irAE

## Cohort and data

All patients on immunotherapy

Created separate model for each irAE


## Method

Elastic net regression

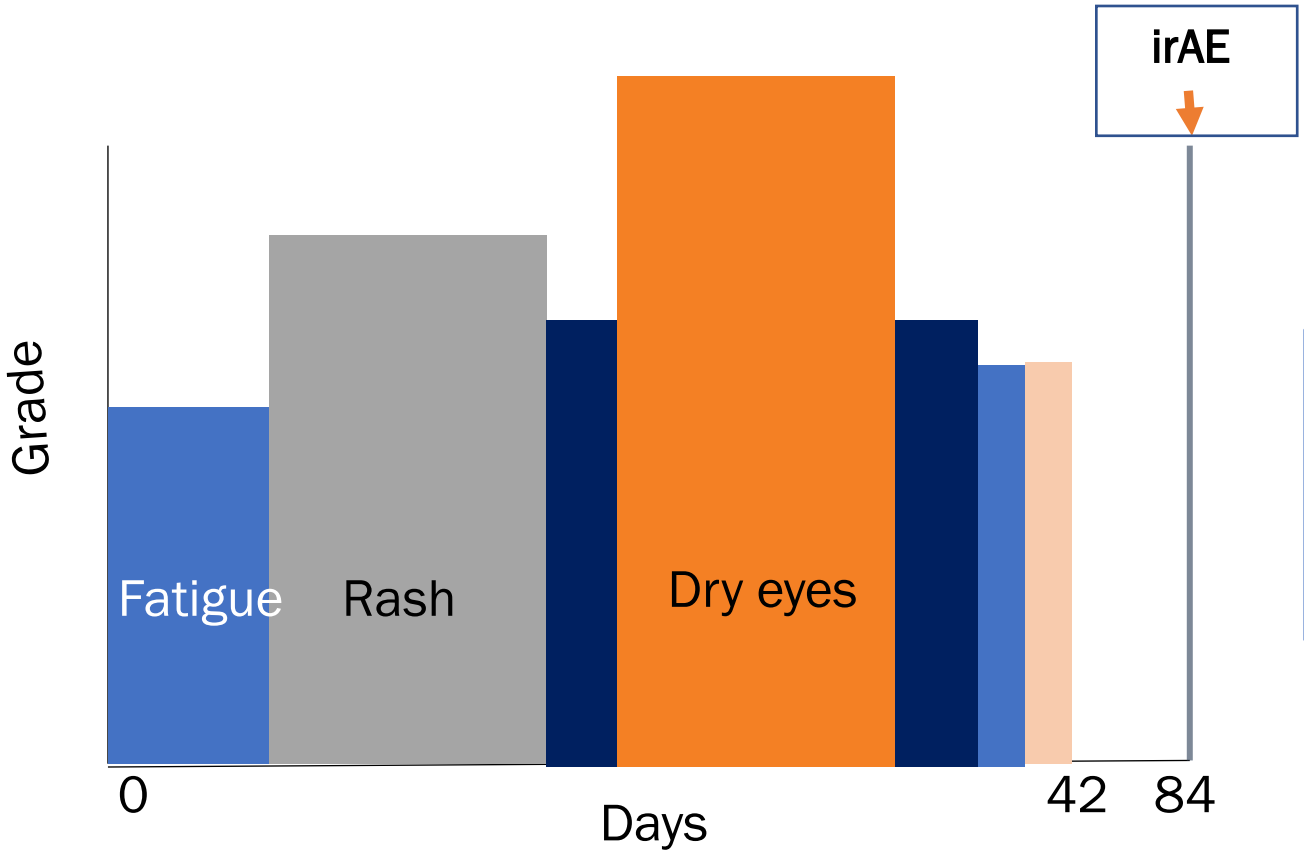
Input: Area under curve for each symptom

