How can we study the effects of new treatments on suicidal behavior?

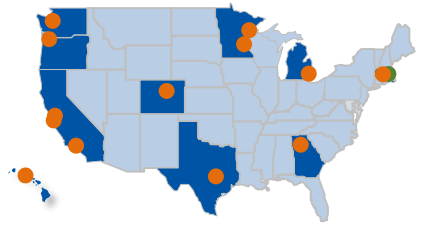
Gregory Simon MD MPH

Kaiser Permanente Washington Health Research Institute

MHRN Mental Health Research Network

KAISER PERMANENTE®

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY



KP Washington
- Yates Coley
- Eric Johnson
- Belinda Operskalski
- Robert Penfold
- Julie Richards
- Susan Shortreed
- Chris Stewart
- Rod Walker
- Rob Wellman
- Rebecca Ziebell

Univ. of Washington
- Noah Simon

KP Southern California
- Karen Coleman
- Jean Lawrence
- Tae Yoon

KP Northwest
- Greg Clarke
- Phil Crawford
- Frances Lynch
- Bobbi Jo Yarborough

KP Colorado
- Arne Beck
- Jennifer Boggs
- David Tabano

Henry Ford Health System
- Brian Ahmedani
- Bin Liu

KP Hawaii
- Yihe Daida
- Beth Waitzfelder
- Carmen Wong

HealthPartners
- Rebecca Rossom
- Sheryl Kane

Microsoft Research
- Rani Gilad-Bachrach
- Rich Caruana

Supported by NIMH Cooperative Agreement U19 MH092201, and by FDA Contract under BAA 18-00123

MHRN Mental Health Research Network

KAISER PERMANENTE®

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Disclosures:

- Employee of Permanente Medical Group
- Research funding:
  - US National Institute of Mental Health
  - US Food and Drug Administration
  - Janssen Scientific Affairs
- Consulting fees/honoraria:
  - UpToDate / Wolters Kluwer Publishing

MHRN Mental Health Research Network

KAISER PERMANENTE®

Outline

- Predicting suicidal behavior from health records data
- Pragmatic trials using randomized encouragement design
- Assessing treatment effects on suicidal behavior: Clarifying the questions and methods
- Use of prediction models in observational studies of treatment effects on suicidal behavior
- Use of prediction models in clinical trials evaluating treatment effects on suicidal behavior

Prediction vs. Inference

- Inference is about generalizable knowledge:

  What does this mean? What should I believe?

  Interpretation is the whole point.

- Prediction is about practical and action:

  What will happen? What could I do about it?

  Interpretation is beside the point.

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

MHRN Suicide Risk Calculator Project

- Setting:
  - 7 health systems (HealthPartners, Henry Ford, KP Colorado, KP Hawaii, KP Northwest, KP Southern California, KP Washington) serving 8 million members
- Visit Sample
  - Age 13 or older
  - Specialty mental health visit OR primary care visit with MH diagnosis
  - 20 million visits by 3 million people
- Outcomes
  - Encounter for self-inflicted injury/poisoning in 90days
  - Death by self-inflicted injury/poisoning in 90 days
- Predictors
  - Demographics (age, sex, race/ethnicity, neighborhood SES)
  - Mental health and substance use diagnoses (current, recent, last 5 yrs)
  - Mental health inpatient and emergency department utilization
  - Psychiatric medication dispensings (current, recent, last 5 yrs)
  - Co-occurring medical conditions (per Charlson index)
  - PHQ8 and item 9 scores (current, recent, last 5 yrs)

