Screen, triage and treat – a digital paradigm for risk stratification in CKD

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Disclosures

Consultant

- Roche
- AZ
- Janssen
- Bayer
- BI-Lilly
- Otsuka
- Tricida
- Mesentech
- Pulsedata
- Renibus

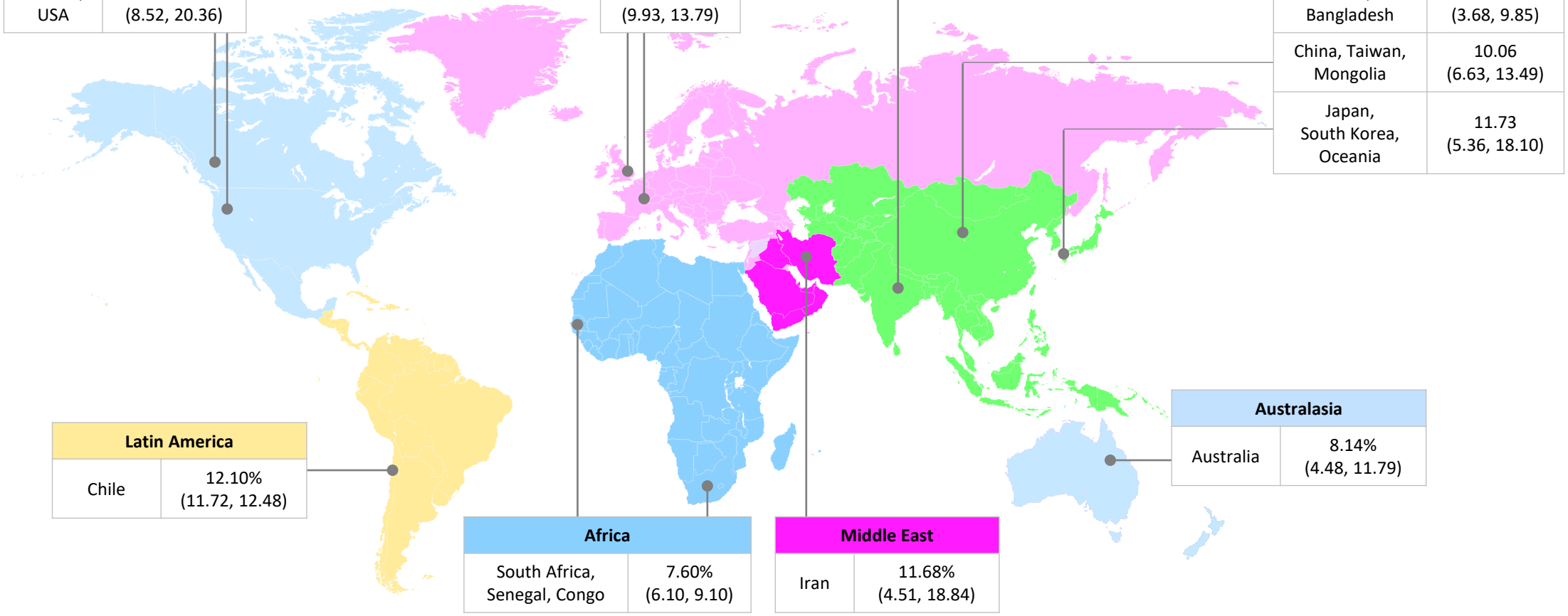
Equity

- Tricida
- Pulsedata
- Mesentech
- Renibus
- Quanta
- Healthlogic

Founder: Klinrisk, Clinpredict

Over 840 million people suffer from CKD worldwide[1]…

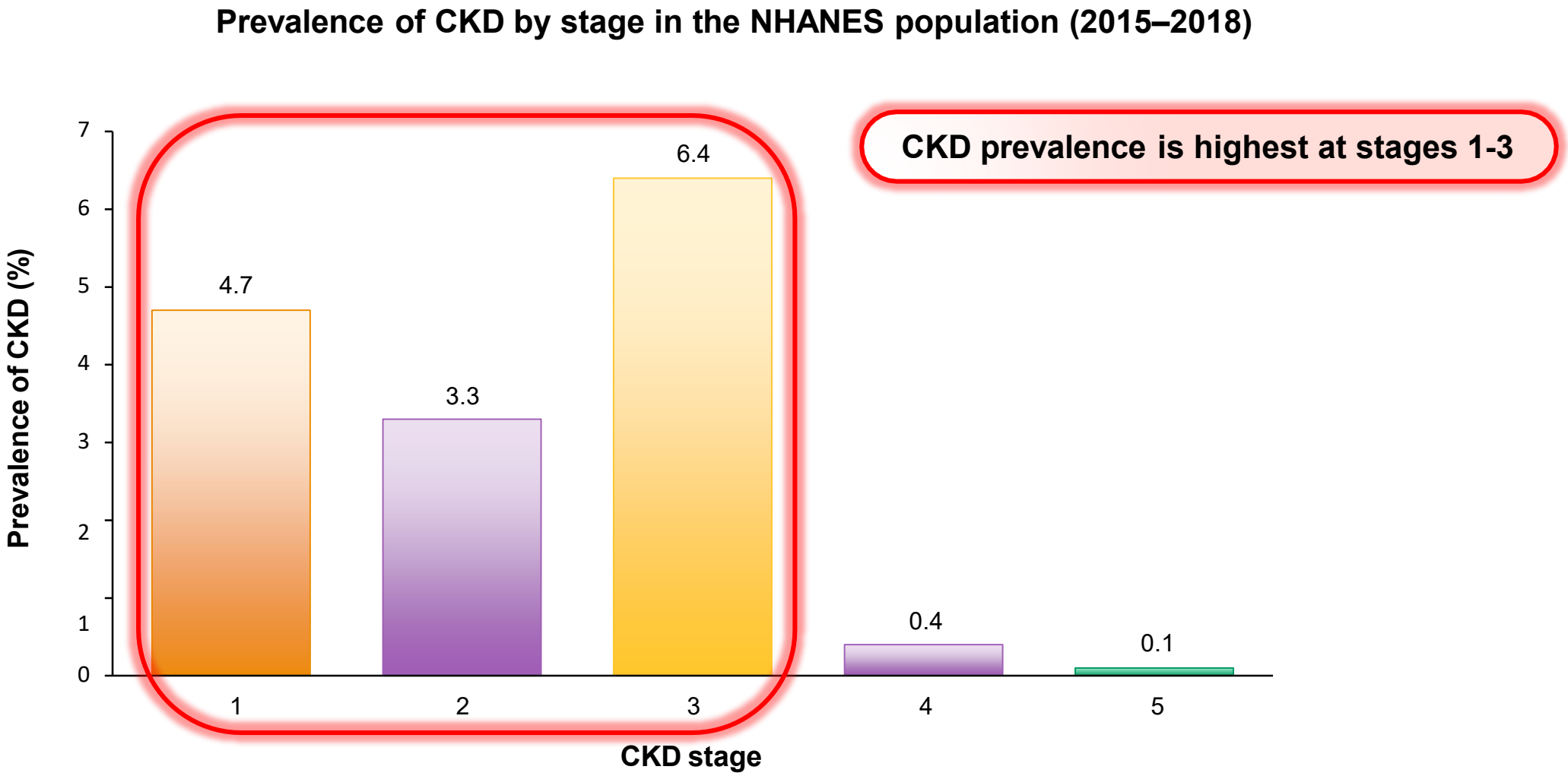
Meta-analysis estimating the global prevalence of CKD (stages 3–5)[2]



