doi.org/10.58931/cpct.2025.3142

ABOUT THE AUTHOR

Navdeep Tangri, MD, PhD

Dr. Navdeep Tangri, MD, PhD, is working on a clinical research program that is also translational, focusing on the improvement of clinical decision making for patients with advanced chronic kidney disease. He developed and validated the Kidney Failure Risk Equation (KFRE) to predict the need for dialysis in patients with chronic kidney disease, and is currently engaged in multiple validation and implementation exercises to increase the uptake of the KFRE.

Affiliations: Department of Internal Medicine, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba
Chronic Disease Innovation Centre, Seven Oaks General Hospital, Winnipeg, Manitoba

Risk Prediction for Chronic Kidney Disease: Considerations for Primary Care

Navdeep Tangri, MD, PhD

Introduction

Chronic Kidney Disease (CKD) affects more than one in ten Canadians and is largely managed in primary care.[1] Diabetes is the leading cause of CKD, and primary care providers often manage the underlying causes and comorbid conditions related to kidney disease, as well as the adverse consequences of CKD itself.

It is important to recognize that CKD has a variable course. While most adults lose approximately 1 mL/min of kidney function every year after the age of 40, some patients lose kidney function rapidly, leading to hospitalizations due to heart failure and progression to kidney failure, whereas others remain stable for decades, requiring minimal additional intervention. Recent[2] advances in risk prediction for CKD allows all providers to accurately identify high risk individuals. These innovations enable the use of highly effective therapies that slow down, and in many cases, normalize the rate of kidney function loss, leading to potential lifetime risk reduction for kidney failure. **(Figure 1)**.

This review will cover key considerations in screening, risk stratification, and treatment of CKD in primary care, with an emphasis on tools that are readily available in clinical settings. We believe that a screen-triage-treat paradigm for CKD can lead to optimal outcomes for patients and health systems.

Screening

Mortality rates for kidney failure requiring dialysis exceed rates for Stage 3 colorectal cancer, yet there are no recommendations for universal CKD screening in Canada.[4] As such, current clinical guidelines recommend a case finding approach, which suggests screening with eGFR and albumiunuria (urine albumin to creatinine ratio) in certain groups at high risk of developing CKD.[5]

Guidelines from Diabetes Canada and global kidney disease guidelines strongly endorse screening individuals with diabetes for CKD with eGFR and albuminuria on an annual basis. Additional guidance recommends screening should be expanded to include adults with hypertension, cardiovascular disease, individuals with a strong family history (first degree relative with kidney failure), as well as high risk ethnic groups such as indigenous Canadians **(Figure 1)**.

