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# Early diagnosis of chronic kidney disease in patients with diabetes in France: multidisciplinary expert opinion, prevention value and practical recommendations

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## ABSTRACT

Diabetes is the leading cause of end-stage kidney disease (ESKD), accounting for approximately 50% of patients starting dialysis. However, the management of these patients at the stage of chronic kidney disease (CKD) remains poor, with fragmented care pathways among healthcare professionals (HCPs). Diagnosis of CKD and most of its complications is based on laboratory evidence. This article provides an overview of critical laboratory evidence of CKD and their limitations, such as estimated glomerular filtration rate (eGFR), urine albumin-to-creatinine ratio (UACR), Kidney Failure Risk Equation (KFRE), and serum potassium. **eGFR** is estimated using the CKD-EPI 2009 formula, more relevant in Europe, from the calibrated dosage of plasma creatinine. The estimation formula and the diagnostic thresholds have been the subject of recent controversies. Recent guidelines emphasized the combined equation using both creatinine and cystatin for improved estimation of GFR. **UACR** on a spot urine sample is a simple method that replaces the collection of 24-hour urine. Albuminuria is the preferred test because of increased sensitivity but proteinuria may be appropriate in some settings as an alternative or in addition to albuminuria testing. **KFRE** is a new tool to estimate the risk of progression to ESKD. This score is now well validated and may improve the nephrology referral strategy. Plasma or **serum potassium** is an important parameter to monitor in patients with CKD, especially those on renin-angiotensin-aldosterone system (RAAS) inhibitors or diuretics. Pre-analytical conditions are essential to exclude factitious hyperkalemia. The current concept is to correct hyperkalemia using pharmacological approaches, resins or diuretics to be able to maintain RAAS blockers at the recommended dose and discontinue them at last resort. This paper also suggests expert recommendations to optimize the healthcare pathway and the roles and interactions of the HCPs involved in managing CKD in patients with diabetes.

## ARTICLE HISTORY

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Healthcare pathway; chronic kidney disease; diabetes; early diagnosis; estimated glomerular filtration rate; kidney failure risk equation (KFRE); hyperkalemia; hypokalemia; urine albumin-to-creatinine ratio (UACR)

## 1. Introduction

Diabetes is estimated to affect more than 8% of the global population (more than 450 million people) and is expected to affect over 700 million people by 2045. Worldwide, the rising prevalence of type 2 diabetes (T2D) is mainly driven by obesity, sedentary lifestyle, and population aging [1–3]. Up to 40% of people with diabetes will likely develop chronic kidney disease (CKD) [1–3].

CKD often manifests a decade post T1D diagnosis but can be present at T2D onset [4]. In France, 2022 data indicates that 6% of adults have diabetes [5], with a 29% CKD prevalence among T2D patients [6]. T2D patients constitute half of those with end-stage kidney disease (ESKD) [7], with renal failure being a significant contributor to cardiovascular (CV) morbidity and mortality in diabetics [8,9]. For diabetics, CKD elevates risks like cardiovascular disease (CVD), cardiorenal syndrome,

expensive kidney replacement therapy (KRT), and shortened lifespan [8,10,11].

The primary goals in CKD management for T2D patients are to mitigate ESKD risks, preserve kidney function, and decrease CV events and mortality. Numerous international guidelines advocate a combination of lifestyle changes and pharmacological measures to curb CKD progression and CV events in T2D patients [1,12–15]. Given the efficacy of these interventions, CKD screening is paramount. Public health policies should emphasize CKD screening and risk stratification. KDIGO endorses assessing the estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (UACR) [16]. This article offers insights into laboratory evidence of CKD and guidelines to enhance CKD diagnosis and management in T2D patients.

## 2. Methodology

During 2022, an external task force of pharmacists, representatives of patient groups, and seven practitioners from France in general medicine, cardiology, biology, diabetology and nephrology experts attended three virtual meetings organized by Bayer as part of the 'Carré Biologie' program. The participants practice in various settings, including private and public clinics, university departments and government hospitals. The overarching aim of this program was to optimize the detection, early diagnosis, follow-up and prevention of CKD in patients with T2D in France.

The objectives of these medical boards were (1) to harmonize biological analyses allowing early diagnosis and monitoring of CKD in France; (2) to improve the readability of the biological results with clear alerts and definition of established high and low limits; (3) to improve knowledge on the interpretation of these values and the actions to be implemented to 'correct' them; (4) to discuss the need to monitor renal function with follow-up of eGFR over time; and (5) to optimize the referral of patients to nephrologists, by stratifying renal and CV risk. The task force discussed and provided opinions on each of the four biological parameters: eGFR, UACR, Kidney Failure Risk Equation (KFRE), and serum potassium, and their preventive value to improve and standardize the management of CKD in patients with T2D in France.

## 3. Results and discussion

### 3.1. Estimated glomerular filtration rate (eGFR)

Assessing renal function is a crucial problem in cardiology and nephrology because the decline in renal function is one of the strongest predictors of the risk of progression to ESKD and CV events. In addition, reduced renal function implies dosage adjustment for many drugs, the dose of which must be reduced (e.g. digoxin) or, on the contrary, increased (e.g. diuretics). Also, renal failure is associated with a change in the behavior of physicians (called 'renalism'), including the underuse of examinations involving the injection of iodinated contrast products or revascularization procedures, and the use of sub-maximal dosages of CV or renal protective drugs (angiotensin-converting-enzyme inhibitors, statin, aspirin), probably due to side effects or drug interactions [17].