CKD, chronic kidney disease

1. Jager KJ, et al. *Nephrol Dial Transplant* 2019;34:1803–1805; 2. Hill NR, et al. *PLoS One* 2016;11:e0158765

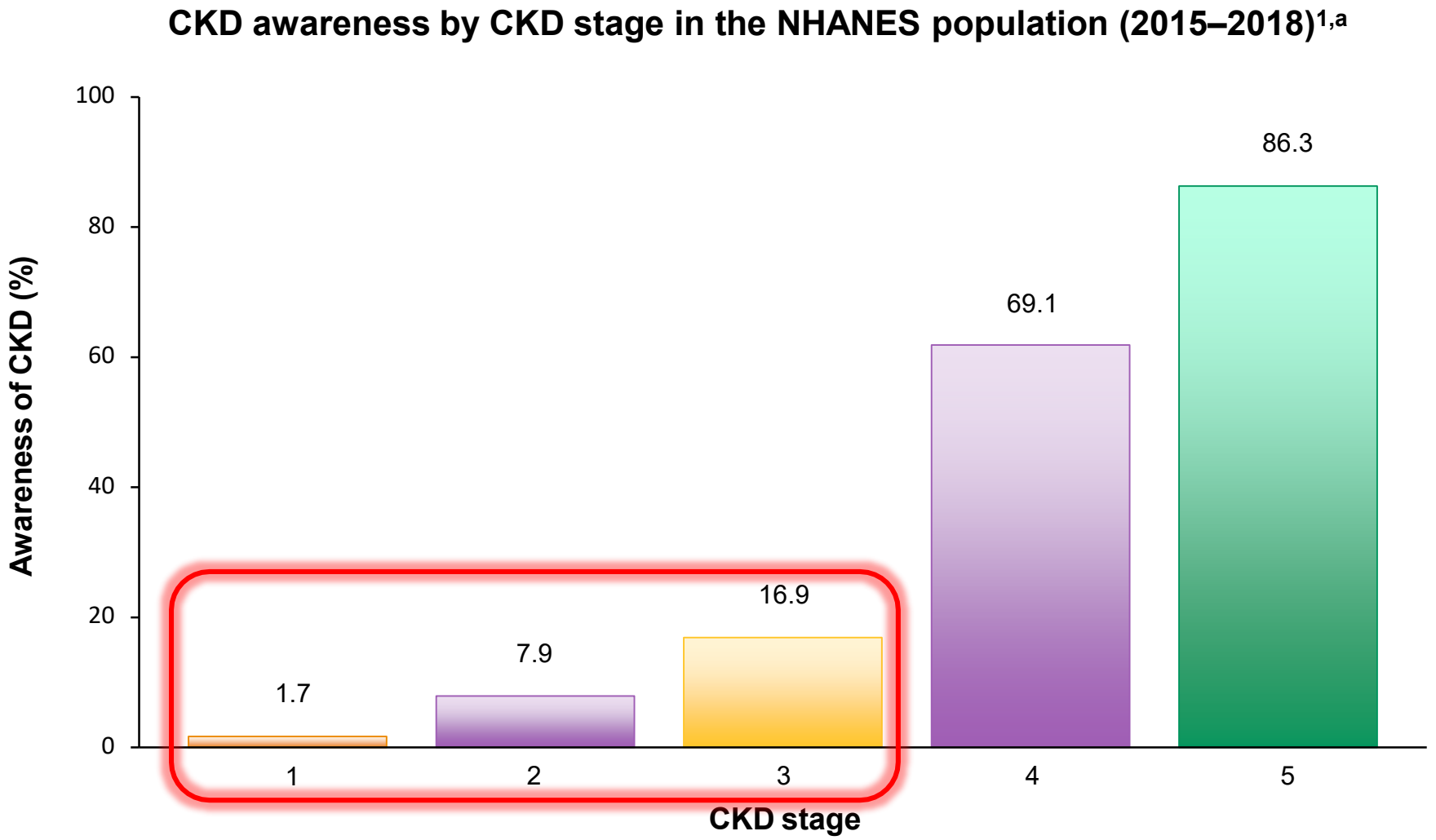
CKD prevalence is significantly higher in the early stages



CKD, chronic kidney disease; NHANES, National Health and Nutrition Examination Survey

USRDS. 2020 Annual data report: CKD in the general population. Available at: https://adr.usrds.org/2020/chronic-kidney-disease/1-ckd-in-the-general-population (Accessed March 2021)

…with patient awareness of CKD significantly lower at early-stage CKD compared with late-stage CKD

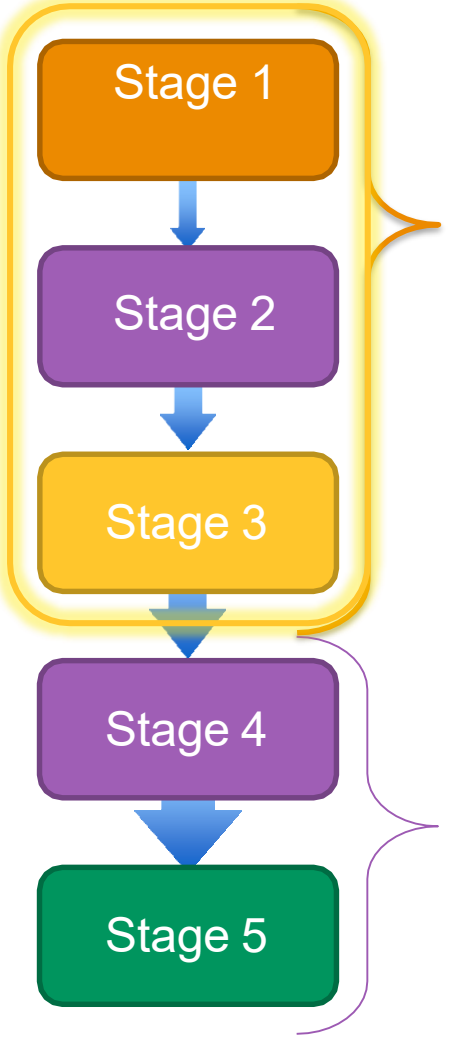


[a]Awareness was assessed as those who reported being told that they had kidney disease

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; NHANES, National Health and Nutrition Examination Survey

1. USRDS. 2020 Annual data report: CKD in the general population. Availalble at: https://adr.usrds.org/2020/chronic-kidney-disease/1-ckd-in-the-general-population (Accessed March 20210); 2. Pavkov M, et al. *Am J Kidney Dis* 2011;57:71–77; 3. Ryan TP, et al. *Am J Med* 2007;120:981–986

Therefore, diagnosis of CKD predominantly occurs at the appearance of symptoms at CKD stage 4–5



CKD stages 1–3 are often asymptomatic[1]

Detection of CKD to optimize patient outcomes requires active screening in the early stages of CKD…

…especially in at-risk asymptomatic patients such as those with diabetes, hypertension, and cardiovascular disease[4]

Therefore, the diagnosis of CKD is likely to occur at the appearance of symptoms[2]

Once late-stage CKD is reached, there are few opportunities to delay further progression and avoid complications[3]