In Canada, and in the United States, the rate

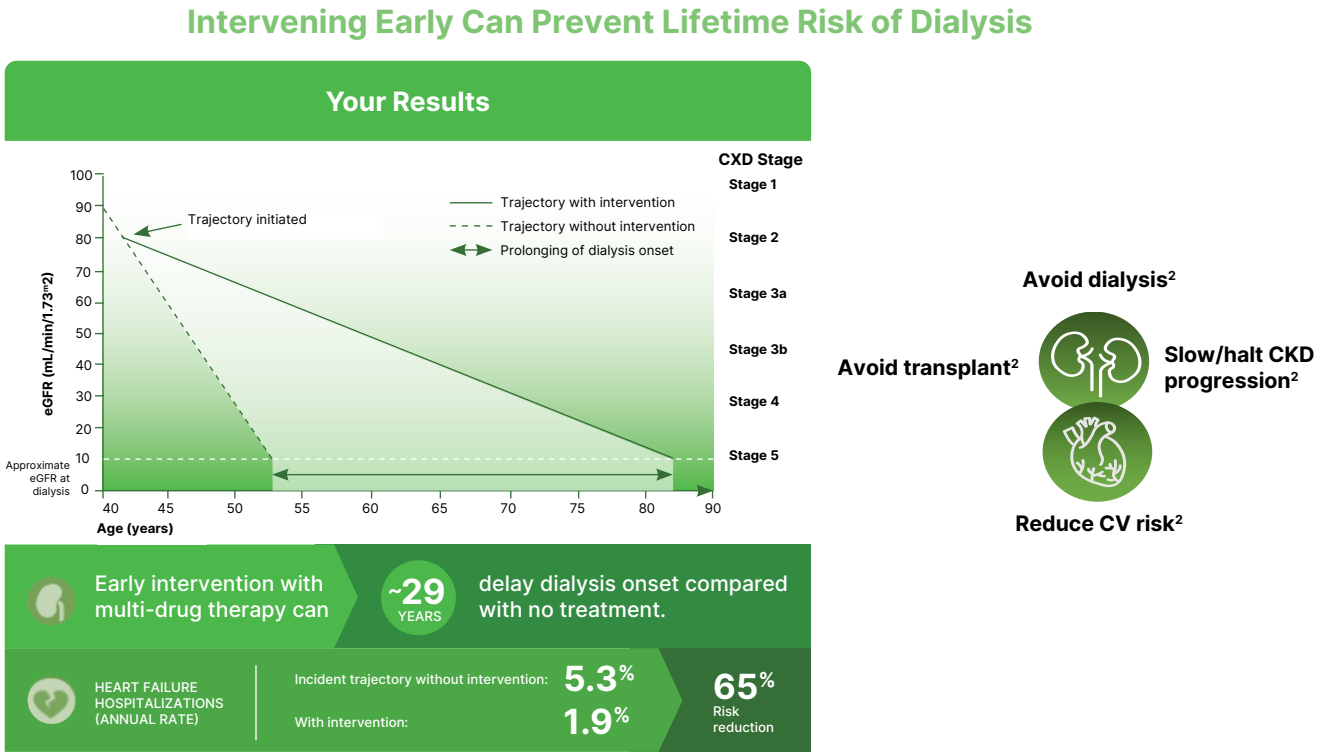

Figure 1. Benefits of early intervention in high risk patients with CKD (actearlyonkidney.com); *courtesy of Navdeep Tangri, MD, PhD*

of albuminuria testing, even among people with diabetes, remains below 50%, which suggests a major gap in implementing appropriate CKD screening.[6] We believe that automating processes, such as alerts in electronic medical records, and the addition of urine ACR into to routine annual bloodwork, can help close this gap in primary care.

Risk Stratification

It is now possible to estimate the risk of progression for all patients with CKD using routinely collected lab data. For patients in the later stages of disease (eGFR 15-60 ml/min), we developed the kidney failure risk equation (KFRE) to estimate the risk of dialysis or transplantation within the next 2-5 years.[7]

The KFRE was developed in patients from Ontario and originally validated in an independent sample of adults with CKD from British Columbia. Since the original publication in 2011, the KFRE has been validated in more than 30 countries involving 2 million individuals and has been used in more than 180 countries worldwide. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines and Diabetes Canada recommend it.[8]

The KFRE requires spot eGFR, urine ACR, age, and sex for calculation, without needing historical data or information on comorbid conditions or blood pressure. It can be automatically calculated in laboratory information systems and electronic medical records, and is included in all routine labs in Ontario, and in leading EMR software platforms, such as EPIC. Primary care providers can use the KFRE to determine the need for nephrology referrals (> 5 % risk in 5 years), as well as to counsel older adults who may have low risk CKD and do not need education or planning for dialysis.[9]

Risk Prediction for Earlier Stages of Disease

Awareness of CKD among both patients and physicians remains limited. As a result, most patients go undiagnosed and suboptimally treated until their eGFR falls below 45 mL/min, by which point more than half of kidney function is already lost. Furthermore,[10] the benefits of disease-modifying therapies for CKD progression are greatest when initiated earlier in the disease course, a stage when CKD goes unrecognized. To accurately identify patients at high risk of CKD progression at all stages of disease, we have

