

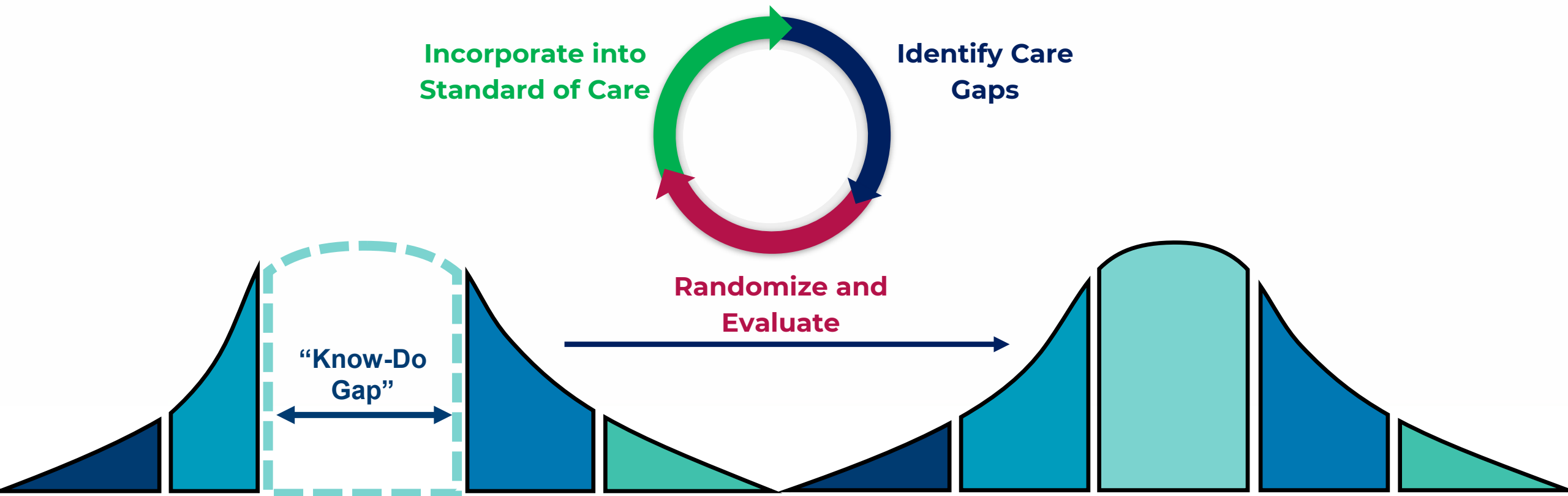
# **Embedding Randomization into Clinical Care in a Learning Healthcare System: Insights from the KP-VACCINATE Trial**

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**Research Scientist, KPNC Division of Research**  
**Adjunct Professor, Stanford University School of Medicine**

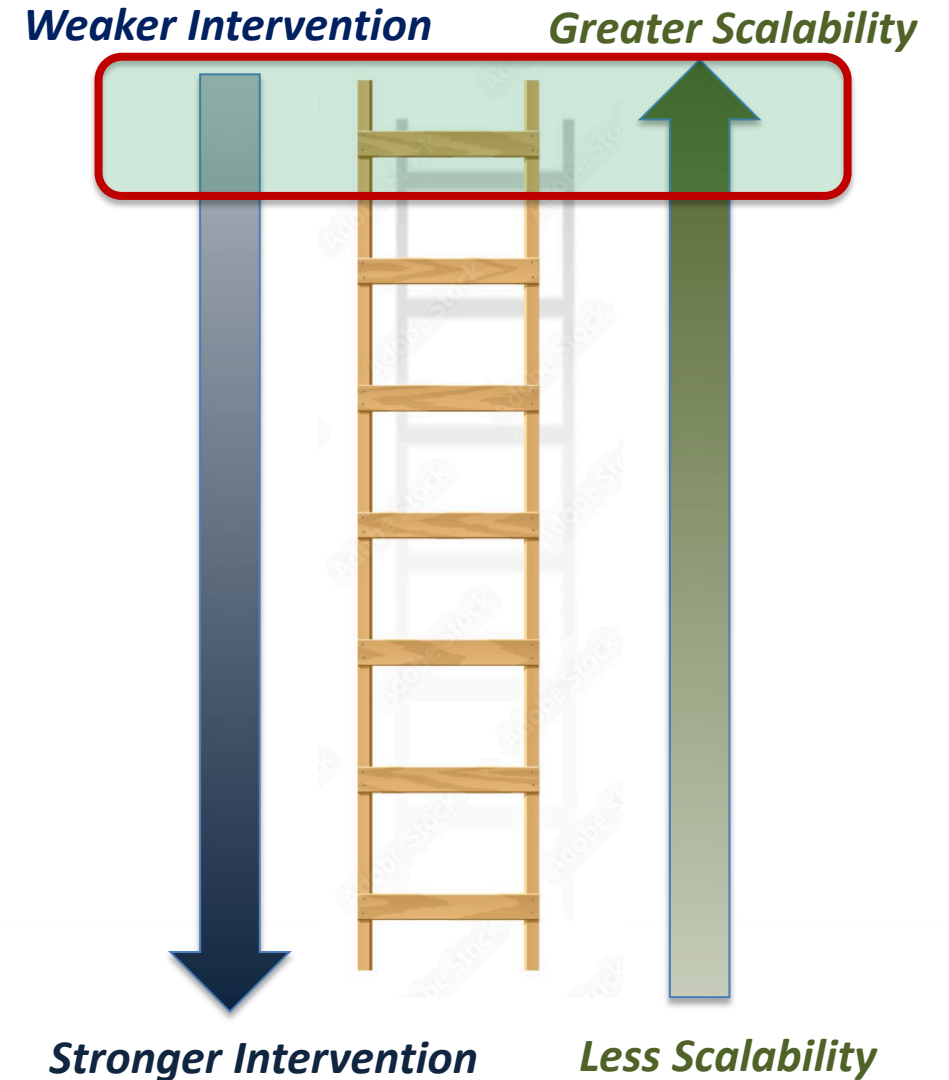
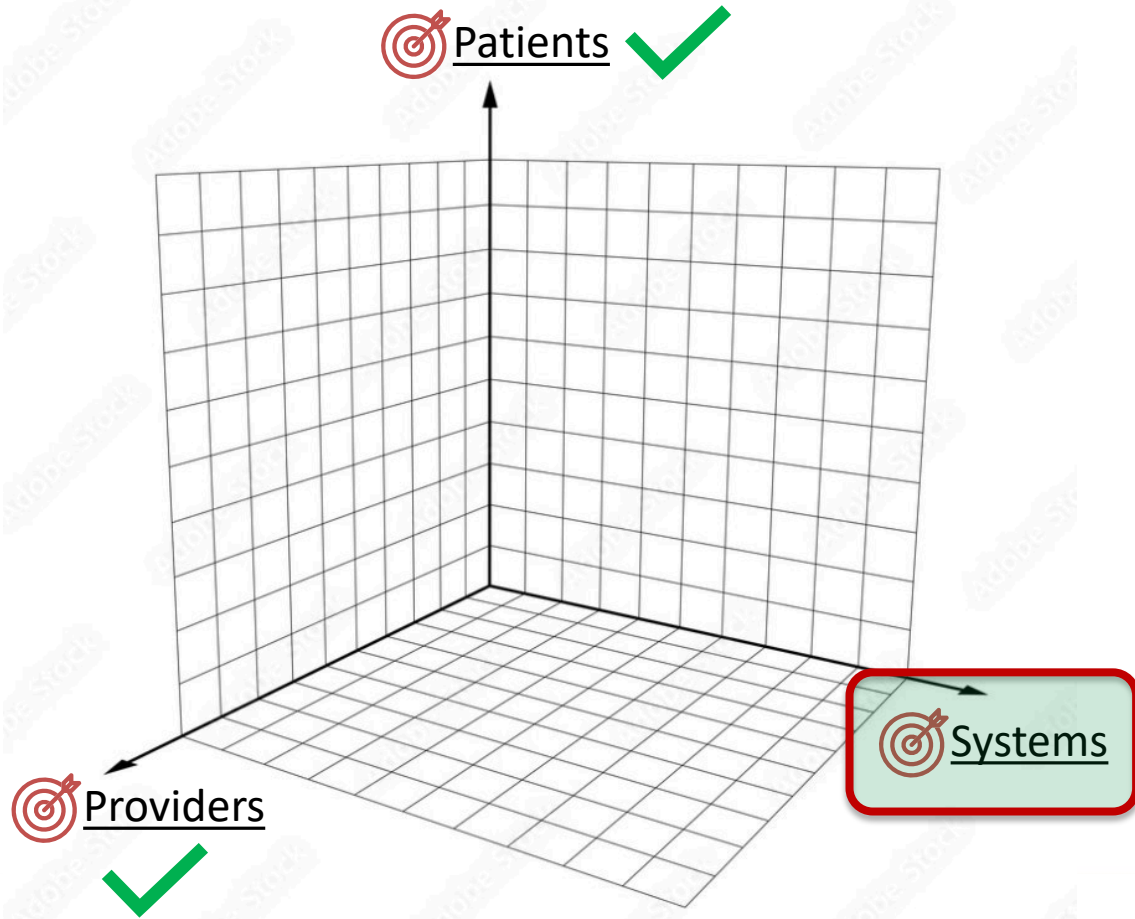
**NIH Collaboratory Grand Rounds**  
**May 30, 2025**  
**Virtual**

# Implementation Science

“...the scientific study of methods and strategies that facilitate the uptake of evidence-based practice and research into regular use by practitioners and policymakers.”




# Implementation Science Frameworks




# Behavioral Science in Everyday Life

## Loss Aversion







RECOMMENDED: ADD TRIP INSURANCE

\*REQUIRED: PLEASE SELECT YES OR NO TO CONTINUE

Protect your trip to New York for \$51.25 total.  Highly Recommended


Several reasons to upgrade your trip to include protection:

-  Reimbursement of cancelled trip costs due to covered injury, illness, or other covered reasons
-  Up to 150% trip interruption protection of ticket costs
-  Travel delay protection
-  Benefits for pre-existing medical conditions

"Buy travel insurance. It can protect you against trip cancellation costs." – USA Today, May 2016

Terms, conditions and exclusions [apply](#). Benefits underwritten by BCS Insurance Company or Jefferson Insurance Company, depending on your state of residence. Recommended by AGA Service Company, the licensed producer and administrator of this plan.

By selecting Complete Purchase, you agree to all the Terms and Conditions and the Hazardous Materials policy outlined below. Federal law forbids the carriage of hazardous materials including explosives, compressed gases, flammable liquids and solids, oxidizers, poison, corrosives and radioactive materials aboard the aircraft, in your luggage, or on your person.

 CURRENCY CALCULATOR

Amount Due \$ 788<sup>00</sup> USD

COMPLETE PURCHASE

## Saliency/Social Norming

### Frequently bought together



Total price: \$49.98

Add both to Cart

Add both to List

## Gamification



# Project M&Ms™: Small change, large impact

Technology

## Google crunches data on munching in office

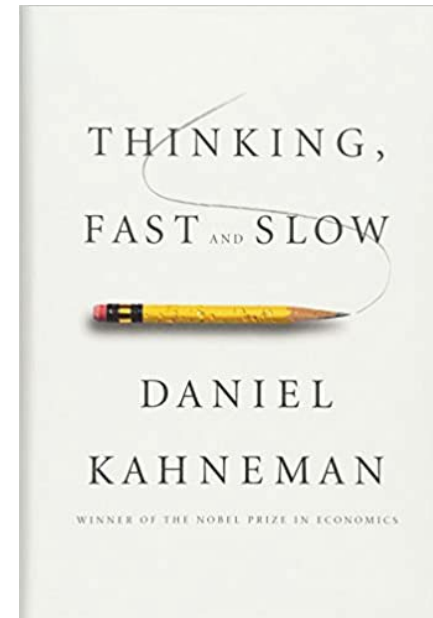
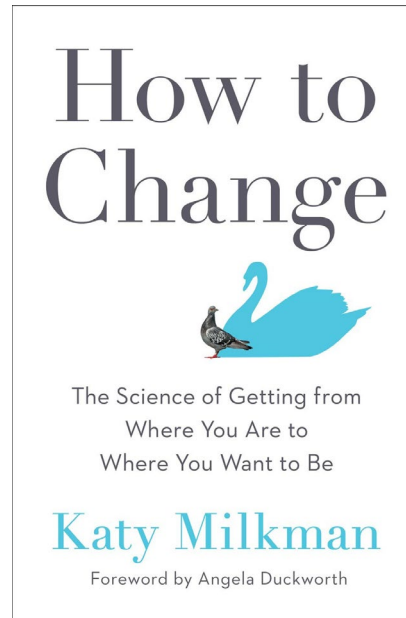
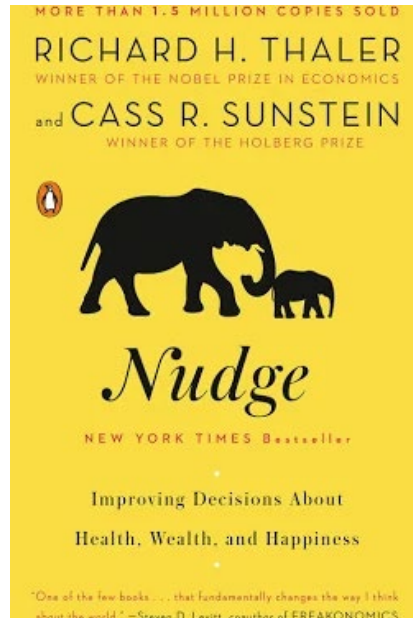


Employees talk near snack jars in one of the office's microkitchens. Google co-founder Sergey Brin insists that every employee be no more than 200 feet away from free food. The idea is that food brings people together, and new products and services could be imagined when workers meet in kitchens and dining halls. (Yana Pashina / For The Washington Post)

What if the company kept the chocolates hidden in opaque containers but prominently displayed dried figs, pistachios and other healthful snacks in glass jars?

The results: In the New York office alone, employees consumed **3.1 million fewer calories** from M&Ms over seven weeks.