**Assessment of renal function in clinical practice** is usually based on the estimation of glomerular filtration rate (eGFR). In France and as early as 2012, in parallel with the KDIGO 2012 guidelines, the French National Authority for Health (Haute Autorité de Santé - HAS) proposed estimating the GFR using the CKD-Epidemiology Collaboration (CKD-EPI) 2009 equation, recommending the isotope dilution mass spectrometry (IDMS) calibrated assay of plasma creatinine, but also favoring the use of an enzymatic technique [18–22]. This enzymatic assay eliminates chromogen interference and ensures better accuracy and reproducibility among laboratories. The post-analytical report must mention the creatinine assay technique and give a GFR estimated by the CKD-EPI 2009 formula, expressed in ml/min indexed for a body surface area of 1.73 m<sup>2</sup>. The 'racial' correction proposed in the U.S.

A. for African Americans is generally not used in Europe: this 'corrective' factor was mainly established from the MDRD and CKD-EPI studies. In the CKD-EPI study, a vast majority of black people were issued from the AASK study with possible methodological flaws due to the high prevalence of obesity and low GFR [23]. Recent European data suggest a minimal difference on average between white subjects and people of African descent living in Europe [24–26].

The CKD-EPI formula is less well validated in specific patient populations: (1) subjects of Asian origin, children and people aged over 75 years, for whom other equations are more suitable, for example, European Kidney Function Consortium (EKFC) [27]; (2) people of extreme weight (obesity, malnutrition) or whose muscle mass is high or low (bodybuilding, sarcopenia, amputation); and (3) vegetarians (lower plasma creatinine at the same level of renal function).

The KDIGO 2012 guidelines proposed a classification of renal function in 6 stages of severity (G1, G2, G3a, G3b, G4 and G5), the value of 60 ml/min/1.73 m<sup>2</sup> defining the threshold for renal failure independently of age and gender [18]. This epidemiological definition is based on an increase in the relative risk of ESKD and CV events in proportion to the reduction in eGFR below 60 ml/min/1.73 m<sup>2</sup>. It was necessary to subdivide the G3 stage into G3a (45 to 59 ml/min/1.73 m<sup>2</sup>) and G3b (30 to 44 ml/min/1.73 m<sup>2</sup>) to refine the prognostic stratification due to significant epidemiological differences. Stage G3a represents the vast majority (70%) of patients with reduced eGFR, and these patients have a relatively low risk of renal progression and a predominant CV risk, especially when albuminuria is normal. Patients at stage G3b, much less numerous (24%), present much higher renal and CV risks.

Keeping a single threshold regardless of age or considering the decline in GFR, which is frequent with age (but not 'physiological' since it does not affect all individuals), was controversial. Some authors suggest different thresholds for renal failure at 75 ml/min/1.73 m<sup>2</sup> in people below 55 years and, conversely, 45 ml/min/1.73 m<sup>2</sup> in people older than 65 years [28]. Introducing such a differentiation into clinical practice is a potential source of confusion. The CKD Prognosis Consortium, which defined the threshold at 60 ml/min/1.73 m<sup>2</sup> maintains its universal position by arguing that the relative risk of CV and renal complications is similar at identical eGFR regardless of age [29].

**The dose adjustment** indicated in the summary of product characteristics (SmPC Vidal) is currently done according to the clearance of creatinine estimated using the Cockcroft-Gault (CG) equation (HAS). However, SmPCs do refer specifically to the CG equation for dose adjustment in only 15% of cases [30].

In France, the National Authority for Health still recommends dose adjustment to the values of the CG equation [31], which estimates creatinine clearance and notoriously underestimates the GFR [20]. This recommendation requires biology laboratories to continue to report this result, which is confusing, especially when the CKD-EPI and CG values diverge sharply. Some pharmacologists and geriatricians defend the CG equation since they are very sensitive to the iatrogenic risk in their populations of elderly patients. The underlying idea is that a formula which underestimates the GFR avoids overdosing. This is misleading reasoning because systematic under-

dosing carries increased risks of ineffectiveness for many therapeutic classes, or even their contraindications due to a threshold effect (eGFR <30 ml/min/1.73 m<sup>2</sup>), for example, for metformin or direct anticoagulants. Another issue is that the colorimetric reagents available at the time of Cockcroft have not been marketed for several decades. An enzymatic assay for creatinine using the CG formula underestimates the eGFR by an additional 10–15%. Therefore the clinical use of this formula should be formally discouraged, in our opinion.

**Another problem of practical importance pertains to the CKD-EPI formula, which gives an eGFR value indexed to a theoretical body surface area of 1.73 m<sup>2</sup>, leading to significant deviations** in obese or underweight patients [32,33]. The National Kidney Disease Education Program (NKDEP) in the U.S.A. recommends drug dosage adjustment in adults, according to GFR estimated using either the Modification of Diet in Renal Disease (MDRD) or CG formulas; this approach is more straightforward but carries a risk of error as highlighted above. For people with extreme body weight, the NKDEP recommends de-indexing eGFR to account for the patient's body surface area to obtain a 'raw' eGFR in ml/min. The new KDIGO CKD 2023 guidelines suggest, as practice points, that 'for most people and clinical settings, validated eGFR equations using serum creatinine are appropriate for drug dosing.' They also propose that, 'where accuracy is required for dosing (e.g. due to narrow therapeutic or toxic range) and/or estimates may be unreliable, the use of equations that combine both creatinine and cystatin C or measured GFR may be indicated.'