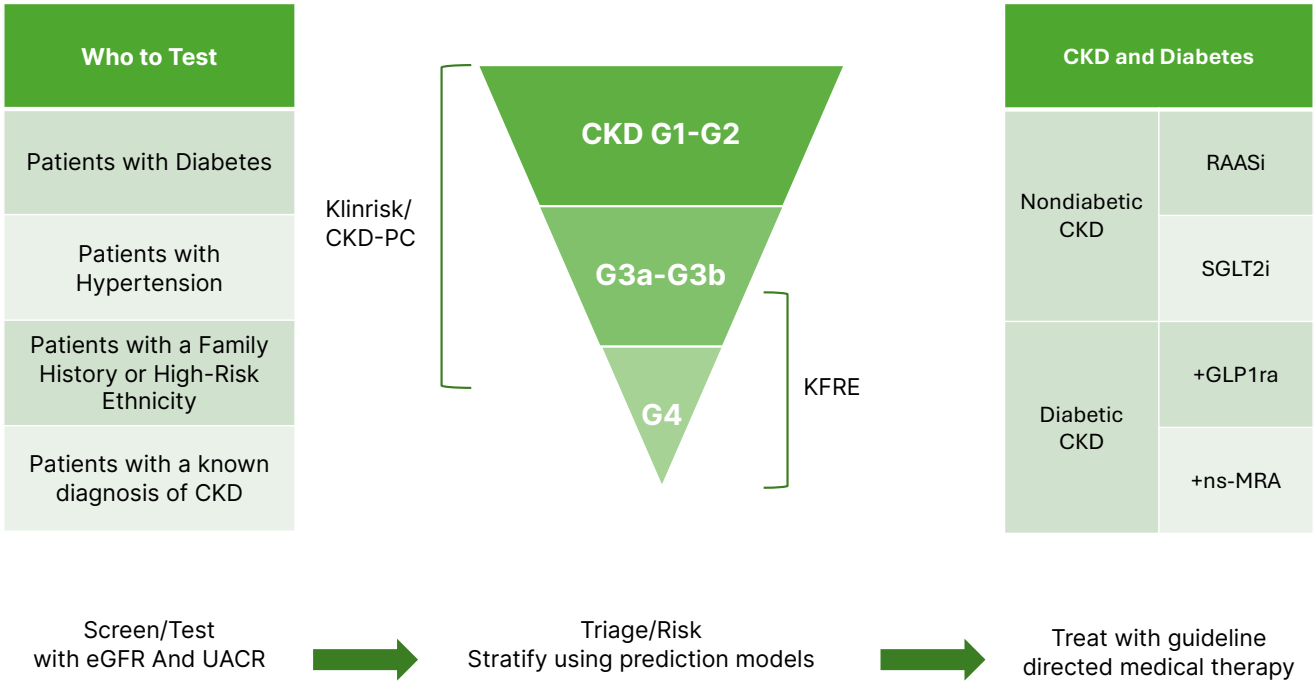

Figure 2. A screen, triage and treat paradigm for management of CKD in primary care; *courtesy of Navdeep Tangri, MD, PhD*

Abbreviations: CKD: chronic kidney disease; **GLP-1 RAs:** GLP-1 receptor agonists; **KFRE:** kidney failure risk equation; **ns-MRA:** Non-steroidal mineralocorticoid receptor antagonists; **RAASi:** Renin-angiotensin-aldosterone system inhibitors; **SGLT2i:** Sodium-Glucose Transport Protein 2 Inhibitors

developed highly accurate models that can be used in clinical care.

The Klinrisk models, which are machine learning based, use data from routine CBC, metabolic panels and urine ACR to predict the likelihood of CKD progression in the next 5 years. CKD progression is defined as a loss of 40% or more in kidney function, an outcome which has been validated as an appropriate surrogate for dialysis/kidney failure by regulatory bodies and is appropriate at any level of eGFR.[11]

These models were developed in Manitoba and Alberta and have subsequently been validated in clinical trial populations, as well as more than 6 million adults from Canada and the United States, with a wide range of age, underlying disease, and socioeconomic status. In the overall population, and in these subpopulations, the models have consistently showed excellent discrimination (AUC > 0.8) as well as good calibration/agreement between the predicted risk of event and the actual observed risk.[12-14]

Importantly, these models fill a key gap in care – by ensuring the appropriate blood and urine tests are ordered (CBC, metabolic panel, urine ACR), the interpretation is accurate (low, intermediate or high-risk CKD), and by connecting the tests to relevant clinical practice guidelines. The combination of these three key processes results in meaningful improvements in quality of care, focused on the patients with the highest need. In Ontario, these models are available through Lifelabs Inc., a leading provider of laboratory services.

In addition to these laboratory-based models, we developed models that use routinely collected demographic data and comorbid conditions that are freely available as an online risk calculator. These models (available from CKD-PC Models) use 14 routinely available variables, and predict the same outcome of CKD progression with good discrimination (AUC 0.74-0.77) in patients with or without diabetes.[15]

Using the Klinrisk or the CKD-PC models, primary care providers can identify patients who have intermediate or high-risk CKD at the point of care and take appropriate actions. Today, these actions can include the prescription of highly effective therapies that both slow CKD progression and address the underlying comorbid conditions **(Figure 2)**.

How Do We Approach Treatment in The 4 Drug Era By Delivering Risk-based Care

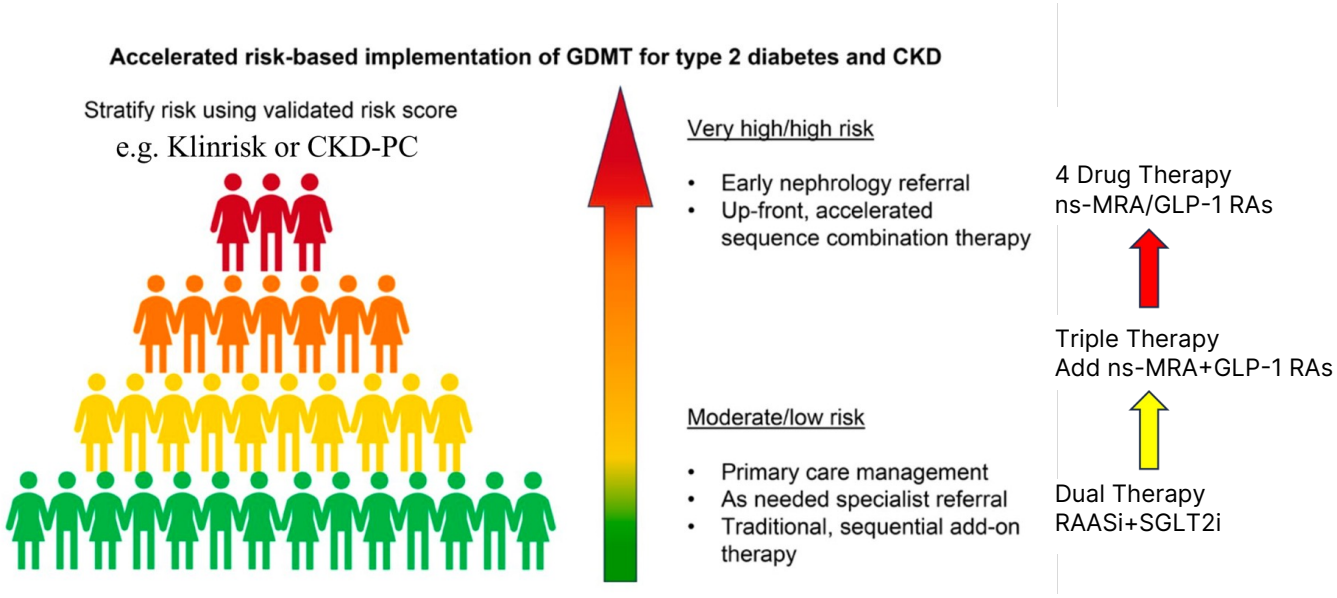

Figure 3. An approach to delivering risk based care; *Adapted from Neuen et al. Circulation 2024*

Abbreviations: CKD: chronic kidney disease; **GLP-1 RAs:** GLP-1 receptor agonists; **ns-MRA:** Non-steroidal mineralocorticoid receptor antagonists; **RAASi:** Renin-angiotensin-aldosterone system inhibitors; **SGLT2i:** Sodium-Glucose Transport Protein 2 Inhibitors

A Risk Based Treatment Paradigm

We now have access to four highly effective classes of treatment that slow CKD progression in patients with diabetes **(Figure 1)**. Trils of Non-steroidal mineralocorticoid receptor antagonists (ns-MRAs) and GLP-1 receptor agonists (GLP-1 RAs) for non-diabetic CKD patients are ongoing and will report findings in the next 12-24 months.

