Model-Based Medicine:

Leveraging Analytics and Modeling To Support Decision Making in Healthcare

Tuan Dinh, PhD
Vice President of Analytics and Modeling
Archimedes Inc

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Today's Topics

- A Brief History of Decision Making in Medicine
- Review the Basic Types of Models used for Making Decisions
- Archimedes Implementation of Model-Based Medicine
- Case study I: Forecasting Health Outcomes and Utilization in Uninsured Populations in California
- Case study II: Design of Kaiser Permanente ALL/PHASE Program

A brief history of clinical decision making

- ***1970's-1980's and earlier: Expert-based medicine***
  - Based on "clinical judgment", "expert opinion", or "expert consensus"
    - Not supported by evidence
    - Errors in reasoning
    - Gross oversimplifications
  - Wide variations in beliefs and practice

A brief history of clinical decision making

- ***1990's-present: Evidence-based medicine***
  - Based on "conscientious, explicit, and judicious use of current best evidence"
  - Systematic reviews supply synthesized evidence
    - E.g. Cochrane Collaboration
    - ***Randomized control trials (RCTs)*** are gold-standards
  - Evidence-based guidelines become ubiquitous
    - Care processes/pathways, EHRs, gap analyses, pay for performance
    - Designed for use in a pre-computer area so doctors can memorize: focusing on one variable at a time (e.g., BP), and using sharp thresholds (e.g., SBP > 140, FPG > 126)
    - Despite 20,000 RCTs per year, "lack of evidence" is frequently seen in guidelines

A brief history of clinical decision making

- ***2010's-?: Model-based medicine***
  - Why ?
    - Limitations of Randomized Control Trials:
      - RCTs are designed for FDA drug approval and enroll "healthy" patients
      - RCTs are not designed to answer standard or common clinical questions – the patients you see
    - Inability of current paradigm of systematic review to handle data explosion due to advances in Health IT
    - Inputs into medical decision making have become increasingly complex
      - E.g. laboratory and imaging results, disease history, genetic/genomic information, family history, presence of comorbidities, and patient preference
      - Sharp threshold guidelines are too blunt
    - Information retrieval and patient communication can be expedited through computers

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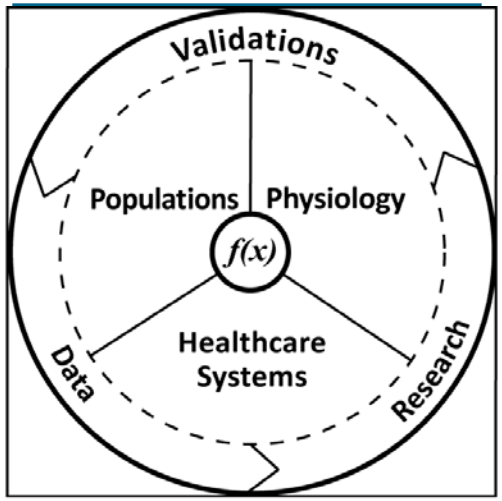
MBM *vs* EBM

Raw Evidence
Clinical Trials,
Case-Control Studies
Observational Studies
EMRs
Databases, Registries
Genomic/Physiologic/Pathology Studies
Medical Expertise



Individualized Guidelines
Take inputs from EMR
Use models to calculate risks and treatment benefits for individual patients
Patient engagement

MBM:

- use of **analytics and mathematical modeling** to synthesize **knowledge and evidence** into a unified and logical framework,
- which will then be used to support clinical decision making at population and patient levels

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Examples of models used in clinical decision making today

- For individuals
  - Many regression-based models are already integrated into physician's workflow
    - Framingham risk score for heart attack
    - Gail risk score for breast cancer
    - Apgar score for newborn
    - Adjuvant! Online for cancer treatments
    - Pooled Cohort Risk Equation for ACC/AHA guidelines on statin use
  - Typically developed based only one data source and focus on one disease and one decision

Examples of models used in clinical decision making today

- For populations
  - Cancer screenings
    - US Preventive Service Task Force cancer screening guidelines are based on Cancer Intervention and Surveillance Modeling Network (CISNET) models
      - Biennial vs annual mammogram screening
      - Lung cancer screening
  - UK NICE's Health Technology Assessments of new products rely on submission of model-based cost-effectiveness analyses
  - Wide range of techniques
    - Statistical prediction models
    - Markov models
    - Discrete event microsimulation
    - Agent-based simulation
  - Focus on one disease and one decision

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Key challenges

- Data availability "fuel" model proliferation
  - Cardiovascular diseases: 10 established models, including Framingham (2 variants), ASSIGN, SCORE, PROCAM, QRISK1, QRISK2, Reynolds, Pooled Cohort, …
  - Diabetes onset: ~50
  - Prostate cancer: ~100
  - 2000 papers published using Markov models in the past 5 years
- A growing concern that the majority of models are poorly developed
  - based on a small and inappropriate selection of the cohort,
  - lack of transferability to another population or setting
  - use questionable statistical methods
  - questionable handling/selection of risk predictors, and missing data

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Key challenges

- Despite the large number of models being developed, only a very small minority are adopted by physicians in clinical practice
  - Many models lack face validity and are inconsistent with medical knowledge
  - Few physicians have the training needed to understand and evaluate a model
  - Different models give different answers
  - Lack of transparency :
    - ‘‘There is no way that an observer can directly understand why an artificial neural network might reach a particular decision’’ (Musen, 2006)
    - Doctors prefer logistic regressions
- Need to develop consensus guidelines and standardized platforms for developing and evaluating prediction models in healthcare

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Model Based Medicine: A Wish List

- *Organically integrating data from ALL sources/scales with medical knowledge*
- *Accurate*
  - Extensive validation and uncertainty quantification
  - Accuracy and uncertainties are quantified using standard measures and clearly communicated
- *Fully integrated with EMR*
  - EMR is used to drive hypothesis testing, and model calibration and validation.
  - EMR will be used with RCT as the new "gold-standard" of empirical evidence.
  - EMR data (structured + unstructured) requires careful analysis to control for errors, missingess and biases
- *Easy to use*
  - User-friendly, accessible to decision makers (patients, physicians, policy makers)
  - Minimize erroneous interpretation of the results.