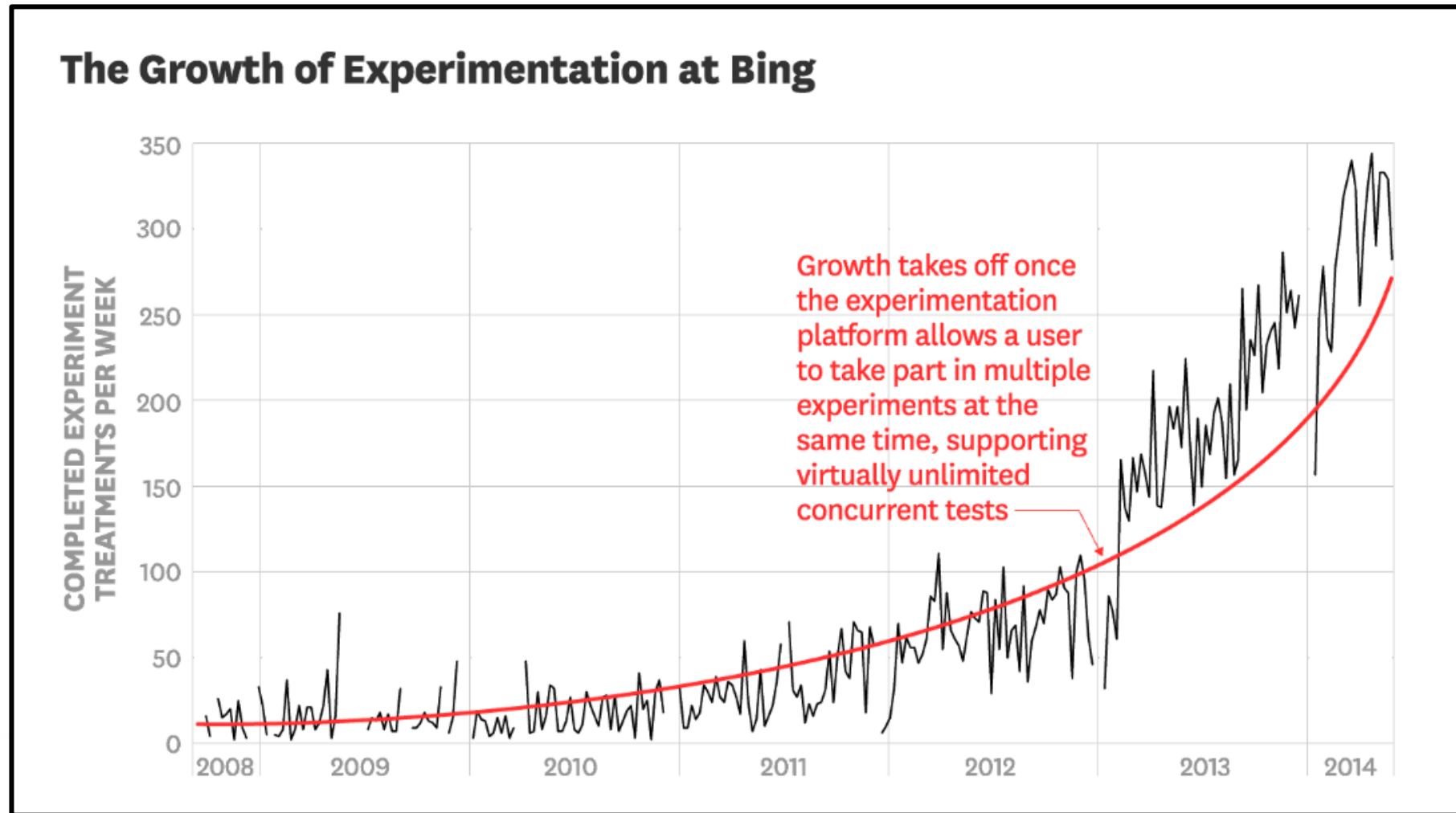
# Behavioral nudges are increasingly embraced by the public



***A nudge is a subtle change in design that can have an outsized impact on human behavior. They can influence behavior without restricting choice.***

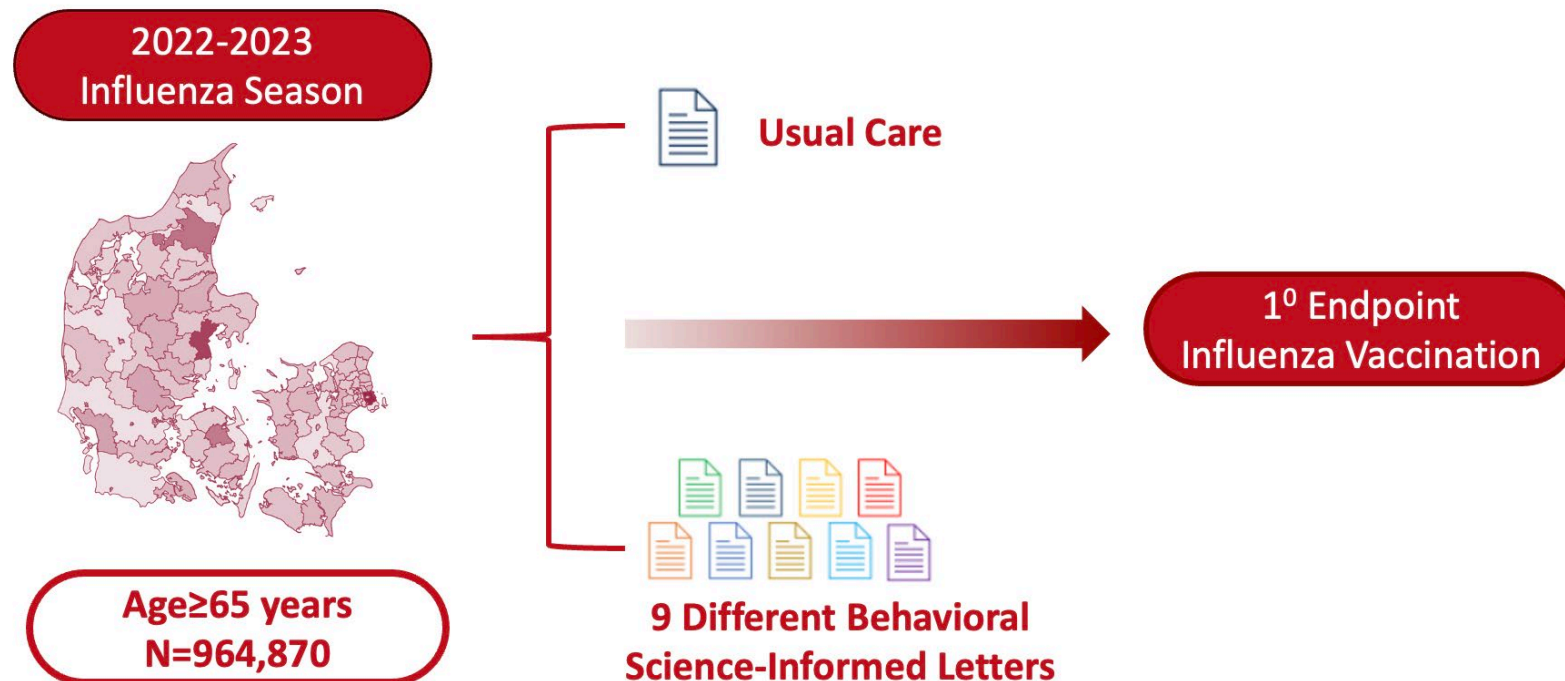


# A/B Randomization



# The NUDGE-FLU Experience: A Nationwide Trial

**Trial: Randomizing ~1 million Danish Citizens to different messaging strategies to improve influenza vaccination.**



**Most effective letter strategies: CV gain frame and repeat letter each resulting in ~1% absolute increase in vaccination rate. *Based on these findings, the Danish gov't changed vaccine messaging in the 2023-2024 season.***

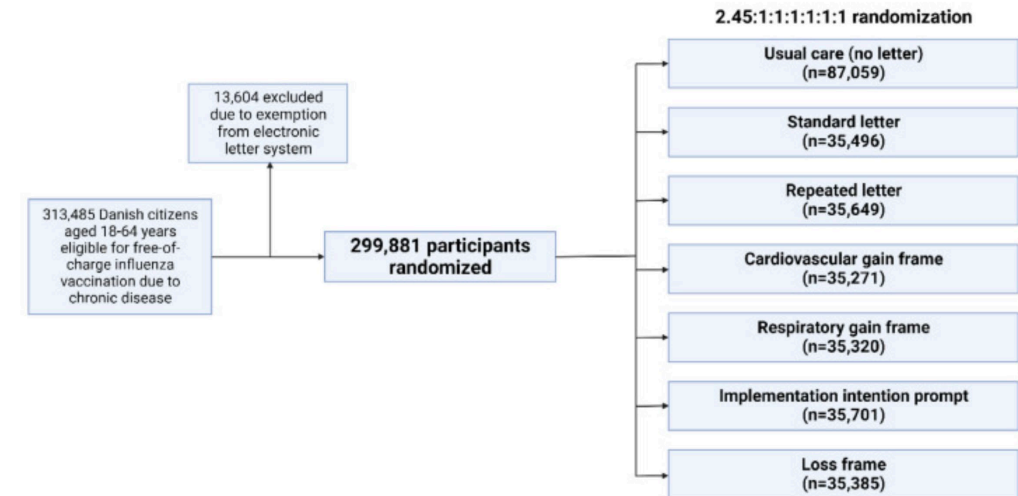


# The NUDGE-FLU Experience: Sequential Randomization

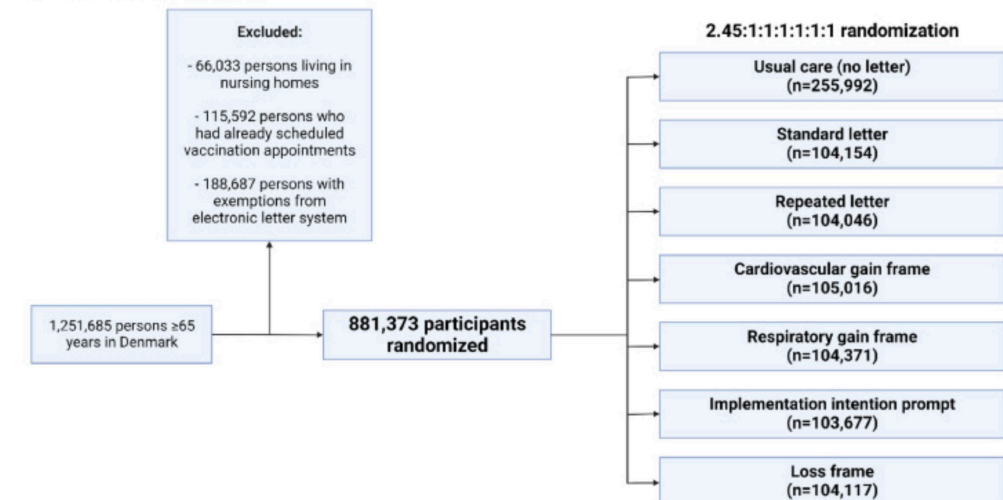
## Trial Designs

Rationale and design of NUDGE-FLU-CHRONIC and NUDGE-FLU-2: Two nationwide randomized trials of electronic nudges to increase influenza vaccination among patients with chronic diseases and older adults during the 2023/2024 influenza season

### A – NUDGE-FLU-CHRONIC



### B – NUDGE-FLU-2



# Eligibility Criteria: NUDGE FLU CHRONIC

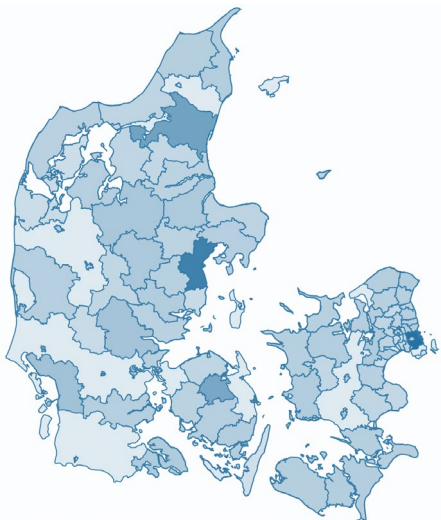
Meeting  $\geq 1$  of following criteria for free-of-charge influenza vaccination in Denmark:

Chronic lung disease
Chronic cardiovascular disease other than hypertension
Type 1 or type 2 diabetes mellitus
Congenital or acquired immunodeficiency
Impaired breathing due to muscular weakness
Chronic renal or hepatic insufficiency
Other chronic conditions with an increased risk of severe influenza as determined by the treating physician

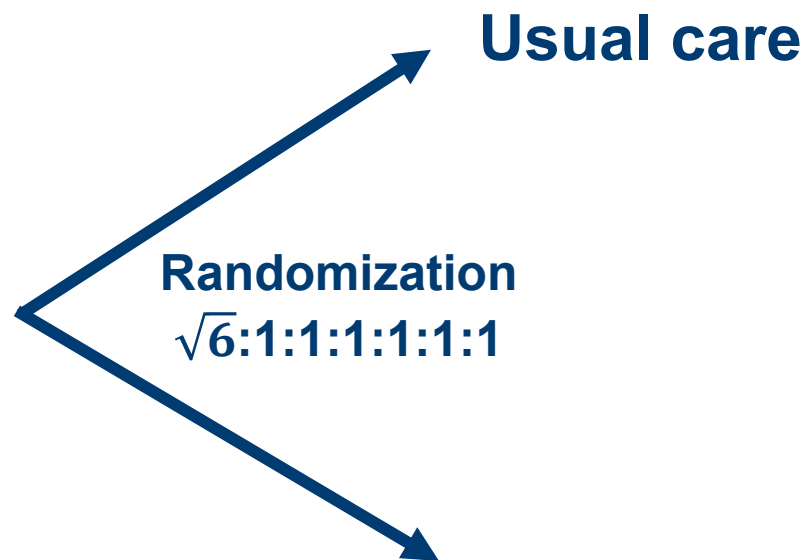
Enrolled in Danish governmental electronic letter system

# NUDGE-FLU Chronic: A Nationwide Trial

2023-2024  
influenza season



Eligible Danish citizens  
aged 18-64 years with  
chronic diseases  
n = 299,654



