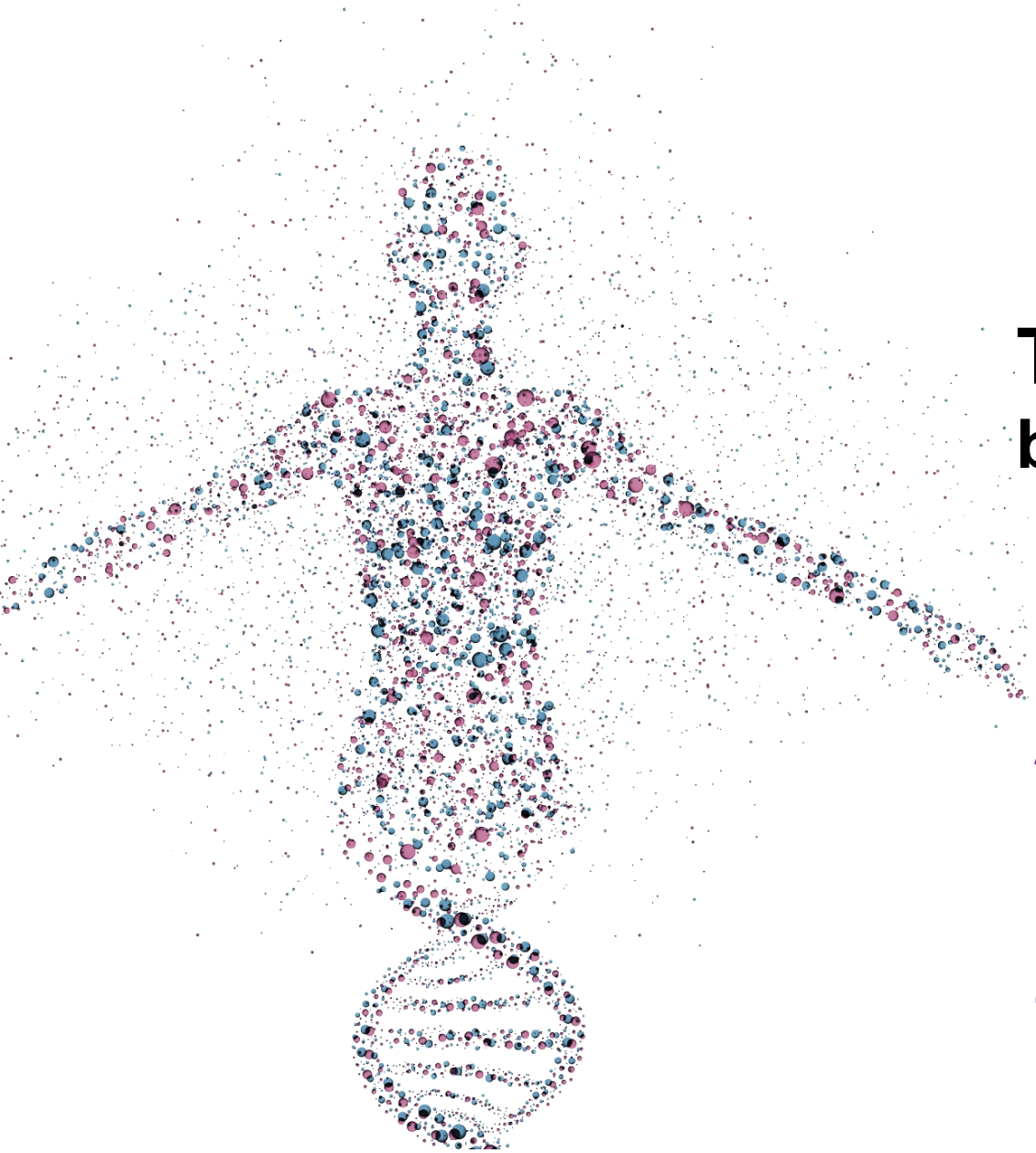

The Road to Precision Medicine
by a Continuous Learning System

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PI, I SPY family of Trials, WISDOM Study