Output: Grade of irAE

## Evaluation of Results

Error estimates for each model

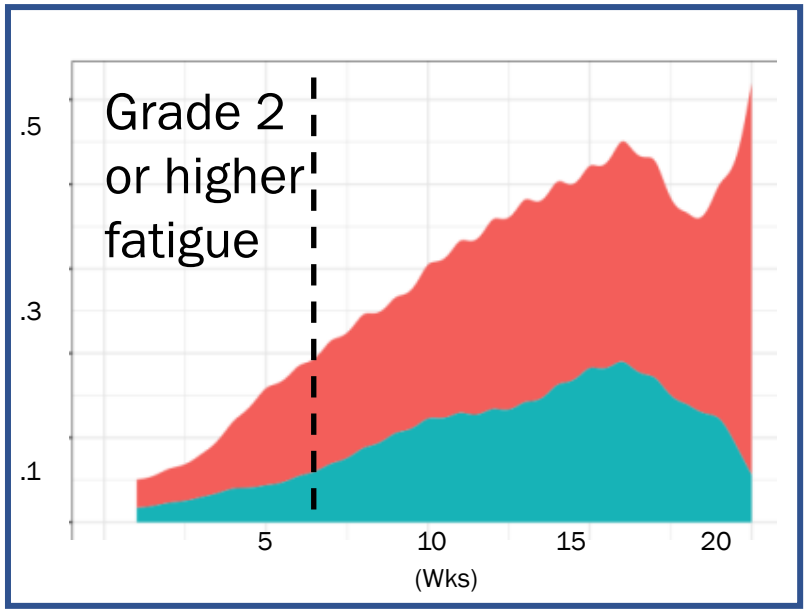
# Methods: Calculation of Symptom Burden

