CHANGE THE FUTURE:

SAVING LIVES BY BETTER DETECTING DIABETES-RELATED KIDNEY DISEASE

Rodney Kwok
Professor Richard MacIsaac
Professor Elif Ekinci

diabetesaustralia.com.au

diabetes australia

Contents

Acknowledgements

This report

Diabetes Australia commissioned the Australian Centre for Accelerating Diabetes Innovations Research Centre to develop this report on the impact of diabetes-related kidney disease on Australia and to outline some potential options for a diabetes-related kidney disease screening that would reduce the impact of the epidemic. Diabetes Australia staff and its network of expert diabetes researchers and health professionals provided key insights and feedback to assist with the development of this report. This initiative has been supported with an educational grant from Bayer Australia Ltd.

About Diabetes Australia

Diabetes Australia is dedicated to reducing the incidence and impact of diabetes on people, health systems and society. Diabetes Australia works with people living with, or at risk of, diabetes, their families and carers, health professionals, researchers, funders, other diabetes organisations and the community to positively change people's lives.

About the Australian Centre for Accelerating Diabetes Innovations Research

The Australian Centre for Accelerating Diabetes Innovations (ACADI) Research Centre was established through Medical Research Future Fund funding from the Australian Government's Targeted Translation Research Accelerator (TTRA) program, delivered by MTPConnect. ACADI is a virtual collaborative diabetes centre uniting over 70 partners and supporters spanning all Australian States and Territories and four international sites. Its purpose is to deliver novel interventions for timely diagnosis, prevention and treatment of diabetes and its complications.

ACADI
Australian Centre for Accelerating Diabetes Innovations

Professor Elif Ekinci is the Director of ACADI. ACADI headquarters is at the University of Melbourne, Australia.

Suggested citation: Kwok, R, MacIsaac, R, and Ekinci, E. (2023) *Change the Future: Saving Lives By Better Detecting Diabetes-related kidney disease*. Diabetes Australia, Australia.

Diabetes Australia acknowledges the Traditional Owners of the lands on which we live and work. We recognise their connection to land, waters and culture. We pay the upmost respect to them, their cultures and to their Elders past and present. We recognise that Australia is made up of hundreds of different Aboriginal and Torres Strait Islander peoples, each with their own culture, language and belief systems. Their relationship with country remains of utmost importance as it is the foundation for culture, family and kinships, song lines and languages.

Foreword

Diabetes-related kidney disease is one of the most widespread and, potentially most debilitating and costly, diabetes complications. An estimated 330,000 Australians living with diabetes have chronic kidney disease. Around 10,000 people in this cohort will experience kidney failure and require dialysis or a kidney transplant. This is about 37% of the total number of people experiencing kidney failure. This report estimates diabetes-related kidney disease costs the Australian economy around $2.68B a year. Kidney failure accounts for around $1.9B of this. This has a huge impact on hospital capacity as people living with diabetes requiring dialysis account for around 5% of all hospitalisations.

However, much of this is preventable. Early detection can help slow or prevent most kidney disease. Unfortunately, less than one in four Australians living with diabetes are getting their kidneys checked within recommended timeframes – we want to change this. Several factors contribute to this including the complexity of the checks, the overall challenges of living with diabetes and a low level of awareness about chronic kidney disease. We need to make kidney checks an easier, routine part of life for people living with diabetes.

Australia has one of the world's best health systems. Most of the health infrastructure needed to build a national diabetes-related kidney disease screening program is already in place. Firstly, the National Diabetes Services Scheme (NDSS), delivered by Diabetes Australia on behalf of the Australian Government, is a world-leading diabetes self-management support and services scheme. Utilising the existing NDSS database to support a recall and reminder system could significantly increase the number of people getting kidney checks. We have highly qualified specialists and well-trained primary care providers, evidence-based guidelines and effective medicines available

on the Pharmaceutical Benefits Scheme to prevent kidney disease or delay its progression. This puts Australia in an enviable position.

Australia already delivers disease screening and awareness programs, utlising central databases to contact and mobilise people at risk of health conditions, that we can learn from and build on including KeepSight, Diabetes Australia's national diabetes eye check recall and reminder program. Other examples include the National Bowel Cancer Screening Program and the National Cervical Cancer Screening Program.

International research and local modelling from Kidney Health Australia demonstrate the cost-effectiveness of diabetes-related kidney disease screening. People living with diabetes and kidney failure account for 70% of the cost burden. If we could prevent even 30% of people from progressing to kidney failure it would have huge benefits for Australians and our health system. The time for action and to drive change is now.

Together we can improve quality of life, save lives and reduce the impact of diabetes. It's time to unite in the fight to change rates of preventable diabetes-related kidney disease.

Justine Cain
Diabetes Australia Group CEO

DIABETES-RELATED KIDNEY DISEASE IMPACT

PEOPLE

1.5M
living with all types of diabetes[1]

330K
living with diabetes and chronic kidney disease[2]

1.1M
not getting their kidneys checked within recommended time frames[3]

5x
Aboriginal and Torres Strait Islander people are more likely to live with kidney failure[4]

8.7M
hours people living with diabetes spent in dialysis every year

2,024
number of people dying from kidney disease[6]

COMPLICATIONS EVERY YEAR

710K
admissions to hospital for dialysis[5]

324
people living with diabetes undergoing kidney transplants[7]

256K
other kidney-related hospital admissions[6]

10,249
people living with diabetes undergoing kidney replacement therapy[8]

25%
of people living with diabetes and chronic kidney disease will experience depression[9]

ANNUAL COST

$2.68B
diabetes-related kidney disease[10]

$1.9B
diabetes-related kidney replacement therapy[10]

$788K
early-stage kidney disease[10]

$182K
kidney failure per person[8]

$500M
in savings from the early detection of kidney disease[8]

A funded **Diabetes Kidney Disease Screening Program** and access to effective medicines will help **reduce the impact** of diabetes-related kidney disease on the **1.5 million Australians** living with diabetes.

1. National Diabetes Services Scheme 2023, National Diabetes Services Scheme data snapshot – March 2023, viewed 19 June 2023, https://www.ndss.com.au/wp-content/uploads/ndss-data-snapshot-202303-all-types-diabetes.pdf
2. Kidney Health Australia. (2019). Make the Link: Diabetes, Kidneys, and Heart. Executive Summary. Retrieved from https://kidney.org.au/uploads/resources/KHA-Executive-Summary-Make-the-Link-Diabetes-Kidneys-and-Heart.pdf
3. Colagiuri, S. et al. (2018) Burden of Diabetes in Australia: It's Time for More Action. rep. Sydney, NSW. Living with Chronic Kidney disease.
4. Maple-Brown LJ, Hughes JT, Ritte R, Barzi F, Hoy WE, Lawton PD, et al. Progression of Kidney Disease in Indigenous Australians: The eGFR Follow-up Study. Clin J Am Soc Nephrol. 2016;11(6):993-1004.
5. Australian Institute of Health and Welfare (2023) Diabetes: Australian Facts, AIHW, Australian Government, accessed 11 June 2023.
6. Australian Institute of Health and Welfare (2023) Chronic kidney disease: Australian facts, AIHW, Australian Government, accessed 11 June 2023.
7. Australia and New Zealand Dialysis and Transplant Registry. Dialysis and Kidney Transplantation in Australia 2021 Summary. 2022.
8. Deloitte Access Economics, Changing the chronic kidney disease landscape: The economic benefits of early detection and treatment (report commissioned by Kidney Health Australia, February 2023).
9. Kidney Health Australia. Transforming Australia's kidney health: A call to action for early detection and treatment of chronic kidney disease. Kidney Health Australia; 2023.
10. Diabetes Australia analysis.

Diabetes and diabetic kidney disease

The diabetes epidemic is one of the most complex health care challenges globally. Worldwide more than 537 million people are living with diabetes, including 1.5 million Australians.[1] These numbers are forecast to double by 2045, leading to 1,074 million people living with diabetes worldwide.

Diabetes can lead to life-threatening complications such as chronic kidney disease which leads to dialysis and kidney transplantation. This type of chronic kidney disease is called diabetic kidney disease or diabetic nephropathy because it is directly caused by diabetes.[2] Globally, diabetic kidney disease is the leading cause of kidney failure in most countries and accounts for 50% of all chronic kidney disease and end-stage kidney disease cases.[3]

While it is known that high glucose levels in the blood, coupled with other risk factors for a sustained period of time, can damage the small blood vessels in the kidneys, the exact mechanisms that lead to diabetic kidney disease are still not fully understood.

In the early stages, chronic kidney disease is asymptomatic but, if detected early, treatments and lifestyle changes can slow or halt the progression of the condition. As the condition progresses, its impacts on a person become much more serious and kidney damage is often irreversible.

There is an urgent need for effective screening and management of kidney disease in people with diabetes to support early detection when treatments are most effective. This would help prevent the progression of kidney disease to kidney failure requiring dialysis and transplantation.

Diabetic kidney disease in Australia

In Australia, around 330,000 people living with diabetes have chronic kidney disease.[4] This is approximately 22% - 25% of Australians living with diabetes.[5]

Dialysis, the most common treatment for kidney failure, is the most frequent source of hospitalisation in Australia accounting for around 14% of all hospitalisations.[6] Diabetes Australia estimates dialysis to support people living with diabetes-related kidney disease accounts for around 5% of all hospitalisations in Australia.