CKD, chronic kidney disease

1. Qaseem A, et al. *Ann Intern Med* 2012;159:835–847; 2. Ryan TP, et al. *Am J Med* 2007;120:981–986; 3. Fishbane S, et al. *Clin Kidney J* 2015;8:54–60; 4. Shlipak MG, et al. *Kidney Int* 2021;99:34–47

Can Machine Learning Help

Machine learning can enable better prognostication when

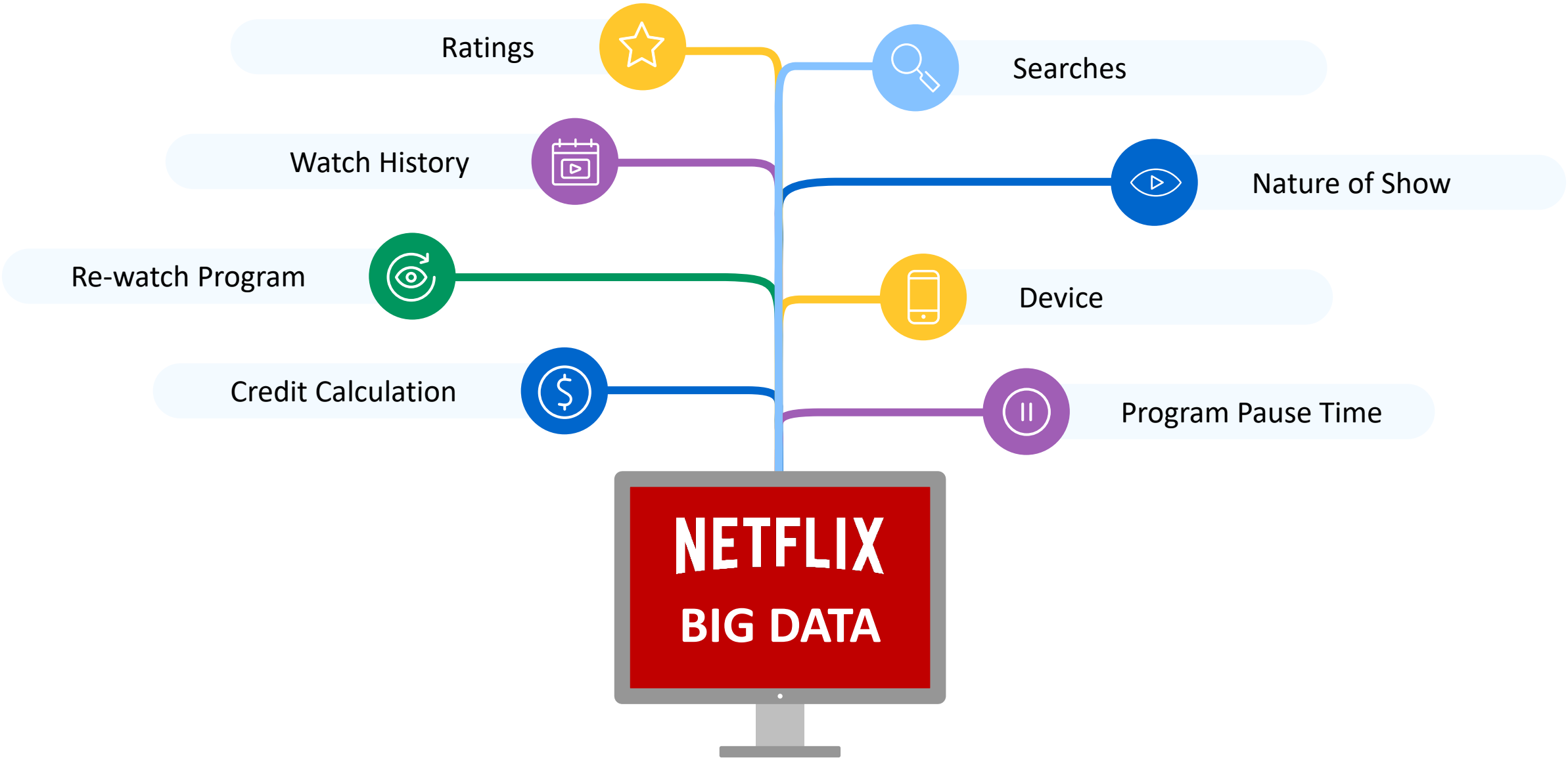
Data is high dimensional

Non linear interactions exist

Missingness is common

Machine learning models are already a part of our everyday lives

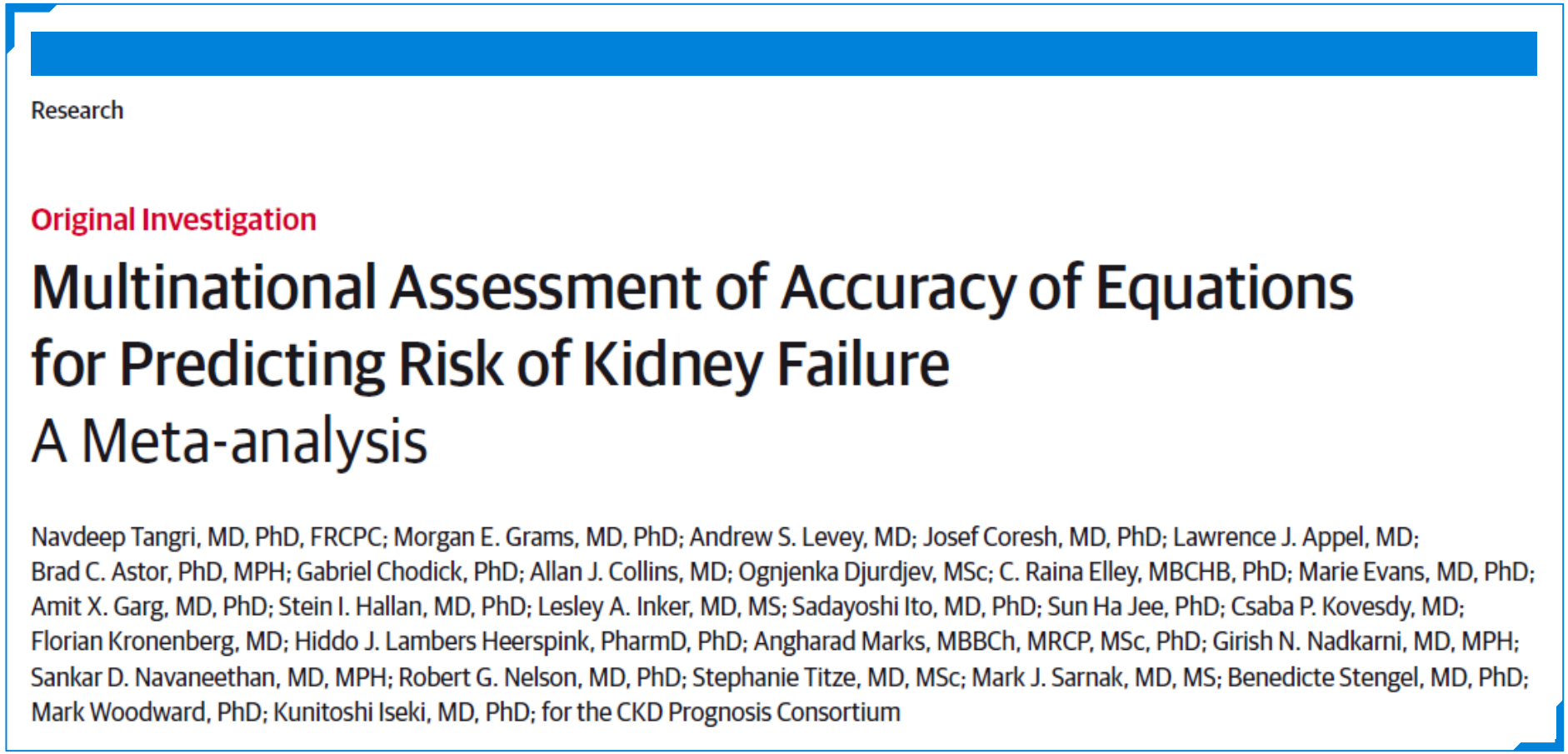
Machine Learning based Prediction



Applications of machine learning to the CKD problem

- Can we identify patients with late stage CKD (G3B-G5) who will progress to dialysis?
- Can we identify patients at earlier stages of CKD who will progress to the later stages?
- Can we create a solution that enables risk based care and truly prevents kidney failure

