Pragmatic Care Embedded Randomization: Insights From the KP-VACCINATE Megatrial & Beyond

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Virtual

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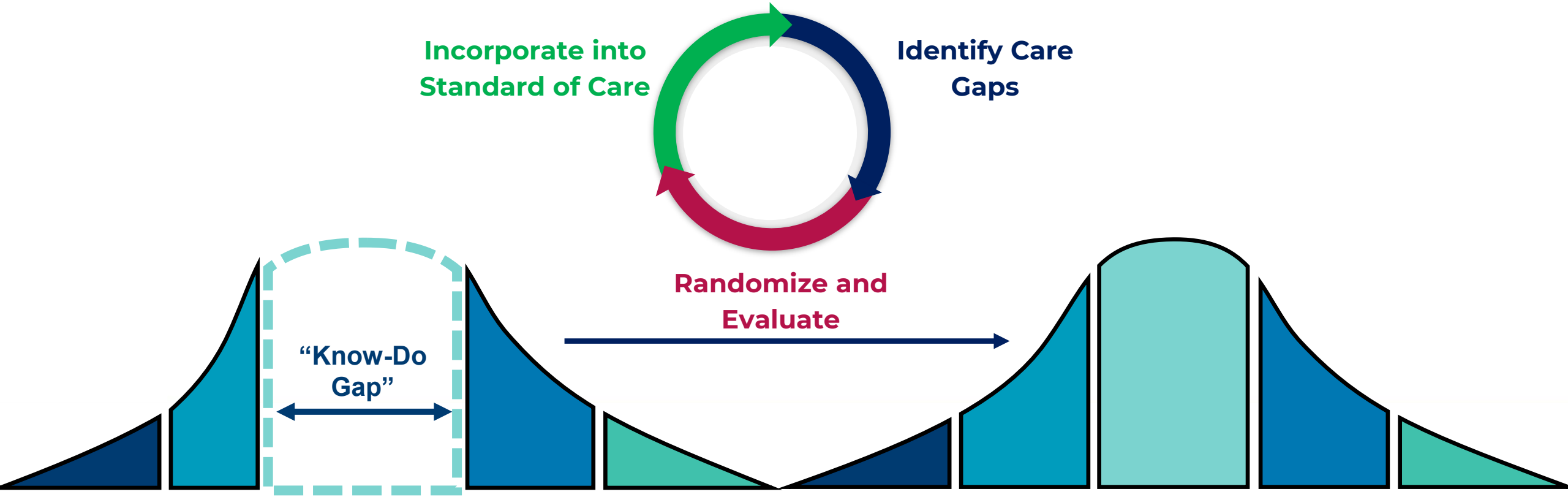
KAISER PERMANENTE®

Implementation Science

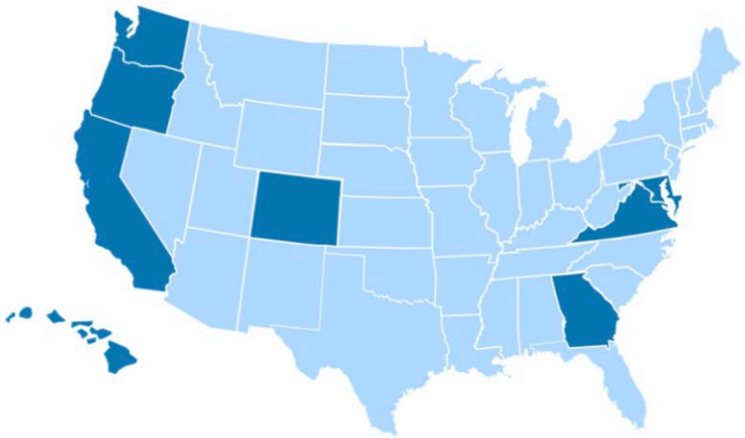
"…the scientific study of methods and strategies that facilitate the uptake of evidence-based practice and research into regular use by practitioners and policymakers."



Implementation Science. University of Washington.

KP as a Learning Healthcare Lab

Mission: To provide affordable high-quality health care services and to improve the health of our members and the communities we serve.



12.5 million members (2023)