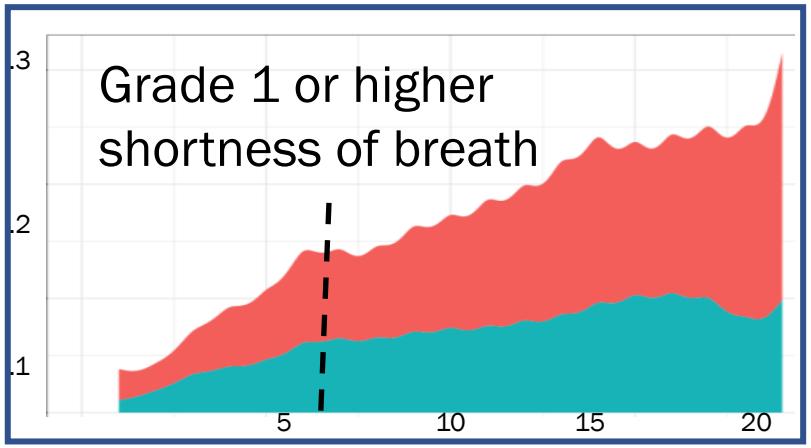


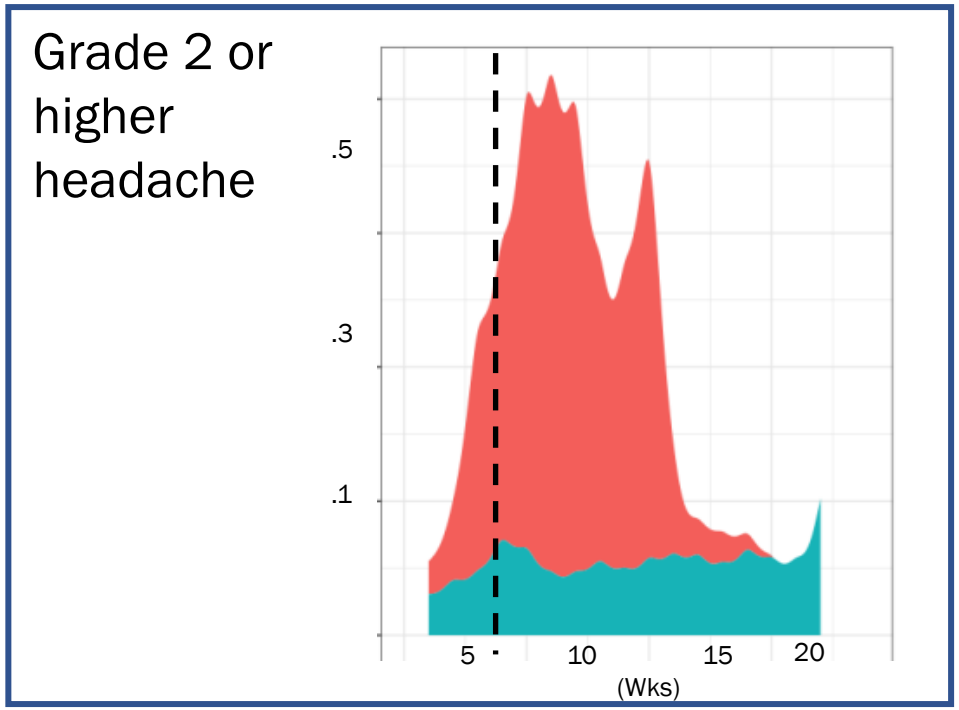

$$AUC(\text{symptom}) = \sum_{n=1}^{n} Grade * Duration$$

- Incorporated duration of symptom (days)
- Symptoms only up to the diagnosis of the irAE
- 4-12 weeks after treatment Initiation

# Results: Early Symptoms Associated with Hypothyroidism




Early onset of symptoms by 6 weeks was associated with subsequent development of hypothyroidism