They also suggest that "in people with extremes of body weight, eGFR unadjusted for body surface area (BSA) may be indicated, especially for medications with a narrow therapeutic range or requiring a minimum concentration to be effective. Use of non-indexed eGFR values (ml/min) should be considered for drug dosing decisions.

The authors suggest de-indexing eGFR to have a more accurate estimate of renal function of drug clearance. The de-indexed eGFR is given by the formula:  $de(eGFR) = eGFR \times A / 1.73 \text{ m}^2$ , where  $de(eGFR)$  is the de-indexed eGFR, and  $A$  is the body surface area of the patient.  $A$  is readily available online or on smartphones (QxMed application, for example) but requires weight and height, which are not always reported in the lab reports. **Ideally, the biology laboratory should render the de-indexed CKD-EPI directly instead of the CG formula.**

### 3.2. Urine albumin-to-creatinine ratio (UACR)

Urinary protein excretion, or proteinuria, is an early biomarker of CKD. Albumin, the most abundant circulating plasma protein, is also the most abundant protein in the urine, with a physiological level of less than 10 mg/day in most healthy individuals. A urinary albumin excretion higher than 30 mg/day is considered pathological and is associated with podocyte alterations, glomerular capillary pressure rise [35] but also diffuse endothelial dysfunction and widespread microvascular disease in the eyes, brain, and heart [36].

The evaluation of urinary albumin excretion or albuminuria is preferable to that of protein because measuring serum

albumin by immunological methods is **more sensitive** than proteinuria in case of mild to moderate increases. In addition, urinary albumin excretion is a **more specific** marker of changes in glomerular permeability.

The general limits of the evaluation of albuminuria, like proteinuria, are related to its significant intra-individual variability, up to 30%, which requires repeating this examination 2 or 3 times over 3 to 6 months to confirm abnormal values [4]. The leading causes of variability are physical exercise, fever, hyperglycemic or blood pressure peaks, some medications, and changes in dietary sodium intake.

The mode of assessment of urine albumin is essential. Classically, a 24-h urine sample is collected for urine albumin measurement, but collecting urine over 24 hours is cumbersome. UACR is reasonably well correlated with 24-hour urinary albumin excretion [37] and can be done on a urine sample, best on morning urine, or otherwise at random [4,18,38]. As early as 2008, French clinical practice guidelines were published [39], and in 2011, the French National Authority for Health proposed using UACR for the diagnosis and monitoring of CKD [38]. However, this practice remains insufficiently widespread, including among people with diabetes, because general practitioners (GPs) do not always know the simplicity of UACR compared to 24-hour proteinuria, and biology laboratories continue to report urinary protein values, particularly when urinary albumin values exceed 300 mg/g, for reimbursement reasons.

Another strong argument for using UACR in renal risk stratification is that this parameter has been used as an inclusion criterion in many clinical trials and that many therapeutic indications and marketing authorizations are now based on UACR values, such as gliflozins or non-steroidal mineralocorticoid antagonists (nsMRAs).

The authors suggest expressing UACR in milligrams of albumin per gram of urinary creatinine (mg/g) rather than the SI units (milligrams of albumin per millimoles of urinary creatinine, mg/mmol). This suggestion is made to avoid the risk of confusion between the two systems of units (which vary from 1 to 10) and because the value in mg/g is roughly equivalent to that in milligrams per 24 hours and, therefore, **more intuitive for the practitioners.**

The international KDIGO classification distinguishes three stages of albuminuria: A1 for physiological values below 30 mg/g, A2 for values from 30 to 300 mg/g, and A3 for values above 300 mg/g [40]. This classification can be easily used to stratify the risk, but these threshold values are arbitrary since the increase in risk is continuous and proportional to the value of the UACR and without a threshold [40,41]

Overall, albuminuria is a risk marker, for renal progression, CV events and mortality [40,41], in addition to its role in risk profiling for new-onset heart failure [42].

Noteworthy, **changes in albuminuria or uACR have predictive value.** For example, in diabetic nephropathy, a 50% reduction in albuminuria is associated with an equivalent decrease in the risk of CKD progression and CV events [43]. In its latest 2023 recommendations, the American Diabetes Association (ADA) suggests that reducing albuminuria by at least 30% should be a therapeutic target in CKD patients with diabetes [4]. The authors



## **Controversy Which formula for estimating eGFR?:**

GFR estimation is a complex and controversial subject around the world.

The original 2009 CKD-EPI formula using the racial correction factor generates a minimal bias in White people and an average overestimation of +4 ml/min in African-Americans. This bias was recognized as a factor of inequity in the diagnosis of renal insufficiency and registration on the transplant list. The new 2021 CKD-EPI formula that has no race coefficient ('race-free') has been validated and quickly recommended in the U.S.A. [34]. This new formula performs slightly worse as it underestimates GFR in African-Americans, overestimates it in White populations by 4 ml/min, and does not provide additional benefits in European populations where it is not recommended [24].

Other formulas than CKD-EPI have recently been proposed and seem promising, particularly the EKFC formula named after the European Kidney Function Consortium. The EKFC equation is a new equation developed and validated on all age groups (from 2 to 90 years) and levels of renal function (40 to 490  $\mu\text{mol/L}$ ) [25]. The originality of this equation is that it recalibrates the plasma creatinine value (by dividing the plasma creatinine by the median creatinine value in the general control population) to adjust for variations linked to differences in age, sex or race. This method makes it easy to transpose specific reference values to various populations [26].