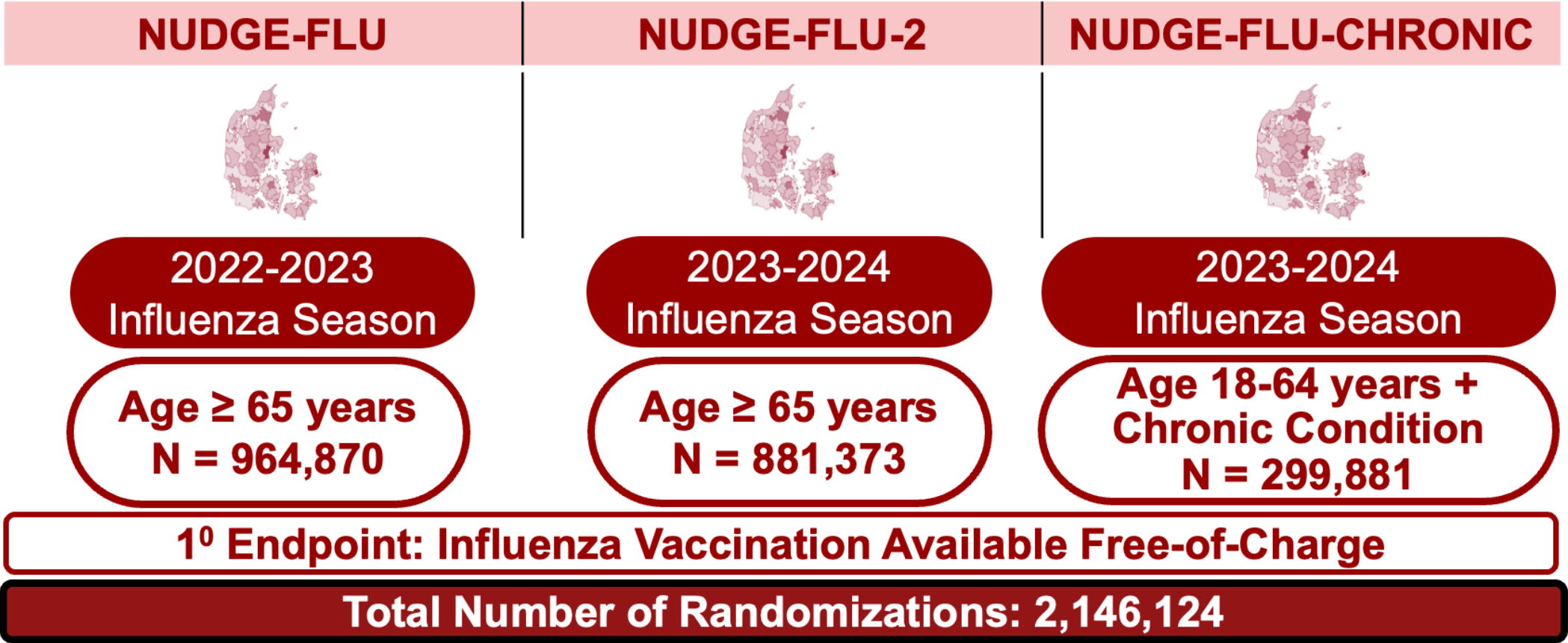
Usual care

Primary endpoint:  
Receipt of influenza  
vaccination



6 different behaviorally  
informed letter strategies

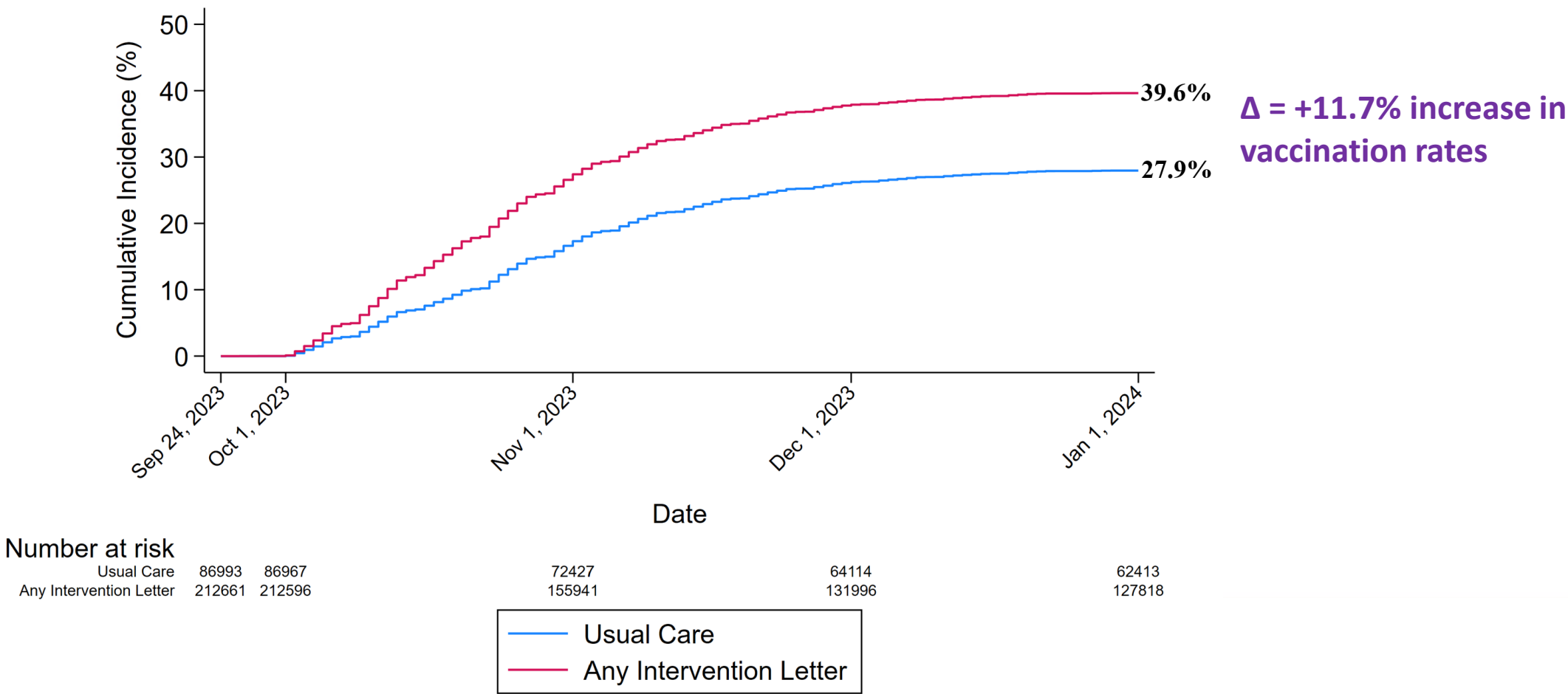
# Sequential Iterative Randomization: The NUDGE-FLU Program



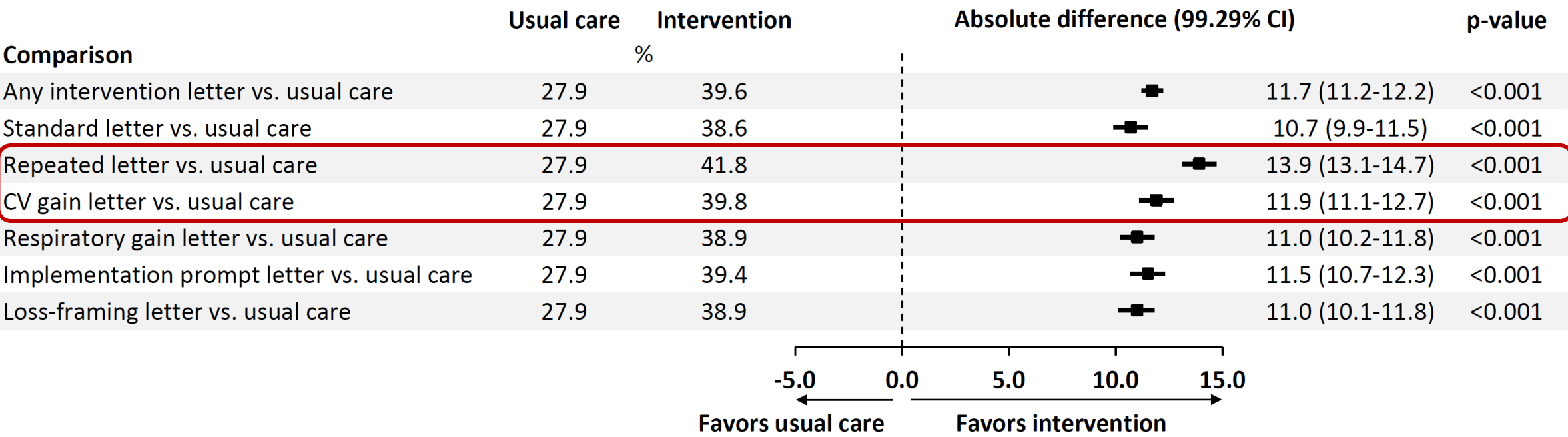
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# Results from NUDGE-FLU Chronic

All Intervention Arms Pooled vs. Usual Care



# Results from NUDGE-FLU Chronic





# Example Text

Dear [name]



The annual flu season is approaching, and with this letter we want to remind you that you can get vaccinated against the flu for free. The offer applies to everyone aged 65 and over. The offer also applies if you turn 65 by 15 January 2023 at the latest.

You can be vaccinated against influenza at vaccination clinics across the country. No specific number of days need to pass between this vaccine and a covid-19 and/or pneumococcal vaccine. The vaccines can therefore be given at the same time.

[Placeholder for text-based nudges]

**Vaccination against influenza**

For most people, the flu is harmless, but for people at particular risk, including people aged 65 or older, the disease can be serious. We therefore hope that you will take up the offer of free vaccination, which is valid from 1 October 2022 to 15 January 2023.

Influenza viruses change (mutate) over time, which is why it is important that you get vaccinated every year.

**Vaccination protects both yourself and others**

When you get vaccinated against the flu, you protect yourself first and foremost. But you also reduce the risk of infecting others who may be more vulnerable.

Over the next few days, you will receive more information about where you can be vaccinated. Until then, you can find more information at [minvaccination.dk](https://minvaccination.dk), [vacciner.dk](https://vacciner.dk) or [ssi.dk/influenzavaccination](https://ssi.dk/influenzavaccination).

**Bliv vaccineret mod influenza**

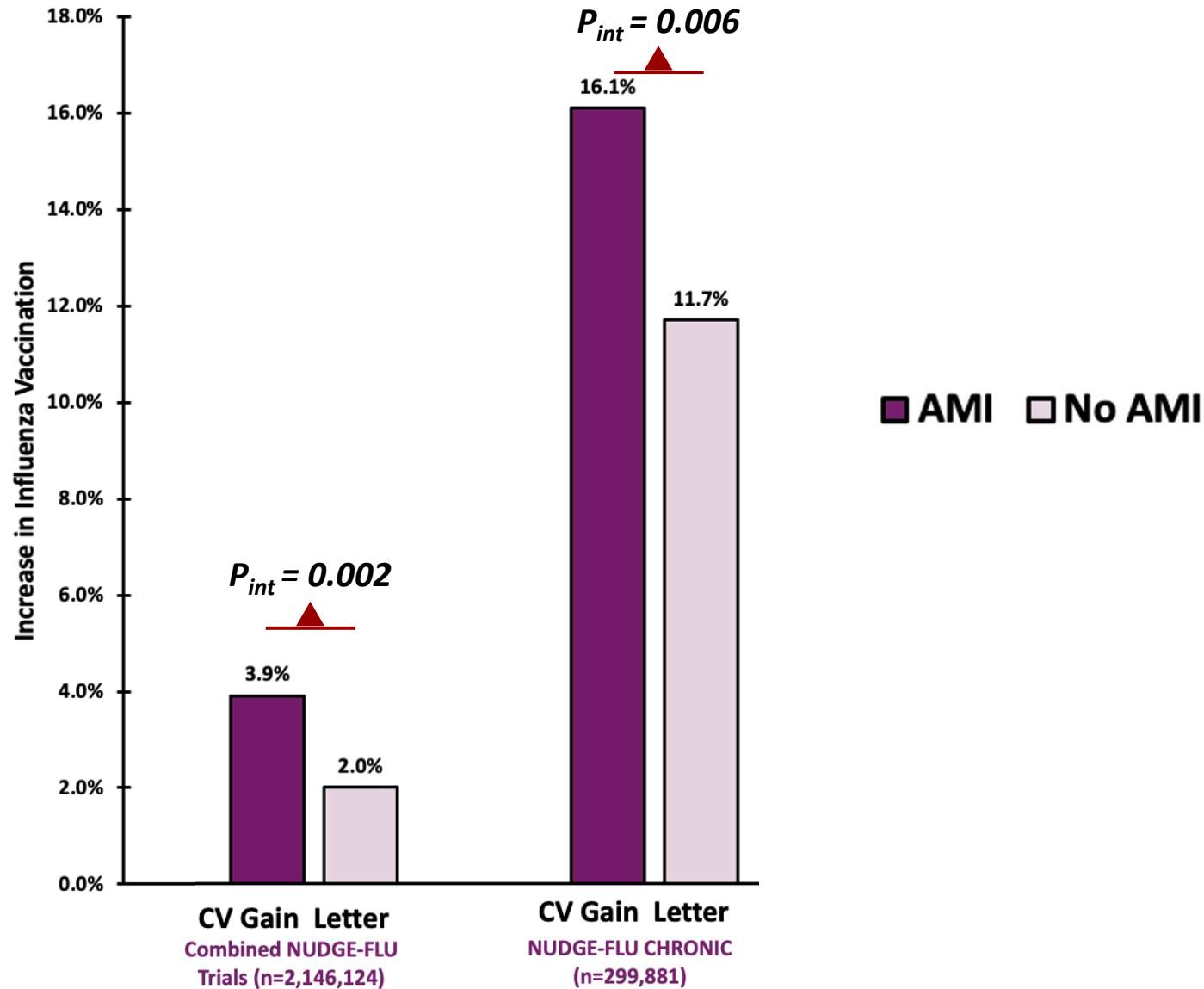
De danske sundhedsmyndigheder anbefaler, at 75% af alle over 65 år bliver vaccineret mod influenza.

Det lykkedes i 2021 – vi håber også, det lykkes i år.

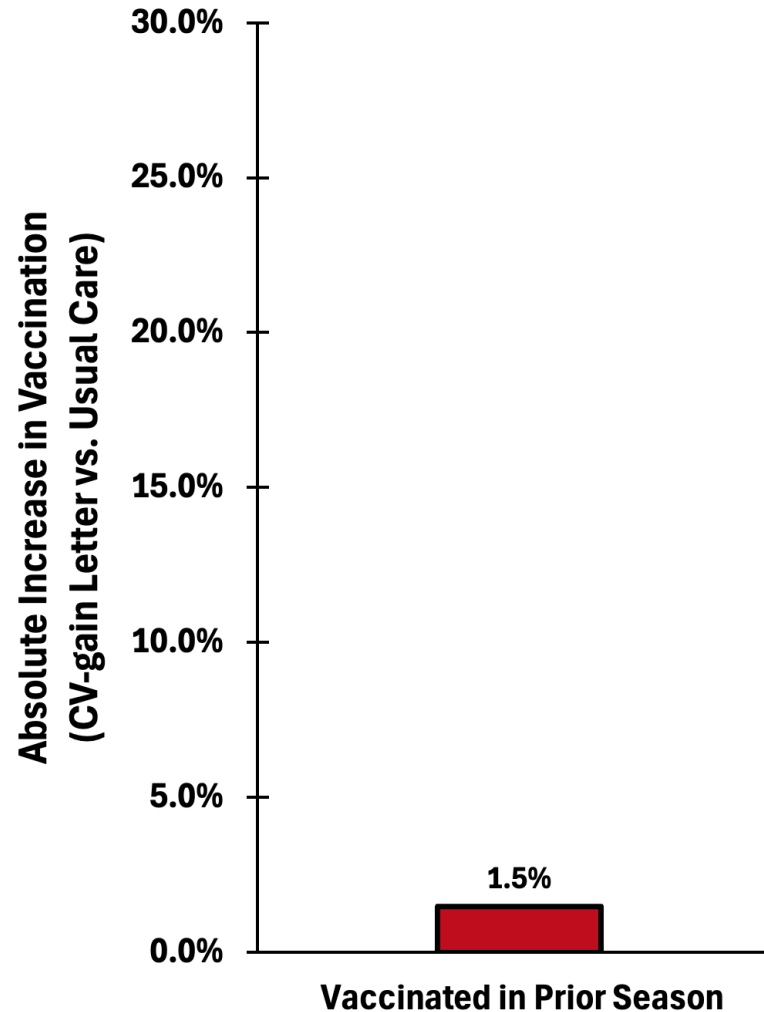


**CV-Gain Frame Letter:**  
***“In addition to its protection against influenza infection, vaccination also seems to protect against cardiovascular disease such as heart attacks and heart failure.”***