In 2020, diabetes was an underlying or associated cause of death in 2024 people living with chronic kidney disease in Australia.[6]

These numbers are expected to rise due to the increasing prevalence of type 2 diabetes and the strong association between type 2 diabetes and diabetic kidney disease.[7] One report estimates the number of Australians living with kidney failure is expected to increase by 42% by 2030.[8]

More than 14% of all Australian hospitalisations are people requiring dialysis.

Aboriginal and Torres Strait Islander people with diabetes

The social determinants of health including access to healthcare and medications, food insecurity, significant cultural losses and dispossession, racial discrimination and other ongoing effects of colonisation contribute to suboptimal diabetes management in Aboriginal and Torres Strait Islander people.[9,10]

Aboriginal and Torres Strait Islander Australians are more likely to develop type 2 diabetes and much more likely to develop complications such as chronic kidney disease when compared to non-Indigenous populations.[11]

According to the Australian Institute of Health and Welfare (AIHW), between 2018-2019, 65,284 Aboriginal and Torres Strait Islander adults self-reported having diabetes; however, the actual number of people living with diabetes is likely to be significantly higher. Over this period, diabetes led to more than 157,282 hospitalisations.

Aboriginal and Torres Strait Islander people living with diabetes are five times more likely to be living with kidney failure compared to other Australians. The overall burden of disease including social and economic factors is around 7.8 times higher in Aboriginal and Torres Strait Islander Australians compared with the non-Indigenous population.[11]

It has also been noted that Aboriginal and Torres Strait Islander Australians living in remote areas are more likely to need treatment for kidney failure which is reflected in the higher hospitalisation rates.

> My little granddaughter came to me and started crying. 'I don't want you to die, *DaTo* (Grandad). Please.' That was the moment that changed me. I really don't want to leave my grandies behind. I have eight children, 28 grandchildren, and three great-grandchildren. They are very beautiful, each one. God has been very good to me.

Jaffa
Torres Strait Islander,
lives with type 2 diabetes

Aboriginal and Torres Strait Islander people are up to four times more likely to die from chronic kidney disease.

Diabetic kidney disease leading to kidney failure

Diabetic kidney disease is the most common cause of kidney failure in Western and high-income Asian countries. It accounts for 40% of individuals receiving kidney replacement therapies.[12,13,14,15]

Kidney failure is defined as permanent kidney damage requiring dialysis or transplantation.[16] The Kidney Disease: Improving Global Outcomes (KDIGO) classifies kidney failure under stage 5 of chronic kidney disease classification whereby individuals have an estimated glomerular filtration rate less than 15 ml/min/1.73m^2 or individuals who require dialysis irrespective of their glomerular filtration rate.[14]

The reasons for the development of diabetic kidney disease are not fully understood. It is commonly believed that the progression of kidney failure in diabetes is due to a combination of metabolic and haemodynamic factors.[17] Additionally, studies have also demonstrated that inflammation caused by diabetes can lead to direct or indirect kidney damage. Inflammation can increase the amount of white blood cells and inflammatory markers in the kidneys and thus, increase kidney damage.[18,19]

Stages of CKD	Things to look out for
Stage 1	• Early-stage kidney disease • No obvious signs of kidney failure • Speak to doctor if unsure
Stage 2	• Early-stage kidney disease • No obvious signs of kidney failure • Speak to doctor if unsure
Stage 3	• Onset of kidney damage • Kidney disease most likely diagnosed • Will feel unwell due to high blood pressure and more waste in the body
Stage 4	• Severe kidney damage • Potential swelling in hands and feet and lower back pain • Likely develop other complications such as cardiovascular disease, bone disease and anaemia
Stage 5	• Kidney failure • Will require dialysis and transplantation

A lower proportion of people living with type 2 diabetes will progress to kidney failure compared with people living with type 1 diabetes.[20,21] This can be attributed to the different baseline characteristics such as age and onset of diabetes, duration of the disease, as well as the severity of other comorbid diseases.[21] Therefore, the main objective of current guidelines is to promote clinical care that aims to slow the progression of diabetic kidney disease to kidney failure. This will reduce diabetic kidney disease-related morbidity and mortality.

The treatments for kidney failure, including dialysis and kidney transplantation, are extremely expensive. However, without these treatments people living with kidney failure will die. Although only around 0.03% of people in developed countries live with kidney failure, treatments for it account for around 2% of the annual health-care budget. Currently, there are more than 2 million people worldwide receiving these therapies.[12,13,14,15]

> About 17 years ago, a doctor in emergency gave me five years to live if I didn't change my life. That was the wake-up call for me. I started to do things better. But unfortunately, the disease had set in so much that you can't reverse damage to the organs. You can't reverse heart and kidney damage.

Joseph
Lives with type 2 diabetes

Dialysis has a huge personal cost

5 hours a day

15 hours a week

60 hours a month

780 hours a year

Cost of diabetic kidney disease in Australia

Diabetic kidney disease is associated with a high personal and economic burden in Australia. A recent report produced by Deloitte Access Economics for Kidney Health Australia estimated the annual cost of total kidney disease at around $9.9B per annum, almost one quarter of this (23.6%) or $2.3B is the cost to the Australian health system.[8] This equates to an average per person cost of $4,800 per annum.

Studies have demonstrated that the cost of managing chronic kidney disease and diabetes is drastically greater than managing only chronic kidney disease.[22] There is a 70% higher individual cost relating to managing the condition and 56% longer length of hospital stays for people living with diabetes and chronic kidney disease compared with people who are living with chronic kidney disease without diabetes.[23,24] This is because a greater proportion of people living with diabetes will progress to kidney failure.

The Deloitte Access Economics report found the cost of providing kidney replacement therapy to treat kidney failure was about $182,000 per person per annum.[8] More than a third (37%) of the 27,700 Australians receiving kidney replacement therapy are living with diabetes.[25]

A similar analysis in the United States also demonstrates the escalating cost impact of chronic kidney disease as it progresses. It found the average cost per person per year for someone in stages 0-2 was approximately US$4,569, whereas for someone with stage 3 CKD, it increased to US$12,617 and jumped to US$33,162 for people living with stage 4 CKD.[26] This clearly highlights the economic benefit of early detection and intervention to prevent or delay the progression of diabetes-related CKD.

Based on available data Diabetes Australia estimates diabetes-related kidney disease costs Australia approximately $2.68B per annum. This includes $1.9B for people receiving kidney replacement therapy and $788M for people with early-stage kidney disease. People receiving kidney replacement therapy account for about 3.7% of people living with diabetes-related kidney disease but account for around 70% of the cost burden.

A significant amount of kidney failure can be prevented if detected early when treatments are most effective. Investment in early detection of chronic kidney disease in Australia could generate savings of $10.2B over 20 years. This equates to a return of around $45 for every $1 invested in early detection.[8]

Diabetes-related kidney disease costs Australia around $2.68 billion a year.

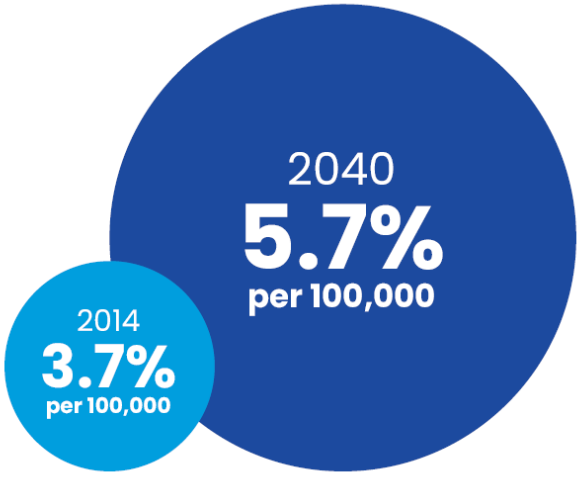
Impact on hospitals

Diabetes-related kidney disease has a major impact on Australia's hospital system.

Dialysis, the most common treatment for kidney failure, is the leading cause of hospitalisation in Australia accounting for around 14% of all hospitalisations. In Australia in 2020-21 there were 1,617,723 dialysis-related hospitalisations.[5] An estimated 598,000 of these involved people living with diabetes. That means around 5% of all hospitalisations in Australia are for dialysis to treat people living with diabetes-related kidney disease.

The number of all dialysis-related admissions has increased from 1,184,000 in 2010-11, which is an increase of 36.6% to 2020-21.[27] This is part of a longer-term trend. In 2006-07 there were 943,000 dialysis-related admissions, which shows they have increased by more than 70% to 2020-21.[28] The number of dialysis-related admissions, as a percentage of total hospital admissions, has increased by about 6% since 2006-07.

Worrying, this trend is expected to increase in the future with a recent study projecting an increase in kidney failure from 3.7 per 100,000 in 2014 to 5.7 by 2040, an increase of more than 45%.[29]



It is projected that more than 3.1 million people will be living with diabetes in Australia by 2050.[30] If roughly 30% of these people develop diabetic kidney disease, 930,000 people will be living with diabetic kidney disease by 2050, an increase of around 181%. Consequently, the health care expenditure to manage and treat diabetic kidney disease will ultimately increase.