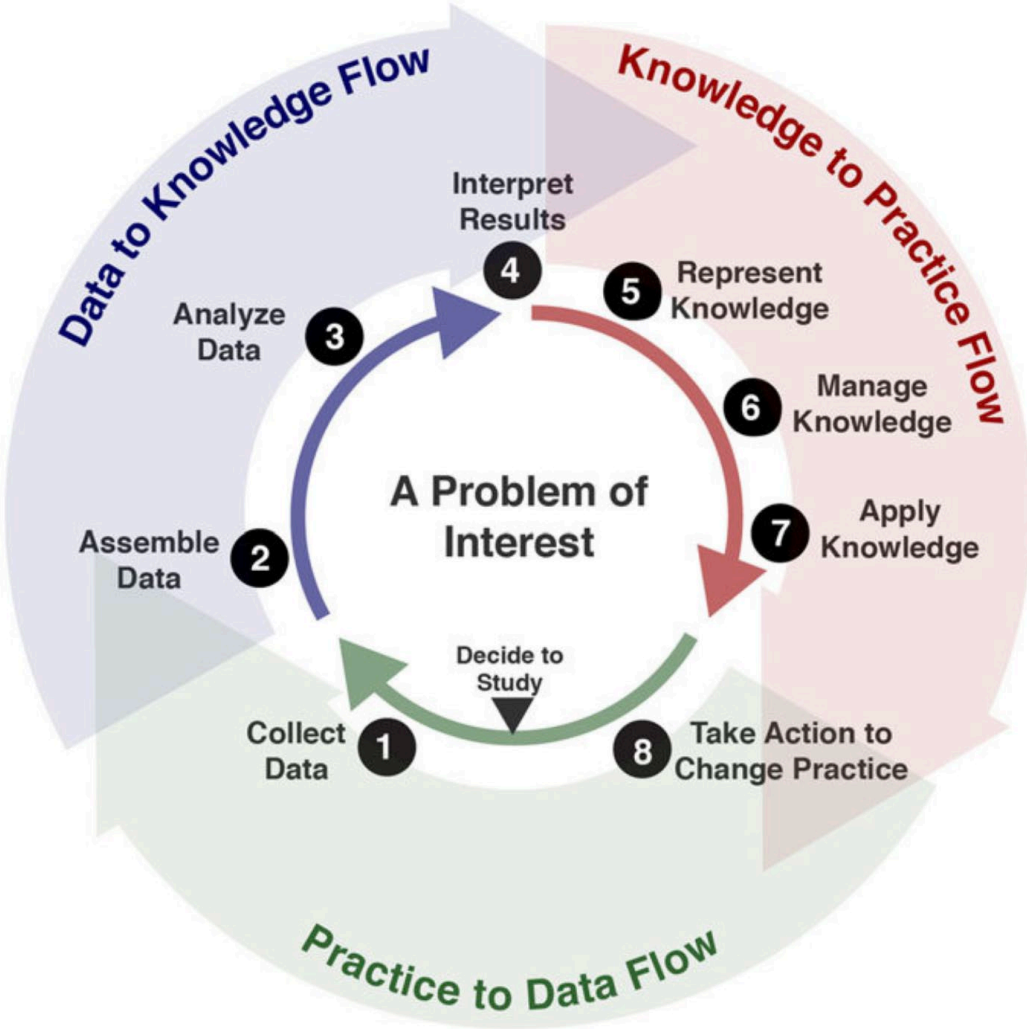
24,605 physicians

73,618 nurses

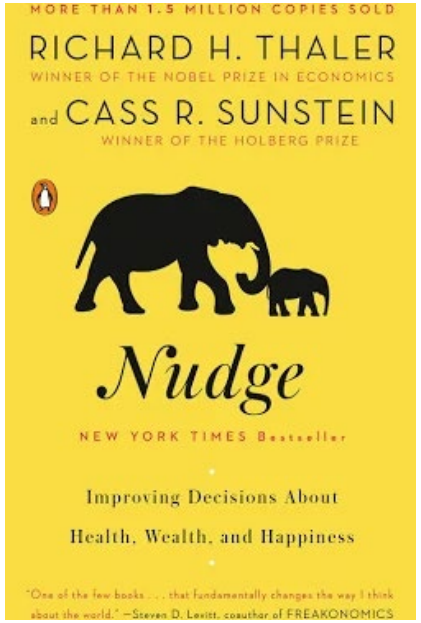
216,000 employees

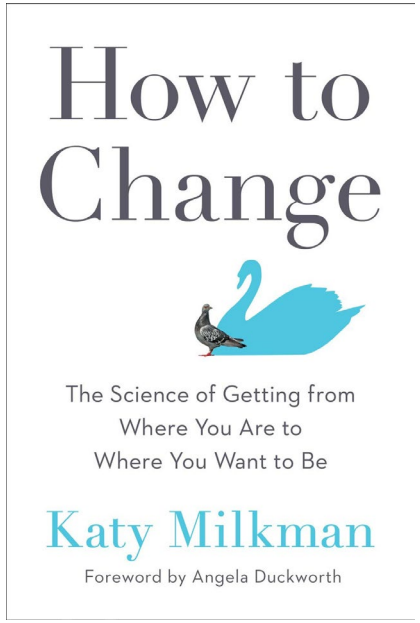
618 medical facilities

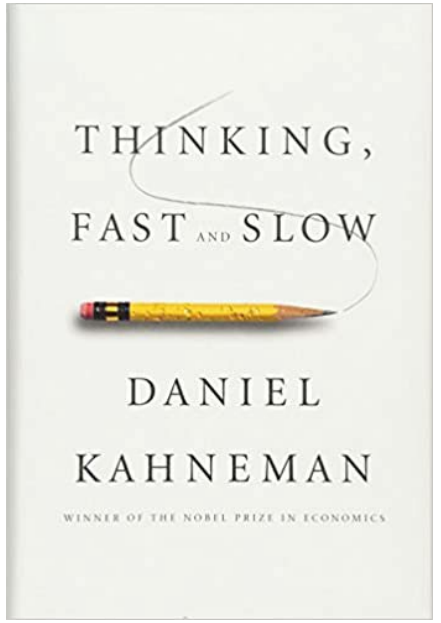
40 hospitals



Behavioral nudges are increasingly embraced by the public

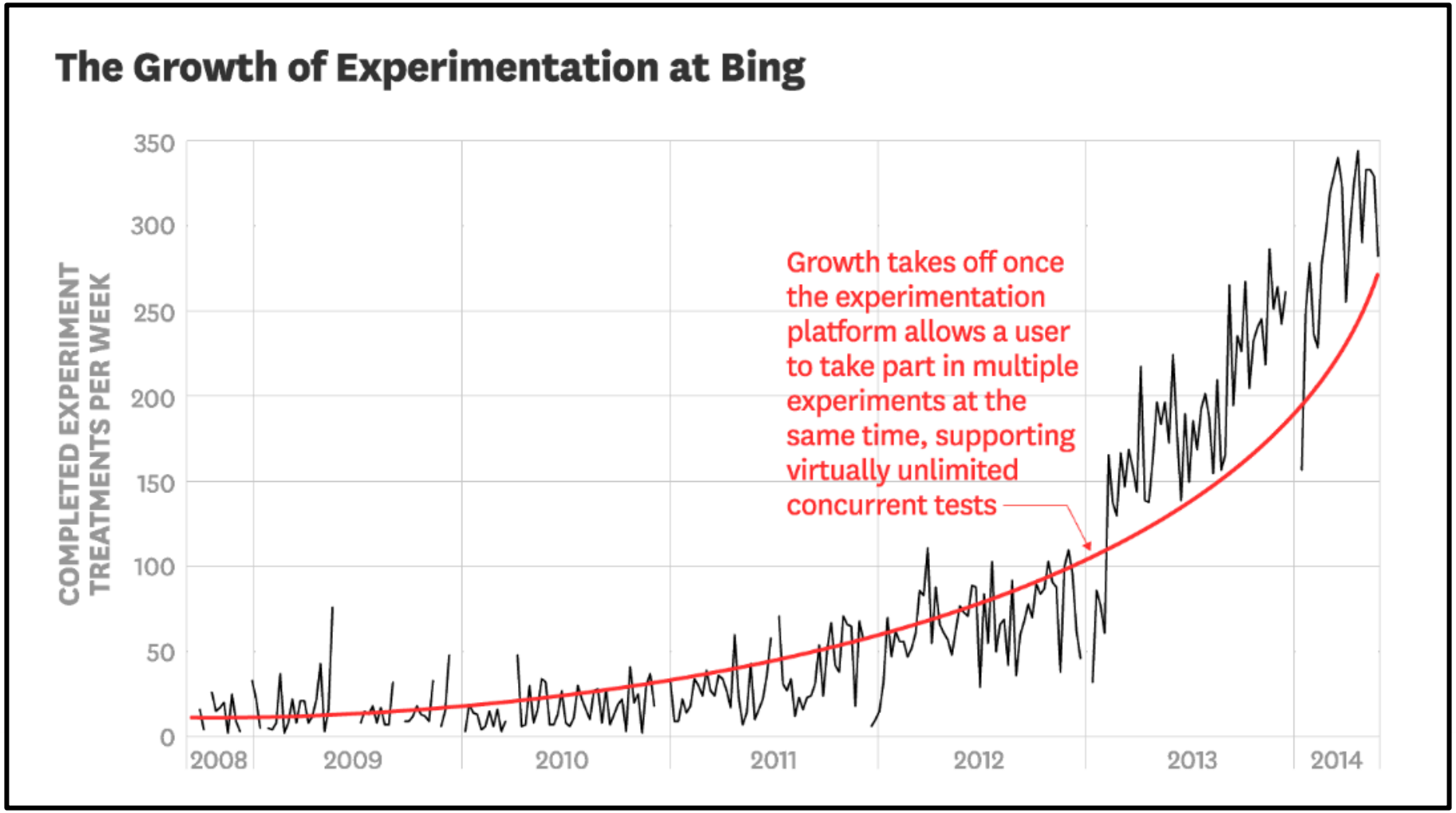






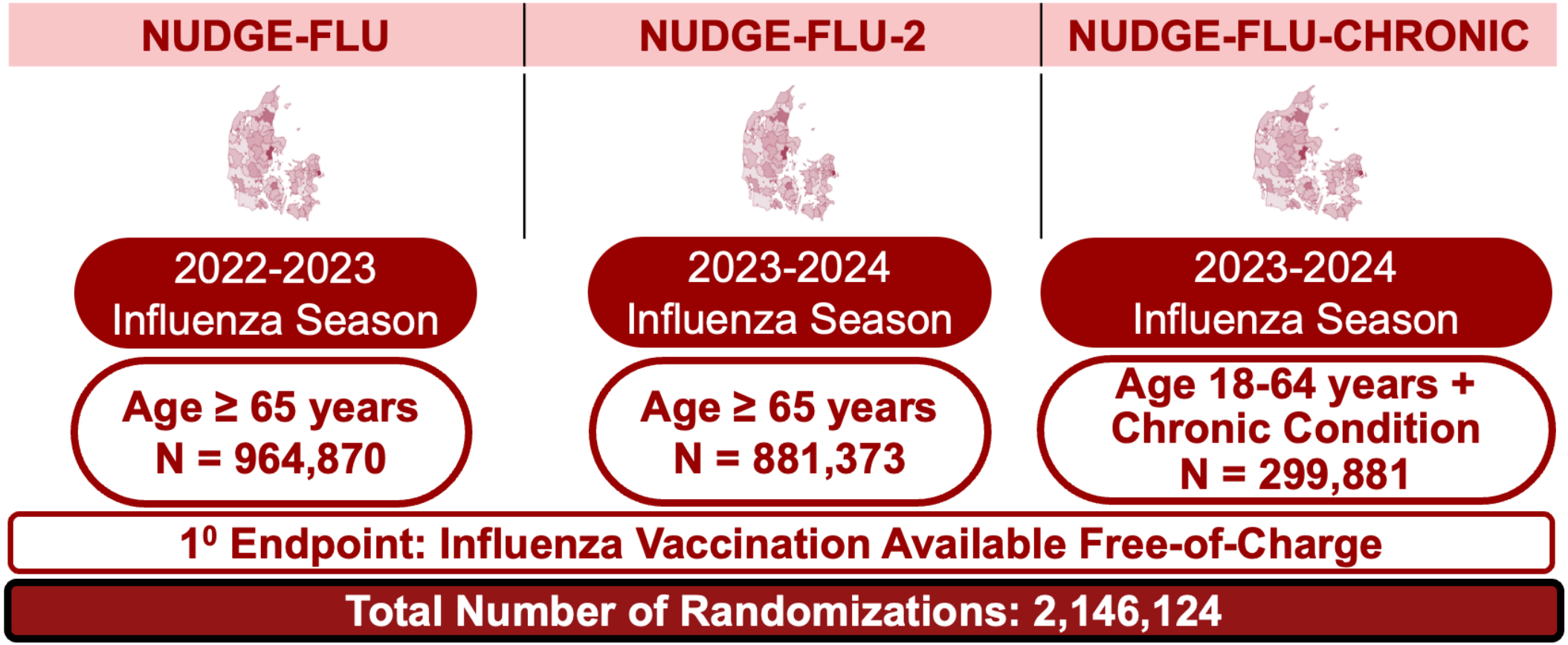
A nudge is a subtle change in design that can have an outsize impact on human behavior. They can influence behavior without restricting choice.

Experimentation Platforms Exist In Other Industries



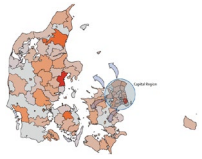
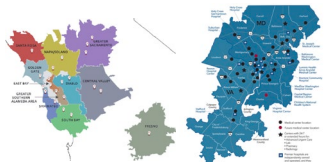
Kohavi R and Thomke S. Harvard Business Review. 2017.

System Wide Randomization: The Danish NUDGE-FLU Program

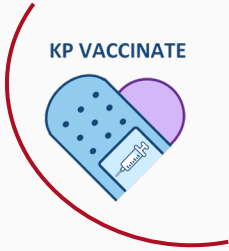


Johansen ND, Vaduganathan M, Bhatt AS, et al. Am Heart J. 2024.

Learning Labs in Healthcare

	Denmark 	Kaiser Permanente 
Size	*~5.9M*	*~5.3M*
Standardized Data	✓	✓
Centralized Payer	✓	✓
Full Endpoint Capture	✓	✓
Electronic Communication	✓	✓
Diverse Racial/Ethnic Population		✓
Rich Fully Searchable EHR Data		✓

Background

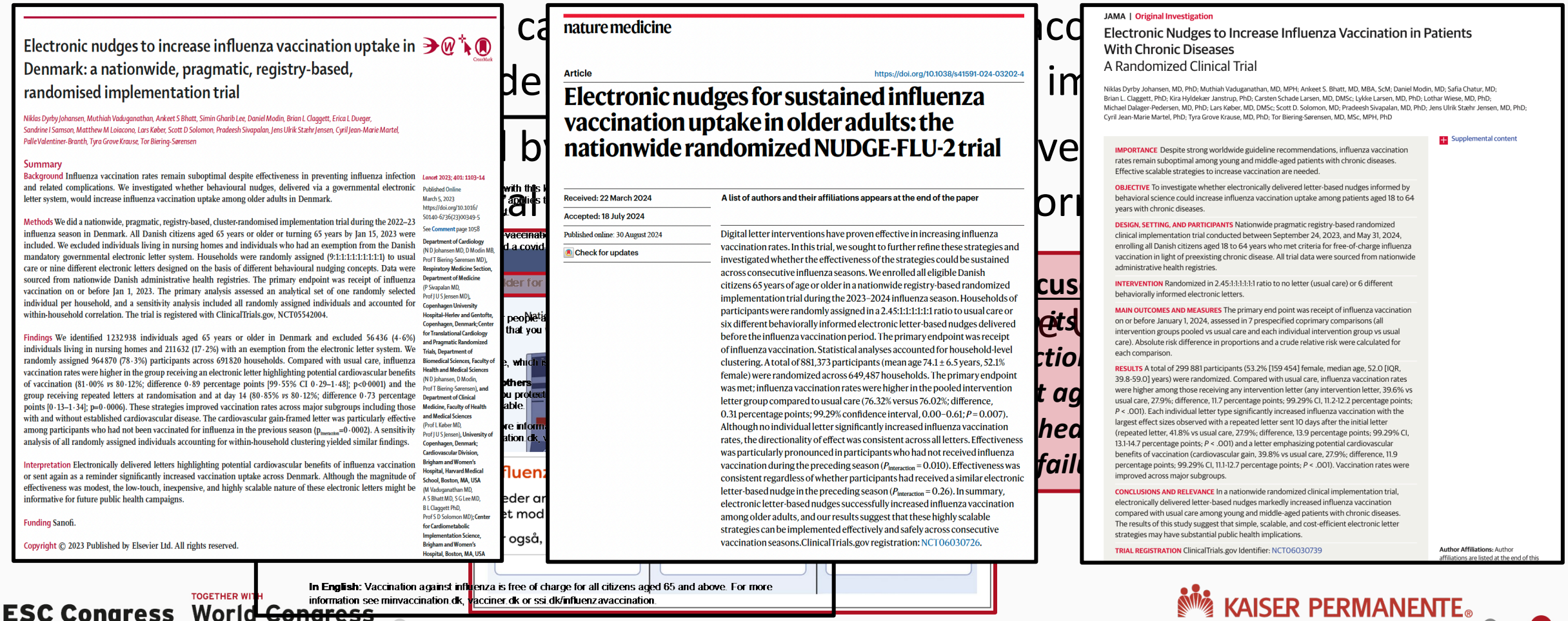


- The World Health Organization estimates **~3-5M severe cases** and **500,000+ deaths** related to influenza worldwide.[1]
- Influenza increases the risk of CV events, including MI and HF.[2]
- Guidelines strongly recommend routine, yearly influenza vaccination.[3]
- Despite this, vaccination rates remain suboptimal globally and persistent inequities exist.[4]
- Urgent need exists for novel, effective, and scalable strategies that improve vaccination rates and promote cardiovascular prevention.

[1] World Health Organization. 2025
[2] Kwong JC et. al. *N Eng J Med*. 2018.
[3] Frobert O et. al. *Circulation.* 2021.
[4] Ghandi GR et. al. *JAMA Cardiol*. 2021.

Background

- 3 recent Danish RCTs established behavioral-science informed “nudges” boosted influenza vaccination rates across 2 seasons.



Electronic nudges to increase influenza vaccination uptake in Denmark: a nationwide, pragmatic, registry-based, randomised implementation trial

Niklas Dyrby Johansen, Muthiah Vaduganathan, Ankeet S Bhatt, Simin Gharib Lee, Daniel Modin, Brian L Claggett, Erica L Dueger, Sandrine I Samson, Matthew M Loiacono, Lars Køber, Scott D Solomon, Pradeesh Sivapalan, Jens Ulrik Stæhr Jensen, Cyril Jean-Marie Martel, Palle Valentiner-Branth, Tyra Grove Krause, Tor Biering-Sørensen

Summary

Background Influenza vaccination rates remain suboptimal despite effectiveness in preventing influenza infection and related complications. We investigated whether behavioural nudges, delivered via a governmental electronic letter system, would increase influenza vaccination uptake among older adults in Denmark.