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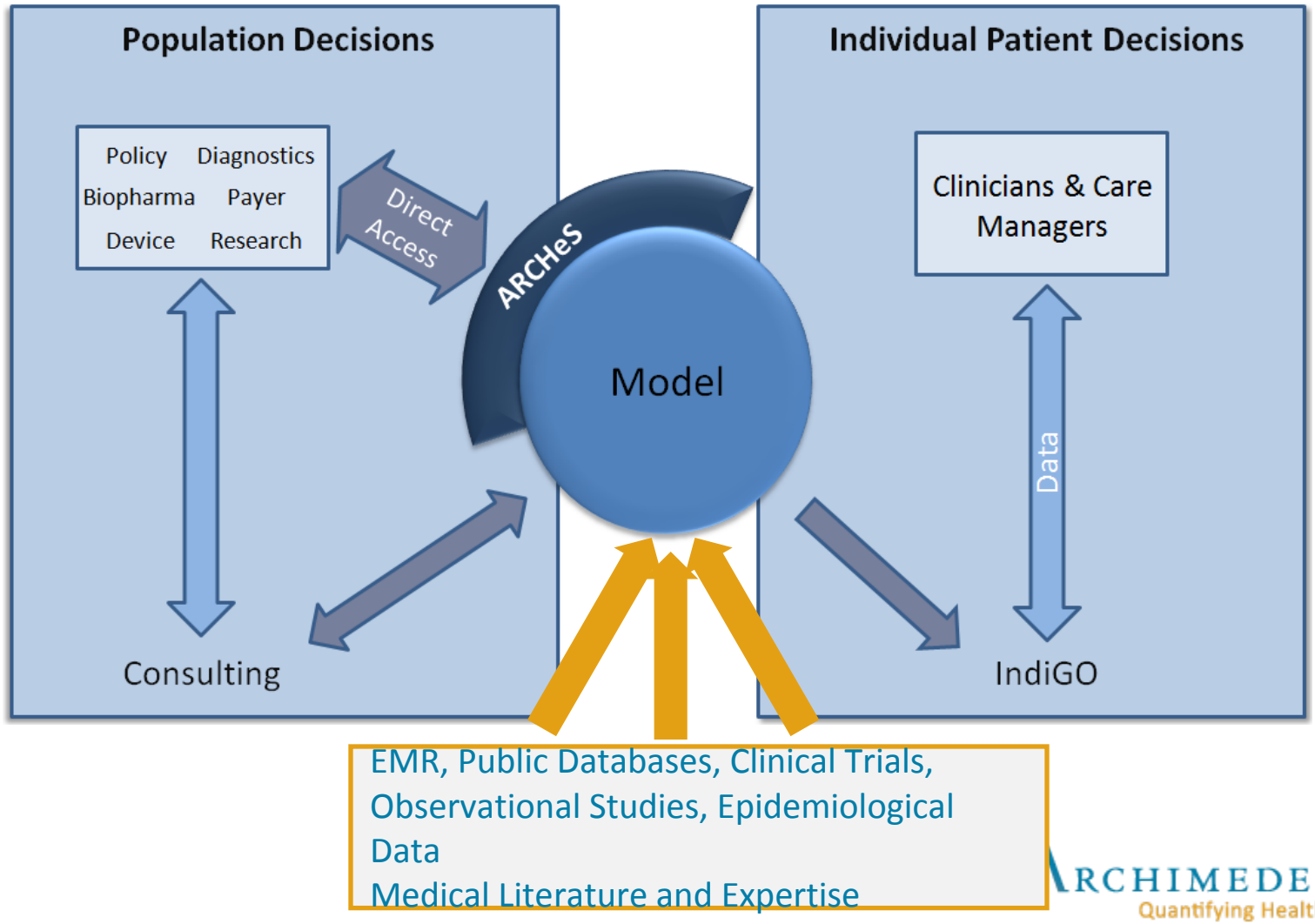
Archimedes Implementation of MBM



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Archimedes Model Basics

- A continuous time discrete event simulation model with coupled components with well-defined interfaces
  - Pathophysiology
  - Interventions
  - Patient and physician behaviors
  - Healthcare system
- Comprehensive validation and continuously updated
- Provides insight into likely health outcomes and costs under various interventions and assumptions
- Coded in Java
  - Object oriented design
  - 150,000 lines of code – completely rewritten in the past 5 years
  - Externalized parameterization
  - Parallelized by individual and engineered to run on a grid

Integrating Multiple Diseases

- Diabetes (type 1 and 2)
- Diabetes complications
- Coronary artery disease
- Atrial fibrillation
- Hypertension
- Stroke (ischemic and hemorrhagic)
- Lung cancer
- Breast cancer
- Colon cancer
- Bladder Cancer
- Lynch Syndrome
- Congestive heart failure
- Dyslipidemia
- Obesity
- Metabolic syndrome
- Hypertriglyceridemia
- Asthma
- COPD
- Major Depressive Disorder

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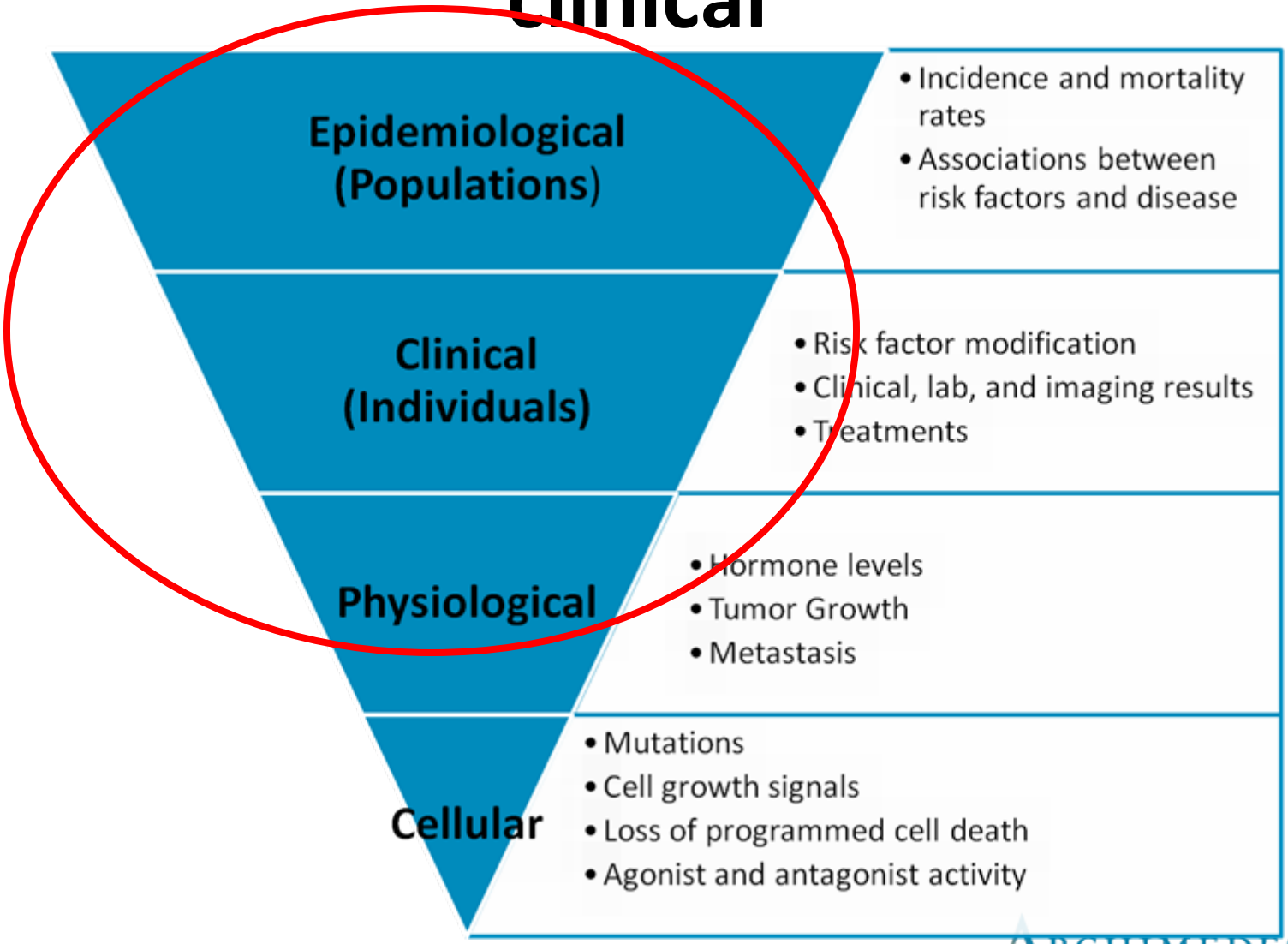
Pragmatic modeling approach