MHRN Mental Health Research Network

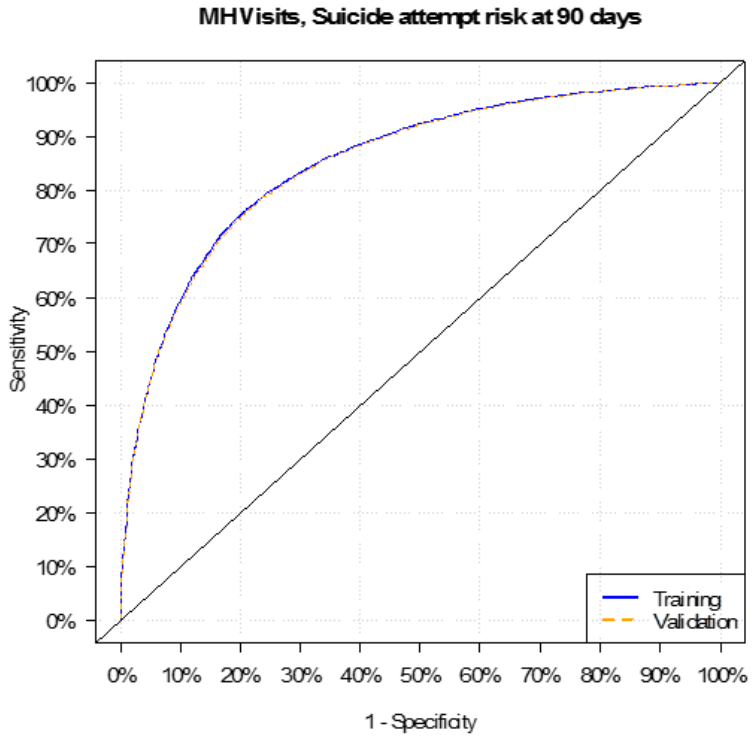
KAISER PERMANENTE®

The math (briefly)

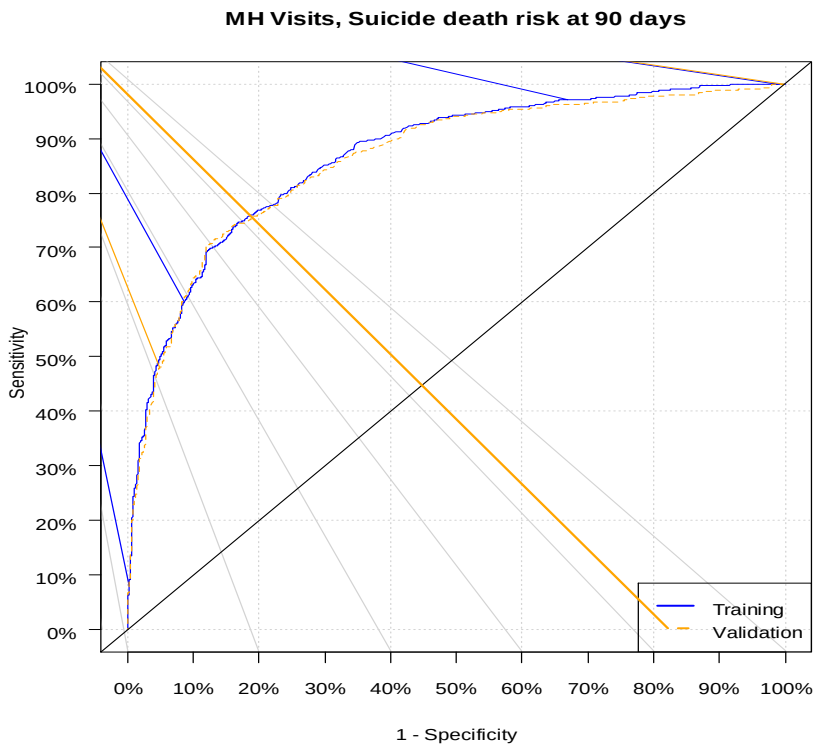
- Consider 200 predictors and 150 interaction effects
- Separate MH specialty and general medical visit samples
- Separate models for suicide attempts and suicide deaths
- Develop in 65% random sample
  - Logistic regression with penalized LASSO variable selection
  - Tuning with 10-fold cross-validation
  - Coefficients re-calibrated with GEE to account for clustering
- Validate in “held out” 35%

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Predicting suicidal behavior in 90 days after outpatient visit



AUC=0.851 (0.848 - 0.853)



AUC=0.861 (0.848 - 0.875)

MHRN Mental Health Research Network

KAISER PERMANENTE®

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Predicting suicidal behavior in 90 days after outpatient visit

Suicide attempt following MH visit

Percentile of Visits	Predicted Risk	Actual Risk	% of All Attempts
>99.5th	13.0%	12.7%	10%
99th to 99.5th	8.5%	8.1%	6%
95th to 99th	4.1%	4.2%	27%
90th to 95th	1.9%	1.8%	15%
75th to 90th	0.9%	0.9%	21%
50th to 75th	0.3%	0.3%	13%
<50th	0.1%	0.1%	8%

Suicide death following MH visit

Percentile of Visits	Predicted Risk	Actual Risk	% of All Attempts
>99.5th	0.654%	0.694%	12%
99th to 99.5th	0.638%	0.595%	11%
95th to 99th	0.162%	0.167%	25%
90th to 95th	0.068%	0.088%	16%
75th to 90th	0.031%	0.029%	16%
50th to 75th	0.014%	0.015%	13%
<50th	0.003%	0.003%	6%