Methods We did a nationwide, pragmatic, registry-based, cluster-randomised implementation trial during the 2022–23 influenza season in Denmark. All Danish citizens aged 65 years or older or turning 65 years by Jan 15, 2023 were included. We excluded individuals living in nursing homes and individuals who had an exemption from the Danish mandatory governmental electronic letter system. Households were randomly assigned (9:1:1:1:1:1:1:1:1) to usual care or nine different electronic letters designed on the basis of different behavioural nudging concepts. Data were sourced from nationwide Danish administrative health registries. The primary endpoint was receipt of influenza vaccination on or before Jan 1, 2023. The primary analysis assessed an analytical set of one randomly selected individual per household, and a sensitivity analysis included all randomly assigned individuals and accounted for within-household correlation. The trial is registered with ClinicalTrials.gov, NCT05542004.

Findings We identified 1 232 938 individuals aged 65 years or older in Denmark and excluded 56 436 (4·6%) individuals living in nursing homes and 211 632 (17·2%) with an exemption from the electronic letter system. We randomly assigned 964 870 (78·3%) participants across 691 820 households. Compared with usual care, influenza vaccination rates were higher in the group receiving an electronic letter highlighting potential cardiovascular benefits of vaccination (81·00% *vs* 80·12%; difference 0·89 percentage points [99·55% CI 0·29–1·48]; p<0·0001) and the group receiving repeated letters at randomisation and at day 14 (80·85% *vs* 80·12%; difference 0·73 percentage points [0·13–1·34]; p=0·0006). These strategies improved vaccination rates across major subgroups including those with and without established cardiovascular disease. The cardiovascular gain-framed letter was particularly effective among participants who had not been vaccinated for influenza in the previous season ($p_{interaction}$=0·0002). A sensitivity analysis of all randomly assigned individuals accounting for within-household clustering yielded similar findings.

Interpretation Electronically delivered letters highlighting potential cardiovascular benefits of influenza vaccination or sent again as a reminder significantly increased vaccination uptake across Denmark. Although the magnitude of effectiveness was modest, the low-touch, inexpensive, and highly scalable nature of these electronic letters might be informative for future public health campaigns.

Funding Sanofi.

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See Comment page 1058

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nature medicine

Article

https://doi.org/10.1038/s41591-024-03202-4

Electronic nudges for sustained influenza vaccination uptake in older adults: the nationwide randomized NUDGE-FLU-2 trial

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Accepted: 18 July 2024

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Check for updates

A list of authors and their affiliations appears at the end of the paper

Digital letter interventions have proven effective in increasing influenza vaccination rates. In this trial, we sought to further refine these strategies and investigated whether the effectiveness of the strategies could be sustained across consecutive influenza seasons. We enrolled all eligible Danish citizens 65 years of age or older in a nationwide registry-based randomized implementation trial during the 2023–2024 influenza season. Households of participants were randomly assigned in a 2.45:1:1:1:1:1:1 ratio to usual care or six different behaviorally informed electronic letter-based nudges delivered before the influenza vaccination period. The primary endpoint was receipt of influenza vaccination. Statistical analyses accounted for household-level clustering. A total of 881,373 participants (mean age 74.1 ± 6.5 years, 52.1% female) were randomized across 649,487 households. The primary endpoint was met; influenza vaccination rates were higher in the pooled intervention letter group compared to usual care (76.32% versus 76.02%; difference, 0.31 percentage points; 99.29% confidence interval, 0.00–0.61; $P = 0.007$). Although no individual letter significantly increased influenza vaccination rates, the directionality of effect was consistent across all letters. Effectiveness was particularly pronounced in participants who had not received influenza vaccination during the preceding season ($P_{interaction} = 0.010$). Effectiveness was consistent regardless of whether participants had received a similar electronic letter-based nudge in the preceding season ($P_{interaction} = 0.26$). In summary, electronic letter-based nudges successfully increased influenza vaccination among older adults, and our results suggest that these highly scalable strategies can be implemented effectively and safely across consecutive vaccination seasons.ClinicalTrials.gov registration: NCT06030726.

JAMA | Original Investigation

Electronic Nudges to Increase Influenza Vaccination in Patients With Chronic Diseases

A Randomized Clinical Trial

Niklas Dyrby Johansen, MD, PhD; Muthiah Vaduganathan, MD, MPH; Ankeet S. Bhatt, MD, MBA, ScM; Daniel Modin, MD; Safia Chatur, MD; Brian L. Claggett, PhD; Kira Hyldekær Janstrup, PhD; Carsten Schade Larsen, MD, DMSc; Lykke Larsen, MD, PhD; Lothar Wiese, MD, PhD; Michael Dalager-Pedersen, MD, PhD; Lars Køber, MD, DMSc; Scott D. Solomon, MD; Pradeesh Sivapalan, MD, PhD; Jens Ulrik Stæhr Jensen, MD, PhD; Cyril Jean-Marie Martel, PhD; Tyra Grove Krause, MD, PhD; Tor Biering-Sørensen, MD, MSc, MPH, PhD

Supplemental content

IMPORTANCE Despite strong worldwide guideline recommendations, influenza vaccination rates remain suboptimal among young and middle-aged patients with chronic diseases. Effective scalable strategies to increase vaccination are needed.

OBJECTIVE To investigate whether electronically delivered letter-based nudges informed by behavioral science could increase influenza vaccination uptake among patients aged 18 to 64 years with chronic diseases.

DESIGN, SETTING, AND PARTICIPANTS Nationwide pragmatic registry-based randomized clinical implementation trial conducted between September 24, 2023, and May 31, 2024, enrolling all Danish citizens aged 18 to 64 years who met criteria for free-of-charge influenza vaccination in light of preexisting chronic disease. All trial data were sourced from nationwide administrative health registries.

INTERVENTION Randomized in 2.45:1:1:1:1:1:1 ratio to no letter (usual care) or 6 different behaviorally informed electronic letters.

MAIN OUTCOMES AND MEASURES The primary end point was receipt of influenza vaccination on or before January 1, 2024, assessed in 7 prespecified coprimary comparisons (all intervention groups pooled vs usual care and each individual intervention group vs usual care). Absolute risk difference in proportions and a crude relative risk were calculated for each comparison.

RESULTS A total of 299 881 participants (53.2% [159 454] female, median age, 52.0 [IQR, 39.8-59.0] years) were randomized. Compared with usual care, influenza vaccination rates were higher among those receiving any intervention letter (any intervention letter, 39.6% vs usual care, 27.9%; difference, 11.7 percentage points; 99.29% CI, 11.2-12.2 percentage points; $P < .001$). Each individual letter type significantly increased influenza vaccination with the largest effect sizes observed with a repeated letter sent 10 days after the initial letter (repeated letter, 41.8% vs usual care, 27.9%; difference, 13.9 percentage points; 99.29% CI, 13.1-14.7 percentage points; $P < .001$) and a letter emphasizing potential cardiovascular benefits of vaccination (cardiovascular gain, 39.8% vs usual care, 27.9%; difference, 11.9 percentage points; 99.29% CI, 11.1-12.7 percentage points; $P < .001$). Vaccination rates were improved across major subgroups.

CONCLUSIONS AND RELEVANCE In a nationwide randomized clinical implementation trial, electronically delivered letter-based nudges markedly increased influenza vaccination compared with usual care among young and middle-aged patients with chronic diseases. The results of this study suggest that simple, scalable, and cost-efficient electronic letter strategies may have substantial public health implications.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT06030739

Author Affiliations: Author affiliations are listed at the end of this

In English: Vaccination against influenza is free of charge for all citizens aged 65 and above. For more information see minvaccination.dk, vacciner.dk or ssi.dk/influenzavaccination.

Kaiser Permanente VACCination Improvement with Nudge-based CardiovAscular Targeted Engagement

KP VACCINATE is a pragmatic, prospective, individually randomized, open-label, operationally conducted trial to assess the efficacy & timing of CV-focused messaging vs. usual care messaging on influenza vaccine uptake.

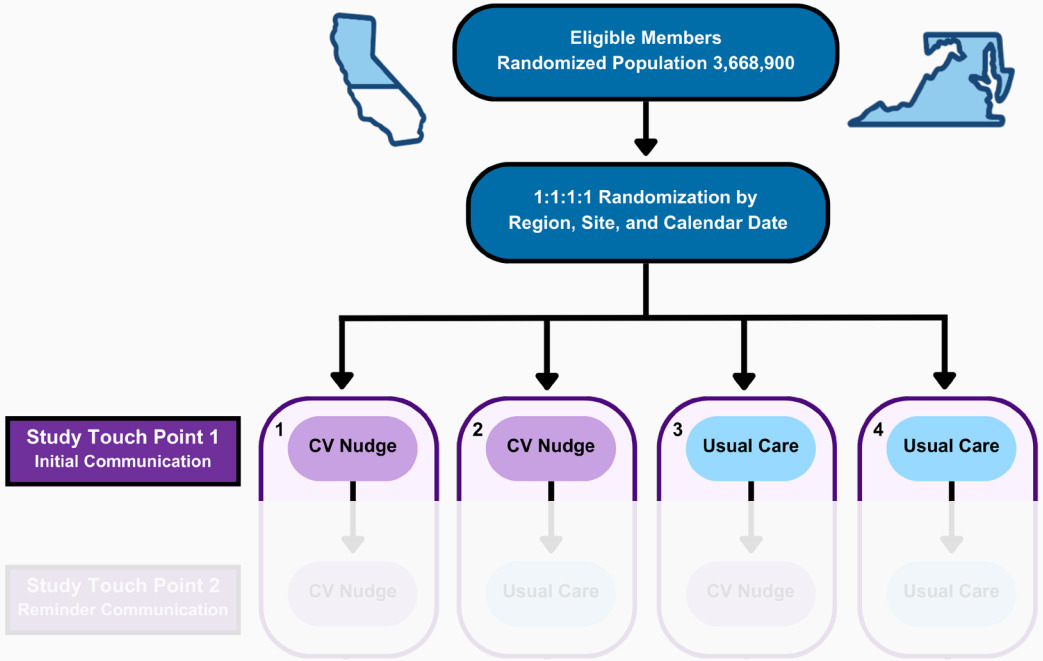
KP Northern California (KPNC)

- Integrated healthcare delivery system caring for >4.6M members in California.
- 21 hospitals, >260 outpatient clinics.
- Single electronic health record.

KP Mid-Atlantic States (KPMAS)

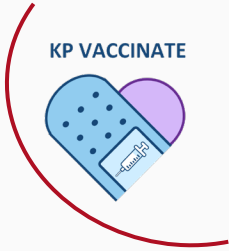
- Integrated healthcare delivery system caring for >800K members in Washington DC, Maryland, & Virginia.
- Care across 13 hospitals and 34 medical office building.
- Single electronic health record.

KP-VACCINATE Design



[1] Bhatt AS et. al. *Am. Heart J*. 2025.