## **Justification for Incorporating Cystatin C in Equations for Chronic Kidney Disease (CKD) Staging**

Creatinine, which is directly linked to muscle mass, may be misleading at extremes of body composition, or in specific conditions (spinal cord injuries, sarcopenia). Conversely, cystatin C is influenced by distinct factors, including steroid administration, thyroid disorders, and malignancies. Since neither is a perfect marker for estimating clearance, their combined assessment provides a more precise estimation of the GFR relative to measured values.

Very low serum creatinine levels frequently signify adverse health conditions, including frailty or sarcopenia, which curtail creatine production. This characteristic of serum creatinine, i.e. relation with muscle mass, has limited its prognostic relevance and results in reducing the risk associations for eGFRcr 45 to 60 ml/min/1.73 m<sup>2</sup> and elevating risks for eGFRcr >110 ml/min/1.73 m<sup>2</sup>. These limitations are not observed when risk is assessed using combined creatinine and cystatin C-based eGFR (eGFRcr-cys) or cystatin C-based eGFR (eGFRcys).

Comparing GFR estimations derived from these two filtration markers, risk gradients for eGFRcys consistently exhibit greater strength for the majority of outcomes compared to eGFRcr. Hence, for the purpose of evaluating the association of eGFR with outcomes (i.e. projecting prognosis for people with CKD), the eGFRcys or eGFRcr-cys can be considered most accurate.

In the French medical landscape, the measure of cystatin C for GFR estimation remains minimal. This is primarily due to the lack of standardization in assay methodologies and the absence of reimbursement for this assay. However, in light of the enhanced stratification potential of equations incorporating cystatin C, and the recent KDIGO guidelines, we strongly advocate for a comprehensive national reassessment of the cost-effectiveness of cystatin C measurement, with a view to broadening reimbursement provisions.

CKD is classified based on: • Cause (C) • GFR (G) • Albuminuria (A)				Albuminuria categories		
				Description and range		
				A1	A2	A3
				Normal to mildly increased <30 mg/g <3 mg/mmol	Moderately increased 30–299 mg/g 3–29 mg/mmol	Severely increased ≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73 m <sup>2</sup> ) Description and range	G1	Normal or high	≥90	Screen 1	Treat 1	Treat and refer 3
	G2	Mildly decreased	60–89	Screen 1	Treat 1	Treat and refer 3
	G3a	Mildly to moderately decreased	45–59	Treat 1	Treat 2	Treat and refer 3
	G3b	Moderately to severely decreased	30–44	Treat 2	Treat and refer 3	Treat and refer 3
	G4	Severely decreased	15–29	Treat and refer* 3	Treat and refer* 3	Treat and refer 4+
	G5	Kidney failure	<15	Treat and refer 4+	Treat and refer 4+	Treat and refer 4+

■ Low risk (if no other markers of kidney disease, no CKD)    ■ High risk  
■ Moderately increased risk    ■ Very high risk

**Figure 1. KDIGO GA matrix according to eGFR and albuminuria stages.** [1]. Heat map reflects the risk of progression by intensity of coloring (green: low risk [if no other markers of kidney disease, no CKD]; yellow: moderately increased risk; orange: high risk; red/deep red, very high risk). The numbers in the boxes are a guide to the frequency of monitoring (number per year). Treatment and referral indications are given in plain text (with the publisher permission).

**Abbreviations:** CKD: chronic kidney disease; GFR: glomerular filtration rate; KDIGO: Kidney Disease Improving Global Outcomes; UACR: urine albumin-to-creatinine ratio.

emphasize that the therapeutic objective is to reduce albuminuria to its lowest possible value, considering the direct relationship with the reduction of renal and CV risk [44,45]. In addition, the FDA now recognizes a reduction in UACR of more than 30% as a relevant surrogate for renal and CV events [46].

Follow-up of people with diabetes should include the measurement of UACR and eGFR at least once a year, independently of treatment, following French [31] and international guidelines [1,4]. In people with diabetes and CKD, these two biomarkers should be monitored more frequently to guide therapeutic decisions [1,4]. The GA classification can be represented in a heat map. Each part of the heat map is associated with a discrete risk of CKD progression, CV events and all-cause mortality [1] (Figure 1). In addition, the GA heat map specifies the treatment and referral indications [1].

### 3.3. Scoring and risk of progression

Most cases of CKD are progressive, and the **progression rate has a predictive value** indicating, in particular the risk of ESKD and the time to KRT as well as a higher risk of CV events [47]. Identifying patients at risk of CKD progression allows optimal nephrology care, including the early start of treatment for nephroprotection, triage for nephrology referrals and appropriate timing of dialysis access and living donor kidney transplantation. Early nephrology referral has been shown to improve overall survival, survival on dialysis [48], and to reduce healthcare costs in patients requiring KRT [49,50].

The slope of the inverse of plasma creatinine, have been proposed for several decades as tools for assessing the progressive risk of CKD. Using a graphic representation with a semi-logarithmic scale, a slope of decrease in plasma creatinine can be drawn to roughly estimate the time duration up to KRT. Tools are available to calculate annual GFR loss online (<https://www.sfdiabeto.org/renalfunctiondeclinecalculator>).

A 5 mL/min/1.73 m<sup>2</sup> or more loss over one year is considered rapid progression and requires specialist advice [18]. The advantage of this representation is linked to its ease of implementation and its easy-to-understand visual aspect. The main limitation is that the evolution of renal function loss is not linear in approximately 30% of individuals. The second limitation is that several points spaced months or years apart are necessary to draw a slope, which can lead to delaying the referral to a nephrologist [51].