5% of all hospitalisations in Australia are for dialysis for people living with diabetes.

Dialysis

Dialysis removes waste products and excess fluid from a person's blood. There are two main types of dialysis: haemodialysis and peritoneal.

Once dialysis is commenced, it must be continued until a kidney transplant is performed or, in cases where a kidney transplant is not possible, it is continued indefinitely.[31] Without dialysis people with kidney failure will die rapidly.

Haemodialysis

Haemodialysis is the most common and well-known type of dialysis.

This procedure requires a tube with a needle attached to a patient's arm drawing blood into an external machine. The machine filters and cleans out the waste products and excess fluid before passing it back into the body through another tube in the arm.

The major drawback with haemodialysis is the time required for the procedure. A typical dialysis

schedule requires a patient attending a hospital or health care service for three to four sessions a week with each session taking around four hours. This equates to around 60 hours a month where a person is connected to the dialysis machine.

Peritoneal dialysis

Peritoneal dialysis is the other major type of dialysis. It can be done at home.

It involves a tube connected to the lining of the abdomen and dialysis fluid is used to absorb waste and extra fluid from the body. A few hours later, the solution and the collected waste is drained out of the same tube into an empty bag and can be thrown away easily. The flexibility of being able to do the procedure at home is increasing its popularity.

Emotional health impact of dialysis

A study exploring the experiences and expectations of patients who have recently started dialysis found many experienced loss of independence, disruption of daily life and loss of time. As it was the only option available to survive, many did not view dialysis as a choice.[32]

In addition to the personal impact, dialysis is very expensive. The per person cost to the health system can range from $76,000 per annum or up to $150,000 per annum depending on factors such as remoteness and ease of access.[8]

Furthermore, dialysis not only affects the patients' quality of life but also the caregivers' quality of life. For instance, a Japanese study found that both people receiving dialysis and their carers experienced poorer mental health outcomes than the general population.[33]

Kidney transplantation

The other primary treatment for kidney failure is kidney transplantation. The procedure and post-surgery medications are demanding on the recipient's body and unfortunately many people are unsuitable for transplantation.

In Australia, an individual can receive transplantation from a deceased or living donor. Waiting lists to receive a transplantation can vary between 2.5 to 7 years, unless a kidney is donated by a relative/living donor.[33]

According to the AIHW the average cost of kidney transplantation in the public hospital system is about $81,000.[28] This includes the cost of the surgery, patient's hospital stay and post-transplant medications.

> Dialysis was my life. That's what it felt like, day in, day out. But a kidney transplant in 2007 changed my life. It feels fantastic. But I can never speak of the transplant without thinking of the family who donated their loved one's organs for me to have the operation.

Brad
Double amputee, lived with type 1 diabetes before kidney and pancreas transplant

Measurement of kidney function

The primary methods of determining a person's kidney health function are the measurement of their glomerular filtration rate (GFR) and the presence of albumin (a type of protein) in the urine. A combination of both tests is considered the best available method to screen for and diagnose diabetic kidney disease.

Glomerular filtration rate

The GFR indicates how well a person's kidneys are filtering or working to remove waste products from the circulation. It can be provided from routine pathology reports when a person has a blood test. People who develop a very low GFR will progress to kidney replacement therapy (dialysis or kidney transplantation). Although direct measurements of GFR using clearance of markers take time and require invasive procedures, these would be considered as the "gold standards" of direct kidney function measurements. In routine clinical practice, equations which estimate kidney function (based on a serum marker cleared by the kidneys called creatinine) are used to calculate an estimated glomerular filtration rate (eGFR).[55] However, there have been concerns about the accuracy of these estimating equations in people living with diabetes, especially in people with relatively preserved kidney function.[34,35] It is important to remember that the above equations are not direct measurements of GFR; they can only provide estimates.

Albuminuria

The presence of the protein albumin in urine (albuminuria) should be regularly measured in people with diabetes to determine if there is kidney damage. High albuminuria is a sign of kidney damage.[36] However, levels of albuminuria do not always reflect the filtering power of the kidneys (i.e., GFR).[37]

Urinary albumin levels can be categorised into three groups – micro-albuminuria, macro-albuminuria, and normo-albuminuria, also referred to as chronic kidney disease categories A1, A2, and A3 respectively, to measure severity of kidney disease (*Figure 1*).[15] The level of albumin in the urine is also an important risk marker for cardiovascular disease in people with diabetes.

It is recommended people with diabetes provide the first morning urine sample of albuminuria but this is often either overlooked or impractical. Urinary albumin levels also have a high degree of day-to-day variability so if an abnormal albumin creatinine ratio value is detected, additional tests should be performed over the next three months. At least two out of three measurements should be abnormal before the presence of 'albuminuria' can be diagnosed. Additional, sex-specific cut-offs for albuminuria which are either not reported or vary depending on the pathology lab can confuse clinicians.[38]

In clinical practice, an early morning spot urine sample is typically sent off to measure for albuminuria at a pathology laboratory and the report comes back as a ratio of albumin to creatinine in the urine. Sometimes timed urine collections, typically over a 24-hour period, to measure the excretion rate of albumin (mcg per min or mg per 24 hours) are also used. These timed collections have traditionally been considered as the gold standard methods for assessing albuminuria but have generally been replaced by spot urine collections for ease and convenience.

Dip stick tests of urine lack sufficient sensitivity and specificity to optimally detect and measure the amount of albumin in the urine. Many people may progress through the stages of diabetic kidney disease without albuminuria.[39]

Table and figures.

GFR categories (ml/min/1.73m^2)	Albuminuria Categories (mg/mmol)		
	Normo-albuminuria (A1) <3.39	**Micro-albuminuria (A2)** 3.39 – 33.9	**Macro-albuminuria (A3)** >33.9
Normal (≥ 90)	**Screen**	**Treat**	**Treat and refer**
Mildly decreased (60 – 89)	**Screen**	**Treat**	**Treat and refer**
Mildly to Moderately decreased (49 – 59)	**Treat**	**Treat**	**Treat and refer**
Moderately to Severely decreased (30 – 44)	**Treat**	**Treat and refer**	**Treat and refer**
Severely decreased (15 – 29)	**Treat and refer**	**Treat and refer**	**Treat and refer**
Kidney failure (<15)	**Treat and refer**	**Treat and refer**	**Treat and refer**

Low Risk **High risk**

Moderate risk **Very high risk**

Albuminuria testing

A recent study reported that measurement of albuminuria is currently performed in only a small proportion of people with type 2 diabetes.[34] In one registry of patients, the Centre for Kidney Disease Research, Education and Hope at UCLA, only 8.7% of people with type 2 diabetes had completed an albuminuria check.

This lack of testing has also been highlighted in a global study including participants with diabetes from Australia where only 35.1% of patients had an albumin creatinine ratio test during the two-year period of this study.[40] Another study found only 27% of Australians living with diabetes had received an albuminuria test in the past 12 months.[41]

Low rates of screening

This low prevalence of albumin to creatinine ratio testing may be due to lack of awareness among people with diabetes and health practitioners regarding the importance of having regular urinary albuminuria tests. The practical inconvenience of providing a urine sample is another barrier that health professionals and people living with diabetes need to overcome. Often facilities at local clinics may not be designed or have simple protocols in place for a straightforward collection of urine samples. Thus, this inconvenience and the inefficient procedures make it harder for people with diabetes providing a urine sample.[37]

Another challenge is that kidney disease often develops asymptomatically. It is estimated that up to 90% of kidney function can be lost before symptoms become apparent.

Low awareness

A European survey found that 91% of respondents were experiencing symptoms for more than two months before their diagnosis, while 38% experienced symptoms for more than six months.[42] The same survey found almost one in five (18%) knew nothing about chronic kidney disease prior to their diagnosis while 36% had heard of chronic kidney disease but did not know anything about it.

An unpublished Australian survey of more than 1000 people living with type 2 diabetes found that less than half (47%) were aware that chronic kidney disease was a complication of the condition. There was also a low level of awareness about what chronic kidney disease is with more than a third (39.4%) saying they did not know or were unsure of what CKD was. Alarmingly, 70.3% were not very concerned about developing diabetes-related chronic disease.

Only 47% of people living with type 2 diabetes were aware of their risk of chronic kidney disease.

Risks associated with diabetic kidney disease

Although global guidelines are in place to detect and manage diabetic kidney disease, this condition is often high risk and can progress to permanent kidney failure.[14] It can also contribute to the development of other chronic diseases such as cardiovascular disease.[43] People living with diabetes, both with and without chronic kidney disease, are at a significantly higher risk of adverse cardiovascular events.

However, the risk of cardiovascular events such as heart attacks, strokes and cardiovascular death is greatest when both chronic kidney disease and diabetes are present.[15, 44] An estimated 213,000 Australians are living with all three conditions.[45] Cardiovascular disease can compound the disease burden and the social and economic burden already associated with diabetic kidney disease and further impact an individual's quality of life and increase the strain on the health system.