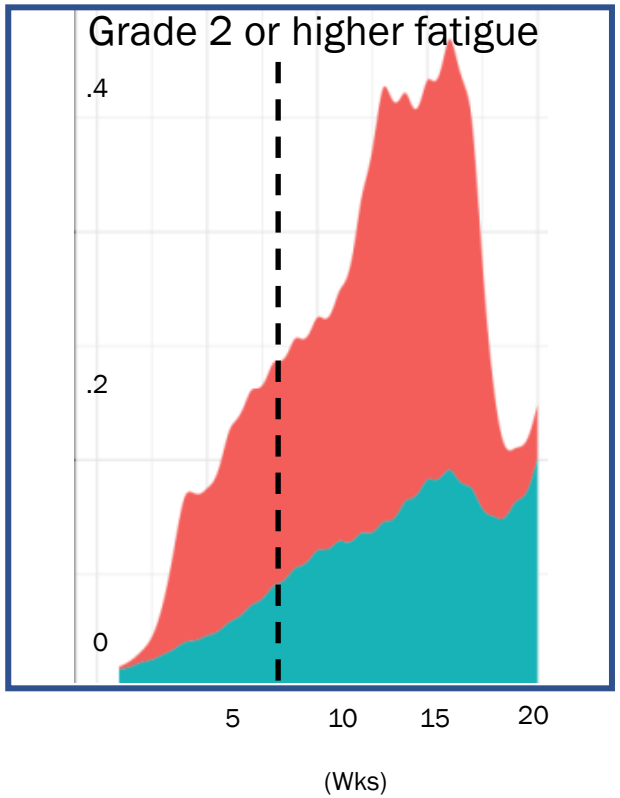
Error Estimate: 30%

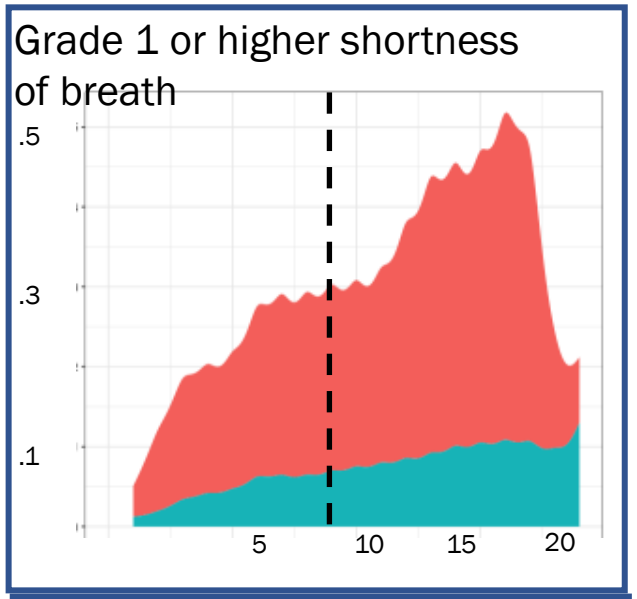
Developed hypothyroidism

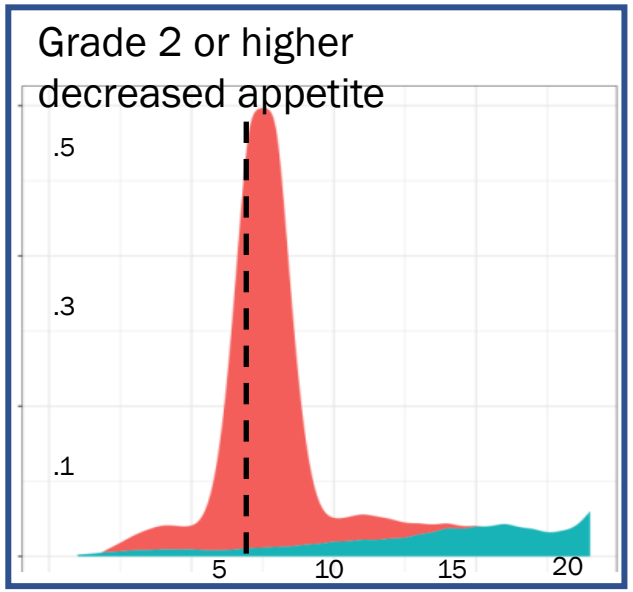
No hypothyroidism

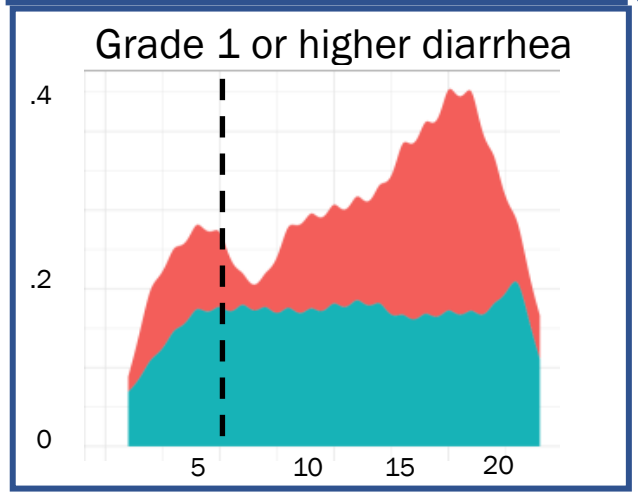
X axis – weeks
Y axis – proportion of patients