Triage – Who will develop CKD Progression



Research

Original Investigation

Multinational Assessment of Accuracy of Equations for Predicting Risk of Kidney Failure
A Meta-analysis

Navdeep Tangri, MD, PhD, FRCPC; Morgan E. Grams, MD, PhD; Andrew S. Levey, MD; Josef Coresh, MD, PhD; Lawrence J. Appel, MD; Brad C. Astor, PhD, MPH; Gabriel Chodick, PhD; Allan J. Collins, MD; Ognjenka Djurdjev, MSc; C. Raina Elley, MBCHB, PhD; Marie Evans, MD, PhD; Amit X. Garg, MD, PhD; Stein I. Hallan, MD, PhD; Lesley A. Inker, MD, MS; Sadayoshi Ito, MD, PhD; Sun Ha Jee, PhD; Csaba P. Kovesdy, MD; Florian Kronenberg, MD; Hiddo J. Lambers Heerspink, PharmD, PhD; Angharad Marks, MBBCh, MRCP, MSc, PhD; Girish N. Nadkarni, MD, MPH; Sankar D. Navaneethan, MD, MPH; Robert G. Nelson, MD, PhD; Stephanie Titze, MD, MSc; Mark J. Sarnak, MD, MS; Benedicte Stengel, MD, PhD; Mark Woodward, PhD; Kunitoshi Iseki, MD, PhD; for the CKD Prognosis Consortium

Tangri et al. JAMA 2011, Tangri et al. JAMA 2016

The Kidney Failure Risk Equation

Laboratory based equation – Age, Sex, eGFR, Urine ACR

Validated in more than 30 countries, > 1 M individuals

C statistics 0.85-0.92 – Validated in pediatric, transplant and ethnically diverse populations

Incorporated in national and international clinical practice guidelines

Part of the updated UK NICE CKD guidance

Used by > 50’000 physicians worldwide

KidneyFailureRisk.com

HOW CAN I REDUCE MY RISK OF KIDNEY FAILURE?

There are things you can do to reduce your risk of kidney failure over the next five years. Click below to see how the following will decrease your risk.

- Your current 5 year risk based on the answers you provided is **26.8%**
- Achieving good blood pressure control can reduce your 5 year risk from **26.8%** to **21.17%.**
- An ACE inhibitor (pril) or ARB (sartan) can reduce your 5 year risk from **26.8%** to **18.76%.**
- An SGLT2 inhibitor (gliflozin) can reduce your 5 year risk from **26.8%** to **14.74%.**

The benefits of these changes can add up over time.

LEARN MORE ABOUT YOUR RESULTS

WATCH THE FOLLOWING VIDEO

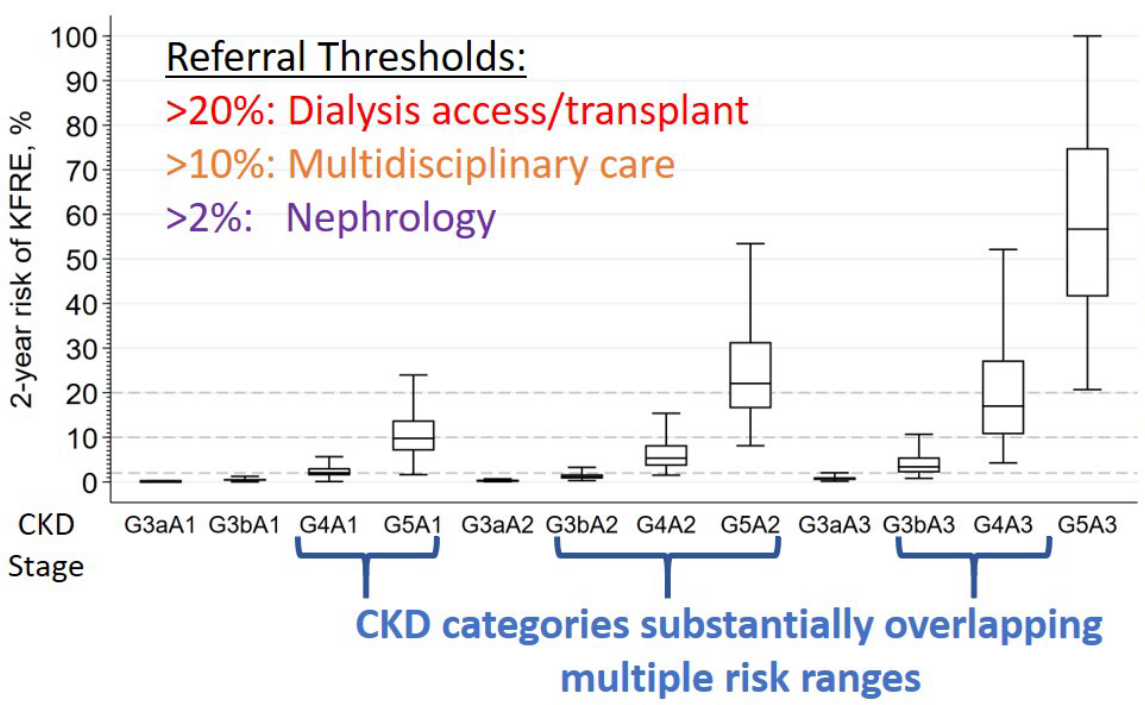
Who with early stage CKD will develop progression

- The KFREs do not predict CKD progression in earlier stages of CKD
- Patients with CKD Stage 1-5
- Predict kidney function decline
  - Composite of 40 % decline in eGFR or kidney failure
  - FDA approved endpoint
- Use routinely collected laboratory data
- Do not require biomarkers – difficult to assay, impractical cost
- Do not require EHR access – difficult to obtain
- Models for everyone

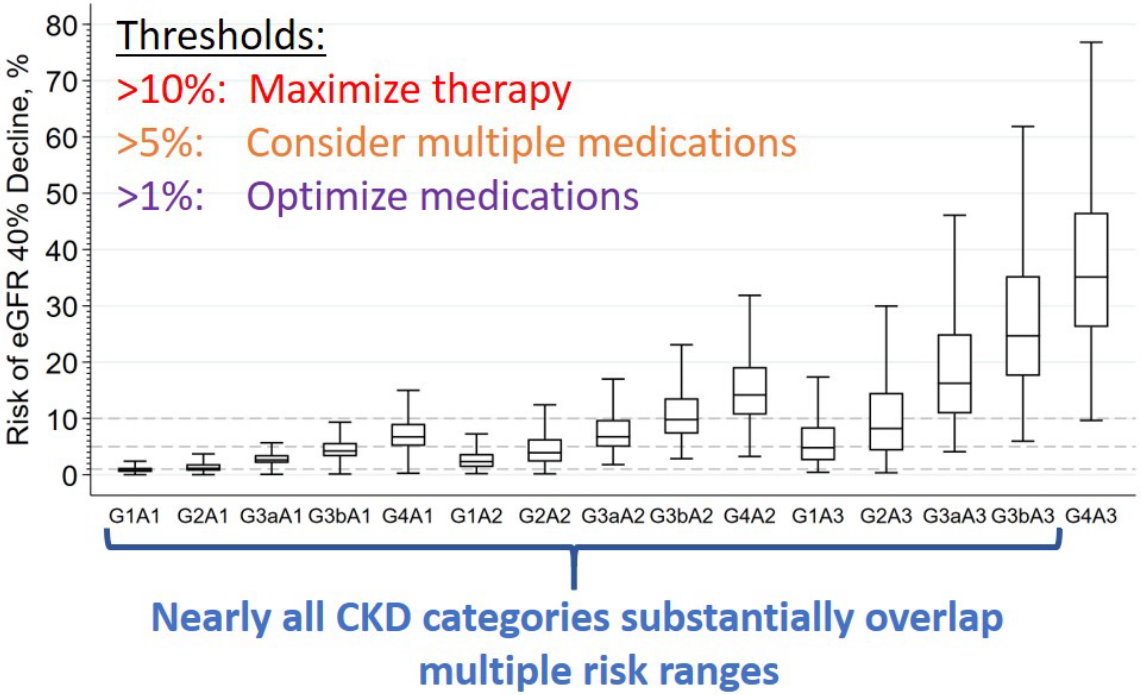
Why not just use albuminuria/heatmap

Figure. Predicted risk of kidney failure (panel A) and >=40% decline in eGFR (panel B) by CKD eGFR (G1 to G5) and ACR (A1 to A3) stage in OLDW. Lines show potential risk thresholds for clinical decisions.

A. Kidney Failure Replacement Therapy Risk among patients with eGFR<60 ml/min/1.73m2 (N=350,232)



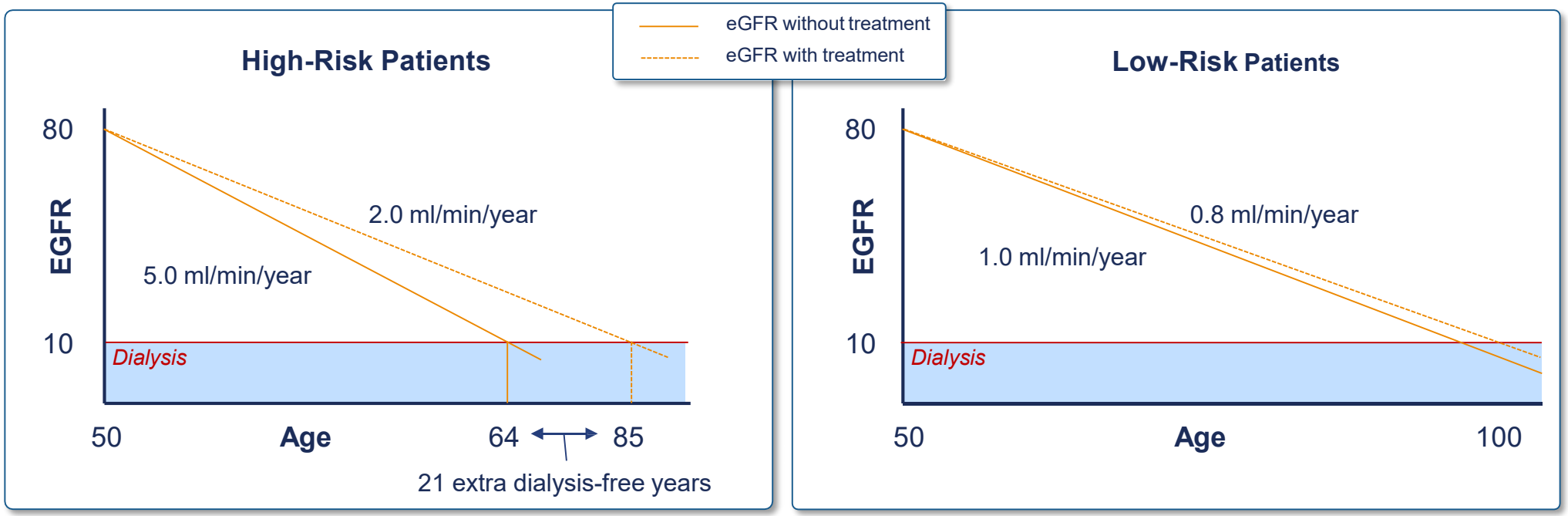
A. Risk of 40% decline in eGFR among patients with eGFR>15 ml/min/1.73m2 (N=1,365,272)



Care is not aligned with risk

	Low Risk*	Intermediate Risk*	High Risk*
BP control	73%	66%	58%
Statins	37%	47%	40%
RAASi	52%	60%	47%

**Data from 7,384 patients in primary care practices*



Patients are not recognized as high risk till eGFR < 30-45 – by that time, majority of kidney function is lost and window to start effective therapeutics is narrowed significantly

Our Datasets

Manitoba Population Health repository

- > 1.2 million individuals
- Population wide coverage
- Every claim, drug, lab test, encounter captured

77’000 individuals with eGFR > 10 and urine ACR data available

- Nearest lab tests acquired within 12 months
- External validation in 100,167 individuals in Alberta

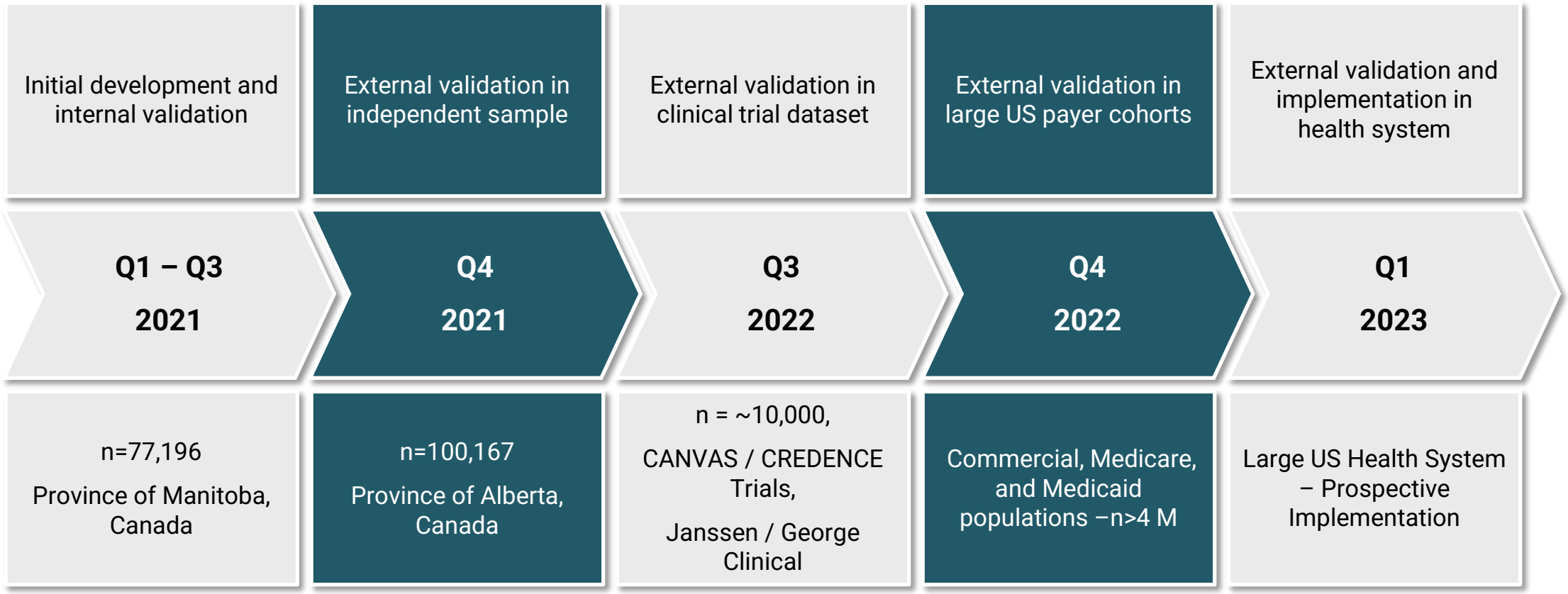
Random Forest Survival Analysis

Our Machine Models are accurate, accessible and generalizable

	Our Machine Models	renalytix
Accuracy	C statistic 0.87	C statistic 0.77
Sample Size	77’196 internal, 100,167 external	1’146 internal only
Predictors and Outcomes	4’000 events	171 events
Require	Require commonly ordered lab tests (LIS or EHR)- CBC, Chemistry panels, LFTs, urine	Require 3 biomarkers, multiple clinical, demographic and laboratory tests over time, medication data, complete EHR access

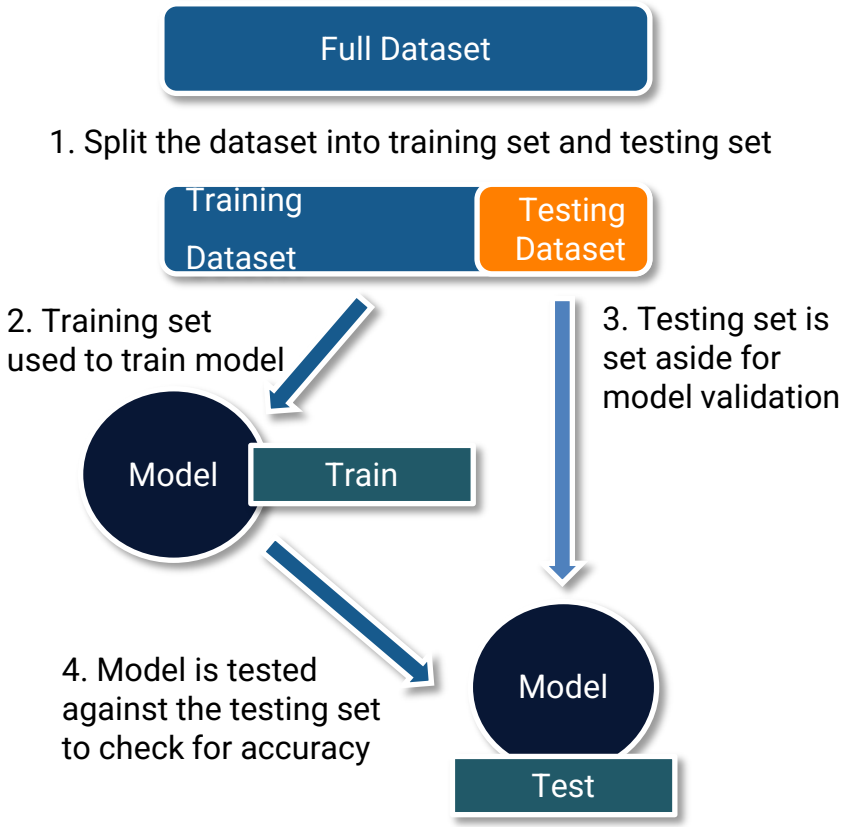
* Both models are not FDA approved and this is not a claim of superiority

Our models are widely validated across clinical trials and representative US Populations

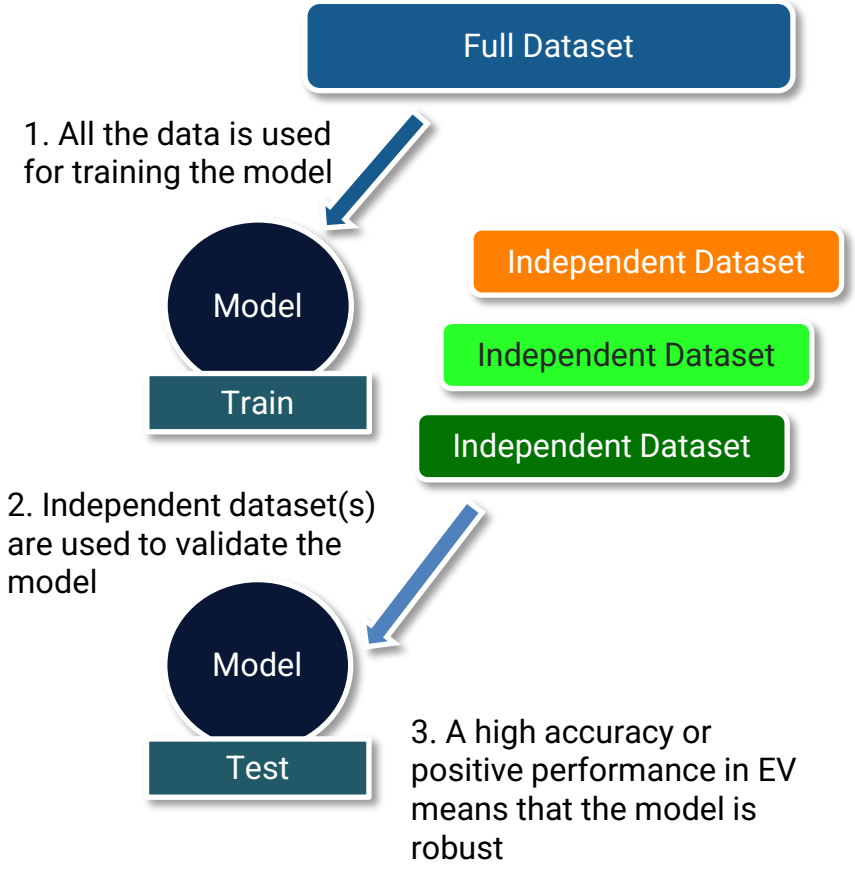


External Validation is essential for machine models

Internal Validation



External Validation



Highlights

External validation is the gold standard for assessing reliability and generalizability of models

Particularly important in machine models which have a tendency to overfit data

Our models are externally validated in an independent sample of 100,000+ individuals

No loss of discrimination accuracy was found confirming that the models are robust to new datasets

