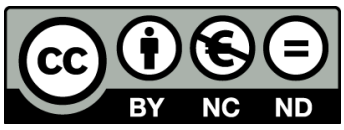
Universitat Internacional de Catalunya
Facultat de Medicina i Ciències de la Salut -
Departament de Medicina

Tesi doctoral

Out of the shell:

spreading renal knowledge into the community

Josep-Maria Galcerán Gui



uic
barcelona

DOCTORAL THESIS

Out of the shell:
spreading renal knowledge into the community

Author
Josep-Maria Galceran, MD

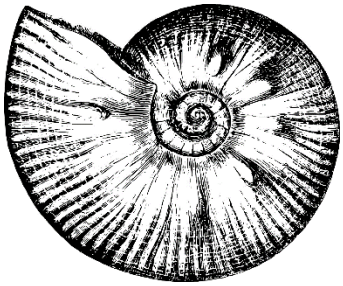


Image by Emmie Norfolk from Pixabay

Director
Xavier Corbella, MD, PhD, MBA

Doctoral Program in Health Sciences
Area of research: Translational, clinical and applied research

Universitat Internacional de Catalunya

2023

Abstract (English)

Chronic kidney disease (CKD) is a fast-growing condition, highly underdiagnosed and not optimally managed. Nephrology knowledge is quite variable among Primary Care physicians (PCPs) and patients tend to ignore their condition and may find difficult to follow the appropriate recommendations. Traditional organization leaves Primary Care with the task of CKD detection and management of patients at initial stages of the disease. Whenever a PCP needs to seek advice, this can only be formally done by initiating a referral, which, in turn, may result in extending the waiting list. As Nephrology workforce is scare and not expected to grow, it is important to ensure that patients who benefit most from in-person nephrologist consultation receive timely care while those at lower risk of progression are attended in Primary Care according to guidelines.

This PhD thesis evaluates the efficacy of a multifaceted intervention carried out along 10 years to avoid long waiting lists and ensure quick appropriate management of patients, consisting of a) a system of quick evaluation of referrals (referral filtering) that included the review of the patient's electronic health records and the return of inadequate ones with a recommendation of management, b) the launch of an electronic consultation platform from PCPs to hospital nephrologists, c) developing and spreading clinical practice guidelines for CKD manage into PCPs, and d) an app to help CKD patients and caregivers with diet requirements (PUKONO). It also describes the app usability and the referral profile to a Nephrology outpatient clinic and their adequacy rates.

The referral filtering system resulted in a quick 50% waiting time reduction for a first in-person appointment, but it was not until the full operational capacity of the e-consultation platform that traditional referral rate was reduced, mostly driven by a 44% traditional referral reduction from Primary Care. Eight years after the introduction of both measures, e-consults and traditional referrals represent 37% and 63% of all outpatient queries to Nephrology respectively. Mean response time for an e-consult has been 25.5 hours and most of them have been solved without the need for further in-person visit. Referral adequacy rates were 60-65% for both PCPs and other Hospital based specialties and did not change throughout the study. Both stable mild CKD (stage 3a) and moderate CKD (stage 3b) in the elderly are the most common cause of inadequate referral. Referral filtering and e-consultation have also achieved a shorter time to implementation of recommendations and important economic savings for both Hospital and patients.

CKD management guidelines have been developed and released to provide a useful source of knowledge for PCPs. Several issues were introduced which make a difference with most other guidelines published at that time i.e., the involvement of the government Department of Health, suggestion of clinical indicators to be used for quality evaluation and a proposal of models of shared management of patients between Primary Care and Nephrology Departments. PUKONO, the app, has been designed and released free of charge to help patients with CKD diet requirements; to avoid sodium, potassium and/or phosphorus intake in those patients with the need of restrictions. According to available data, PUKONO is the world's most widely downloaded app for CKD diet.

Providing PCPs and patients of useful tools to better manage CKD and improving Nephrology resource efficiency is a first step to try to delay CKD progression in the community, but if intelligent algorithms could be linked to electronic health records, it would further improve early detection and management, and hopefully would result in reducing the end stage renal disease burden.

Abstract (Catalan)

La malaltia renal crònica (MRC) és una patologia creixent, molt infradiagnosticada y no òptimament manejada. Els coneixements nefrològics son variables entre metges i metgesses d'Atenció Primària (MAP) i els pacients solen ignorar la seva condició i poden tenir dificultats per seguir les recomanacions. El sistema organitzatiu tradicional deixa en mans d'Atenció Primària les tasques de detecció i maneig de la MRC en els estadis inicials. Quan es vol formalment consell especialitzat, cal iniciar una derivació, amb el risc d'augmentar la llista d'espera. Com que les plantilles de Nefrologia son limitades i no es preveu ampliar-les, és important garantir la vista ràpida dels pacients que més es beneficien de la consulta especialitzada presencial, mentre que aquells en menor risc de progressió siguin atesos a Atenció Primària d'acord amb les directrius de les guies.

Aquesta tesi doctoral avalua l'eficàcia d'una intervenció multifactorial realitzada al llarg de 10 anys per evitar llargues llistes d'espera i garantir una gestió ràpida i adequada dels pacients, consistent en a) un sistema d'avaluació ràpida de les derivacions (filtratge) que inclou la revisió de la història clínica electrònica i el retorn de les inadequades amb una recomanació de maneig, b) la posada en funcionament d'una plataforma de consulta electrònica dels MAP als nefròlegs, c) l'elaboració i difusió de guies de pràctica clínica per al maneig de la MRC a Atenció Primària i d) una aplicació per a mòbils i tauletes (PUKONO) per ajudar a pacients amb restriccions dietètiques. També descriu la usabilitat de l'aplicació i el perfil de les derivacions.

El sistema de filtratge va comportar una ràpida reducció del 50% del temps d'espera per primera visita, però no va ser fins a la plena capacitat operativa de la plataforma de consulta electrònica que es va reduir la taxa de derivacions, impulsada fonamentalment per una reducció del 44% en derivacions clàssiques des d'Atenció Primària. Vuit anys després de la implantació d'ambdues mesures, les consultes electròniques i les derivacions tradicionals representen el 37% i el 63% de totes les consultes ambulatòries a Nefrologia, respectivament. El temps mitjà de resposta per a una consulta electrònica ha estat de 25.5 hores i la majoria d'elles s'han resolt sense necessitat de posterior visita presencial. Les taxes d'adequació de les derivacions van ser del 60-65% i no van canviar al llarg de l'estudi. Tant la MRC lleu estable (estadi 3a) com la MRC moderada (estadi 3b) en població d'edat avançada són la causa més freqüent de derivació inadequada. Les mesures adoptades també han aconseguit una reducció del temps per a la implementació de les recomanacions i un estalvi econòmic important tant per a l'hospital com per als pacients.

S'han elaborat i disseminat unes guies de pràctica clínica de que inclouen apartats diferencials amb la majoria d'altres guies de l'època, com son el suggeriment d'indicadors clínics de qualitat i una proposta de models de gestió compartida dels pacients entre Atenció Primària i Nefrologia, i la implicació del Departament de Salut. L'aplicació PUKONO s'ha dissenyat i posat en funcionament de manera gratuïta per ajudar als pacients a restringir la ingesta de sodi, potassi i/o fòsfor. Segons les dades disponibles, és l'aplicació més descarregada del món per a la dieta de la MRC.

Proporcionar eines als MAP i pacients per gestionar la MRC i millorar l'eficiència dels recursos de Nefrologia és un primer pas per intentar frenar la progressió de la MRC, però una eventual integració d'algorismes intel·ligents en la història clínica electrònica milloraria més la detecció precoç i el maneig adequat en les fases inicials, i es podria reduir així l'elevada càrrega que comporta la malaltia renal sobre els pacients i el sistema sanitari.

Index

1. Abbreviations

ABPM: Ambulatory Blood Pressure Monitoring

ACEI: Angiotensin Converting Enzyme Inhibitor

AKI: Acute kidney injury

ARB: Angiotensin Receptor Blocker

BP: Blood Pressure

CAMFiC: Catalan Society of Family and Community Medicine

CDSS: Clinical Decision Support Systems

CKD: Chronic kidney disease

CrCl: Creatinine clearance

DALYs: Disability-Adjusted Life-Years

eGFR: Estimated glomerular filtration rate

ESC: European Society of Cardiology

ESH: European Society of Hypertension

ESRD: End stage renal disease

GBD: Global Burden of Disease

GFR: Glomerular filtration rate

HbA1c: Glycated hemoglobin A1c

HTN: Hypertension

KDIGO: Kidney Disease Improving Global Outcomes

KDOQI: Kidney Disease Outcomes Quality Initiative

KFRE: Kidney Failure Risk Equation

MDRD: Modification of Diet in Renal Disease equation

MRA: Mineralocorticoid Receptor Antagonist

NSAID: Non-Steroidal Anti-inflammatory Drugs

PCPs: Primary Care physicians

RAS: Renin Angiotensin System

RAAS: Renin Angiotensin Aldosterone System

SCatHTA: Catalan Society of Hypertension

SCN: Catalan Society of Nephrology

sCr: Serum creatinine

SD: Standard Deviation

SEDEN: Spanish Society of Nephrology Nursing

SEN: Spanish Society of Nephrology

WHO: World Health Organization

2. Introduction

Not that long ago we didn't exist.
Still, we are just only a few, and that could be a serious problem…or not.
(JM. Galceran)

2.1. A brief history of Nephrology

Nephrology is quite a modern specialty; it started in the late 1940s with the initial approaches to treat severe acute renal failure with a rudimentary dialysis procedure (1,2). At the beginning, some internal medicine physicians who were interested in the field became progressively more focused on dialysis and also on rapidly progressive kidney diseases. It is thought that the first Nephrology unit was created by Jean Hamburger at the Hôpital Necker in Paris in 1951 (3); first long-term successful renal transplantation was done in Boston in 1954 (4) and first successful treatment with chronic dialysis for end stage renal disease (ESRD) in 1960 (5).

It took several years to follow those steps in Spain, and it was not until 1957 that the first hemodialysis procedure was carried out at Hospital Dos de Maig in Barcelona, the first Nephrology Department created at Fundación Jimenez Diaz in Madrid in 1962 and first successful human renal transplantation performed at Hospital Clinic in Barcelona in 1965 (6). Those initial crucial events were followed by a continuous movement of creation of new Nephrology Units and Departments in different Hospitals, the foundation of the Catalan Society of Nephrology (SCN) in 1963 and of the Spanish Society of Nephrology (SEN) in 1964, and finally the official recognition of Nephrology as an independent specialty in 1977 (6). From then on, Medicine graduates could choose to become nephrologists and to receive specific recognized education and training at certified hospitals.

2.2. A small army

Even expanding the area of knowledge to less severe renal damage and related comorbidities such as hypertension, and also becoming a reference not only for acute and chronic kidney disease but also for electrolyte and acid-base disorders and secondary and resistant hypertension, nephrologists have never been present in Primary Care centers in Spain and Nephrology Departments remain a facility only in middle-big size hospitals where hemodialysis is provided for ESRD. Certainly, roughly 0.1 % of the population is on renal replacement therapy (either dialysis or renal transplantation) (7) and only 1.5% has either important increases in serum creatinine or very high proteinuria (8); acute kidney injury (AKI) is highly incident in the hospital setting but not that much in the community (9) and although

resistant hypertension might affect 10-15% of treated hypertensive patients (10), these patients can also be referred to Hypertension Units in Internal Medicine Departments. According to this limited expected need, nephrologist training in Spain has also been quite restricted, in 1985 only 17 graduates could choose to undergo the Nephrology residency program; and although this figure was doubled quickly, only an average of 46 nephrologists/year were admitted until 2003 (11), much less than cardiologists (average 78/year), and even less than dermatologists (average 47/year) through the same time period (12). Not many Nephrology Units, not many nephrologists.

2.3. Nephrology, the great unknown

The general approach in Spain is that Primary Care physicians (PCPs) take care of detection of renal disease and management of mild and slow progressive chronic kidney disease (CKD). Whenever they feel the need to refer a patient to Nephrology they can, but even in some areas there will be an Internal Medicine physician filtering this request. As renal diseases are mostly asymptomatic until the most advanced stages, PCPs knowledge in CKD risk factors and management is a crucial issue. Population at risk has to be identified and markers of renal damage have to be tested regularly. Abnormal values have to be detected and adequate measures to prevent CKD progression have to be implemented. The Spanish official Family and Community Medicine Training Program does not include a compulsory rotation in Nephrology, and leaves this possibility to be chosen as an optional rotation (13). This may result in major differences in nephrological skills among PCPs and indeed, some observations suggest that these skills could be quite poor (14). Therefore, renal damage might not be detected until severely established, thus losing the possibility of implementing earlier corrective measures; or minor abnormalities might be overestimated and generate inadequate referrals.

2.4. To refer or not, the importance of how to measure renal function

The referral issue is of greater importance. If Nephrology units with outpatient clinic facilities are few, it is crucial that these resources would be efficient. Visiting patients with minor abnormalities or low risk of CKD progression does not add value to patient care and in any way, it should not result in excessive delay in visiting patients with significant renal damage. In fact, for many years first appointment request to Nephrology outpatient clinics had been quite restrained. Traditional way of evaluating renal function was to measure serum creatinine level (sCr), an easy and unexpensive laboratory test. Still, it had been long known that sCr is quite an imperfect marker, it does not only depend on kidney function but on many other factors such as muscle mass, protein intake, drug interference and extrarenal removal (15). Even in terms of

renal excretion, creatinine is mainly eliminated due to glomerular filtration without tubular reabsorption, thus reflecting glomerular filtration rate (GFR), but also by active tubular secretion, which grows with increasing sCr concentrations (15). Moreover, sCr does not follow a linear but an exponential relationship with creatinine clearance (CrCl), it hardly ever rises before CrCl is clearly below 60 ml/min/1.73m^2, and it increases extremely quickly at CrCl <15 ml/min/1.73m^2 (15). Thus, CrCl would appear to be a better approach to real renal function, but it does also show some problems, mainly a greater variability than sCr and the difficulty to rely on a real 24-hour urine collection by the patient (15). As muscle mass is a major confounding for the usefulness of sCr to measure renal function, in 1976 Cockcroft and Gault developed a simple equation that modulated sCr values with patient's age, weight and sex (all of them related with muscle mass), thus showing a better correlation with real renal function (16). However, the need to know the patient's weight to make the calculation prevented this equation to be widely adopted and, apart from nephrologists, it was just used for drug dose adjustment in patients with impaired renal function (17).

A major change began in 1999 with the publication of the Modification of Diet in Renal Disease equation (MDRD), a quite accurate estimate of renal function based on sCr that did only take into account items that any lab can obtain from a usual request: age, gender and race (18). MDRD clearly showed that people with very mild increases of sCr, even within normal values (mostly in the elderly women group), did have indeed significant reductions of GFR.

A second landmark point occurred when evidence was shown that that mildly impaired renal function was an ominous prognostic factor, not only for eventual progression to ESRD but mainly for both cardiovascular and all-cause mortality (19-21). With the strength of that evidence coming from numerous studies, in 2007 the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) put a statement in their guidelines emphasizing that "estimated GFR constitutes a very potent predictor of future cardiovascular events and death even in treated patients. Therefore, it is recommended that glomerular filtration rate is estimated, and the presence of urinary protein sought in all hypertensive patients" (22). By that time, the SEN and the Spanish Society of Clinical Biochemistry and Molecular Pathology had already delivered a document encouraging all Spanish clinical labs to report estimated GFR (eGFR) along with sCr values (23). In a few years this recommendation had been widely implemented and any physician would know his/her patient's eGFR whenever they ordered a sCr lab test.

2.5. The referral tsunami

The “fire” had been set. PCPs came to know that an important percentage of general population had a significant reduction in renal function (<60 ml/min/1.73m^2), as much as 11-15% in the 65-74 age group and even >30% in people 75 and over (24), and this was associated to a significant increase in morbidity and mortality. For years they hadn’t paid much attention to those “nearly normal” sCr values and all of a sudden, they realized that many of their patients had renal failure. They became seriously alarmed and most of them were absolutely unfamiliar with the management of CKD. The solution was clear: refer all those patients to the nephrologist.

In just 2 years, referrals to Nephrology units increased as much as 270% (25-30), many of them became oversaturated and the outpatient waiting time increased exponentially.

2.6. The clinical significance of CKD, strengths and weaknesses of CKD staging

Reduced eGFR clinical significance is synthetized in Figure 1, as shown in the Kidney Disease Improving Global Outcomes (KDIGO) guidelines (31). The more reduced eGFR and/or the greater amount of proteinuria, the greater renal and cardiovascular risk.

Figure 1. KDIGO Chronic Kidney Disease classification and prognosis (ref. 31).

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/ 1.73 m^2) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

However, this useful and easy to remember classification does not take into account two important factors: patient’s age and rate of GFR decline. Aging is associated with reductions in the glomerular capillary plasma flow rate, loss of renal mass, arteriolar hyalinization and a

certain degree of glomerular sclerosis and tubulointerstitial fibrosis (32). Consequently, GFR declines by approximately 1 ml/min/m^2 per year in the general population, beginning in the third decade of life (33). Certainly, this mean reduction includes both CKD patients and healthy people, but even in healthy subjects a 0.7- 0.9 ml/min/m^2 per year decline is observed (34). As for CKD progression rate, it has also been shown that a slower decline in GFR is associated with a lower cardiovascular risk (35,36). Therefore, patients allocated in the same KDIGO classification box might indeed show a much different renal and cardiovascular risk, a very important issue when considering referrals.

Having observed the great impact of automated eGFR reporting on Nephrology referrals, us and others tried to modulate this request by remarking that the added risk for progression to ESRD and cardiovascular morbidity and mortality is very low in aged patients with mild GFR decrease (45-60 ml/min/1.73m^2) and no proteinuria (33,37-40), which account for a big amount of those referrals. But all these efforts had very little effect on PCPs' practice, and the problem didn't change much.

2.7. The patient factor

A better medical practice in CKD management is of paramount importance, but the "Health equation" does not only include medical skills and knowledge, it does also include patients. The patient factor is frequently ignored or undervalued but patients manage their health on their own most of the time, making decisions daily that affect their health… and costs. Patients who are more engaged and with a deeper subject matter knowledge have better health outcomes and care experiences (41-44). Personal health literacy is "the degree to which individuals have the ability to find, understand, and use information and services to inform health-related decisions and actions for themselves and others" (45). Levels of health literacy vary among chronic disease patients according to sociodemographic and disease characteristics (46), and have been shown to be quite low in CKD patients (47,48), even in those attending Nephrology clinics regularly (49). In order to improve patient's health literacy, "educational materials must be developed and disseminated to patients" (50), this being one of several actions that have to be taken (47).

2.8. The importance of a correct diet, and the difficulty of a good adherence

Hydro-electrolytic disturbances are a matter of great concern in CKD patients. As CKD progresses, electrolyte abnormalities become more prevalent (51) due to impaired excretion. Increased sodium intake is related to high blood pressure and weight gain, hyperkalemia may

induce fatal arrhythmias and hyperphosphatemia promotes hyperparathyroidism and vascular calcification. Thus, control of sodium, potassium and phosphorus intake is essential in CKD patients. Following these recommendations might be difficult (48) because of the large list of foods that have to be restricted, particularly added to other dietary restrictions as it is for diabetic or dyslipidemic subjects. Patients are expected to memorize those lists or carry with them nutritional booklets which can also be cumbersome. With the arrival of new technologies, more comfortable and practical tools can be developed to help improve patients' adherence to diet.

2.9. How to overcome, spreading renal knowledge into the community

CKD is hence a serious problem for patients and Health systems. Poor patient's Health literacy and engagement could result in worse clinical outcomes and insufficient PCPs knowledge on CKD management may result in less detection of renal diseases and excess of referrals, pushing the waiting list for an outpatient visit to unacceptable standards, with the threat that patients who would benefit from a quick visit to the nephrologist for a prompt diagnose and treatment face a dangerous delay because other patients with no clear benefit (but still specific needs due to the reduced GFR) collapse the agendas.

As the Nephrology workforce is not expected to grow significantly despite the increasing prevalence of CKD and ESRD (even a reduction in the number of nephrologists per 1,000 ESRD patients can be observed in countries like the USA) (52), something has to be done. The nephrologist cannot wait in the office while the problem grows outside. We have to come out of the shell, teach other physicians, mainly PCPs, how to deal with renal issues and also teach patients how to do to better delay CKD progression and associated morbidity risk. And while doing so, actions have to be taken to ensure efficient use of resources.

3. Hypothesis

Providing PCPs, CKD patients and caregivers of useful tools to help improve renal knowledge and management will avoid visiting patients with mild conditions and low added value at the Nephrology outpatient clinic, thus preventing saturation of the outpatient clinic capacity, reducing waiting lists, and also ensuring a quicker implementation of recommended treatments and cost reductions.

4. Aim

Primary Objective

To evaluate the efficacy of a multifaceted intervention consisting of 1) a system of quick evaluation of referrals, 2) the launch of an electronic consultation platform from PCPs to hospital nephrologists, 3) spreading clinical practice guidelines for CKD manage into PCPs, and 4) a new electronic guidance tool for CKD patients and caregivers in preventing avoidable hospital referrals of CKD patients with mild conditions and low added value at 2 counties in Catalonia (Bages and Solsones; population n= 168,087).

Secondary Objectives

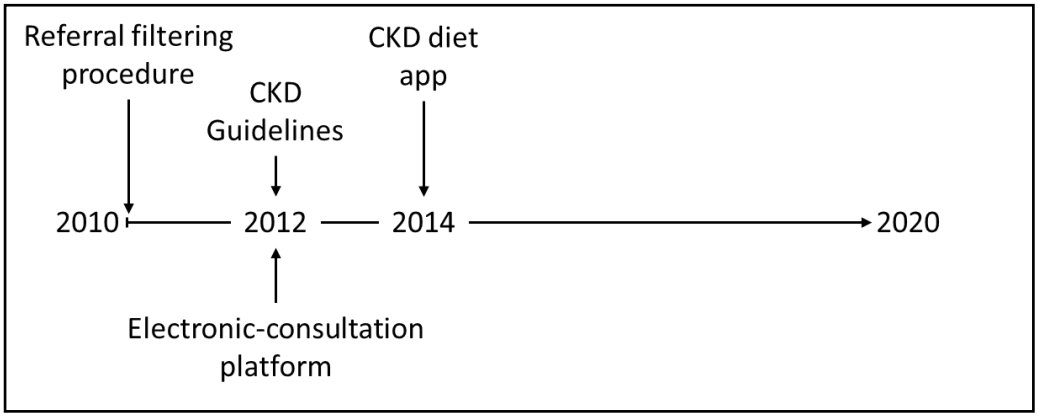
To describe the referral profile to a Nephrology outpatient clinic and their adequacy rates.

To evaluate the amount and type of consultation of an electronic specific tool for helping CKD patients with diet compliance.

5. Methods

Starting 2010, progressive measures were introduced to reduce avoidable referrals to the Nephrology outpatient clinic and to improve CKD patients' management.

Figure 2. Action schedule



5.1. Referrals and electronic consultation to Nephrology outpatient clinic

5.1.1. Referral profile and filtering procedure

Study Design: observational, descriptive and longitudinal

Study population: Referrals from 2 counties in Catalonia (Bages and Solsones; population n= 168,087) to the Nephrology outpatient clinic at Fundació Althaia, Manresa in a 10-year period (April 2010 – March 2020).

Referral requests were evaluated by a single nephrologist and considered appropriate or not according to the previously mentioned CKD guidelines (53). Inappropriate requests could be discarded and sent back with recommendation of management, providing a way of feedback (whether e-mail or consultation in a specific electronic platform) to allow further doubts to be worked out.