# Results: Early Symptoms Associated with Adrenal Insufficiency



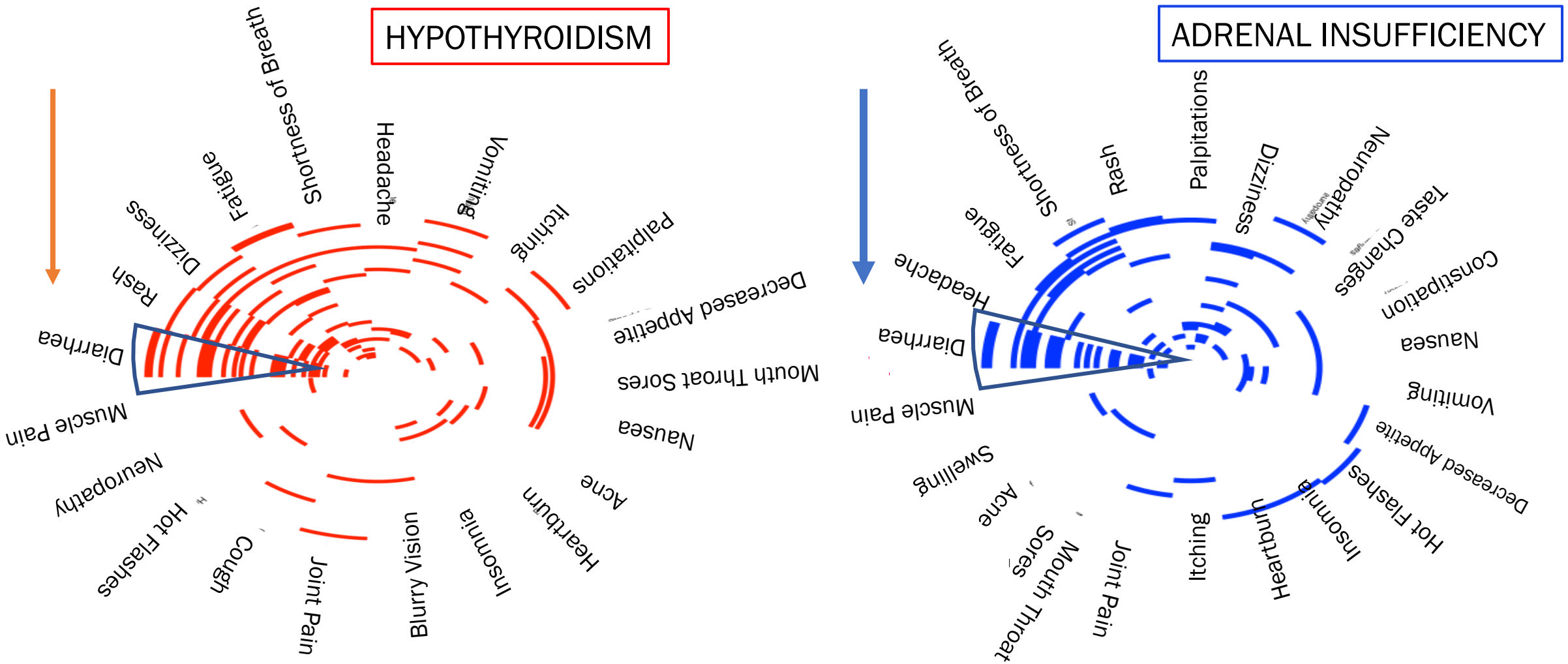



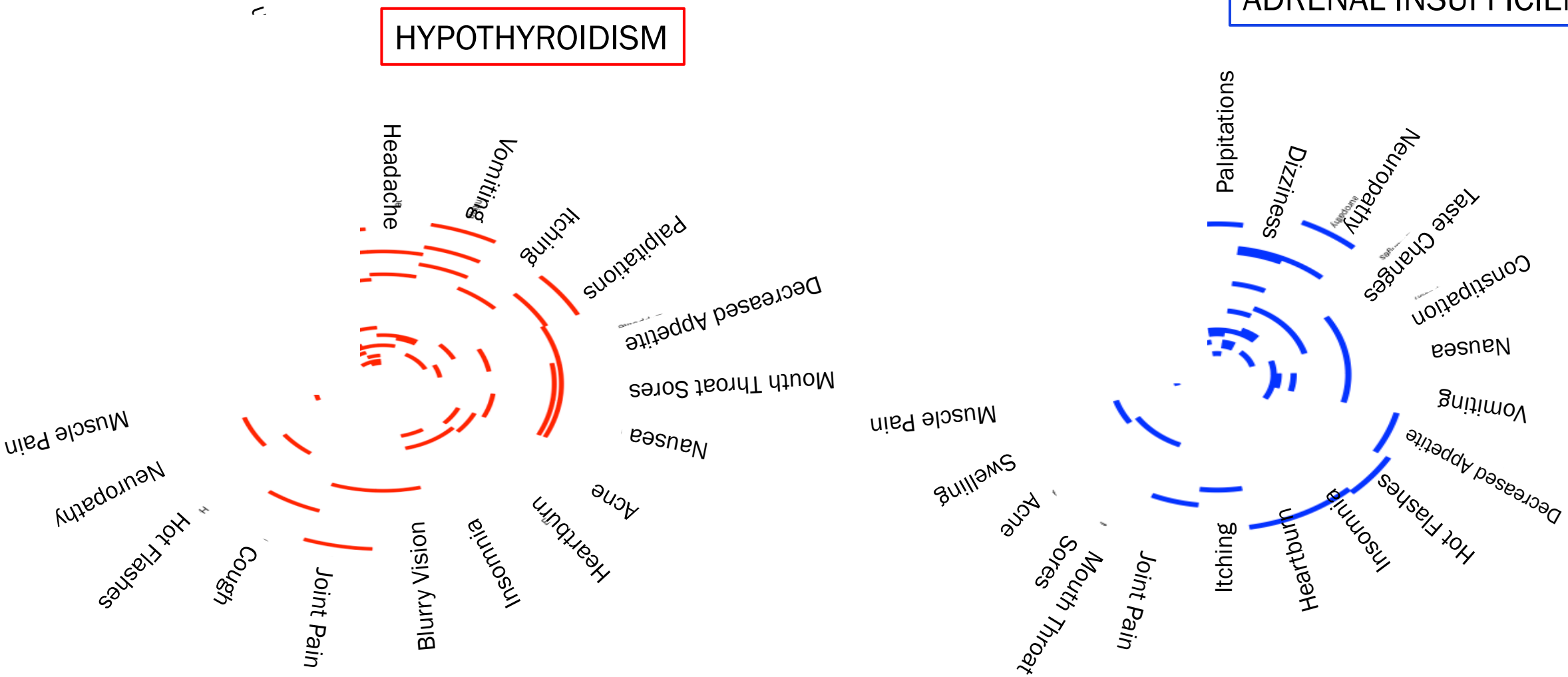

Early onset of symptoms by 6 weeks was associated with subsequent development of adrenal insufficiency