Psychosocial and emotional impact

Diabetic kidney disease increases a person's risk of developing mental and emotional health challenges including depression and anxiety.[46]

Kidney Health Australia reports almost 25% of people living with chronic kidney disease and 50% of people on dialysis will experience depression.[47] A study conducted in Tasmania has identified that depression may be an independent predictor for both mortality and morbidity in people living with chronic kidney disease before receiving any kidney replacement therapies.[42] A European study of people living with chronic kidney disease found that the experience of diagnosis caused more than one in three people to feel anxious (42%), scared (41%), stressed (36%) or depressed (36%).[48] The same study found the leading psychosocial impacts of a diagnosis with chronic kidney disease included concerns about losing independence, becoming a burden to family and friends and concerns about the ability to travel.

> I felt overwhelmed and scared when I was diagnosed with kidney disease. I was horrified at the prospect of needing dialysis due to my needle phobia and having had a fit on the one occasion I tried to donate blood. I really felt I would not be able to cope emotionally.
>
> 
>
> **Maire**
> Lives with type 1 diabetes

Additionally, there is a social and psychological burden associated with maintaining the multiple interventions required to delay the start and progression of diabetic kidney disease and to minimise the risk of developing co-occurring diseases.[49]

Diabetic kidney disease can also negatively affect a person's quality of life by reducing their immune function and physical performance, changing their appetite, affecting their memory and lead to fluid build-up which results in life-threatening abnormalities in blood chemistry and can affect bone structure and increase the risk of fractures.[50]

Management of diabetic kidney disease

Effective management of diabetic kidney disease involves multiple interventions to address the risk factors driving its progression. Interventions include:

- Lifestyle management (increased physical activity, diet modification and smoking cessation)
- Blood glucose management
- Lipid and blood pressure management
- Use of medications.

The combination of these treatments can slow the development and progression of diabetic kidney disease for people with type 1 or type 2 diabetes particularly in the earlier stages of the disease.

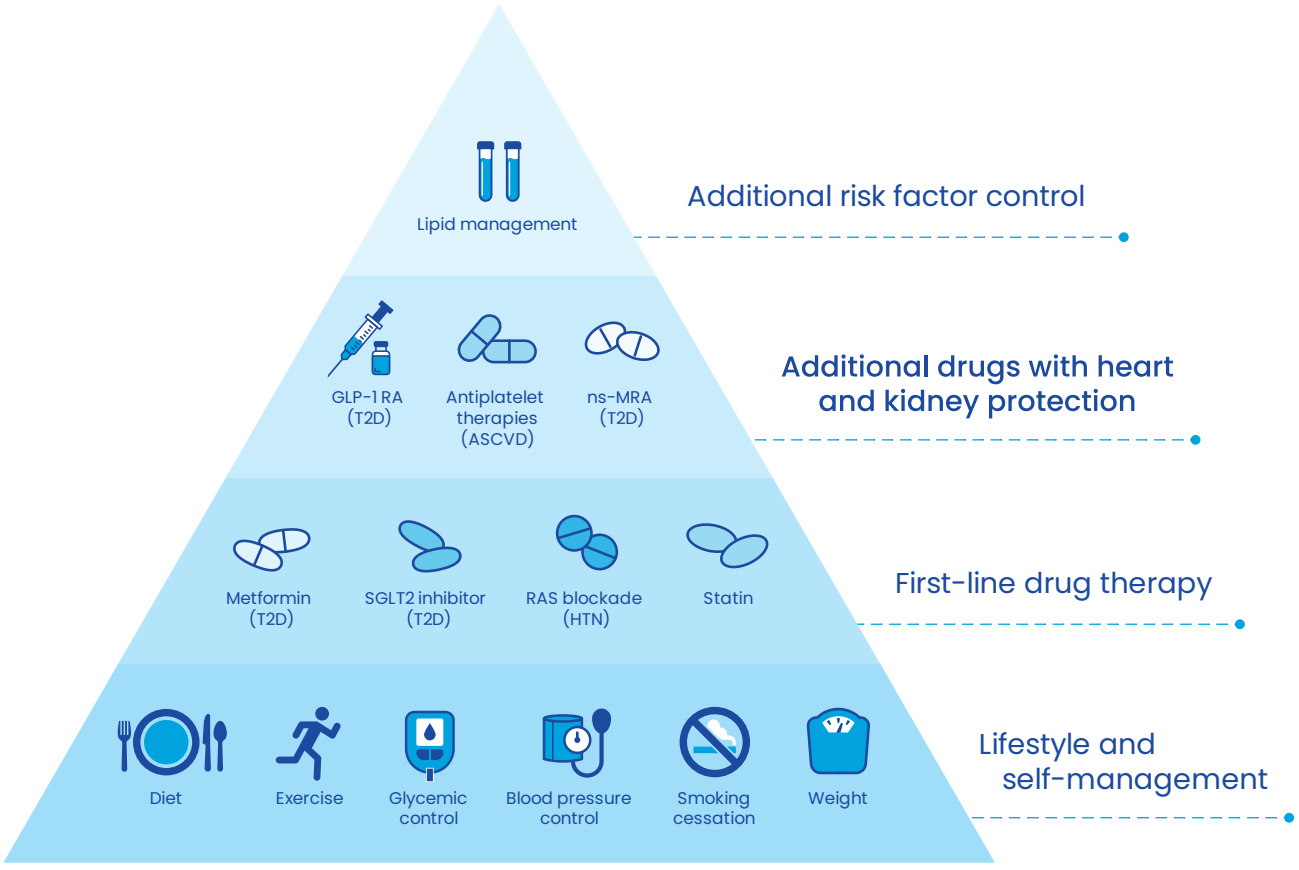
Kidney Disease: Improving Global Outcomes (KDIGO) and the American Diabetes Association (ADA) are the leading global non-profit organisations in kidney diseases and diabetes, respectively. These organisations have been working collaboratively to develop and implement evidence-based clinical practice guidelines for diabetes-related kidney disease. There are many other kidney-focused organisations around the world providing management guidelines for kidney disease. However, in this report we will focus on the KDIGO and ADA guidelines as they are the most recently published and updated guidelines.

Current KDIGO and ADA guidelines define chronic kidney disease as the presence of abnormalities of kidney structure and function for more than three months. Chronic kidney disease is further classified into four categories (low, moderate, high risk, and very high risk) in terms of risk of chronic kidney disease progression based on GFR and urinary albumin levels (*Figure 1*).

Current guidelines focus on an evidence-based, complete care approach by integrating best available clinical research with clinical expertise and the lived experience of people living with diabetic kidney disease.

These guidelines are tiered, the pyramid shape indicating the multiple treatments required to effectively manage the disease (*Figure 2*). The first interventions, at the bottom of the pyramid, should be lifestyle interventions followed by first-line drug therapy and then additional heart and kidney protective drugs and finally managing diabetes-specific risk factors. Addressing these interventions are the key to preventing progression of kidney disease.

Kidney Disease Improving Global Outcomes 2022 Clinical Practice Guidelines for Diabetes Management in Chronic Kidney Disease



RAS Renin-angiotensin system
GLP-1 RA Glucagon-like peptide-1 receptor agonists
Ns-MRA Nonsteroidal mineralocorticoid receptor antagonists

Kidney-heart risk factor management

A comprehensive approach should be used to improve kidney and cardiovascular outcomes for people with diabetes. This approach is shaped in a pyramid where the foundation of lifestyle management should be implemented before layering on other treatments.

Lifestyle management

Certain lifestyle factors can increase a person's risk of diabetic kidney disease. These include living with obesity, smoking and physical inactivity.[51,52,53]

Overweight and obesity

Diabetic kidney disease is more prevalent and progresses more rapidly in people living with diabetes who are also living with obesity than those who are not.[54] Obesity is often defined as abnormal or excessive accumulation of fat that presents a health risk.[55] However, it is not known why people living with obesity are at higher risk of developing kidney disease or why it progresses faster when compared to people without obesity. This may be related to the intra-abdominal fat leading to changes in insulin resistance and higher genetic propensity to a range of serious chronic diseases including diabetes and cardiovascular disease and higher risk of dying earlier. It may also be due to obesity significantly increasing the risk of diabetes and hypertension and these two factors contribute greatly to the development of kidney failure.[56,57,58] This is why weight reduction is so important.

Weight reduction achieved either through lifestyle changes, the use of weight lowering medicines and/or bariatric surgery can help manage diabetes and its complications.[59] Bariatric surgery, which aims to make the stomach smaller and affect the way food is digested, may also contribute to a reduction in serum creatinine and albuminuria. This has been observed in people following the procedure.[60] It is unclear whether this is a protective effect against progression and development of diabetic kidney disease or whether it reflects body mass changes.[60] A more recent study with a five-year follow up period suggested that bariatric surgery can improve or delay the development of diabetic kidney disease.[59] Therefore, the potential for bariatric surgery to improve the management of diabetes and its complications is widely accepted.