Pragmatic Systemwide Inclusion

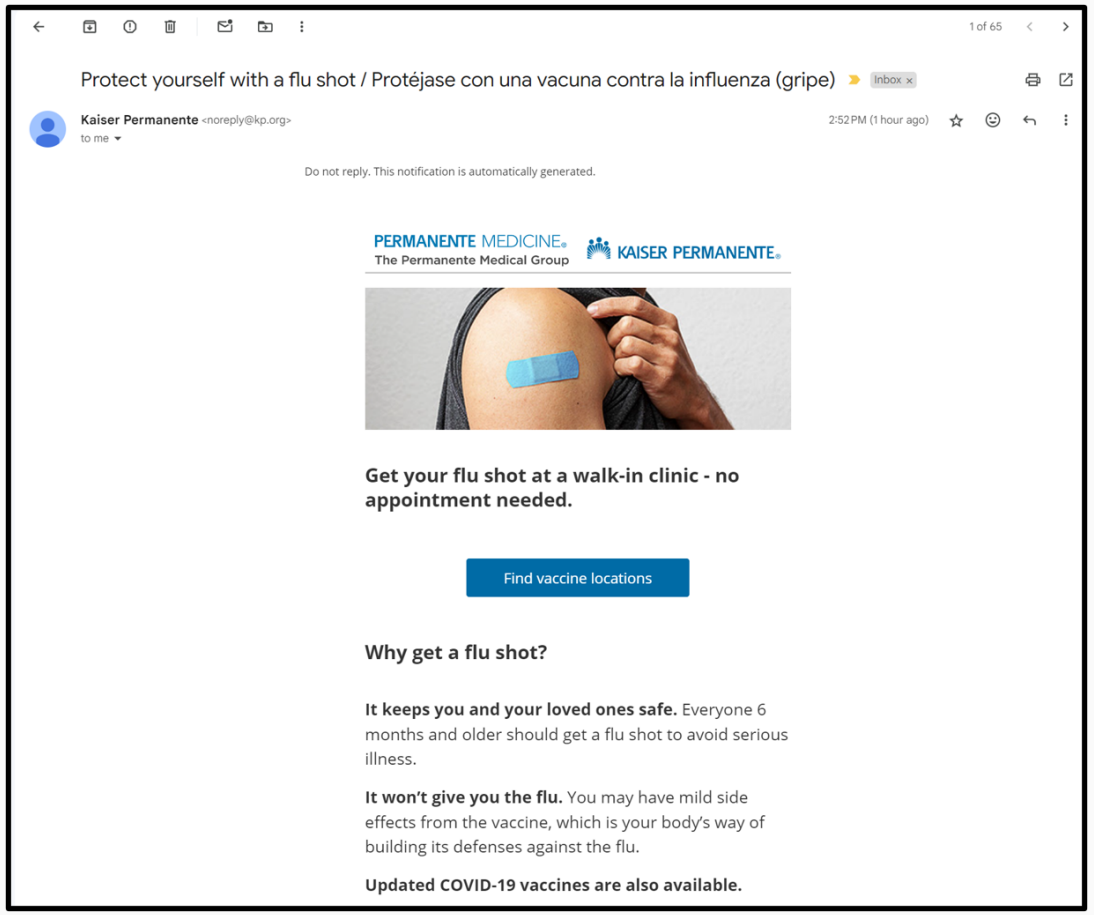


Inclusion Criteria	Exclusion Criteria
Age ≥18 years	Unable to receive or opted out of receiving health system messaging
Active KPNC or KPMAS health plan member as of September 1, 2024	Other exclusion that prevents messaging outreach
≥6 months of continuous health plan coverage and prescription drug benefit before September 1, 2024	Unknown service area or medical center affiliation
Evidence of member access of the KP HealthConnect® 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	

Randomization: Kaiser Permanente Northern California

KP VACCINATE

Usual Care Communication



Protect yourself with a flu shot / Protéjase con una vacuna contra la influenza (gripe)

Inbox ×

Kaiser Permanente <noreply@kp.org>
to me

2:52 PM (1 hour ago)

Do not reply. This notification is automatically generated.

PERMANENTE MEDICINE
The Permanente Medical Group
KAISER PERMANENTE

Get your flu shot at a walk-in clinic - no appointment needed.

Find vaccine locations

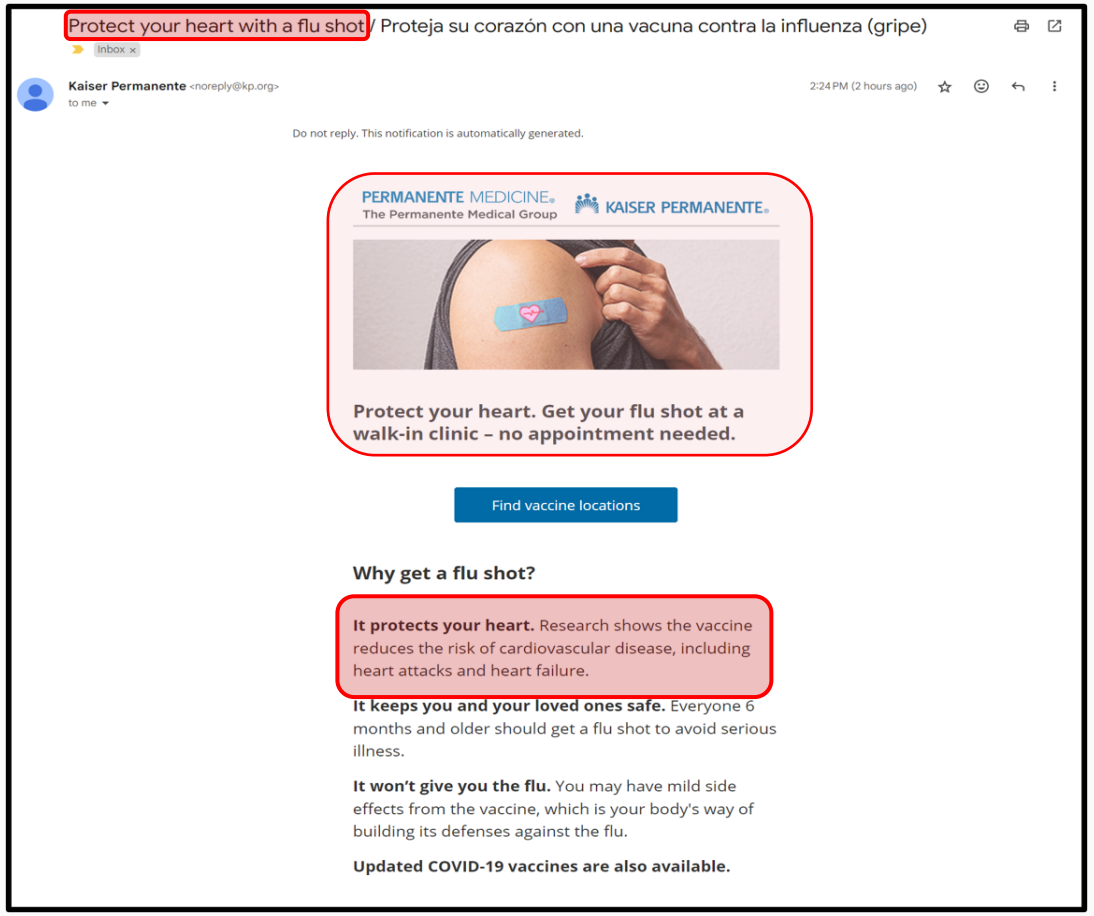
Why get a flu shot?

It keeps you and your loved ones safe. Everyone 6 months and older should get a flu shot to avoid serious illness.

It won't give you the flu. You may have mild side effects from the vaccine, which is your body's way of building its defenses against the flu.

Updated COVID-19 vaccines are also available.

Cardiovascular-Focused Communication



Protect your heart with a flu shot / Proteja su corazón con una vacuna contra la influenza (gripe)

Inbox ×

Kaiser Permanente <noreply@kp.org>
to me

2:24 PM (2 hours ago)

Do not reply. This notification is automatically generated.

PERMANENTE MEDICINE
The Permanente Medical Group
KAISER PERMANENTE

Protect your heart. Get your flu shot at a walk-in clinic – no appointment needed.

Find vaccine locations

Why get a flu shot?

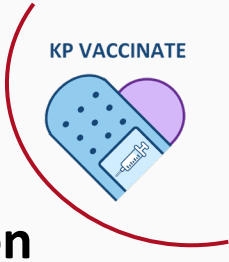
It protects your heart. Research shows the vaccine reduces the risk of cardiovascular disease, including heart attacks and heart failure.

It keeps you and your loved ones safe. Everyone 6 months and older should get a flu shot to avoid serious illness.

It won't give you the flu. You may have mild side effects from the vaccine, which is your body's way of building its defenses against the flu.

Updated COVID-19 vaccines are also available.

Randomization: Kaiser Permanente Mid Atlantic States



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:

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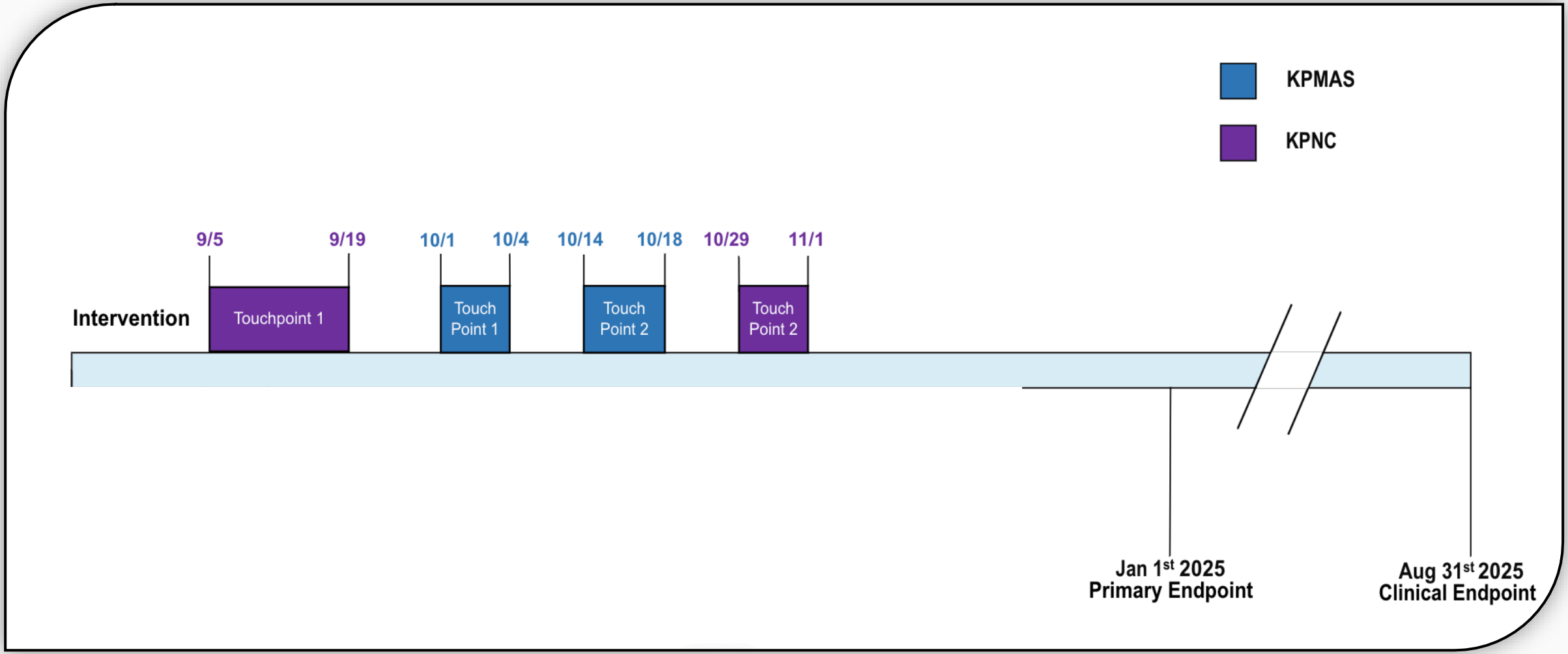
Randomization & Usual Care Vaccination Efforts



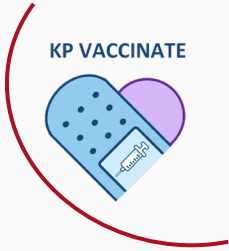
Outcomes

Primary Outcome — Vaccination Rate through January 1, 2025

6 Co-Primary Endpoints

- Each Individual Arm vs. Usual Care (3 Comparisons)
- Repeat vs. One-time CV-Focused Nudge
- Two vs. One CV-Focused Nudge
- Any CV-Focused Nudge vs. Usual Care