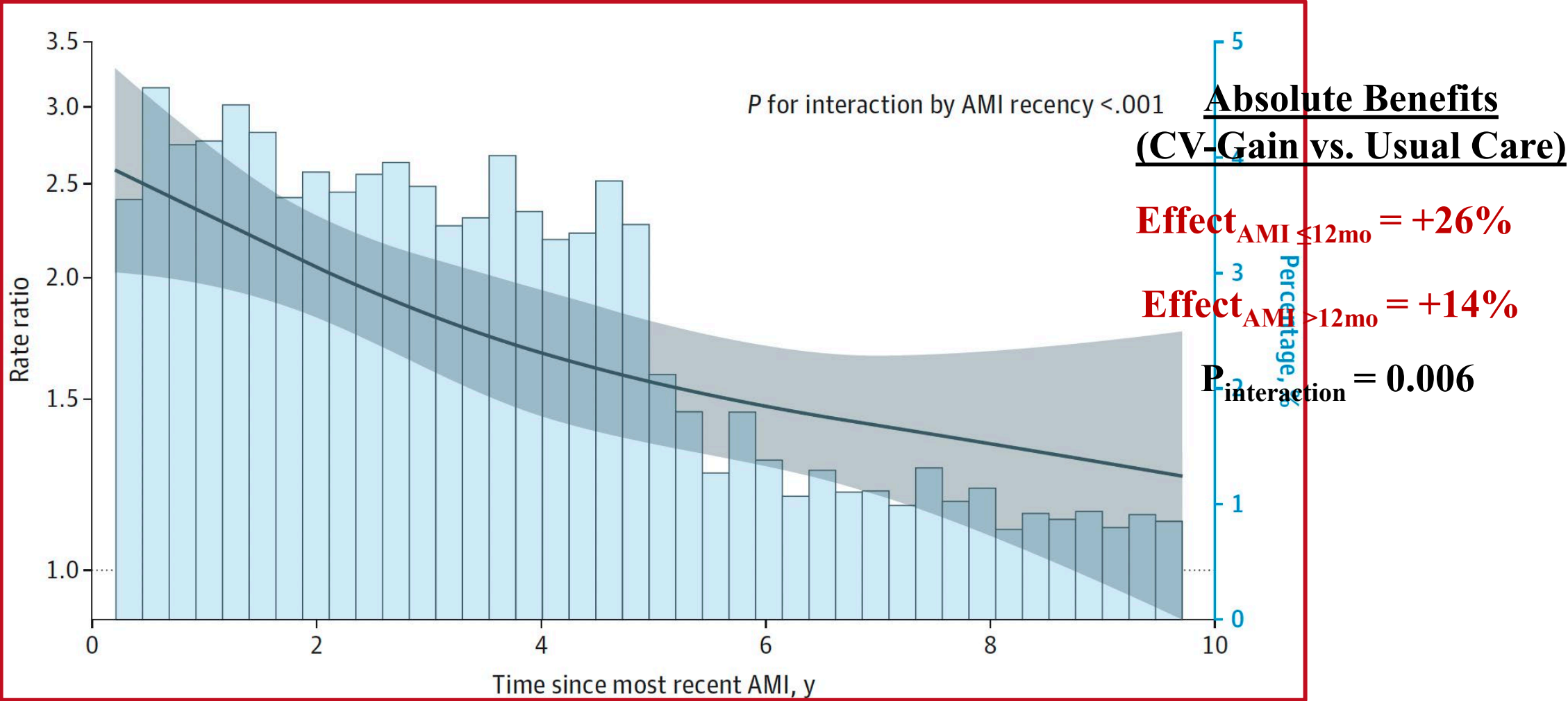
# EFFECTS OF CV-GAIN NUDGE BY AMI STATUS



# IN PTS WITH AMI, CV-GAIN NUDGE MORE EFFECTIVE NOT VACCINATED IN PRIOR SEASON



# CV-GAIN NUDGE MORE EFFECTIVE IN WITH RECENT AMI IN NUDGE-FLU-CHRONIC



# Extending Beyond Vaccination

## The NUDGE Trial Concept

Nationwide Utilization of Danish Government Electronic Letter System

### Nationwide Health Registries



Identification of population of interest, source of all baseline and outcome data

### Letter Interventions



Letters designed with behavioral science, delivered to patients and/or clinicians to influence health-related behavior

### Government Electronic Letter System



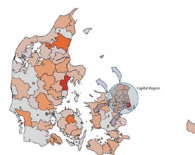
Secure nationwide delivery of behaviorally informed letter interventions

Table 1. Current and Planned NUDGE Trials.\*

Trial name	ClinicalTrials.gov	Study Aim	Population	Intervention(s)	Randomization	Primary End Point	Status
NUDGE-FLU <sup>51</sup>	<a href="#">NCT05542004</a>	Increase influenza vaccination rates	Adults ≥65 years (n=964,870)	9 different nudging letters delivered prior to influenza vaccination period	Cluster randomization at household level (n=691,820 households)	Receipt of an influenza vaccine	Completed follow-up for primary end point (main findings published in <i>Lancet</i> <sup>52</sup> )
NUDGE-FLU-2	<a href="#">NCT06030726</a>	Increase influenza vaccination rates	Adults ≥65 years	6 different nudging letters delivered prior to influenza vaccination period	Cluster randomization at household level	Receipt of an influenza vaccine	Ongoing
NUDGE-FLU-CHRONIC	<a href="#">NCT06030739</a>	Increase influenza vaccination rates	Adults 18–64 years with chronic disease	6 different nudging letters delivered prior to influenza vaccination period	Individual randomization at patient level	Receipt of an influenza vaccine	Ongoing
NUDGE-DM	TBD	Increase uptake of novel antidiabetic medication	T2DM patients with ASCVD, HF, or CKD with no prior use of GLP-1 RA or SGLT2i	Nudging letter delivered to patients and/or their general practitioner in a two-by-two factorial design	Patient letter, individual randomization at patient level; general practitioner letter, cluster randomization at general practitioner level	Filled prescription for GLP-1 RA or SGLT2i	Planned
NUDGE-DM-Persistence	TBD	Increase adherence and persistence to GLP-1 RA therapy	T2DM patients who fill their first prescription for a GLP-1 RA	3 consecutive nudging letters delivered at 12, 24, and 36 weeks after initiation	Individual randomization at patient level stratified on injectable/oral and daily/weekly treatment	GLP-1 RA persistence at 12 months	Planned
NUDGE-CKD	TBD	Increase GDMT uptake	CKD patients with no current GDMT use	Nudging letter delivered to patients and/or their general practitioner in two-by-two factorial design	Patient letter, individual randomization at patient level; general practitioner letter, cluster randomization at general practitioner level	Filled prescription for SGLT2i or RASi	Planned
NUDGE-Ischemia	TBD	Increase use of statin therapy	T2DM and ASCVD patients eligible for statin with no current statin use	Nudging letter delivered to patients and/or their general practitioner in a two-by-two factorial design	Patient letter, individual randomization at patient level; general practitioner letter, cluster randomization at general practitioner level	Statin prescription	Planned