There is also an increase in use of obesity medications such as Glucagon like peptide-1 (GLP-1) analogues, dual receptor antagonists such as tirzepatide and newer incretin therapies for weight control. These medications are likely to play a significant part in helping people manage both diabetes and obesity.[61,62,63,64]

Dietary changes

Healthy dietary choices can also help manage diabetic kidney disease. A healthy eating plan to support the management of diabetic kidney disease should aim to stabilise blood glucose levels and reduce waste and fluid for the kidneys to process.[65] Both the ADA and KDIGO recommend individualised balanced diets high in vegetables, whole grains, and fruits, but also low in sugar-sweetened beverages and refined carbohydrates. Salt intake may need to be lowered to help manage blood pressure in people with advanced kidney disease. Protein intake also needs to be monitored as increases in protein intake may increase the risk of kidney function decline. The KDIGO and ADA recommended targeting dietary protein intake of 0.8 g/kg/day for people with diabetes and eGFR rate of less than 30 ml/min/1.73m^2 which is the same as the World Health Organisation's recommendation for people without diabetes or chronic kidney disease.[14,32] 14 above It is accepted that this target is often hard to achieve in clinical practice.

Zero tobacco intake

Smoking can increase the risk of diabetic kidney disease by worsening inflammation in the small vessels of the body. It is essential people with diabetes do not smoke.[14,32]

Increasing physical activity

Physical activity improves physical health, lipid profiles, blood pressure, insulin sensitivity and cardiovascular events in people living with diabetes.[4] The ADA suggests a minimum of 150 minutes per week of moderate to vigorous exercise for people living with diabetes.[13] The Look AHEAD (Action for Health in Diabetes) study determined whether intentional weight loss reduced cardiovascular morbidity and mortality in overweight people with type 2 diabetes. This study also showed participants who were randomised to intensive lifestyle changes resulted in a weight loss of approximately 9% which led to a reduction in the development of high-risk chronic kidney disease measures compared to people receiving usual care.[66]

Generally, any physical activity is better than no physical activity and people with diabetic kidney disease should start at a level they can tolerate and build upon this steadily. They should also consult with their diabetes healthcare teams about adjusting their medications, as increased physical activity may require dosages to be decreased.

Management of glucose levels

High blood glucose levels are one of the most important modifiable risk factors for the development of diabetic kidney disease.[55,67] Current guidelines generally suggest keeping haemoglobin A1c (HbA1c) levels to 7% or less for people living with type 1 or type 2 diabetes to reduce the damage to small blood vessels in the kidney and other parts of the body which can lead to the development and progression of diabetic kidney disease.[13,14,68] This recommendation is supported by the results of numerous randomised controlled trials, providing the best evidence to guide practice.[13,69,70,71]

However, the level of blood glucose management should also be individualised, based on the person's underlying chronic kidney disease or cardiovascular status, age, and blood glucose levels, and especially risk for hypoglycaemia.[72]

Management of blood pressure

Management of blood pressure also plays an important role in the development and progression of diabetic kidney disease. People living with diabetes are at a three times higher risk of high blood pressure than people without diabetes and many studies have shown a strong association between high systemic blood pressure and development of diabetic kidney disease (*Table 1*).[73,74]

The KDIGO and ADA have similar recommendations for target blood pressure levels. Both guidelines mainly focus on using correct blood pressure measurement techniques, preferred medication for treatment and personalised blood pressure target for each patient.[75] There has been controversy regarding recommended blood pressure targets for people with diabetes. The most recent ADA recommendation is a blood pressure target of <130/80 mmHg for people with diabetes.[13] The current KDIGO guidelines suggest a target systolic blood pressure of 120 mmHg or less for people with diabetes not receiving dialysis based on large clinical trial results.[7575] However, as noted above, there have been conflicting results regarding the benefits of reducing blood pressure targets to below the previous general target of <140/90 mmHg (*Table 1*).[76]

Most importantly, the shared conclusion of blood pressure lowering guidelines is the adoption of personalised targets based on a person's individual characteristics and consideration of the benefits and potential adverse effects of achieving tight blood pressure management.[75]

Management of lipids

Kidney lipid metabolism may play a direct role in the progression of diabetic kidney disease.[64,77,78] Research suggests that both quality and quantity of lipids can contribute to increased inflammation and cell death.[79] This disruption can increase cholesterol and fats in the blood, a well-known risk factor for cardiovascular disease but also common in people with diabetic kidney disease.[80] Hence, the management of lipids is a crucial treatment goal to delay the progression of diabetic kidney disease. It is important to note optimal management of the lipid profile in people with diabetes and chronic kidney disease is essential to reduce the exaggerated cardiovascular disease risk that accompanies the development of chronic kidney disease.

The use of statins is recommended by the KDIGO and the ADA as a lipid-lowering intervention. This is supported by many clinical trials which showed statins' ability to preserve glomerular filtration rate and reduce albuminuria in people with diabetic kidney disease (*Table 1*).[81,82,83]

Role of medications

There are a range of medications that can help slow the development and progression of diabetic kidney disease. These include renin-angiotensin-system (RAS)-acting agents, sodium glucose cotransporter 2 inhibitors (SGLT-2s), spironolactone, finerenone, glucagon-like peptide-1 receptor agonists (GLP1-RA) and twincretins.[84] They should be used in combination with other management treatments.

Renin-angiotensin-system (RAS)-acting agents

- The renin-angiotensin-aldosterone system (RAAS) regulates blood pressure, fluids, and inflammation.[85,86]
- Angiotensin receptor blockers and angiotensin-converting enzyme inhibitors effectively lower blood pressure and protect kidneys.[87,88,89,90]
- These medications are the preferred treatment for diabetic kidney disease and high blood pressure.[13,14,44]

Spinolactone

- An agonist of aldosterone's action. It is used to treat high blood pressure, fluid build-up and reduce albuminuria.
- Studies show that combining it with RAS-acting agents can significantly reduce albuminuria in people living with diabetes and have protective benefits for both kidney and heart disease.

Finerenone

- Newer medication that works by blocking the action of aldosterone.
- Associated with a lower risk of hyperkalemia compared to spironolactone.
- Studies have shown improved kidney and cardiovascular outcomes in people living with diabetes.

Finenerone

- Newer medication that works by blocking the action of aldosterone.
- Associated with a lower risk of hyperkalemia compared to spironolactone.
- Studies have shown improved kidney and cardiovascular outcomes in people living with diabetes.

Sodium-glucose Cotransporter-2 (SGLT-2) inhibitors

- SGLT-2 inhibitors decrease glucose absorption by the kidneys, leading to improved blood glucose management.
- Multiple high-quality randomised controlled trials demonstrate these benefits.
- KDIGO guidelines recommend using SGLT-2 inhibitors for people living with type 2 diabetes and CKD regardless of albuminuria and eGFR.

Glucagon-like peptide-1 receptor agonists

- GLP-1 is a hormone released by the gut after meals that regulate various metabolic pathways.
- GLP1-RAs may have kidney-related benefits, including reducing albuminuria and slowing decline of kidney function.
- Kidney-specific trails are currently underway. Studies have shown improved kidney and cardiovascular outcomes in people living with diabetes.

Twincretins

- Twincretins, such as tirzepatide, are newer medications that have shown effectiveness in managing diabetes and weight.
- The SURPASS-4 trial demonstrated the safety of tirzepatide in people with diabetic kidney disease, compared to insulin glargine.
- Twincretins like tirzepatide have shown promise in improving kidney and cardiovascular outcomes in individuals with diabetes.

Future implications

The future implications of inaction on diabetes-related kidney disease are clear. If we do not improve awareness of diabetes-related kidney disease among people living with diabetes and health professionals and increase rates of screening, the incidence and impact of diabetes-related kidney disease will continue to increase placing an ever-greater burden on our health system.

There are well-researched, evidence-backed lifestyle measures, guidelines and clinically tested medications available on the Pharmaceutical Benefits Scheme that support the prevention and delay progression of diabetes-related kidney disease; however, the disease must be detected early when treatments are most effective.

Evidence presented shows the most important factor in successfully implementing the available treatment recommendations is effective screening and early diagnosis of diabetic kidney disease. Regularly assessing the amount of albumin in urine is especially important. All the cited management strategies depend on the level of eGFR, degree of urinary albumin and presence of other conditions. It must be noted that there are deficiencies in the implementation of the current methods of accurately measuring kidney health and function which are the fundamental tools to help clinicians determine the optimal management plan for individual patients.

Rates of screening for urine albumin, as outlined above, are relatively low compared to measurements of eGFR. Additionally, the lack of continuity and harmonisation of reporting of urine albumin between different pathology laboratories creates a barrier that hinders the interpretation of ACR testing, which need to be overcome. It may be helpful to improve the methods used to estimate kidney function and develop a simple system for clinicians with standardised albumin test results values to encourage improving testing rates.

While large-scale, whole-of-population kidney disease screening programs are not cost-effective there is strong evidence for their cost-effectiveness in high-risk populations such as people living with diabetes.[91,92] A diabetes-related kidney disease screening program would increase rates of screening, improve detection and enable early intervention to prevent or delay CKD.

Diabetes Australia currently delivers KeepSight, a diabetes-related eye check recall and reminder program that is increasing rates of regular diabetes eye checks. A similar program focused on CKD in people living with diabetes would make a major impact.