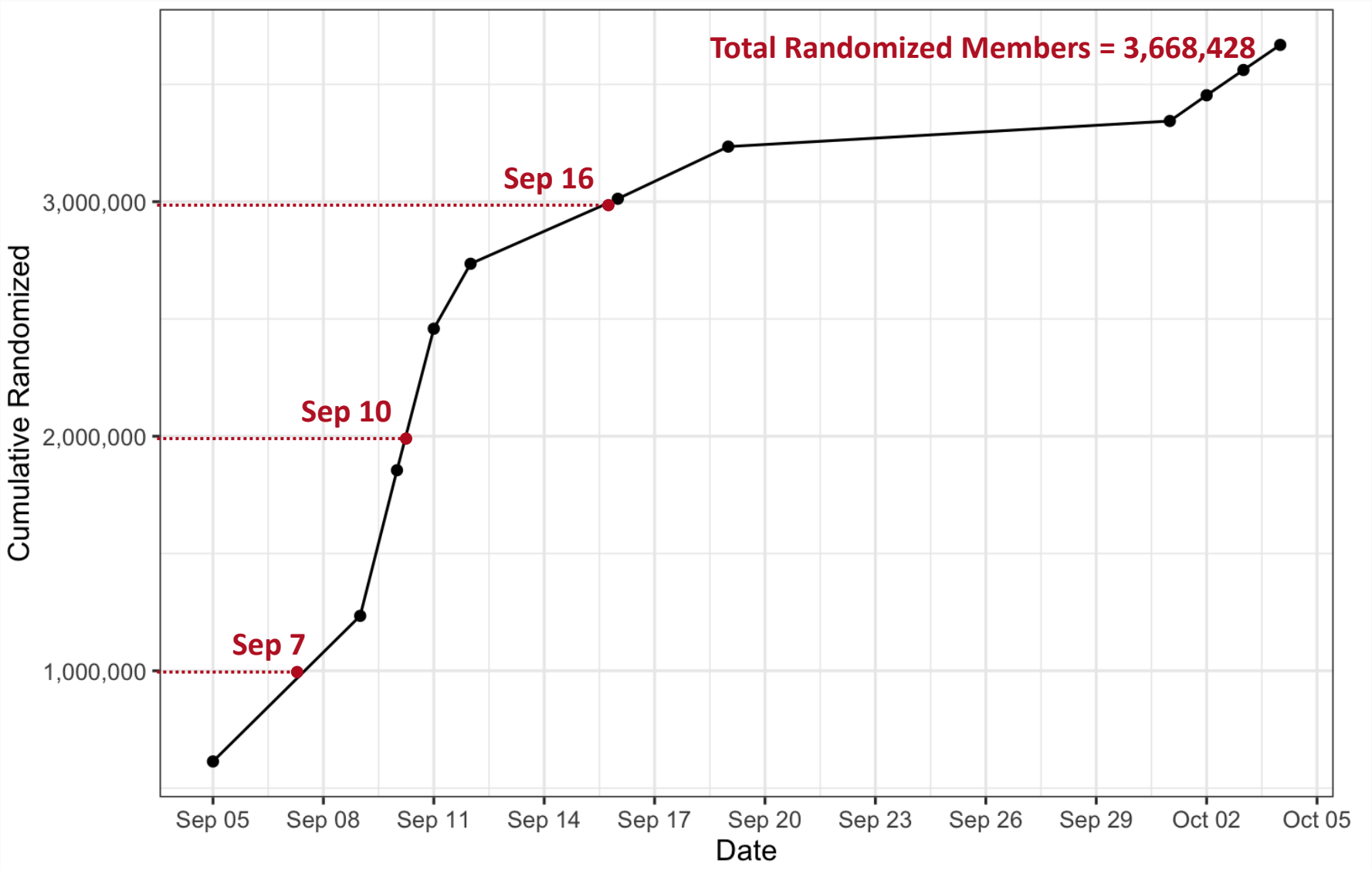
KP VACCINATE: Pragmatic Embedded Clinical Trial Elements



- Intervention Coordinated with Existing Vaccine Promotion Efforts
- Randomization Performed by Operational (Non-Research) Health System Teams
- Endpoint Capture Fully Embedded in EHR (Claims + Natural Language Processing
- Vital status known in >90% of patients at 1 year follow-up.

KAISER PERMANENTE®

>3.6 Million Members Randomized in <30 Days

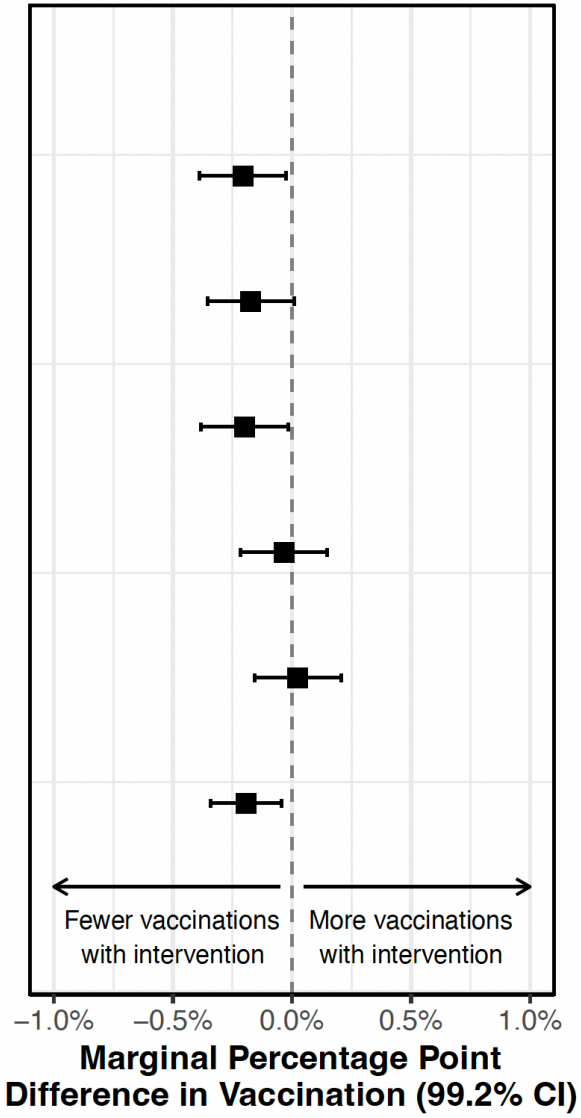


Baseline Characteristics

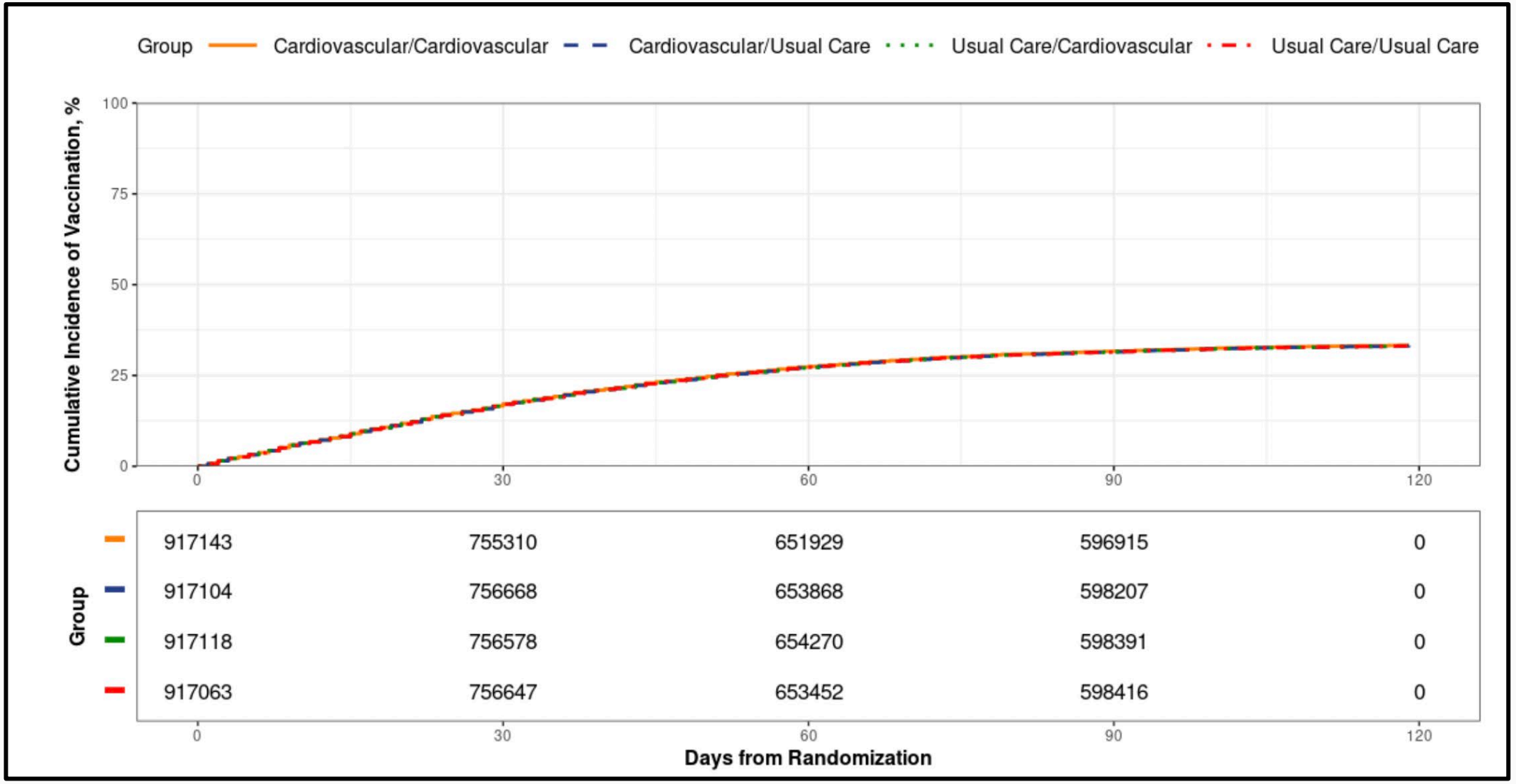
Characteristic	Cardiovascular/ Cardiovascular	Cardiovascular/ Usual Care	Usual Care/ Cardiovascular	Usual Care/ Usual Care
Number of individuals	917,063	917,104	917,118	917,143
Age, years, mean (±SD)	48 (18)	48 (18)	48 (18)	48 (18)
Female (%)	53	53	53	53
Race (%)				
Asian	21	21	21	21
Black	11	11	11	11
White	40	40	40	40
Hispanic ethnicity (%)	21	21	21	21
Vaccination history (%)				
Vaccinated for all 3 prior yrs	26	26	26	26
Vaccinated for some prior yrs	27	27	27	27
Not vaccinated in last 3 yrs	45	45	45	45
Prior influenza vaccinations (%)				
2022–23 season	40	40	40	41
2023–24 season	38	38	37	38
Chronic cardiovascular disease (%)	19	19	19	19