- Disease models are a blend of “statistical” and “physiological, mechanistic” models
  - Examples with more mechanistic focus:
    - Heart function and circulation: Pressure, volume, inotropy, etc.
    - Colorectal cancer model: Growth and development of adenomas, transition to malignant tumors
  - Examples with more statistical focus:
    - CHF
    - Diabetes and diabetic complications
- Match epidemiology while improving predictive capability by capturing basic causal relationships
- Event examples:
  - Arrival at a threshold value, e.g. FPG=126
  - Scheduled health care appointment, e.g. for mammogram
  - Occurrence of an acute event, e.g. an MI
- Multiple interacting trajectories evolving simultaneously
  - Biomarkers: Typically clinical variables such as FPG, HDL, urinary albumin, …
  - Maintains NHANES distributions of biomarkers through time
  - Preserves biomarker covariance structure

The scope of the Archimedes Model is clinical



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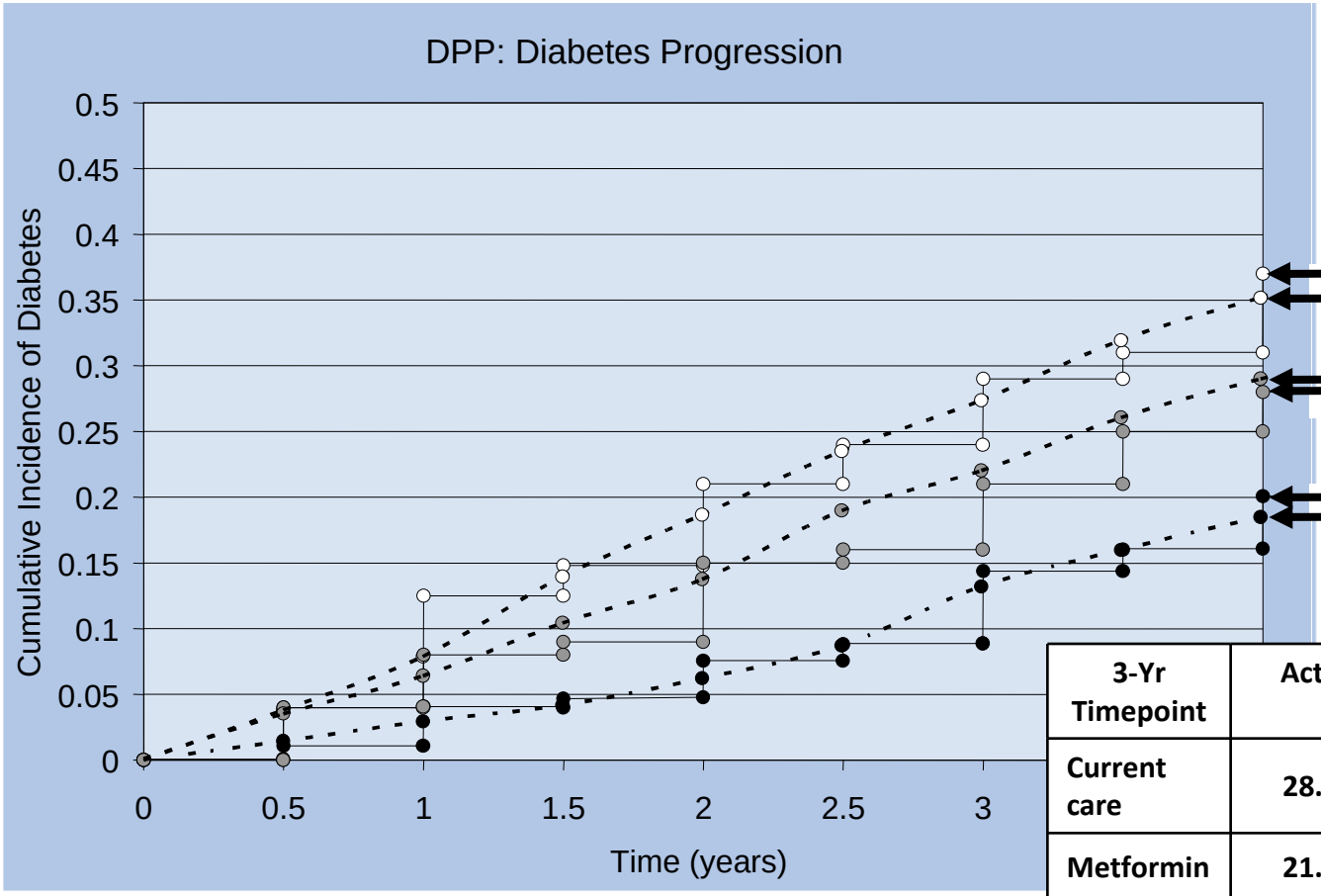
We successfully validate the Archimedes Model prospectively many times, …



3-Yr Timepoint	Actual	Simulated
Current care	28.9%	27.4%
Metformin	21.7%	21.9%
Lifestyle	14.4%	13.2%

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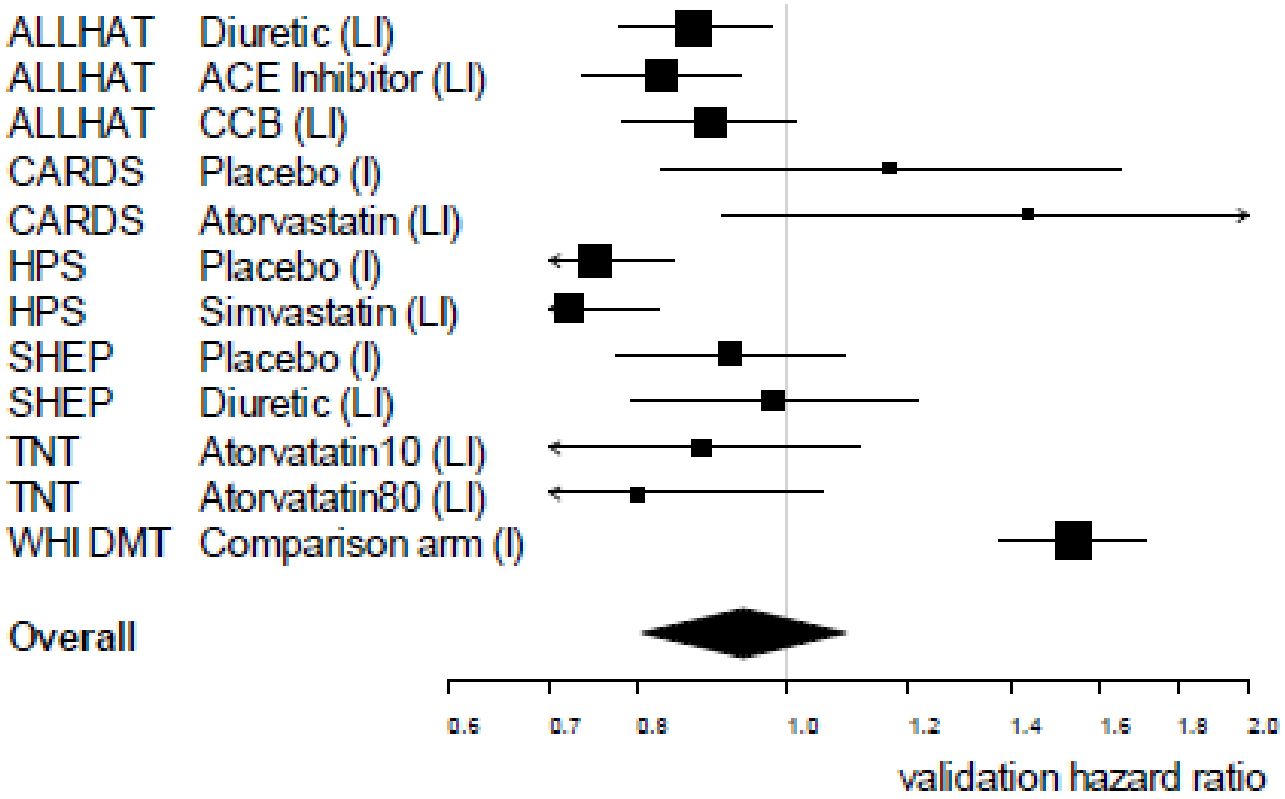
The validations do not always look like DPP



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Examples of data sources used to independently validate the Archimedes Model

Clinical trials (~80)
CARDS
TNT
SHEP
UK Flex Sig
ALLHAT
PLCO
ATBC
HOPE
DPP
WESDR
HPS
ACCORD

Observational studies (~30)
CPS-II
WHS
WHI
NPS
LHS
EORTC
CUETO

EMRs, claim databases, and disease registries (~10)
KP Southern California
SEER-Medicare
Leiden Registry

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ARCHeS Trial Designer

My Projects | Help | Support | Change Password | Sign Out

Project: Test

Save for Later

1. Description | 2. Population | 3. Background Care | 4. Interventions | 5. Trial Arms | 6. Subpopulations | 7. Submit

Enter the criteria used to limit the patient population eligible for the project. Use the drop-down list and the buttons in the shaded area to build a logical expression that defines the population of interest. *More Information*

Select from library | Save to Library

Inclusion/Exclusion Criteria

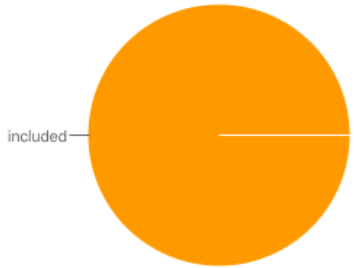
NOT | AND | OR | (|)

Clear

(Select One) | Add

Validate & Update

100.0% of the population between ages 20 and 85 will be included based on the criteria



Baseline Population Characteristics

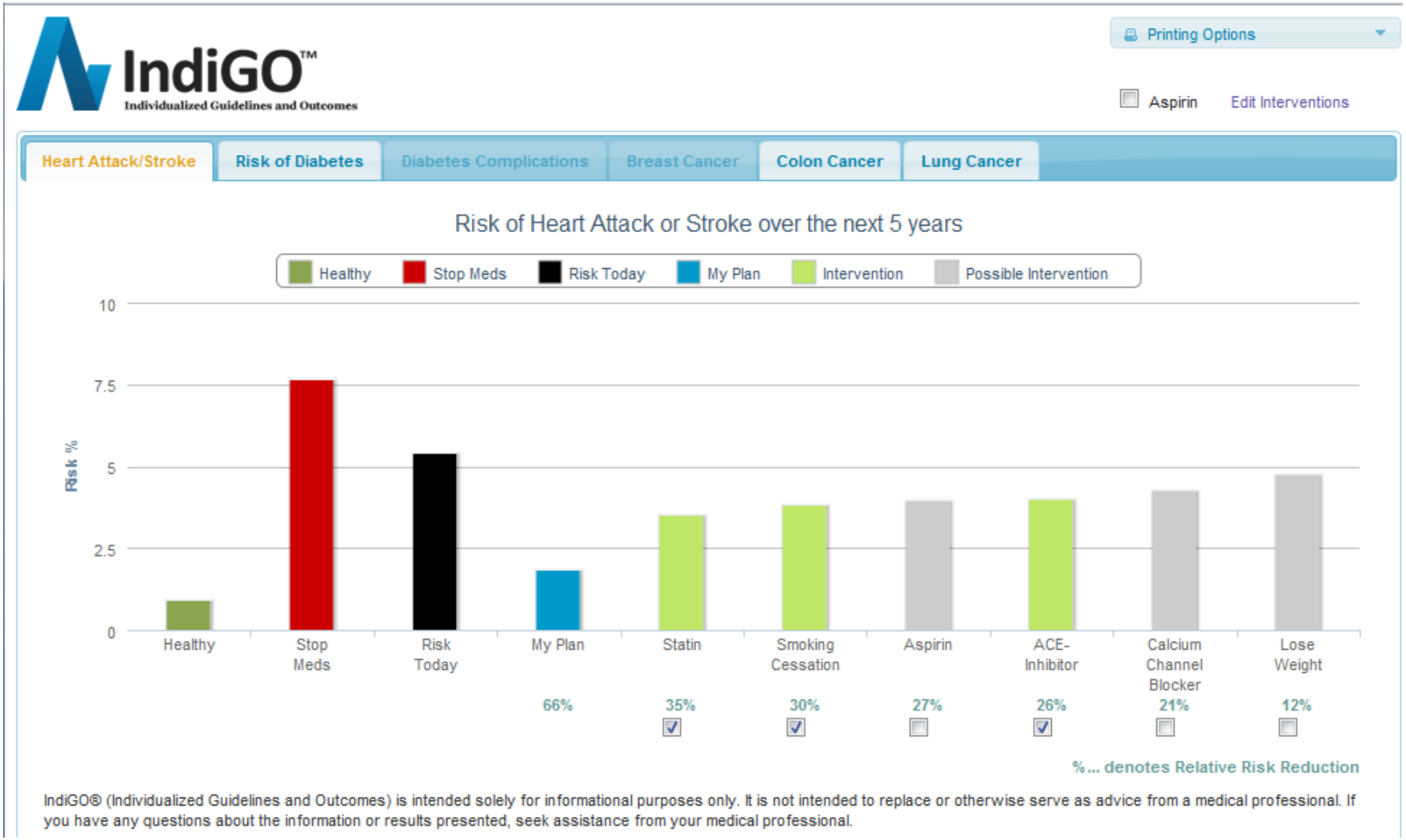
Biomarkers | Medical History | Medication Use

Default values for these characteristics are based on the included population. Use the sliders to modify them.

		use default
Age Mean (yr)	46.6	☑
Current Smoker (%)	23.9	☑
Male Fraction (%)	48.3	☑
BMI (kg/m^2)	28.2	☑
Weight (kg)	80.6	☑
Waist (cm)	97.2	☑
Systolic blood pressure (mm Hg)	121.6	☑
Diastolic blood pressure (mm Hg)	71.5	☑
LDL (mg/dL)	116.5	☑
HDL (mg/dL)	54.0	☑

IndiGO: Archimedes Model for Individual Patient

- Personalized decision support tool derived from the Archimedes Model
- In use by Kaiser, Intermountain Health, CDC, and other organizations
- Used for risk stratification and patient adherence



Current IndiGO Decision Support Information

Inputs from EMR

Demographics:
- Age, gender, height, weight

Biomarkers
- Cholesterol, HDL, LDL, TG
- Blood pressure
- A1c and FPG
- Creatinine, urinary albumin
- FEV1
- PHQ-9

Medical history
- Prior MI, Prior Stroke, CHF, Atrial Fibrillation, history of Revascularization
- Diagnosis of diabetes, neuropathy, retinopathy, COPD,
- depression
- Family history

Behaviors
- Smoking
- Physical activity

Allergies and contraindications

Risk of Outcomes

Cardiovascular Disease (CVD)
- MI
- Stroke

Diabetes Onset

Diabetes Complications
- Foot ulcers
- Retinopathy

Renal Disease

Cancers
- Breast
- Colon
- Lung

Chronic obstructive pulmonary disease (COPD)
- Exacerbations
- Hospitalizations

Major depressive disorder
- Treatment response
- Recurrence
- Suicidality

Benefit of Interventions

- Statins
- Anti-hypertensives
- Aspirin
- Niacin
- HbA1c Reduction
- Weight Loss
- Smoking Cessation
- Exercise
- Fish Oil
- Cancer Screening
- Antidepressants
- Psychotherapy

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Independent Evaluation of IndiGO

- Validation
  - Accurately predict risks of cardiovascular diseases and diabetic complications for ~1,000,000 patients in KPSC
- Qualitative assessment
  - High physician acceptance: *"IndiGO helped make **the best clinical decisions** for patients."*
  - Positive patient focus: *"It was pretty impressive… it showed what is going on in my life regarding health issues. **For me it made an impact**."*
  - Doctor and patient engagement: *"[IndiGO] brought out not only the negative side of **what could happen**, but also showed if I lose x amount of weight I will fall within this category of being well."*
  - Personalized information is powerful: *"It was **very informative.** I didn't realize **how dangerously close** I was to having heart or high blood pressure problems."*
- Quantitative assessment
  - Increased compliance
    - Patients who had a care gap for statins under standard guidelines were **6 times more likely to close the gap** after a PCP visit that included IndiGO
    - For high risk patients identified by IndiGO, there was a **7 times improvement in prescription dispenses** as compared to EHR and panel support tool alone
  - Improved outcomes
    - A **13% reduction in 5-year CVD** more than EHR and panel support tool alone
    - For every 1 million members, we estimate 1400 heart and strokes averted annually

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Case Study I: Estimating Disease Burden and Medical Utilization in Newly Insured Population in California

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Project Context

- In Jan 2014, hundreds of thousands of Californians who currently do not have health insurance coverage will be insured through the Health Insurance Exchange.
- For planning purposes, it is important to estimate disease burden and demands for services in uninsured populations.
  - Demographics: younger, more male, higher smoking prevalence
  - Low income, higher proportions
  - Long history of lack of access to preventive care – Pent up demand
- How pricing might affect characteristics of populations who choose to join a specific insurer

General Methodology

- Collect California-specific data on health, demographics and socioeconomic status at county level
  - California Health Interview Survey (CHIS)
  - National Health and Nutrition Examination Survey
  - Current Population Survey
  - US Census Bureau
  - California Hospital Inpatient
- Use the Archimedes Model as a platform to synthesize all information available for each Health Insurance Exchange pricing region
- Leverage the California-calibrated Archimedes Model to
  - Generate a virtual population, representative of the California uninsured population for each county and
  - Forecast clinical outcomes, health care utilization and medical expenditures in the next 2 years for this population

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Type of information extracted

- **Demographic:** age, race, ethnicity, gender
- **Socioeconomic status:** income, education
- **Insurance status:** Medicare, Medicaid, insured through employer-sponsored plans, insured through nongroup package, uninsured
- **Biomarkers:** A1C, FPG, BMI, cholesterols, triglycerides, BPs
- **Disease diagnosis:** diabetes, cancers, cardiovascular diseases
- **Medication usage and medical utilization:** including pregnancy, child birth complications
- **Performance measures**
- **Medical expenditures**

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Examples of outcome predicted for uninsured populations

- Coronary artery disease,
- Diabetes and its complications,
- Congestive heart failure,
- Stroke,
- Hypertension,
- Chronic obstructive pulmonary disease,
- Colorectal, lung, and breast cancers
- Pregnancy utilization
- Annual medical expenditure

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Sample predictions: Baseline characteristics of newly insured populations in Alameda County

Characteristics	Join KP	Join non-KP
Number Joining	12,500	17,000
Age (%)		
18 to 24	15	19
25 to 34	22	27
35 to 44	24	21
45 to 54	26	21
55 to 64	14	11
Male (%)	58	65
Diagnosed Diabetes (%)	6.0	5.5
Diagnosed Hypertension (%)	20	22.0
Number of Births	320	450
PM Medical Expenses	$3,500	$3,400

Average per member (PM) medical cost for KP enrollees

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Sample predictions of expected medical expenses for individual members

General Information	Conditions	Expected Medical Expenses
44 y.o. Female, Excellent Health	Obese (BMI > 35), High Blood Pressure, COPD	$3,183
60 y.o. Male, Good Health	Obese (BMI > 30), Diabetic, High Blood Pressure, High Cholesterol, COPD	$8,273
26 y.o. Female, Good Health	Gave Birth	$12,126
26 y.o. Female, Good Health	None	$984
20 y.o. Male, Excellent Health	None	$870

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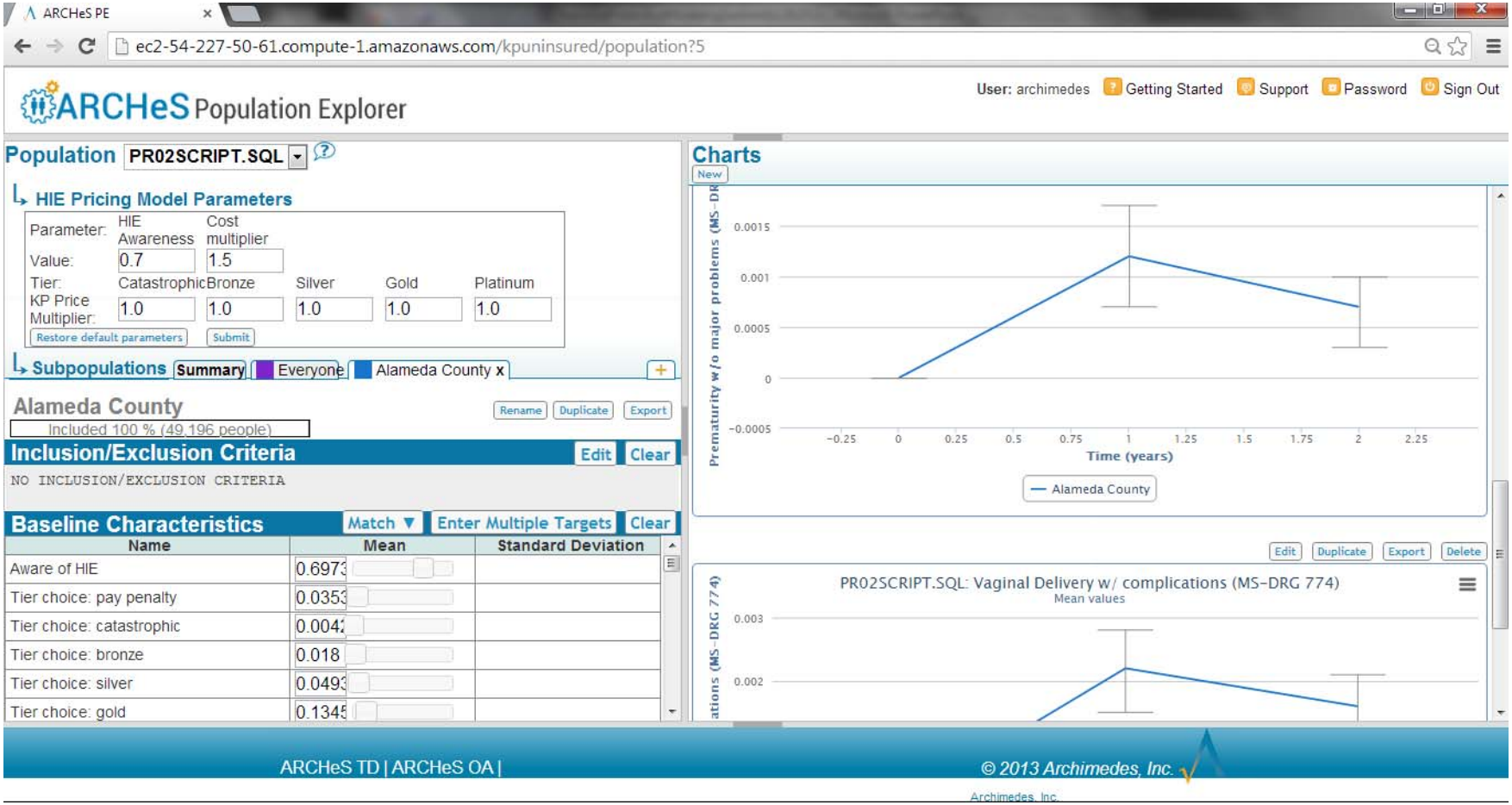
Demo



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Case Study

Health Economics & Outcomes Research

Targeting a Specific Population with a Drug Combination to Improve Health Outcomes and Reduce Costs (A-L-L)

Structure of Simulation

WHO

Patients with CAD and all diabetics over 55 years in KP California

WHAT

- Experimental Group: Aspirin, Lisinopril, Lovastatin
- Reference Group: 1% HbA1c reduction
- Control Group: Current care

WHEN

25-year simulation
(followed by 2-year real trial)

OUTCOMES

- Annual risk of: MI, stroke, ESRD, blindness, death
- Annual cost

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Setup

- For Patients with CAD and/or DM (for diabetics over 55 years of age)
  - Aspirin
  - Lovastatin
  - Lisinopril
- Keep it simple
  - As few visits and tests as possible
  - Don’t strain to reach a goal
  - Just make sure they get it

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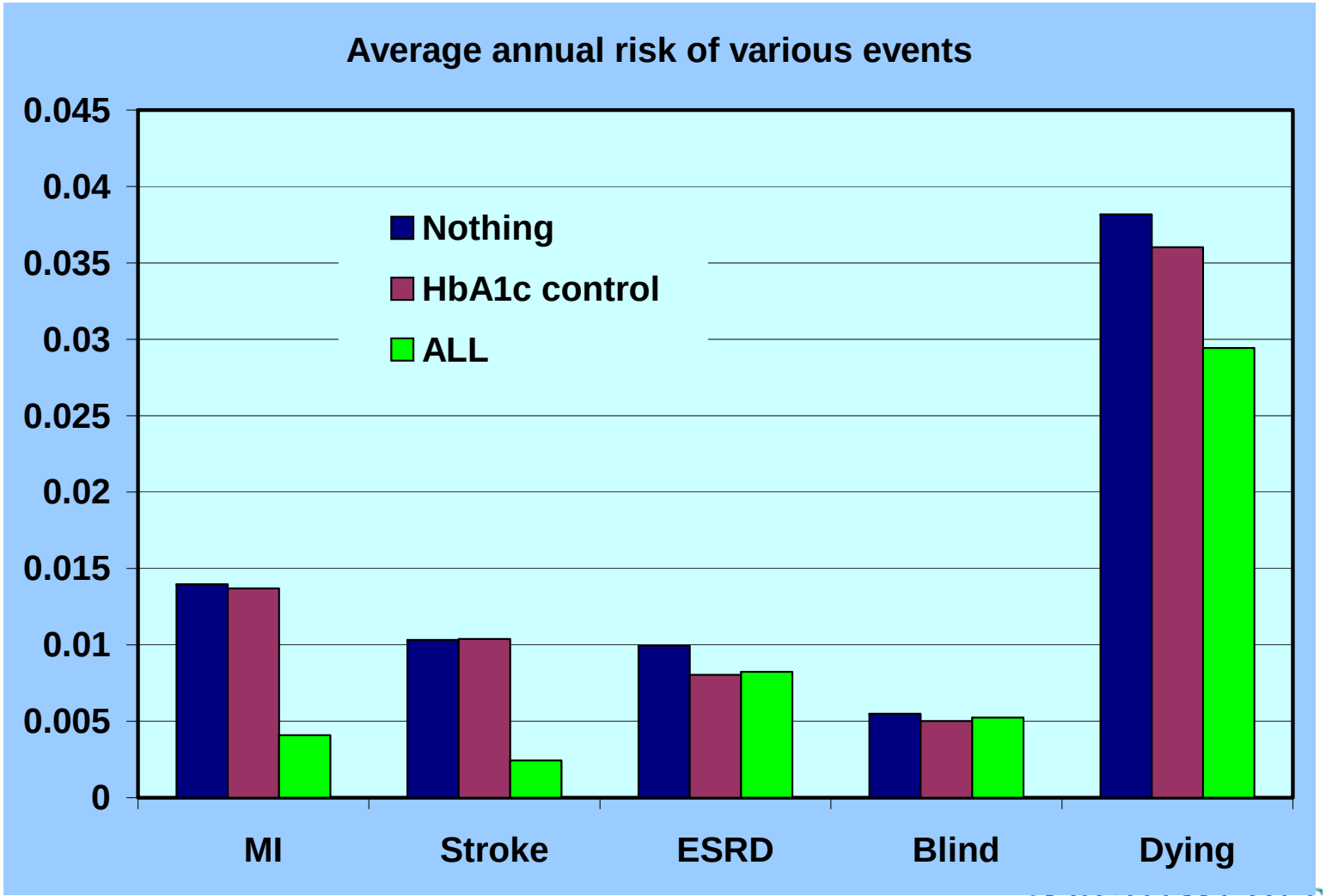
A-L-L has a Bigger Effect than 1% HbA1c Reduction



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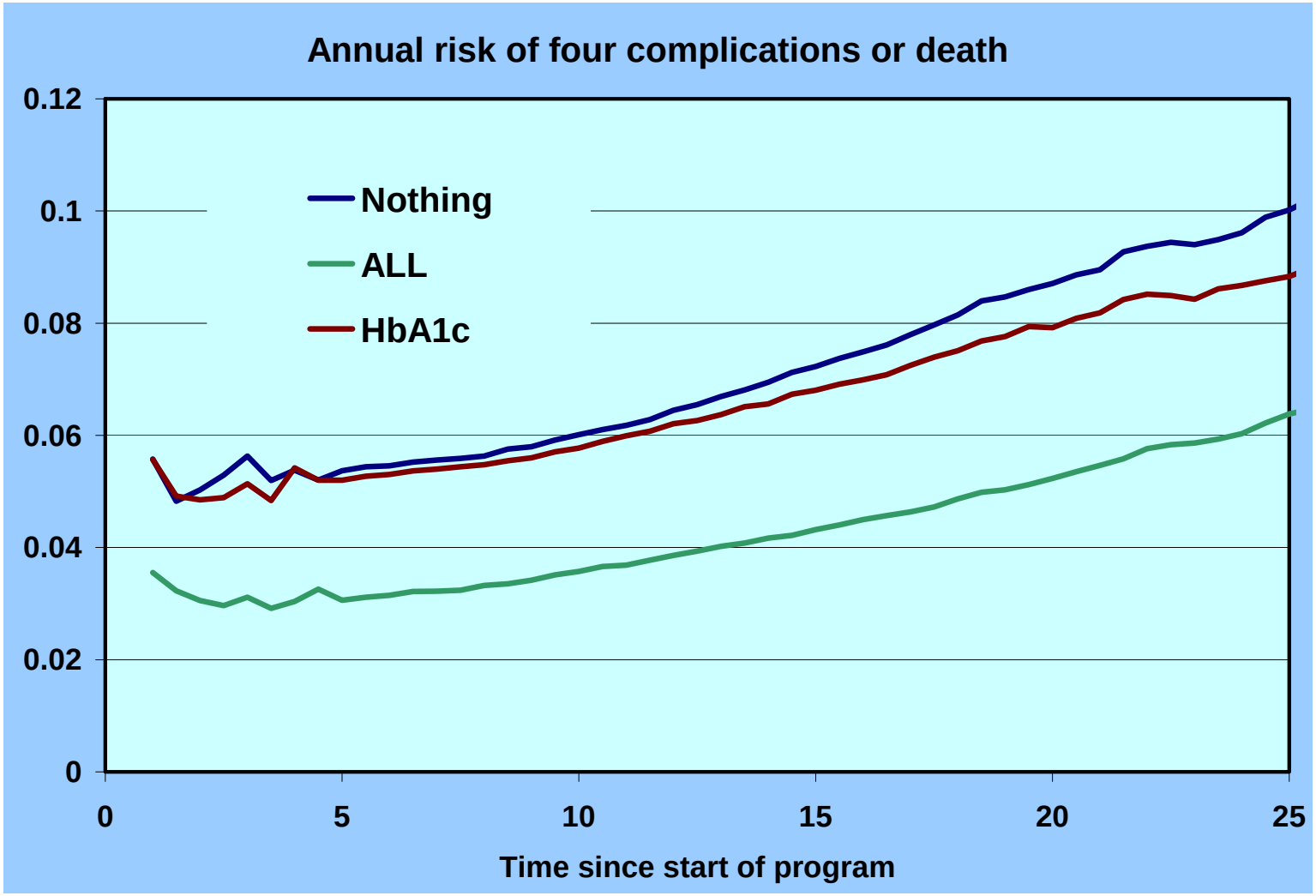
The Effect Begins Immediately



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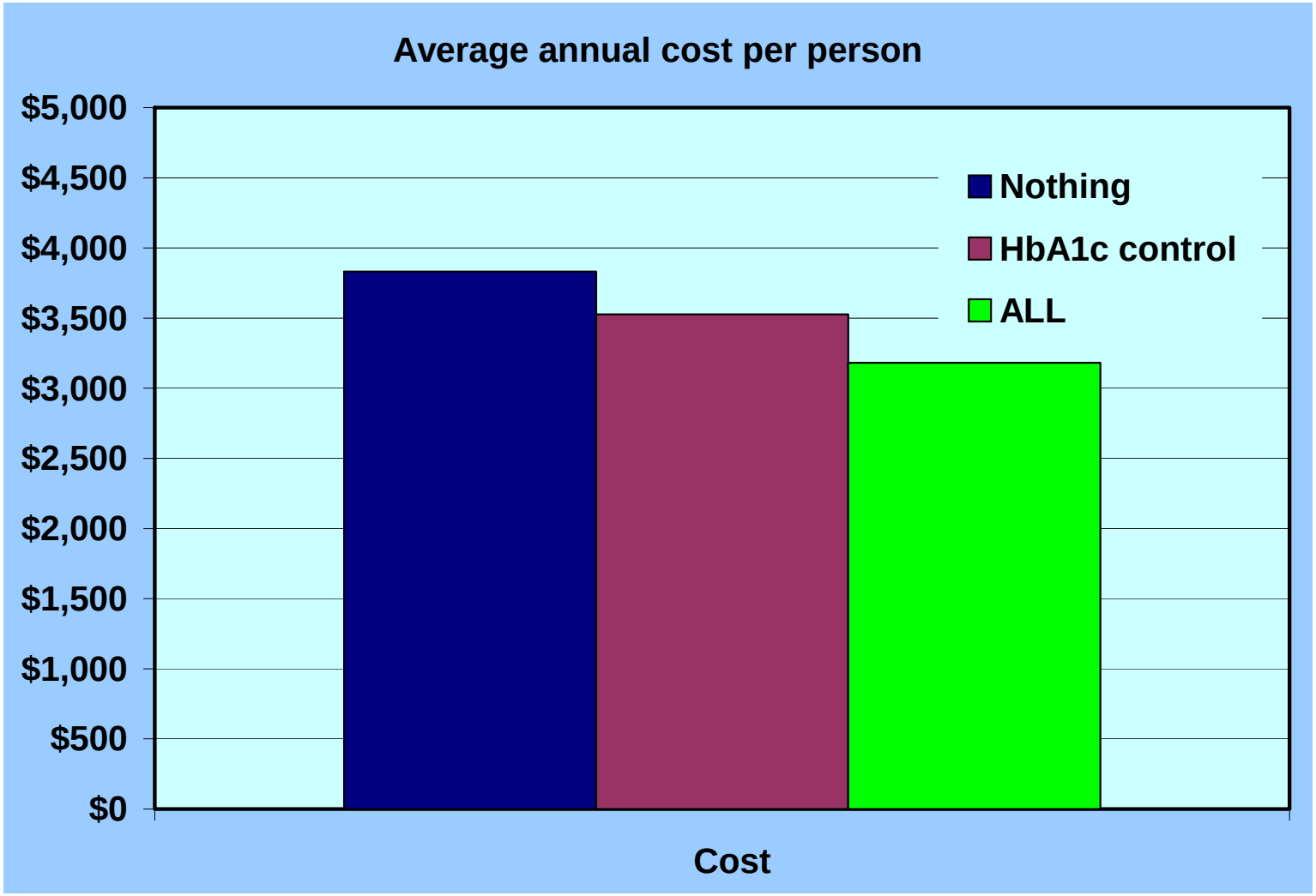
It Saves More Money



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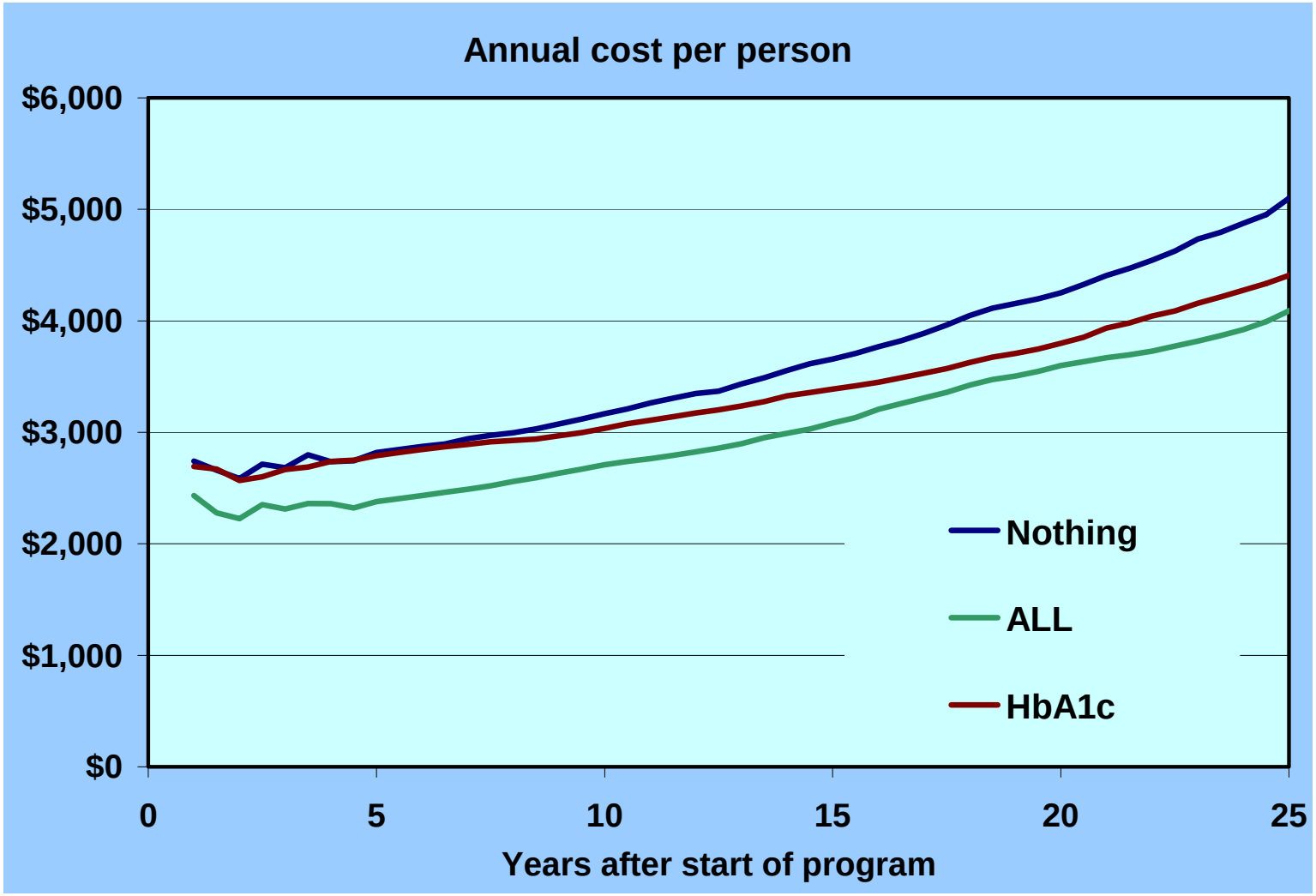
The Savings Begin Immediately



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CMI Independent Evaluation

- In 2004-2005, 28% of KP's eligible study population in Northern + Southern CA (n=170,024) had received A-L-L at low exposure, 13% at high exposure (59% no exposure)
- Modeled results consistent with actual findings by CMI:
  - By 2006, heart attacks and strokes decreased by 15 per 1000 members for the low-exposure group ($p<0.05$), and 26 per 1000 for the high-exposure group ($p<0.05$)
  - 1,271 hospitalizations prevented in 2006
  - Net savings of $38M/year among the study population
- Estimated net savings of $120M per year if fully implemented among all of Kaiser's eligible patients
- Kaiser extends A-L-L to become the PHASE (Prevent Heart Attacks and Strokes Everyday) program at all KP locations
- If extended to 10% of U.S. diabetics, potential savings of $1B/yr

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CMI Publication of Findings, 2009

- National publicity of Archimedes' modeling for Kaiser's A-L-L intervention
  - Dudl JR, Wang MC, Wong, M, Bellows, J. Preventing Myocardial Infarction and Stroke with a Simplified Bundle of Cardioprotective Medications. **The American Journal of Managed Care, 2009** Oct 1;15(10):e88-94.
  - The Care Continuum Alliance honored Kaiser Permanente's ALL/PHASE initiative with the Quality Impact Award for the "Greatest Impact on Health"
- George Halvorson, KP CEO in an email to KP employees:

  "Archimedes saves lives….We are now spreading this work across all of Kaiser Permanente. We now have more than a quarter of a million people in all eight regions signed up to take this regimen. So this week, I'm celebrating the researchers and caregivers who followed the Archimedes model to improve care for our members and patients."

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Conclusions

- Extremely bullish about Model Based Medicine
  - MBM= EBM2
- Despite initial successes, there are a lot of work to be done
  - Archimedes is one of many possible implementations of MBM
  - Advanced machine learning can greatly improve accuracy and robustness of models
  - Love to collaborate to develop tools, standards, etc. to push the field forward
- Key challenges:
  - Collecting and synthesizing evidence from multiple data sources
  - Standards/regulations for and model development, validation and calibration
    - Learning from other industries (e.g. nuclear and aerospace industries)
    - Some organizations like International Society of Pharmacoeconomics Outcomes Research are already pushing these standards
  - Physicians' acceptance: integrating models into physician's work flows, making sure models consistent with medical reality, training/education

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