Variables:

- Total amount of referrals by origin (primary care, private insurers, emergency unit, other hospital-based departments, long-term care hospitals, penitentiary and others) and annual, seasonal, monthly and daily variation
- Referrals by groups of age and sex

- Diagnosis on referral (or reason for referral) by origin and annual variation
- Diagnosis on referral (or reason for referral) by groups of age and sex
- Referrals with previous electronic consultation
- Adequacy ratio by origin and annual variation
- Rate of discarded referrals
- Inappropriate referrals by reason, referrals' origin and annual variation
- Accepted inappropriate referrals by reason, referrals' origin and annual variation

5.1.2. Communication platform for electronic queries from PCPs

A communication platform was developed to enable PCPs to send electronic queries to specialists. All nephrologists in our department attend these e-consults, which are assigned in a rotating basis. When accessing the general Electronic Health Record System, a pop-up message notifies that there is an e-consult, which can be opened at that time or left aside for a later response. When the e-consult is accepted, the specialists access the patient's electronic medical records so as to have full information and leave their recommendations recorded.

Analyzed items have been:

- Total amount of electronic queries and annual variation
- Query response time and annual variation
- Electronic queries solved without a resultant referral

5.1.3. Referral filtering and electronic guidance efficiency

- Number of visits avoided by the referral filtering scheme
- Nephrology outpatient clinic waiting list evolution
- Within discarded referrals sent back with specific recommendation of management, time to implementation of recommendations (days). In these cases, Primary Care electronic medical records were reviewed to identify if recommendations had been carried out and when.
- Hospital cost savings by avoided visits. Costs: Direct (Nephrology physician-nurse human outpatient-related resources, materials…) and indirect (structure and support services such as administrative resources, information technology, amortization, maintenance services, laundry and cleaning) Hospital costs have been calculated since 2018 with SAP Product Lifecycle Costing (SAP trademark software services).

5.2. Spreading renal knowledge into PCPs by CKD guidelines

Development and release of comprehensive clinical practice guidelines for CKD manage in Primary Care, with the participation of the main Catalan scientific societies concerned, together with the involvement of the Department of Health, Generalitat de Catalunya (53, Annex 1a-1b). A working group was appointed, which reviewed the compelling literature, wrote the sections and the final document was amended by reviewers before guidelines were presented, released and published.

5.3. Spreading renal knowledge into CKD patients and their environment

5.3.1. Development of an app for mobile phones to help adherence to CKD diet

A group of investigators from the Nephrology Department at the Fundació Althaia, Manresa, elaborated a list of useful functionalities regarding dietary counselling for CKD patients, including fluid, sodium, potassium and phosphorus restriction, along with food preparation techniques to reduce the content of these elements. The initial list was submitted to dialysis and non-dialysis CKD patients through interviews for feedback and improvement. A joint venture was set with the Alicia Foundation, a local institution devoted to the improvement of eating habits and food challenges in specific illness so as to include an attractive list of suitable menus for CKD patients. Finally, we brought the project to practice with app and graphic designers (Sixtemia Mobile Studio), the Legal Department at Fundació Althaia, and financial support (AMGEN Spain).

Backend: The database is hosted on a web server with the contents of the application (food, recipes…), which can be modified at any time thanks to a web content manager (CMS), which allows to synchronize the server with the database in the mobile phone or tablet app via REST-JSON webservices. Food database is provided by the Spanish Society of Hypertension.

Frontend: Formed for a mobile app for iOS and Android. It has been developed using Apple's development tools and Google (SDK's). The app is designed in a way that it can run without internet access once synced for the first time with the backend.

The app (PUKONO) is available free of charge on iOS and Android in three languages (Catalan, Spanish and English) and provides instant graphic information about specific contents of P, K and Na by type of food and serving; a safety degree color code for CKD patients and tips for food preparation along with demonstrating videos. It does also provide suitable recipes and menus and allows sharing and mail interaction.

5.3.2. App usability

Study Design: observational, descriptive and longitudinal

Study period: Since app release in July 2014 till June 2021 (7 years)

Study population: Users who have downloaded the application

Variables:

- Number of downloads, total monthly rate (± SD) and by origin
- Patient/caregivers use ratio and other users profile details
- Rates of consultation of functionalities

5.4. Statistics

Data collected and unified in Access Database. Debugging process with elimination of duplicates and wrong records. Subsequently, tables and graphs have been produced by statistical exploitation. Statistical treatment of the data has been carried out with the support of Access (SQL) queries and Microsoft Excel's Pivot Charts and Tables (2016 version). For the description of continuous variables, mean, standard deviation, 95% confidence interval of the mean, median, and the minimum and maximum were used, including the total number of valid values. Comparison between groups has been performed with Chi-square and Fisher tests. Data is presented as Grouped Data & Frequency Distribution Tables. Dynamic graphics were created to better understand the results' evolution over time. App usability data analyzed through Flurry Analytics platform.

6. Results

6.1. Referrals and electronic consultation to Nephrology outpatient clinic

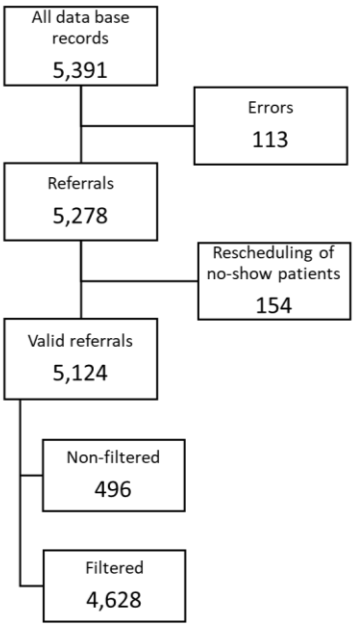
The Nephrology Department at Fundació Althaia, a University Hospital in Catalonia, Spain, covers an area of five counties and 253,083 total population. It has an outpatient clinic in the main hospital at Manresa, Barcelona, and 2 other outpatient clinics in hospitals at Berga, Barcelona, and Puigcerda, Girona. These latter clinics run autonomously. Results are offered for a 10-year period (April 2010 – March 2020) at the main outpatient clinic at Manresa, which covers an area of 3 counties and 194,981 total population (168,087 >15 years, real target population for an adult Nephrology Department) (54). Population is attended in 15 Primary Care Areas which can refer patients to specialties. Other facilities that can refer patients to Nephrology are long-term care hospitals, a penitentiary, private insurers and other university hospital-based departments, as well as the Emergency Unit.

6.1.1. Referral profile, adequacy and filtering procedure

6.1.1.1. Total amount of referrals

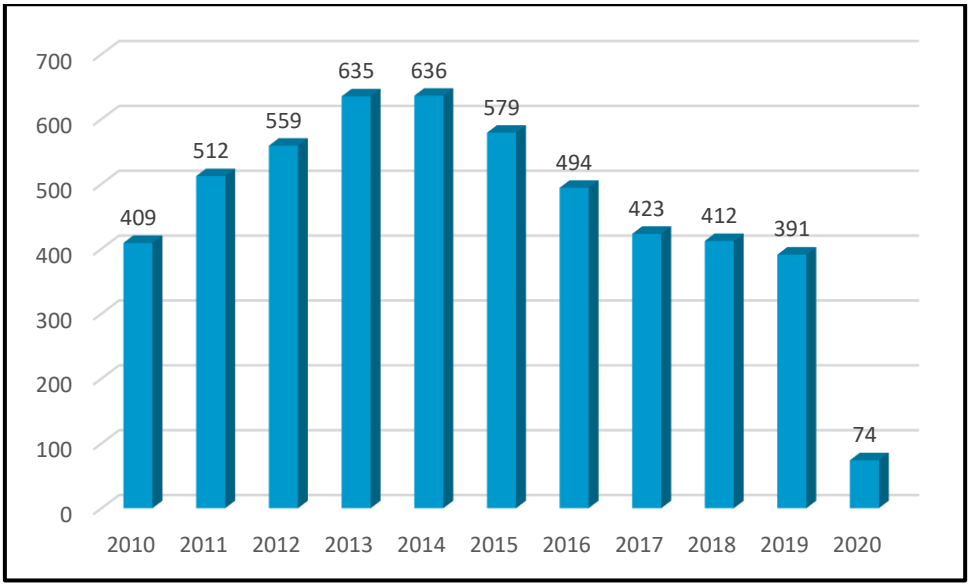
From April 2010 till March 2020, 5,391 referrals to the Nephrology outpatient clinic were registered. The database debugging and workout process is shown in Figure 3; 113 records are considered errors due to several reasons: a) a virtual visit was created for other purposes, or b) the referral request was not found and visit was not scheduled, or c) were indeed subsequent visits, or d) were really addressed to other agendas within the Nephrology Department (i.e., echography, advanced CKD…). 154 records are rescheduling of no-show patients, which should not be taken into account for the analysis as they are really duplicates, but they do have an impact on the waiting time for a first appointment. The remaining 5,124 records are considered valid referrals. A single nephrologist evaluated and filtered all referrals except for those received during summer holidays (in order not to delay appointments) and those which were automatically scheduled avoiding the protocol.

Figure 3. Database workout flowchart.



Valid referrals distribution along the study period and monthly rates are shown in Figure 4 and Figure 5. A significant trend for reduction over time is seen, mainly concentrated in the time period 2014-2017. Monthly variation is shown In Figure 6; an important reduction is observed during the usual summer holiday period (August till mid-September). The number of referrals received per day varied mainly between 0 and 4, but as many as 10 were occasionally received (data not shown).

Figure 4. Referrals yearly distribution*.



* 2010 includes referrals April-December. 2020 includes referrals January-March.

Figure 5. Referrals monthly rates and trend line.

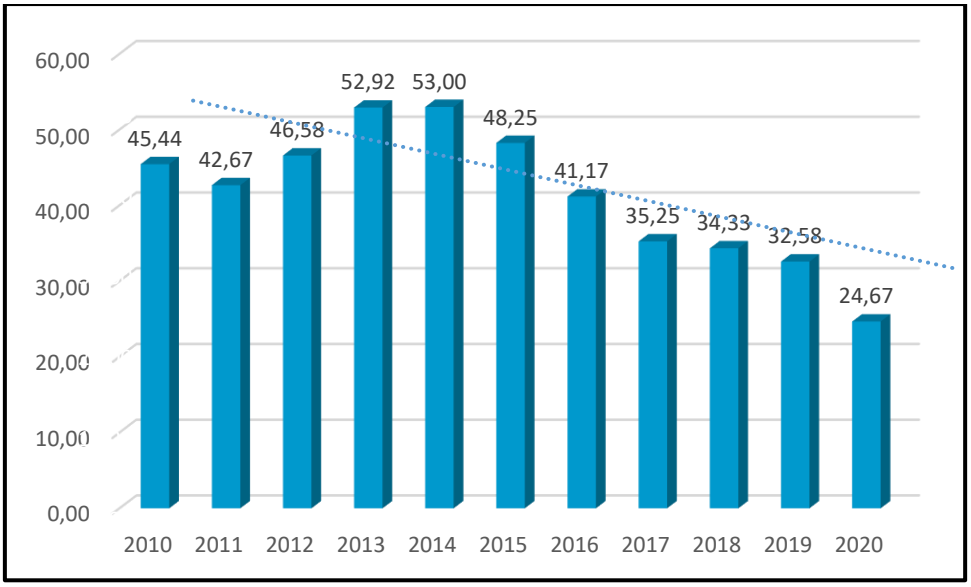
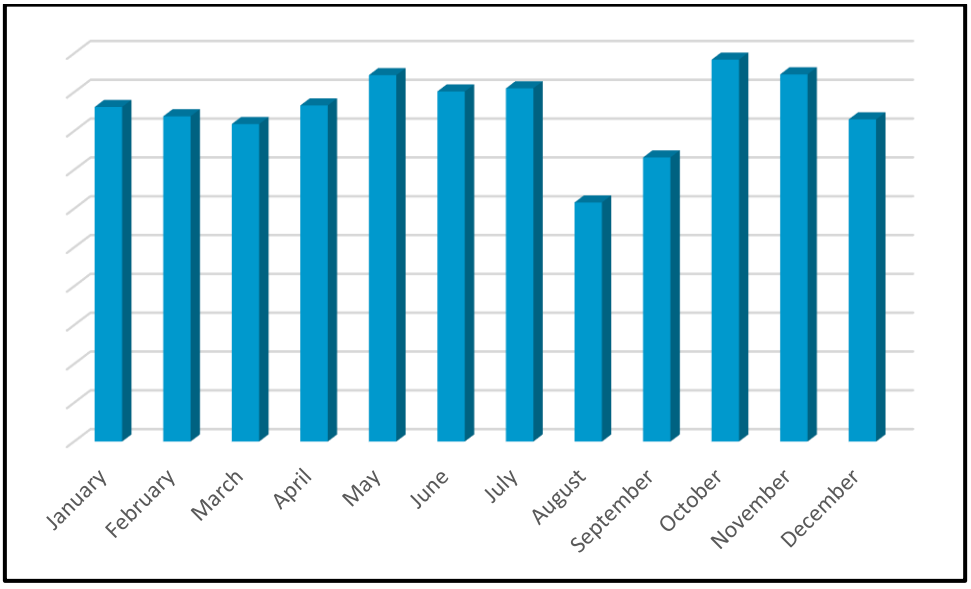


Figure 6. Referrals seasonal variation.



As for the type of requesters profile, the majority of referrals come from Primary Care (63.33%), followed by other Hospital-based Departments (29.16%). The Emergency Unit accounts for 4.74% referrals and Private insurers 1.09%, the rest coming from other institutions (Figure 7).

Detailed distribution of other Hospital-based Departments referring patients to Nephrology is shown in Figure 8. The Internal Medicine Department is the main requester (16.98%), closely followed by Urology (14.74%). Smaller Departments as Endocrinology (10.73%) and Hematology (9.04%) are also frequent requesters. Importantly, the Occupational Health Unit accounts for an important volume of referrals (11.62%).

Figure 7. Referral requesters profile.

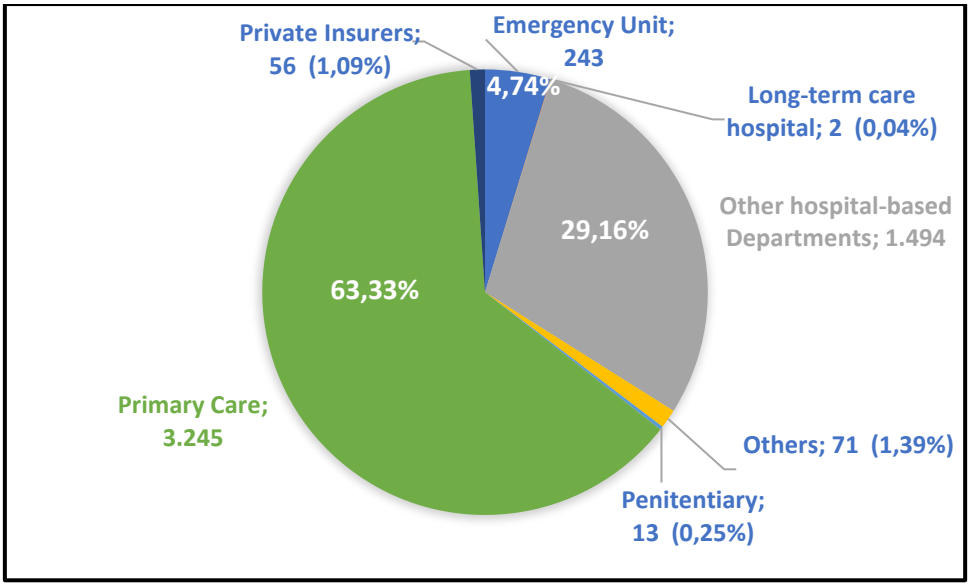
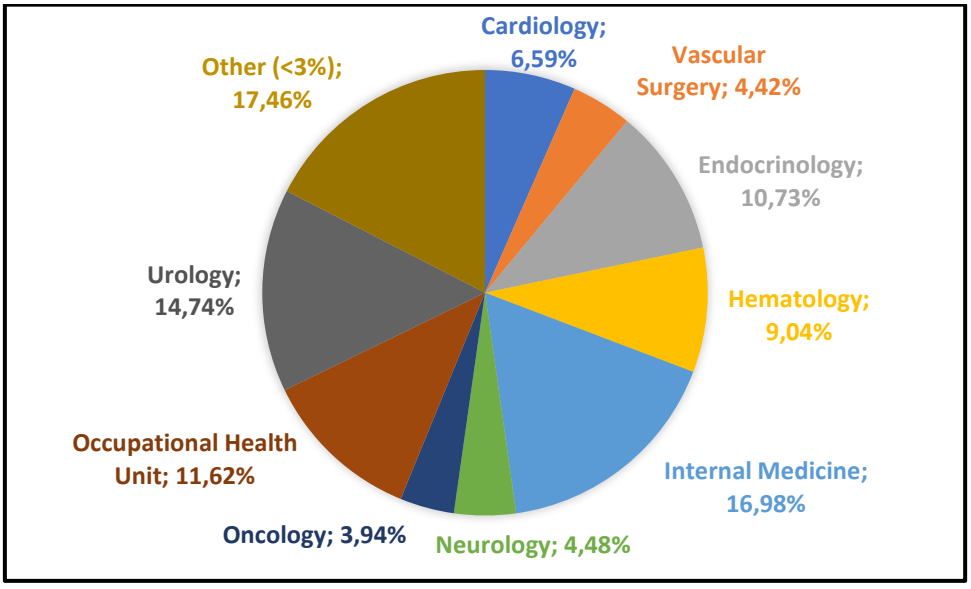
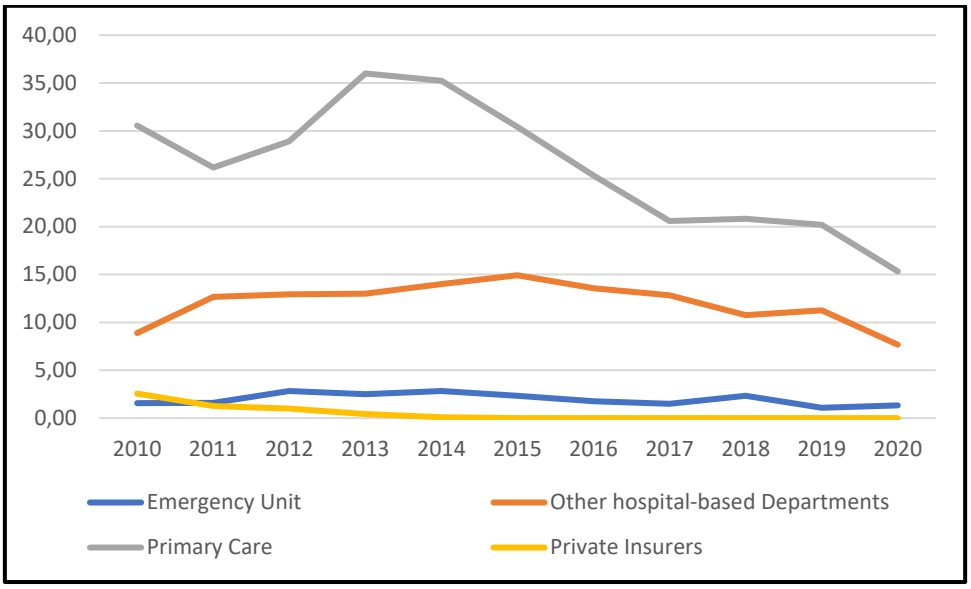


Figure 8. Hospital-based Department's referrals to Nephrology.



When looking at the evolution of referrals by type of requester over time (Figure 9), both the Emergency Unit and other Hospital-based Departments show a fairly stable pattern. Main changes are seen for Primary Care behavior, with a mild increase in referrals rate from 2010 till 2013, a significant decrease from 2014 till 2017 and stability thereafter. Data from 2020 should be interpreted cautiously as it does only come from 3 months, including the first month of the COVID-19 pandemic. Thus, the aforementioned reduction in referrals over time shown in figure 5 is mostly due to Primary Care behavior. Private insurers referrals were attended by a single nephrologist who retired in 2013.

Figure 9. Referrals by requester profile over time (monthly rates/year). Only data for main requesters is shown.



6.1.1.2. Referrals by groups of age and sex

The proportion of male and female patients is quite balanced (51.2%/48.8% respectively). Age distribution is showed in Figure 10; the majority of referrals involve people over 50 years old (78.5%). Considering distribution by groups of age and sex, females tend to be older than males (Figure 11).

Figure 10. Referrals by age group (years).

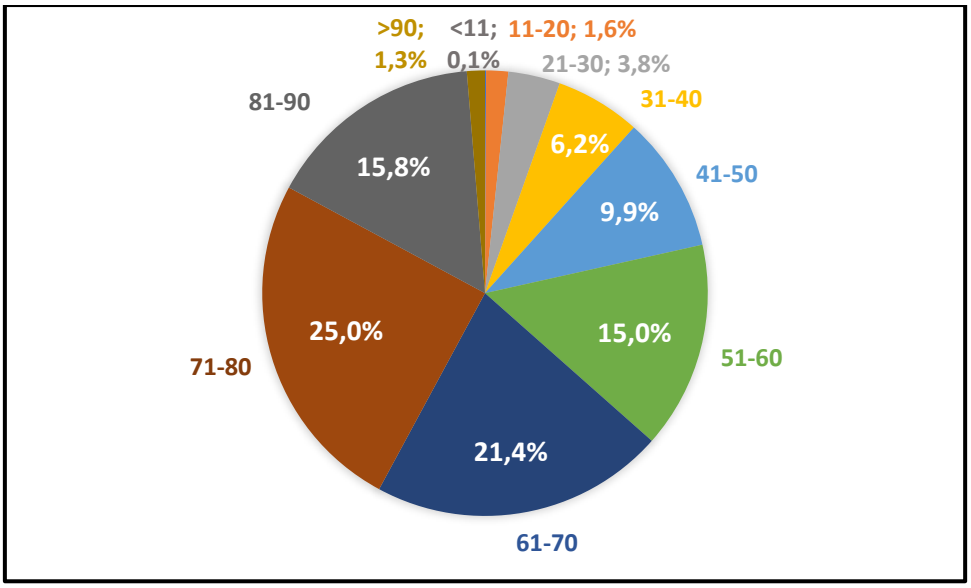
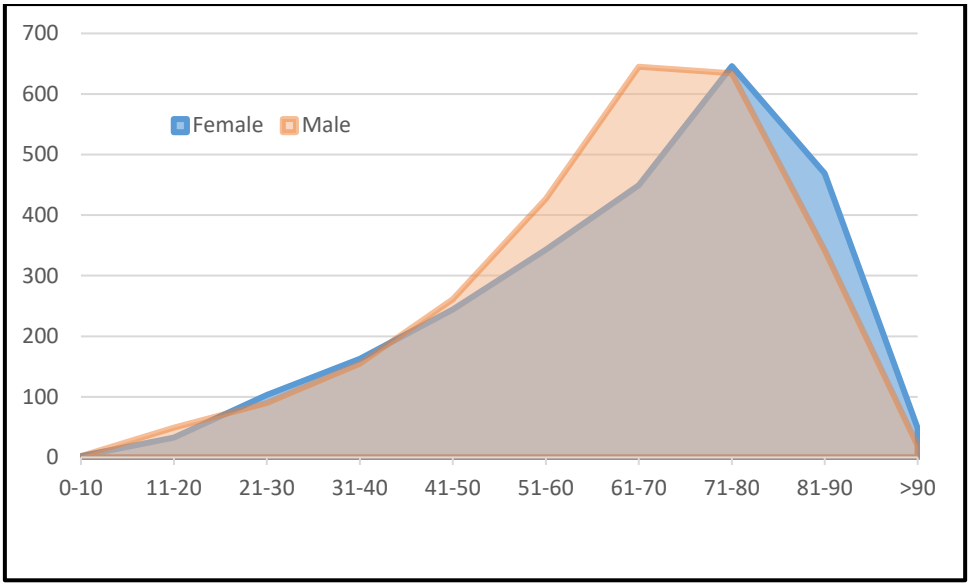


Figure 11. Distribution by groups of age and sex.



6.1.1.3. Diagnosis on referral (or reason for referral) by origin and annual variation

Reasons for referral are shown in Tables 1-2 and Figure 12. As expected, CKD with reduced eGFR, worsening of renal function, HTN and proteinuria account for the majority of referrals (73.51%). Remarkably, electrolyte disorders represent only a very small percentage (1.80%). Loss of follow-up is also a major reason for referral (7.30%). In our institution, patients who have not been scheduled during 12 months need a new referral to be revisited. Finally, the similarity between the words “Neurology” and “Nephrology” generates quite a frequent mistake (1.03% of referrals).