Vaccination Rates By Randomized Treatment

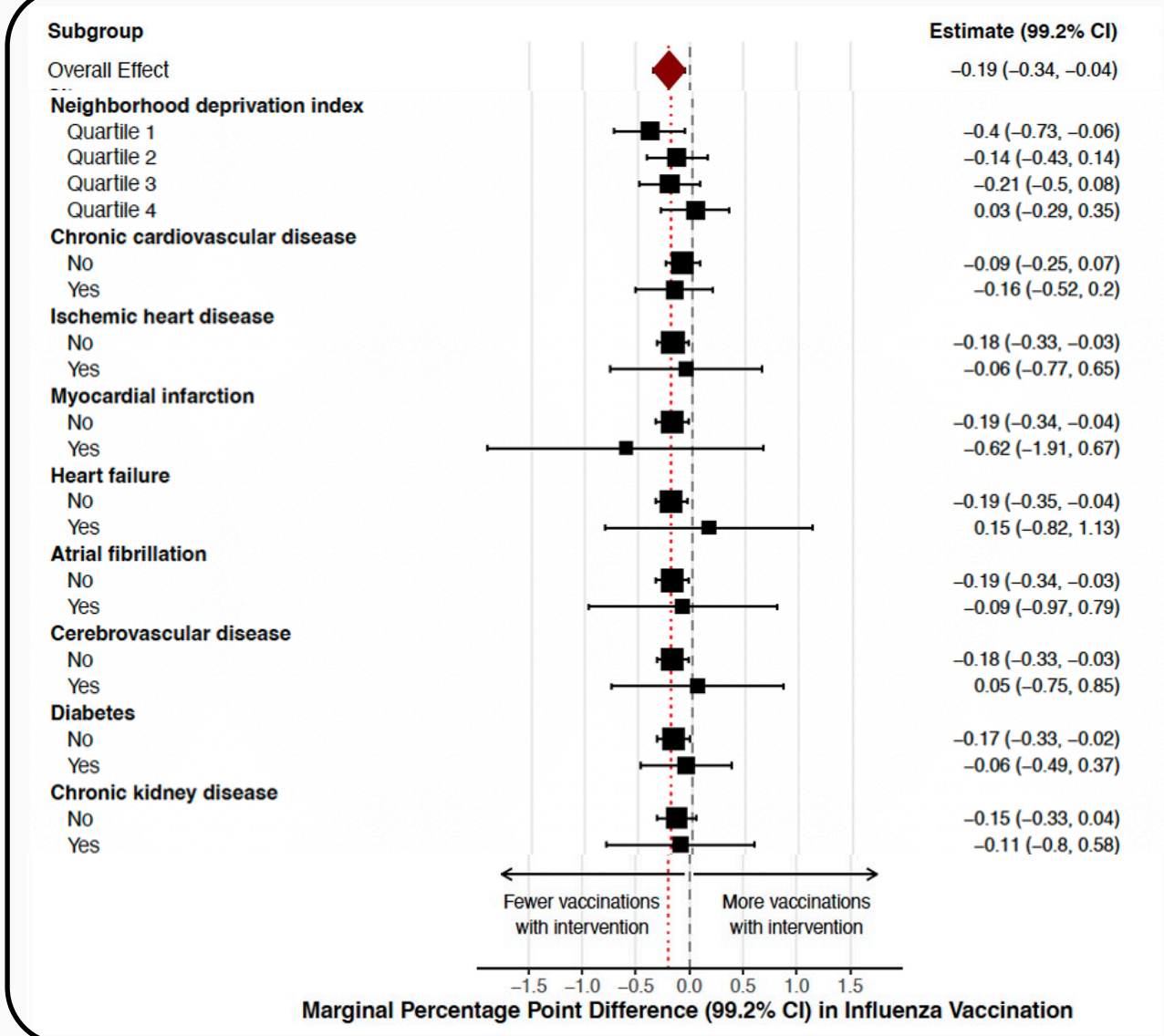
Co–primary Comparison	Vaccination Rate	Point Estimate (99.2% CI)
Comparison 1		
Cardiovascular/Cardiovascular	32.39%	–0.21 (–0.39, –0.02)
Usual Care/Usual Care	32.60%	Ref
Comparison 2		
Cardiovascular/Usual Care	32.43%	–0.17 (–0.35, 0.01)
Usual Care/Usual Care	32.60%	Ref
Comparison 3		
Usual Care/Cardiovascular	32.40%	–0.20 (–0.38, –0.01)
Usual Care/Usual Care	32.60%	Ref
Comparison 4		
Cardiovascular/Cardiovascular	32.39%	–0.03 (–0.22, 0.15)
Cardiovascular/Usual Care	32.43%	Ref
Comparison 5		
Cardiovascular/Usual Care	32.43%	0.03 (–0.16, 0.21)
Usual Care/Cardiovascular	32.40%	Ref
Comparison 6		
All cardiovascular arms	32.41%	–0.19 (–0.34, –0.04)
Usual Care/Usual Care	32.60%	Ref