Error Estimate: 25%

# Results: Co-occurring Symptoms up until 6 week timepoint



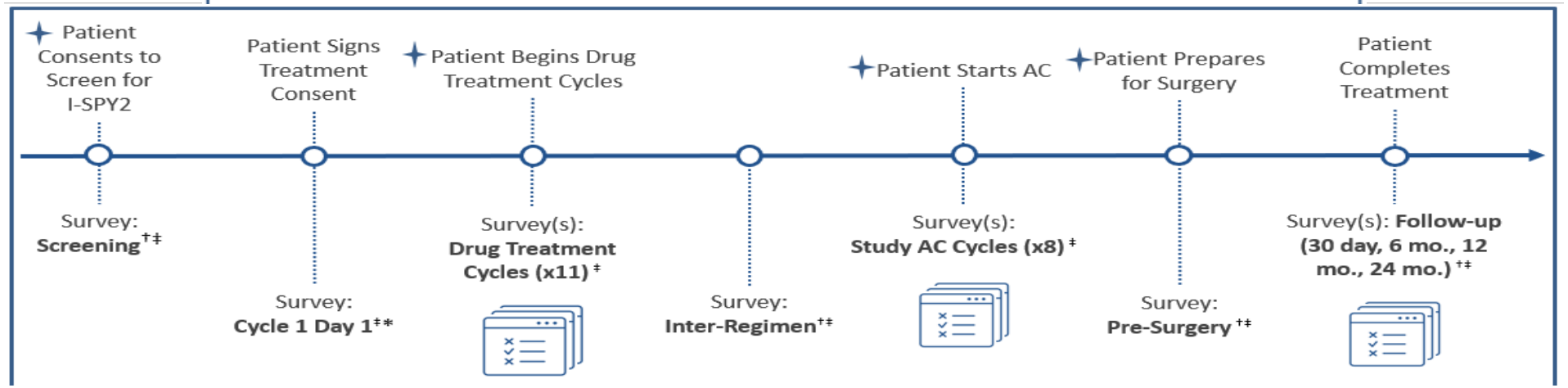
# Results: Removal of specific symptoms significantly decreases model performance