# Learning Labs in Healthcare

## Denmark



**~5.9M**

***Size***

***Standardized Data***



***Centralized Payer***



***Full Endpoint Capture***



***Electronic Communication***



***Diverse Racial/Ethnic Population***

***Rich Fully Searchable EHR Data***

## Kaiser Permanente

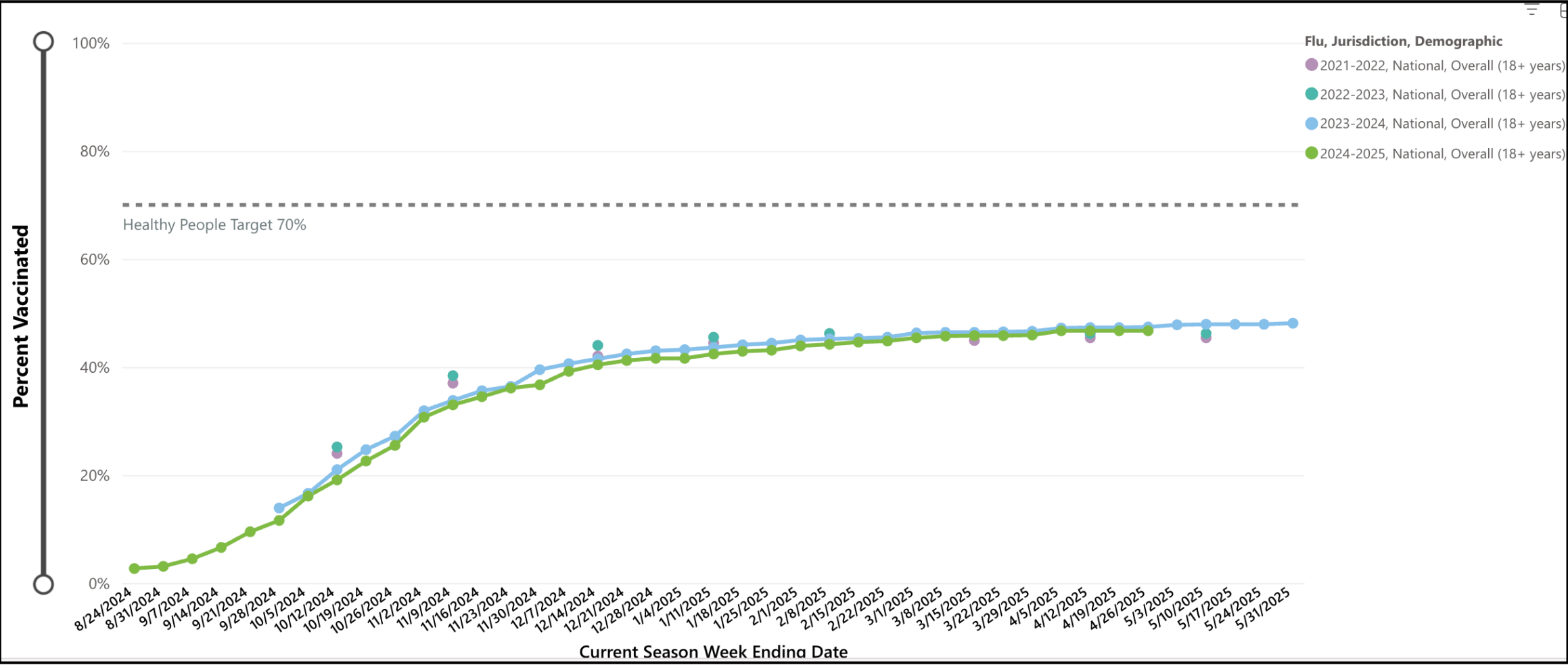


**~5.3M**

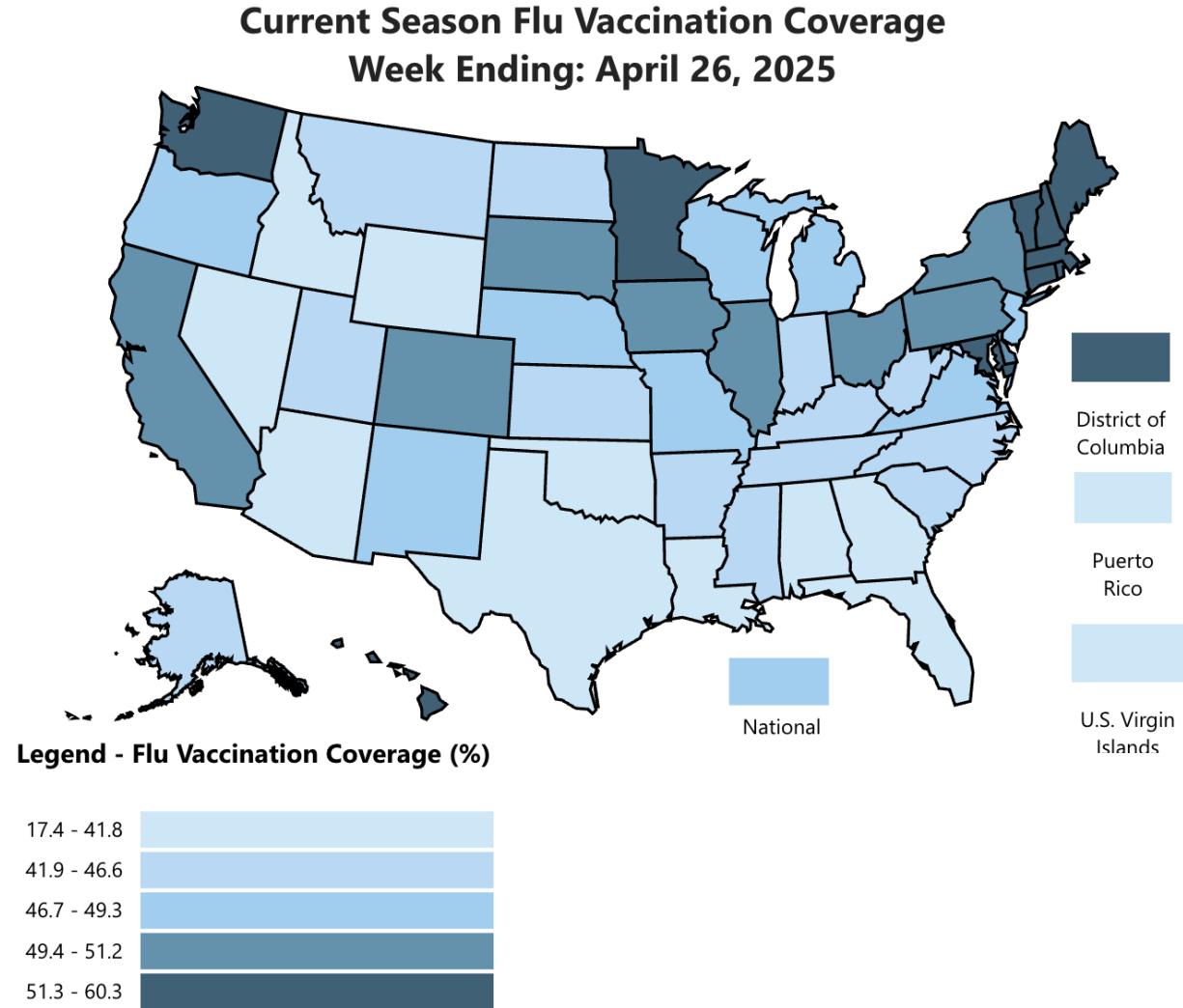




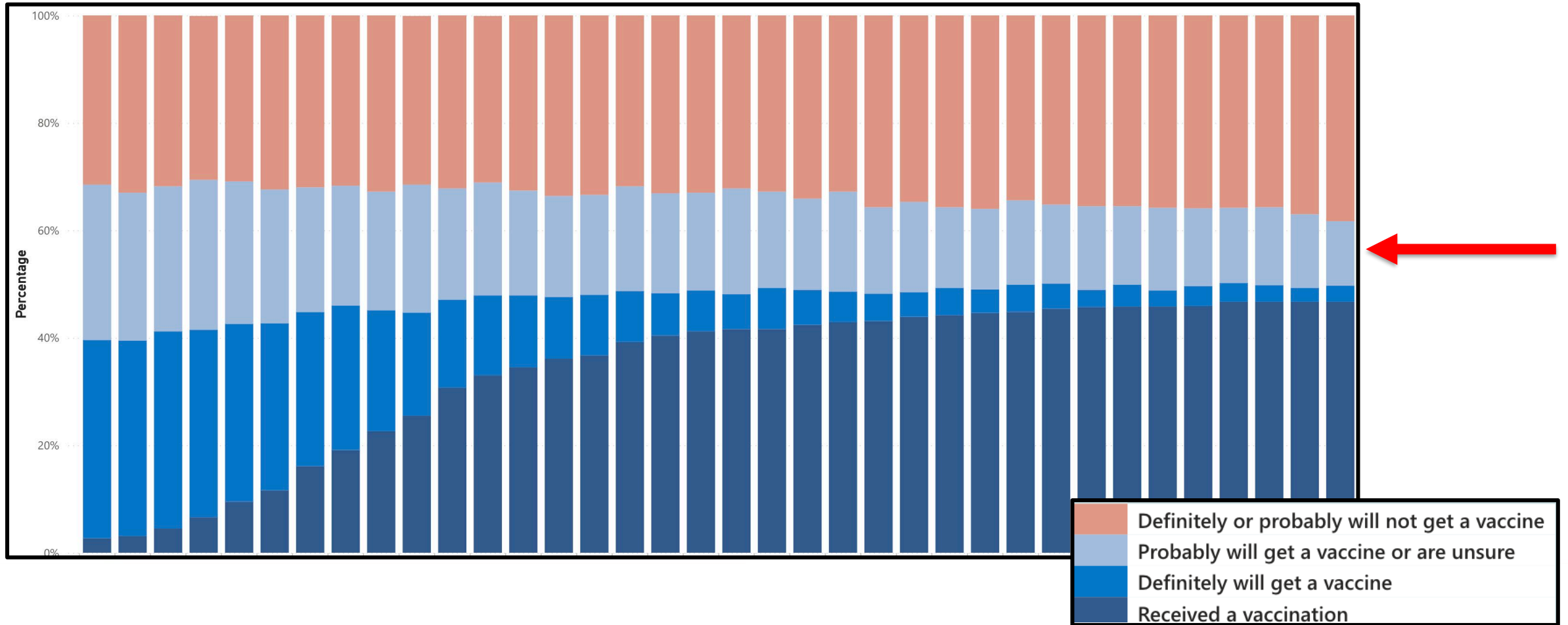
# Vaccination in the United States



# Vaccination in the United States

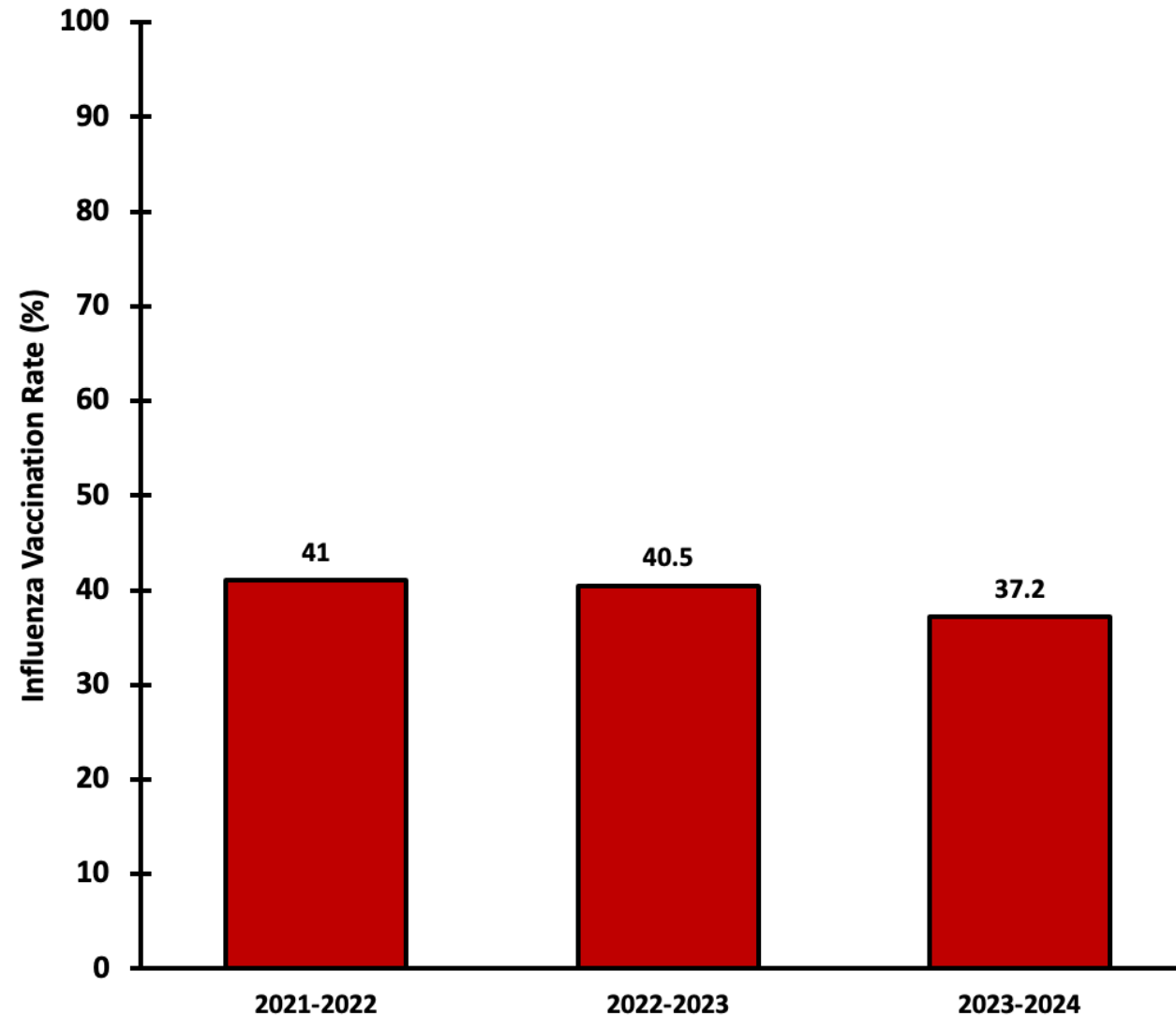


# Vaccination in the United States



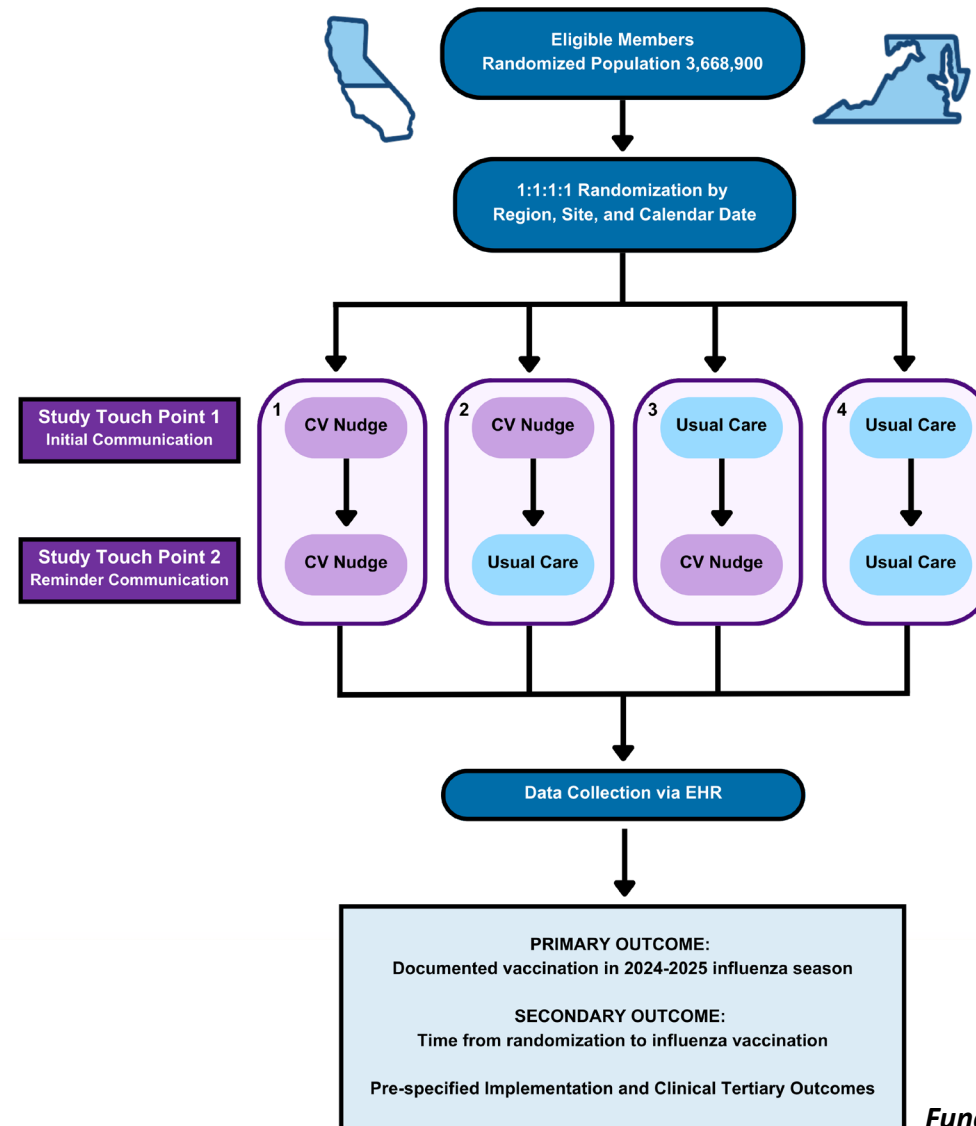
# Baseline Vaccination Rates

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# KP VACCINATE: Fully Care Embedded RCT at Scale

**Kaiser Permanente**  
**VACCination Improvement**  
**with Nudge-based**  
**Cardiovascular Targeted**  
**Engagement**  
**(NCT06571747)**

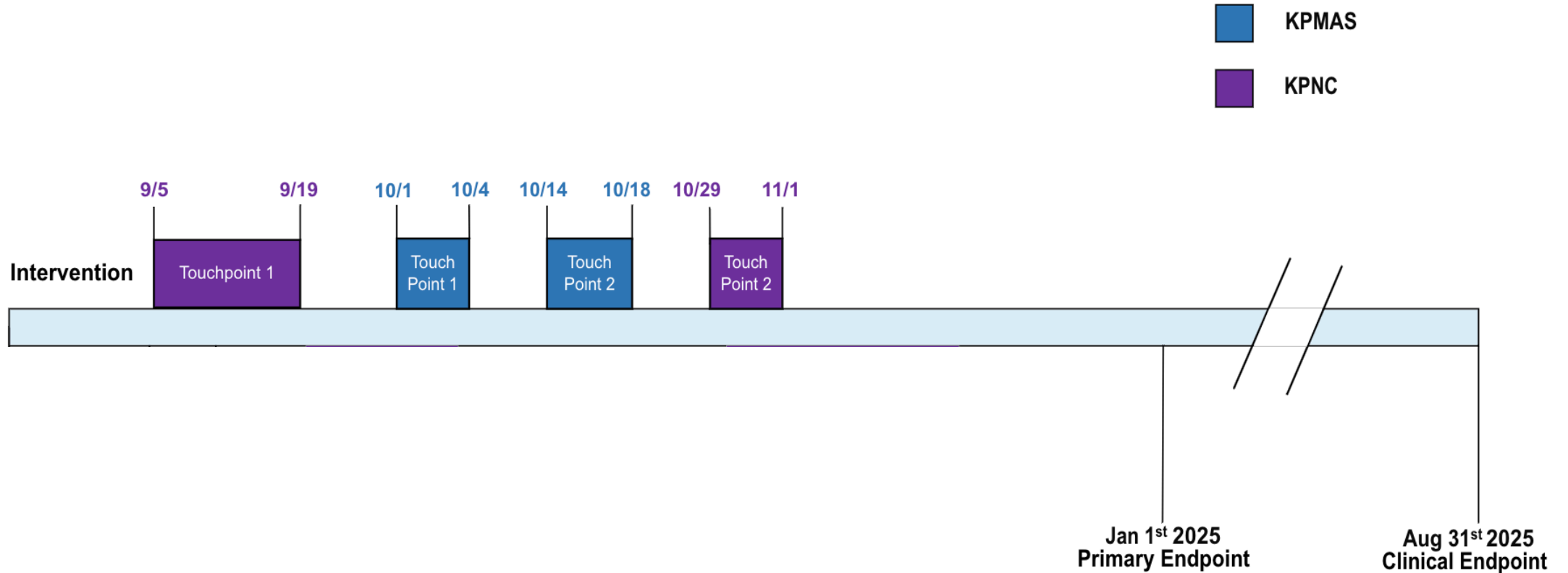


# Pragmatic Systemwide Inclusion

Inclusion Criteria	Exclusion Criteria
Age $\geq 18$ years	Unable to receive or opted out of receiving health system messaging
Active KPNC or KPMAS health plan member as of September 1, 2024	Other exclusion that prevents messaging outreach
$\geq 6$ months of continuous health plan coverage and prescription drug benefit before September 1, 2024	Unknown service area or medical center affiliation
Evidence of member access of the KP HealthConnect <sup>®</sup> Portal and/or a listed registered email address	History of diagnosed Guillain-Barre Syndrome
No documented influenza vaccination during the 2024–2025 influenza season prior to randomization	