The existence of the National Diabetes Services Scheme (NDSS), a long-established, world-leading diabetes support scheme built around a register of more than 1.5 million Australians living with all types of diabetes, puts Australia in an excellent position to target such a program. The NDSS includes key personal information such as age as well as contact details. This database could form the backbone of a diabetes-related kidney disease screening program.

A diabetes-related kidney disease screening program would increase rates of screening, improve detection, and enable early intervention to prevent or delay CKD.

Options for improving screening

Australia needs a diabetes-related kidney disease screening program to increase rates of kidney screening and detect early kidney damage to prevent or delay its progression to kidney failure. A successful program would mobilise people to complete kidney screening checks within recommended time frames with awareness raising and recall and reminder programs. The checks should be easier and more convenient for people living with diabetes.

While there are currently no identified, world-leading national diabetes-related kidney disease screening programs suitable for adaptation in Australia, there are a range of existing programs, established health infrastructure and emerging technologies that could support a new national program.

The core pillars of a successful program are:

1. Make kidney screening easy
2. Mobilise people with diabetes to get regular kidney health checks.

A recent report from Kidney Health Australia forecasts savings of $509M per annum over 20 years based on a screening program targeting 1.7 million people at high risk and detecting an additional 400,000 people living with chronic kidney disease. This works out to $25,457 per person detected. Based on these figures, a National Diabetes Kidney Disease Screening Program could generate savings of around $30.3M per annum.

1. Make kidney screening easy

Emerging diagnostic tools

There are a number of new diagnostic tools that are being used overseas or under development that could help simplify kidney screening checks, particularly around ACR checks.

Minuteful Kidney

Minuteful Kidney is an ACR urine check developed by Healthy IO which combines accessible technology, at-home kits, and health professional consultations. Eligible patients receive the check kit by mail. The check is taken using the kit and a smartphone. Results are available immediately for discussion with a person's health professional. The check kit has been approved by the Food and Drug Administration (US) and is being trialled through the National Health Service in the United Kingdom.

Promarker D

Promarker D, developed by Proteomics, is a predictive screening tool. While yet to be approved by the Therapeutic Goods Administration, it offers an insight into the growing ability to use blood checks as a preventive diagnostic. It claims the ability to predict the development of diabetic kidney disease up to four years in advance, allowing people the chance to act on medications and lifestyle changes earlier, diminishing the extent of kidney damage. Promarker D is conducted through a routine blood check which is sent to a laboratory for analysis, with results returned to the health professional.

Algorithmic health screening

There are a number of algorithmic disease screening tools for chronic kidney disease either under development or in the early stages of deployment. These tools can be used in a variety of medical settings, from primary care clinics to large scale population health programs, to identify people at elevated risk of chronic kidney disease. Some of these tools can be integrated with large general practice management software to better target kidney disease screening programs.

RenoTrue®

RenoTrue® is a machine learning algorithm under development by the Australian Centre for Accelerating Diabetes Innovation (ACADI), at the University of Melbourne. This algorithm is trained on direct measurements of kidney function as well as readily available markers from routine blood tests. It aims to help improve the estimation of GFR for people with diabetes compared to current estimating equations and to help detect, manage and delay kidney disease for people with diabetes.

Following the example of existing Australian screening programs

A national diabetes kidney disease screening program could be adapted from the models employed by existing Australian screening programs such as the National Bowel Cancer Screening Program and the National Cervical Cancer Screening Program. This could involve a test kit including instructions, urine sample jars and a return reply paid mailing bag being mailed out annually to people living with diabetes or being available for collection from a person's health professional. The person would then have the option of mailing back their sample or taking it to their general practitioner, if the general practitioner has point-of-care diagnostic equipment. If the sample is mailed, a person would be sent a copy of their results and their nominated general practitioner would also be notified.

2. Mobilise people to get regular kidney health checks

A national awareness raising program

Raising awareness of the risks and impacts of diabetes-related kidney disease is an essential part of a diabetes-related kidney disease screening program.

This should include:

- broad marketing across multiple channels to the Australian population and people living with diabetes, their families and carers,
- targeted marketing for priority groups of people including Aboriginal and Torres Strait Islander people, people from culturally and linguistically diverse backgrounds, people with a disability, older Australians and young people, and
- targeted engagement to people living with diabetes, their families and carers, and their health professionals via centralised databases such as the National Diabetes Services Scheme and other health specific channels

A national personalised recall and reminder program

Personalised recall and reminder programs are a well-established proven method of improving rates of screening among people at risk of certain health conditions. Diabetes Australia currently delivers KeepSight, a targeted eye check recall and reminder program for people living with diabetes that is reducing rates of preventable diabetes-related blindness. Utilisation of a central database could enable a personalised national recall and reminder program to be established to mobilise people living with diabetes to get regular kidney screening checks. Recall and reminder push alerts can also be sent to each person's nominated health professional.

An app-driven approach

An app-driven approach would use a specially developed mobile phone app to send push alerts to people living with diabetes when they are due for a kidney check. This approach would leverage the ubiquity of smartphones. However, it would require the person living with diabetes to be engaged in the process. This includes initially downloading the app, providing key details to generate recall and reminders, and then following through with booking appointments. The app could also send recall and reminder push alerts to each person's nominated health professional.

Integration with practice management software

Another opportunity for national screening is working with the general practice management software to integrate a recall and reminder function that would support general practices in generating reminder notices to patients when kidney checks are needed.

The challenges with this approach are that not every person has a regular general practitioner and the fragmented nature of the practice management market would require working with a range of providers to develop and deliver a comprehensive program across Australia.

The National Bowel Cancer Screening Program (NBCSP)

The National Bowel Cancer Screening Program (NBCSP) was established in 2006 to support early diagnosis of bowel cancer by making testing more accessible and private. Australians aged 50 to 74 are sent a test kit every two years. The text kit contains sample tubes, instructions, toilet liners and a return mailing bag.

The program has effectively raised awareness of the importance of screening for bowel cancer. Around 92% of people in the target cohort are aware of the program, while almost 44% participate.

The National Cervical Cancer Screening Program (NCCSP)

The National Cervical Cancer Screening Program (NCCSP) was introduced in 2017, replacing the Pap Smear Program. Originally designed to support biennial screening for all women aged 26 to 74 years, this was changed in 2017 to every five years. Coordinated through a reminder mailout to visit a GP for a test.

In 2022, a new arm of the Program was initiated allowing self-testing, with a health professional serving as both the supplier of the at-home test and the drop-off and follow-up point. This allowed a procedure to be undertaken privately, to overcome trauma, discomfort, or embarrassment, increasing the participation rate among those people who would not seek the procedure from a health professional.

References

1 Diabetes Australia. Diabetes globally. https://www.diabetesaustralia.com.au/about-diabetes/diabetes-globally/ Accessed 23 June 2023.

2 Phillips J, Chen JHC, Ooi E, Prunster J, Lim WH. Global Epidemiology, Health Outcomes, and Treatment Options for Patients With Type 2 Diabetes and Kidney Failure. Frontiers in Clinical Diabetes and Healthcare. 2021;2.

3 Hoogeveen EK. The Epidemiology of Diabetic Kidney Disease. Kidney and Dialysis. 2022;2(3):433-42.

4 White SL. Chronic Kidney Disease, Diabetes & Cardiovascular Disease: Evidence Report 2021. Kidney Health Australia, Melbourne, Australia, August 2020.

5 Lecamwasam A, Ekinci EI, MacIsaac RJ, Saffery R, Dwyer KM. The threat among us: significance and scale of diabetic chronic kidney disease in Australia. Internal Medicine Journal. 2017;47(12):1339-41.

6 AIHW. Australian Institute of Health and Welfare (2023) Chronic kidney disease: Australian facts, AIHW, Australian Government, accessed 11 June 2023.

7 Reutens AT. Epidemiology of diabetic kidney disease. Med Clin North Am. 2013;97(1):1-18.

8 Deloitte Access Economics, Changing the chronic kidney disease landscape: The economic benefits of early detection and treatment (report commissioned by Kidney Health Australia, February 2023).

9 Cass A, Cunningham J, Snelling P, Wang Z, Hoy W. Exploring the pathways leading from disadvantage to end-stage renal disease for Indigenous Australians. Social Science & Medicine. 2004;58(4):767-85.

10 Cass A, Cunningham J, Wang Z, Hoy W. Regional variation in the incidence of end-stage renal disease in Indigenous Australians. Medical Journal of Australia. 2001;175(1):24-7.

11 Maple-Brown LJ, Hughes JT, Ritte R, Barzi F, Hoy WE, Lawton PD, et al. Progression of Kidney Disease in Indigenous Australians: The eGFR Follow-up Study. Clin J Am Soc Nephrol. 2016;11(6):993-1004.

12 Ayodele OE, Alebiosu CO, Salako BL. Diabetic nephropathy--a review of the natural history, burden, risk factors and treatment. Journal of the National Medical association. 2004;96(11):1445.

13 El Sayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 11. Chronic Kidney Disease and Risk Management: Standards of Care in Diabetes—2023. Diabetes Care. 2022;46(Supplement_1):S191-S202.

14 Rossing P, Caramori ML, Chan JC, Heerspink HJ, Hurst C, Khunti K, et al. Executive summary of the KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease: an update based on rapidly emerging new evidence. Kidney international. 2022;102(5):990-9.

15 Thomas MC, Brownlee M, Susztak K, Sharma K, Jandeleit-Dahm KA, Zoungas S, et al. Diabetic kidney disease. Nature reviews Disease primers. 2015;1(1):1-20.

16 Abbasi MA, Chertow GM, Hall YN. End-stage renal disease. BMJ clinical evidence. 2010;2010.

17 Raptis AE, Viberti G. Pathogenesis of diabetic nephropathy. Exp Clin Endocrinol Diabetes. 2001;109(Suppl 2):S424-S37.

18 Yu Y, Lin Q, Ye D, Wang Y, He B, Li Y, et al. Neutrophil count as a reliable marker for diabetic kidney disease in autoimmune diabetes. BMC Endocrine Disorders. 2020;20(1):158.

19 Chow FY, Nikolic-Paterson DJ, Ozols E, Atkins RC, Tesch GH. Intercellular adhesion molecule-1 deficiency is protective against nephropathy in type 2 diabetic db/db mice. J Am Soc Nephrol. 2005;16(6):1711-22.

20 Ruggenenti P, Remuzzi G. Nephropathy of type 1 and type 2 diabetes: diverse pathophysiology, same treatment? Nephrology Dialysis Transplantation. 2000;15(12):1900-2.

21 R Radcliffe NJ, Seah Jm, Clarke M, MacIsaac RJ, Jerums G, Ekinci EI. Clinical predictive factors in diabetic kidney disease progression. Journal of diabetes investigation. 2017;8(1):6-18.

22 Lee CM, Colagiuri R, Magliano DJ, Cameron AJ, Shaw J, Zimmet P, et al. The cost of diabetes in adults in Australia. Diabetes Res Clin Pract. 2013;99(3):385-90.

23 Comino EJ, Harris MF, Islam MDF, Tran DT, Jalaludin B, Jorm L, et al. Impact of diabetes on hospital admission and length of stay among a general population aged 45 year or more: a record linkage study. BMC Health Services Research. 2015;15(1):12.

[24] Wyld MLR, Lee CMY, Zhuo X, White S, Shaw JE, Morton RL, et al. Cost to government and society of chronic kidney disease stage 1–5: a national cohort study. Internal Medicine Journal. 2015;45(7):741-7.

[25] Australia and New Zealand Dialysis and Transplant Registry. Dialysis and Kidney Transplantation in Australia 2021 Summary. 2022.

[26] Vupputuri, S. et al. (2014) 'The economic burden of progressive chronic kidney disease among patients with type 2 diabetes', Journal of Diabetes and its Complications, 28(1), pp. 10–16. doi:10.1016/j.jdiacomp.2013.09.014.

[27] Australian Institute of Health and Welfare 2012. Australia's hospitals 2010–11, at a glance. Health services series no. 44. Cat. no. HSE 118. Canberra: AIHW.

[28] Australian Institute of Health and Welfare 2008. Australian hospital statistics 2006–07. Health services series no. 31. Cat. no. HSE 55. Canberra: AIHW.

[29] Morton, J.I. et al. (2021) Projecting the incidence of type 2 diabetes–related end-stage kidney disease until 2040: A comparison between the effects of diabetes prevention and the effects of diabetes treatment [Preprint]. *doi:10.2337/figshare.14363783.*

[30] Diabetes Australia. (2022) Change The Future: Reducing the Impact of The Diabetes Epidemic. Canberra: Diabetes Australia.

[31] Australian Institute of Health and Welfare. (2021). Kidney transplant recipients in Australia 2020. Canberra: AIHW. Retrieved from https://www.aihw.gov.au/reports/kidney-data/kidney-transplant-recipients-in-australia-2020/contents/table-of-contents

[32] Alsing JFL, Hayes Bauer E, Brandt F, Kampmann JD. Expectations and Experiences of Patients Recently Initiated to Centre-Based Dialysis Treatment. Healthcare (Basel). 2022;10(5):897.

[33] Nagasawa H, Sugita I, Tachi T, Esaki H, Yoshida A, Kanematsu Y, et al. The Relationship Between Dialysis Patients' Quality of Life and Caregivers' Quality of Life. Frontiers in Pharmacology. 2018;9.

[34] Zafari N, Lotfaliany M, O'Keefe GJ, Kishore K, Torkamani N, MacIsaac RJ, Churilov L, Ekinci EI. Performance of 4 Creatinine-based Equations in Assessing Glomerular Filtration Rate in Adults with Diabetes. J Clin Endocrinol Metab. 2021 Jan 1;106(1):e61-e73.

[35] Zafari N, Churilov L, Wong LY, Lotfaliany M, Hachem M, Kiburg KV, Kong L, Torkamani N, Baxter H, MacIsaac RJ, Ekinci EI. Evaluation of the diagnostic performance of the creatinine-based Chronic Kidney Disease Epidemiology Collaboration equation in people with diabetes: A systematic review. Diabet Med. 2021 Jan;38(1):e14391.

[36] Christofides EA, Desai N. Optimal Early Diagnosis and Monitoring of Diabetic Kidney Disease in Type 2 Diabetes Mellitus: Addressing the Barriers to Albuminuria Testing. Journal of Primary Care & Community Health. 2021;12:21501327211003683.

[37] Ekinci E I, Jerums G, Skene A, Dayan S, Power D, Panagiotopoulos S, McNeil K, Clarke S, Levidiotis V, Baker S, Fioretto P, MacIsaac RJ. Renal structural changes in normoalbuminuric and albuminuric patients with type 2 diabetes and impaired renal function. Diabetes Care 2013; 36(11): 3620-3626. (70%, IF=19.112)

[38] Johnson DW, Jones GR, Mathew TH, Ludlow MJ, Chadban SJ, Usherwood T, et al. Chronic kidney disease and measurement of albuminuria or proteinuria: a position statement. Medical Journal of Australia. 2012;197(4):224-5.

[39] MacIsaac RJ, Ekinci EI. Progression of Diabetic Kidney Disease in the Absence of Albuminuria. Diabetes Care. 2019;42(10):1842.

[40] Shin J-I, Chang AR, Grams ME, Coresh J, Ballew SH, Surapaneni A, et al. Albuminuria Testing in Hypertension and Diabetes: An Individual-Participant Data Meta-Analysis in a Global Consortium. Hypertension. 2021;78(4):1042-52.

[41] Colagiuri, S. et al. (2018) Burden of Diabetes in Australia: It's Time for More Action. rep. Sydney, NSW.

[42] European Kidney Patient Federation (EKPF). The Reality of Living with CKD: People with T2D and CKD Speak Up. EKPF-Designed Patient Insights Report, 2023. Available at: https://ekpf.eu/wp-content/uploads/2023/03/EKPF-Designed-Patient-Insights-Report_FINAL.pdf

[43] Libianto R, Davis TM, Ekinci EI. Advances in type 2 diabetes therapy: a focus on cardiovascular and renal outcomes. Med J Aust. 2020 Feb;212(3):133-139.

[44] Radbill B, Murphy B, LeRoith D, editors. Rationale and strategies for early detection and management of diabetic kidney disease. Mayo Clinic Proceedings; 2008: Elsevier.

[45] Kidney Health Australia. (2019). Make the Link: Diabetes, Kidneys, and Heart. Executive Summary. Retrieved from https://kidney.org.au/uploads/resources/KHA-Executive-Summary-Make-the-Link-Diabetes-Kidneys-and-Heart.pdf

[46] McKercher C, Sanderson K, Jose MD. Psychosocial factors in people with chronic kidney disease prior to renal replacement therapy. Nephrology. 2013;18(9):585-91.

[47] Kidney Health Australia. Transforming Australia's kidney health: A call to action for early detection and treatment of chronic kidney disease. Kidney Health Australia; 2023.

[48] European Kidney Patient Federation (EKPF). The Reality of Living with CKD: People with T2D and CKD Speak Up. EKPF-Designed Patient Insights Report, 2023. Available at: https://ekpf.eu/wp-content/uploads/2023/03/EKPF-Designed-Patient-Insights-Report_FINAL.pdf

[49] Zoungas S, Patel A, Chalmers J, De Galan BE, Li Q, Billot L, et al. Severe hypoglycemia and risks of vascular events and death. New England Journal of Medicine. 2010;363(15):1410-8.

[50] Helou N, Talhouedec D, Zumstein-Shaha M, Zanchi A. A Multidisciplinary Approach for Improving Quality of Life and Self-Management in Diabetic Kidney Disease: A Crossover Study. J Clin Med. 2020;9(7):2160.

[51] Hallan S, de Mutsert R, Carlsen S, Dekker FW, Aasarød K, Holmen J. Obesity, smoking, and physical inactivity as risk factors for CKD: are men more vulnerable? American journal of kidney diseases. 2006;47(3):396-405.

[52] Tozawa M, Iseki K, Iseki C, Oshiro S, Ikemiya Y, Takishita S. Influence of smoking and obesity on the development of proteinuria. Kidney International. 2002;62(3):956-62.

[53] Stengel B, Tarver-Carr ME, Powe NR, Eberhardt MS, Brancati FL. Lifestyle factors, obesity and the risk of chronic kidney disease. Epidemiology. 2003:479-87.