KDIGO guidelines have proposed risk stratification with the GA heat map [18]. The GA heat map visually represents the risk with a colorimetric scale representing both the renal and CV risks or the risk for all-cause mortality (Figure 1). Each GA stage indicates a relative risk of renal or CV event compared to a G1A1 reference. This GA representation is modeled on the CV risk scales used in cardiology to stratify the risk of CV events. The significant advantage of this representation is to stratify the risk in all individuals with an easy-to-understand visual representation. The major limitation is that this heat map only indicates a relative risk, making it possible to stratify individuals among themselves but not to predict the individual absolute risk.

While lower eGFR and higher UACR identify patients with CKD, these biomarkers only provide a 'snapshot' of the disease. Risk scores have therefore been developed to consider multiple progression factors dynamically. The Kidney Failure Risk Equation (KFRE) was developed as a risk-predictive model to measure the 2-year and 5-year risk of developing ESKD in people with CKD stages G3-G4 (eGFR 15–60 ml/min/1.73 m<sup>2</sup>). The KFRE score was developed in Canada on a large cohort of patients with CKD stages 3 to 5 [52]. After comparing numerous models, two equations were retained: a score of 4 variables including gender, age, eGFR and UACR, and a score using variables adding four serum parameters (albumin, calcium, phosphate, and bicarbonate). The 8-variable model performed marginally better in net reclassification improvement and calibration. Later on, a meta-analysis extended the validity of the 4-variable score from 31 international cohorts covering almost 720,000 participants from 4 continents [53]. The score was calibrated for non-North American cohorts due to a lower basal risk of 32.9% at 2 years and 16.5% at 5 years. This meta-analysis found C statistics very satisfactory (4-variable score: 0.90 at 2 years and 0.88 at 5 years; 8-variable score: 0.89 at 2 year, and 0.86 at 5 years) [53].

The score (4 variables) has now been externally validated in numerous multiethnic populations in Europe, North America and Asia [54–56]. The score has also been validated in various types of kidney diseases and is very performant in diabetic nephropathy and chronic glomerular diseases but slightly less efficient in interstitial nephropathy and polycystic kidney disease, for which other tools are available [57,58]. KFRE is convenient, easy to use and reliable in most populations over a wide age range (KFRE @ qxmed). However, the KFRE has not been studied or validated in people with an eGFR >60 ml/min/1.73 m<sup>2</sup> and may be slightly less effective in pediatric patients [59] or in very elderly subjects (>80 years) due to the competitive risk of CV mortality [60,61]. Another drawback of this risk equation is that it does not account for post-intervention changes in UACR. Finally, this risk equation may require a recalibration in France and other low-risk countries [62].

In Canada, Tangri et al. proposed a 5% risk threshold at five years for nephrology referral, while lower risk patients were referred to the treating physician for follow-up [63]. This triage strategy reduced the wait time for the first nephrology visit from 9 months to less than 4 months. This research group also proposed a KFRE threshold of 40% at two years for planning vascular access and transplantation. However, this threshold has not been formally validated nor universally adopted. In the United Kingdom, the 2021 NICE guidelines for managing CKD assessed KFRE as a triage and referral tool and recommended rapid implementation in all electronic medical records [64]. The National Institute for Health and Care Excellence (NICE) found that the best referral rule was '**KFRE ≥5% at 5 years or UACR ≥650 mg/g**,' which allows to identify patients with CKD but whose eGFR is >60 ml/min/1.73 m<sup>2</sup>. In France, the French National Authority for Health has recognized KRFE as a predictive tool to optimize triage and referral to a nephrologist but has not made it mandatory [31]. As part of an experiment in some regions of France, KRFE has been routinely implemented in laboratory reports for practitioners

and patients with a comment to consider referral to the nephrologist when the 5-year KFRE is ≥5%. The authors suggest extending this practice to all laboratory reports, including eGFR and UACR measurements, as part of the post-analytical reporting.

### 3.4. Blood potassium

Factors associated with an increased likelihood of developing hyperkalemia include predisposing conditions (diabetes, CKD, heart failure), medications, potassium-rich foods, and potassium-enriched salt substitutes. CKD as early as G3a and G3b stages are one of the most important predictors of hyperkalemia [65]. Potassium-sparing diuretics, MRAs, and RAAS inhibitors are the drugs most frequently associated with hyperkalemia, but diabetes itself may promote hyperkalemia in some patients resulting from hyporeninemic hypoaldosteronism [66]. Other common drugs can interfere with renal potassium excretion and worsen hyperkalemia, including non-steroidal anti-inflammatory drugs (NSAIDs), COXIBs, cotrimoxazole, heparin and low molecular weight heparins, drospirenone, and calcineurin inhibitors (cyclosporin and tacrolimus).

Measuring serum or plasma potassium for diagnosis is acceptable, but the laboratory reports should state clearly which method was used, a practice not currently done in France. Since potassium is released from platelets during coagulation, serum potassium is higher than plasma potassium by 0.1 to 0.7 mmol/L [67]. Point-of-care devices have until now had limited accuracy and precision, which may have limited their widespread adoption [65], but new devices look promising [68]. A falsely elevated potassium level (pseudohyperkalemia) may occur with a clenched fist during phlebotomy, mechanical trauma, small gauge needle, use of a tourniquet for more than 1 minute, clotting, or hyperleukocytosis or thrombocytopenia. A significant factor of pseudohyperkalemia is samples taken at home and measured too late, a frequent but not recommended practice. Generally, any factor tending to promote hemolysis or even minimal passive diffusion during the pre-analytical phase of the assay falsely increases blood potassium.