External Validation in Clinical Trial Dataset

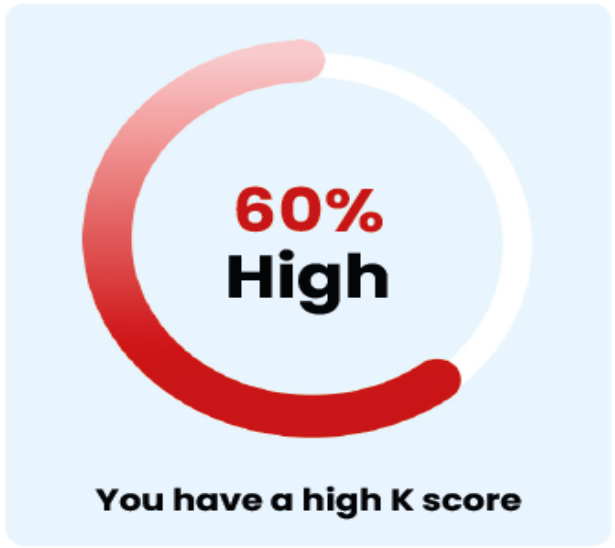
Preliminary Results from CANVAS/CREDENCE

- We were able to score 14,000 participants in the combined CANVAS/CREDENCE population
- We achieved an AUC of >0.80 with optimal calibration
- 15 fold separation in risk between high and low risk groups
- Low risk group eGFR slope benefit (0.4 ml/min.year) vs intermediate risk group (1.5 ml/min/year) and high risk group (3.5 ml/min/year)
- Clear statistically significant change in risk profile between drug/placebo groups over time
  - Treatment group risk decreased by 5.4 % over time
  - Placebo group increased by 13.2 % over time
  - Separation of risk significant at all time points (>15-20 %)
- Replicating same analyses in FIDELITY (Bayer-Finerenone) in Q3/Q4 2022

Enabling Risk Based Care

Test report

Risk of Progressive decline in kidney function



Low	Medium	High
0 → 10	11 → 29	30+

Patients with a high K score are at increased risk, but can work with their physician on a care plan focused on improving their kidney health.

The K score from the Klinrisk device ranges from 0–100 and describes the probability of kidney function loss of up to 40% or kidney failure in the next 5 years. The risk categories and recommendations are provided to alert patients and providers to complications of kidney disease, and associated care pathways recommended by clinical practice guidelines.

This test was developed by Klinrisk Inc, and has been tested for accuracy in independent populations. It is not cleared or approved by the FDA and is not required to be. The test is for clinical care, and should be considered an aid to help with clinical decision making. It should not be regarded as investigation.

Integrating risk based care into workflow

Clinical decision support

Frequency of monitoring

3 times per year

Blood Pressure Target

Target standardized systolic BP< 120

Referral

Nephrology referral is indicated

Complications of CKD

Anemia | Hyperkalemia | **Metabolic Acidosis** | CKD-MBD

Anemia - Hb 10.5
Metabolic Acidosis - HCO3 - 21

Other Recommendations

- **Measure iron studies and replete iron if needed**
- **Treat metabolic acidosis**
- **Recommend statin therapy for CV risk reduction**

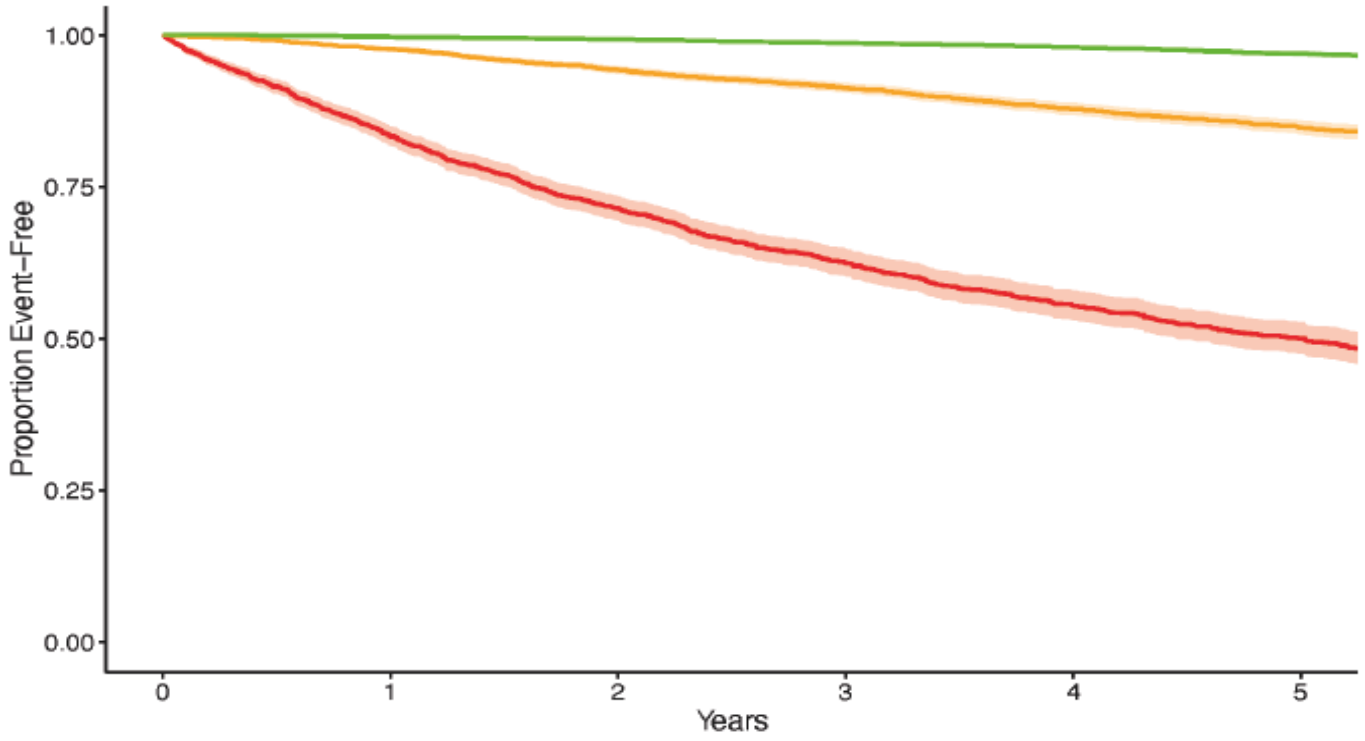
Disease modifying treatment to slow CKD progression

RAASi | **SGLT2i Therapy** | **Non Steroidal MRA**

- **Titrate RAASi or ARB to maximally tolerated dose**
- **Strongly consider SGLT2i therapy**
  Empagliflozin 1x 10 mg daily
  Dapagliflozin 1x 10 mg daily
  Canagliflozin 1x 100 mg daily
- **Strongly consider non steroidal MRA**
  Finerenone 10 mg once daily

Our test identifies high risk patients early before eGFR declines

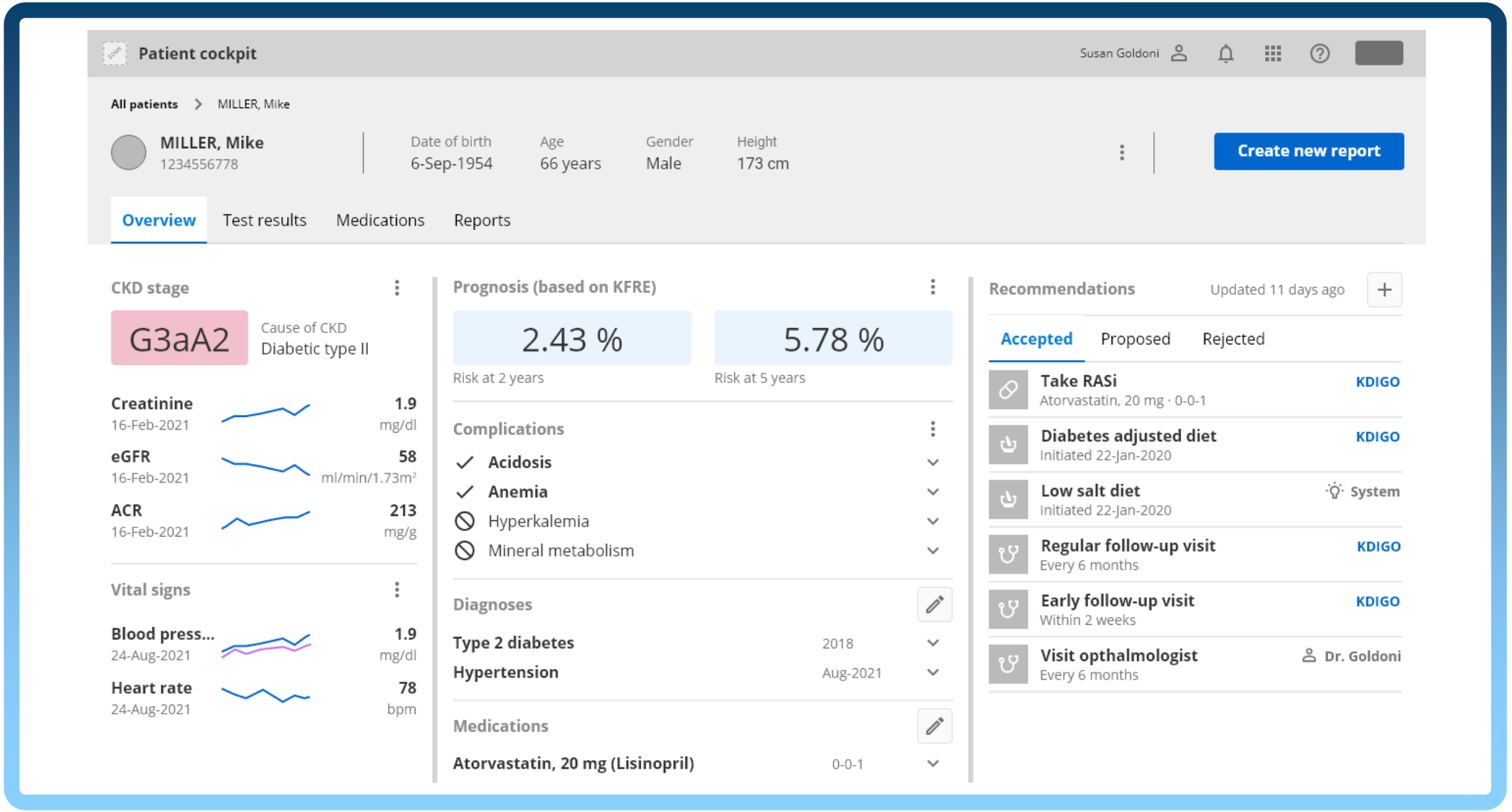
Relationship between Categories of Predicted Risk (Low, Intermediate, and High) from the Random Forest Algorithm and the Occurrence of the Primary Outcome (40% Decline in eGFR or Kidney Failure) over 5 Years



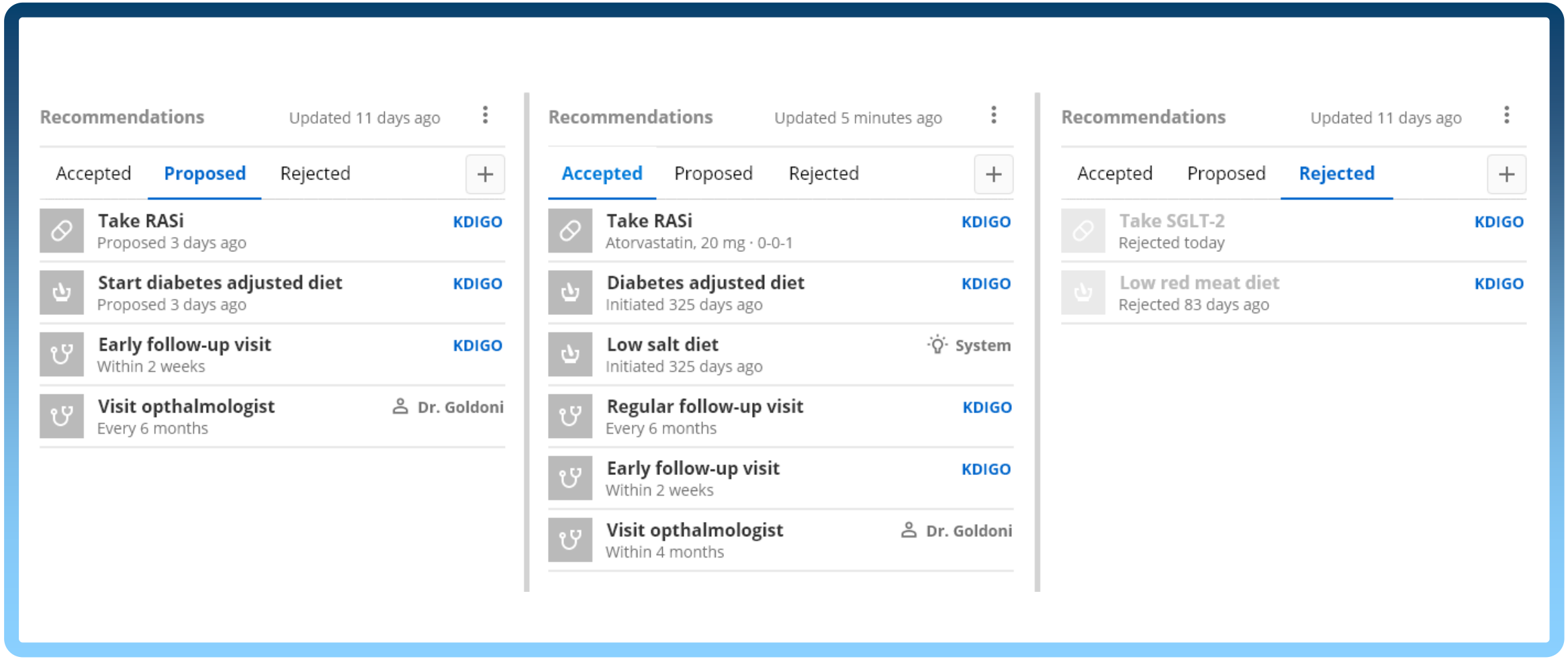
When applying the Klinrisk test, patients who are classified at the highest risk (≥30% risk over 5 years) had a 20-fold higher risk of the 40% decline in eGFR or kidney failure event at 5 years compared to those classified as low risk, and those classified as intermediate risk (10 – 30% risk over 5 years) had a 5-fold higher risk of the event at 5 years. This relationship is observed immediately and persists over the entire 5-year period.

- High risk
- Intermediate risk
- Low risk

Enabling Risk Based Care



Integrating risk based care into workflow



Summary

Accurate risk prediction tools can help physicians make better treatment decisions

For risk prediction in CKD – eGFR and albuminuria are essential and should be part of screening and ongoing management

Our disease progression models are entirely lab based and can be operationalized easily in labs or EMRs

All models only work when they are integrated in clinical workflow

Making risk visible