Table 1. Comprehensive list of diagnosis on referral (or reason for referral) by frequency.

Reason for referral	n	%
Significant impairment of renal function	752	14.68%
Proteinuria	625	12.20%
CKD stage 3b	463	9.04%
Loss of follow-up	374	7.30%
Resistant HTN	371	7.24%
CKD stage 4	355	6.93%
Progressive deterioration of renal function	307	5.99%
Difficult to control HTN	278	5.43%
CKD stage 3a	189	3.69%

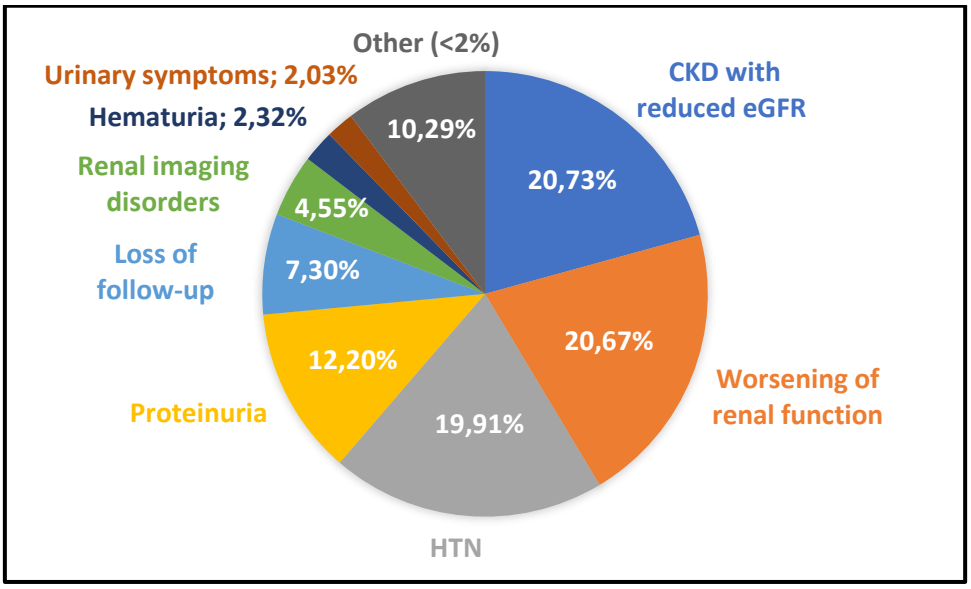
Suspected secondary HTN	152	2.97%
Hematuria	119	2.32%
Renal cysts	106	2.07%
Anemia	88	1.72%
HTN in young adults (<35 y)	88	1.72%
Vascular risk	84	1.64%
Other renal imaging disorders	78	1.52%
Others	63	1.23%
CKD stage 5	55	1.07%
Error (mistaken for Neurology)	53	1.03%
Recurrent urinary tract infections	53	1.03%
Hyperkalemia	47	0.92%
Kidney transplant, shared visits with transplantation center	47	0.92%
Renal colic	32	0.62%
HTN with target organ damage	30	0.59%
High BP and pregnancy	30	0.59%
HTN with multiple side effects	29	0.57%
BP variability	28	0.55%
Edema	25	0.49%
Renal lithiasis	24	0.47%
Kidney donor study	23	0.45%
Solitary kidney	21	0.41%
Other electrolyte disorders	20	0.39%
Reason for referral not stated	28	0.55%
Hypokalemia	15	0.29%
Hyperparathyroidism	13	0.25%
ABPM request	13	0.25%
Transfer from Pediatric Nephrology	13	0.25%
Hyponatremia	10	0.20%
Polyuria	8	0.16%
Oliguria	7	0.14%
Family history of polycystic kidney disease	4	0.08%
Lower urinary tract symptoms	4	0.08%

Table 2. Diagnosis on referral (or reason for referral) grouped by disease or condition and frequency.

CKD		**20.73%**
	Stage 3a	3.69%
	Stage 3b	9.04%
	Stage 4	6.93%
	Stage 5	1.07%
Worsening of renal function		**20.67%**
	Significant impairment	14.68%
	Progressive deterioration	5.99%
HTN		**19.91%**
	Resistant	7.24%
	Difficult to control	5.43%
	Suspected secondary	2.97%
	Young (<35 y)	1.72%
	With target organ damage	0.59%
	High BP and pregnancy	0.59%
	With multiple side effects	0.57%
	BP variability	0.55%
	ABPM request	0.25%
Proteinuria		**12.20%**
Loss of follow-up		**7.30%**
Renal imaging		**4.55%**
	Cysts	2.07%
	Lithiasis	0.47%
	Solitary kidney	0.41%
	Family history of polycystic kidney disease	0.08%
	Other	1.52%
Hematuria		**2.32%**
Urinary symptoms		**2.03%**
	Recurrent urinary tract infections	1.03%
	Renal colic	0.62%

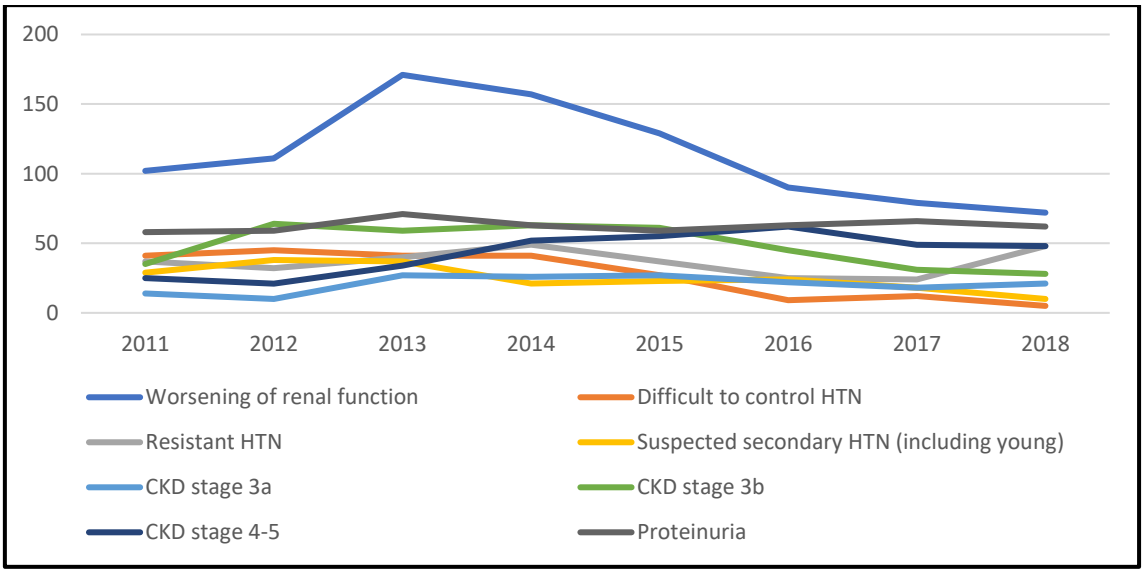
	Polyuria	0.16%
	Oliguria	0.14%
	Lower urinary tract symptoms	0.08%
Electrolyte disorders		**1.80%**
	Hyperkalemia	0.92%
	Hypokalemia	0.29%
	Hyponatremia	0.20%
	Other	0.39%
Anemia		**1.72%**
Vascular risk		**1.64%**
Kidney transplant		**1.37%**
	Shared visits with transplantation center	0.92%
	Kidney donor study	0.45%
Others		**1.23%**
Error (mistaken for Neurology)		**1.03%**
Reason not stated		**0.55%**
Edema		**0.49%**
Hyperparathyroidism		**0.25%**
Transfer from Pediatric Nephrology		**0.25%**

Figure 12. Main groups of diagnosis on referral.



Annual variation according to reason for referral is shown in Figure 13. The mild increase in referrals rate from 2010 till 2013, the significant decrease from 2014 till 2017 and stability thereafter is mostly driven by "Worsening of renal function" referrals. Other referrals which show an important decrease over time are both "Difficult to control HTN" and "Suspected secondary HTN", and also "CKD stage 3b". "Proteinuria" referrals remain stable over the study period while "CKD stage 4-5" referrals increase from 2011 till 2014 and remain stable thereafter.

Figure 13. Main reasons for referral over time (only years with full 12-month data).



6.1.1.4. Diagnosis on referral (or reason for referral) by groups of age and sex

Reasons for referral in males and females are shown in table 3. Some differences are either obvious (i.e., high BP and pregnancy) or to be expected (recurrent urinary tract infections). Males are significantly more frequently referred because of CKD stage 3b, proteinuria and vascular risk, while females because of anemia, BP variability and other renal imaging disorders. Interestingly, females are significantly more frequently referred for kidney donor study. In terms of suspected secondary HTN, females seem significantly more frequently referred but HTN in young adults (which indeed is a specific form of suspected secondary HTN) seems more frequent in males.

Table 3. Reason for referral in males and females.

	Female (n=2500)	Male (n=2624)	p-value
ABPM request	9	4	0.17
Anemia	60	28	<0.001
BP variability	20	8	0.016
CKD stage 3a	87	102	0.440
CKD stage 3b	205	258	0.042
CKD stage 4	170	185	0.724
CKD stage 5	21	34	0.114
Difficult to control HTN	144	134	0.302
Edema	17	8	0.054
Error (mistaken for Neurology)	24	29	0.608
Family history of polycystic kidney disease	3	1	0.363
Hematuria	52	67	0.261
High BP and pregnancy	30	0	<0.001
HTN in young adults	27	61	<0.001
HTN with multiple side effects	16	13	0.491
HTN with target organ damage	12	18	0.334
Hyperkalemia	22	25	0.785
Hyperparathyroidism	9	4	0.17
Hypokalemia	10	5	0.165
Hyponatremia	6	4	0.540
Kidney donor study	17	6	0.016
Kidney transplant, shared visits	23	24	0.984
Loss of follow-up	191	183	0.360
Lower urinary tract symptoms	3	1	0.363
Oliguria	5	2	0.278
Other electrolyte disorders	9	11	0.734
Other renal imaging disorders	58	20	<0.001
Polyuria	4	4	1.000
Progressive deterioration of renal function	154	153	0.620
Proteinuria	208	417	<0.001
Recurrent urinary tract infections	49	4	<0.001

Renal colic	17	15	0.623
Renal cysts	59	47	0.153
Renal lithiasis	13	11	0.597
Resistant HTN	180	191	0.913
Significant impairment of renal function	378	374	0.381
Solitary kidney	14	7	0.101
Suspected secondary HTN	94	58	0.001
Transfer from Pediatric Nephrology	6	7	0.849
Vascular risk	25	59	<0.001
Reason for referral not stated	17	11	0.206
Other	32	31	0.749

Reasons for referral by groups of age are shown in Table 4 (comprehensive list) and Figure 14 (main reasons for referral percentage by group of age). Suspected secondary HTN is the major cause for referral in both 21-40 and <21y age groups, followed by transfer from Pediatric Nephrology in <21y and loss of follow up in 21-40y. Remarkably, hematuria is a much more frequent reason for referral in these young patients compared with the rest, probably driven by suspected IgA nephropathy, a disease that frequently appears when people are in their teens to late 30s.

In patients 41-60y, HTN is still the major cause for referral but mostly due to the difficulty to achieve control rather than to discard a secondary etiology. Proteinuria is the second most important reason for referral in this group.

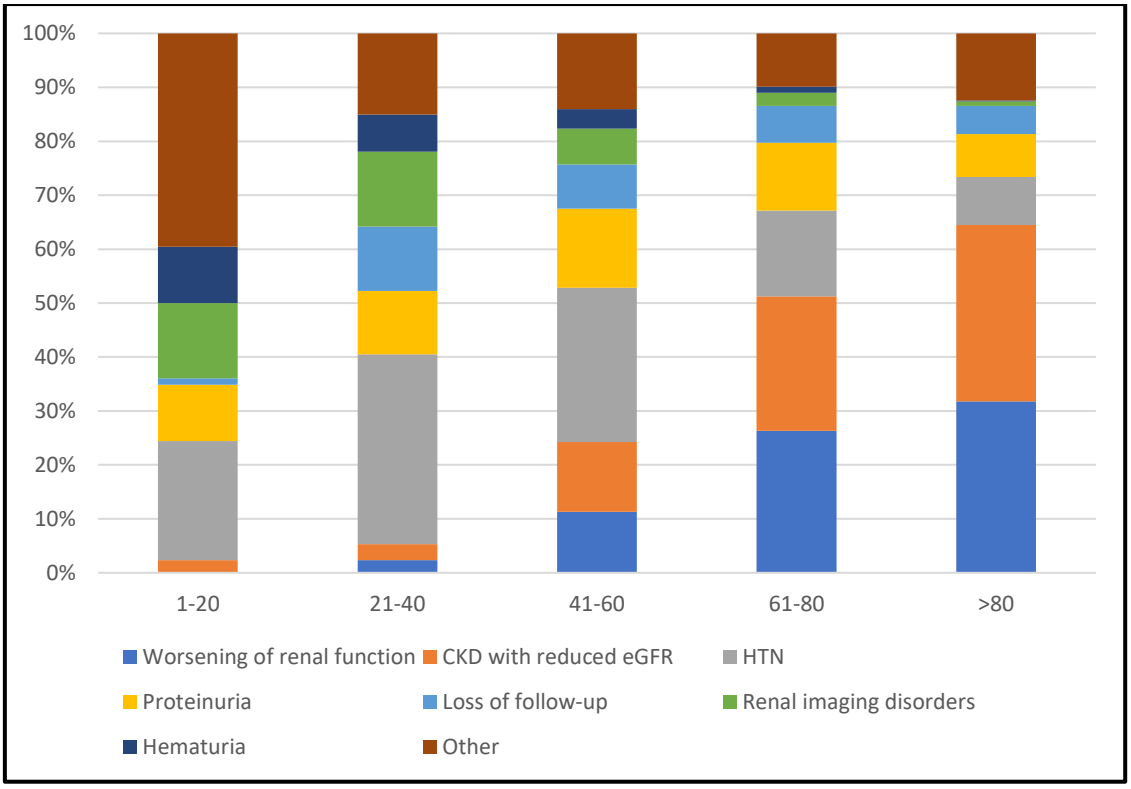
Worsening of renal function and CKD with reduced eGFR are the main reasons for referral in people >60y. Anemia is quite an infrequent reason for referral except for patients >80y, reflecting the common association of reduced hemoglobin levels and reduced renal function in this population.

Table 4. Reason for referral by groups of age. Comprehensive list.

Age (y)	1-20	21-40	41-60	61-80	>80
Progressive deterioration of renal function	0	2 (0.39%)	31 (2.43%)	202 (8.51%)	72 (8.20%)
Significant impairment of renal function	0	10 (1.96%)	113 (8.86%)	422 (17.78%)	207 (23.58%)
CKD stage 3a	1 (1.16%)	5 (0.98%)	53 (4.16%)	108 (4.55%)	22 (2.51%)
CKD stage 3b	1 (1.16%)	7 (1.37%)	81 (6.35%)	275 (11.58%)	99 (11.28%)
CKD stage 4	0	0	21 (1.65%)	178 (7.50%)	156 (17.77%)
CKD stage 5	0	3 (0.59%)	10 (0.78%)	32 (1.35%)	10 (1.14%)
Resistant HTN	0	10 (1.96%)	122 (9.57%)	192 (8.09%)	47 (5.35%)
Difficult to control HTN	0	18 (3.52%)	134 (10.51%)	103 (4.34%)	23 (2.62%)
Suspected secondary HTN	1 (1.16%)	49 (9.59%)	65 (5.10%)	33 (1.39%)	4 (0.46%)
HTN in young adults (<35 y)	17 (19.77%)	71 (13.89%)	0	0	0
HTN with target organ damage	0	1 (0.20%)	16 (1.25%)	13 (0.55%)	0
High BP and pregnancy	0	28 (5.48%)	2 (0.16%)	0	0
HTN with multiple side effects	0	1 (0.20%)	13 (1.02%)	14 (0.59%)	1 (0.11%)
BP variability	0	0	11 (0.86%)	14 (0.59%)	3 (0.34%)
ABPM request	1 (1.16%)	2 (0.39%)	2 (0.16%)	8 (0.34%)	0
Proteinuria	9 (10.47%)	60 (11.74%)	187 (14.67%)	299 (12.59%)	70 (7.97%)
Loss of follow-up	1 (1.16%)	61 (11.94%)	104 (8.16%)	162 (6.82%)	46 (5.24%)
Renal cysts	5 (5.81%)	31 (6.07%)	45 (3.53%)	23 (0.97%)	2 (0.23%)
Renal lithiasis	0	7 (1.37%)	15 (1.18%)	1 (0.04%)	1 (0.11%)
Solitary kidney	2 (2.33%)	13 (2.54%)	2 (0.16%)	4 (0.17%)	0
Family history of polycystic kidney disease	1 (1.16%)	2 (0.39%)	1 (0.08%)	0	0
Other renal imaging disorders	4 (4.65%)	18 (3.52%)	22 (1.73%)	30 (1.26%)	4 (0.46%)
Hematuria	9 (10.47%)	35 (6.85%)	46 (3.61%)	27 (1.14%)	2 (0.23%)
Recurrent urinary tract infections	3 (3.49%)	21 (4.11%)	17 (1.33%)	11 (0.46%)	1 (0.11%)

Renal colic	1 (1.16%)	15 (2.94%)	9 (0.71%)	6 (0.25%)	1 (0.11%)
Polyuria	1 (1.16%)	1 (0.20%)	4 (0.31%)	2 (0.08%)	0
Oliguria	0	1 (0.20%)	0	3 (0.13%)	3 (0.34%)
Lower urinary tract symptoms	1 (1.16%)	0	2 (0.16%)	1 (0.04%)	0
Hyperkalemia	1 (1.16%)	0	8 (0.63%)	28 (1.18%)	10 (1.14%)
Hypokalemia	1 (1.16%)	0	7 (0.55%)	5 (0.21%)	2 (0.23%)
Hyponatremia	0	0	2 (0.16%)	4 (0.17%)	4 (0.46%)
Other electrolyte disorders	1 (1.16%)	2 (0.39%)	10 (0.78%)	7 (0.29%)	0
Anemia	0	0	1 (0.08%)	23 (0.97%)	64 (7.29%)
Vascular risk	0	5 (0.98%)	36 (2.82%)	39 (1.64%)	4 (0.46%)
Kidney transplant, shared visits with transplantation center	0	4 (0.78%)	20 (1.57%)	23 (0.97%)	0
Kidney donor study	0	2 (0.39%)	16 (1.25%)	5 (0.21%)	0
Edema	1 (1.16%)	2 (0.39%)	3 (0.24%)	15 (0.63%)	4 (0.46%)
Hyperparathyroidism	0	0	0	11 (0.46%)	2 (0.23%)
Transfer from Pediatric Nephrology	13 (15.12%)	0	0	0	0
Error (mistaken for Neurology)	1 (1.16%)	9 (1.76%)	15 (1.18%)	22 (0.93%)	6 (0.68%)
Others	8 (9.30%)	10 (1.96%)	22 (1.73%)	18 (0.76%)	5 (0.57%)
Reason for referral not stated	2 (2.33%)	5 (0.98%)	7 (0.55%)	11 (0.46%)	3 (0.34%)

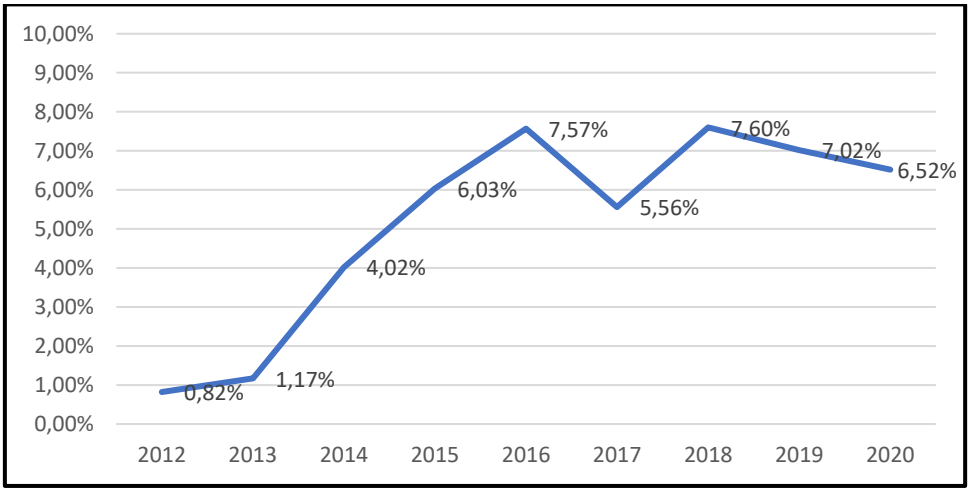
Figure 14. Main reasons for referral percentage by group of age.



6.1.1.5. Referrals with previous electronic consultation

Since March 2012, PCPs can send an electronic consultation previous to an eventual referral; it took though a couple of years till all PCPs were fully aware of the existence of this a tool and how to proceed. Since 2015, 5-8% of Primary Care referrals have been preceded by an electronic consultation (Figure 15).

Figure 15. Primary Care referrals with previous electronic consultation.



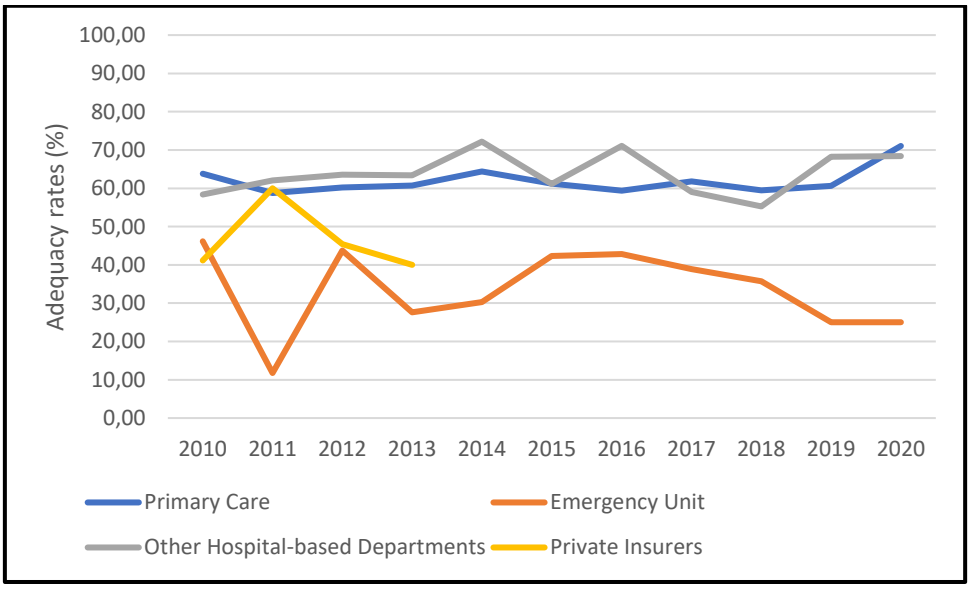
6.1.1.6. Adequacy ratio according to CKD guidelines by origin and annual variation

As previously stated, a single nephrologist evaluated and filtered all referrals except for those received during summer holidays (in order not to delay appointments) and those which were automatically scheduled avoiding the protocol. 4,628 referrals (90.3% of all referrals) were filtered and considered appropriate or not, according to CKD guidelines (ww). Globally, 2,779 (60.05%) of evaluated referrals were considered appropriate. Adequacy rates by origin is shown in Table 5. Best adequacy rates are shown by Primary Care (61.23%) and other Hospital-based Departments (63.86%) rather than the Emergency Unit, which shows a quite low adequacy rate (34.76%). These rates have been quite stable along the study period (Figure 16).

Table 5. Adequacy rates by origin.

	Filtered referrals	Appropriate (%)
Primary Care	2,969	1,818 (61.23%)
Emergency Unit	233	81 (34.76%)
Other Hospital-based Departments	1,320	843 (63.86%)
Private Insurers	48	23 (47.92%)
Penitentiary	12	5 (41.67%)
Other	46	9 (29.57%)
All	4,628	2,779 (60.05%)

Figure 16. Adequacy rates by requester profile over time (only main type of requesters are shown).