The definition of hyperkalemia is based on the distribution of potassium values in the general population. Hyperkalemia is generally defined as a plasma or serum potassium level higher than 5.0 mmol/L and is further classified as mild hyperkalemia (5.0 to 5.9 mmol/L), moderate hyperkalemia (6.0 to 6.4 mmol/L), and severe hyperkalemia (≥6.5 mmol/L) in the absence of suggestive ECG signs [65].

There is no international consensus on the magnitude, duration and frequency of elevated potassium values that define chronicity. A consensus was achieved by a Delphi panel of French nephrologists defining 'Persistent hyperkalemia as the recurrence of an episode of hyperkalemia two times or more within a year, despite the use of chelating resins or available loop diuretics in the same year' [69].

A definition based on prognosis should reflect the gradual association with adverse events, but the risk increases continuously with higher potassium levels, and CKD alters both the distribution of potassium levels and the associated risk [70]. Hyperkalemia is associated with an increased risk of



adverse events and mortality [71,72]. The likelihood of the association is explained by the electrophysiological role of potassium and the known cardiac abnormalities that can be induced by very high or very low potassium levels, especially after rapid changes.

Incorporating risk factors into predictive models can contribute to better individual risk stratification. In the Swedish SCREAM cohort, 70000 patients were evaluated after taking a RAAS inhibitor, and the incidence of hyperkalemia increased continuously as kidney function declined [73]. These authors developed a hyperkalemia risk score integrating eGFR, baseline potassium level, gender, diabetes, heart failure, and concurrent use of potassium-sparing diuretics in new users of RAAS blockers. This score accurately predicted the risk of hyperkalemia at one year in the SCREAM cohort (area under the curve: 0.85, 95% CI: 0.84 to 0.87) and in a validation cohort. This score is promising for predicting the risk of hyperkalemia before starting an RAAS inhibitor, but it is not yet available as a calculator. The more convenient **45/4.5 rule** predicts a 4- to 8-fold increased risk of hyperkalemia on RAAS inhibitors in patients with a baseline eGFR  $\leq 45$  ml/min/1.73 m<sup>2</sup> and serum potassium  $>4.5$  mmol/l under diuretics at adequate doses [74].

Chronic hyperkalemia is usually asymptomatic and more likely to be detected in patients with more frequent dosing [65]. In patients at risk of hyperkalemia, it is recommended that serum potassium be measured before and 1 to 2 weeks after initiation and each titration of RAAS inhibitors, based on expert opinion in several guidelines [65]. However, epidemiological data show that adherence to these recommendations is limited. To prevent hyperkalemia in patients with advanced CKD, recommendations based on expert opinion call for low-diet potassium, with reduced intake of fruits, vegetables, and plant-derived bioactive compounds, such as fiber, vitamin C and carotenoids. However, randomized data on the effectiveness of this approach are lacking, and observational studies in people with CKD or ESKD report weak associations between dietary potassium intake and potassium levels [75,76], which challenges the belief that dietary potassium intake strongly influences potassium levels.

Numerous observational studies on patients with different degrees of CKD severity have explored the association between dietary potassium intake and prognosis [75,76]. In most of these studies, markers of high potassium intake were associated with a lower risk of death or progression of kidney disease. It is unclear whether the observed associations are explained by potassium intake or by greater consumption of specific plants or diets associated with a better prognosis in people with or without kidney disease [70]. Few trials, limited to short-term and small cohorts, have assessed the impact of altering dietary potassium in people with CKD and generally found no alterations in plasma potassium and no adverse hyperkalemic events [65].

The current recommendation to limit dietary potassium in patients with CKD is not supported by any direct evidence. However, no evidence supports the safety of increasing potassium intake or liberalizing potassium restrictions in patients with advanced CKD.

RAAS inhibition improves prognosis in patients with heart failure with reduced ejection fraction, including patients with advanced CKD (eGFR  $<30$  ml/min/1.73 m<sup>2</sup>) [77], as well as in

patients with albuminuric kidney disease, including diabetes. A recent meta-analysis has established the benefit of RAAS inhibition in advanced stages of CKD with albuminuria [78]. Improved control of serum potassium could allow higher use of RAAS blockers in eligible patients. In observational cohorts, hyperkalemia is the leading cause of reduction or discontinuation of RAAS inhibitors [79,80], which are associated with an increased risk of CKD progression and mortality [81,82].

Recent retrospective and observational studies have suggested that continuing RAAS blockers may help to reduce the need for KRT [83,84]. In the randomized STOP-ACEi study, in 410 participants with CKD stages G4-G5 receiving RAAS inhibitors, continuation or cessation of RAAS inhibitors had no impact on the rate of CKD progression and the risk of hyperkalemia [85], however, the small sample size limited the power of this study.

KDIGO 2022 guidelines for the management of diabetes in CKD recommend initiating therapy with RAAS inhibitors and titrating to the highest approved dose tolerated by hypertensive and albuminuric diabetic patients [1]. Hyperkalemia induced by RAAS inhibitors can usually be corrected by dietary or pharmacological measures (increase/introduction of the dose of loop diuretics, correction of acidosis or chelators) rather than by dose reduction or stopping the RAAS inhibitors, and discontinuation should only be considered as a last resort. Randomized trials support that chronic hyperkalemia can be corrected in people with normal or reduced eGFR, with durations up to one year for the new agents, patiromer and sodium zirconium cyclosilicate, and a less proven level of evidence from short-term studies (up to one week) for sodium polystyrene sulfonate (SPS) [86–88]. A recent editorial controversy discussed the arguments for or against the use of these new chelators vs SPS [89]. Gliflozins, which are now part of the standard of care in patients with diabetes and CKD, could mitigate the risk of hyperkalemia when combined with other RAAS inhibitors, such as ACE inhibitors, ARB, spironolactone, eplerenone, finerenone, and sacubitril-valsartan [90]. Therapeutic algorithms have been recently developed to implement new potassium chelators on the cardiorenal continuum [65], although these new potassium chelators are not yet available in France.