Primary care providers are very familiar with prescribing both Renin-angiotensin-aldosterone system inhibitors (RAASi) and Sodium-Glucose Transport Protein 2 Inhibitors (SGLT2i), but rates of SGLT2i use, particularly in those with non-diabetic kidney disease remain low. Our work, and work by others shows that the benefits of SGLT2i are independent of diabetes status, and that patients at all levels of risk have an improvement in their rate of kidney function decline with SGLT2i use. As such, we recommend that RAASi and SGLT2i be considered foundational therapy for all patients with CKD.

For patients with intermediate and high-risk disease, we believe that a risk-based care paradigm should be applied and can most effectively balance the benefits of additional therapy (GLP-1 RAs or ns-MRA) vs the risks of side effects, polypharmacy and costs. **(Figure 3)** For intermediate risk patients, the choice of ns-MRA vs GLP-1 RAs should be made on patient preferences regarding injection, body mass index, glyemic control and serum potassium.

For high risk patients, there is likely to be benefit for both cardiovascular and kidney events with use of GLP-1 RAs and ns-MRA. These patients typically lose ~ 3 mL/min/year even with RAASi and SGLT2i therapy, and additional treatment can further reduce albuminuria and risk, and potentially lower the risk of all cause death. Communication of risk including the use of visual aids **(Figure 3)** can help engage the patients in shared decision making and thereby improve initiation and reduce discontinuation of these highly effective therapies.

It is important to note that no data to date demonstrates any interactions between these therapies (SGLT2i, GLP-1 RAs, ns-MRA) with respect to safety and efficacy and physicians should assume that these treatments, with their independent mechanisms of action have additive effects on slowing the progression of disease. Nonetheless, the benefit is the largest in the patients at the highest risk of progression, further supporting the intensification of treatment in high risk individuals.

Summary

Of the more than 4 million Canadians with CKD, less than 500,000 receive care from a nephrologist. We believe that accurate and usable risk prediction tools like the KFRE and the Klinrisk model can enable primary care providers to deliver the same quality of care as a kidney specialist for the vast majority of patients with, or at risk for, CKD.

In addition, risk prediction tools can help engage the patient in their care journey, improve awareness and shared decision making, and also provide valuable reassurance to patients and families who may perceive CKD to be equivalent to kidney failure. Ultimately, a risk-based care paradigm will lead to more personalized care for this vulnerable population.

Correspondence

Navdeep Tangri, MD, PhD
Email: ntangri@sogh.mb.ca

Financial Disclosures

Consultancy: Prokidney Corp., PulseData Inc, Mesentech Inc., Marizyme, Roche; **Ownership Interest:** Prokidney Corp., PulseData Inc, Mesentech Inc., Marizyme, Klinrisk, Quanta; **Research Funding:** Astra Zeneca Inc., Tricida Inc, Janssen, Otsuka, BI-Lilly, Bayer, Roche; **Honoraria:** Astra Zeneca Inc., BI-Lilly, Bayer, Renibus; **Patents or Royalties:** Mar- izyme, Klinrisk; **Other Interests or Relationships:** National Kidney Foundation