6.1.1.7. Rate of discarded referrals

1,569 requests (84.90% of inappropriate referrals) were discarded and sent back with an explanation and a recommendation of management. The remaining 15.1% is analyzed in section 6.1.1.9.

6.1.1.8. Inappropriate referrals by reason, referrals' origin and annual variation

A comprehensive list of inappropriate discarded referrals is shown in Table 6. The most single specific frequent reason is referring a patient to Nephrology when he/she should have been addressed to another specialty (14.53%), Urology in most cases (but also quite often a mistake when writing Nephrology instead of Neurology).

In many cases (14.40% of inappropriate discarded referrals), an identifiable nephrotoxic agent was detected that could have been withdrawn previous to referral (Table 7).

HTN is also an important source of inadequate referrals, mostly due to inappropriate treatment. Many patients are referred because of alleged resistant HTN without having reached the recommended treatment of RAAS blockade + Dihydropyridine Calcium Channel blocker + diuretic (22), or in order to discard secondary HTN when there are no symptoms or signs of suspicion for an underlying cause of HTN.

Mild slow or non-progressive CKD (stage 3a), moderate slow or non-progressive CKD (stage 3b) in the elderly and albuminuria <300 mg/g creatinine do also generate an important number of inappropriate referrals. If we consider Stage 3a and 3b in the elderly as a group, this would be the most common cause of inadequate referral.

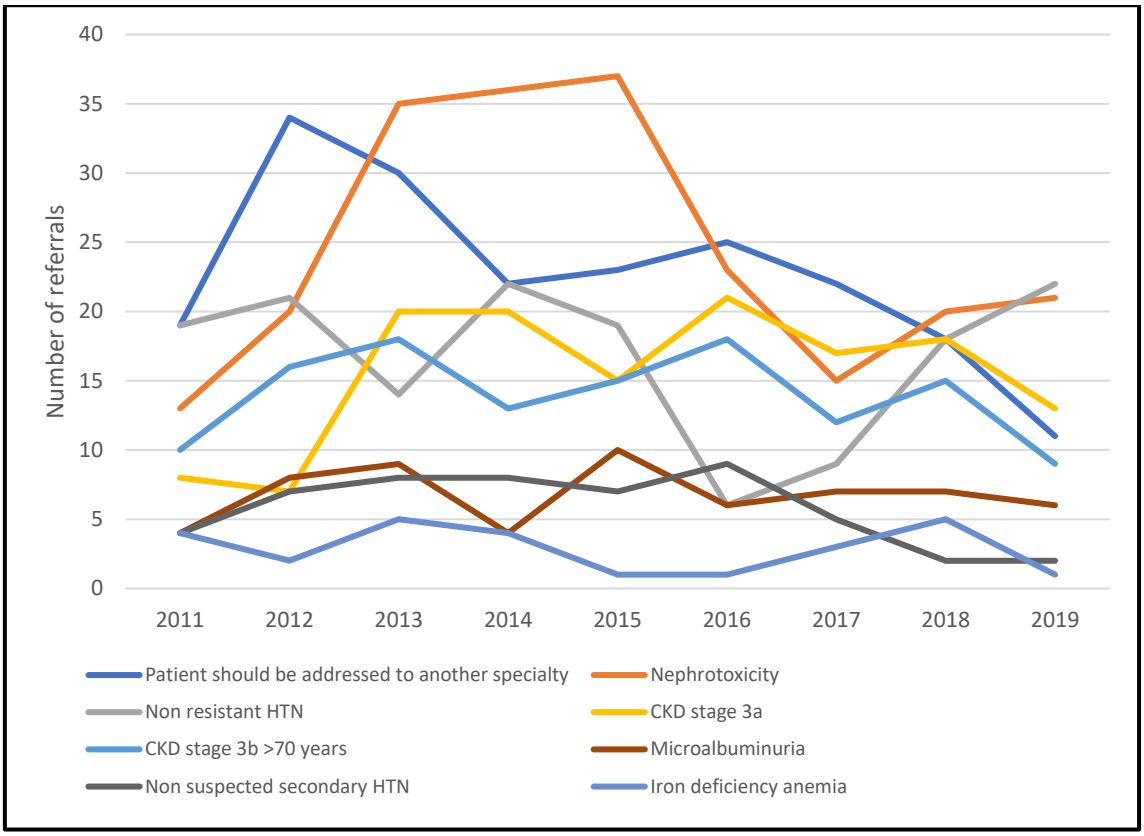
Table 6. Comprehensive list of inappropriate discarded referrals by frequency.

	n	%
Patient should be addressed to another specialty	228	14.53
Nephrotoxicity	226	14.40
Non-resistant HTN	169	10.77
CKD stage 3a	144	9.18
CKD stage 3b >70 years	142	9.05
Already visited	89	5.67
Non-significant disorder	87	5.54
Microalbuminuria	66	4.21
Non suspected secondary HTN	56	3.57
Recovering from AKI	43	2.74
No confirmation of the altered parameter	31	1.98
Non synergistic HTN treatment combination	28	1.78
Iron deficiency anemia	26	1.66
Out of zone	25	1.59
Wrong definition (no oliguria/polyuria/hematuria)	24	1.53
Stable patient	23	1.47
Solitary kidney	20	1.27
Simple renal cysts	19	1.21
Edema with no sign of renal disease	16	1.02
Insufficient information provided	15	0.96
BP variability	14	0.89
Patient in follow-up by another Nephrology Department	14	0.89
Albuminuria with no RAAS blockade	13	0.83
Hemodynamic disorder	10	0.64
Other	41	2.61

Although adequacy rates were quite stable along the study period, interesting differences can be seen from the evolution of inappropriate discarded referrals over time (Figure 17). While some types of inadequate referrals remain stable over time in absolute numbers (i.e., CKD 3a and CKD 3b in >70y, and also microalbuminuria), some other show an important decrease during

the last years of the study period: those patients that should be referred to other specialties and most importantly, patients with identifiable nephrotoxicity.

Figure 17. Reason for inappropriate referral over time*#.



* Minor reasons for inappropriate referral are not shown.

Only full-year (12 months) data are shown.

Table 7. Referrals with an identifiable nephrotoxic or renal hemodynamic agent.

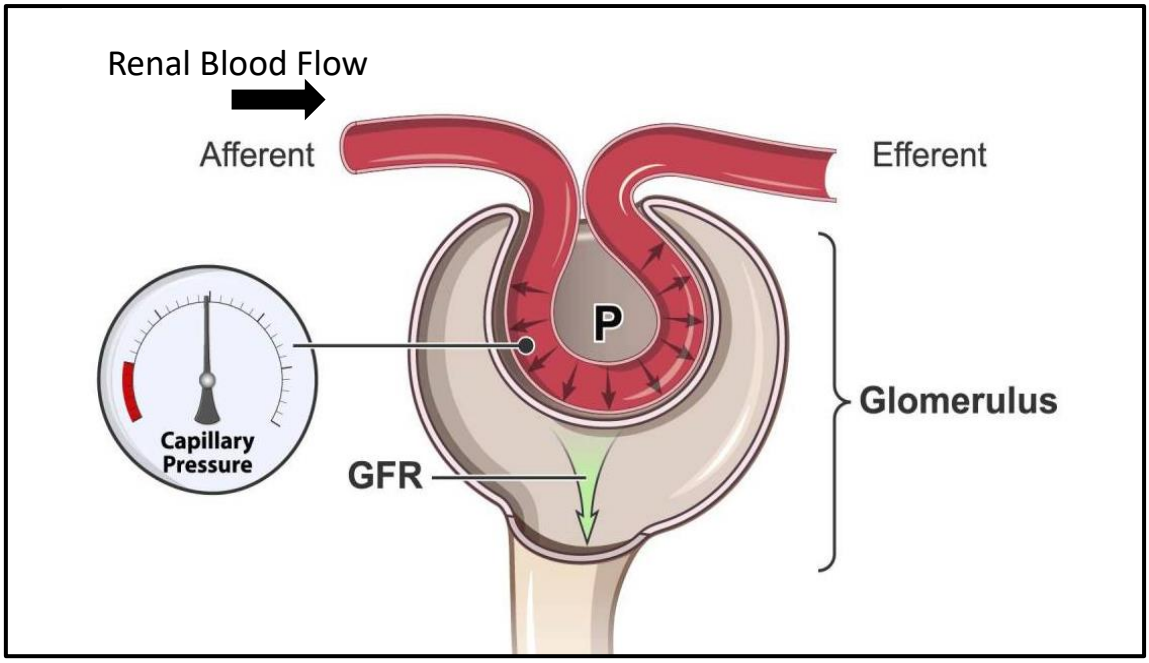
		n	%
1 agent	NSAID alone	38	16.81
	Single RAS blockade	17	7.52
	MRA alone	26	11.50
	Diuretic alone	28	12.39
	Other*	7	3.10
2 agents	ACEI + ARB	3	1.33
	MRA + RAS blockade	5	2.21
	RAS blockade + Diuretic	28	12.39
	MRA + Diuretic	8	3.54
3 agents	RAS blockade + MRA + Diuretic	13	5.75
	ACE I+ ARB + Diuretic	8	3.54
	RAS blockade + Diuretic + NSAID	40	17.70
4 agents	ACEI + ARB + Diuretic + NSAID	5	2.21

* Cyclosporin A or Ranolazine

NSAID are well known nephrotoxic agents which may be identified and withdrawn before referral, but still they have been involved in 83 referrals over the study period, 5.29% of inappropriate discarded referrals and 36.72% of requests with an identifiable nephrotoxic agent.

To better understand why otherwise considered “nephroprotective” agents like RAAS blockers or even diuretics are listed here as nephrotoxic, renal hemodynamics have to be considered (Figure 18). The main driving force for filtration is the hydrostatic pressure of the glomerulus, which depends mostly on renal blood flow and the afferent/efferent arterioles’ tone. Excessive diuretic treatment may result in volume depletion and renal blood flow reduction. As Angiotensin II exerts its vasoconstrictive effect mainly in the efferent arteriole, RAAS blockers induce efferent arteriole vasodilation and hydrostatic glomerular pressure reduction. This effect has been shown to be beneficial for proteinuria reduction and slowing down CKD progression, but in the short term it can result in transient eGFR decline, mostly in the elderly and in patients with already reduced eGFR (55). Thus, guidelines recommend sCr and potassium monitoring after RAAS blockade treatment initiation or increase for dose adjustment and monitoring of side effects (56). Inappropriate referrals because of potential nephrotoxicity include those where RAAS blockade initiation or dose increase (of either RAAS blockade or loop diuretic) was detected previous to renal function deterioration.

Figure 18. Renal hemodynamics scheme.



6.1.1.9. Accepted inappropriate referrals by reason, referrals' origin and annual variation

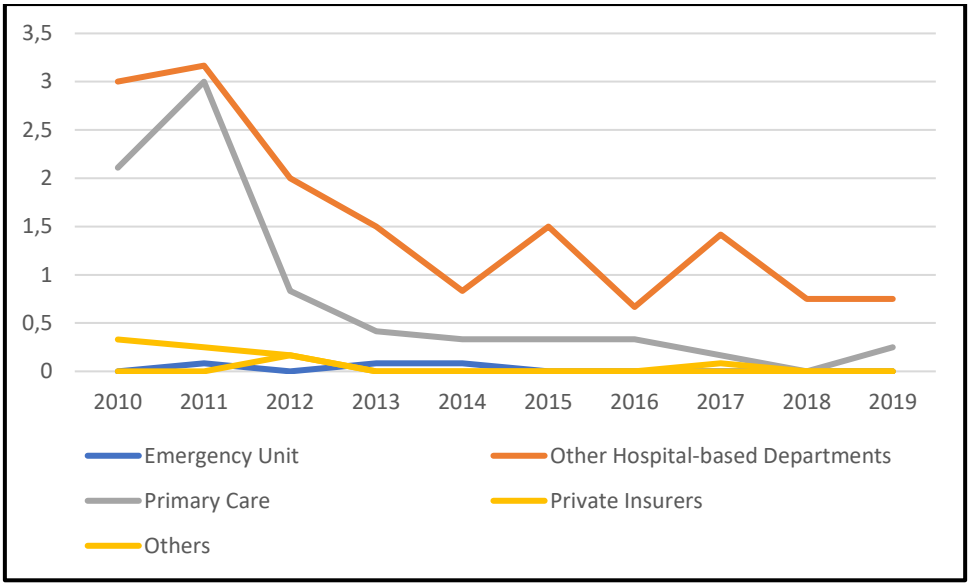
280 inappropriate referrals were however accepted and scheduled (Table 8). Most of them coming from other Hospital-based departments (63.93%). Main reason for doing so was referral coming from colleagues with closer relation with the Nephrology Department (88.93%), followed by being the referred patient a relative of the Hospital staff (8.57%). The results show that most inappropriate referrals coming from the Emergency Unit and Primary Care are effectively sent back with a recommendation, while more than one third of referrals coming from other Hospital staff colleagues are accepted despite being inappropriate.

Table 8. Accepted inappropriate referrals.

	n	% of inadequate referrals
Emergency Unit	3	1.97
Other Hospital-based Departments	179	37.53
Primary Care	87	7.56
Private Insurers	8	16.67
Others	3	8.11

Nevertheless, this favoritism to closer colleagues was much more common at the beginning of the study period and clearly reduced afterwards (Figure 19).

Figure 19. Mean monthly accepted inappropriate referrals by origin.

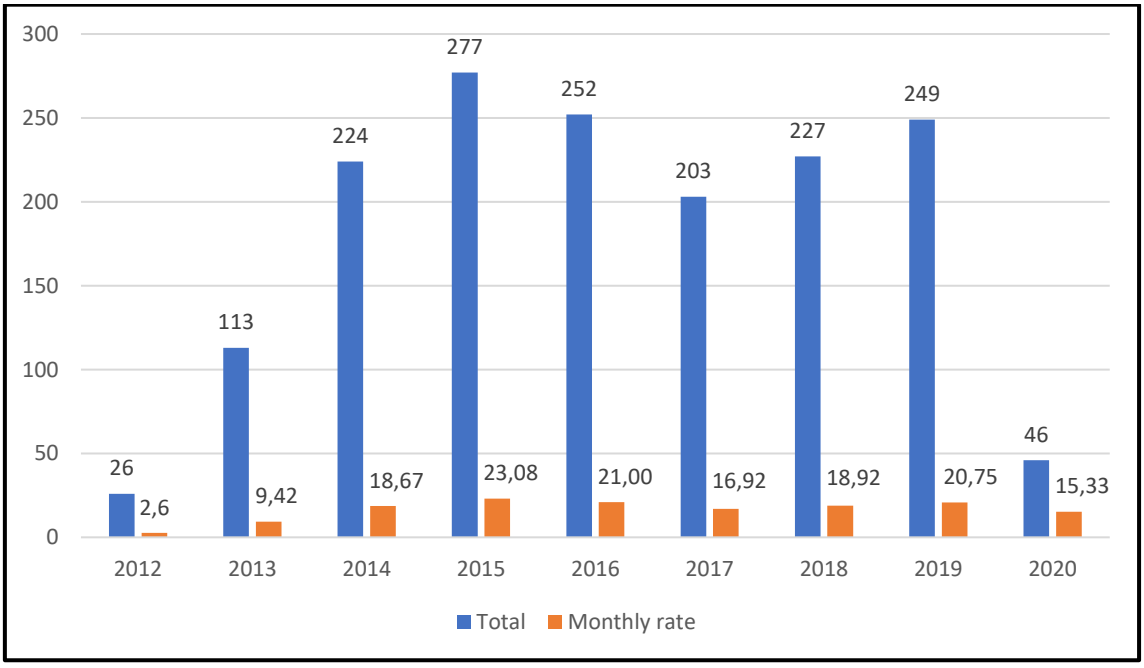


6.1.2. Electronic queries

6.1.2.1. Total amount and annual variation

Since the platform began to operate in March 2012, 1,617 e-consults had been addressed to Nephrology as of March 2020. Evolution over time is shown in Figure 20: after the 2 initial years, an average of 19.24 queries have been addressed monthly to Nephrology.

Figure 20. Electronic queries over time*

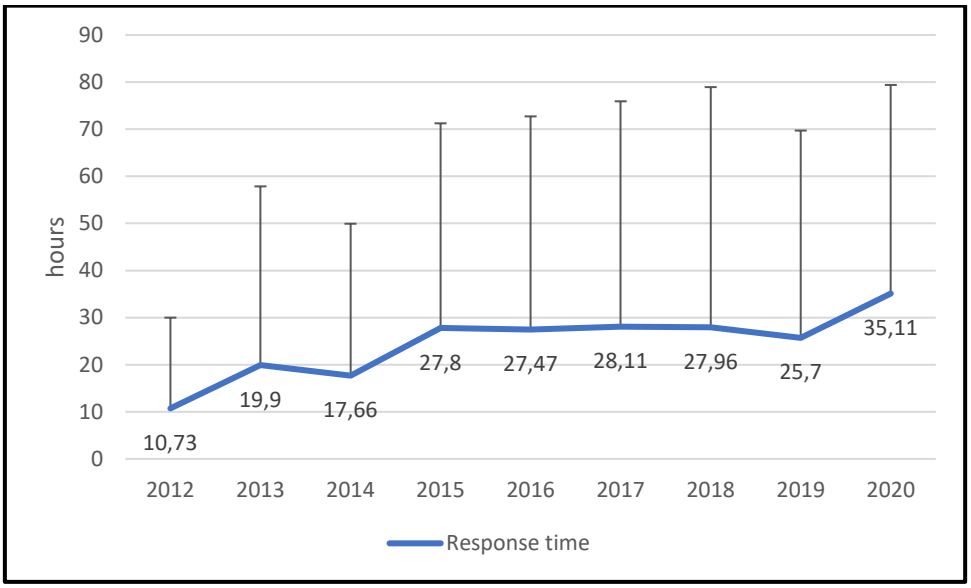


*From March 2012 till March 2020.

6.1.2.2. Query response time and annual variation

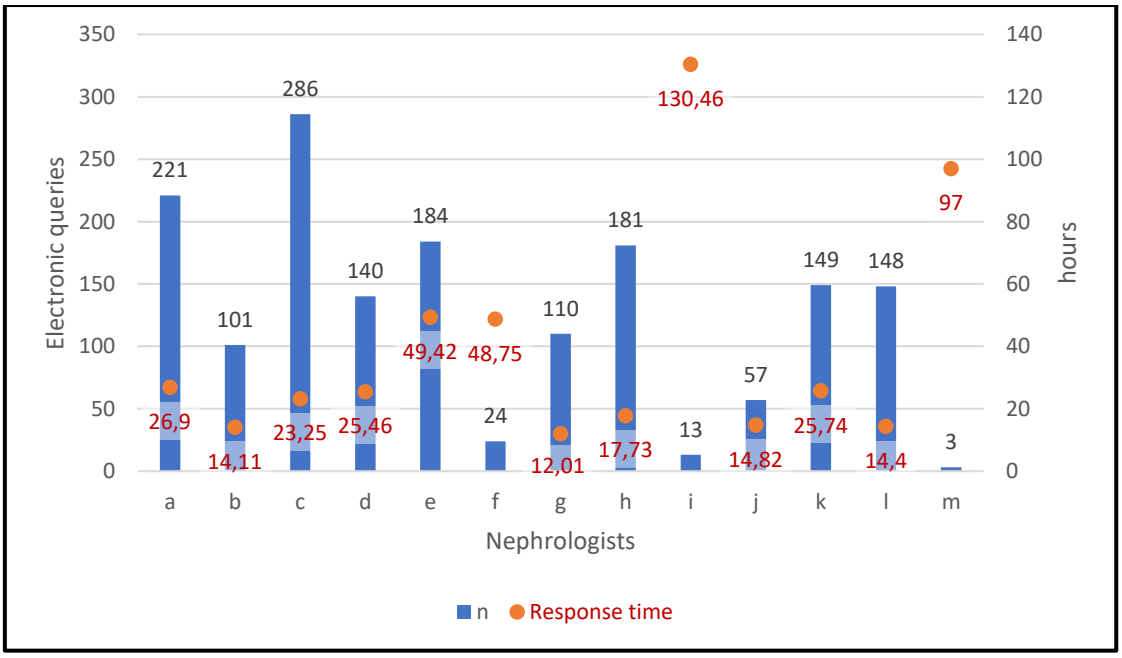
Mean response time was 25.46 hours; SD 43.71 (Rank 0 – 334). Most frequent response time was 1 hour. Annual variation is shown in Figure 21.

Figure 21. Query response time, annual variation.



A wide difference between nephrologists who take care of electronic queries is seen in terms of response times (Figure 22). As expected, those with temporary part-time contracts working fewer days per working week show longer response times.

Figure 22. Electronic queries per nephrologist and response time (hours).



6.1.2.3. Electronic queries solved without a resultant referral

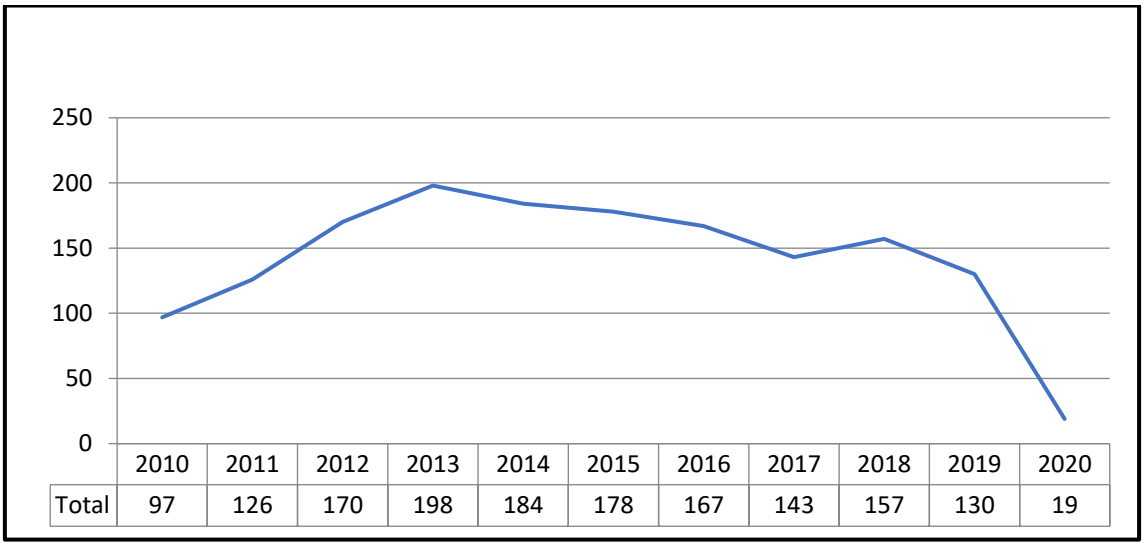
1,496 electronic queries could be solved without the need to refer the patient (92.52%).

6.1.3. Procedure efficiency

6.1.3.1. Number of visits avoided by the referral filtering scheme

1,569 referrals were avoided (84.90% of inappropriate referrals). A trend towards less avoided first visits is seen over time.

Figure 23. Discarded referrals and annual variation*.



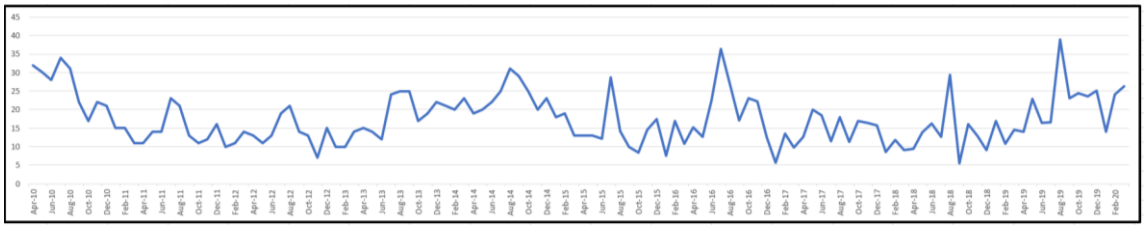
	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Total	97	126	170	198	184	178	167	143	157	130	19

* 2010 includes April-December. 2020 includes January-March

6.1.3.2. Nephrology outpatient clinic waiting list evolution

Outpatient waiting time throughout the study is shown in Figure 24. Shortly after the onset of the referral filtering procedure, waiting time was reduced by 50% (from 30 to 15 days). There was a trend to increase during 2013 and 2014, coinciding with the increase in referrals' rate during those years, and improved thereafter to keep within 10-15 days, except for the summer periods when waiting time increased due to several reasons: firstly, less availability for appointments because of closed agendas due to summer holidays; secondly because the filtering procedure was temporarily stopped during the evaluator's summer holidays; and thirdly because referrals addressed to a specific nephrologist during his/her summer holidays had to wait until the nephrologist's return to work.