Finally, it should be noted that drug interactions are possible, resulting from a direct binding (patiromer and SPS) or a change in gastric pH (sodium zirconium cyclosilicate). These interactions have led manufacturers to recommend taking all other drugs orally at least 3 hours before or after patiromer and SPS, and at least 2 hours before or after sodium zirconium cyclosilicate for drugs whose absorption depends on gastric pH, such as atorvastatin, azole antifungals, dabigatran, furosemide, protease inhibitors and tyrosine kinase inhibitors [65].

### 3.5. 'Tuning' the healthcare pathway

The prevalence of CKDs is escalating, largely attributed to the rise in diabetic nephropathy and, secondarily, to an aging population. In France, major chronic diseases, including

**Table 1.** Situations in which CKD screening is recommended by HAS 2021 [28]. Screening includes plasma creatinine assay to estimate GFR and urine albumin-to-creatinine ratio (UACR). Screening is recommended once a year for all patients with diabetes and, at the time of diagnosis, then every five years (if initially normal) in hypertensive patients. The three first conditions (bold text) represent ~90% of patients diagnosed with CKD.

1	<b>Diabetes (every year)</b>
2	<b>Hypertension (at diagnosis and every 5 years thereafter)</b>
3	<b>Age &gt;60 years</b>
4	Obesity >30 kg/m <sup>2</sup>
5	Cardiovascular disease
6	Family history of chronic renal failure (e.g. polycystic kidney disease)
7	Obstructive uropathy
8	Systemic/inflammatory diseases (e.g. myeloma, lupus, amyloidosis)
9	Nephrotoxic drugs (e.g. non-steroidal anti-inflammatory drugs, COXIB, lithium, iodinated contrast products)
10	History of acute renal failure

**Table 2.** Referral to a nephrologist based on the guidelines for CKD management established by the French National Authority for Health [28]. These recommendations generally suggest referring patients at late stages of CKD (1-5-8), which misses opportunities for optimal pharmacological interventions. The use of the KFRE could replace recommendations 1, 3 and 4.

1	eGFR <45 mL/min/1.73 m <sup>2</sup>
2	UACR >500 mg/g (>45 mg/mmol)
3	Rapid decline in eGFR: annual loss >5 ml/min/1.73 m <sup>2</sup>
4	Decline in eGFR > 30% in 4 months without obvious explanation
5	Complications (hyperkalemia >5.5 mmol/l resistant to treatment; anemia, etc.)
6	Resistant hypertension
7	A doubt about the cause or management in a patient with suspected renal disease
8	Suspicion of hereditary nephritis/lithiasis, monoclonal gammopathy
9	Potential eGFR <20 ml/min/1.73 m <sup>2</sup> or renal replacement therapy within the next 12 months

**Abbreviations:** CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; UACR: urine albumin-to-creatinine ratio.

diabetes and CKDs, are fully reimbursed under the 'ALD 30' provision. Patients have direct GP access, but this is constrained by GP availability and the expansion of 'medical deserts' in underserved regions. Notably, 11000 patients initiate dialysis annually, with half being diabetic [7]. This disparity between a comprehensive health system and persistent chronic disease complications underscores the need for healthcare system refinement.

GPs are the central point of the patient's care pathway for screening and diagnosing chronic diseases, implementing the first treatments, and organizing the follow-up in coordination with the specialists. The French National Authority for Health has issued recommendations for screening CKD (Table 1) and referring patients to a specialist (Table 2). These recommendations are poorly known and applied, as evidenced by the persisting 30% of patients starting chronic dialysis in emergency conditions [91].

The practice of GPs is still too often isolated and not relayed by other healthcare professionals (HCPs). The health authorities encourage GPs to provide primary care in 'multi-professional health centers (Maison de Santé Pluriprofessionnelle – MSP)' with the possibility of optimizing the care pathway thanks to team coordinators and advanced practice registered nurses (APRNs) or therapeutic education nurses. Involving users (such as expert patients, health mediators, receptionists, peer helpers, and adapted physical education specialists) to support patients with diabetes within these MSPs appears promising.

Effective management of complex diabetes necessitates multidisciplinary collaboration. Yet, care remains disjointed

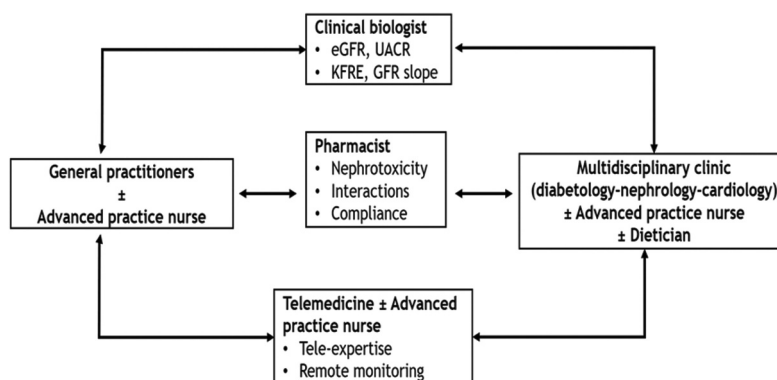
due to specialists' disparate locations. Financial incentives could foster collaboration in multidisciplinary clinics, aligning with KDIGO 2022 recommendations [1]. The COORDINATE study highlighted the efficacy of such clinics, noting a 21% reduction in cardiovascular complications within a year [91].

Other HCPs may be called upon to intervene in the care pathway of patients with diabetes and CKD, such as clinical biologists, pharmacists, dietitians, and nurses, including APRNs.

Other HCPs, including clinical biologists and pharmacists, play integral roles in diabetes and CKD management. Clinical biologists can proactively measure albuminuria annually in at-risk patients, ensuring systematic CKD screening. Pharmacists, with frequent patient interactions, can advise on drug interactions and monitor medication adherence. Advanced practice nurses (APRNs), post their specialized training, have demonstrated significant patient care improvements [92–94].

With the development of new computer technologies and the large number of smartphone users, the role of telemedicine needs to be unraveled. Telemedicine includes tele-expertise to quickly answer a specific question from the GP to the specialist. It can also involve remote monitoring for blood pressure, glycemia, continuous interstitial glucose measurement, weight or edema. APRNs or therapeutic education nurses play a central coordinating role in this telemonitoring.

Telemedicine's potential, bolstered by technological advancements, remains untapped. It encompasses tele-



**Figure 2.** Coordinated care pathway model for CKD in patients with diabetes.

**Abbreviations:** eGFR: estimated glomerular filtration rate; GFR: glomerular filtration rate; KFRE: Kidney Failure Risk Equation; UACR: urine albumin-to-creatinine ratio.

**Table 3.** Expert recommendations to improve the management of CKD in patients with T2D.

1	To raise awareness of kidney disease among healthcare providers, including nurses and pharmacists
2	To improve the fragmented journey of the diabetic patient using a well-coordinated multidisciplinary and pluriprofessional approach
3	To improve poor and late follow-up of kidney disease in patients with diabetes
4	To facilitate access of patients to the specialist, including the set-up of a helpline for nephrology advice
5	To strengthen patient autonomy and promote therapeutic education
6	To involve local health professionals as much as possible in the management of CKD in patients with diabetes
7	To standardize the practice of lab specialists: <ul style="list-style-type: none"> <li>• To assess eGFR using the CKD-EPI equation and validated analytic methods</li> <li>• To measure UACR on spot urine expressed in mg/g, instead of proteinuria</li> <li>• To calculate slopes of eGFR with an automatic calculation of the annual decline of eGFR</li> <li>• To calculate the KFRE score with comments for referral</li> <li>• To help clinicians by indicating 'Think about rechecking eGFR' when eGFR is found abnormal for the first time in a patient</li> <li>• Implement a comment 'Mind about measuring UACR' when eGFR or HbA1c is found abnormal for the first time</li> </ul>
8	To inform healthcare professionals on the availability of additional biological parameters and tools to promote early detection and monitoring of CKD: <ul style="list-style-type: none"> <li>• To advise on the follow-up frequency of laboratory tests according to KDIGO guidelines</li> <li>• Calculator of the renal function decline: <a href="https://www.sfdiabete.org/renalfunctiondeclinecalculator">https://www.sfdiabete.org/renalfunctiondeclinecalculator</a></li> <li>• Monitoring graph of eGFR with a non-linear scale for a more accessible demonstration of renal function decline</li> <li>• eGFR slope as a predictive indicator of cardiovascular risk and mortality by differentiating steep slope versus chronic slope</li> <li>• KFRE:               <ul style="list-style-type: none"> <li>◦ <a href="https://kidneyfailurerisk.com">https://kidneyfailurerisk.com</a></li> <li>◦ <a href="https://qxmd.com/calculate/calculator_308/kidney-failure-risk-equation-4-variable">https://qxmd.com/calculate/calculator_308/kidney-failure-risk-equation-4-variable</a> (also available as a mobile application: QxMed)</li> </ul> </li> </ul>
9	To develop a map of biological parameters by region in France to draw the attention of Regional Health Authorities on kidney diseases

**Abbreviations:** CKD: chronic kidney disease; CKD-EPI: chronic kidney disease-epidemiology collaboration; eGFR: estimated glomerular filtration rate; KeGFR: kinetic estimated glomerular filtration rate; KeUACR: kinetic urine albumin-to-creatinine ratio; KFRE: Kidney Failure Risk Equation; T2D: type 2 diabetes; UACR: urine albumin-to-creatinine ratio.

expertise, facilitating swift GP-specialist consultations, and remote monitoring, with nurses central to this coordination.

This manuscript delineates a model encapsulating HCP roles in diabetes and CKD management (Figure 2) and offers recommendations for enhanced patient care (Table 3).

#### 4. Conclusion

The progressive nature of CKD in patients with T2D and its association with an increased risk of CV and adverse kidney outcomes leads to shortened life expectancy, poor quality of life for these patients and sky-rocketing management costs. This paper raises awareness and informs HCPs on the importance of early diagnosis, monitoring renal function/damage (GPs and non-nephrologist specialists) using four biological parameters (eGFR UACR, KFRE, and blood potassium) to ensure an early biological diagnosis of CKD in patients with

diabetes in France. New tools such as KFRE represent a step forward for proper referral and optimal therapeutic intervention in most patients with renal impairment. Moreover, this project leverages input of HCPs (biologists, pharmacists, and nurses). It highlights the need to improve the coordination and communication between all HCPs involved in managing renal disease (specialists, interdisciplinary and multidisciplinary approaches).

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## Author contributions

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