MHRN Mental Health Research Network

KAISER PERMANENTE®

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

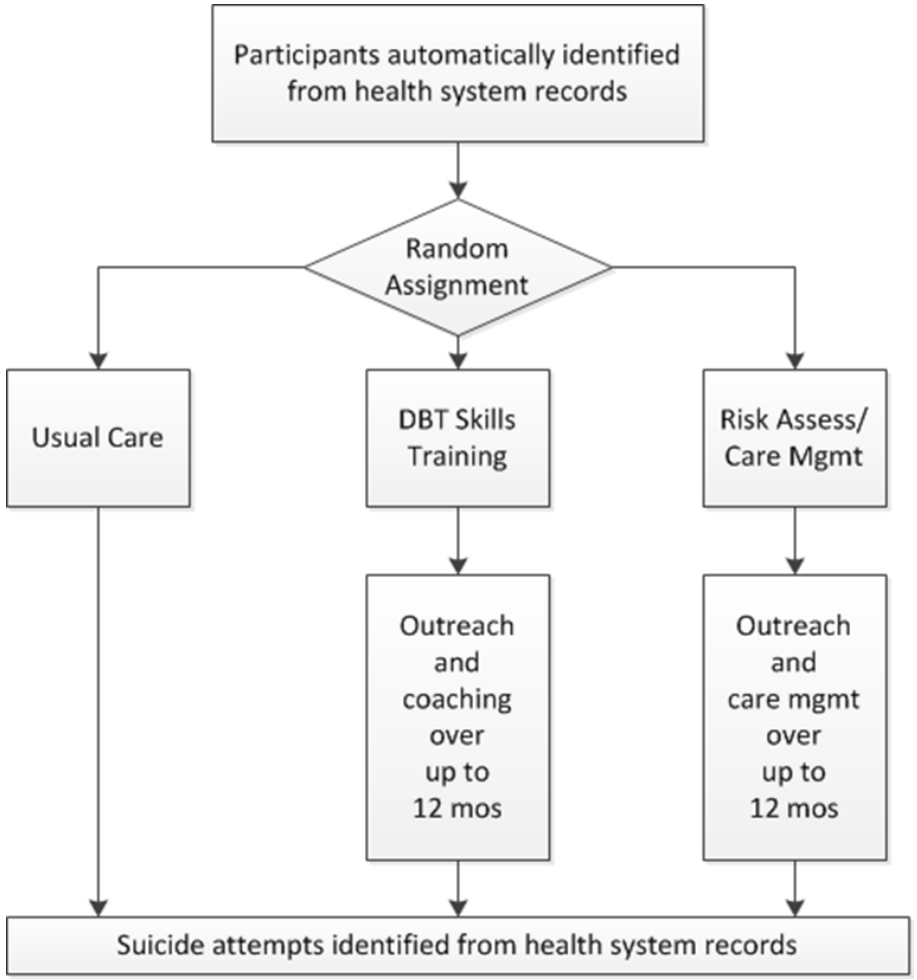
Next generation of risk prediction models:

- Wider range of predictors (medical diagnoses, additional medication classes, etc.)
- More detailed temporal encoding (monthly counts for each of prior 60 months)
- Alternative model-fitting methods (random forest, neural net, generalized additive models)
- Additional PRO measures (GAD, Audit, CSSRS)
- New cohorts of emergency department visits and inpatient discharges

MHRN Mental Health Research Network

KAISER PERMANENTE®

Pragmatic trial of population-based selective prevention programs (funded by NIH Collaboratory)



Ongoing at four MHRN sites:

- KP Washington
- HealthPartners
- KP Colorado
- KP Northwest

18,887 enrolled

Results expected in early 2020

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Randomized encouragement design (aka Modified Zelen design)

- Eligible participants identified automatically from real-time records (in this case, by response to PHQ9)
- Everyone eligible randomized to usual care or to offer of intervention
- Those assigned to usual care are never contacted
- Those assigned to intervention are encouraged to participate, but can refuse or discontinue
- Outcomes ascertained from health system records
- Analysis by intent-to-treat, regardless of intervention uptake or participation

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Randomized encouragement design is appropriate when:

- We are asking a practical question about practice or policy ("What should we do?" rather than "What should we believe?")
- Varying uptake or adherence is feature, rather than a bug
- Outcomes can be ascertained from health system records

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Effects of new treatments on suicidal behavior: Different questions for different stakeholders

- Regulators (causal): Can the manufacturer make a claim regarding prevention of suicidal behavior?
- Clinicians (clinical): Should I recommend or prescribe this new treatment for my patients at high risk of suicidal behavior?
- Payers and Health Systems (policy): Should coverage or guidelines restrict or encourage use of this new treatment?

MHRN Mental Health Research Network

KAISER PERMANENTE®

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Treatment effects on suicidal behavior: Different counter-factuals for different questions

- Regulators (causal): Comparison to placebo
- Clinicians (clinical): Comparison to alternative treatment choice
- Payers and Health Systems (policy): Comparison to alternative policy

MHRN Mental Health Research Network

KAISER PERMANENTE®

Traditional placebo-controlled clinical trial:

- Not feasible: Detecting reduction in risk from 5% to 3% would require a total sample of over 3,000
- Not ethical: Would require randomly assigning high-risk patients to placebo and allowing suicidal behavior to occur

So regulatory decisions will likely rely on indirect evidence.

Randomized trial comparing alternative treatments:

- Practically challenging: Would need to identify/recruit/randomize at the point of care across a very large population.
- Ethically challenging: Patients and clinicians would have to accept random assignment about a choice they may have already made.

So we may have to rely on observational comparisons.

Pragmatic trial of alternative policies:

- Randomized encouragement design
- Analyze by original assignment
- Effects diluted by “non-compliers”

So we’d need large sample and high “compliance” rate.

Two uses for risk prediction models

- Reducing bias in observational comparisons of treatments
- Enriching samples in clinical trials comparing practices or policies

Observational comparison of treatments

- Easy
  - Identifying exposure to new treatment of interest
  - Estimating/predicting risk at any time point
  - Identifying outcomes of interest (suicidal behavior, hospitalization)
- Hard:
  - Defining and identifying the comparison group or counterfactual
  - Balancing precision and bias when we want an early answer

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

New design alternatives

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2017; **26**: 459–468
Published online 9 September 2016 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.4107

ORIGINAL REPORT

Prevalent new-user cohort designs for comparative drug effect studies by time-conditional propensity scores

Samy Suissa[1,2,3]*, Erica E. M. Moodie[1] and Sophie Dell'Aniello[2,3]

[1] *Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Quebec, Canada*
[2] *McGill Pharmacoepidemiology Research Unit, McGill University, Montreal, Quebec, Canada*
[3] *Centre for Clinical Epidemiology, Jewish General Hospital, Montreal, Quebec, Canada*

ABSTRACT

Purpose Studies of the real-world comparative effectiveness of drugs conducted using computerized healthcare databases typically involve an incident new-user cohort design for head-to-head comparisons between two medications, using exclusively treatment-naïve patients. However, the desired contrast often involves one new drug compared with an older drug, of which many users of the new drug may have switched from, seriously restricting the scope of incident new-user studies.

Methods We introduce prevalent new-user cohort designs for head-to-head comparative drug effect studies, where incident new users are scarce. We define time-based and prescription-based exposure sets to compute time-conditional propensity scores of initiating the newer drug and to identify matched subjects receiving the comparator drug. We illustrate this approach using data from the UK's Clinical Practice Research Datalink to evaluate whether the newer glucagon-like peptide-1 receptor agonists (GLP-1 analogs) used to treat type 2 diabetes increase the risk of heart failure, in comparison with the older similarly indicated sulfonylureas.

Results Of the 170 031 users of antidiabetic agents from 2000 onwards, 79 682 used sulfonylureas (first use 2000), while 6196 used GLP-1 analogs (first use 2007), 75% of which had previously used a sulfonylurea. After matching each GLP-1 analog user to a sulfonylurea user on the time-conditional propensity scores from prescription-based exposure sets, the hazard ratio of heart failure with GLP-1 use was 0.73 (95% CI: 0.57–0.93).

Conclusion The proposed prevalent new-user cohort design for comparative drug effects studies allows the use of all or most patients exposed to the newer drug, thus permitting a more comprehensive assessment of a new drug's safety.

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Using prediction models to enrich clinical trial samples: Two new questions

- Setting a threshold or cut-point
- Considering heterogeneity of treatment effects

MHRN Mental Health Research Network

KAISER PERMANENTE®

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Using prediction models to enrich clinical trial samples: Setting a threshold or cut-point

Suicide attempt following MH visit

Percentile of Visits	Predicted Risk	Actual Risk	% of All Attempts
>99.5th	13.0%	12.7%	10%
99th to 99.5th	8.5%	8.1%	6%
95th to 99th	4.1%	4.2%	27%
90th to 95th	1.9%	1.8%	15%
75th to 90th	0.9%	0.9%	21%
50th to 75th	0.3%	0.3%	13%
<50th	0.1%	0.1%	8%

99th percentile
- 10.4% event rate
- But only 1% of MH specialty patients

OR

95th percentile
- 5.4% event rate
- 5% of MH specialty patients

MHRN Mental Health Research Network

KAISER PERMANENTE®

Using prediction models to enrich clinical trial samples: Heterogeneity of treatment effects