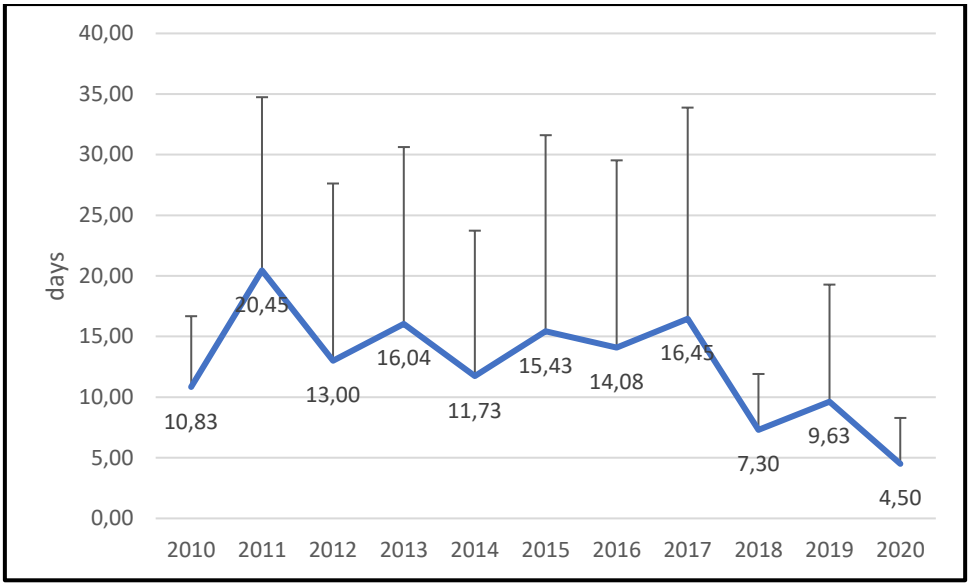
Figure 24. Waiting time (days) for first outpatient appointment throughout the study



6.1.3.3. Time to implementation of recommendations

Discarded referrals (n= 1,569) were sent back with recommendation of management, in most cases a general recommendation that included links to CKD guidelines (57) or ESH/ESC HTN treatment algorithm (22). In 297 cases (18.93%), specific recommendations were given related to potential nephrotoxic agents that might be withdrawn or particular antihypertensive agents that could be introduced. Primary Care electronic medical records were available in 245 of those cases (82.49%). Within the cases that could be reviewed, no reference to provided recommendations was founded in 63 patients (25.71%). In the rest of patients, mean time to implementation of recommendations was 12.96 days (SD 13.21; Rank 1-67 days), with a significant improvement in the last 3 years (Figure 25), coinciding with a change in the system by which these recommendations reached PCPs. Initially, counseling came in the form of a paper report, and physicians had to remember to open the patient's electronic chart to transfer it. Sometimes these documents could get lost or the doctor forget to implement them. Currently, a virtual visit is opened in the PCP's agenda with the recommendation, so it is easier and faster to notice and apply them.

Figure 25. Time to implementation of recommendations annual variation.



Most recommendations (70.88%) were implemented within the first two weeks (Table 9).

Table 9. Time to implementation of recommendations by speed.

≤ 7 days	8-14 days	15-21 days	22-28 days	≥ 28 days
80	49	21	12	20

6.1.3.4. Health system cost savings

Throughout the 10-year period of the study, 1,569 first visits at the Nephrology outpatient clinic were avoided. The cost of a single visit varies depending on several factors as staff volume and number of visits performed. From 2010 till 2014, the hospital billed the government Department of Health 54.88 € per visit, therefore those savings (42,532 €, corresponding to 775 avoided visits) were for the Catalan public Health system, although representing an income reduction for the hospital. Since 2015, a change on the Catalan health services purchase system allowed the hospital to charge a fixed amount for outpatient activity per year, so reducing the number of visits results in direct hospital savings. However, no accurate cost per visit was calculated till 2018, so we are not able to estimate savings corresponding to years 2015-2017 (488 avoided visits). Interestingly, from 2018 on, licensed software services (SAP™) have been used to estimate outpatient visits cost that take into account human resources, structure and support services such as administrative resources, information technology, amortization, maintenance services, laundry and cleaning. Calculated costs were 81.51 €/visit for 2018 (total savings

12,797.07 €; 157 avoided visits); 113.4 €/visit for 2019 (total savings 14,742 €; 130 avoided visits) and 102.43 €/visit for 2020 (total savings 1,946.17 € from January till March; 19 avoided visits).

When a first visit is performed, most of the time a follow up visit is generated with a lab safety test, after which the patient is discharged if there is no further follow-up indication. The cost of a basic Nephrology lab follow-up test including blood count, blood chemistry (creatinine, urea, sodium and potassium), urine sediment and urine albumin/creatinine ratio was a mean 7.86 € during the study period.

6.1.3.5. Patients' travel savings

Our hospital covers an area of 2,431 square kilometers and, even though 37.4% of the population lives in the same city as the hospital, patients can be referred from quite distant towns and villages. Avoided visits resulted in a total of 54,486 km saved for patients (roundtrip distance from patients' residence address to the hospital). Our institution has estimated a 0.19 € gas compensation cost per km for health professionals who have to move from the main hospital to other health facilities. Applying this scale, avoided visits would have resulted in 10,352.34 € savings for patients and caregivers. Potential expenses for parking and meals have not been contemplated, neither cost associated with lost wages or productivity for patients or caregivers.

6.2. Spreading renal knowledge into PCPs by CKD guidelines

Between June 2010 and January 2012, the author leaded a consensus between the 5 local scientific societies which more frequently deal with patients with CKD, i.e., the SCN, the Catalan Society of Family and Community Medicine (CAMFiC), the Catalan Society of Hypertension (SCatHTA), the Catalan Diabetes Association and the Catalan Nursing Association; together with the Department of Health, Generalitat de Catalunya. The final document (*Consensus document on attention to chronic kidney disease*) was amended by reviewers before guidelines were presented, released (Annex 1a) and published (53, Annex 1b).

The guidelines aim to improve CKD detection in the population at risk; help identify reversible causes of kidney failure; give specific recommendations for therapeutic management; promote measures to slow down the progression of CKD and reduce the associated cardiovascular risk. They also define referral criteria to specialists (Table 10). These criteria have been used to evaluate referral adequacy to our Nephrology outpatient clinic and to send back referrals with recommendation of management.

Table 10. Criteria for Referral of CKD Patients to Specialized Care (53, Annex 1a-1b).

	Criteria	Specialty
CKD stage 3	<45 ml/min/1.73m^2 and <70 years	Nephrology
CKD stage 4	<75 years ≥75 years depending on comorbidities	Nephrology
CKD stage 5	All	Nephrology
Progression rate	CKD 3-4 with quick progression (>5 ml/min/1.73m^2/year)*	Nephrology
Acute kidney injury	sCr increase >25% in <1 month	Nephrology
Proteinuria	>500 mg/g or >1 g/24h	Nephrology
Hematuria	Hematuria with albuminuria >300 mg/g	Nephrology
Hypertension	Uncontrolled hypertension despite the use of 3 synergistic drugs, including a diuretic, at fully tolerated dose Suspected renal artery stenosis	Hypertension unit or Nephrology
Anemia	Hb <11 g/dl without iron deficiency or other causes of anemia	Nephrology
Hyperkalemia	K > 5.5 mmol/l despite treatment	Nephrology
Other	Suspected genetic etiology	Nephrology

* Particularly on those in whom the rate of decline would lead to the need for renal replacement therapy according to their life expectancy.

Finally, models of communication between Primary Care and Nephrology Departments and shared management of CKD patients are proposed, as well as a set of clinical indicators that can be used to evaluate quality improvement (Table 11).

Table 11. CKD healthcare quality indicators.

Detection	Percentage of people with assessment of eGFR and albuminuria in relation to total population at risk
Diagnosis	Percentage of people with eGFR <60 ml/min/1.73 m^2 for ≥ 3 months with diagnosis of CKD
Treatment	Percentage of patients with CKD and very high albuminuria or proteinuria treated with RAAS blockade in relation to all patients with CKD and very high albuminuria or proteinuria Percentage of CKD (stage 4-5) diabetic patients treated with metformin in relation to total number of diabetic patients with CKD 4-5
Follow-up	Percentage of patients with CKD 3-5 with controlled HTN Percentage of CKD diabetic patients with HbA1c <7%

	Percentage of CKD diagnosed patients with annually assessment of eGFR and albuminuria in relation to total CKD diagnosed patients Percentage of CKD patients with hypercholesterolemia and LDL-cholesterol <100 mg/dl in relation to total CKD patients with hypercholesterolemia
Referrals	Percentage of patients referred to Nephrology according to the guidelines criteria in relation to total number of referrals to Nephrology (referrals' adequacy)
Primary Care – Nephrology coordination	Percentage of Primary Care centres with a referral/electronic consultation protocol in relation to total Primary Care centres which depend on a single Nephrology Department Percentage of centres that carry out at least one biannual meeting with the reference Nephrology Department in relation to total Primary Care centres which depend on a single Nephrology Department

Guidelines are available at SCN website (57).

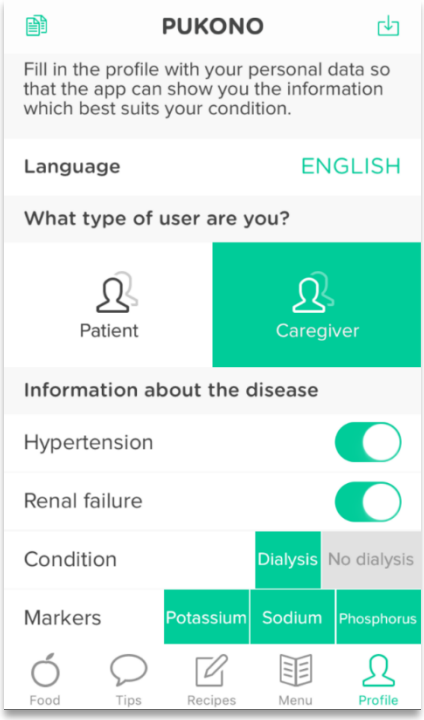
6.3. Spreading renal knowledge into CKD patients and their environment

6.3.1. Development of an app for mobile phones and tablets to help adherence to CKD diet

From November 2012 till July 2014, we designed and carried out an app for mobile phones and tablets to help patients and their caregivers to have a handy reliable source of information about an appropriate CKD diet at all times. The app was released in summer 2014 and it is available free of charge at the App Store and Google Play websites.

When downloading the app, the user profile interface can be set according to the language (Catalan, Spanish or English), user type (patient or caregiver) and condition (CKD and/or HTN). The HTN condition activates the Sodium "traffic light" and the corresponding counseling. Within CKD condition, there is a choice between Dialysis and Non -Dialysis (which activates fluid intake counseling or not), and options for activation of any or all of the following "traffic lights" and counseling: Potassium, Sodium and Phosphorus. Figure 26.

Figure 26. PUKONO user profile interface.



At this point, users can navigate the following functionalities (bottom Fig. 26):

- Food database: Predictive text input helps selection of the desired type of food. Instant information is shown about the contents of activated elements (K, Na, P) per 100 grams of food, along with a safety traffic light code (green for safe, orange for caution, red for dangerous). Further information is offered concerning the reference values and maximum recommended daily intake. It does also allow to create a list of favorite foods. Figure 27.
- Tips: Includes a large set of tips for reducing the amount of the desired element in food, organized in five sections: potassium, sodium, phosphorus, fluid intake and general counseling for a healthier cooking. Example shown in Figure 28.
- Recipes: Appropriate recipes for main dishes, side dishes, deserts and breakfast are offered in 2 sections: recipes from Fundació Alicia and from app users. The latter are pre-reviewed for adequacy by the app managers before being published.
- Menu: Full season menus provided by Fundació Alicia.

Figure 27. PUKONO food database finder screenshot.

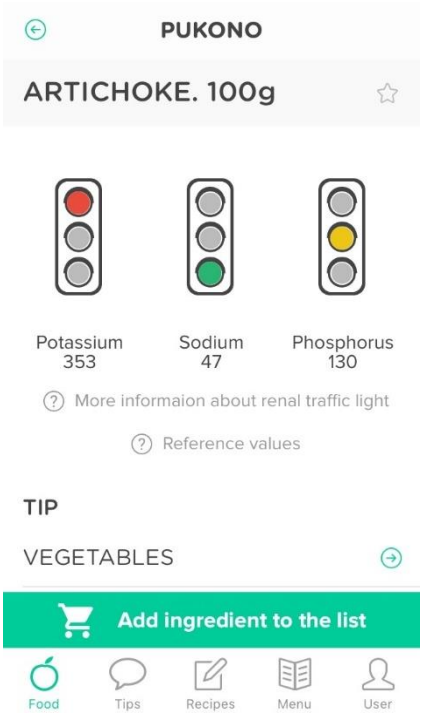
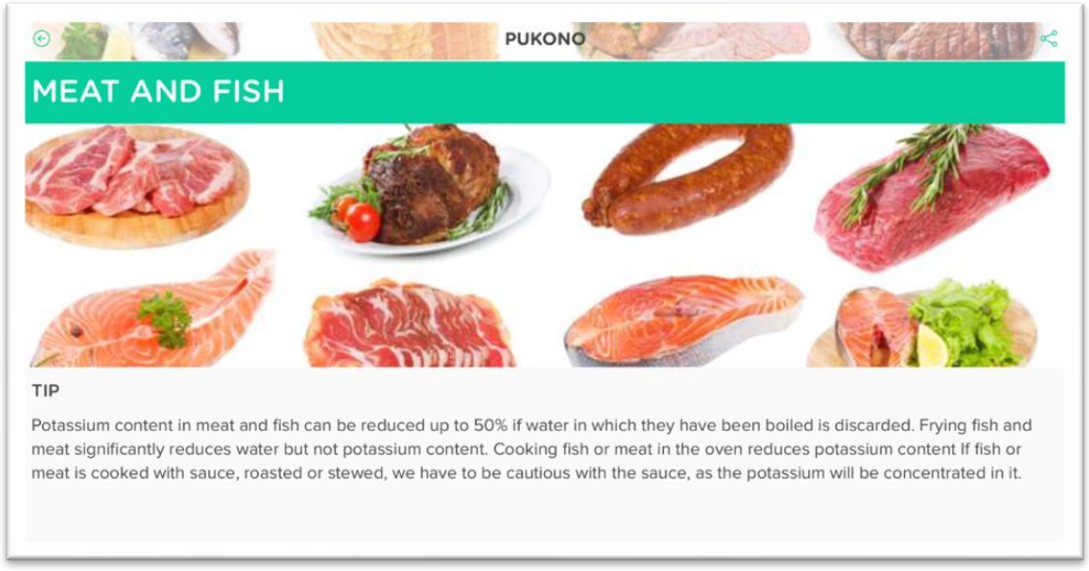


Figure 28. PUKONO tips example screenshot.



PUKONO was presented in 2014 at several local scientific meetings (SCN, SEN, SCatHTA, Spanish Society of Nephrology Nursing) and is recommended by the SEN at the website (58).

6.3.2. App usability

New users (downloads): PUKONO was released in July 2014 and after a strong start, it maintained an average download rate around 600 new devices/month. Since September 2016,

a continuous growing tendency is seen, reaching a maximum of 1769 downloads in November 2019 (Figure 29). During the last 12 months of analysis (July 2020 – June 2021) there has been a mean of 1,322 ± 128 new users/month. PUKONO is being downloaded mostly in Europe (around 75%) but North, Central and South America account actually for 12%, 1%, and 12% downloads respectively (Figure 30). Total downloads since the app was released had reached 78,788 by June 2021. In terms of users' profile, 57.5% are patients and 42.5% caregivers (Figure 31a); 90.3% are configured in Spanish, 9.3% in Catalan and only 0.4% in English (Figure 31b). Most users activate both Renal failure and HTN condition (77.8%). Within Renal failure condition, 52.1% activate the Dialysis profile. The most frequently activated "traffic light" is Sodium (95.4%), followed by Potassium (80.8%) and Phosphorus (75.2%).

Figure 29. PUKONO new users.

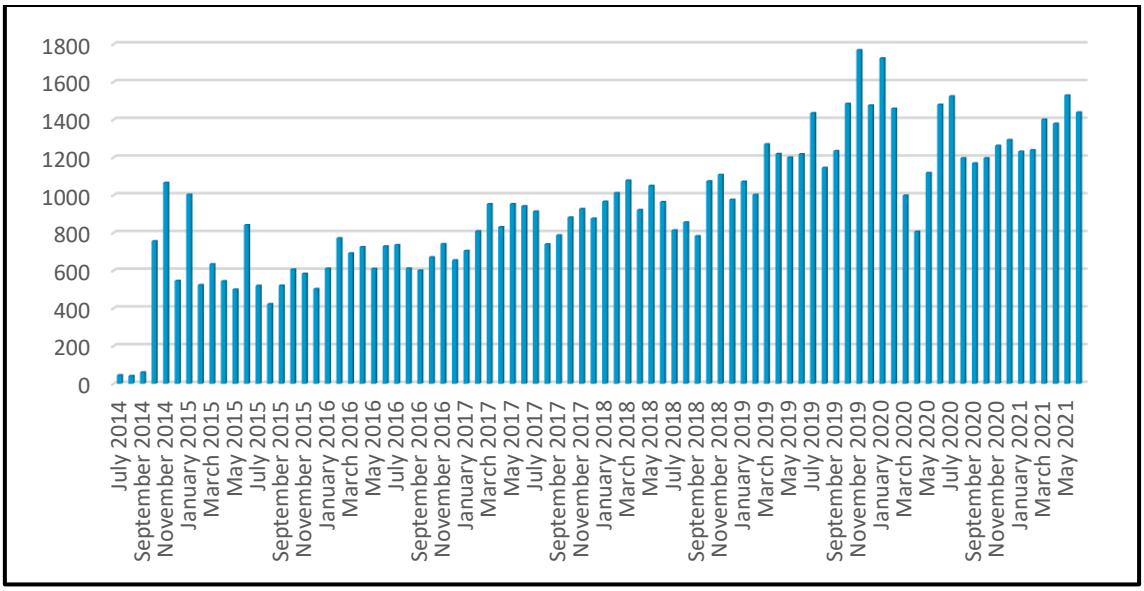


Figure 30. PUKONO users by region.

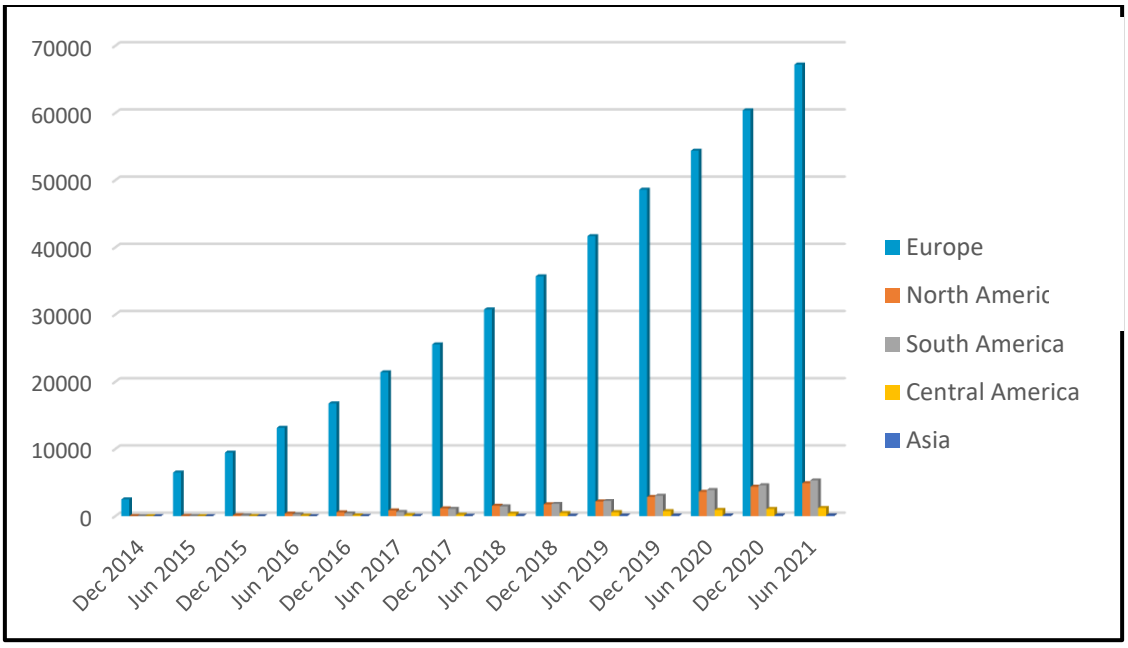
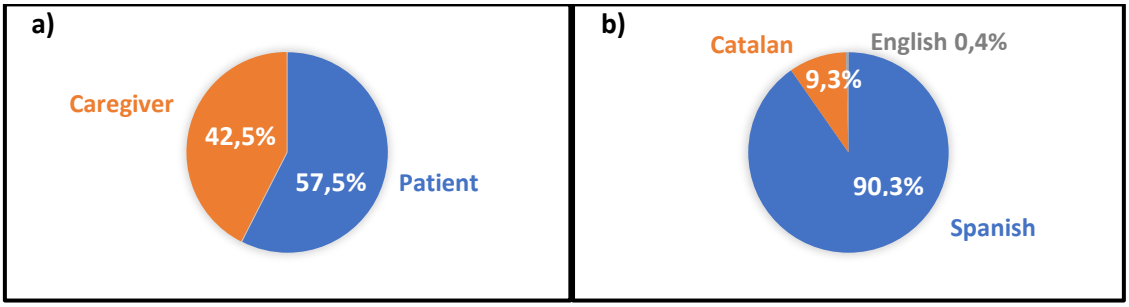


Figure 31. PUKONO user profile: a) patient/caregiver; b) language.



Activity: Since its release in July 2014 till June 2021 (7 years), a total of 2,443,644 sessions had been developed, with a continuous increase rate except for the first wave of the COVID-19 pandemic (Figure 32). During the last 12 months of analysis (July 2020 – June 2021), active users per month represent 6,876 ± 375, carrying out 41,672 ± 3,402 sessions/month. Average session length is 57 seconds, being the majority of them 1-3 minutes (Figure 33). As for the type of consulted functionality, 88% are food database searches, 6% tips, 3% recipes and 3% full menus (Figure 34).

Figure 32. PUKONO monthly sessions.