References

1. Kitzler TM, Chun J. Understanding the current landscape of kidney disease in Canada to advance precision medicine guided personalized care. *Can J Kidney Health Dis*. 2023;10:20543581231154185. doi:10.1177/20543581231154185. PMID: 36798634; PMCID: PMC9926383.
2. Li L, Astor BC, Lewis J, Hu B, Appel LJ, Lipkowitz MS, et al. Longitudinal progression trajectory of GFR among patients with CKD. *Am J Kidney Dis*. 2012;59(4):504–12. doi:10.1053/j.ajkd.2011.12.009. PMID: 22284441; PMCID: PMC3312980.
3. Tangri N. Risk stratification to improve care and outcomes in diabetic kidney disease. *Can Diabetes Endocrinol Today*. 2024;2(1):5–10. Available from: https://canadiandiabetesandendocrinologytoday.com/article/view/2-1-Tangri
4. Naylor KL, Kim SJ, McArthur E, Garg AX, McCallum MK, Knoll GA. Mortality in incident maintenance dialysis patients versus incident solid organ cancer patients: a population-based cohort. *Am J Kidney Dis*. 2019;73(6):765–76. doi:10.1053/j.ajkd.2018.12.011. PMID: 30738630.
5. Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes Canada 2018 clinical practice guidelines for the prevention and management of diabetes in Canada. *Can J Diabetes*. 2018;42(Suppl 1):S1–S325.
6. Chu CD, Xia F, Du Y, et al. Estimated prevalence and testing for albuminuria in US adults at risk for chronic kidney disease. *JAMA Netw Open*. 2023;6(7):e2326230. doi:10.1001/jamanetworkopen.2023.26230.
7. Tangri N, Stevens LA, Griffith J, Tighiouart H, Djurdjev O, Naimark D, et al. A predictive model for progression of chronic kidney disease to kidney failure. *JAMA*. 2011;305(15):1553–9. doi:10.1001/jama.2011.451. PMID: 21482743.
8. Tangri N, Grams ME, Levey AS, et al. Multinational assessment of accuracy of equations for predicting risk of kidney failure: a meta-analysis. *JAMA*. 2016;315(2):164–74. doi:10.1001/jama.2015.18202.
9. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int*. 2024;105(4S):S117–S314. doi:10.1016/j.kint.2023.10.018. PMID: 38490803.
10. Chu CD, Chen MH, McCulloch CE, Powe NR, Estrella MM, Shlipak MG, et al. Patient awareness of CKD: a systematic review and meta-analysis of patient-oriented questions and study setting. *Kidney Med*. 2021;3(4):576–85.e1. doi:10.1016/j.xkme.2021.03.014. PMID: 34401725; PMCID: PMC8350814.
11. Ferguson T, Ravani P, Sood MM, Clarke A, Komenda P, Rigatto C, Tangri N. Development and external validation of a machine learning model for progression of CKD. *Kidney Int Rep*. 2022;7(8):1772–81. doi:10.1016/j.ekir.2022.05.004.
12. Tangri N, Ferguson T, Leon SJ, Anker SD, Filippatos G, Pitt B, et al. Validation of the Klinrisk chronic kidney disease progression model in the FIDELITY population. *Clin Kidney J*. 2024;17(4):sfae052. doi:10.1093/ckj/sfae052. PMID: 38650758; PMCID: PMC11033844.
13. Tangri N, Ferguson TW, Bamforth RJ, Leon SJ, Arnott C, Mahaffey KW, et al. Machine learning for prediction of chronic kidney disease progression: validation of the Klinrisk model in the CANVAS Program and CREDENCE trial. *Diabetes Obes Metab*. 2024;26(8):3371–80. doi:10.1111/dom.15678. PMID: 38807510.
14. Boehringer Ingelheim, Carelon Research. Novel AI-driven model validated to predict risk of chronic kidney disease progression in large U.S. study [Internet]. PR Newswire; 2023 Nov 4 [cited 2025 May 13]. Available from: https://www.prnewswire.com/news-releases/novel-ai-driven-model-validated-to-predict-risk-of-chronic-kidney-disease-progression-in-large-us-study-301977580.html
15. Grams ME, Brunskill NJ, Ballew SH, Sang Y, Coresh J, Matsushita K, et al. Development and validation of prediction models of adverse kidney outcomes in the population with and without diabetes. *Diabetes Care*. 2022;45(9):2055–63. doi:10.2337/dc22-0698.