# Methods: Patient Reported Outcomes in I-SPY

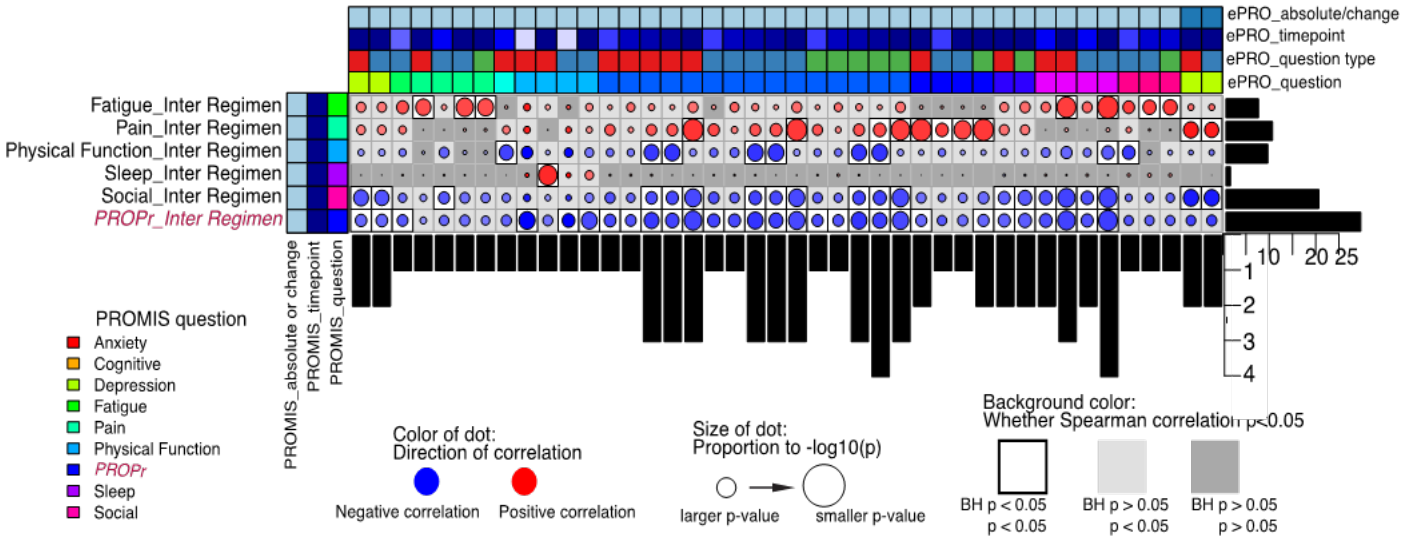
*ePRO launched in 2021  across 28 sites*

| PROMIS† | PRO-CTCAE‡ |
|---|---|
| Pain Interference | Mouth and Throat |
| Sleep Disturbance | Stomach and Digestion |
| Physical Function | Heart and Lungs |
| Anxiety* | Eyes |
| Depression | Skin and Hair |
| Fatigue | Neurologic |
| Cognitive Function | Muscle and Body |
| Social Roles | Bladder |
| Sexual Interest/Function | General/Other |



# Results: PRO enables us to evaluate symptoms and their impact on quality of life longitudinally

Joint Pain




- Joint and muscle pain starting at week 4 is most predictive of reduced QOL at week 12

**Poster ID:** P5-07-03
**Poster Title:** The Association Between Symptom Severity and Physical Function among Participants in I-SPY2
**Thursday, 5 pm CT**

# Conclusions and Next Steps

- **Early onset of symptoms may predict subsequent risk for irAEs**
  - **Understanding the risk factors for developing an irAE will help to optimize intensity of surveillance and potential treatment modification to minimize the impact of toxicity**
- Further confirmation of this model is required
  - Analysis of PRO is ongoing
  - Analysis of genetic predictors to identify who is at risk of developing a severe irAE

# Acknowledgements


## WORKING GROUP CHAIRS

**Study PIs:** L. Esserman
**Agents:** L. Esserman, D. Yee
**Statistics:** C. Yau
**Operations:** C. Isaacs, R. Shatsky
**Patient Advocates:** J. Perlmutter
**Imaging:** N. Hylton
**PRO/QOL:** D. Hershman, A. Basu
**Informatics:** A. Asare, A. Basu
**Biomarkers:** L. van 't Veer
**Ct DNA:** A. DeMichele
**QED:** A. DeMichele
**IP Project Oversight:** A. Barker
**Surgery:** J. Boughey, R. Mukhtar
**Safety :** H. Rugo, R. Nanda
**Clinical Operations:** M. Pitsiouni
**Pathology:** F. Symmans
**IRB Working Group:** T. Helsten
**Return of Results:** A. DeMichele

## SITE PRINCIPAL INVESTIGATORS: 28 sites

**City of Hope:** Jennifer Tseng
**Cleveland Clinic:** Erin Roesch
**Columbia:** Meghna Trivedi
**Denver:** Anthony Elias
**Emory:** Kevin Kalinsky
**Georgetown:** Claudine Isaacs
**HOAG:** Chaitali Nangia
**Huntsman:** Christos Vaklavas
**Loyola:** Kathy Albain
**Mayo:** Judy Boughey
**Moffitt:** Heather Han
**OSU:** Nicole Williams
**OHSU:** Zahi Mitri
**Rutgers:** Coral Omene
**Sanford:** Amy Sanford
**Sparrow:** Brittani Thomas
**UAB:** Erica Stringer-Reasor
**UC Davis:** Mili Arora
**UChicago:** Rita Nanda
**UCSD:** Anne Wallace
**UCSF:** A. Jo Chien
**UMN:** Doug Yee
**URMC:** Carla Falkson
**UPenn:** Amy Clark
**USC:** Evanthia Roussos Torres
**Vanderbilt:** Laura Kennedy
**WakeForest:** Alexandra Thomas
**Yale:** Tara Sanft

## DSMB & INDEPENDENT AGENT SELECTION COMMITTEE (IASC) Members

## PROJECT OVERSIGHT

Anna Barker/USC; Patrizia Cavazzoni/FDA CDER; Reena Phillip/FDA; Janet Woodcock/FDA; Eric Rubin/Merck, FNIH Biomarker Consortium; Lisa LaVange/UNC; Ken Ehlert/UHG

## QUANTUM LEAP HEALTHCARE COLLABORATIVE/ UCSF:

**CEO:** J. Palazzolo

**Director of Clinical Operations:** M. Pitsiouni

**Oncology Clinical Operations:**
T. Nguyen, W. Chang, H. Prisant, A. Hastings, B. Nwaogu, S. Ezrati, Z. Patel, P. Vyas, A. Snew, H. Patel, E. Buell, J. Engleman, N. Allen

**Safety:**
M. Salem (QLHC), A. Kelley, S. Bezawada, B. Smolich, M. Bozorginia (CCSA)

**Site Regulatory:** E. Guerrero, S. Rice

**Drug Management:**
F. Chu, A. Spivak, A. Sangwan, J. Ritchie

**Manuscripts/Strategy:** L. Sit, J. Matthews

**Collaborations**
P. Henderson, S. Jafari, H. Fraser

**Biomarkers/Specimens:**
L. Brown Swigart, G. Hirst, E. Chip Petricoin, J. Wulfkuhle, M. Campbell, M. Magbanua, S. Venters, A. Aye Ma, E. Bergin, C. Yau, D. Wolf, K. Papuga, P. Glenn, L. Torres Altamirano, & collaborators

**Imaging Lab:**
J. Gibbs, W. Li, D.Newitt, N. Onishi, M. Watkins, T. Bareng

**Data Analysis, Data Management & IT:**
C. Yau, A. Basu, G. Peterson, A. Wilson, D. Dimitru, L. Weiss, C. Russell, A. Glowacki, P. Beineke, I. Dunn, A. Asare, T. Gannamaneedi

## PRIOR COLLABORATORS and STAFF

A. Forero-Torres, L. Korde, R. Murthy, D. Northfelt, Q. Khan, K. Edmiston, R. Viscusi, B. Haley, A. Zelnak, J. Sudduth-Klinger, N. Lisser, M. Buxton, M. Paolini, J. Lyanderes , R. Singhrao, S Asare, E. Sponti, F Xu., S. Khozin, R. Califf, Verily Life Sciences, C. Austin, B. Consultants, R. Lu; R. Schwab

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# Participating Organizations

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Stand Up to Cancer
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