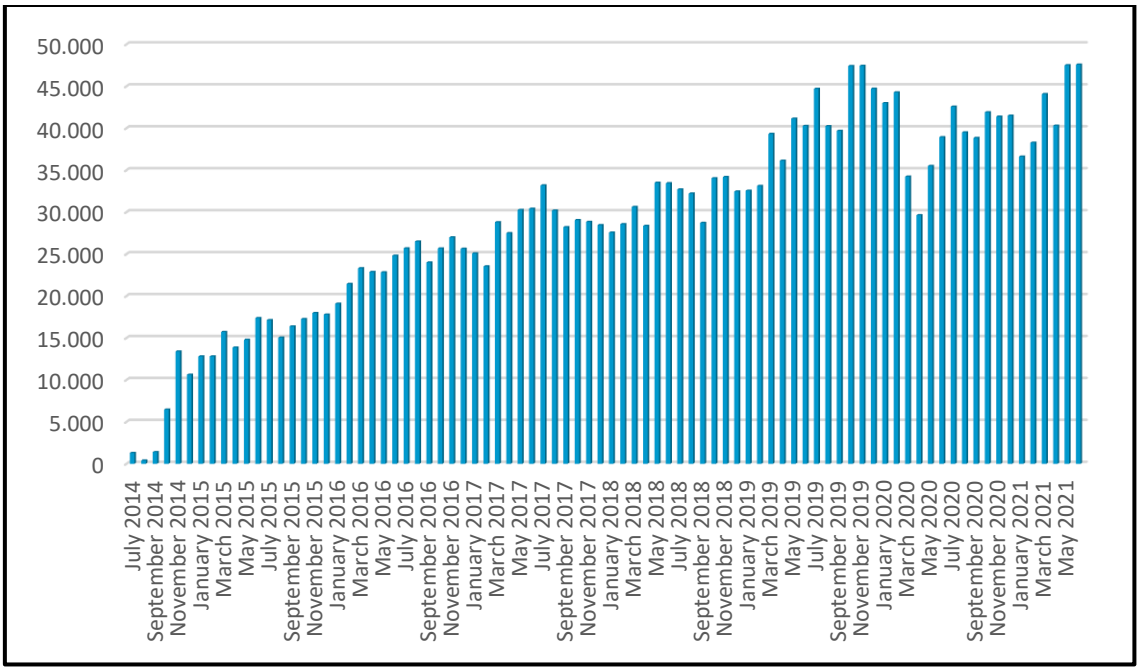


Figure 33. PUKONO session length.

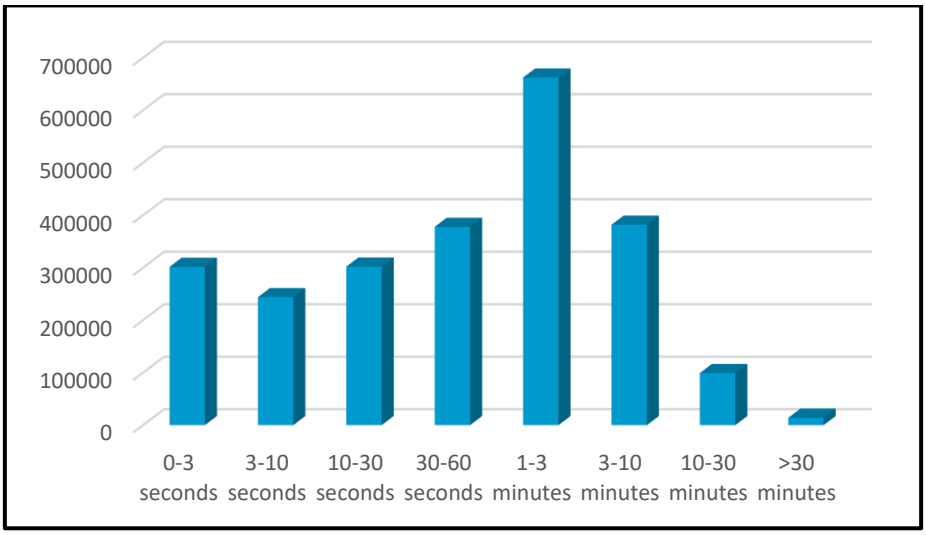
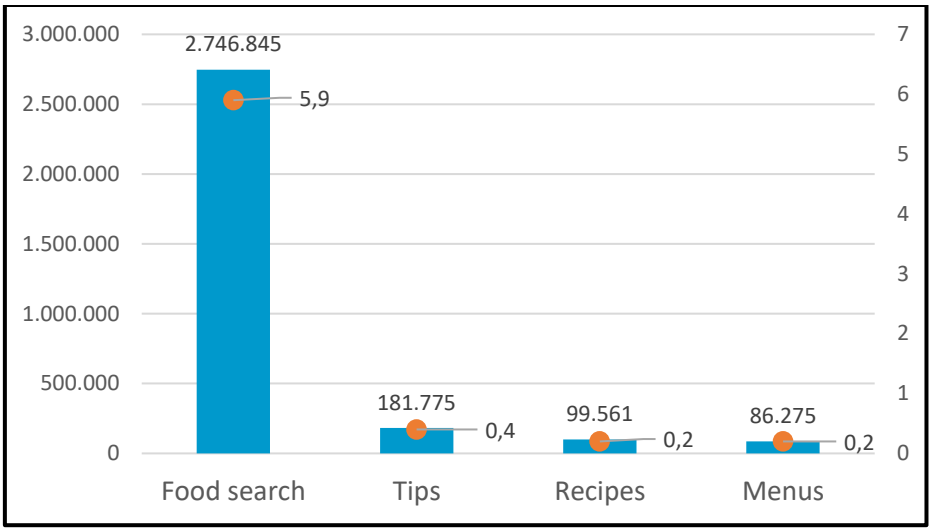


Figure 34. PUKONO type of search (functionalities).



Main axis: events. Secondary axis: average events per session.

Periodic app usability results have been presented at scientific meetings (59,60). Finally, PUKONO has excellent user ratings at Google Play (4.0/5 with 339 reviews) and App Store (4.5/5 with 176 reviews) websites and was awarded the 2015 Cactus prize for the best marketing, communication and new technology app project in Catalonia (61).

7. Discussion

CKD is a major health issue worldwide. As stated in the analysis for the GBD study, in 2017 697.5 million cases of CKD were recorded, for a global prevalence of 9.1% (which represents a 29.3% increase since 1990), and 1.2 million people died from CKD (which represents a 41.5% increase between 1990 and 2017). CKD also resulted in 35.8 million DALYs in 2017. Moreover, 1.4 million cardiovascular disease-related deaths and 25.3 million cardiovascular disease DALYs were attributable to impaired kidney function (62). While this phenomenon might impact diversly in different areas, epidemiology of CKD in Spain is much alike the global study. The EPIRCE study showed an almost identical CKD prevalence in 2010, 9.09% (8). CKD was the 8th cause of death in Spain in 2016, and among the top ten causes of death, CKD was the fastest growing from 2006 to 2016, after Alzheimer disease. So does prevalence, the ENRICA study published in 2018 showed 15.1% CKD prevalence in the Spanish general adult population (63), a 67% increase in just 8 years. At the current pace of growth, CKD is set to become the second cause of death in Spain, after Alzheimer disease, by 2100 (64). This is not only a matter of greater clinical importance but economic as well; the 57,429 persons (i.e., 0.1% of the population) living on dialysis or carrying a kidney graft in Spain in 2016 are estimated to consume 2–5% of the healthcare budget (64). Being CKD a largely preventable and treatable disease, the GBD study concludes that it deserves greater attention in global health policy decision making.

Improving the availability of specialized care, opening new Nephrology facilities throughout the territory and better equipping the existing ones might improve the situation, and certainly a wide panel of actions have been proposed (65), but despite the increasing number of patients reaching dialysis or transplantation, the ratio of nephrologists per capita is stable in some areas and even decreasing in others (52). Therefore, there is the need to organize the existing workforce in a more efficient way, so as to provide a better service for the community.

Referral profile and filtering procedure

The first part of this PhD thesis analyses the work that is being done at a Nephrology outpatient clinic and whether methods of reducing inadequate referrals can improve quality and economic results. Management of non-dialysis ambulatory patients may represent 20-40% of the total Nephrology Department activity and accounts for the Department's external image. Therefore, knowing the external demand is of foremost importance in order to design a Nephrology Department, to choose among the best staff characteristics, to promote knowledge improvement in the most demanded fields and to be more efficient in the investments.

Our principal referral requesters are Primary Care (63.33%) and other Hospital-based Departments (29.16%), with a minor number of requests coming from the Emergency Unit (4.74%). Private insurers and other institutions are residual (Figure 7). Within Hospital-based Departments, Internal Medicine and Urology are the most frequent requesters, but an important percentage of referrals do also come from Endocrinology (mostly because of diabetic nephropathy), the Occupational Health Unit (mostly on the institution workers' demand, whether appropriate or not) and Haematology (where a special concern about reduced eGFR has been detected). The third line of requesters are Neurology (mostly because of HTN and cardiovascular risk in stroke patients), Cardiology (mainly linked to cardiorenal syndrome and renal hemodynamic actions of heart failure treatment) and Oncology (reflecting either indication of certain treatments depending on renal function or secondary HTN induced by cancer therapies) (Figure 8).

Major reasons for referral were CKD with reduced eGFR (20.73%), worsening of renal function (20.67%) and HTN (19.91%), followed by proteinuria (12.20%) (Tables 1-2). A similar proportion of men and women is observed (51.2%/48.8% respectively), most of patients being >50 years old (78.5%) and 42.1% >70 years old (Figure 11). Reasons for referral vary according to sex and age (Tables 3-4, Figure 14).

Similar results have been reported by Ferrer G et al. at Hospital General Universitario Ciudad Real (HGUCR) (66) and Arrizabalaga P et al. at Hospital Clinic Barcelona (HCB) (67). CKD progression was the most frequent referral criteria at HGUCR (66) while, although being Althaia and HGUCR quite alike hospitals in terms of volume and complexity, the percentage of referrals coming from PCPs at HGUCR was greater than in Althaia (85.3% vs. 63.3%), reflecting a smaller number of referrals coming from other HGUCR departments. At HCB, focusing only in PCPs' referrals, eGFR <60 ml/min/1.73m^2 (whether stable or progressing) was the referral reason in 72% of patients while 19% of patients were consulted for proteinuria >1 g/d with a normal kidney function (67). Comparable results have been reported in other countries like Australia, where Lane et al. reported a decline in renal function to be the cause of 44% of referrals and 22% because of HTN management (68); but not in other countries like Canada where HTN clinics are sometimes run by other specialists (cardiologists and internists) (69).

Prevalence of CKD is very high in the general adult population, with the majority of cases being mildly reduced eGFR and either stable or slowly progressive (63). Many of them would be adequately managed by PCPs with the appropriate knowledge and tools. The limited capacity of Nephrology outpatient clinic agendas should therefore be dedicated to patients with more

severe CKD and associated morbidities or at a higher risk of progression. In order to help with this patient selection, guidelines have provided recommendations for adequate referral to specialists (31,53,70).

Communication platform for electronic queries from PCPs

Considering the full period of analysis (2010-2020), 60.05% of referrals were considered appropriate in our study. Primary Care and other Hospital-based Departments (considered as a group) showed comparable adequacy rates (61.23 and 63.86%, respectively) while the Emergency Unit showed a much lower rate (34.76%). CKD stages 3a and 3b in the elderly account for the larger number of inappropriate referrals (18.23%), followed by inadequate referral of hypertensive patients (16.12%), either non-resistant or to discard secondary HTN without reasonable clinical or laboratory suspicion. Addressing the patient to the wrong specialty (i.e., mistaking Nephrology for Urology portfolio) is also common (14.53%). The last large group of inadequate referrals are patients where obvious nephrotoxicity could be detected in electronic health records (14.40%) (Tables 6-7).

Several authors have analysed the issue of referral adequacy to Nephrology in different countries. Ghimire A et al. conducted a retrospective cohort study in Alberta, Canada, and observed a worse adequacy rate, only 41% of patients were referred from Primary Care in a guideline concordant manner (71); just slightly better than the 37.2% observed by Hingwala et al. also in Canada almost a decade before (72). Similar to Canada, low adequacy rates have been reported by Bahiense-Oliveira M et al. in Brazil (47.3%) (73); Schulz C et al. in France (42%) (74) and Kiel S et al. in Germany (27.9%) (75). Interestingly, differences may be seen within the same country. In Australia, Wright J et al. reported a 43.5% adequacy rate in referrals from a rural region in the state of Victoria during 2013-2015 (76). Conversely, Lane C et al. observed a much better adequacy rate (75%) in urban south-east Sydney during 2008-2011 (68), suggesting different PCPs' guidelines knowledge and referral pattern behaviour depending on the area characteristics. In Spain, the 55% adequacy rate reported by Ferrer G et al. at Ciudad Real (66) is quite similar to our 60% rate, but both studies have been conducted in areas with similar urban/rural characteristics. Unfortunately, we cannot compare our results with a more urban area (Barcelona Esquerra) because Arrizabalaga P et al. do not report the referral adequacy rate in their study (67).

Can referral adequacy or referral pattern be improved over time? In our study, where improvement actions were based on a) the rejection of inappropriate referrals and their return to the requester with an explanation, a link to guidelines and recommendation of management

if needed, and b) the development of a nephrology virtual consultancy that can be used previous to an eventual referral; we observed an important 38.5% referral reduction from 2013/2014 (with an average 53.0 referrals/month) till 2019 (with an average 32.6 referrals/month) (Figure 5). 2020 showed an even more reduced rate (24.7 referrals/month) but is not taken into account for comparisons because of the few months analysed, the last of which being highly affected by the COVID-19 pandemic. The reduction in referral rate was mostly due to Primary Care behaviour, as the pattern of both the Emergency Unit and other Hospital-based Departments remained stable throughout the study (Figure 9). The evolution of reasons for referral over time is detailed in Figure 13. The great reduction in referral rates was not accompanied by an equivalent improvement in adequacy rates, which slightly changed from a 57.5-59.8% before 2014 to a 62.0% in 2019 (Figure 16). Taking this into account, along with the great increase in virtual electronic consultation between 2013 and 2019 (Figure 20), we feel that referral reduction rate throughout the study period was mostly due to the success of electronic consultancy rather than on PCPs improvement in guidelines knowledge.

The opposite trend in referrals rate was seen in Alberta, Canada, where no specific correction actions had been implemented. The overall rate showed a 13.4% increase from 2006 to 2019, with an even worsening of guideline concordant/discordant ratio (71). Mixed results were observed in Barcelona, Spain, where an outpatient nephrology programme was set consisting of a referral nephrologist for quick consultancy of case reports by email and also face-to face at certain basic health areas; the programme also included periodic clinical/teaching sessions. A mean 23.6% reduction in new referrals was observed between 2010 and 2014 in areas with virtual and face-to-face nephrology consultancy (and up to 43.6% reduction in some of them) while a 6.6% increase was observed in areas with virtual nephrology consultancy only (67). Other positive results have been reported also in Marbella, Spain, by Oliva-Damaso N et al. with the introduction of a purpose-built smartphone app for use in clinical practice. The referral adequacy rate improved from a 39.6% before the introduction of the app (in 2015) to a 67.8% when the app was in use (in 2017) (77). This study has important limitations though, as all referrals were from other departments within the same hospital, with none coming from PCPs.

The study design that most resembles ours was conducted by Hingwala et al. in Manitoba, Canada (69). From 2012 on, referrals which did not meet adequacy criteria were returned to PCPs with recommendations based on guidelines. No parallel e-consultancy was offered though. The authors compared the pre-triage period (January-December 2011) with the post-triage period (January-December 2013) and observed a reduction in the median wait time for nephrology visit from 230 days in 2011 to 58 days in 2013, along with a 66% referral adequacy

rate in the post-triage period (no adequacy rate is available for the pre-triage period). However, they report that the median number of referrals climbed from 68/month in 2011 to 94/month in 2013. Thus, it is difficult to tell if wait times improvement was attributable to the algorithm for referral triage or rather to other additional changes that the authors admit to have done, which included additional capacity to see new referrals by additional nephrologists (69).

There is a growing number of places where an outpatient Nephrology referral form has been introduced in order to ameliorate referral adequacy. Examples can be found in Ontario, Canada (78); Southern Adelaide, Australia (79); Nova Scotia, Canada (80) or at the NIH National Institute of Diabetes and Digestive and Kidney Diseases, United States of America (81). Still, there is either no available evidence of the benefit of this strategy or the evidence is not positive in the short term. In Ontario, Canada, Brimble KS et al. evaluated the impact of the introduction of the "KidneyWise toolkit", a web-based platform and mobile application to provide guidance on the detection and management of people with CKD in primary care, which includes a standardised referral form. Comparing a 3-month time period immediately prior to and 1 year after the toolkit release, the authors found that referral criteria had not changed significantly (44.7% adequacy vs 45.8%, respectively) (82). A probable explanation for the lack of success could be that only 10.1% referrals used the KidneyWise referral form indeed.

Focus has been put on existent referrals, trying to reduce the burden of patients sent to specialists. But what about patients that meet referral criteria but are actually not referred? In Michigan, USA, Singh K et al. used electronic health record data from the primary care population at Brigham and Women's Hospital to project referral volume if the KDIGO referral recommendations were to be implemented. Among patients with pre-existing CKD (9.9% of all primary care patients), 51% of them met referral criteria, but less than a quarter of them had actually been seen by a nephrologist. The greater mismatch was seen in the group of patients with annual decline of eGFR ≥5 ml/min/1.73m^2. If the additional patients meeting an indication for referral had been referred to a nephrologist, this would have resulted in a 38.0% increase in total nephrology patient volume and 67.3% increase in new referral volume (83). Also in the USA, Duggal V et al. reported that among patients who met laboratory indications for referral, only 17.7% were referred to Nephrology in the following year (84). Likewise, Kiel S et al. in Germany made the observation that implementing KDIGO criteria would lead to more than double increase in referral rate (75). To a certain extent, this is what seemed to happen in the aforementioned study by Hingwala et al. (69).

The aim of setting a referral criterion is to select those patients at risk of complications or progression to ESRD, and patients requiring specific diagnostic work-up or treatments. KDIGO guidelines, the most widely used to define referral adequacy, do not have age-adapted diagnostic criteria for CKD (31), therefore not distinguishing between normal kidney senescence and true kidney disease. An elderly patient with a stable 20-29 ml/min/1.73m^2 eGFR with no electrolyte disturbances would fulfil KDIGO referral criteria but is not expected to benefit from specialised care. In order to better identify patients at risk of CKD progression, an equation (KFRE) has been developed for estimating the absolute risk of kidney failure over 2- and 5- years (85,86). In Germany, adding KFRE to usual referral criteria would reduce potential referrals by almost 30% (75), just about the 42% potential reduction reported by Duggal et al. in the USA (84). In the United Kingdom, Bhachu HK et al. analysed how would referrals change if using the KFRE risk threshold of >3% at 5 years for progression to ESRD. They found out that a similar proportion of individuals would be referred (19.2% of CKD patients with current guidelines and 21.9% with KFRE) but they would not be the same; more than 50% of patients meeting any criteria would have been reclassified between primary and specialty care in either direction if the KFRE-based criteria replaced the current criteria (87), similarly to what Duggal et al. have observed in the USA (84). More recently, using SAIL Databank and UK Biobank data which include 2,311,601 individuals, Sullivan MK et al. report that if the eGFR threshold of 30mL/min/1.73m^2 was replaced by KFRE, between 265 and 456 people per year would no longer need referral (88). A major barrier to adopt KFRE for clinical practice is that the equation requires the albuminuria value, which is still not tested in the majority of CKD patients (73,87,89-91). Nevertheless, if this equation were to be generally adopted, it would probably need a recalibration for usual primary care patients and a decision should be taken about which KFRE threshold should be applied (≥3%, ≥4% or ≥5%) and if additional albuminuria criteria should be added to improve ESRD event prediction (91).

Electronic consultation platform implementation

Electronic consultancy has been a quite successful improvement at our institution. From March 2012 till March 2020, 1,617 requests addressed to Nephrology were attended (mean 19.24 e-consults per month after the initial onset period), with only 7.48% of them needing a further face-to-face visit. Mean response time was 25.46 hours (Figure 21). E-consultancy volume is quite similar to the annual referral reduction volume (Figures 20 and 4) but it doesn't seem that PCPs have changed their pattern of referring patients to Nephrology because most of referrals (92-95%) are still not preceded by an e-consult (Figure 15). Rather, this suggests that e-

consultancy use has been widely adopted by some PCPs while many others continue to proceed in the traditional manner.

One of the first experiences with electronic consultation in Nephrology was carried out by Stoves J et al. in Bradford, United Kingdom, in 2007 (92). The authors developed a system of networked electronic health records and compared referrals from 17 practices (involving 35 PCPs) which implemented e-consultation to 68 non-implementation practices. During the 12 months following the introduction of the service, 68 e-consults and 376 traditional referrals were submitted. Mean response time for an e-consult was 7 days, much longer than our 25.46 hours, but much shorter than their 55.1 days waiting time for traditional referrals. 16% e-consults were finally referred to the clinic as compared to our 7.48%. The total referral rate (counting both traditional and electronic referrals) was marginally higher for the implementation practices during the study period but the ratio of traditional referrals was reduced by 46% compared with 0.02% reduction for the non-implementation practices. In Ontario, Canada, Keely E et al. developed a different system which is not linked to the patients' electronic health records but consists of a secure web browser, where PCPs can enter their questions in a free-text field and attach any files they feel might be relevant. The specialists receive an email notification requesting them to log in and respond. Between May 2011 and January 2015, 97 PCPs submitted 155 eConsults; 68% referrals were avoided and 22% patients required referral following the eConsult (93). In the Netherlands, a group of PCPs and nephrologists conducted a pilot study in 2009-2011 (94), followed by a randomized controlled trial (95). They developed a protected web-based consultation system where family physicians could upload relevant data from the patients' electronic files and nephrologists gave management advice based on the patient's information, and recommended a further referral if needed. In the pilot study involving 28 Family practices and 5 Nephrology departments, 40% of intended referrals were avoided while referral was recommended in 13% of patients where management advice was sought without initial intention to refer. Time investment per consultation amounted a mean of 9 minutes and response time was 1.6 days (94). Most PCPs felt that their knowledge of nephrology had increased by the use of telenephrology and nephrologists perceived a learning curve in the way physicians asked questions (94). The controlled trial following this pilot study involved 47 general practices with 128 PCPs (other than the participants in the pilot study) which were randomized to access to telenephrology or usual care (95). All practices received a previous CKD management course and were instructed on guideline criteria for recommended consultation or referral. Practices served a population of 207,469 people, just slightly less than in our study, with a total of 3,004 identified CKD adult patients, an overview of which was provided to their

PCPs. Overall, no significant differences were observed for referrals (2.3% vs 3.0%) or consultation rates (6.3% vs 5.0%) between the intervention and control group respectively. Differences in the quality of care were neither observed. The authors attribute the lack of results to a probable contamination bias, as the control group also received a CKD management course and overviews of their CKD population, and were intrinsically motivated to participate in the study (95). Nevertheless, the telenephrology tool did not improve results among these PCPs with improved CKD information.

A small pilot study was also conducted in Boston, United States of America, in 2014-2015, involving 49 PCPs and 2 nephrologists. Using an electronic health record integrated platform, 74 nephrology e-consults were completed over 15 months. Referral rates did not change throughout the study but both PCPs and nephrologists thought that the e-consult had been efficient mostly because PCPs sought nephrology advice about patients they would have not referred (96). Finally, Schettini et al. carried out a short 8-month study in 2016-2017 in North Carolina, United States of America (97), with 4 participating Primary Care sites and one nephrologist consultant. They developed a nephrology eConsult workflow embedded within the patients´ electronic health records. 80 e-consults were submitted throughout the study with a median response time of one day. In the 32.5% of patients for whom a face-to-face nephrology visit was recommended, median wait time was 40 days, considerably long but significantly less than the 51-day median wait time for traditional referrals sent from other Primary Care sites (97).

As compared with the other nephrology e-consult experiences reviewed, most of them carried out during the same period, our study is the longest (8 years) and has the larger number of e-consults (n=1,617); response time is quite similar in all cases (mean 1 day) except for the 7 days in Stoves J et al. (92) which was conducted several years before. We did not seek to survey PCPs satisfaction though. When looking at the technical tools developed, shared full electronic health records seem preferrable as they allow nephrologists to review whichever data they feel important, as they could miss relevant data not perceived by PCPs as important in other systems where PCPs do only share the information they select.