The Problems With Most Clinical Trials

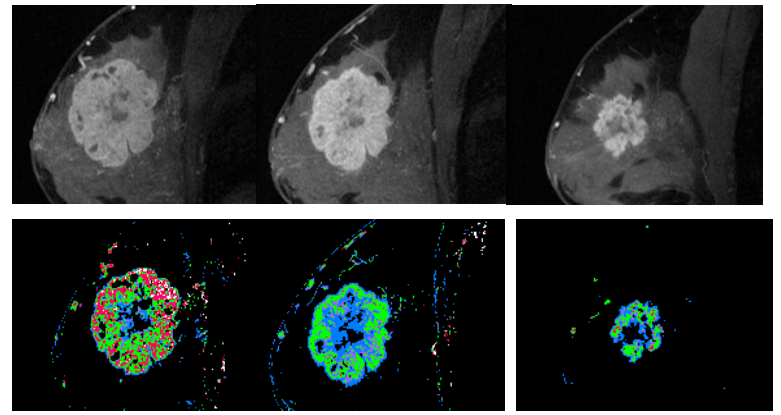
- Most clinical trial design assumes that the disease is the same for all
- Each trial is a “one-off” making knowledge turns slow
  - The process is burdensome and not integrated with care processes
- Most new drugs are tested first in the setting of metastatic disease
  - Where progress is measured in terms of months, rather than cure
- For years, the standard of care was to start with surgery first
- There is little effort to tie progress from treatment to screening and prevention


ragweed
allergy


Allergy

Conceptual Framework of I-SPY

Goal: ***Improve the Way We Evaluate New Treatments***



- Accelerate Knowledge turns: drive urgency and innovation
- Design trials that incorporate disease heterogeneity prospectively
- Move drug development into the earlier stage: high risk neoadjuvant setting
- Identify early endpoints captured in the course of care:
  - Amount of tumor left after treatment (none=pCR)
- Look for big signals
- Design trial to continuously learn: adaptive randomization
- Allow seamless evaluation of new drugs: eliminate “stop and start”
- Building evidence using biomarkers and new statistical methods

ROADMAP

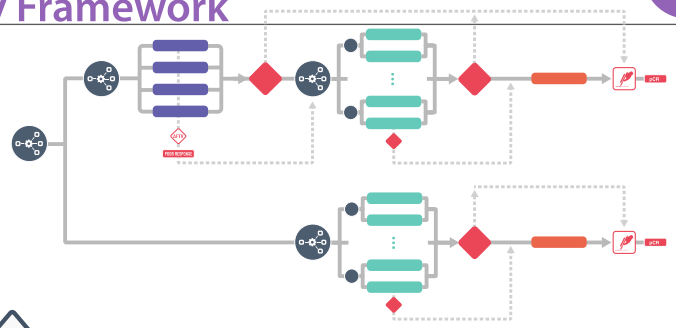
I-SPY 2.3

Optimize Strategy in a Regulatory Framework

2.3

- Randomization to contemporary control at second tx block
- Continue to optimize pCR by subtype
- Integrate PROs in trial and standard of care

GOAL: Minimize toxicity, increase chance of pCR and accelerated approval



- Accelerated approval for agents with optimal pCR rates
- Introduce quantitative measures of toxicity
- Use combined endpoints for efficacy and toxicity
- Equal efficacy with less toxicity is superior

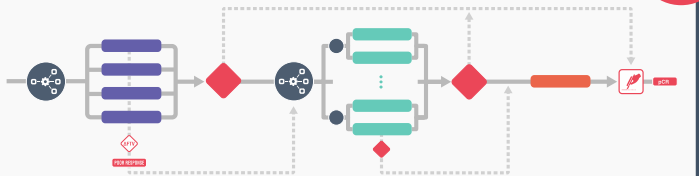
I-SPY 2.2

Adapt therapy within patients

2.2

- RCB, Imaging as a regulatory endpoint for poor & excellent responders ('preRCB')
- Allows early treatment switching and discontinuation depending on interim response to treatment

GOAL: Increase chance of pCR for each individual; reduce unnecessary toxicities



- Optimize pCR for each patient
- Stop at pCR, continue if not
- Confirm DRFS at 3 years ≥92% for pt with pCR

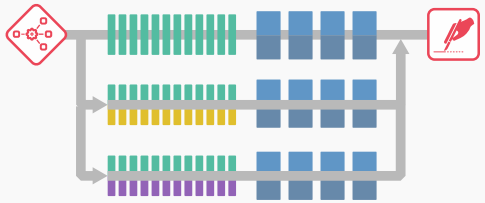
I-SPY 2

Adapt therapy within trial

2

- pCR regulatory endpoint (accelerated approval)
- Test multiple novel agents adaptively
- Operational efficiencies, platform trial, culture of innovation

GOAL: Increase pCR in each biomarker signature



- pCR predicts DRFS HR 0.18 regardless of subtype, therapy
- RCB stratifies outcome
- Many agents identified that improve subtype specific pCR
- Molecular markers better classifiers than receptors

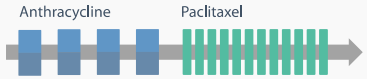
I-SPY 1

Measure outcomes by subtype

1

- Standardize imaging, pathology, biomarkers, data collection

GOAL: create collaborative framework & standards



- Absence of tumor after neoadjuvant chemo (pCR) is optimal early endpoint
- for molecularly high risk disease
- Better by subtype

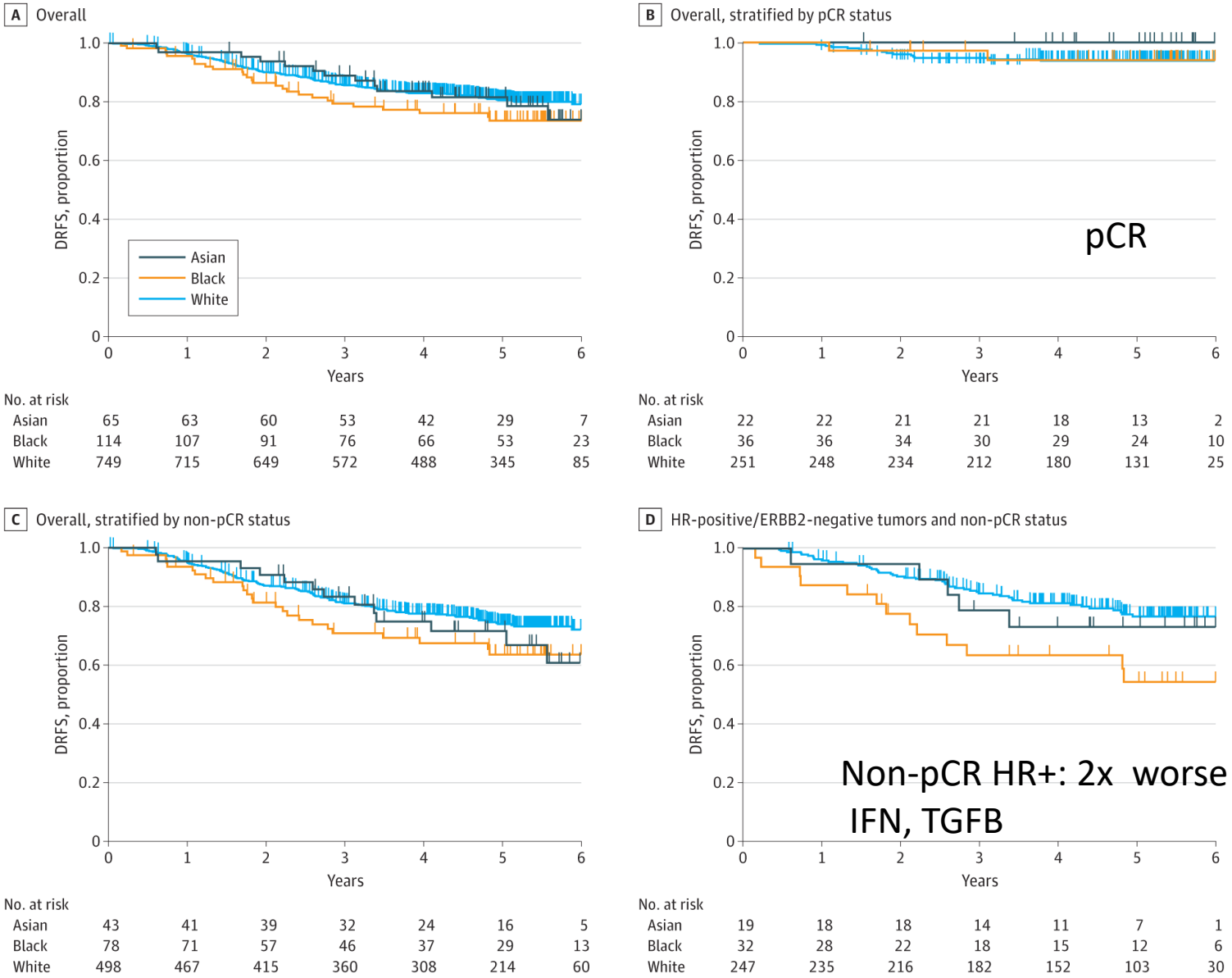
From: **Race, Gene Expression Signatures, and Clinical Outcomes of Patients With High-Risk Early Breast Cancer**

JAMA Netw Open. 2023;6(12):e2349646. doi:10.1001/jamanetworkopen.2023.49646

JAMA Network™

overall

non-pCR



Non-pCR HR+: 2x worse for AA

IFN, TGFB

Figure Legend:

Kaplan-Meier Curves of Distant Recurrence–Free Survival (DRFS) Differences by Race and Pathologic Complete Response (pCR) StatusA, Hazard ratios 1.06 (95% CI, 0.60-1.88; P = .84) and 1.37 (95% CI, 0.90-2.06; P = .14) for Asian and Black patients relative to White patients. B, Hazard ratios 0.00 and 0.93 (95% CI, 0.21-4.07; P = .92) for Asian and Black patients relative to White patients. C, Hazard ratios 1.23 (95% CI, 0.69-2.18; P = .48) and 1.45 (95% CI, 0.95-2.24; P = .09) for Asian and Black patients relative to White patients. D, Hazard ratios 1.26 (95% CI, 0.50-3.17; P = .62) and 2.28 (95% CI, 1.24-4.21; P = .01) for Asian and Black patients relative to White patients. HR indicates hormone receptor.

Evolution of Trial Design

- Identify the right ways to stratify the disease population
- Adapt on agents that work
- Develop biomarkers of response
- Move toward serial treatments by testing SMART strategies
  - Block A Block B Block C
  - Standardize the ways to measure treatment success, failure
  - Mitigates the risk of a less than optimal response on “first line”
  - Reimagine how we propose pCR for drug approval in the setting of serial strategies
- Trials should look more like care

Are these Approaches

?

TRIAL STATUS

- I SPY 2.2
  - We are setting a new standard
  - New strategies are going to evolve that will change breast cancer treatment- our trial design allows this
  - EOP (endocrine optimization pilot): we need to settle on a response adaptive endpoint and grow

- RECAST DCIS
  - Response adaptive, but not segmented as much yet
  - Biomarker rich

- ARDS (I SPY COVID→SPARC→ISPY ARDS)
  - Selected real time biomarkers
  - First network to implement in real time
  - Planning testing of response predictive markers

- Pre I SPY: Phase 1 pipeline→I SPY 2.2
  - Shorten the timeline
  - value

I SPY Efficiencies

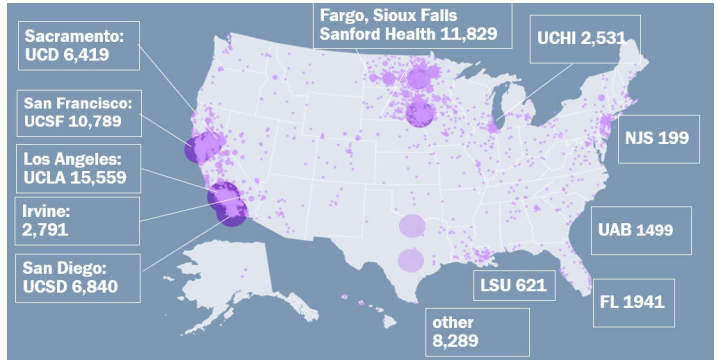
- Academic Consortium partnered with Quantum Leap HealthCare Collaborative (Not for Profit organization)
- Central IRB- approval 20-25 days
- Collaboration with FDA- 30 day notification
- Efficiencies for real time data capture, advancing evidence generation
  - OneSource
- Collaborative engagement of 14 working groups, including Safety
  - Real time management of Aes and AESIs
- Advocate involvement
  - Especially will be powerful in the BRCA space
- Network of 40+ sites with diverse population enrollment
  - 40+ patients enrolled each month

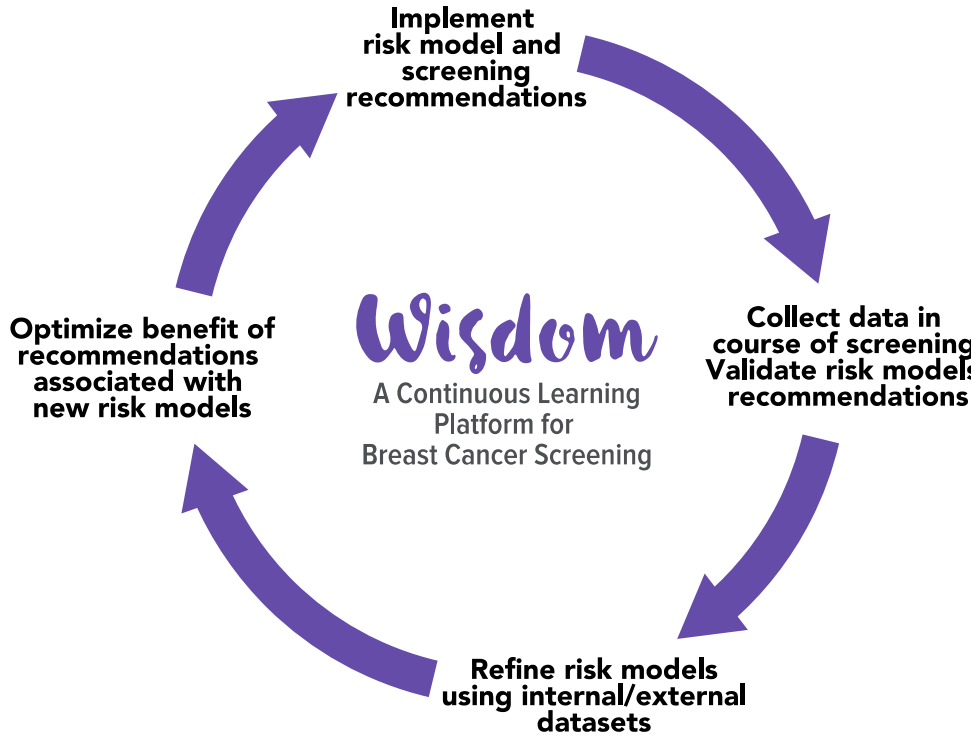
WISDOM: *Women Informed to Screen Depending on Measures of Risk*

- Because if One Size Does Not Fit All . . . For treatment
  - Screening everyone as if it does will not work well

- Personalized Screening vs. Annual Screening:
  - 45,000 women enrolled 2016-2023
  - Open to any women without Breast Ca in the US

- Personalized Screening: Who is at Risk for Fast vs Slow Growing Ca
  - Target prevention based on tumor type
  - Target Screening- when to start, how often, and with what modality
  - Just starting: Fall 2023- . . .





UCSF

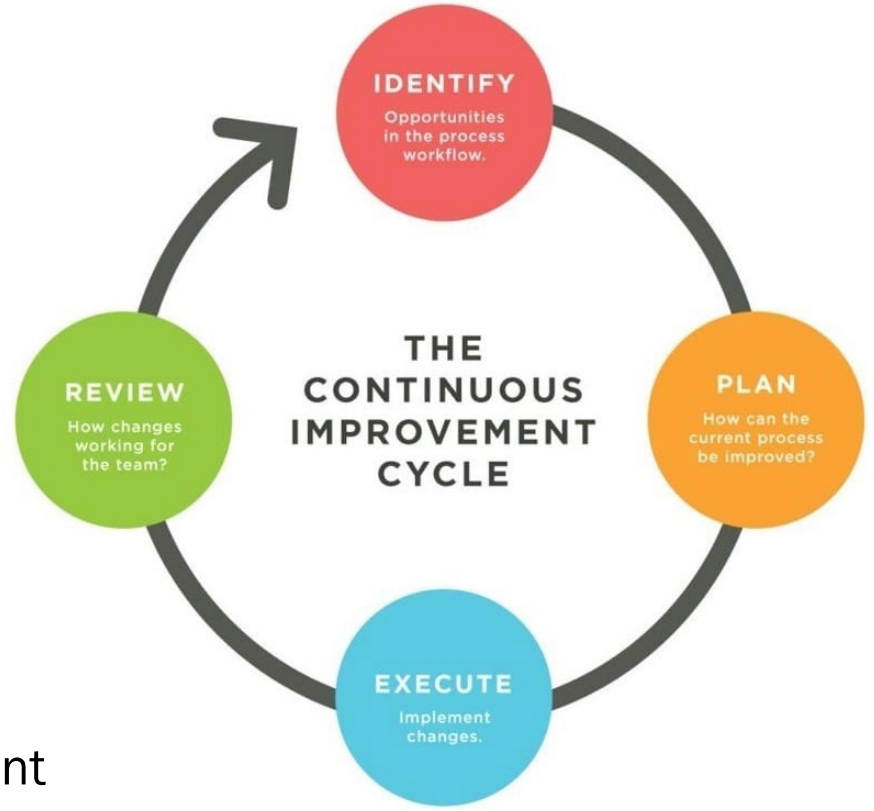
Improvements in Racial and Ethnic Diversity

- Significant improvement in representation since 2020
- 1.7% Black/African American participants through 2019; in Q4 2022, WISDOM included over 16% Black/AA participants
- Overall study numbers show gradual improvement each quarter and year

Year/Timeframe	White alone, non-Hispanic or Latino	Black or African American alone non-Hispanic or Latino	American Indian and Alaskan Native alone non-Hispanic or Latino	Asian alone, non-Hispanic or Latino	Native Hawaiian and Other Pacific Islander alone, non-Hispanic or Latino	Two or More Race, non-Hispanic or Latino	Hispanic or Latino	Unknown, Prefer not to answer, some other race not listed	Total N
Start-2019	81.4%	1.7%	0.2%	4.5%	0.2%	2.9%	7.9%	1.3%	21,399
2020	74.2%	4.2%	0.3%	6.0%	0.1%	3.4%	10.5%	1.3%	7,725
2021	73.4%	8.1%	0.3%	4.0%	0.1%	0.3%	10.1%	0.8%	10,053
2022	67.1%	11.9%	0.5%	4.6%	0.1%	3.7%	11.5%	0.8%	10,108
Q1 2023	57.9%	18.1%	0.1%	5.6%	0.7%	3.8%	12.2%	1.6%	1,076
All Time	**75.3%**	**5.7%**	**0.3%**	**4.7%**	**0.2%**	**3.2%**	**9.5%**	**1.1%**	**50,300**
US Population	*60.1%*	*13.4%*	*1.3%*	*5.9%*	*0.2%*	*2.8%*	*18.5%*	*n/a*	

Bridging the Research-Care Divide

- Research and care are largely separate
- The vast majority of data from clinical care is wasted
- Knowledge transfer is slow and difficult
- Prevention, screening, and treatment are not integrated



The Continuously Learning Healthcare System Model:

- Learn from each patient's care
- Avoids duplication of effort
- Cycle of continuous improvement, Accelerates knowledge turns
- Connect risk assessment to prevention, screening, and treatment

➢ **PLATFORM TRIALS are the ENGINE of the Learning Healthcare System**

Lessons Learned

- No disease is monolithic
- The more you understand the biology, the better you can personalize treatment
  - This must be built into the prospective course of care and trials
- The road is long
- Enrollment diversity is crucial and will not happen by itself
  - Must be intentional and requires effort and change
- Improving the way data is collected in care will increase the ability to conduct trials and learn from real world data