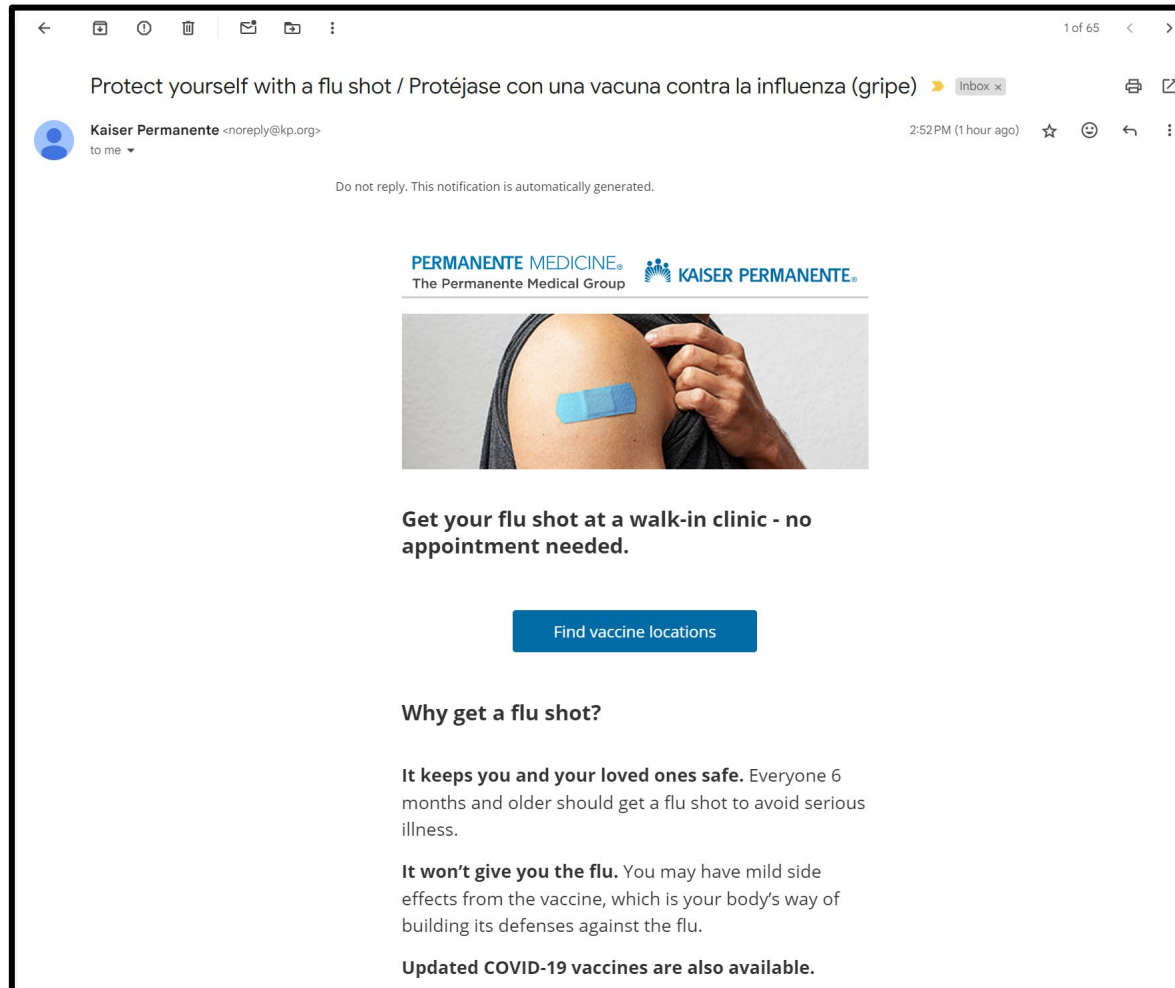


# KP VACCINATE: Randomization Scheme

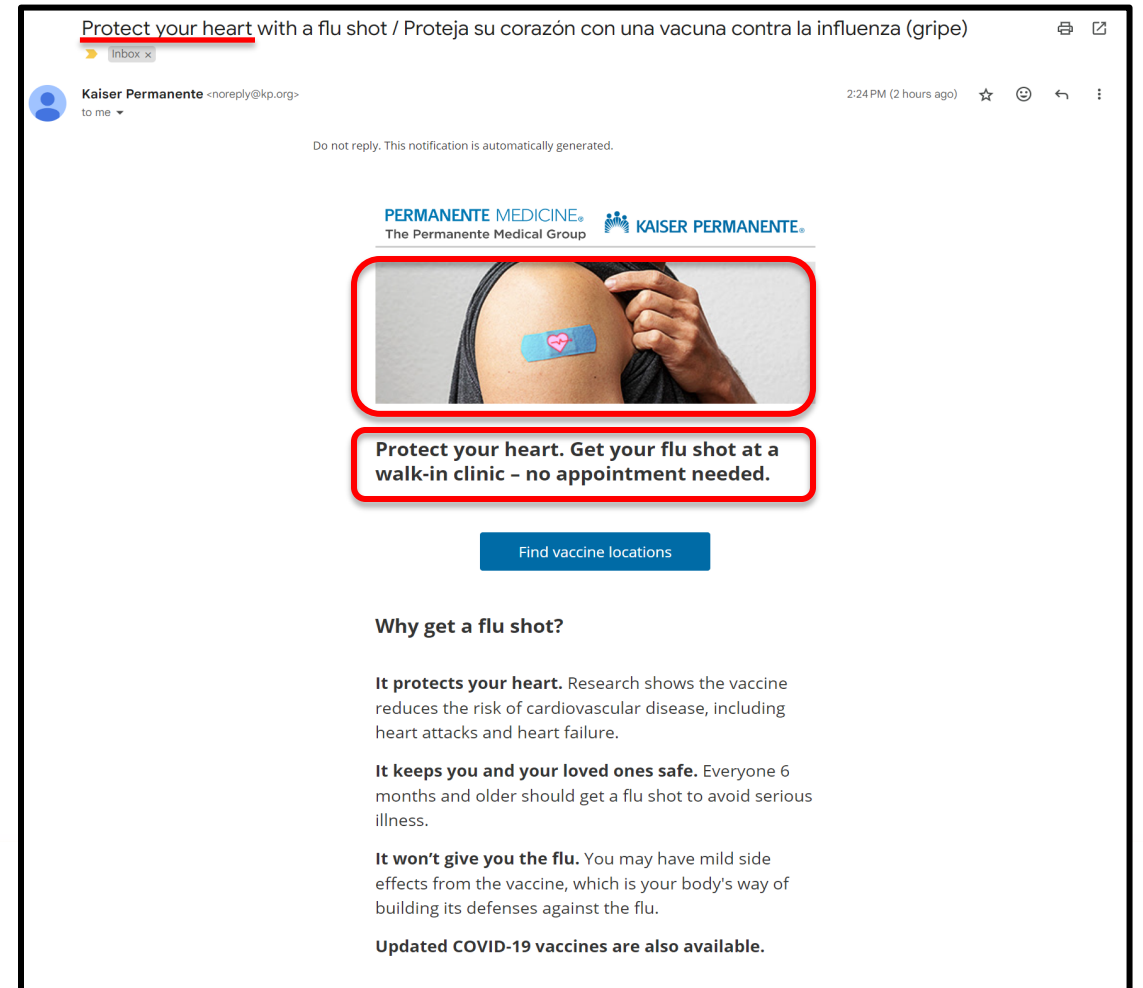


# Randomization Treatment Arms: KP Northern California

## Usual Care Communication



## Cardiovascular Focused Communication



# Randomization Treatment Arms: KP Mid Atlantic

## Usual Care Communication

.KPVACCINATEREG

TITLE: Protect Yourself From The Flu

Dear @NAME@,

According to our records, you have not had a flu shot this season. The flu vaccine can protect you from getting sick from the flu virus. It can also decrease the severity of the symptoms from the flu if you do get sick.

The vaccine is safe, simple, quick, and no additional cost to you. For your safety, you can schedule a no-copay flu shot by [visiting this link](#) or contacting the call center at (703) 359-7878 or toll-free 1-800-777-7904.

Tips to prevent the spread of the flu:

- Wash your hands often with soap and warm water, or use hand sanitizer
- Cough and sneeze into your sleeve or a tissue
- Avoid touching your face unnecessarily
- Distance yourself from others who are sick

If you have already received the flu shot outside of Kaiser Permanente, please click on the attached questionnaire.

We encourage you to watch [this video](#) from Dr. Paul McClain discussing the importance of getting your flu shot every year.

Please [visit us online](#) for more information about the flu shot.

## Cardiovascular Focused Communication

.KPVACCINATECV

TITLE: **Protect Your Heart With a Flu Shot Today!**

Dear @NAME@,

According to our records, you have not had a flu shot this season. The flu vaccine can protect you from getting sick from the flu virus, and **may also protect the heart**. It can also decrease the severity of the symptoms from the flu if you do get sick.

**Research shows the vaccine reduces the risk of cardiovascular disease, including heart attacks and heart failure.**

The vaccine is safe, simple, quick, and no additional cost to you. For your safety, you can schedule a no-copay flu shot by [visiting this link](#) or contacting the call center at (703) 359-7878 or toll-free 1-800-777-7904.

Tips to prevent the spread of the flu:

- Wash your hands often with soap and warm water, or use hand sanitizer
- Cough and sneeze into your sleeve or a tissue
- Avoid touching your face unnecessarily
- Distance yourself from others who are sick

If you have already received the flu shot outside of Kaiser Permanente, please click on the attached questionnaire.

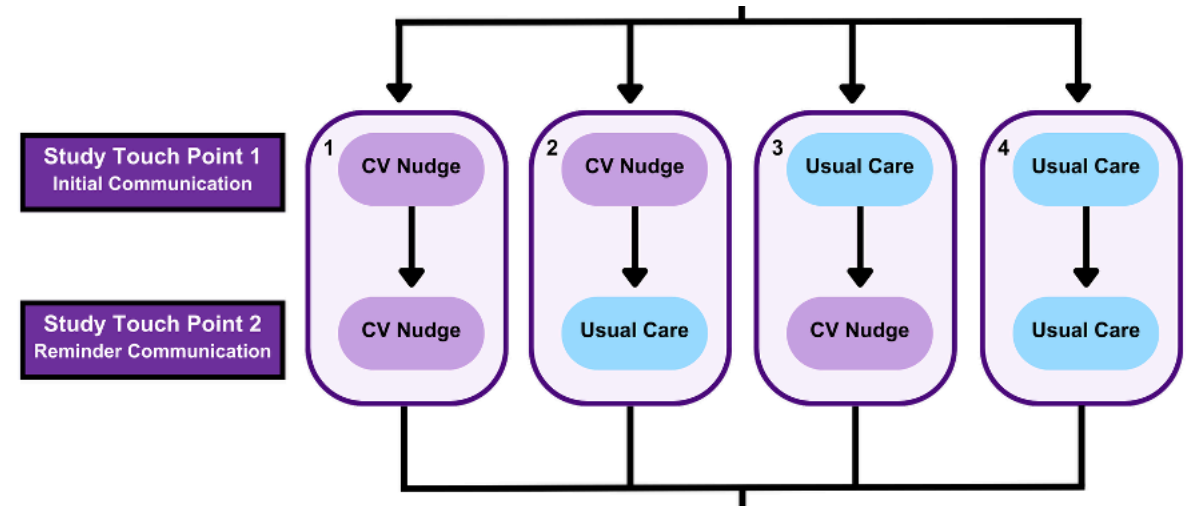
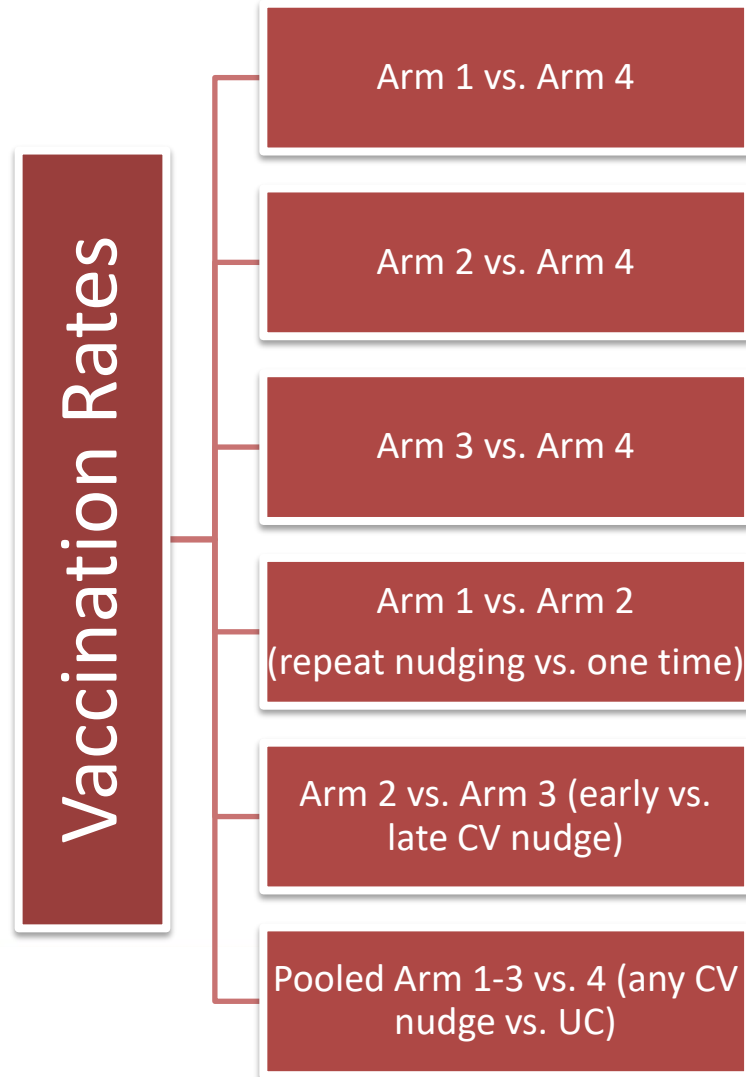
We encourage you to watch [this video](#) from Dr. Paul McClain discussing the importance of getting your flu shot every year.

Please [visit us online](#) for more information about the flu shot.

# Outcomes of Interest

Primary Outcome	Vaccination Rate
Key Secondary Outcome	Time to Vaccination
Prespecified Exploratory Outcomes	Incidence of laboratory-confirmed influenza infection.
	Hospitalization for influenza or pneumonia.
	Adverse CV events: HF, Hosp. for AMI, Afib, VTE, stroke
	All-cause hospitalization, emergency department (ED) visits, and observation stays.
	All-cause intensive care unit (ICU) days.
	Total inpatient days.
	All-cause death, ascertained through a combination of Social Security Administration files, state death certificate files, EHR data, and member proxy reporting.
	Composite of adverse CV events (incident or worsening heart failure events, hospitalization for acute myocardial infarction, atrial fibrillation, venous thromboembolism and hospitalization or acute stroke) and all-cause death.
Implementation Outcomes	Vaccination scheduling link click-through rate.
	Secure messaging read receipt rates.

# Primary Outcome Assessment



# Select Prespecified Subgroups of Interest

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**Age:** <55, 55-64, ≥65 years

**Sex** (self-Identified)

**Race:** White, Black, Asian American and Native Hawaiian/Pacific Islander (AANHPI), Multiracial, other

**Ethnicity:** Hispanic or non-Hispanic

**Socioeconomic Status:** defined using the neighborhood deprivation index (NDI)

**Region** (overall and by service area/facility): KPNC or KPMAS and by service area/medical center

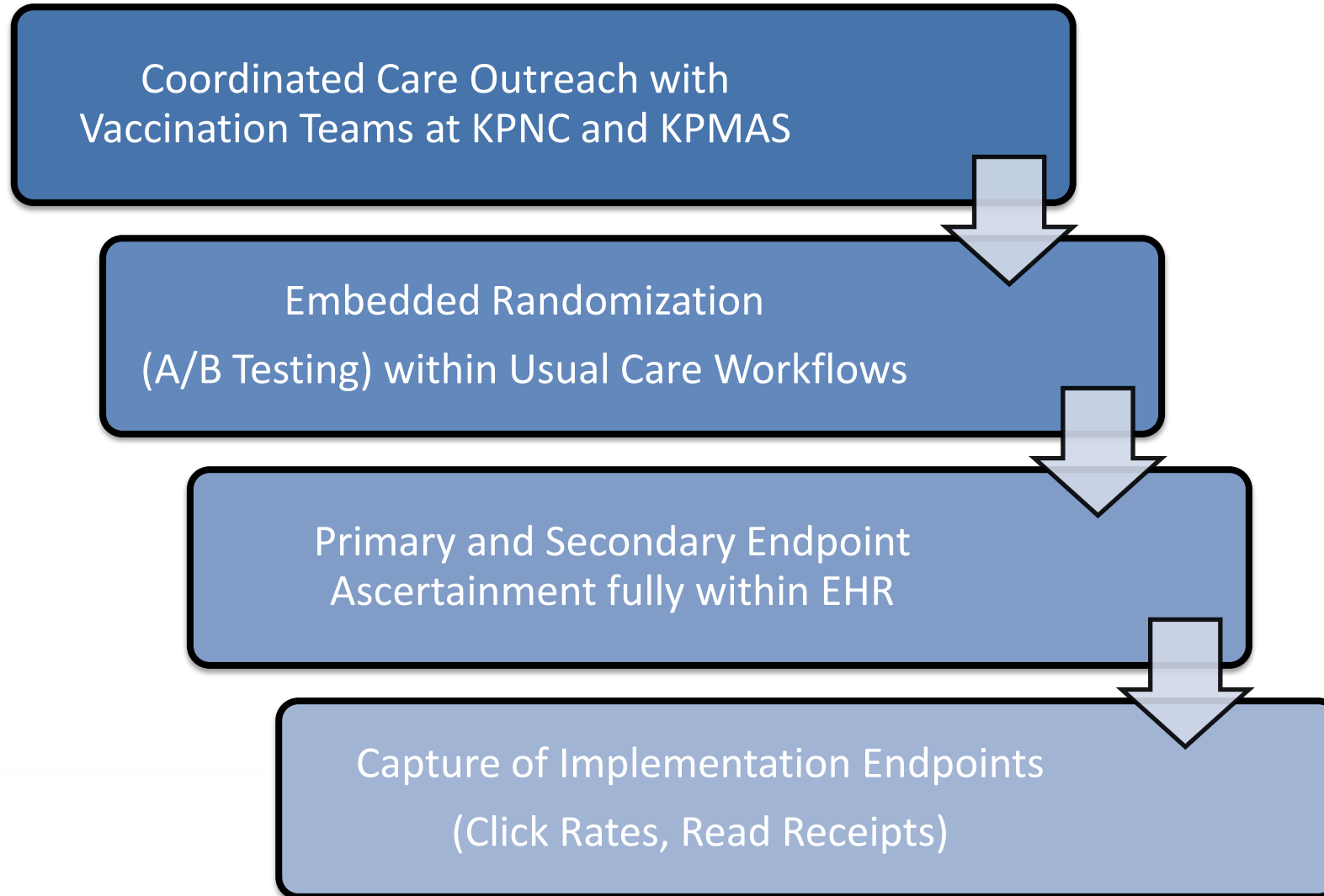
**Chronic obstructive pulmonary disease:** Yes or no

**Prior CV disease:** Yes or no; defined as a documented history of heart failure, acute myocardial infarction, atrial fibrillation, or stroke



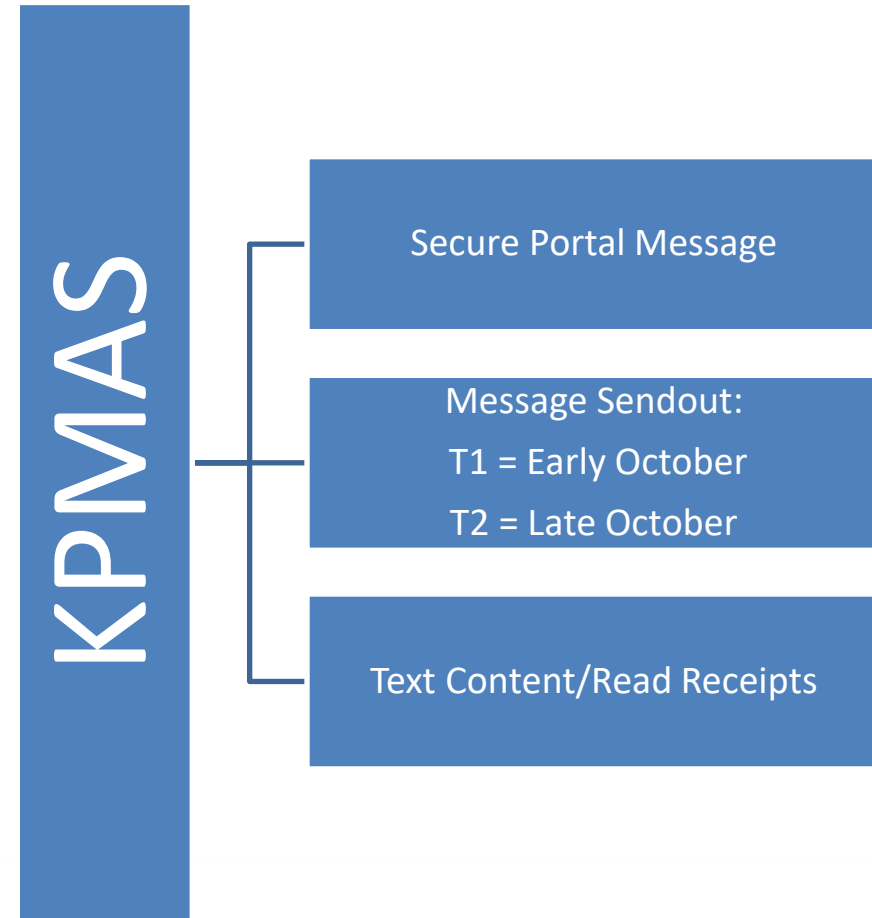
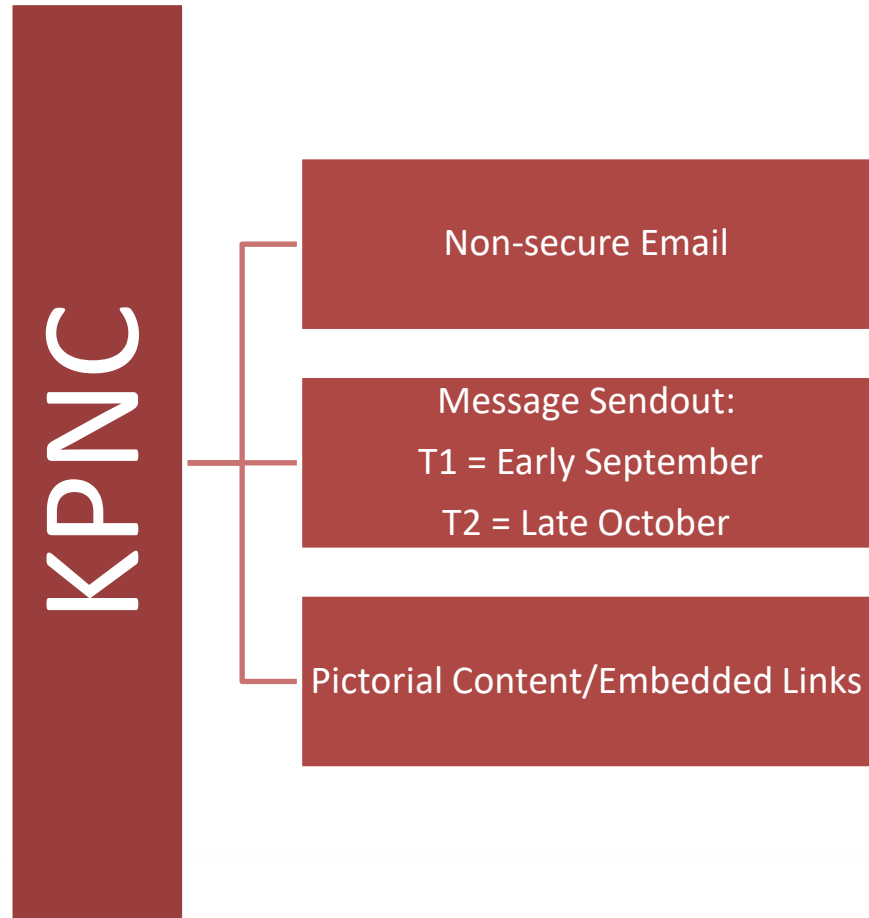
# Pragmatic Embedded Clinical Trial Elements

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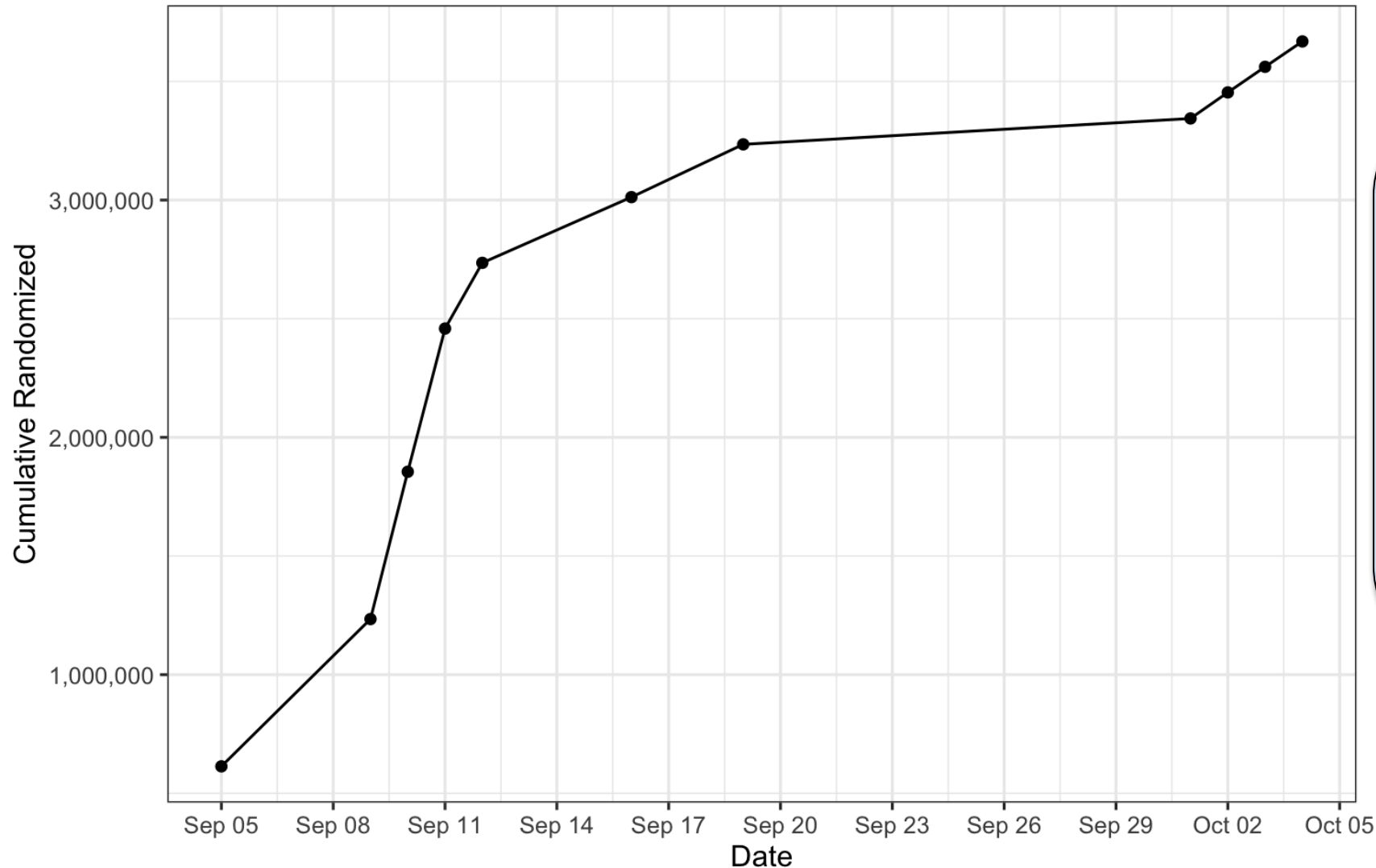


# Local Adaptation to a Unified Protocol

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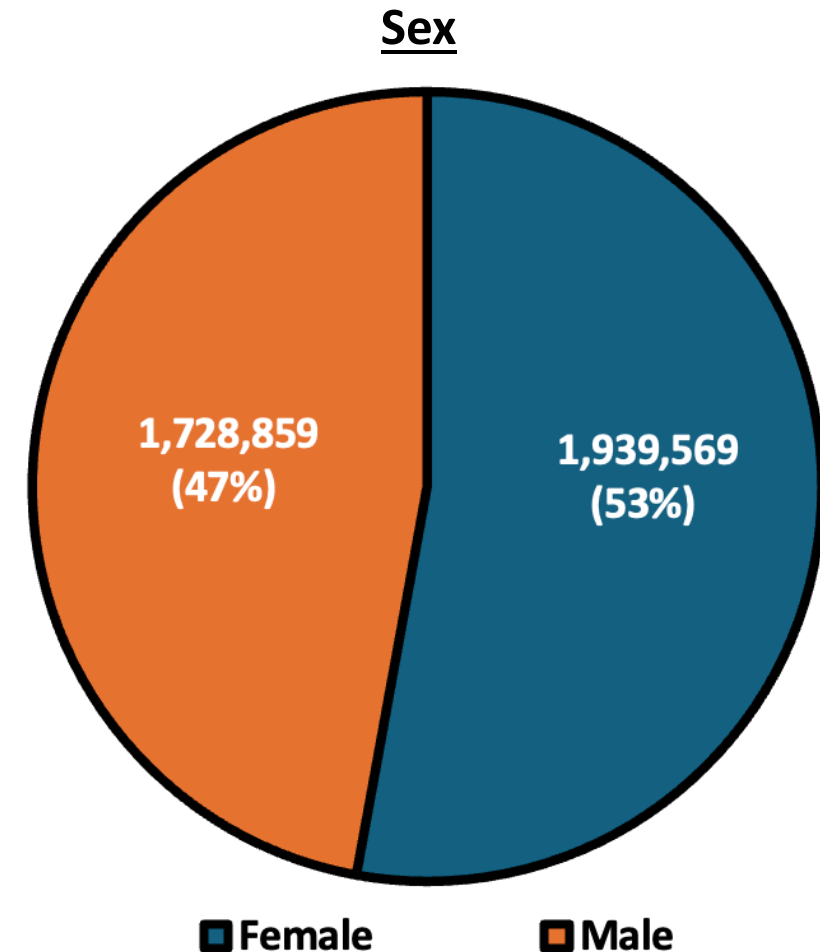
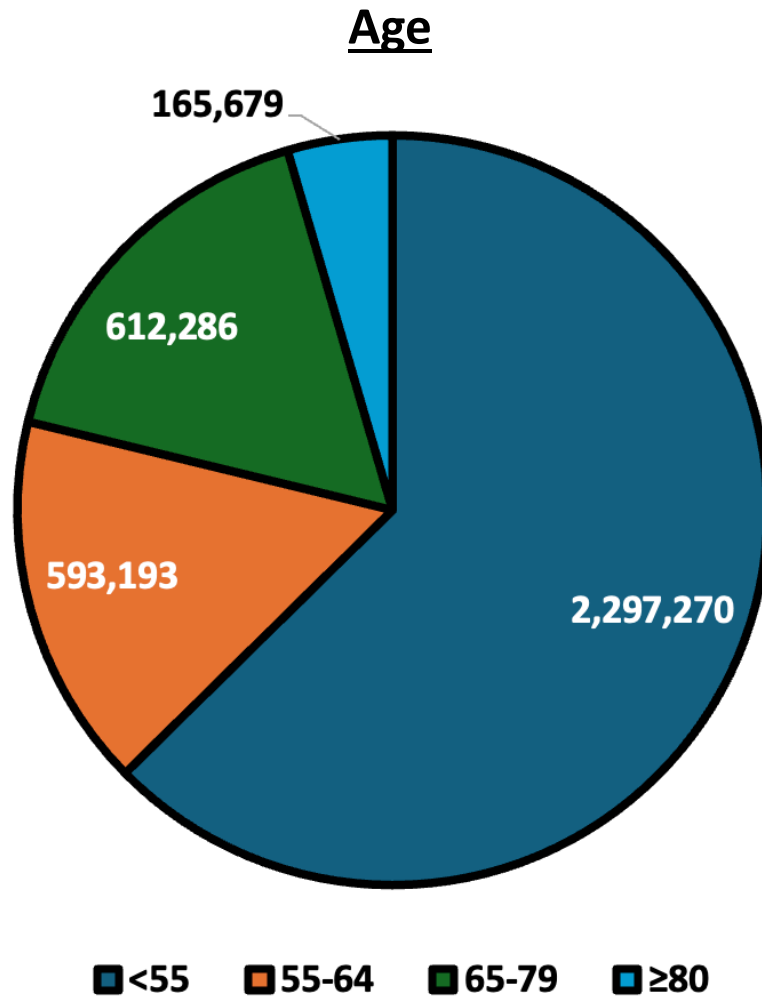
# Randomizations Over Time: >3.6M Randomized in 3 Months



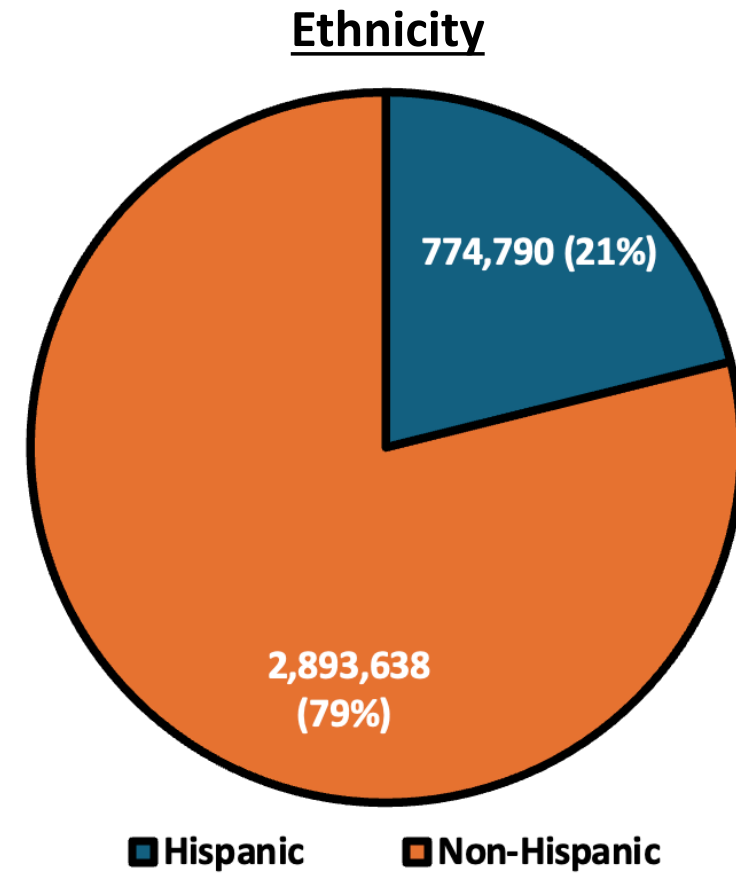
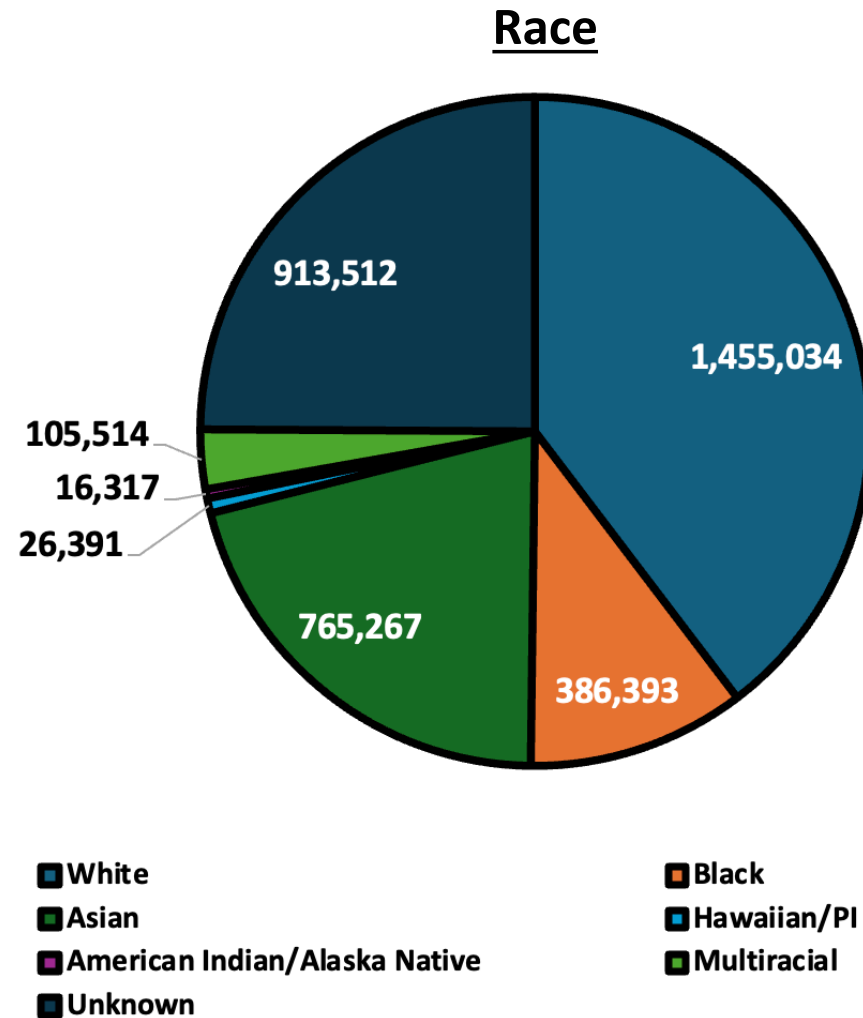
**Study Population:**  
**3,668,428 across 2**  
**diverse care entities**  
**in an integrated**  
**healthcare delivery**  
**system**

# Baseline Characteristics

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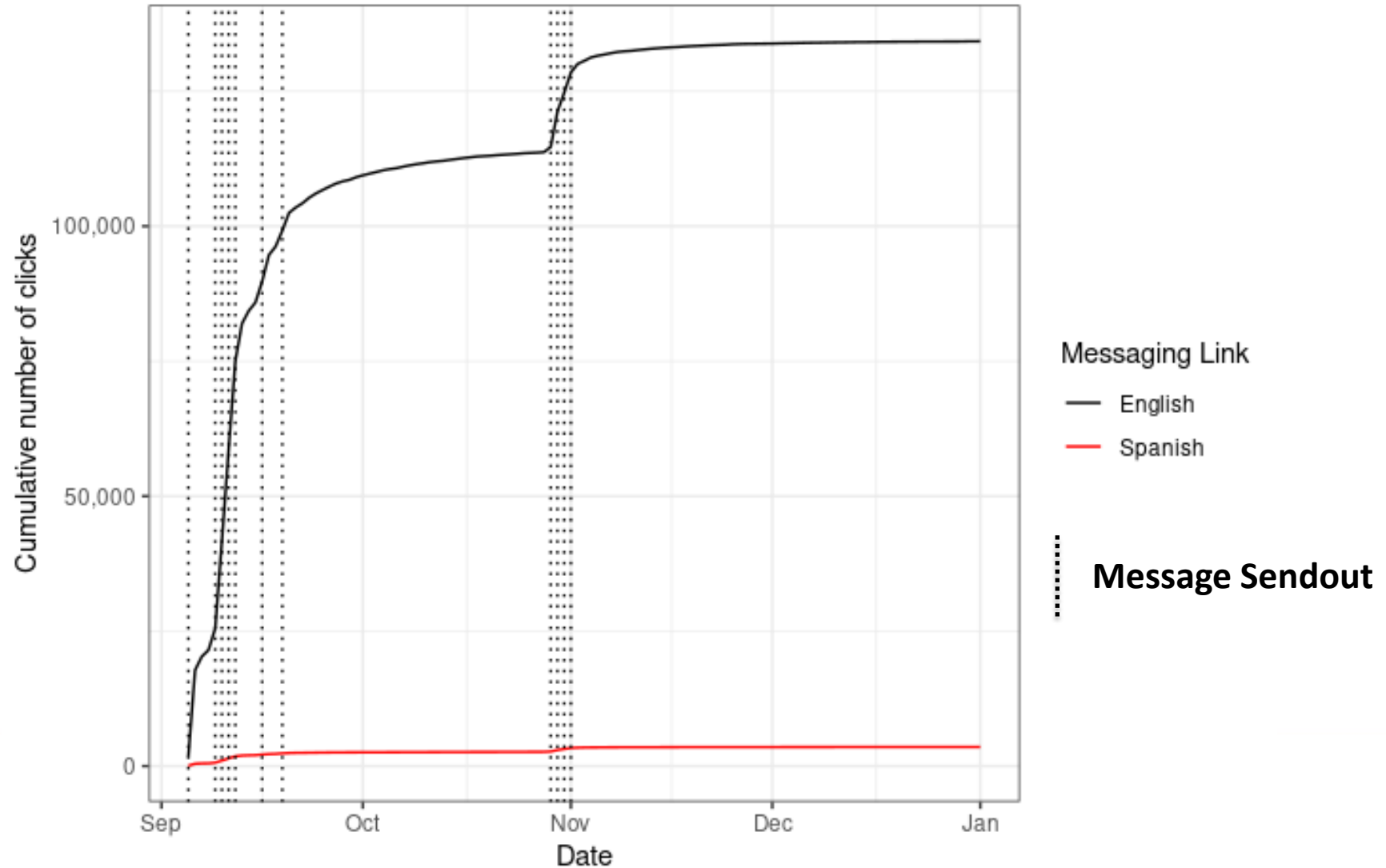
# Baseline Characteristics



# Baseline Characteristics

	KP-VACCINATE	NUDGE-FLU	NUDGE-FLU 2	NUDGE-FLU CHRONIC	Yokum 2018	Milkman 2021
<b>Sample Size</b>	N=3,668,428	N=964,870	N=881,373	N=299,881	N=227,955	N=47,306
<b>Age, years, mean (SD)</b>	48.3 (18.2)	73.8 (6.3)	74.1 (6.5)	48.6 (12.6)	75.7 (7.6)	51.9 (16.3)
<b>Female, n (%)</b>	1,939,380 (52.9)	496,482 (51.5)	458,789 (52.1)	159,454 (53.2)	130,015 (57.0)	26,964 (57.0)
<b>Race, n (%)</b>						
<b>White</b>	1,455,034 (39.7)	--	--	--	191,755 (84.1)	33114 (70.0)
<b>Black</b>	386,393 (10.5)	--	--	--	19,376 (8.5)	8988 (19.0)
<b>Asian</b>	765,267 (20.9)	--	--	--		
<b>Hawaiian or Pacific Islander</b>	26,391 (0.7)					
<b>American Indian/Alaska Native</b>	16,317 (0.4)	--	--	--	0 (0.0)	0 (0.0)
<b>Multi-racial</b>	105,514 (2.9)	--	--	--	0 (0.0)	0 (0.0)
<b>Hispanic ethnicity, n (%)</b>	774,790 (21.1)	--	--	--	0 (0.0)	1892 (4)
<b>Vaccinated in prior season, n (%)</b>	1,423,786 (38.8)	741,659 (76.9)	684,206 (77.6)	95,479 (31.8)	85,566 (37.5)	--
<b>Myocardial infarction, n (%)</b>	55,616 (1.5)	28,481 (3.0)	25,682 (2.9)	13,014 (4.3)	--	--
<b>Heart failure, n (%)</b>	97,244 (2.7)	33,109 (3.4)	30,875 (3.5)	11,727 (3.9)	--	--
<b>Atrial fibrillation or flutter, n (%)</b>	116,130 (3.2)	95,551 (9.9)	88,591 (10.1)	19,481 (6.5)	--	--
<b>Diabetes mellitus, n (%)</b>	497,295 (13.6)	123,974 (12.8)	111,374 (12.6)	43,427 (14.5)	48,977 (21.5)	--
<b>Hypertension, n (%)</b>	969,884 (26.4)	555,437 (57.6)	513,835 (58.3)	106,271 (35.4)	--	--
<b>Chronic lung disease, n (%)</b>	531,842 (14.5)	72,792 (7.5)	65,241 (7.4)	36,541 (12.2)	32,838 (14.4)	--

# Click Through Rates at KPNC



# Conclusions


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- KP-VACCINATE is one of the largest clinical trials ever completed.
  - It will answer the question of the effectiveness and timing of CV-focused nudge communication vs. usual care on vaccine uptake in a diverse US population.
- KP-VACCINATE is a systemwide A/B randomized clinical trial fully embedded in an integrated healthcare delivery system.
  - Systemwide implementation trials are feasible across learning healthcare systems.
  - Collaboration amongst research and operational teams is paramount for stakeholder engagement, implementation, and analysis.
- This model may be readily transferable to other areas of patient, clinician, and health system engagement.
  - A culture of randomization for operational initiative rollouts may provide definitive answers that further health systems priorities and improve patient outcomes.



# Learning to Learn in Learning Healthcare Systems

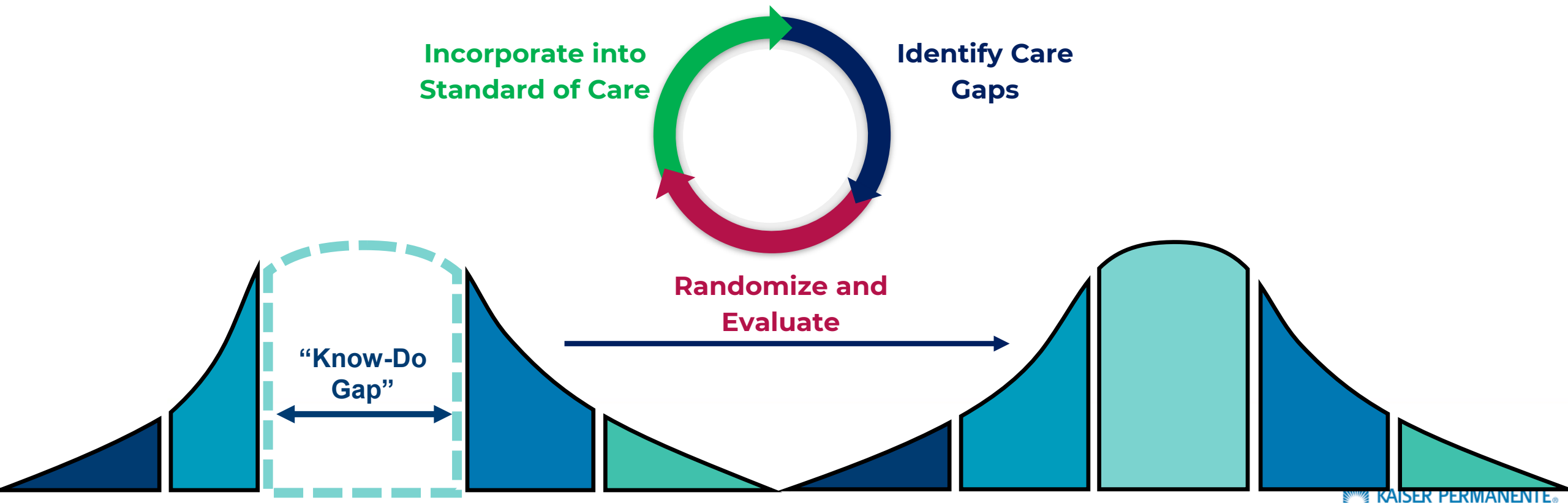
## Creating a Learning Health System through Rapid-Cycle, Randomized Testing

Authors: Leora I. Horwitz, M.D., M.H.S. , Masha Kuznetsova, M.P.H., and Simon A. Jones, Ph.D. [Author Info & Affiliations](#)



## Nudge Units to Improve the Delivery of Health Care

Authors: Mitesh S. Patel, M.D., M.B.A., Kevin G. Volpp, M.D., Ph.D., and David A. Asch, M.D., M.B.A. [Author Info & Affiliations](#)



# Thank You

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**NIH Collaboratory Grand Rounds**  
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# Extra Slides

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# Consort

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