<u>Evolution of waiting times for first appointment referrals</u>

The aim of improving nephrology knowledge among PCPs and reorganize nephrology attention in the community does not only try to improve medical care but to make it more efficient as well. Avoiding inappropriate referrals quickly reduced our waiting time for a first appointment from 30 days to less than 2 weeks (Figure 24), a greater relative reduction than the one observed

by Schettini et al. (22% reduction, from 51 to 40 days) with their e-consultation program (97) but less than the impressive 75% reduction observed by Hingwala et al. rejecting inappropriate referrals (69). Nevertheless, the latter started from a quite long wait time (230 days) to reach 58 days (4 times as much as ours) and part of their improvement might be attributable to an increase of their agenda capacity with additional nephrologists. Similar to Hingwala et al. and also in Canada (Nova Scotia), Poyah et al. observed a 62% reduction in wait time for an elective referral to Nephrology (from 178 to 67 days), but again with a mix of improvements which not only included standardized referral information forms, staff training and returning inadequate referrals but also increasing new referral clinic capacity (98), which is something that was not done in our case (where a reduction in the agenda capacity occurred indeed, as a 20% staff reduction was forced between 2010 and 2015 because of government Health budget cuts). Comparisons between different countries might be somehow puzzling due to the many factors involved, thus a clearer comparison can be made with a nearby similar Nephrology department (PTHU) which did not implement operational changes. During the 3-year period 2016-2018, mean wait time for a first outpatient appointment in Nephrology was 16 days at Althaia and 48/83 days (preferential/ordinary visits respectively) at PTHU (unpublished shared information).

Another important issue which we are not aware to have been analysed in the literature is the speed at which eventual health corrective measures considered necessary are applied. Many inadequate referrals are due to either uncontrolled HTN under a non-appropriate treatment or renal function deterioration with a clear identifiable nephrotoxic or hemodynamic agent (tables 6 and 7). Whether all these patients had had to wait for a first visit at Nephrology to implement the appropriate changes, the poor BP control or the renal toxic effect would have been maintained for longer. Within all discarded referrals which were sent back with a specific recommendation of management (n=297), and had available Primary Care electronic medical records (n=245), recommendations were found to have been implemented in 74.3% of patients, with a mean time to implementation of 13 days (Figure 25). A clear improvement was observed since 2018 (mean time 14.8 days before 2018; 7.1 days since 2018), probably due to the change on how these recommendations reached PCPs. Initially, they received the feedback in a written report, not linked to the patient's electronic health records while progressively since 2018, a new virtual visit of the patient appears on their agenda with the recommendations.

Impact on cost savings

Efficiency is also about cost savings. We have avoided 1,569 in-person visits in a 10-year period. Kiel et al. pointed out that applying different Nephrology referral criteria would result in quite

different costs in Germany (75), thus emphasizing the importance of which guideline is to be followed. Trnka et al. reported a 78.6% cost reduction with paediatric nephrology telehealth consultations carried out by videoconference in Queensland, Australia; most of savings derived from avoided patient and family travel and accommodation expenses (99). A detailed analysis of cost savings associated to a system designed to avoid unnecessary referrals through e-consultation has been done by Liddy et al. in Ontario, Canada (100). They evaluate the Champlain BASE eConsult service, which has been used in the aforementioned Nephrology study by Keely et al. (93). Briefly, they identify direct and indirect savings; being direct those savings for the payer (cost of avoided referrals) and indirect those savings for the patient (travel costs and costs associated with lost wages/productivity for patients under the age of 65). Moreover, they also identify direct and indirect costs; being direct those for the payer (costs required to fully operate the eConsult, to register and train new users and the cost of added referrals – those e-consults where a referral was not initially contemplated but was recommended by the consultant –) and indirect those costs for the patient (travel costs and costs associated with lost wages/productivity for those added referrals). The overall net potential cost savings were estimated by subtracting the total costs from the total savings. 3,487 e-consults were completed during 12 months (April 2014 –March 2015) by 44 different specialty groups, including Nephrology; 39.9% (n=1,393) of e-consults resulted in avoided referrals, and 3.1% (n=109) resulted in added referrals. Total costs were $207,787 and total savings $246,516 for an overall net savings of $38,729 (100). The authors recognize that real savings were expected to be greater as they had not taken into account potential reduction in imaging and laboratory testing.

Savings are quite difficult to compare between countries, as costs vary a lot for the same concept. We have estimated a 0.19 € gas cost per km for our patients, while Liddy et al. estimate 0.37 € in Canada (100). As for the cost for a first outpatient visit, we have calculated a variable amount ranging from 81.51 to 113.4 € per visit depending on the year, while Scherpbier-de Haan et al. estimated a 600 € cost per first visit in the Netherlands (94). Nevertheless, relative figures may be more comparable, and the 15.7% cost reduction estimated by Liddy et al. could provide a fairly precise estimate (100), or even greater in more rural areas where travel distances to the hospital are larger.

Improving the efficiency and accessibility of Nephrology departments would eventually result in shorter waiting lists, quicker implementation of recommendations and cost savings, but the biggest problems to face are the prompt detection and management of earlier stages of kidney disease, and the promotion of reno-protective habits, both mainly corresponding to Primary

Care. As PCPs cover a wide range of health conditions, and their nephrological training in Spain can be somehow deficient (14), there is the need to provide them with useful information based on scientific evidence and presented in a comprehensive way (i.e., clinical practice guidelines) which may help to improve healthcare outcomes and reduce levels of inappropriate practice.

Spreading renal knowledge into PCPs by CKD guidelines

First clinical practice guidelines for CKD were developed in 2002 by the United States National Kidney Foundation: The KDOQI guidelines (101). Those guidelines though were more focused on CKD evaluation, classification and stratification and not much into management. First comprehensive clinical practice guidelines including not only CKD evaluation recommendations but also for management and even referral to specialists and models of care were developed in 2012 by the KDIGO, an independently incorporated non-profit foundation governed by an international volunteer Executive Committee (31). These guidelines, that have not been updated so far, were adopted by most national Nephrology societies, including the Spanish SEN (70). Still, the KDIGO guidelines are mostly targeted to nephrologists, and its implementation by PCPs has been limited elsewhere. Abdel-Kader et al. and Sperati et al. found that 45-51% of PCPs were unfamiliar with CKD guidelines and therefore did not follow them (102,103).

In order to get closer to PCPs, National Health institutions like CARI in Australia & New Zealand or the National Institute for Health and Care Excellence in the United Kingdom have developed their own recommendations (104,105). In other countries without this kind of institutions, which is the case for Spain, Nephrology scientific societies have developed consensus documents with their Primary Care partners (106). This latter document made recommendations on CKD diagnosis, evaluation, classification, management and referral criteria, and also proposed a list of tasks to be completed at PCPs visits. The 10-page document though did only involve one of the three major Spanish Primary Care scientific societies, was not endorsed by Public Administration and was hardly diffused among PCPs, resulting in a very little impact on their practice. An additional problem was the poor rating that the document received with the AGREE II instrument (107).

We felt then that there was the need for a more efficacious work. Being the author the president of the Catalan SCN by that time, a new consensus was developed with the 5 local scientific societies mentioned in section 6.2. and also, with the engagement of the Department of Health, Generalitat de Catalunya (53, Annex 1a-1b) with the aim that if guidelines are supported by Health authorities and their application is encouraged, results are more expected to be achieved. Main differences with the Spanish document besides a wider broad of societies and

Health administration involvement were that a) it was more synthetic (7 pages); b) included a section about diuretic management in CKD; c) proposed models of communication between Primary Care and Nephrology Departments and shared management of CKD patients (i.e., on-line data-base, email consulting…) and d) proposed a series of clinical indicators that can be used to evaluate quality improvement (Table 11).

Main problem with guidelines is their poor implementation in real clinical practice. In Catalonia, only 41% of individuals aged ≥60 years with a diagnosis of HTN and 2 or more years of follow up included in the SIDIAP plus database had an eGFR determination and a BP measurement for 2 years (108). The database contains clinical information about patients treated at 274 primary healthcare centres. Within those patients with eGFR and BP data, albuminuria was only available in 51.6% of the individuals (50.9% in the eGFR≥60 ml/min group and 54.4% in the eGFR<60 ml/min group). Similar results have been seen for diabetic patients; a recent Spanish study shows that only 44.21% of them had a urinary albumin excretion test within the last 12 months, and the rate did only increase to 56.09% if the observation period was lengthened to 24 months (109). This lack of guidelines adherence is indeed a generalized problem; Bramlage et al. have recently published the analysis of a German database of 675,628 patients with type 1 or type 2 diabetes, showing that less than 50% of patients were annually screened correctly for CKD (110). Regular (≥ 1x/year) determination of eGFR was more frequent in type 2 (91.4 %) than in type 1 diabetes (81.6 %) while regular urinary albumin excretion determination was much worse: 44.1% in type 1 and 49.1% in type 2 diabetes. Despite anti-diabetic treatment, only 27.2 % patients with type 1 and 43.5 % patients with type 2 achieved a target HbA1c of < 7.0 %. HTN control varied from 41.1% in type 1 to 67.7 % in type 2 patients and RAAS inhibitors were only used in 24.0 – 39.9% patients with microalbuminuria (type 1 – type 2) and 40.9% – 47.7% patients with macroalbuminuria. Also in the United States, Folkerts et al. analysed type 2 diabetic patients included in the Optum Clinformatics Data Mart, a large administrative claims database representative of the commercially insured population and Medicare Advantage patients in the United States (111). Within 1,881,447 eligible patients, 84.8% had at least one sCr test ordered during the 1-year follow-up period but only 43.3% received a urinary albumin excretion test. Albuminuria testing seems to be the worse accomplished quality indicator, and even worse results have been reported in Canada, where only 18.4% patients with CKD received a urine albumin test within 6 months of CKD diagnosis, and only 39.4% had a second measurement within 6 months of an abnormal baseline albuminuria (112).

If guidelines adherence were greater, better clinical outcomes are to be expected. Lu et al. showed that in 1,128 patients with biopsy proven diabetic nephropathy, adherence to

medication regimen and drug contraindication recommended by the American Diabetes Association and Chinese guidelines was associated with a significantly better HbA1c and BP control after 3–6 months' therapy (113). Using the latent class mixed model (LCMM) and time-dependent Cox models, the authors estimated that the continuous control of proteinuria, low-density lipoprotein cholesterol, systolic BP and uric acid were more likely to reduce the risk of ESRD. Better than mathematical models' estimations, Peeters et al. showed that strict implementation of CKD guidelines (through the aid of nurse practitioners) improves renal outcomes: after a median follow-up of 5.7 years, the intervention group reduced the composite renal endpoint of death, ESRD, and 50% increase in sCr significantly by 20%; following a small but significant differences between the groups in BP, proteinuria, LDL cholesterol, and use of aspirin, statins, active vitamin D, and antihypertensive medications (114). In the intervention group, the decrease in eGFR was 0.45 ml/min per 1.73 m^2 per year less than in the control group, highly significant.

Despite the global observation that adherence to recommendations to slow CKD progression is low, substantial variation among countries can be seen. Analysing data from the CKD Outcomes and Practice Patterns Study (CKDopps), a prospective cohort study of patients with moderate and advanced CKD that is conducted among national samples of nephrology clinics in Brazil, Germany, France and the United States, Stengel et al. showed that albuminuria or proteinuria was routinely measured in fewer than half of the patients in Brazil, Germany, and the United States, but in 89% patients in France (115). BP control ≤140/90 mmHg ranged from 49% in France to 76% in Brazil, ≤130/80 mmHg ranged from 25% in France to 52% in Brazil, and ≤120/80 mmHg ranged from 13% to 35%, also in the same countries. In patients with KDIGO recommendations for use, RAAS inhibitors prescription was 67%, 78%, 81%, and 52%, in Brazil, France, Germany, and the United States, respectively. In nondiabetic patients, achievement of all 3 targets including BP control ≤130/80 mmHg, RAAS inhibition, and dietary advice ranged from 10% in the United States to 32% in Brazil. In treated diabetic patients, achievement of these targets, as well as an HbA1c >6% and <8%, ranged from 6% in the United States to 11% in Brazil (115).

Why are CKD guidelines so poorly implemented? And moreover, why such differences between countries?

When asked about the first question, PCPs refer lack of CKD guidelines awareness and knowledge as one of the main problems (102, 103); they also perceive guidelines to change frequently (103) (though this does not seem to be the case for CKD, with only 2 guidelines – KDOQI and KDIGO – released in the last 20 years). PCPs also describe a fatalistic belief that CKD

is incurable and only likely to worsen, and feel it difficult to engage patients in modification of their CKD risk factors (103). Another common issue is lack of time; the system is not optimized for the management of patients with a multi-faceted disease process such as CKD. As care of the CKD patient needs patient education and management of hypertension, diabetes, anemia, and other comorbid illnesses, there is often insufficient time in a clinic visit to address all relevant medical and behavioural topics (103). Finally, an absence of clear, easily applied algorithms for the management of CKD is also remarked (103).

Some solutions can be foreseen when looking at differences between countries in detail. This is the case for albuminuria testing, with as much as 89% compliance in France (115) and <55% elsewhere (108-111,115). In most places, albuminuria testing is included in the Primary Care initial study protocol in diseases like diabetes mellitus or HTN; however, it is not included in the protocol of follow up. Thus, when a PCP clicks on the button “diabetes (or HTN) follow up” at the clinical analysis petitioner, only a serum sample would be drawn. The PCP will not receive a urinary albumin excretion test result unless she/he specifically orders it. This is not the case for France, where albuminuria testing is called by protocol in follow-up (115).

Improving PCPs’ knowledge and education on CKD facts is also important. Drawz et al. showed significant improvements in parathyroid hormone, phosphorus and urine protein measurements in PCPs given education and access to a CKD registry designed to facilitate guideline adherence (116).

Clinical decision support systems (CDSS) can also be helpful to facilitate delivery of guideline concordant care, and may be particularly useful among PCPs who are often charged with managing patients’ multiple and/or complex medical conditions during brief clinical encounters. Ennis et al. studied the effect of a KDOQI/KDIGO based algorithm-driven advice embedded in laboratory reports and sent to physicians as part of their routine work flow (117). PCPs who used this system ordered all CKD-relevant testing more in accord with guidelines than those who did not use it, ranging from 29% for Transferrin saturation to 88% for serum Phosphorus. Meeting guidelines targets for control rates was not that successful though, CDSS physicians met guideline targets for LDL-Cholesterol and 25-vitD more often than control physicians, but the latter did better in Hemoglobin targets, while CDSS did not affect the achievement of the remaining guideline targets. Better results were observed by Carroll et al. improving CDSS with the TRANSLATE model (Target, use Registry and Reminder systems, get Administrative buy-in, Network information systems, Site coordination, Local physician champion, Audit and feedback, Team approach, and Education), a model which had been shown successful in diabetes care. The

intervention resulted in a slower CKD progression (primary outcome): the mean annual loss of eGFR was 0.95 ml/min/1,73m^2 in the control group and 0.01 ml/min/1.73m^2 in the intervention group ($P < 0.001$) (118). There was also a greater decline in HbA1c for patients in intervention practices compared with control group practice, but not differences for systolic BP, avoidance of NSAIDs, use of RAS blockers and early recognition and diagnosis of CKD, probably because the control group also included the use of CDSS. Intensive nurse practitioner support in strict implementation of CKD guidelines has also been shown effective as previously pointed out (114). Combining both physicians' education and online clinical pathways also showed good results in Alberta, Canada, where albuminuria testing had a larger increase in zones where pathway uptake was greater (119).

While some effective measures require important changes or the involvement of an increased number of professionals (114,118), other like CDSS are much simpler and unexpensive (117). Electronic health records could alert a PCP as she/he orders a sCr that a patient with possible CKD does not have a documented urine albumin test and is not receiving a RAS blocker. The alert could also provide references to guidelines and the studies that informed those guidelines (102). Raising awareness of CKD within the general population with more media coverage and public service announcements might also increase patient engagement in their CKD management (103). Coming back to our guidelines, the board of the SCN tried to engage Public Administration into a system of implementation of recommendations and outcomes analysis. Unfortunately, despite a promising start, personnel changes at both SCN and the Department of Health changed priorities and this was not carried out. Nevertheless, the document has been accessible on scientific societies websites and has been used by the author to evaluate referrals' adequacy and to discard inappropriate referrals along with a recommendation of management or reconsultation.

<u>Spreading renal knowledge into CKD patients and their environment</u>

Along with physicians' lack of knowledge or therapeutic inertia, low patients' adherence and persistence with recommendations is an important cause for not achieving targets. In order to get patients to follow recommendations, it is crucial that they understand the risk of CKD and the main issues involved in its progression. To make matters worse, unlike other chronic diseases, even awareness of their condition is low among CKD patients. The National Health and Nutrition Examination Survey (NHANES) in United States asked laboratory proven CKD patients "Have you ever been told by a doctor or health care professional of weak or failing kidneys?" and showed that only Stage 5 (kidney failure) patients were fully aware (120), while in Stage 1-

3, most of them managed in Primary Care, awareness did not even reach 10% (121). Results were better for stage 4 patients but even in those, fewer than half the subjects were aware that they had CKD (121). The fact that patients' CKD awareness did not change over a 5-year period is particularly disappointing (121). Referring patients to a Nephrology clinic improves their knowledge, but apparently not much. Gray et al. analysed the improvement in patients' CKD knowledge after referral by filling out a questionnaire at first visit and after 12 months. Despite an initial visit (typically a 45 min consultation) and a mean of 3 subsequent visits (15–20 min consultations) during the follow-up, the percentage responding "unsure" to understanding and to management of CKD was only reduced from 57% to 37% and 38% respectively (122). Analysing further in detail, Wright et al. developed a kidney disease knowledge survey for patients attending a Nephrology speciality clinic in Nashville, Tennessee, US, and observed that while some issues were well understood (the risk of HTN and diabetes for kidney function and the importance of achieving BP targets) other important issues were less identified (medications a person with CKD should avoid) and knowledge in some areas was very poor (the importance of proteinuria in CKD progression) (49). Focalising on adherence to nutrition recommendation, Betz et al. recently observed that stage 3-5 CKD patients recruited from a Nephrology clinic were consuming excess sodium (average intake of 3,117 mg; 67% to 91% of patients' intake above goal), and phosphorus (average intake of 1,153 mg; 59% to 70% of patients' intake above goal); and there was no significant difference in the amount of potassium consumed between the group with hyperkalemia and the group without (48).

Why are all these efforts so ineffective? Nephrologists tend to rely on classical learning approaches i.e., providing booklets with information and assuming that it will be memorised, while patients may not be really susceptible to these methods. In the previously commented study by Gray et al., only 50% of patients collected kidney disease booklets from a large display in the clinic area but more interestingly, they couldn't show a difference in knowledge when comparing participants who had and had not collected information material (122). The US Department of Education has recognised that as many as half of the adult population has trouble when using printed materials to deal with everyday tasks, and too often Health materials for the public and patients are written at such complex levels that they cannot be sufficiently understood (123). Health literacy is thus low, and particularly worse among CKD patients (47-49), which constitutes a more serious problem because of the multiple aspects they have to deal with (cardiovascular risk, anemia, electrolytic and metabolic disturbances). Along with medication adherence, diet control is a field where patient's compliance is of paramount importance. Low adherence to CKD-specific dietary recommendations associates with impaired

kidney function, dyslipidemia, higher uric acid, and inflammation (124). Diet issues are usually addressed at specific Nephrology outpatient clinics where specialized nurses instruct patients on adequate type of food and cooking procedures. Results can be somehow disappointing though, Betz et al. showed that greater knowledge of the renal diet was not associated with increased adherence to dietary restrictions; patients consumed excess sodium, phosphorus, and protein, whereas potassium intake was inadequate in people without hyperkalemia (48). Moreover, sometimes intervention might even result in a worsening in the scores of food variety and legume components of the diet quality index (125). Making the effort to improve the usual teaching approach to reach low literacy patients by providing clearer printed materials might not be sufficient, people tend to forget all those recommendations over time and they frequently lose the teaching materials they are given at the clinic, or simply don't have them handy when they need them i.e., at the supermarket or at the restaurant when they have to decide which food to get. Accordingly, some patients will tend to unnecessary restrict to the few items of food that they know safe, a behaviour that may reduce their quality of life, while others may feel frustrated and take risks with any kind of food. Improving self-management seems an important objective because it has been associated to better outcomes (126) but the methods that we have traditionally been using are not efficacious. Therefore, there is an urgent need to improve and switch to clearer and easier models of communication with patients.

Development of an app for mobile phones and tablets

Health information technology or eHealth (using telecommunication technology to provide health communication and services) represents a unique opportunity to improve patients Health literacy and empowerment. Smartphones and tablets have shown a vertiginous penetration over the years, worldwide and particularly in Spain where 85% of the population owned a mobile device in 2014, when PUKONO was released (127). Indeed, it represented a 16% increase compared to just one year before and the greater increase was shown in population from the age of 45 (127). The WHO Executive Board in 2016 considered mobile Health (mHealth) the use of mobile wireless technologies for public health, and remarked the increasing importance of this resource for health services delivery and public health, given their ease of use, broad reach and wide acceptance. The WHO emphasizes that mHealth has been shown to increase access to health information, services and skills, as well as to promote positive changes in health behaviours and manage diseases (128). eHealth tools include patient websites, wearable technology and mobile apps. Among them, apps seem to be particularly useful because as mobile phones are carried by people to all places, they allow everyone to access information every time and everywhere. Lifestyle, Health & Fitness apps are the second most popular apps

after Games (129). According to ©Research2Guidance, 325,000 health apps were available in 2017, with 78,000 new health apps added to major app stores throughout that year, and 3.6 billion health apps expected to be downloaded by users (130). Knowing about the chronic problem to improve results in low Health literacy population, apps should be designed to meet this population's needs (131). This is what we intended to do with PUKONO, to provide CKD patients and caregivers with a simple and wearable tool to improve diet safety and variety.

Major eHealth efforts are dedicated to fitness, exercise and weight loss and healthy diets for the general population, also to certain chronic conditions like diabetes, mental health and cardiovascular disease (132). Apps and websites for patients with CKD are scarce; Singh K et al. conducted a search of the US Apple App Store (iOS) and Google Play Store (Android) in November 2016, looking for apps targeting patients with CKD and identified just 28 suitable apps, the majority of them focused on ESRD patients (already on dialysis or transplantation) (133). To make matters worse, 50% of those apps were no longer available for download as of January 20, 2019, when the manuscript was submitted to the journal, reflecting how hard is to keep an app on the market throughout the years.

If Health apps available in English are few, the choice is even more restricted for those available in Spanish. A search performed on the Apple App Store (iOS) and Google Play Store (Android) as of May 30, 2022, identified just 10 apps available in Spanish targeting patients with CKD, 4 of them strictly focused on dialysis or transplantation. Apart from PUKONO, 5 more apps offered counselling and tools for non ESRD CKD patients:

"Salud Renal" is an app developed in Peru and available free of charge since January 2020. It is just dedicated to monitor the evolution of users' kidney health using data from laboratory results and to alert users about kidney health issues. Since its release it has had less than 500 downloads and has not been rated by users.

"Renal&Go" is an app developed in Spain and available free of charge since September 2019. It just offers personalized exercise training and allows medication adherence monitoring. Since its release it has had 500-1,000 downloads and has been rated a mean of 4.0 out of 5.0 points by 10 users.

"Renal Vi" is an app developed in Colombia and available free of charge since June 2021. It is a digital platform that allows patients to control nutritional facts, daily water intake, daily exercise and medication adherence. Patients can also be reminded of the scheduling of pending appointments and monitor own laboratory results and obtain medical interpretations. Since its

release it has had 1,000-5,000 downloads and has been rated a mean of 4.0 out of 5.0 points by 23 users.

“Dieta renal y diabetes” is an app developed in Spain and available free of charge since September 2019. It contains tables with different types of food content of phosphorus, potassium, proteins, fats, sodium and carbohydrates; also, menus for kidney disease and diabetes and renal function calculators. Since its release it has had 1,000-5,000 downloads and has not been rated by users.

Finally, “Nefrodiet” is an app developed in Spain by Fundación Iñigo Alvarez de Toledo and available free of charge since April 2016. It provides information about food content in sodium, potassium, phosphorus, water, proteins, carbohydrates and calories, and provides a calculator to monitor daily intake of these components. Since its release it has had 10,000-50,000 downloads and has been rated a mean of 3.4 out of 5.0 points by 100 users.