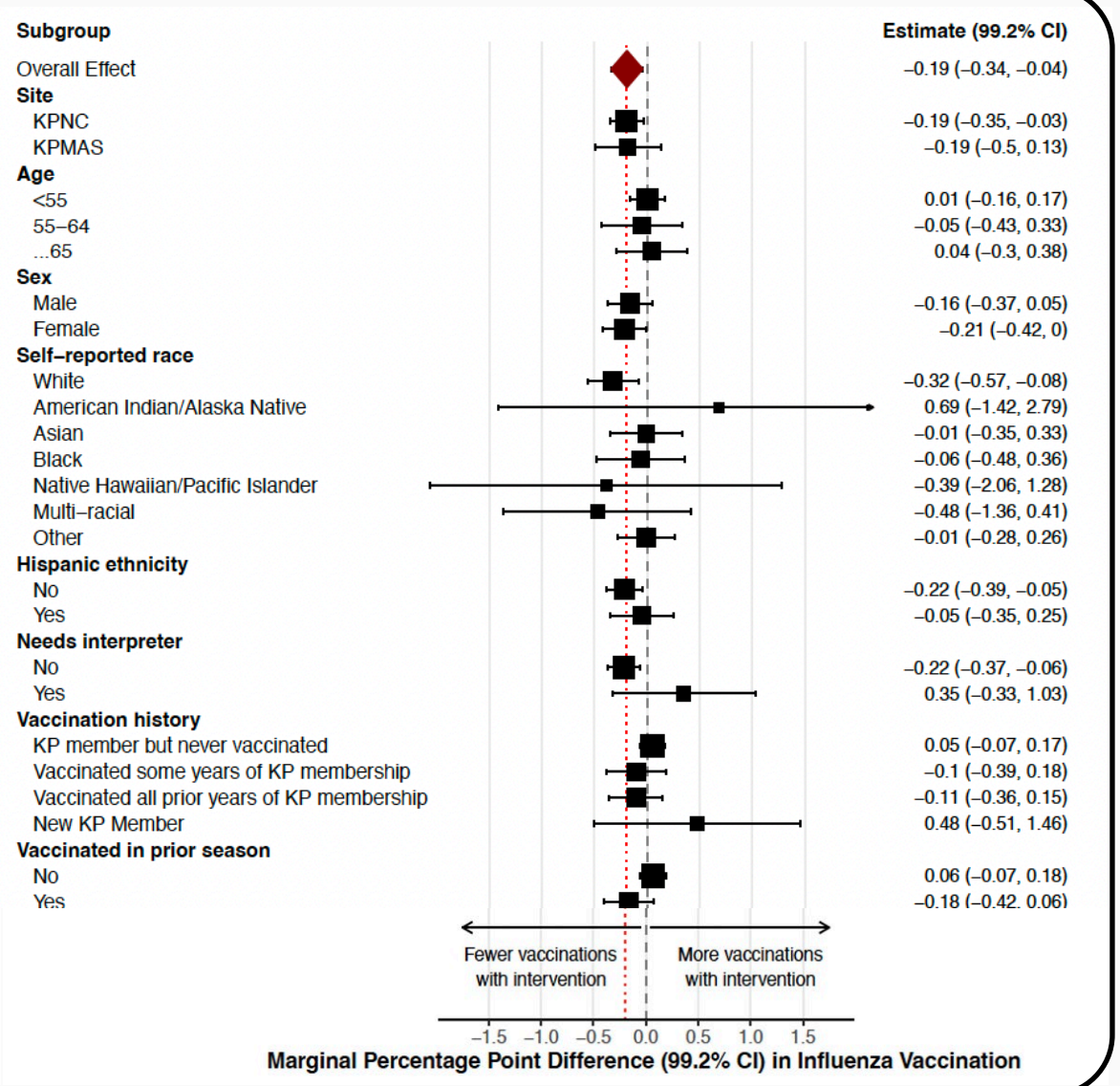


Time to Vaccination



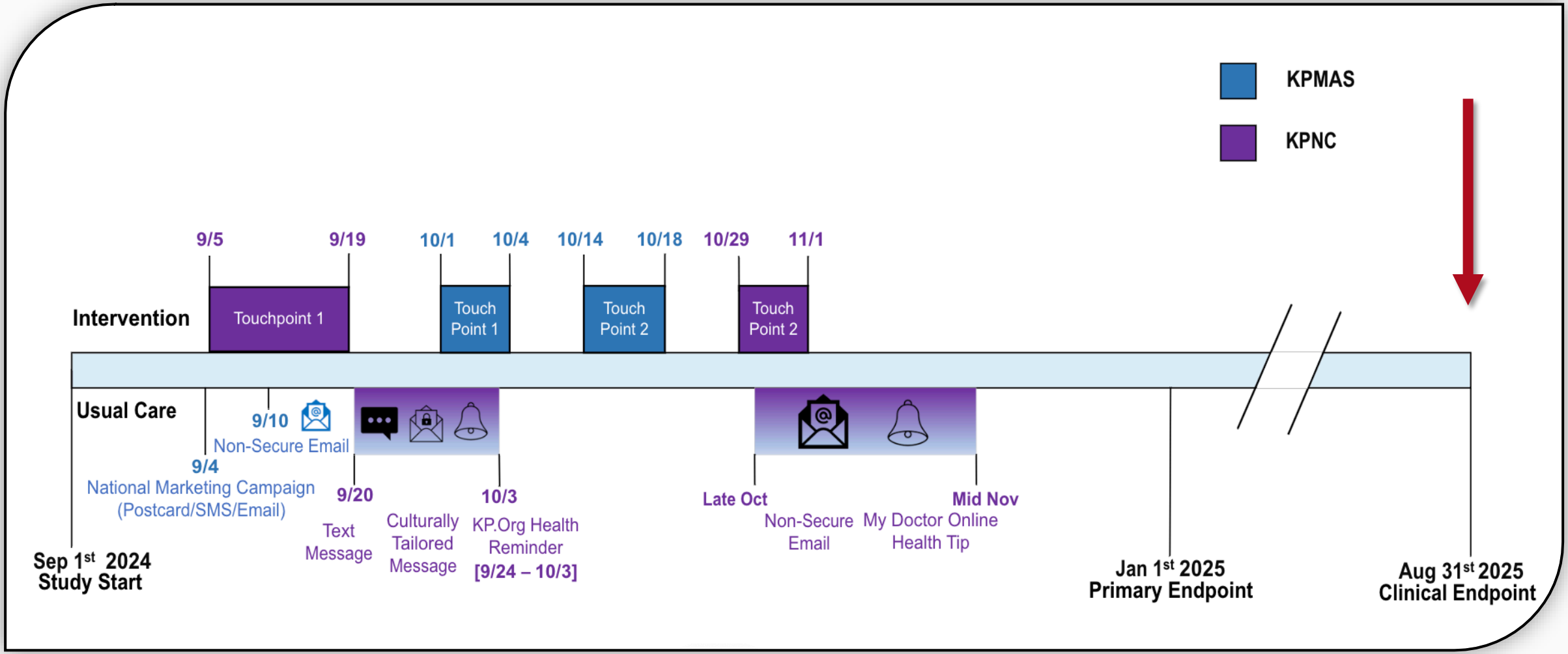
Subgroups



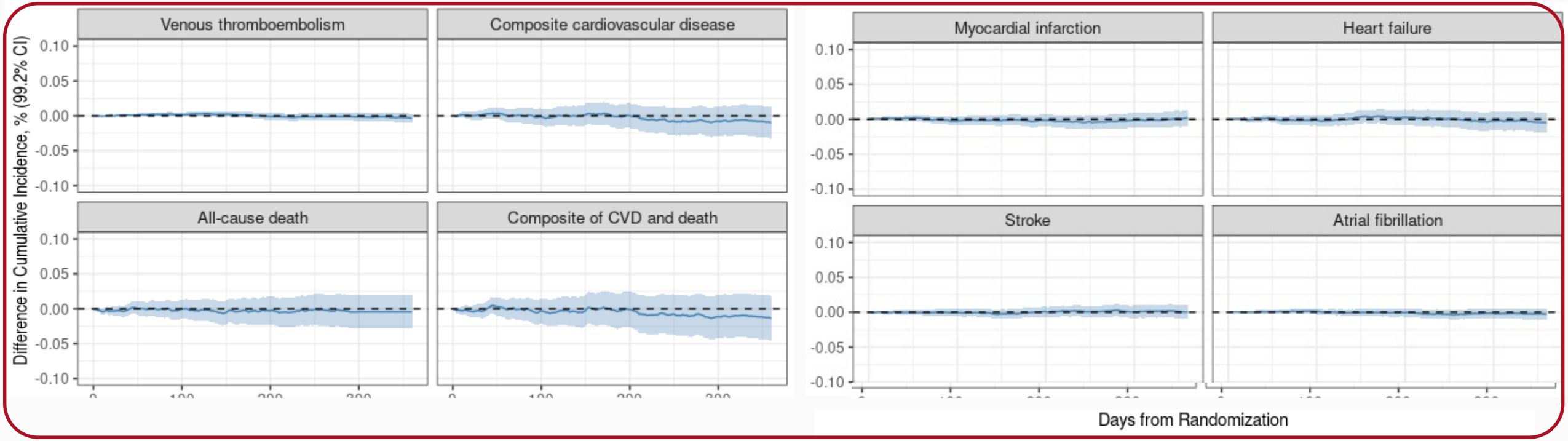


Bhatt, AS. European Society of Cardiology 2025 Scientific Sessions. Madrid, ES.

Long Term Follow-up



Clinical Outcomes By Randomized Treatment



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ORIGINAL ARTICLE

Cardiovascular-Focused Messaging to Improve Influenza Vaccination Rates

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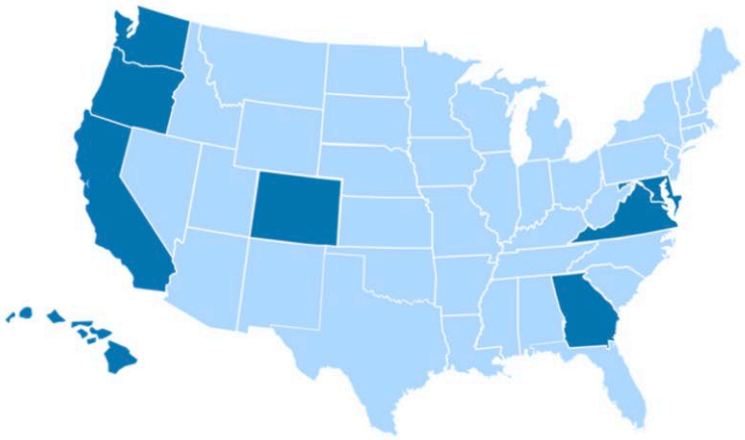
Learning to Learn In a Learning Healthcare System

Mission: To provide affordable high-quality health care services and to improve the health of our members and the communities we serve.



12.5 million members (2023)

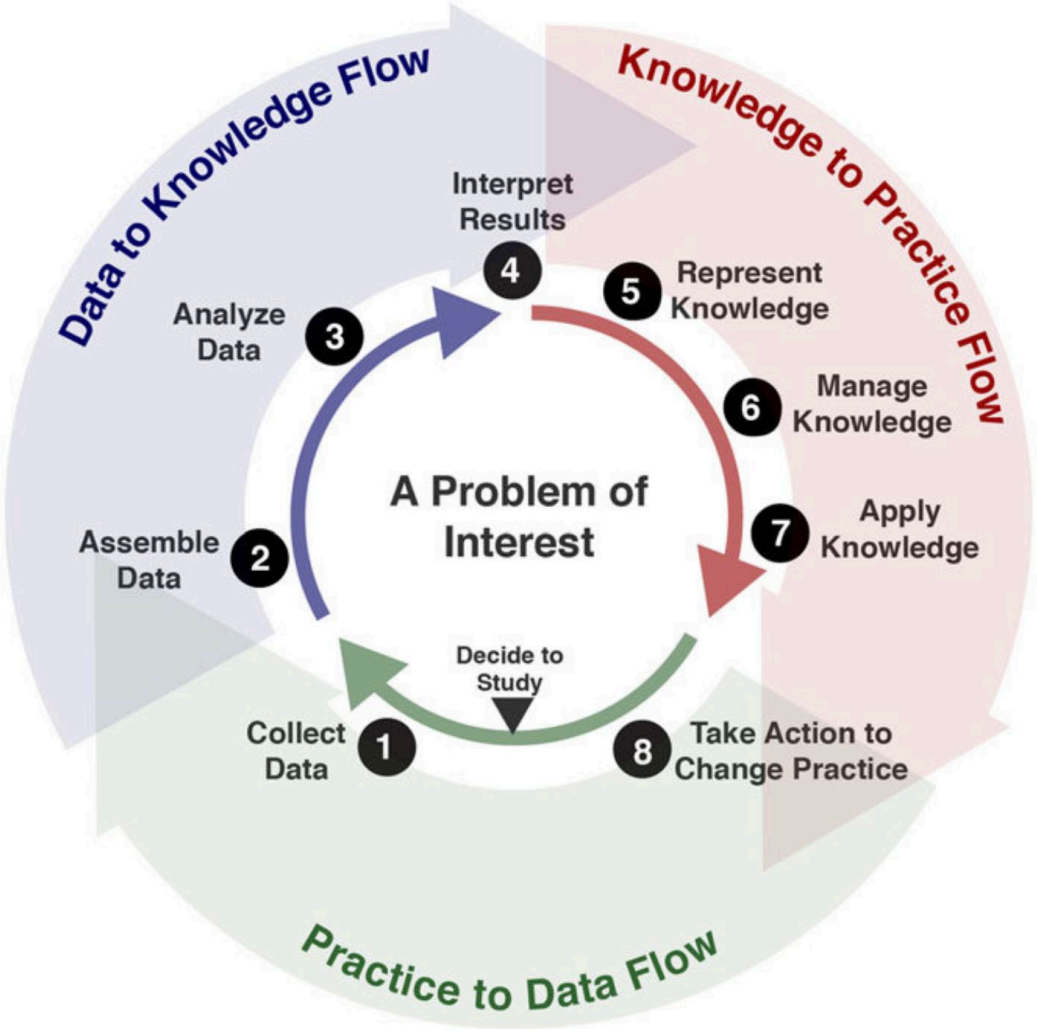
24,605 physicians

73,618 nurses

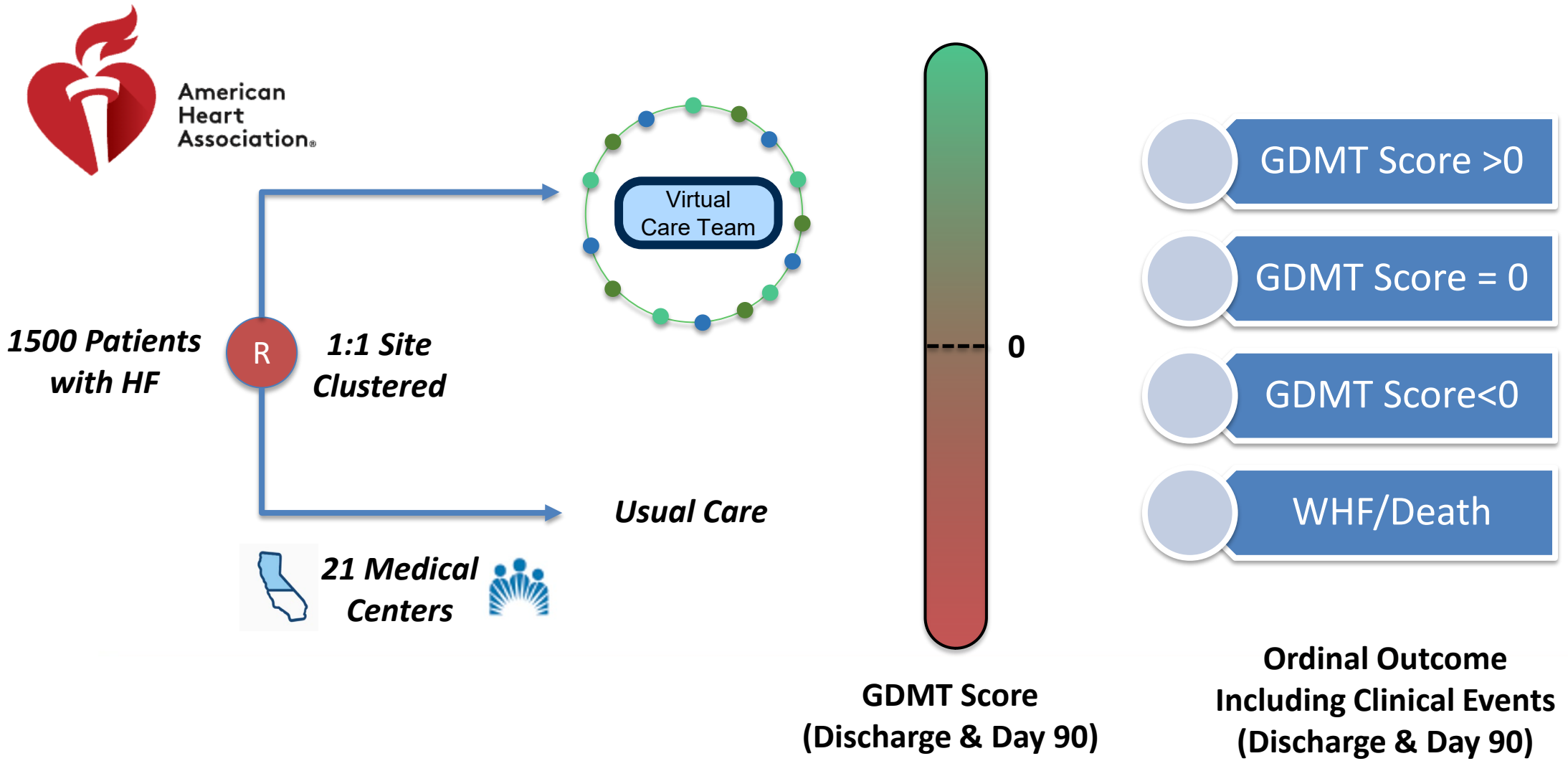
216,000 employees

618 medical facilities

40 hospitals

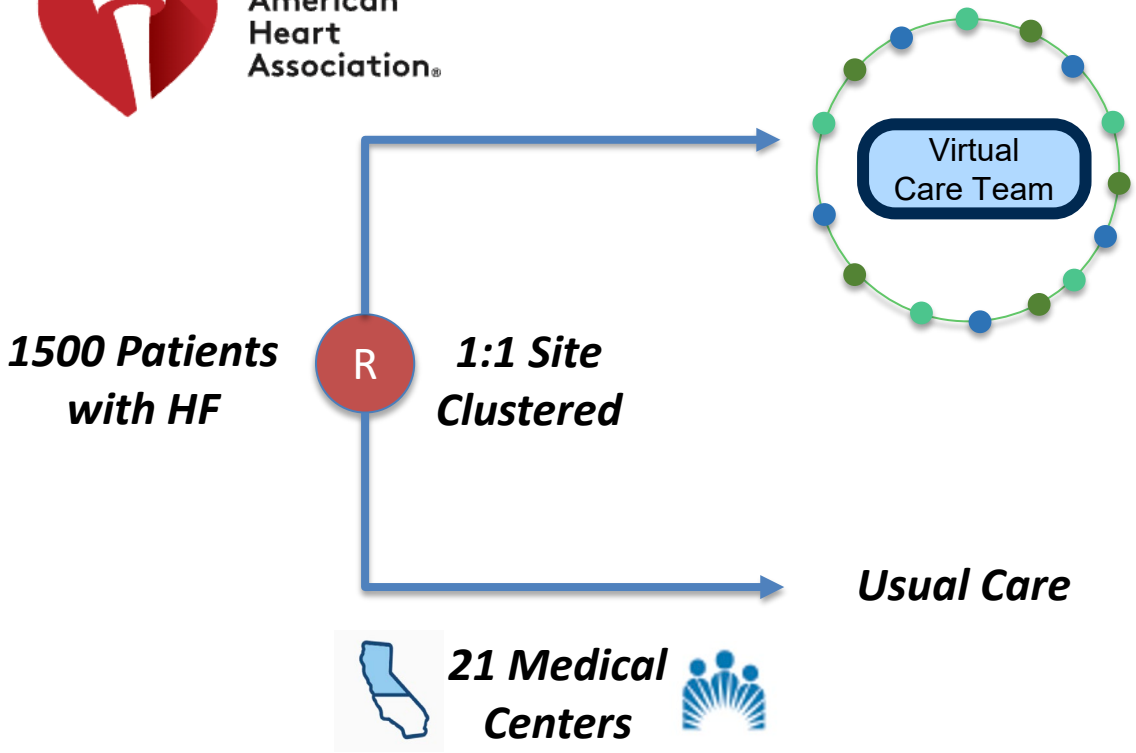


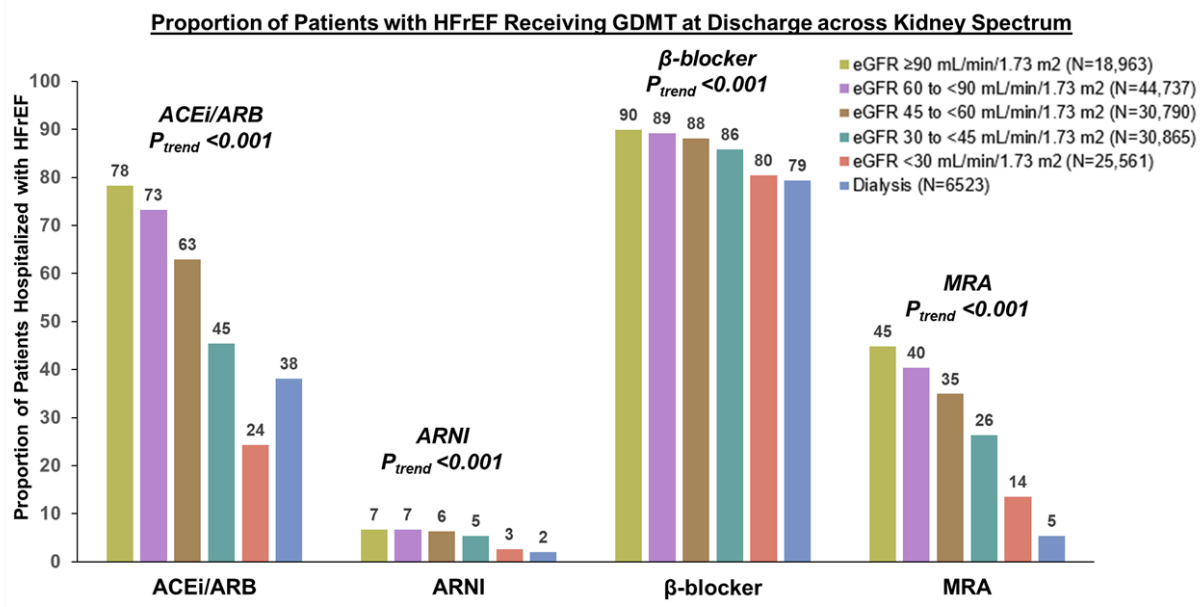
IMPLEMENT-CKM Trial: Virtual Care Team Guided Care



IMPLEMENT at KP: A Specific Focus on CKM Comorbidity

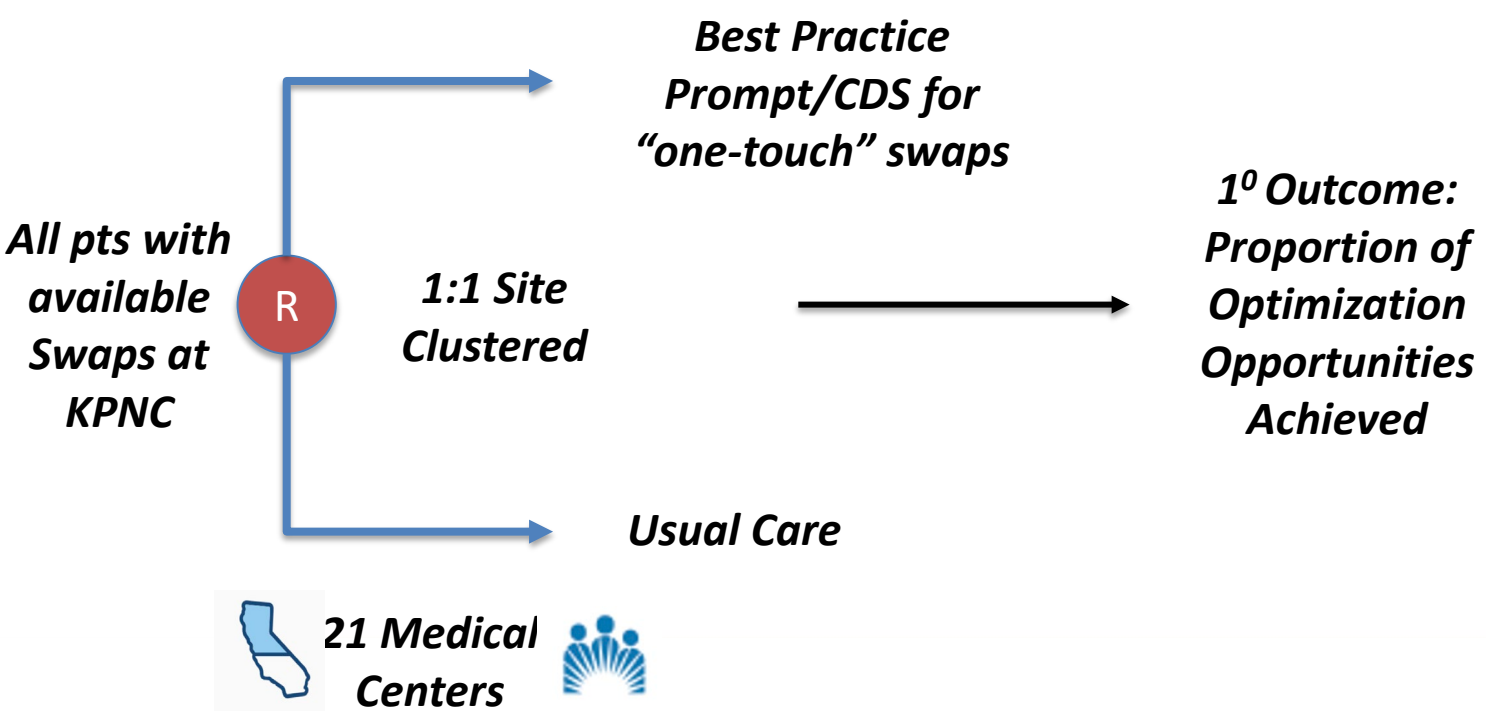
American Heart Association.





SWitching to Appropriate Prescriptions for Cardiovascular- Kidney-Metabolic Health (SWAP-CKM)

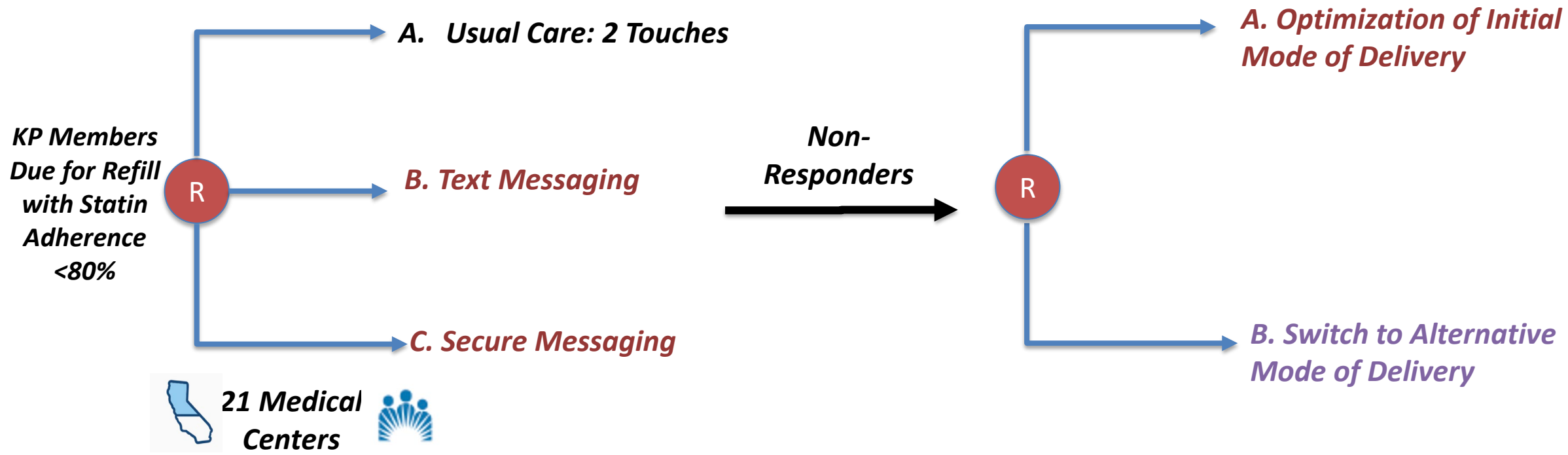
Pairing implementation & de-implementation science for CKM health



Condition	Potentially Inappropriate Treatment	Potentially Appropriate Treatment
HFrEF	Non-dihydropyridine calcium channel blockers or non-evidence-based beta-blockers	Evidence-based beta-blocker
T2DM + HF or CKD	DPP4i/TZD/sulfonylureas	SGLT2i
HF	Loop diuretic + potassium supplementation	Loop diuretic + MRA
HF or CKD	NSAIDs	Alternative non-opioid analgesic

Adherence to **D**yslipidemia therapy: **H**arnessing **E**vidence from **R**andomized **E**valuations in **ASCVD** (**ADHERE-ASCVD**)

Sequential, Multiple Assignment, Randomized Trial (SMART)



Conclusions

- **KP-VACCINATE is the one one largest individually RCT conducted to date.**
- **A cardiovascular-focused nudge communication did not increase influenza vaccination rates compared with usual care communication.**
  - **Reasons may include differing cultural views toward vaccination and increased vaccine hesitancy in the US.**
- **Despite the negative results, this trial establishes that pragmatic and rapid randomization of communication strategies is operationally feasible at scale with routine health care workflows in the US.**
- **Innovative trial designs (cluster randomization, SMART designs) that are intentionally care embedded may help to fully realize the promise of the learning healthcare system.**

Pragmatic Care Embedded Randomization: Insights From the KP-VACCINATE Megatrial & Beyond

Thank You!

Ankeet S. Bhatt, MD, MBA, ScM

NIH Collaboratory Grand Rounds
January 09, 2026
Virtual

@Ankeetbhatt

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