[54] Group LAR. Effect of a long-term behavioural weight loss intervention on nephropathy in overweight or obese adults with type 2 diabetes: a secondary analysis of the Look AHEAD randomised clinical trial. The lancet diabetes & endocrinology. 2014;2(10):801-9.

[55] Harjutsalo V, Groop P-H. Epidemiology and risk factors for diabetic kidney disease. Adv Chronic Kidney Dis. 2014;21(3):260-6.

[56] Sanches FM, Avesani CM, Kamimura MA, Lemos MM, Axelsson J, Vasselai P, et al. Waist circumference and visceral fat in CKD: a cross-sectional study. American Journal of kidney diseases. 2008;52(1):66-73

[57] Iglesias P, Díez JJ. Adipose tissue in renal disease: clinical significance and prognostic implications. Nephrology Dialysis Transplantation. 2010;25(7):2066-77.

[58] Ejerblad E, Fored CM, Lindblad P, Fryzek J, McLaughlin JK, Nyrén O. Obesity and risk for chronic renal failure. J Am Soc Nephrol. 2006;17(6):1695-702.

[59] Heneghan HM, Cetin D, Navaneethan SD, Orzech N, Brethauer SA, Schauer PR. Effects of bariatric surgery on diabetic nephropathy after 5 years of follow-up. Surgery for Obesity and Related Diseases. 2013;9(1):7-14.

[60] Friedman AN, Wolfe B. Is Bariatric Surgery an Effective Treatment for Type II Diabetic Kidney Disease? Clin J Am Soc Nephrol. 2016;11(3):528-35.

[61] Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, et al. Tirzepatide Once Weekly for the Treatment of Obesity. New England Journal of Medicine. 2022;387(3):205-16.

[62] Gupta V. Glucagon-like peptide-1 analogues: An overview. Indian J Endocrinol Metab. 2013;17(3):413-21.

[63] Rayner CK, Horowitz M. Twincretin therapy for type 2 diabetes: how do two do? The Lancet. 2021;398(10300):560-1.

[64] Nauck MA, D'Alessio DA. Tirzepatide, a dual GIP/GLP-1 receptor co-agonist for the treatment of type 2 diabetes with unmatched effectiveness regrading glycaemic control and body weight reduction. Cardiovascular Diabetology. 2022;21(1):169.

[65] Prevention CfDCa. Diabetes and Kidney Disease: What to Eat? 2022 [Available from: https://www.cdc.gov/diabetes/managing/eat-well/what-to-eat.html

[66] Group LAR. Effect of a long-term behavioural weight loss intervention on nephropathy in overweight or obese adults with type 2 diabetes: a secondary analysis of the Look AHEAD randomised clinical trial. The lancet diabetes & endocrinology. 2014;2(10):801-9.

[67] Mitrofanova A, Burke G, Merscher S, Fornoni A. New insights into renal lipid dysmetabolism in diabetic kidney disease. World J Diabetes. 2021;12(5):524-40.

[68] Molitch ME, Adler AI, Flyvbjerg A, Nelson RG, So W-Y, Wanner C, et al. Diabetic kidney disease: a clinical update from Kidney Disease: Improving Global Outcomes. Kidney International. 2015;87(1):20-30.

[69] Gembillo G, Ingrasciotta Y, Crisafulli S, Luxi N, Siligato R, Santoro D, et al. Kidney disease in diabetic patients: from pathophysiology to pharmacological aspects with a focus on therapeutic inertia. International journal of molecular sciences. 2021;22(9):4824.

[70] MacIsaac RJ, Jerums G, Ekinci EI. Effects of glycaemic management on diabetic kidney disease. World J Diabetes. 2017;8(5):172-86.

[71] Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes. New England Journal of Medicine. 2008;358(24):2560-72.

[72] Lin YC, Chang YH, Yang SY, Wu KD, Chu TS. Update of pathophysiology and management of diabetic kidney disease. Journal of the Formosan Medical Association. 2018;117(8):662-75.

[73] King P, Peacock I, Donnelly R. The UK prospective diabetes study (UKPDS): clinical and therapeutic implications for type 2 diabetes. British journal of clinical pharmacology. 1999;48(5):643-8.

[74] Group UPDS. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. Bmj. 1998;317(7160):703-13.

75 de Boer IH, Khunti K, Sadusky T, Tuttle KR, Neumiller JJ, Rhee CM, et al. Diabetes Management in Chronic Kidney Disease: A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). Diabetes Care. 2022;45(12):3075-90.

76 Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus. New England Journal of Medicine. 2010;362(17):1575-85.

77 Stadler K, Goldberg IJ, Susztak K. The evolving understanding of the contribution of lipid metabolism to diabetic kidney disease. Curr Diab Rep. 2015;15(7):40.

78 Tolonen N, Forsblom C, Thorn L, Wadén J, Rosengård-Bärlund M, Saraheimo M, et al. Lipid abnormalities predict progression of renal disease in patients with type 1 diabetes. Diabetologia. 2009;52(12):2522-30.

79 Mitrofanova A, Burke G, Merscher S, Fornoni A. New insights into renal lipid dysmetabolism in diabetic kidney disease. World J Diabetes. 2021;12(5):524-40.

80 Kwan B, Fuhrer T, Zhang J, Darshi M, Van Espen B, Montemayor D, et al. Metabolomic Markers of Kidney Function Decline in Patients With Diabetes: Evidence From the Chronic Renal Insufficiency Cohort (CRIC) Study. American Journal of Kidney Diseases. 2020;76(4):511-20.

81 Fried LF, Orchard TJ, Kasiske BL. Effect of lipid reduction on the progression of renal disease: a meta-analysis. Kidney Int. 2001;59(1):260-9.

82 Qin X, Dong H, Fang K, Lu F. The effect of statins on renal outcomes in patients with diabetic kidney disease: A systematic review and meta-analysis. Diabetes/Metabolism Research and Reviews. 2017;33(6):e2901.

83 Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, W Neil HA, Livingstone SJ, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. The Lancet. 2004;364(9435):685-96

84 Khurana N, James S, Coughlan MT, MacIsaac RJ, Ekinci EI. Novel Therapies for Kidney Disease in People with Diabetes J Clin Endocrinol Metab. 2021 Aug 30:dgab639.

85 Ruggenenti P, Cravedi P, Remuzzi G. The RAAS in the pathogenesis and treatment of diabetic nephropathy. Nat Rev Nephrol. 2010;6(6):319-30.

86 Leoncini G, Viazzi F, De Cosmo S, Russo G, Fioretto P, Pontremoli R. Blood pressure reduction and RAAS inhibition in diabetic kidney disease: therapeutic potentials and limitations. Journal of Nephrology. 2020;33(5):949-63.

87 Björck S, Nyberg G, Mulec H, Granerus G, Herlitz H, Aurell M. Beneficial effects of angiotensin converting enzyme inhibition on renal function in patients with diabetic nephropathy. Br Med J (Clin Res Ed). 1986;293(6545):471-4.

88 Cheung AK, Chang TI, Cushman WC, Furth SL, Hou FF, Ix JH, et al. Executive summary of the KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. Kidney Int. 2021;99(3):559-69.

89 Strippoli GF, Bonifati C, Craig ME, Navaneethan SD, Craig JC. Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. Cochrane Database of Systematic Reviews. 2006(4).

90 Strippoli GF, Bonifati C, Craig ME, Navaneethan SD, Craig JC. Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. Cochrane Database of Systematic Reviews. 2006(4).

91 Galbraith, L. E., Ronksley, P. E., Barnieh, L. J., Kappel, J., Manns, B. J., Samuel, S. M., Jun, M., Weaver, R., Valk, N., & Hemmelgarn, B. R. (2016). The See Kidney Disease Targeted Screening Program for CKD. *Clinical journal of the American Society of Nephrology : CJASN*, *11*(6), 964–972. https://doi.org/10.2215/CJN.11961115

92 Manns, B., Hemmelgarn, B., Tonelli, M., Au, F., Chiasson, T. C., Dong, J., Klarenbach, S., & Alberta Kidney Disease Network (2010). Population based screening for chronic kidney disease: cost effectiveness study. *BMJ (Clinical research ed.)*, *341*, c5869. https://doi.org/10.1136/bmj.c5869

DIABETES AUSTRALIA

Phone: +61 2 6232 3800

Fax: +61 2 6230 1535

E-mail: admin@diabetesaustralia.com.au

Website: diabetesaustralia.com.au

Version August 2023

Science for a better life

Bayer is a global life science company with expertise in healthcare and agriculture. The company has had a presence in Australia since 1925 and has a long-term commitment to the health and nutrition of all Australians and New Zealanders. As people live longer and the population continues to grow both locally and beyond, Bayer is one of the few companies that takes a comprehensive view of these issues. Guided by our purpose – Science for a better life – we apply our global scientific expertise in healthcare and agriculture to deliver innovations locally to help people and the planet thrive.

Bayer employs almost 900 people across Australia and New Zealand and is dedicated to servicing the needs of rural and remote communities. Bayer embraces and encourages its employees' unique identities and advances a culture of inclusion and diversity across gender, LGBTQIA+, generations, disability and race.

For further information visit www.bayer.com.au