App PUKONO usability

Summarizing PUKONO updated results, our app has been downloaded a total of 93,749 times as of May 30, 2022; and a total of 2,957,129 sessions have been performed (Flurry Analytics). Recent activity shows 14,020 active users and 144,921 sessions during the last 3 months. Even considering English apps for CKD patients, no other but PUKONO has had more than 50,000 downloads.

The search for Health apps targeting CKD patients for this discussion has been cross-sectional but 50% of these apps are likely to be no longer available in just 2 years, as it has been shown by Singh Ket al. (133). More than 90% of Health apps are available for free at the stores but keeping an app operative in the market involves fixed costs, and so do periodical updates. 55% of apps have less than 5,000 downloads and 46% report less than 500 mean active users (130), which makes them good candidates to disappear in the medium term. Therefore, the only fair comparison for PUKONO seems to be Nefrodiet, both of apps supported by a prestigious Health institution (i.e., Althaia and Iñigo Alvarez de Toledo foundations respectively), with more than 6 years in the market already and endorsed by Spanish scientific societies SEN and SEDEN. Still, PUKONO is ahead of Nefrodiet in terms of downloads, active users and ratings. In addition to scientific rigor, technological reliability and graphic design, there are several reasons that may explain PUKONO success and its leadership in the field. Having been the first available app is Spanish almost 2 years ahead of Nefrodiet undoubtedly offers an advantage, but one of the most valued issues by users is its simplicity, a point which is aligned with the recommendations

of public administrations and health institutions to also improve Health results in low literacy patients (131). PUKONO has a quick and simple first step to define user's profile and does not need to fill in further information. PUKONO usability data also reflects this feature, the average session length is just 57 seconds, being the majority of them 1-3 minutes (Figure 9), usually just to make a consultation about the safety of a certain type of food (Figure 10). Other issues that contribute to its success are the lack of commercial ads, the ability to share app experiences with other people on social networks and finally that mobile phones and tablets don't need to be connected to the network for the app to work.

Neither PUKONO nor Nefrodiet have been analysed for their efficacy in improving quality of life, clinical parameters or end points. A recent Cochrane review has focused on eHealth interventions to change health behaviours in people with CKD, the review includes 43 studies involving 6,617 participants, 11 studies (26%) were conducted with mobile or tablet apps. They concluded that although a significant reduction in dietary sodium intake of 197 mg/day was found, overall, the evidence for eHealth interventions was of low quality and insufficient to guide clinical practice in kidney disease (89). Nevertheless, some studies show promising results, Ong et al. developed a more complex smartphone-based system application targeting four behavioural elements: monitoring BP, medication management, symptom assessment, and tracking laboratory results. 47 patients completed at least 6 months of follow-up and showed a significant reduction in BP. They also identified 127 medication discrepancies; 59% of which were medication errors that required an intervention to prevent harm. At the end of the study patients felt more confident and in control of their condition and clinicians perceived patients to be better informed and more engaged (134).

Overall, mHealth provides CKD patients with powerful tools to improve their knowledge and outcomes. These tools have to be scientifically reliable, easy to use and positively rated by both patients and Nephrology teams and ideally, they should have to be endorsed by scientific societies and public administration. Generating high quality evidence of effectiveness is not easy, apps do not lend themselves to randomize so we cannot expect randomised controlled trials in this field. Nevertheless, efforts have be taken to promote studies and to standardize measurable outcomes and endpoints that help to compare an analyse results.

8. Limitations

A first limitation concerning the referral filtering procedure and electronic consultation platform should be considered. All Primary Care centers were provided with these improvements but no control group was stablished to compare potential changes in referrals rate, adequacy rates or time to implementation of recommendations. As already described, the system by which counselling reached PCPs was ameliorated during the study. No comparisons were made between Primary Care centers, and no surveys were passed to PCPs to assess their knowledge, attitudes and feelings about the changes introduced.

Secondly, savings calculation has been incomplete as it has only taken into account the cost of first outpatient visits and patients' travel savings, other potential savings like reduced absenteeism have not been considered. Neither have been extra costs calculated, like those required to fully operate the eConsult.

Thirdly, CKD clinical practice guidelines were developed but did not follow a process of systematic dissemination among PCPs, and after several initial informative actions were performed, they were posted for consultation in the respective sections of the participating societies web pages. Therefore, it is not known how wide their knowledge has been on PCPs. Moreover, guidelines included a section of clinical indicators to be used for quality improvement evaluation, but no analysis was carried out before and after their dissemination so their real impact on CKD detection and management is not known.

Finally, the app PUKONO has been largely downloaded and operated, has been awarded and has excellent customers' ratings and comments, but users have not been offered a validated questionnaire on kidney health to be filled out before and after a certain period of utilization, so it is not possible to assess the potential improvements that its use may have brought.

9. Conclusions

1. A quick evaluation system of referrals which includes the review of the patient's electronic health records and the return of inadequate ones with a recommendation of management (referral filtering) resulted in a quick 50% waiting time reduction for a first in-person appointment, which has been maintained with minor variation in less than 15 days thereafter. However, this did neither reduce in the short term the number of referrals nor their adequacy rate.

2. A conflicting increase in referrals monthly rate was observed during the first 4 years. This increasing trend was reversed however 2 years after the introduction of an e-consultation platform for PCPs (when it reached full operational capacity), mostly driven by a 44% traditional referral reduction from Primary Care referrals. Possible reasons for that could be both that it took several years to improve PCPs knowledge of referral criteria through recommendations and/or that many PCPs started to use the e-consult instead of a classic referral for a first approach to the nephrologist.

3. Eight years after the introduction of both measures (referral filtering and e-consultation platform), e-consults and traditional referrals represent 37% and 63% of all outpatient queries to Nephrology respectively. Mean response time for an e-consult has been 25.5 hours and most of them (92.5%) have been solved without the need for further in-person visit.

4. Referral adequacy rates were 60-65% for both PCPs and other Hospital based specialties and did not change in general throughout the study (April 2010 – March 2020), although some inappropriate reasons for referrals did improve, as it is the case for confusing Nephrology with Urology portfolio and worsening of renal function with an identifiable nephrotoxic agent, mostly NSAID. Both stable mild CKD (stage 3a) and moderate CKD (stage 3b) in the elderly are the most common cause of inadequate referral.

5. Referral filtering and e-consultation have also achieved a shorter time to implementation of recommendations and important economic savings for both Hospital and patients, and probably to the community that would benefit from fewer patients requiring time off work.

6. PCPs account for almost two-thirds of referrals to Nephrology, and other Hospital based specialties account for almost one-third, with much less coming from the Emergency Unit. More than 40% of patients referred to Nephrology are over the age of 70 and major reasons for referral are CKD with reduced eGFR, worsening of renal function, HTN and proteinuria. Main diagnoses vary depending on age group, being suspected secondary HTN the major cause for referral in patients younger than 40, difficult to control HTN in patients 41-60 years old, and worsening of renal function in patients over the age of 60.

7. Comprehensive CKD management guidelines have been developed along with other related specialties and released to provide a useful source of knowledge for PCPs. Several important issues were introduced which make a difference with most other guidelines published at that time i.e., the involvement of the government Department of Health, suggestion of clinical indicators to be used for quality improvement evaluation and a proposal of models of communication between Primary Care and Nephrology Departments and shared management of CKD patients.

8. In order to improve patients' knowledge and adherence to recommendations, an e-health tool has been developed to help patients with CKD diet requirements; to avoid sodium, potassium and/or phosphorus intake in those patients with indicated restrictions, while allowing a varied safe diet. This app, PUKONO, is free of charge and available in several languages; has been downloaded almost 80,000 times and almost 2.5 million sessions have been performed during the first 7 years, with a mean of more than 1,300 new users/month. These figures make PUKONO the world's most widely used app for CKD diet, according to available data. Its simplicity and graphic design are aligned with recommendations of public administrations and health institutions to improve health results in low literacy patients, and the fact that it doesn't need connection to the network to work makes it handy at all times.

10. Future directions

This PhD thesis has tried to describe in a large, long-term study the referral profile to a Nephrology department and to improve several factors in order to better detect and manage CKD patients at different levels, and to do this in a more efficient manner. Guidelines and app usability have been published and reported at scientific meetings (59,60), and so is planned for the referral filtering procedure and electronic consultation platform. Ameliorating the efficiency of delivering nephrology services is important but many other issues have to improve to reverse the GBD fateful predictions. Being CKD diagnosing criteria based on biochemical markers, Artificial Intelligence linked to electronic health records could be better used for early detection and thus correct the high rate of underdiagnose. It could also be used to detect if CKD patients are not tested regularly for markers of progression. Guidelines algorithms could also be embedded in electronic health records to detect if patients are not being treated according to recommendations, and if they fulfil referral criteria. Moreover, alerts could be sent to PCPs in case of guideline discordance so as they that could reconsider their treatment strategy, and both nephrologists and PCPs could better work in a method of shared management of patients instead of being separate stages of medical care according to the degree of CKD severity. We are actually involved in a project called “Practice Change Platform” that aims to implement all these improvements at the Althaia Primary Care centers in Manresa. Quality indicators would be compared before and after the new procedure implementation and could also be compared to neighboring areas that will not introduce these changes for the time being. Finally, we are also planning to improve PUKONO functionalities to help patients not only with diet but also to improve treatment adherence and to achieve BP control targets. Only with early detection and good management of patients would we be able to reduce ERDS burden and to contain or even reverse the ominous impact on clinical outcomes, quality of life and healthcare budget.

11. References

1) Kolff WJ, Berk HTJ. The artificial kidney: A dialyzer with a great area. Acta Med Scand. 1944; 117: 121-34.
2) Alwall N. On the artificial kidney; apparatus for dialysis of the blood in vivo. Acta Med Scand. 1947; 128: 317-25.
3) Robinson RR, Richet G. History of the ISN. Kidney Int. 2001; 59 (Suppl. 79): S1-S100.
4) Merrill JP, Murray JE, Harrison JH, Guild WR. Successful homotransplantation of the human kidney between identical twins. JAMA. 1956; 160: 277-82.
5) Blagg C: Preface: The first dialysis for chronic renal failure 50 years ago. Hemodial Int. 2010; 14: 1-2.
6) Botella J. Historia de la Nefrología española. http://enfermosrenales.blogia.com/temas/historia-de-la-nefrologia.php
7) De Francisco ALM. Sostenibilidad y equidad del tratamiento sustitutivo de la función renal en España. Nefrologia. 2011; 31: 241-6.
8) Otero A, de Francisco A, Gayoso P, García F; EPIRCE Study Group. Prevalence of chronic renal disease in Spain: results of the EPIRCE study. Nefrologia. 2010; 30: 78-86.
9) Holmes J, Rainer T, Geen J, Roberts G, May K, Wilson N, et al. Acute Kidney Injury in the Era of the AKI E-Alert. Clin J Am Soc Nephrol. 2016; 11: 2123-31.
10) Noubiap JJ, Nansseu JR, Nyaga UF, Sime PS, Francis I, Bigna JJ. Global prevalence of resistant hypertension: a meta-analysis of data from 3.2 million patients. Heart. 2019; 105: 98-105.
11) Bernis Carro C; Comisión Nacional de la Especialidad de Nefrología en España. Evolución de las plazas asignadas a nefrología en las convocatorias MIR (1985-2008) [Trends in resident positions offered in nephrology (1985-2008)]. Nefrologia. 2011; 31: 155-61.
12) Andreu JL, Silva-Fernandez L, Galla T. Progress of the attractiveness of Rheumatology among medical speciality training candidates (MIR) in Spain. Reumatol Clin (Engl Ed). 2018; 14: 150-4.
13) Itinerario formativo de la especialidad de Medicina Familiar y Comunitaria. https://icsgirona.cat/adjunts/files/ESPprograma_formativo_MFiC.pdf
14) Lopez A, Herrera GL. Conocimientos de los médicos de familia sobre los factores de riesgo de la enfermedad renal crónica. Rev Ciencias Médicas. 2021; 25 (4) Julio-Agosto: e4829. ISSN: 1561-3194.
15) Spencer K. Analytical reviews in clinical biochemistry: the estimation of creatinine. Ann Clin Biochem. 1986; 23: 1-25.
16) Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976; 16: 31-41.
17) Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for industry: pharmacokinetics in patients with impaired renal function - study design, data analysis, and impact on dosing and labeling. 2010. [cited 2021 Aug 8]. Available from: https://www.fda.gov/files/drugs/published/Pharmacokinetics-in-Patients-with-Impaired-Renal-Function.pdf
18) Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999; 130: 461-70.

19) Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004; 351: 1296-305.
20) Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. Arch Intern Med. 2004; 164: 659-63.
21) Hallan SI, Dahl K, Oien CM, Grootendorst DC, Aasberg A, Holmen J, et al. Screening strategies for chronic kidney disease in the general population: follow-up of cross sectional health survey. BMJ. 2006; 333: 1047-52.
22) Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens. 2007; 25: 1105–87.
23) Gracia S, Montañés R, Bover J, Cases A, Deulofeu R, Martín de Francisco AL, et al. Recomendaciones sobre la utilización de ecuaciones para la estimación del filtrado glomerular en adultos [Recommendations for the use of equations to estimate glomerular filtration rate in adults. Spanish Society of Nephrology]. Nefrologia. 2006; 26: 658-65.
24) Cirillo M, Laurenzi M, Mancini M, Zanchetti A, Lombardi C, De Santo NG. Low glomerular filtration in the population: prevalence, associated disorders, and awareness. Kidney Int. 2006; 70: 800-6.
25) Richards N, Harris K, Whitfield M, O'Donoghue D, Lewis R, Mansell M, et al. The impact of population-based identification of chronic kidney disease using estimated glomerular filtration rate (eGFR) reporting. Nephrol Dial Transplant. 2008; 23: 556–61.
26) Noble E, Johnson DW, Gray N, Hollett P, Hawley CM, Campbell SB, et al. The impact of automated eGFR reporting and education on nephrology service referrals. Nephrol Dial Transplant. 2008; 23: 3845–50.
27) Jain AK, McLeod I, Huo C, Cuerden M, Akbari A, Tonelli M, et al. When laboratories report estimated glomerular filtration rates in addition to serum creatinines, nephrology consults increase. Kidney Int. 2009; 76: 318–23.
28) Hemmelgarn BR, Zhang J, Manns BJ, James MT, Quinn RR, Ravani P, et al. Nephrology visits and health care resource use before and after reporting estimated glomerular filtration rate. JAMA. 2010; 303: 1151-8.
29) Phillips LA, Donovan KL, Phillips AO. Renal quality outcomes framework and eGFR: impact on secondary care. QJM. 2009; 102: 415-23.
30) Kagoma YK, Weir MA, Iansavichus AV, Hemmelgarn BR, Akbari A, Patel UD, et al. Impact of estimated GFR reporting on patients, clinicians, and health-care systems: a systematic review. Am J Kidney Dis. 2011; 57: 592-601.
31) Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Inter. Suppl. 2013; 3: 1-150.
32) Weinstein JR and Anderson S. The aging kidney: physiological changes. Adv Chronic Kidney Dis. 2010; 17: 302–7.
33) Raymond NT, Zehnder D, Smith SCH, Stinson JA, Lehnert H, Higgins RM. Elevated relative mortality risk with mild-to-moderate chronic kidney disease decreases with age. Nephrol Dial Transplant. 2007; 22: 3214-20.

34) Eriksen BO, Palsson R, Ebert N, Melsom T, van der Giet M, Gudnason V, et al. GFR in Healthy Aging: an Individual Participant Data Meta-Analysis of Iohexol Clearance in European Population-Based Cohorts. J Am Soc Nephrol. 2020; 31: 1602-15.
35) Matsushita K, Selvin E, Bash LD, Franceschini N, Astor BC, Coresh J. Change in estimated GFR associates with coronary heart disease and mortality. J Am Soc Nephrol. 2009; 20: 2617-24.
36) Cabrera CS, Lee AS, Olsson M, Schnecke V, Westman K, Lind M, et al. Impact of CKD Progression on Cardiovascular Disease Risk in a Contemporary UK Cohort of Individuals With Diabetes. Kidney Int Rep. 2020; 5: 1651-60.
37) Tovillas-Morán FJ, Vilaplana-Cosculluela M, Dalfó-Pibernat A, Zabaleta-del-Olmo E, Galcerán JM, Coca A, et al. El filtrado glomerular reducido según las fórmulas de Cockcroft-Gault y MDRD no siempre predice la morbimortalidad cardiovascular en los pacientes hipertensos atendidos en atención primaria [Decreased glomerular filtration rate using the Cockckroft-Gault and MDRD formulas does not always predict cardiovascular morbidity and mortality in hypertensive primary care patients]. Nefrologia. 2010; 30: 653-60.
38) Galceran JM. Riesgo por enfermedad renal crónica: la epidemia revisada. Hipertens riesgo vasc. 2010; 27: 183–6.
39) O'Hare AM, Bertenthal D, Covinsky KE, Landefeld CS, Sen S, Mehta K, et al. Mortality risk stratification in chronic kidney disease: one size for all ages? J Am Soc Nephrol. 2006; 17: 846-53.
40) Roderick PJ, Atkins RJ, Smeeth L, Mylne A, Nitsch DD, Hubbard RB, et al. CKD and mortality risk in older people: a community-based population study in the United Kingdom. Am J Kidney Dis. 2009; 53: 950-60.
41) Mosen DM, Schmittdiel J, Hibbard J, Sobel D, Remmers C, Bellows J. Is patient activation associated with outcomes of care for adults with chronic conditions? J Ambul Care Manage. 2007; 30:21-9.
42) Hibbard JH, Mahoney ER, Stock R, Tusler M. Do increases in patient activation result in improved self-management behaviors? Health Serv Res. 2007; 42: 1443-63.
43) Rogvi S, Tapager I, Almdal TP, Schiøtz ML, Willaing I. Patient factors and glycaemic control--associations and explanatory power. Diabet Med. 2012; 29: e382-9.
44) Berkman ND, Sheridan SL, Donahue KE, Halpern DJ, Crotty K. Low health literacy and health outcomes: an updated systematic review. Ann Intern Med. 2011; 155: 97-107.
45) Office of Disease Prevention and Health Promotion, Office of the Assistant Secretary for Health, Office of the Secretary, U.S. Department of Health and Human Services. History of Health Literacy Definitions. [cited 2021 Aug 16]. Available from: https://health.gov/our-work/healthy-people/healthy-people-2030/health-literacy-healthy-people-2030/history-health-literacy-definitions
46) Heijmans M, Waverijn G, Rademakers J, van der Vaart R, Rijken M. Functional, communicative and critical health literacy of chronic disease patients and their importance for self-management. Patient Educ Couns. 2015; 98: 41-8.
47) Taylor DM, Fraser SDS, Bradley JA, Bradley C, Draper H, Metcalfe W, et al. ATTOM investigators. A Systematic Review of the Prevalence and Associations of Limited Health Literacy in CKD. Clin J Am Soc Nephrol. 2017; 12: 1070-84.

48) Betz M, Steenes A, Peterson L, Saunders M. Knowledge Does Not Correspond to Adherence of Renal Diet Restrictions in Patients With Chronic Kidney Disease Stage 3-5. J Ren Nutr. 2021; 31: 351-60.
49) Wright JA, Wallston KA, Elasy TA, Ikizler TA, Cavanaugh KL. Development and results of a kidney disease knowledge survey given to patients with CKD. Am J Kidney Dis. 2011; 57: 387-95.
50) Costa-Requena G, Moreso F, Cantarell MC, Serón D. Health literacy and chronic kidney disease. Nefrologia. 2017; 37: 115-7.
51) Sofue T, Nakagawa N, Kanda E, Nagasu H, Matsushita K, Nangaku M, et al. Prevalences of hyperuricemia and electrolyte abnormalities in patients with chronic kidney disease in Japan: A nationwide, cross-sectional cohort study using data from the Japan Chronic Kidney Disease Database (J-CKD-DB). 2020; PLoS ONE 15(10): e0240402.
52) Sharif MU, Elsayed ME, Stack AG. The global nephrology workforce: emerging threats and potential solutions! Clin Kidney J. 2016; 9: 11-22.
53) Galceran JM, Felip A, Tovillas X. En nombre de la Sociedad Catalana de Nefrología (SCN), la Sociedad Catalana de Medicina Familiar y Comunitaria (CAMFiC), la Sociedad Catalana de Hipertensión Arterial (SCHTA), la Asociación Catalana de Enfermería (ACI), la Asociación Catalana de Diabetes (ACD), y con el apoyo del Departament de Salut de la Generalitat de Catalunya. Documento de consenso sobre atención a la enfermedad renal crónica. Hipertens riesgo vasc. 2013; 30: 107-14.
54) Indicadors demogràfics i de territory. Estructura per edats, envelliment i dependència. Institut d'Estadística de Catalunya. https://www.idescat.cat/pub/?id=inddt&n=915&by=com
55) Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? Arch Intern Med. 2000; 160: 685-93.
56) Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int. 2020; 98: S1-S115.
57) Consens català sobre atenció a la malaltia renal crònica. https://www.socane.cat/pdfs/document_de_consens1.pdf
58) APPs para pacientes. https://senefro.org/modules.php?name=apps&op=detalle&id=17
59) Casals G, Fenollar M, Morera A, Galceran JM. Impacto de una aplicación (APP) para el enfermo renal. Enferm Nefrol. 2015; 18, suppl. 1: 13.
60) Fenollar M, Casals G, Morera A, Galceran JM. New technologies to improve the diet of patients with hypertension or chronic kidney disease. 45th EDTNA/ERCA International Conference 2016. https://www.edtnaerca.org/resource/edtna/files/O%2070%20-%20Marina%20Fenollar.pdf
61) https://premiscactus.com/primera-edicio-premis-cactus/
62) GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2020; 395: 709-733.
63) Gorostidi M, Sánchez-Martínez M, Ruilope LM, Graciani A, de la Cruz JJ, Santamaría R, et al. Chronic kidney disease in Spain: Prevalence and impact of accumulation of cardiovascular risk factors. Nefrologia (Engl Ed). 2018; 38: 606-15.
64) Ortiz A, Sanchez-Niño MD, Crespo-Barrio M, De-Sequera-Ortiz P, Fernández-Giráldez E, García-Maset R, et al. The Spanish Society of Nephrology (SENEFRO) commentary to the

Spain GBD 2016 report: Keeping chronic kidney disease out of sight of health authorities will only magnify the problem. Nefrologia (Engl Ed). 2019; 39: 29-34.

65) El libro blanco de la Nefrología española. (II). Sociedad Española de Nefrología [The white book of Spanish nephrology. (II). Spanish Society of Nephrology]. Nefrologia. 2000; 20: 214-33.
66) Ferrer G, Herráez L, Castro MP, Moral E, Olazo E, Sidel D, et al. Referral criteria to Nephrology and matching degree with the consensus document for chronic kidney disease detection and management. Nephrol Dial Transplant. 2021; 36 (Suppl. 1), gfab087.0047
67) Arrizabalaga P, Gómez M, Menacho I, Pallisa L, Jorge V, Poch E. The contribution of outpatient nephrology to the control of demand: Analysis of the comprehensive Health Area of Barcelona Esquerra (AISBE). Nefrologia (Engl Ed). 2019; 39: 192-7.
68) Lane C, Pirabhahar S, Robins J, Tranter S, Brown M, Katz I. Improving nephrology service delivery - Accessing the specialist. Aust Fam Physician. 2016; 45: 223-8.
69) Hingwala J, Wojciechowski P, Hiebert B, Bueti J, Rigatto C, Komenda P, Tangri N. Risk-Based Triage for Nephrology Referrals Using the Kidney Failure Risk Equation. Can J Kidney Health Dis. 2017; 4: 2054358117722782.
70) Gorostidi M, Santamaría R, Alcázar R, Fernández-Fresnedo G, Galcerán JM, Goicoechea M, et al. Spanish Society of Nephrology document on KDIGO guidelines for the assessment and treatment of chronic kidney disease. Nefrologia. 2014; 34: 302-16.
71) Ghimire A, Ye F, Hemmelgarn B, Zaidi D, Jindal KK, Tonelli MA, et al. Trends in nephrology referral patterns for patients with chronic kidney disease: Retrospective cohort study. PLoS One. 2022; 17: e0272689.
72) Hingwala J, Bhangoo S, Hiebert B, Sood MM, