Team Science: A Case History

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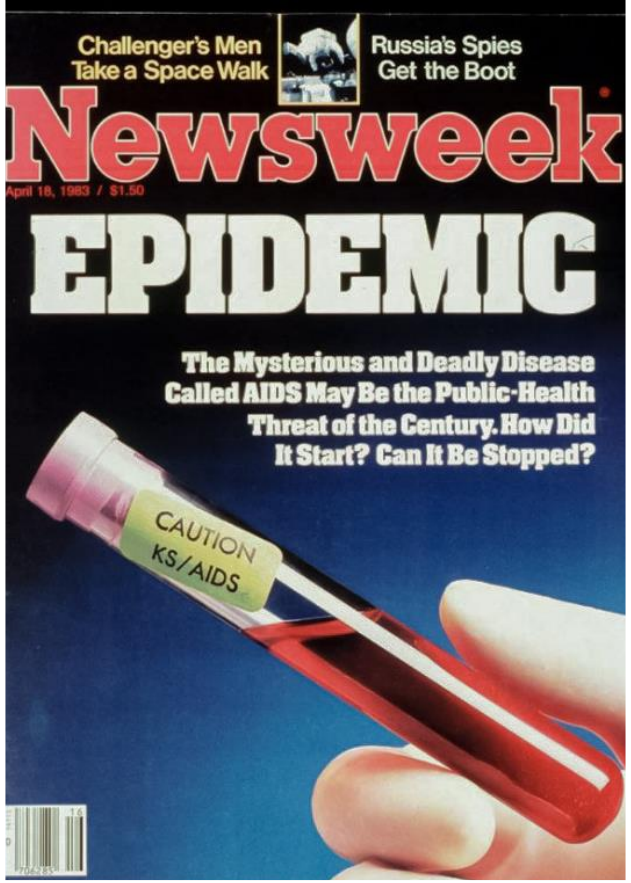
A Long and Winding Road…

1. HIV prognosis
2. +Aging
3. +Alcohol in HIV/aging context
4. =Polypharmacy



The Bad Old Days of AIDS

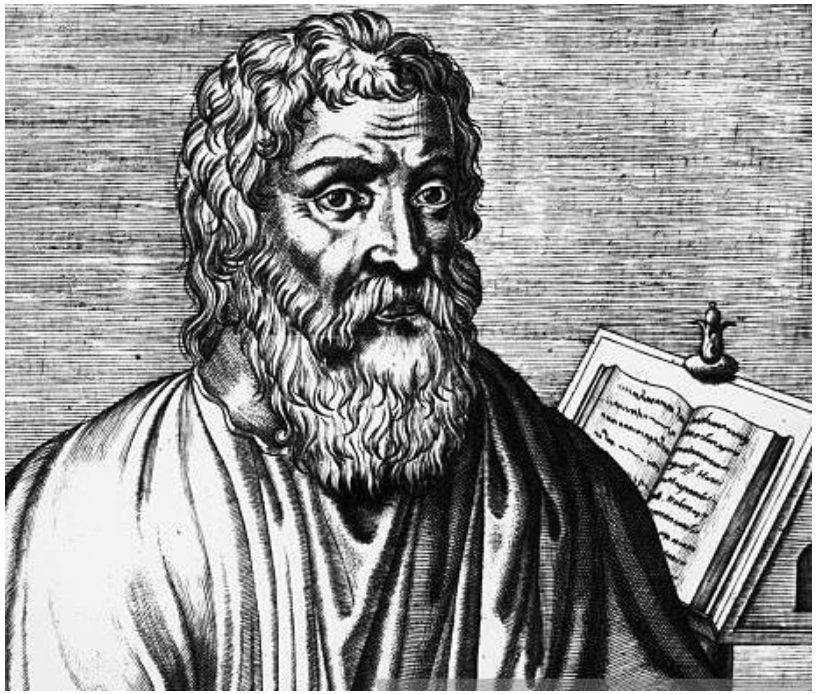
1981-87: The Beginning of the AIDS Epidemic

- “Gay-Related Immune Deficiency (GRID)” targeting 4-H’s: haemophiliacs, heroin users, homosexuals, and Haitians—highly stigmatized
- As a med student I was reprimanded for touching a patient
- One woman my age was admitted with a history of injection drug use and cryptococcal meningitis and said,

  “I know I have AIDS and I am going to die…I need to know how long I have so I can make plans for my children.”

  --This question launched my research career, how would <u>you</u> have answered her?

The First Question After Diagnosis: Prognosis



It appears to me a most excellent thing for the physician to cultivate Prognosis:…he will manage the cure best who has foreseen what is to happen from the present state of matters. For it is impossible to make all the sick well …but since men die, …it becomes necessary to know the nature of such affections, how far they are above the powers of the constitution…

---- from The Book of Prognostics, a Hippocratic treatise

Why study prognosis?

- Gives the patient an added sense of control
- Informs personal and health care decision making
- May provide mechanistic insight to inform treatment
- Provides a means of detecting changes in health

SPECIAL ARTICLE

A NEW PROGNOSTIC STAGING SYSTEM FOR THE ACQUIRED IMMUNODEFICIENCY SYNDROME

Amy C. Justice, M.D., Alvan R. Feinstein, M.D., and Carolyn K. Wells, M.P.H.

Abstract An improved prognostic staging system is needed for patients with the acquired immunodeficiency syndrome (AIDS). To construct such a system, we analyzed the course of 117 consecutive adults who received a diagnosis of AIDS at Yale–New Haven Hospital from 1981 through 1987. The staging system was developed from the data on the first 76 patients, confirmed in the remaining 41 patients, and then applied to the entire cohort.

The staging system, which is based on physiologic deficits rather than demographic or diagnostic features, gives one point for each of the following: severe diarrhea or serum albumin level under 2.0 g per deciliter, any neurologic deficit, arterial oxygen tension of 50 mm Hg or less, hematocrit below 30 percent, lymphocyte count below 150 per microliter, white-cell count below 2500, and platelet count below 140,000. The total score determines the presence of Stages I (0 points), II (1 point), or III (2 to 7 points). The three stages had distinctive prognostic gradients in our cohort. For patients in Stages I, II, and III, the median survival times were 11.6, 5.1, and 2.1 months, respectively, with one-year survival rates of 50, 30, and 8 percent. When the staging system was tested with a proportional-hazards model, no other descriptive or laboratory variable added any additional predictive power.

Although this new staging system requires further validation in other populations, we believe it will be useful in evaluating new therapies and improving the precision of prognosis in patients with AIDS. (N Engl J Med 1989; 320:1388-93.)

- N=117
- Severe Diarrhea (albumin<2 g/dL)
- Neurologic deficit
- Hypoxia
- Cytopenias
  - Total White Blood Cells
  - Lymphocytes
  - Platelets
  - Red cells

--Cited 130 times

0 citations since 2019

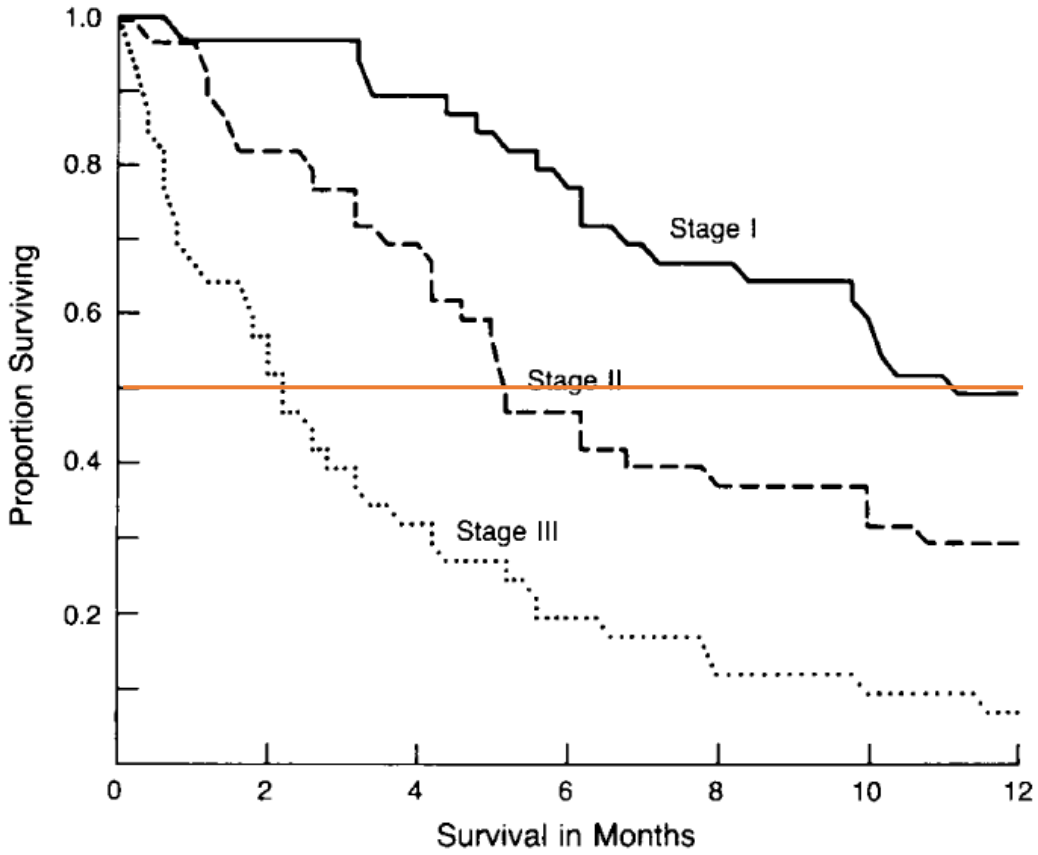


Figure 1. Survival of Patients with AIDS in the Three Prognostic Stages.

Patients were assigned to stages according to their physiologic-deficit scores at the time of diagnosis: 0 = Stage I, 1 = Stage II, and ⩾2 = Stage III. Survival is plotted at intervals of 0.1 month.

al of Medicine

AIDS in the 80s to Early 90s

- 1986 the first test was licensed for HIV
- 1987 AZT (too toxic for cancer!) repurposed to HIV--modest benefit
- During residency, 1988-91, half my service was people with AIDS
- Median survival after first hospitalization was 6 months
- By 1992, AIDS was the leading cause of death for men in the US 25-44 yrs
- More benefit seen with 2 drug regimens but toxicity problematic
- By mid 90s, providers were burning out
- I wanted to know whether my prognostic index still applied

--This question was the basis for my PhD; how would you answer it?

The Development, Validation, and Evaluation of Prognostic Systems: An Application to the Acquired Immunodeficiency Syndrome (AIDS)

A Dissertation in Health Systems for the Graduate Group in Managerial Science and Applied Economics

(Wharton School of Management, University of Pennsylvania)

1996

PhD Dissertation 1994-96

Project

- Develop candidate indices using 3 approaches in 1 sample
  - Classification and regression trees
  - Neural networks
  - Conventional regression techniques
- Validate in 4 independent samples
- Ability to discriminate short vs. longer term mortality fair (AUC 0.65-.75)
- Accuracy not always consistent in development and validation samples

Limitations

- **DATA!**
  - **Few predictors**
  - **Sample size (largest sample ~1000 pts)**
  - **All academic sites**
- **Collaborators**
  - **Programming and statistical experts**
  - **Clinical experts**
- **Faster, stronger, smarter computers**

At the time, these limitations seemed insurmountable. What could I do?

Hierarchy of Generalizability

Table 1. Definitions of Accuracy and Generalizability

Term	Definition or Criteria
Accuracy	The degree to which predicted outcomes match observed outcomes
Calibration	Predicted probability is neither too high nor too low (commonly shown with calibration curves)
Discrimination	Relative ranking of individual risk is in correct order (observed event rates in those with higher scores are higher); commonly measured with the area under the receiver-operating characteristic curve
Generalizability	Ability of a prognostic system to provide accurate predictions in a new sample of patients
Reproducibility	The system is accurate in patients who were not included in development but who are from an identical population
Transportability	The system is accurate in patients drawn from a different but related population or in data collected by using methods that differ from those used in development
Historical	Accuracy is maintained when the system tested in data from different calendar time
Geographic	Accuracy is maintained when the system is tested in data from different locations
Methodologic	Accuracy is maintained when the system is tested in data collected by using different methods
Spectrum	Accuracy is maintained in a patient sample that is, on average, more or less advanced in disease process or that has a somewhat different disease process or trajectory
Follow-up interval	Accuracy is maintained when the system is tested over a longer or shorter period

Table 2. A Hierarchy of External Validity for Predictive Systems

Level of Validation	Cumulative Generalizability Evaluated
0. Internal validation	Reproducibility
1. Prospective validation	Reproducibility, historic transportability
2. Independent validation	Reproducibility, historic transportability, geographic transportability, methodologic transportability, spectrum transportability
3. Multisite validation	Reproducibility, historic transportability, geographic transportability, methodologic transportability, spectrum transportability
4. Multiple independent validations	Reproducibility, historic transportability, geographic transportability, methodologic transportability, spectrum transportability
5. Multiple independent validations with life-table analyses	Reproducibility, historic transportability, geographic transportability, methodologic transportability, spectrum transportability, follow-up period transportability

Annals of Internal Medicine, March 16, 1999

Cited >800 times, 35 times in 2022

Assessing the Generalizability of Prognostic Information

Amy C. Justice, MD, PhD; Kenneth E. Covinsky, MD, MPH; and Jesse A. Berlin, ScD

Physicians are often asked to make prognostic assessments but often worry that their assessments will prove inaccurate. Prognostic systems were developed to enhance the accuracy of such assessments. This paper describes an approach for evaluating prognostic systems based on the accuracy (calibration and discrimination) and generalizability (reproducibility and transportability) of the system's predictions. Reproducibility is the ability to produce accurate predictions among patients not included in the development of the system but from the same population. Transportability is the ability to produce accurate predictions among patients drawn from a different but plausibly related population. On the basis of the observation that the generalizability of a prognostic system is commonly limited to a single historical period, geographic location, methodologic approach, disease spectrum, or follow-up interval, we describe a working hierarchy of the cumulative generalizability of prognostic systems.

This approach is illustrated in a structured review of the Dukes and Jass staging systems for colon and rectal cancer and applied to a young man with colon cancer. Because it treats the development of the system as a "black box" and evaluates only the performance of the predictions, the approach can be applied to any system that generates predicted probabilities. Although the Dukes and Jass staging systems are discrete, the approach can also be applied to systems that generate continuous predictions and, with some modification, to systems that predict over multiple time periods. Like any scientific hypothesis, the generalizability of a prognostic system is established by being tested and being found accurate across increasingly diverse settings. The more numerous and diverse the settings in which the system is tested and found accurate, the more likely it will generalize to an untested setting.

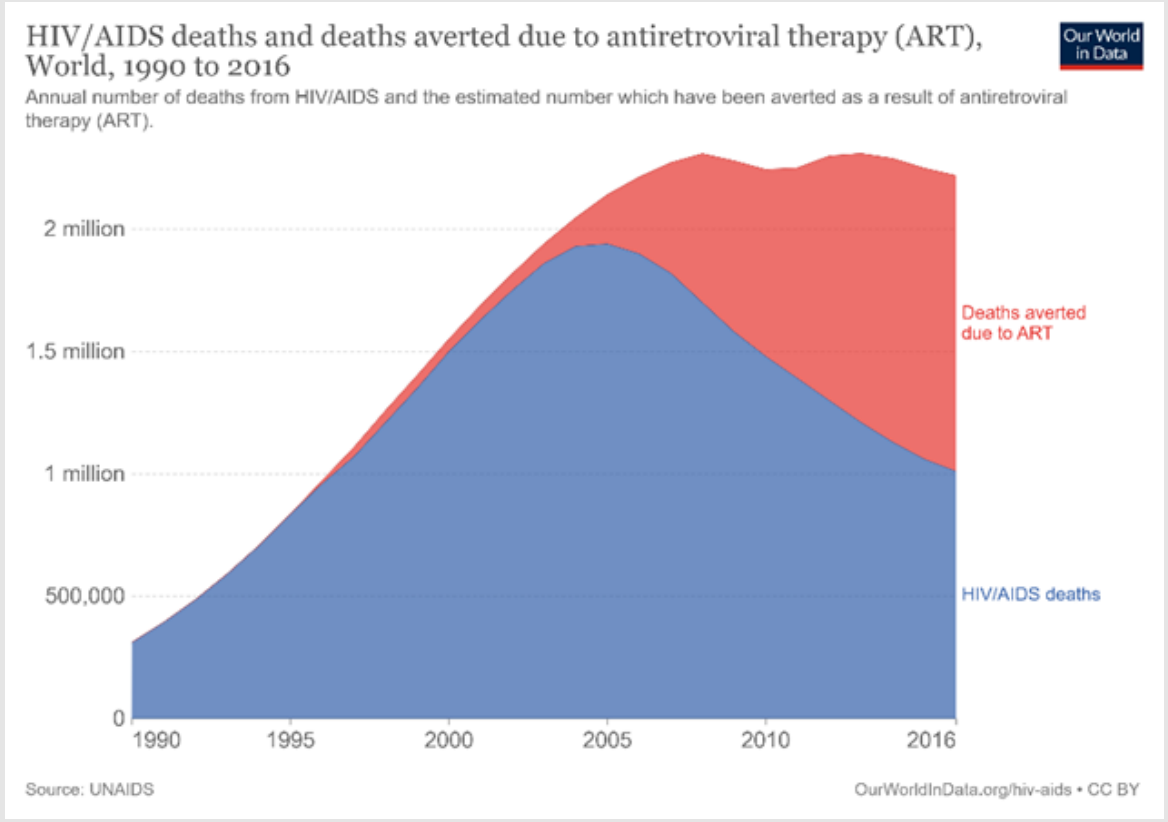
Your secretary just called to say that a favorite patient of yours (a 45-year-old high school teacher) with colon cancer dropped off his surgical and pathologic reports. She reminds you that he is scheduled this afternoon for a second opinion about his prognosis. Scanning the reports, you note that the surgeon staged the cancer at Dukes stage C1 on the basis of negative margins and 1 positive out of 28 lymph nodes and that the pathologist staged the microscopic tissue at Jass stage IV. You are not sure how to translate these stages into useful prognostic information for your patient.

Time is short. You log on to MEDLINE, type "Dukes and Jass," and select the years 1966 to 1997. The combined terms generate 18 references (1–18). Of these, 4 are independent reports of observed mortality rates (8, 11, 17, 19). You also track down the original reports of the Dukes and Jass systems (20, 21) and learn that both systems were developed at St. Mark's Hospital in London more than 30 years ago (20, 21). The Dukes system is based on histology and extent of local, lymphatic, and venous spread seen in the surgical specimen (20), and the Jass system is based on microscopic pathologic staging (21). However, the reported mortality rates by stage for these systems vary widely. How do you tell which report and which system are most likely to pertain to a 45-year-old teacher from Cleveland, Ohio?

Physicians are frequently asked for prognostic assessments and often worry that their assessments

Two Miracles Occurred…

Miracle #1: Highly Effective Antiretroviral Therapy



- 1996 three drug class regimens first recommended
- Dramatic shift in ability to suppress virus with concomitant CD4 response
- Treatment as prevention
- Testing now an opportunity for treatment and survival
- Mortality rates have plummeted
- Can prevent transmission
  - U = U: Undetectable = Untransmittable
  - mother to child transmission
  - PrEP to prevent sexual transmission
- Aging with HIV now possible

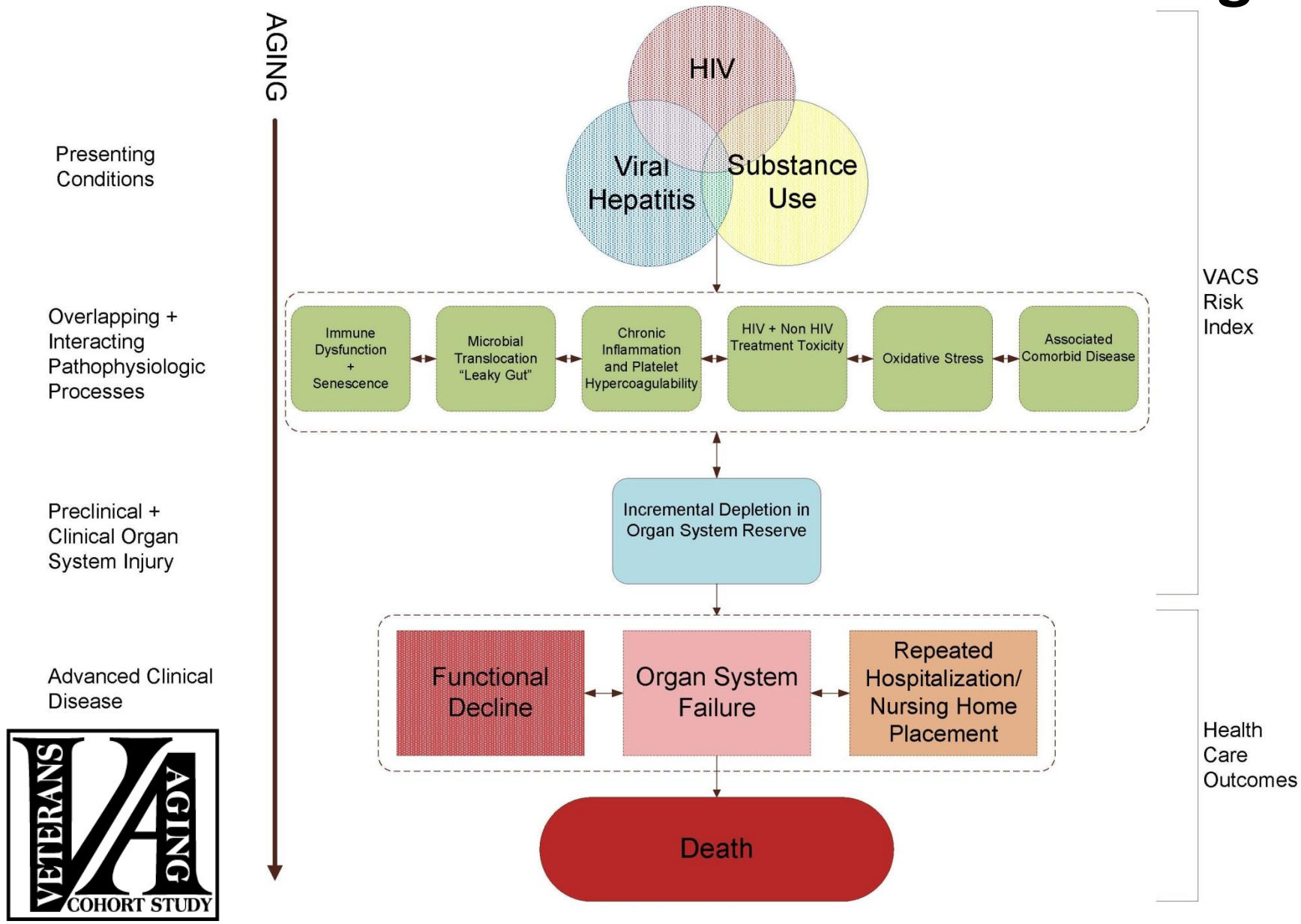
Miracle # 2:
US Veterans Healthcare System Institutes a National "Paperless" Electronic Health Record (EHR) in 1999

9 million individuals/year—since 1999 >33 million users

An Idea! Use VA EHR Data to Create a National Cohort of People Aging with and without HIV

This idea launched a cohort that I have studied for 25 years.

CD4 & Viral Load Insufficient: How to Monitor Aging with HIV?



VETERANS AGING COHORT STUDY

Justice AC. HIV and Aging: Time for a New Paradigm. Curr HIV/AIDS Rep. 2010 May;7(2):69-76

VACS Cohorts: HIV Came First

- Full national sample
- N~13.5 million
- All Veterans in the VA system

VACS-*Full VA*

- 1945-1965 HCV birth cohort
- N~3.1 million
- All Veterans born between 1945-1965

VACS-*Birth cohort*

- HIV study
- N~60,000 PWH, 120,000 PWoH
- 1 PWH:2 PWoH demographically-matched

VACS-*HIV*

- 2,554 PWH, 3,037 PWoH
- Consented substudy
- 1 PWH:1 PWoH
- 9 VA sites
- Patient & provider surveys

VACS-*HIV Survey*

- 1,050 PWH, 577 PWoH
- Survey substudy
- 2 PWH:1 PWoH
- Banked specimens, select labs, DNA

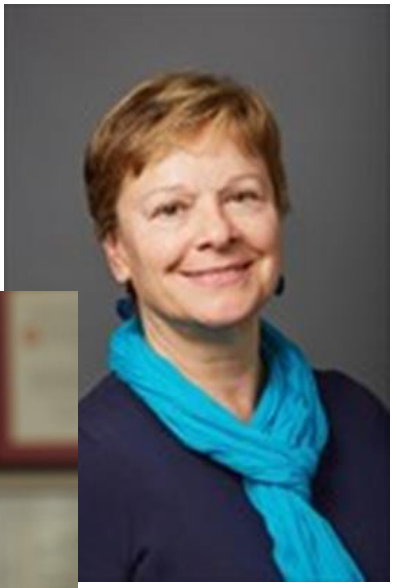
VACS-*HIV Biomarker*

VACS
Veterans Aging Cohort Study

PWH = Persons with HIV (HIV+)
PWoH = Persons without HIV (uninfected)

VACS Index

- Begin with **CD4 count**, **HIV-1 RNA**, and **age**
- Add clinical indicators of physiologic frailty
  - **Hemoglobin**
  - **Liver tests (transaminases, albumin)**
  - **Renal function (creatinine)**
  - **Bone marrow (white blood cells, platelets)**
  - **Body mass index**
  - **Hepatitis C**
- Identify optimal functional form
- Validate in ART CC and NA ACCORD (40+ independent international cohorts)



VETERANS AGING COHORT STUDY

ART Cohort Collaboration

NA ACCORD North American AIDS Cohort Collaboration on Research and Design

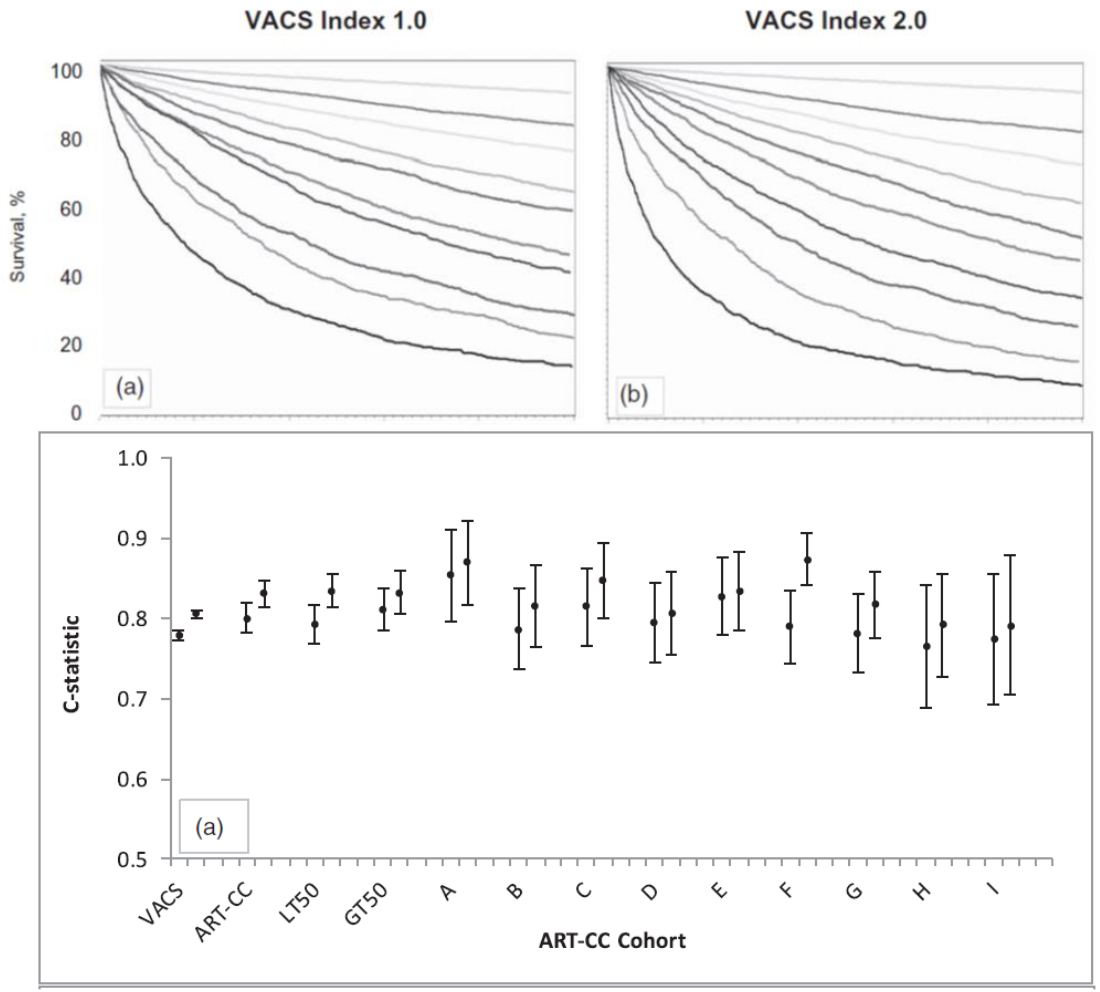
Veterans Aging Cohort Study Index (VACS Index 1.0)

- Goal: use laboratory values that are routine ordered on people with HIV to more accurately predict mortality
- For comparison, we created a restricted index: Cd4 cell count, HIV-1 viral load, and age

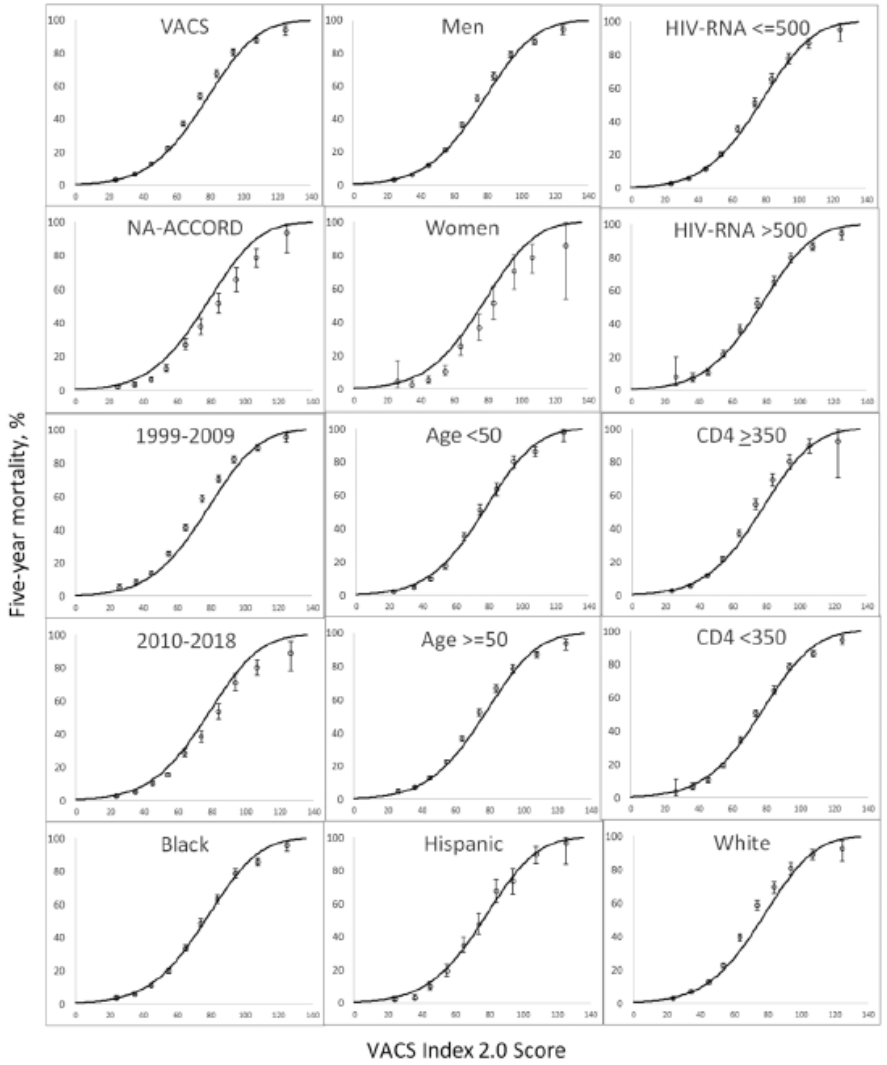
		Index Score	
		Restricted	VACS
Age (years)	<50	0	0
	50 to 64	23	12
	≥ 65	44	27
CD4 cells/mm^3	≥ 500	0	0
	350 to 499	10	6
	200 to 349	10	6
	100 to 199	19	10
	50 to 99	40	28
	< 50	46	29
HIV-1 RNA copies/ml	< 500	0	0
	500 to 1x10^5	11	7
	≥ 1x10^5	25	14
Hemoglobin g/dL	≥ 14		0
	12 to 13.9		10
	10 to 11.9		22
	< 10		38
FIB-4	< 1.45		0
	1.45 to 3.25		6
	> 3.25		25
eGFR mL/min	≥ 60		0
	45 to 59.9		6
	30 to 44.9		8
	< 30		26
Hepatitis C Infection			5

VACS Index 2.0

Albumin, white blood cell count, and body mass index improve discrimination of mortality in HIV-positive individuals



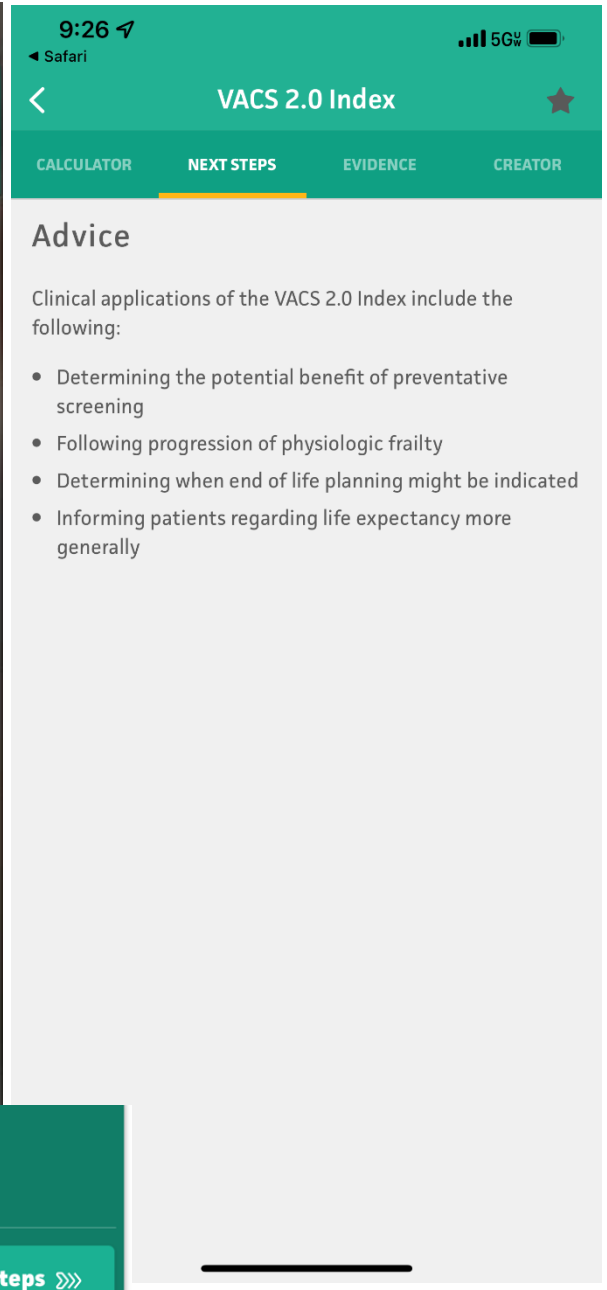
AIDS 2019, **33**:903–912

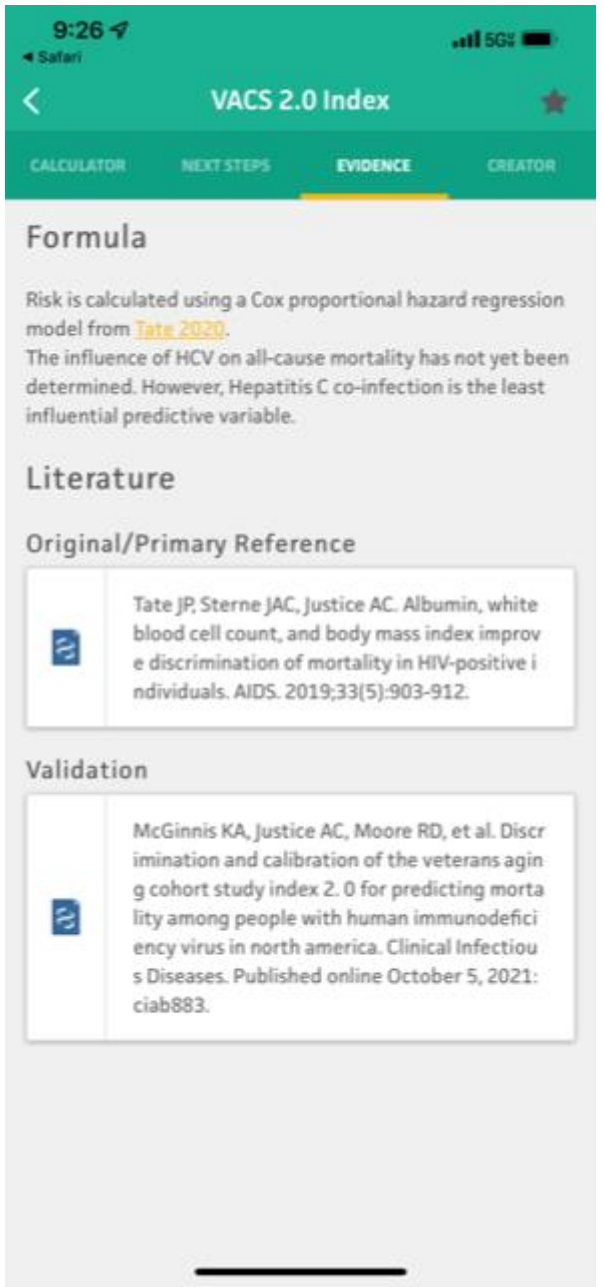


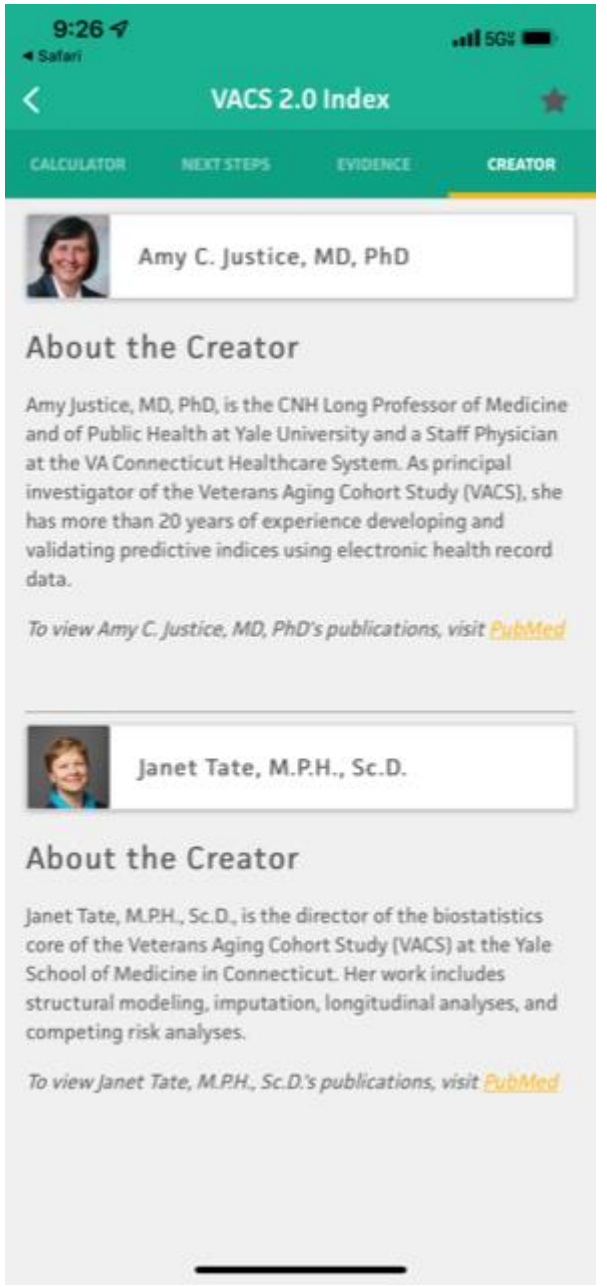
Discrimination and Calibration of the Veterans Aging Cohort Study Index 2.0 for Predicting Mortality Among People With Human Immunodeficiency Virus in North America

Clinical Infectious Diseases® 2022;75(2):297–304

MD Calc Application (and our prior VACS Index website) >95,000 hits since 6/1/12







VACS Cohorts: Newer Cohorts Using Same Methods

- Full national sample
- N~13.5 million
- All Veterans in the VA system

VACS-*Full VA*

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- All Veterans born between 1945-1965

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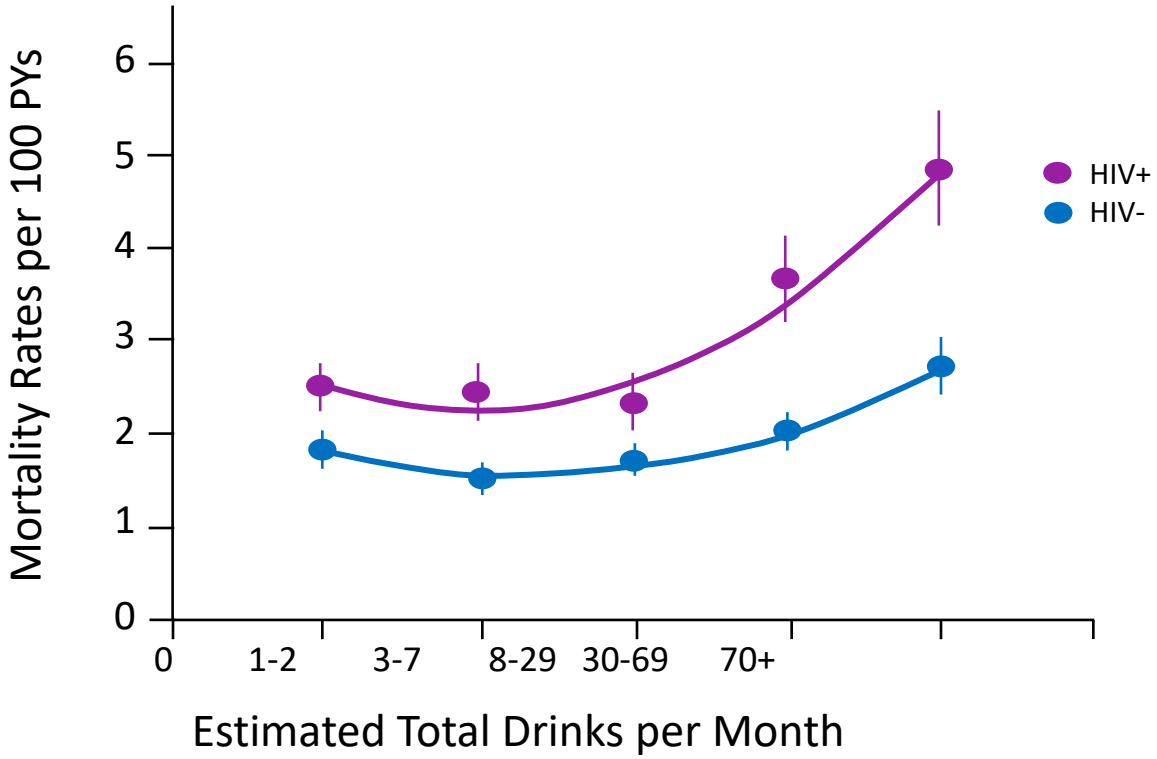
Recent Work on Prognosis

- VACS + Charlson Comorbidity Index (VACS-CCI) in general patients
- VACS-CCI in men with non-metastatic prostate cancer
- VACO Index for pre-existing risk of mortality with COVID-19

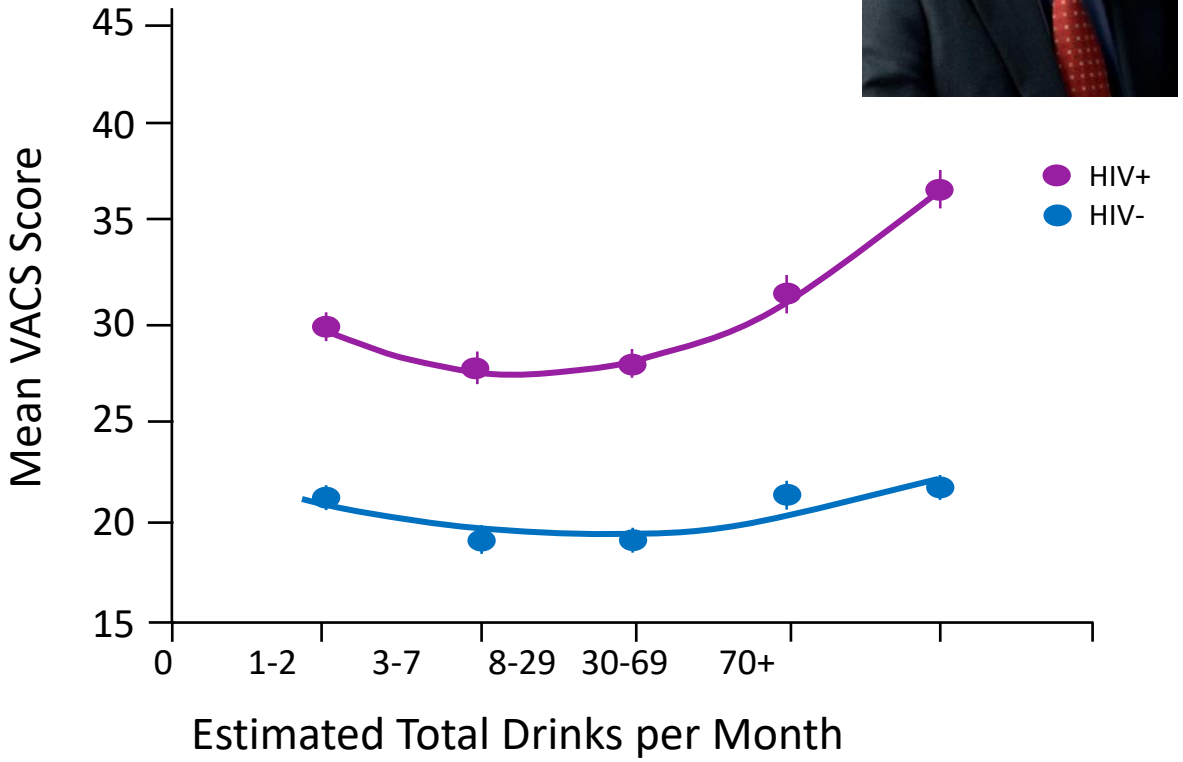
Why Not Include Smoking, Alcohol, Injection Drug Use Etc. in VACS Index?

Harm from Alcohol is Greater Among HIV+ than Uninfected

Mortality

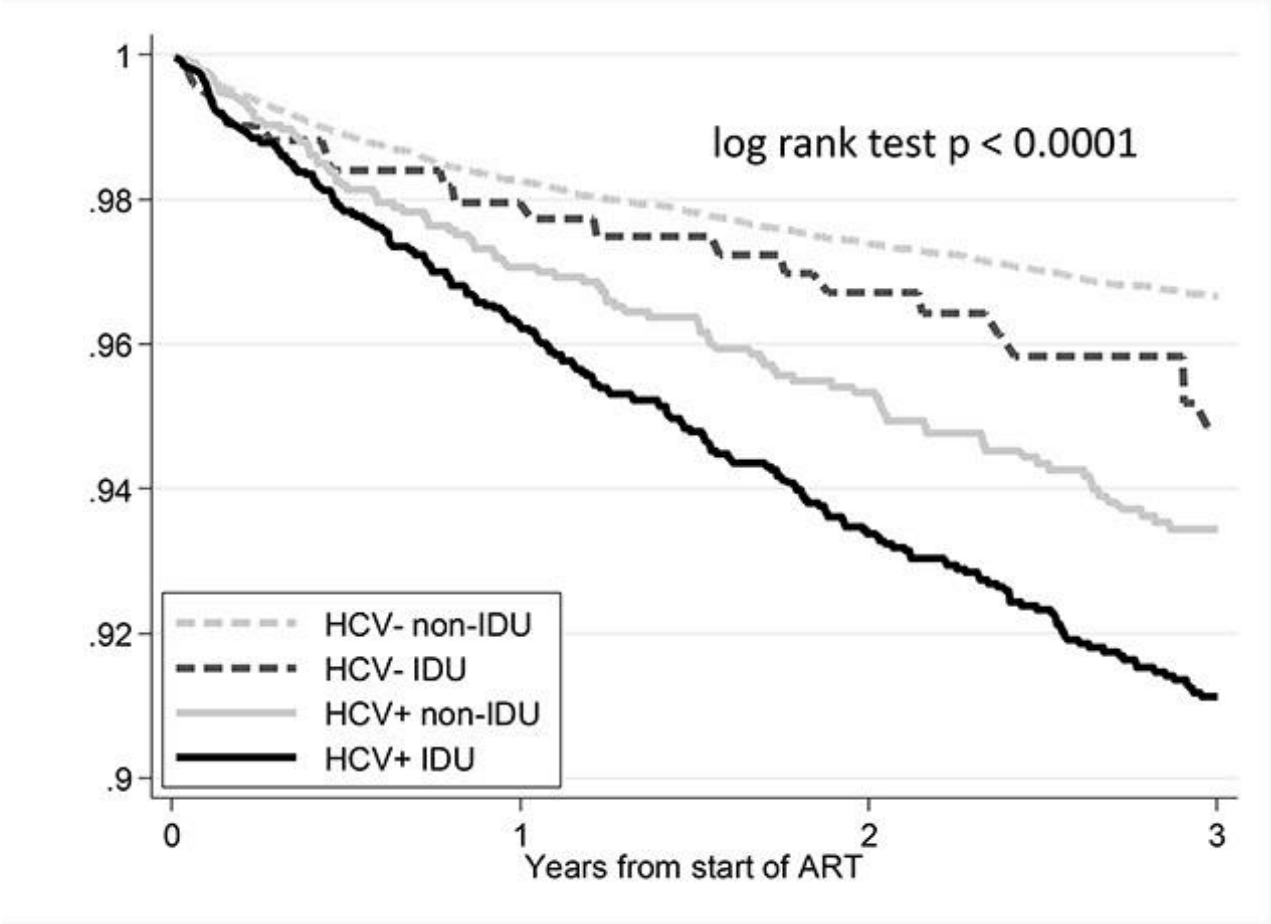


Physiologic Frailty (VACS Index)



Justice AC, et al. Risk of Mortality and Physiologic Injury Evident with Lower Alcohol Exposure Among HIV+ Compared with Uninfected Men. Drug Alcohol Depend. 2016;161:95-103.

Injection Drug Use and Hepatitis C as Risk Factors for Mortality in People with HIV

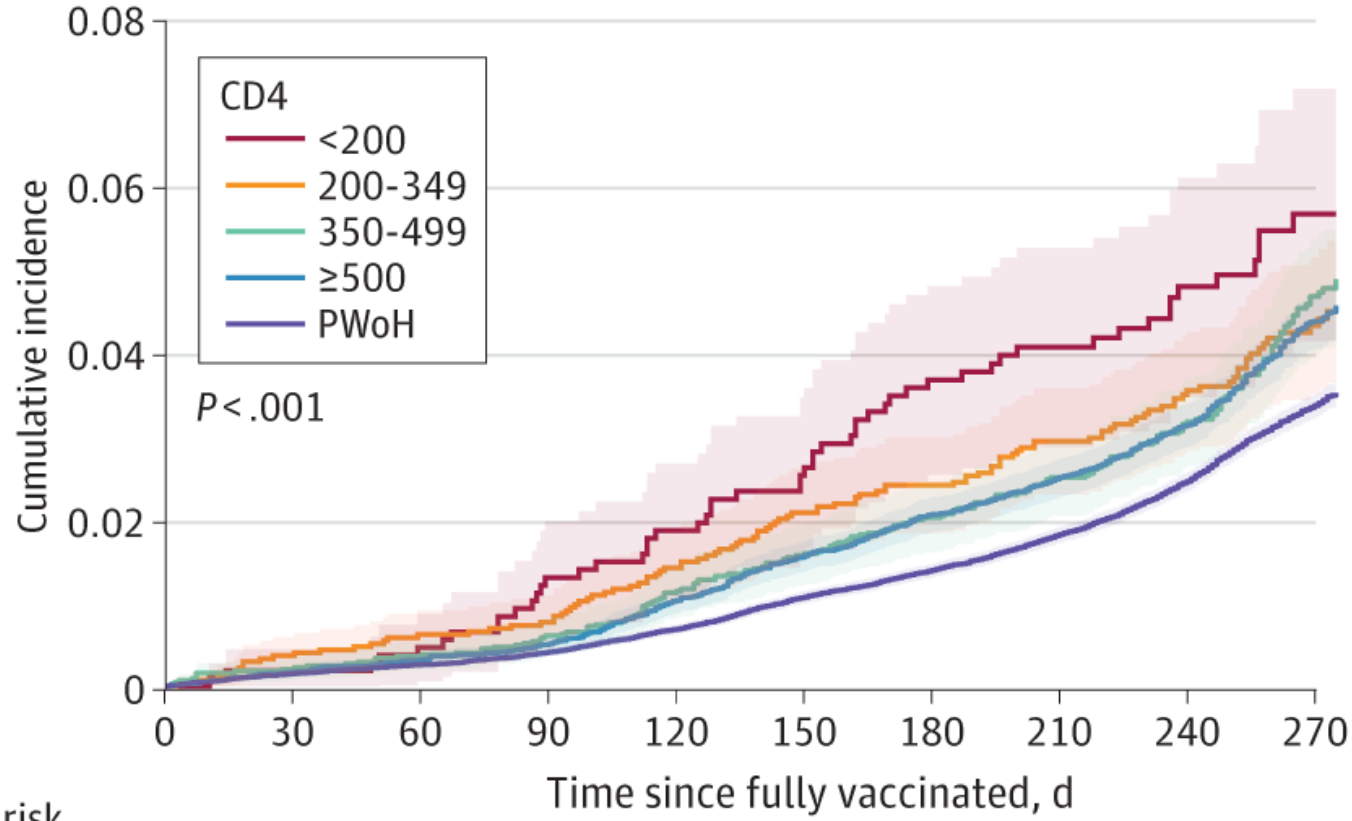


Number at risk:	Yr 0	Yr 1	Yr 2	Yr 3
HCV- non-IDU	27567	23729	19625	15919
HCV- IDU	506	426	353	289
HCV+ non-IDU	1762	1485	1209	953
HCV+ IDU	2868	2400	1958	1553

May, MT. et al. JAIDS Journal of Acquired Immune Deficiency Syndromes69(3):348-354, July 1, 2015.doi: 10.1097/QAI.0000000000000603

Cumulative Incidence of SARS-CoV-2 Vaccine Breakthrough by CD4 Count and HIV Status

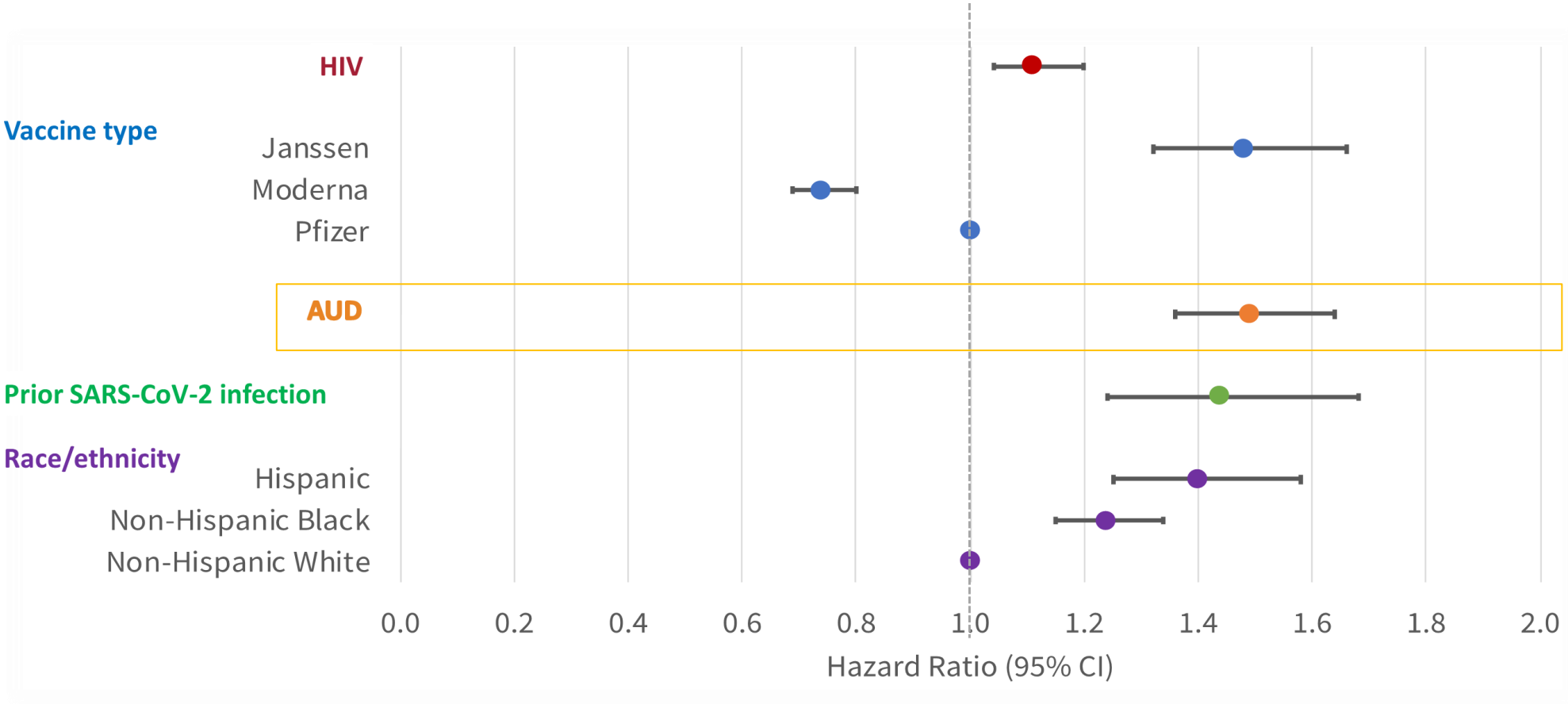
A Cross Cohort Analysis



No. at risk

<200	1086	1080	1067	1047	1037	1017	998	915	720	409
200-349	2753	2734	2718	2703	2677	2652	2632	2470	2021	1143
350-499	4488	4467	4439	4413	4377	4338	4303	4071	3467	1960
≥500	18309	18242	18186	18107	17953	17806	17649	16752	13997	7321
PWoH	80965	80678	80394	80071	79601	79046	78550	74674	61777	32305

JAMA Netw Open. 2022;5(6):e2215934. doi:10.1001/jamanetworkopen.2022.15934



Alcohol consumption and risk of breakthrough SARS=CoV-2 Infection among Persons with and without HIV

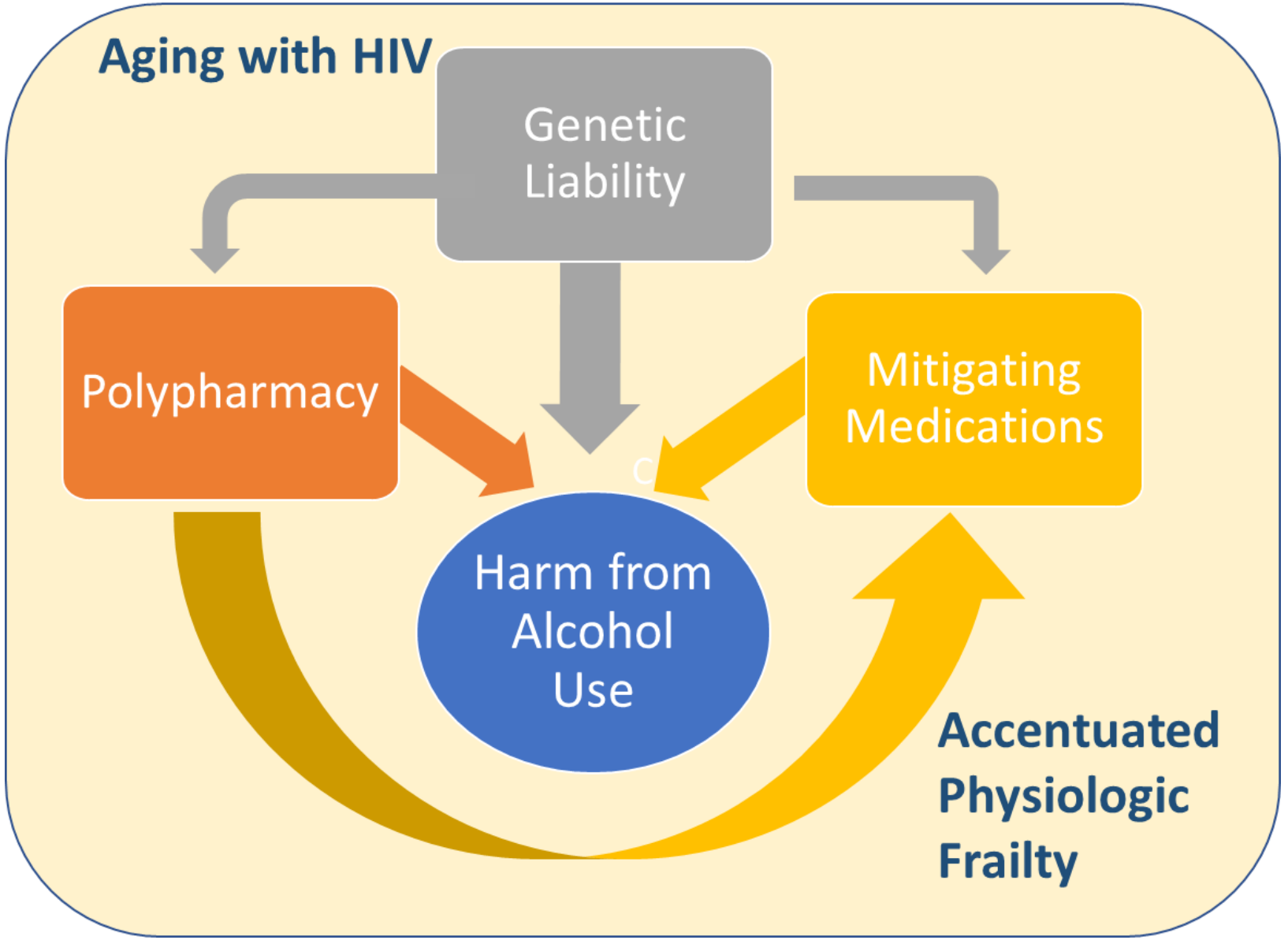
Poster, Park L. et al. Research Society on Alcohol 2022

+

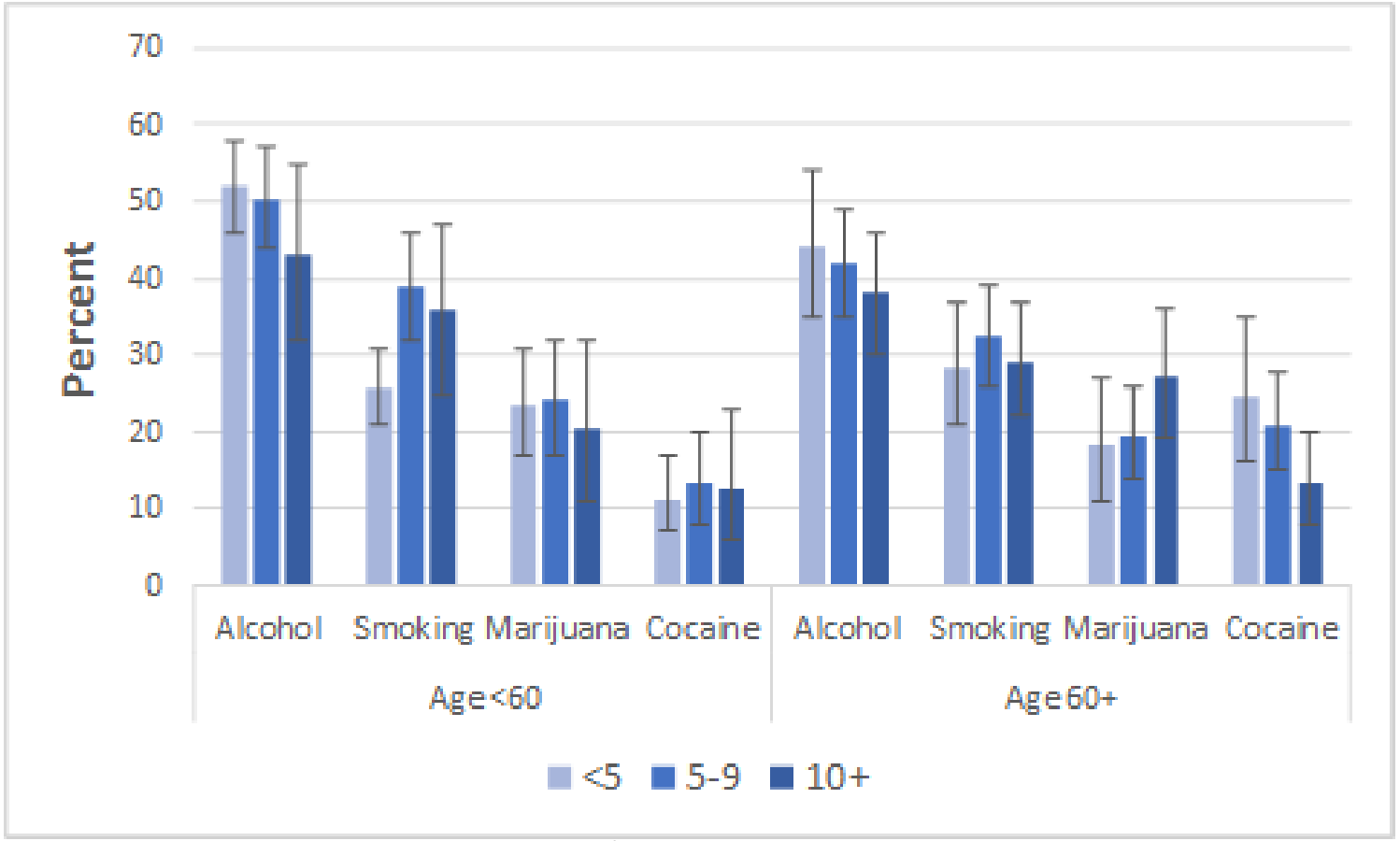
Alcohol & Polypharmacy Harm Among PAH

- Alcohol interacts with many medications
- People aging with HIV may be particularly susceptible
  - Antiretrovirals interact with many medications
  - Experience polypharmacy a decade earlier
  - Have greater physiologic frailty than uninfected
- Two ways to mitigate these harms
  - Deprescribe medications that interact with alcohol
  - Decrease or stop drinking alcohol
- Effectively communicated, personalized interventions, will improve health behaviors more than population-based interventions

HIV, Alcohol & Polypharmacy



Substance Use and Polypharmacy Among PWH



- **M**edications, **A**lcohol, **S**ubstance use in **H**IV Study (MASH)
- Extends VACS to include Kaiser Permanente Northern California and Swiss Cohort
- Prospectively collect data on:
  - ARV & non ARV medications
  - Self report and biomarker verified substance use

		Medication Count		
		<5	5-9	10+
Age <60	Alcohol	52	50	43
	Smoking	26	39	36
	Marijuana	24	24	20
	Cocaine	11	13	13
Age 60+	Alcohol	44	42	38
	Smoking	28	33	29
	Marijuana	18	19	27
	Cocaine	25	21	13

Alcohol, Polypharmacy, and Delirium

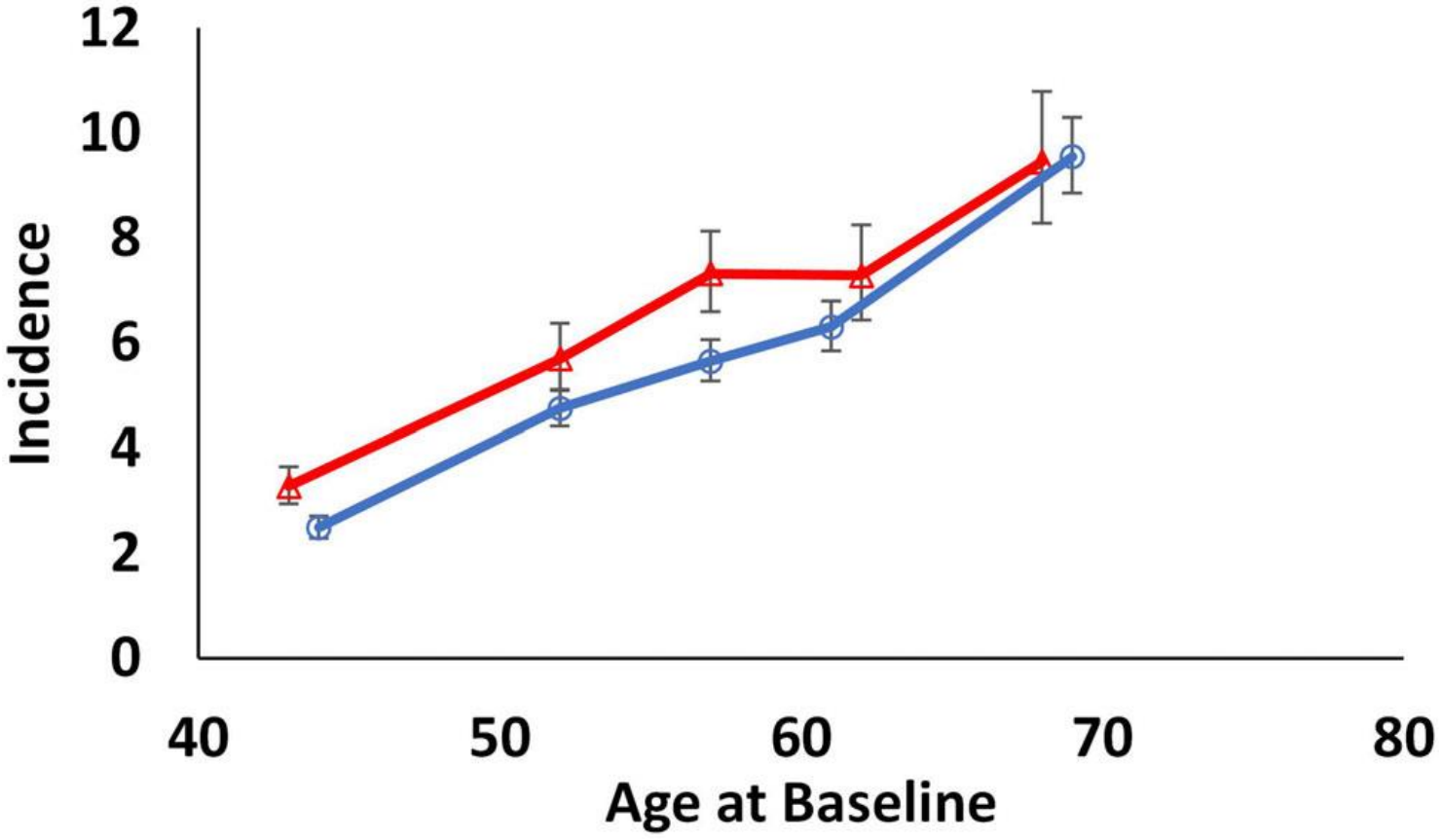


FIGURE 1 Delirium incidence per/1000 person years, by HIV status. PWH, people with HIV; PWoH, people without HIV. Red line = PWH and Blue line = PWoH.

J Am Geriatr Soc. 2023;1–12.

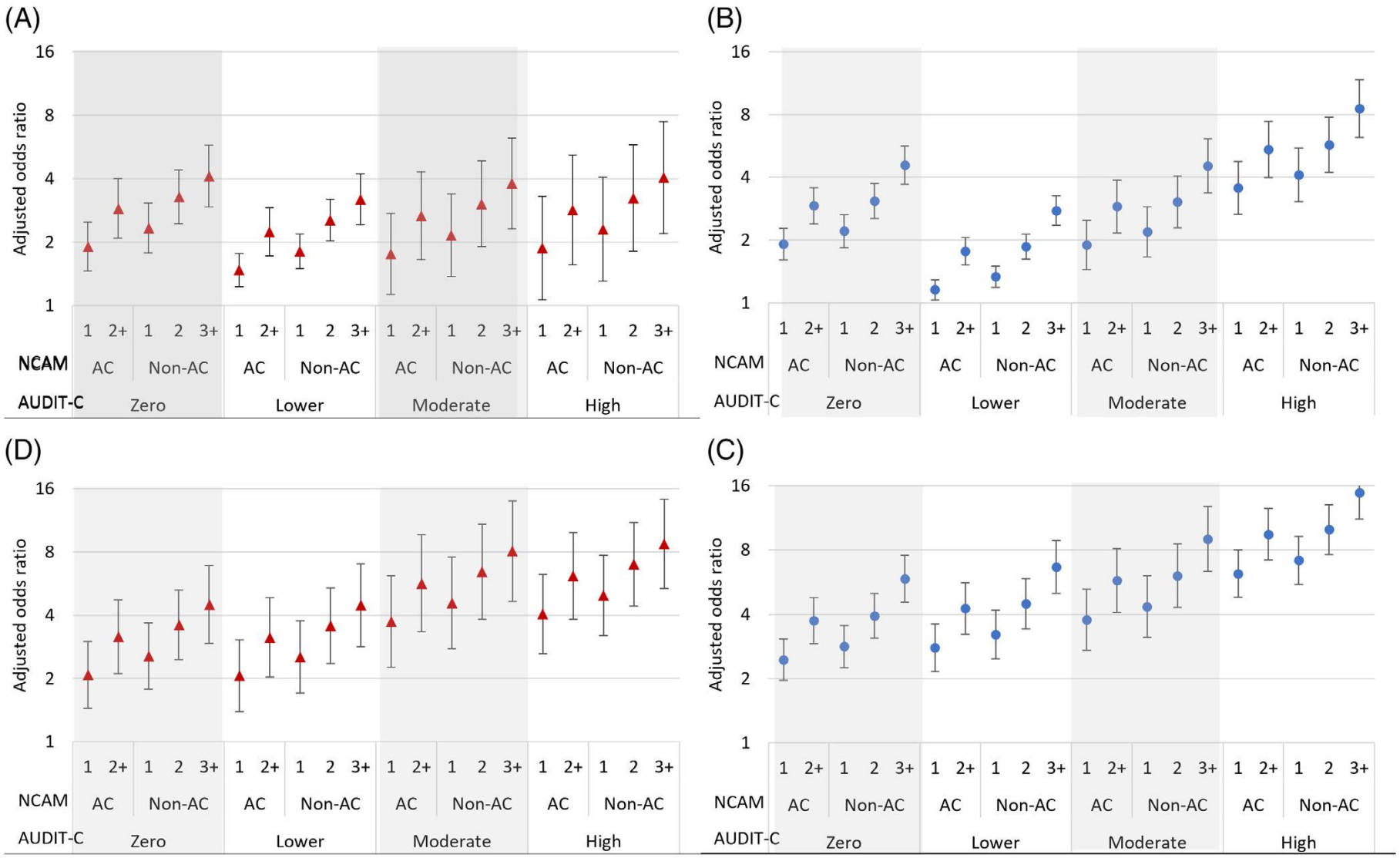


FIGURE 3 Multivariable association showing additive effects of medications and alcohol use patterns with incident, inpatient delirium; stratified by HIV status and history of alcohol use disorder (AUD), adjusted for age, sex, race, severity of illness. Red triangle = People with HIV; Blue circle = People without HIV; AC, anticholinergic; AUDIT-C, alcohol use disorder test, Consumption; NCAM, neurocognitively active medication; Non-AC, non-anticholinergic; lower 1–3 men, 1–2 women; moderate 4–5men, 3–5 women; high 6+.

J Am Geriatr Soc. 2023;1–12.

NIAAA FUNDED:
HIV & Alcohol Research center focused on Polypharmacy

HARP

Goal: To design and implement effective personalized interventions for people aging with HIV experiencing medical harm from unhealthy alcohol use and polypharmacy.

Program Director: A. Justice, MD, PhD

Project 1. Alcohol & Polypharmacy Risks

Aim 1. Summarize risks (including pharmacogenomic risk) for decompensated liver cirrhosis, serious falls, pneumonia, and dementia by level of alcohol use (AUDIT-C and alcohol use disorder) and HIV status

Aim 2. Identify patients with high genetic liability for unhealthy alcohol use (develop and apply a polygenic risk score)

Aim 3. Pilot interventions incorporating personalized risk information (including phosphatidylethanol and genetic liability) in the context of a theory-based behavioral intervention

IMPACT: By providing personalized summaries of alcohol and polypharmacy risks for relevant outcomes and communicating these within a theory-based intervention, we hope to more effectively intervene on unhealthy alcohol use and polypharmacy among PAH

New Core: Genetics

- Originated as part of MVP 004 (Justice A, Kranzler R Multi-PI)
- Chaired by Drs. Henry Kranzler (U Penn) & Ke Xu (Yale)
- 11 publications including Nature Medicine, JAMA Psychiatry, ACER, Addiction, Addiction Biology, AIDS and Behavior and PLOS One

Project 2. Repurposed Medications for Mitigating Harm from Alcohol

Aim 1. Identify candidate medications to repurpose for Alcohol Use Disorder using systems biology

Aim 2. Conduct propensity score matched analyses, by HIV status, of the safety and effectiveness of prazosin, pioglitazone, verapamil on drinking and metformin for mitigating Alcohol Associated Liver Disease among HIV+/-

Aim 3. Pilot interventions incorporating risk information and promising repurposed medications identified through Aims 1 and 2

Impact: this project will yield timely data to identify accessible novel medication options to address harm from alcohol among PAH exposed to polypharmacy.

Expanded Data Analytics Core: Artificial Intelligence

- Originated as part of VA-DOE Exemplar Projects (Dr. Justice Scientific Liaison)
- Drs. Daniel Jacobson (Oak Ridge National Laboratory) and Cynthia Brandt (Yale) co-leading
  - Systems biology
  - Iterative random forests
  - Explainable artificial intelligence

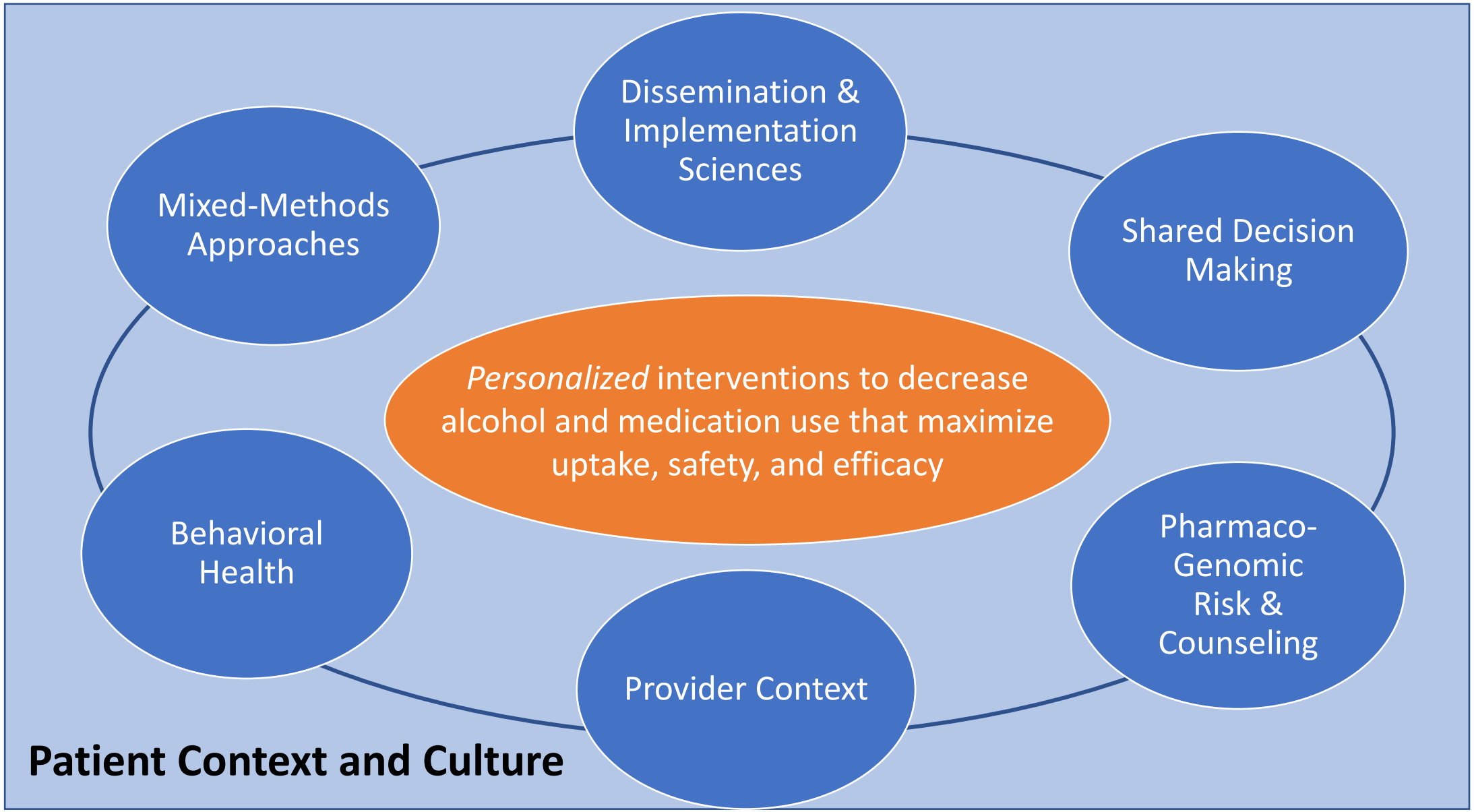
Rapid Cycle Learning: Pilot Studies

- Aim 3 of Projects 1 & 2
- 3 rapid cycle waves
- Each wave informed by prior wave
- Personalized risk within a theory-based intervention
  - Project 1: Counseling only
  - Project 2: Counseling + medication

New Core: Risk Communication

- Lead by Drs. Julie Womack and Evelyn Hsieh
- Bridges multiple domains
- Prior research, across domains, suggests that messaging must be
  - Salient –personalized risk estimates for relevant outcomes
  - Understandable—accounting for health literacy and numeracy
- A Risk Communication Core will bridge these domains and optimize risk communication for pilot studies

Risk Communication Core (RCC)



Dr. Jeffrey Fisher

Information
- Objective information about current level of alcohol use and polypharmacy
- Level of information about risks and consequences of alcohol consumption, polypharmacy, and their interaction
- Level of information about preventing risks associated with alcohol consumption, polypharmacy, and their interaction

Motivation
- Level of personal vulnerability to the risks of alcohol consumption, polypharmacy, and their interaction
- Favorability of attitudes towards behaviors needed to avoid risks of alcohol consumption, polypharmacy, and their interaction
- Level of social normative support for lowering alcohol use and polypharmacy

Behavioral Skills
Objective skills and sense of self-efficacy to use them when needed to lower alcohol use and polypharmacy behavior

Moderating Factors
- Mental health
- Multi-substance use
- Unstable living situations

Behavior
Lower objective levels of alcohol use and polypharmacy behavior

Short Term Outcomes
- PEth
- VACS Index
- Symptoms
- Medication count
- Alcohol interactive medications
- AUDIT-C

Information, Motivation, Behavioral Skills Model Applied to Alcohol Use and Polypharmacy

Project 1 Pilot 1:
PEth, Polypharmacy, and Symptoms

- 50 Prior MASH Participants
  - HIV+
  - 5+ medications
  - Positive PEth (8+ microgms/L)
- Remote intervention
  - Verbal consent
  - Self completed surveys + PEth
  - Phone based intervention
    - 1 hour initial
    - ½ booster 2 weeks later
- Fidelity monitoring throughout

- Pharmacist led IMB targeting
  - Alcohol & medications that likely cause/exacerbate patient's symptoms
- Prior to 1st call
  - Patient completes PEth and survey
    - Bothersome symptoms
    - Alcohol use
    - Readiness to change
  - Pharmacist reviews meds and obtains pre-approval for change from MD
- 30-day Outcome: change in…
  - PEth, active medications, symptoms

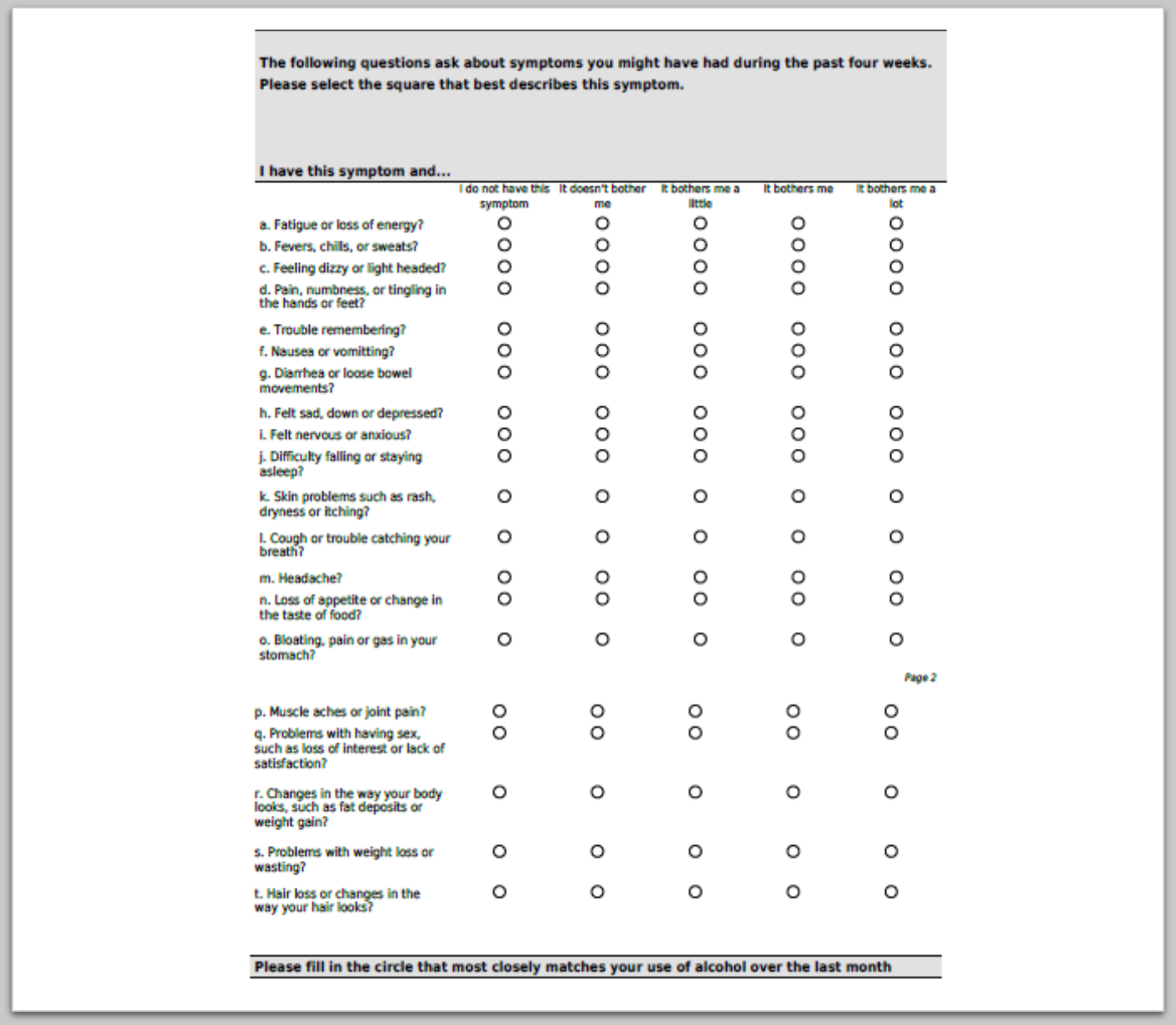
Critical Components of Intervention

Steve Maisto

- Be Respectful
- Review personalized information
- Avoid arguing
- Make the connection between alcohol, polypharmacy and bothersome symptoms
- Re-Assess readiness to change
- Develop discrepancy between medications/alcohol and symptoms
- Reflective listening, open-ended questions
- Discuss changes to alleviate symptoms
- Negotiate goals, create agreement form
- Introduce concept of self monitoring and walk through worksheet

Information Provided Pharmacists in Support of ***Personalized*** IMB Intervention

Participants Self Reported, Currently Active, Bothersome Symptoms



The following questions ask about symptoms you might have had during the past four weeks. Please select the square that best describes this symptom.

I have this symptom and...	I do not have this symptom	It doesn't bother me	It bothers me a little	It bothers me	It bothers me a lot
a. Fatigue or loss of energy?	O	O	O	O	O
b. Fevers, chills, or sweats?	O	O	O	O	O
c. Feeling dizzy or light headed?	O	O	O	O	O
d. Pain, numbness, or tingling in the hands or feet?	O	O	O	O	O
e. Trouble remembering?	O	O	O	O	O
f. Nausea or vomitting?	O	O	O	O	O
g. Diarrhea or loose bowel movements?	O	O	O	O	O
h. Felt sad, down or depressed?	O	O	O	O	O
i. Felt nervous or anxious?	O	O	O	O	O
j. Difficulty falling or staying asleep?	O	O	O	O	O
k. Skin problems such as rash, dryness or itching?	O	O	O	O	O
l. Cough or trouble catching your breath?	O	O	O	O	O
m. Headache?	O	O	O	O	O
n. Loss of appetite or change in the taste of food?	O	O	O	O	O
o. Bloating, pain or gas in your stomach?	O	O	O	O	O

Page 2

p. Muscle aches or joint pain?	O	O	O	O	O
q. Problems with having sex, such as loss of interest or lack of satisfaction?	O	O	O	O	O
r. Changes in the way your body looks, such as fat deposits or weight gain?	O	O	O	O	O
s. Problems with weight loss or wasting?	O	O	O	O	O
t. Hair loss or changes in the way your hair looks?	O	O	O	O	O

Please fill in the circle that most closely matches your use of alcohol over the last month

Participant's Self Reported Current Alcohol Use (AUDIT-C)

Please fill in the circle that most closely matches your use of alcohol over the last month

WHAT IS A STANDARD DRINK?

1 Standard Drink equals:

drink made with 1.5 oz. of alcohol (whiskey, gin, etc.) | 12 oz. Beer | 5 oz. wine

Conversions

Ounces (oz.)		Cups (C.)		Tablespoons (tbs.)
12 oz.	=	1.5 C.	=	24 tbs.
5 oz.	=	0.6 C.	=	10 tbs.
1.5 oz.	=	0.2 C.	=	3 tbs.
1 oz.	=	0.13 C.	=	2 tbs.

1. How often do you have a drink containing alcohol?	○ Never ○ Monthly or less ○ 2-4 times a month ○ 2-3 times a week ○ 4 or more times a week
2. How often do you have six or more drinks on one occasion?	○ Daily or almost daily ○ Weekly ○ Monthly ○ Less than monthly ○ Never
3. How many standard drinks containing alcohol do you have on a typical day? (See figure below for definition of standard drink)	○ 1 or 2 ○ 3 to 4 ○ 5 to 6 ○ 7 to 9 ○ 10 or more

Participant's PEth Value

- If 0, rely on AUDIT-C
- If 8-20 suggests moderate use, check AUDIT-C
- If >20 suggests potentially harmful use regardless of AUDIT-C

Participant's Readiness to Change Meds & Alcohol Use

1. If your provider felt it was a good idea, how ready are you to decrease your medications?

- ◯ 1 Not at all ready
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5, Moderately ready
- ◯ 6
- ◯ 7
- ◯ 8
- ◯ 9
- ◯ 10, Extremely ready

1. How ready are you to decrease how much you drink?

- ◯ 1 Not at all ready
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5, Moderately ready
- ◯ 6
- ◯ 7
- ◯ 8
- ◯ 9
- ◯ 10 Extremely ready

Participants Medications in Order of Association with Patient's Reported Symptoms

	Drug	Drug Associated Symptom	Symptom Reported on Survey	Alcohol Interaction	Reconciliation
Edit Delete	METOPROLOL SUCCINATE 50MG SA TAB TAKE ONE-HALF TABLET BY MOUTH EVERY DAY MAY BE DIVIDED, BUT SWALLOW WHOLE WITHOUT CRUSHING OR CHEWING	CognitiveImpairement Diarrhea Fatigue Headache Insomnia NauseaVomitting Sexual Dysfunction Shortness Of Breath Weight gain	Yes (It bothers me a lot)	Yes	Difference in dose or schedule
Edit Delete	TERAZOSIN HCL 10MG CAP TAKE ONE CAPSULE BY MOUTH AT BEDTIME FOR PROSTATE. CAN INCREASE DOSE IF URINATION STILL NOT IMPROVED. CAN INCREASE TO 10 MG (2 CAPS) IF CONTINUE TO HAVE FREQUENT NIGHTTIME URINATION. PLEASE MONITOR FOR DIZZINESS.	CognitiveImpairement Diarrhea Headache NauseaVomitting Sexual Dysfunction Weight gain	Yes (It bothers me a lot)	Yes	
Edit Delete	HALOPERIDOL 0.5MG TAB TAKE FOUR TABLETS BY MOUTH AT BEDTIME	Muscle Joint Pain Sexual Dysfunction Weight gain	Yes (It bothers me a lot)	Yes	
Edit Delete	SILDENAFIL CITRATE 100MG TAB TAKE ONE TABLET BY MOUTH EVERY DAY AS NEEDED FOR ERECTILE DYSFUNCTION. TAKE ONE HOUR BEFORE SEX. DO NOT EXCEED MORE THAN ONE TABLET IN 24 HOURS.	Bloating Headache	Yes (It bothers me)	Yes	
Edit Delete	AMLODIPINE BESYLATE 10MG TAB TAKE ONE TABLET BY MOUTH EVERY DAY FOR HEART/BLOOD PRESSURE.	Bloating CognitiveImpairement Cough Diarrhea Headache NauseaVomitting Sexual Dysfunction	Yes (It bothers me)	Yes	Home medication: not on VA CPRS list Other pharmacy
Edit Delete	ASPART INSULIN 100UNIT/ML PEN NOVO 3ML INJECT 12 UNITS UNDER THE SKIN BEFORE MEALS	Nausea Vomitting	Yes (It bothers me)		
Edit Delete	ERGOCALCIF 1,250MCG (D2-50,000UNIT) CAP TAKE ONE CAPSULE BY MOUTH ONCE A WEEK FOR VITAMIN D	Bloating	Yes (It bothers me)		
Edit Delete	CHOLECALCIF 25MCG (D3-1,000UNIT) TAB BY MOUTH	Bloating	Yes (It bothers me)		
Edit Delete	TRAZODONE HCL 50MG TAB TAKE ONE TABLET BY MOUTH AT BEDTIME AS NEEDED FOR INSOMNIA	Fatigue FC Sweats Insomnia Sexual Dysfunction Sweats	Yes (It bothers me)	Yes	
Edit Delete	ASPIRIN 81MG EC TAB TAKE ONE TABLET BY MOUTH EVERY DAY TO PREVENT BLOOD CLOTS.	Bloating Diarrhea Headache NauseaVomitting Skin problems	Yes (It bothers me)	Yes	
Edit Delete	FLUOXETINE HCL 20MG CAP TAKE ONE CAPSULE BY MOUTH EVERY DAY FOR DEPRESSION	Bloating Diarrhea Fatigue FC Sweats Headache Insomnia Sexual Dysfunction Sweats Weight gain Weight loss	Yes (It bothers me)	Yes	
Edit Delete	IBUPROFEN 800MG TAB TAKE ONE TABLET BY MOUTH THREE TIMES A DAY AS NEEDED FOR GOUT FLARE OCCURRENCES ONLY. TAKE WITH FOOD.	Bloating Diarrhea Headache NauseaVomitting Skin problems	Yes (It bothers me)	Yes	
Edit Delete	INSULIN,GLARGINE 100 UNT/ML 3ML SOLOSTAR INJECT 30 UNITS UNDER THE SKIN EVERY MORNING	Nausea Vomitting	Yes (It bothers me)		
Edit Delete	METFORMIN HCL 500MG 24HR SA TAB TAKE TWO TABLETS BY MOUTH EVERY DAY	Bloating Diarrhea NauseaVomitting Weight loss	Yes (It bothers me)	Yes	
Edit Delete	EMPAGLIFLOZIN 25MG TAB TAKE ONE TABLET BY MOUTH EVERY DAY	NauseaVomitting Weight loss	Yes (It bothers me)	Yes	
Edit Delete	ROSUVASTATIN CA 20MG TAB TAKE ONE TABLET BY MOUTH EVERY DAY FOR CHOLESTEROL.	Hair Loss Headache Loss in Apetite Muscle Joint Pain NauseaVomitting Skin problems	Yes (It bothers me)	Yes	
Edit Delete	HCTZ 12.5/LISINOPRIL 20MG TAB TAKE 2 TABLETS BY MOUTH EVERY DAY FOR HEART/BLOOD PRESSURE.				
Edit Delete	COAL TAR 2% OINTMENT (MG217) APPLY SMALL AMOUNT TO SKIN EVERY DAY TO AFFECTED AREA AS NEEDED AS DIRECTED				

HARP Agreement Form

I agree to have my provider [stop/taper] the following medications to see if my symptoms improve and I feel better: [list medications]

I also agree to [cut down/stop] drinking alcohol for the next 30 days to see if my symptoms improve. To help achieve this, I will use a worksheet to monitor my alcohol use and symptoms over the next 30 days. Specifically:

> I will drink alcohol no more than ___xx___ days/week.
>
> I will have no more than __xx__ drinks/day on average on days I am drinking alcohol.
>
> If I have a heavy alcohol use day, I will drink no more than __xx__ drinks/day. I will aim to reduce my heavy alcohol use days to __xx___/month.

The pharmacist and I also discussed some strategies or changes that can help me achieve my goals, including: [list strategies/behavior changes that were brainstormed during session]

I agree to have the pharmacist check back with me approximately 2 weeks to see how I am doing.

HARP Data Collection Overview

- Main data points are:

Demographics, Alcohol symptom checklist, Shipping, tracking, payment information

Tools: REDCap

- Medication Reconciliation
- Clinician Feedback
- Personalized Feedback
- Participant Agreement
- Post interview Survey

Tools: MedRec. Website, REDCap, Teams

Participant feedback of Intervention

Tools: ATLAS-ti, REDCap

- Survey data is entered electronically from paper to REDCap
- PEth data from lab

Tools: REDCap

- Survey data (30 days post interview)
- PEth data from lab

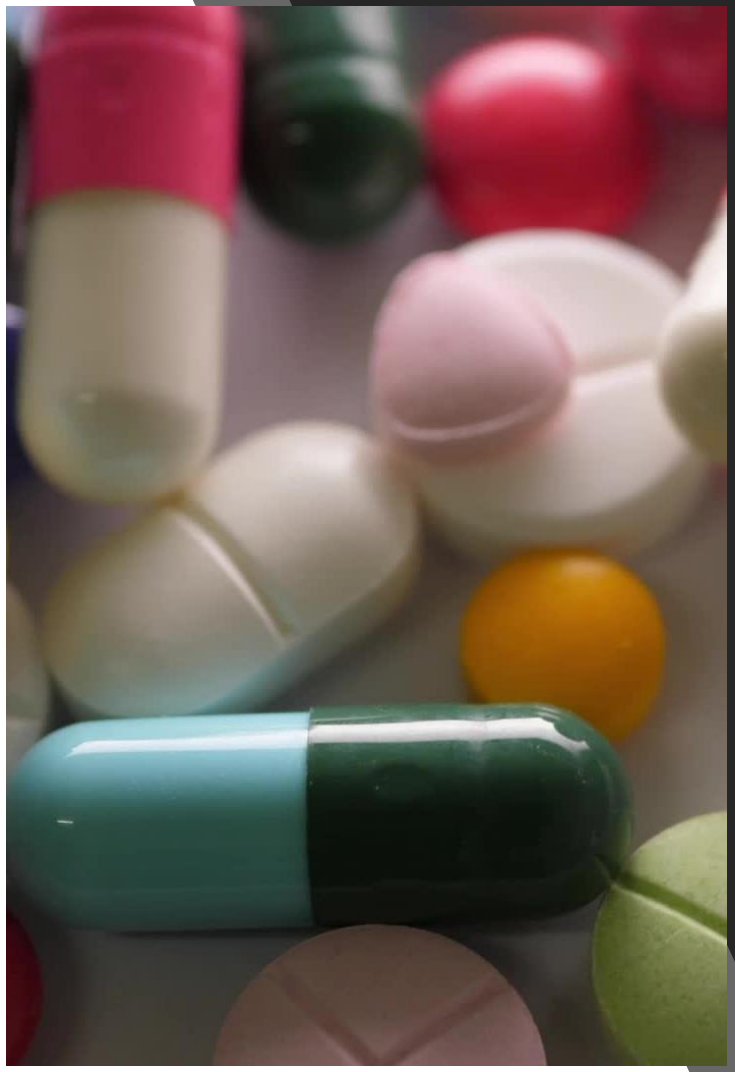
Tools: REDCap

Fidelity Monitoring

Verbal consent and both intervention calls recorded and reviewed

Weekly review will include

- Critical content
- Pharmacist feedback from patients
- Feedback provided to pharmacist



We Hope to Learn

- Feasibility of self testing PEth at home
- Which aspects of intervention faciliatate:
  - Discontinuing medication?
    - Knowledge of alcohol-medication interactions
    - Connecting bothersome symptoms with specific medications
    - Pre-approval of MD
    - Conversation with pharmacist
  - Decreased alcohol use?
    - PEth
    - Concerns about polypharmacy
    - Connecting bothersome symptoms with alcohol use

Opportunities for Collaboration

It starts with a proposal…

Proposal form: m.yale.edu/vacs-proposal

VACS
Veterans Aging Cohort Study

VACS Proposal

m.yale.edu/vacs-proposal

Thank you for your interest in collaborating with VACS. Once you have submitted your concept sheet, VACS research leadership will review for feasibility before distributing to the relevant VACS Core or Workgroup for full review and approval. If approved by the workgroup/core, the chairs of the committee will continue to work with you on developing the project proposal and methods, analysis, and manuscript review.

Note: all public dissemination of research (abstracts, manuscripts, presentations) must receive approval from the VACS publications committee. Please visit m.yale.edu/vacs-pubs for more information.

About the 5 cohorts

VA National Cohort (full national sample, N~13.5 million) - all Veterans in the VA system

- Sample pub: Covid-19 by Race and Ethnicity: A National Cohort Study of 6 Million United States Veterans

VA 1945-1965 Birth Cohort (1945-1965, N~3.1 million) - all Veterans born between 1945-1965

- Sample pub: Regional and Rural-Urban Differences in the Use of Direct-acting Antiviral Agents for Hepatitis C Virus: The Veteran Birth Cohort

VACS-HIV (~60,000 HIV+, 120,000 uninfected) - Veterans Aging Cohort Study, 1 HIV+:2 uninfected demographically-matched

Research question *

Ex. Is early initiation of prophylactic anticoagulation compared with no anticoagulation associated with decreased risk of death amongst patients admitted to hospital with COVID-19?

Short title *

Please provide a short title or list key words (separated by a space) associated with your proposal (5 words or less)

Submission date *

Is this a feasibility request?

Select this checkbox if you are requesting potential sample sizes or preliminary data for a feasibility request. Please continue to complete this proposal form, which you will have an opportunity to update after the request is fulfilled.

☐

Contact information

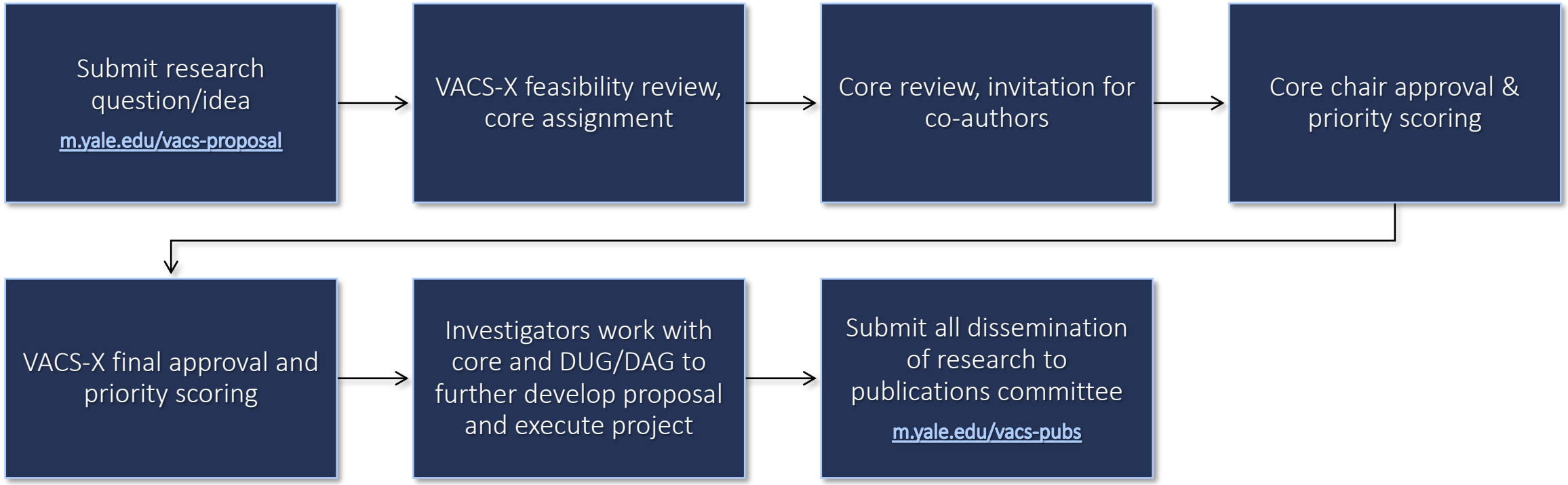
Lead Investigator Name *

Lead Investigator Email Address *

Lead Investigator Telephone Number *

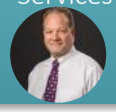
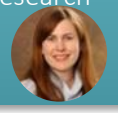
+1 (___) ___-____

VACS Project Process



VACS Cores & Workgroups

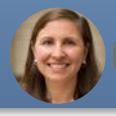
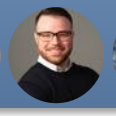
ABHSR
Alcohol, Behavior Intervention, & Health Services Research

Cancer


Cardiovascular


Covid-19

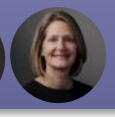




HARP Risk Communication


Liver


Opioids





PEPI
Pharmacoepidemiology

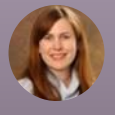

Pulmonary


REGS
Rheumatology, Endocrine, & Geriatrics


Translational


Uniform Services


VACS Index




Resources: DUG & DAG

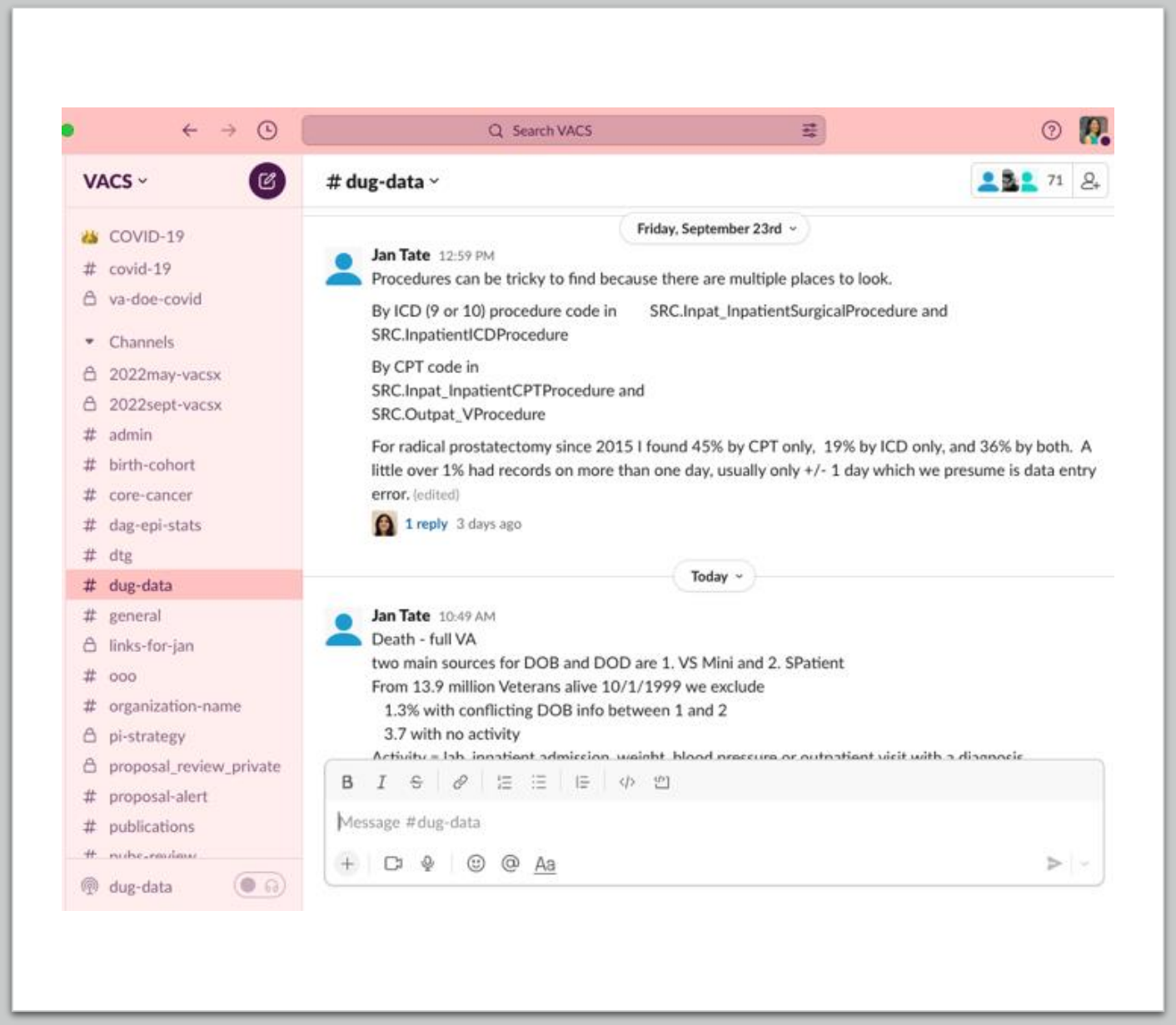
	DUG (Data User Group)	DAG (Data and Analysis Group)
Goal	To consolidate, expand, and grow knowledge base of VA and other linked data	To consolidate, expand, and grow knowledge base of epidemiologic and statistical methods

Key activities	• Discuss data/cohort updates, where data live
	• Develop and maintain VACS Sharepoint, data storage/access plans
	• Discuss operational issues (server, data access)
	• Ask about any data element/variable
	• Mini presentations/walkthroughs, e.g.:
	  • Labs for non-biologists
	  • Overlap of sources of death data
		• Informal webinars
		• Internal & external members invited
		• Works-in-progress
		• Mini IWHOD
		• Additional space for feedback beyond core/workgroup
		• Practice conference presentations

Attendees	Programmers & analysts	Project PIs, epidemiologists, biostatisticians, bioinformaticians
Schedule	Semi-monthly 1st/3rd Tuesdays @ noon	Semi-monthly 2nd/4th Tuesdays @ noon

Slack

vacshq.slack.com



Organizational Structure of HARP

A Justice, MD, PhD
Consortium PD

Program Advisory Committee
To Be Determined

Steering Committee
J Edelman, MD: Project 2 PI
D Fiellin, MD: Project 2 Co-PI
J Womack, PhD, MSN, MA: RCC Director
E Hsieh, MD, PhD: RCC Co-Director
H Kranzler, MD: Site PI, Genetics Core Director
C Brandt, MD, PhD: AI/Machine Learning Director
J Tate, ScD: Epi/Biostatistics Director
V LoRe, MD, MSCE: Liver Core Director
D Jacobson, PhD: Site PI, AI/Machine Learning Co-Director
V Marconi, MD: Site PI
C Rentsch, PhD: Polypharmacy and Antiviral Therapy Co-Director

Administrative/Data Analytics (ADA) Core
Amy Justice, MD, PhD, Director

Administrative Subsection
A Consorte
J Ciarleglio
A Wrona
R Sutton

Data Analytics Subsection

Data	Epi/Biostat	AI/ Machine Learn.
M Skanderson	**J Tate**	**C Brandt**
F Kidwai-Khan	C Rentsch	D Jacobson
F. Levin	K Gordon	M Garvin
	L Park	R Kember
	K McGinnis	B McMahon
		K Xu

Supported and Assigned Cores and Workgroups: Directors

Alcohol and Behavior Change & Health Services Research: D Fiellin, MD, K. McGinnis, DrPH
Liver Disease: V Lo Re, MD, MSCE & J Tate, ScD
VACS Index: A Justice, MD, PhD & J Tate, ScD
Polypharmacy: V Lo Re, MD, MSCE & C Rentsch, PhD
Antiviral Therapy: E Cartwright, MD & C Rentsch, PhD

Additional Existing Cores and Workgroups: Directors

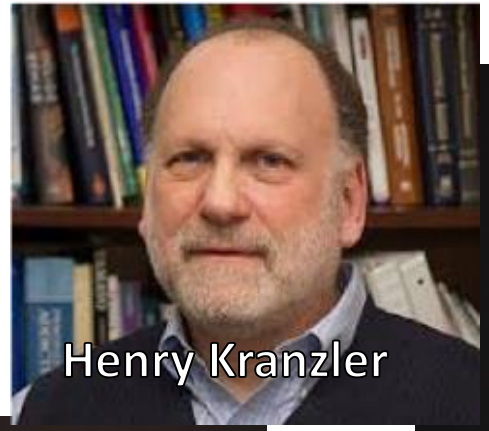
Cancer Disease: K Sigel, MD & L Park, PhD, MPH
Cardiovascular Disease: M Freiberg, MD, MSc
Opioids: W Becker, MD & J Edelman, MD
Pulmonary Disease: K Crothers, MD
Prostate Cancer Workgroup: R Wadia, MD
Endocrine and Frailty: B Gulanski, MD & J Womack, PhD, MSN, MA
Rheumatology Workgroup: E. Hsieh, MD, PhD, J Hanberg MD
Uniform Services: B Agan, MD, FACP & V Marconi, MD
Longitudinal Analyses: K Gordon, PhD
Translational Research: M Freiberg, MD, MSc & K Armah, PhD

New Cores: Directors

Risk Communication Core (RCC): J Womack, E. Hsieh
Genetics Core: R Kranzler, K Xu

National VACS Team


Ke Xu


Henry Kranzler


Steve
Martino


Jeffrey Fisher


Daniel Jacobson


Rebecca Pulk


Michael
Virata


Lydia
Aoun-Barakat


Liana
Fraenkel


Shan-Estelle Brown


Anne Murphy


Michael
Murray

HARP

Team Science: Lessons Learned

- Don’t try to be an expert in everything—be honest and collaborate
- Communication is ESSENTIAL—it is the life blood of collaboration
- Effective communication requires
  - Careful thought
  - Ongoing monitoring
  - Organization
  - Humility
  - Time and economic resources

Questions?
vacs@yale.edu

Lesley Park, Executive Director

VACS

Veterans Aging Cohort Study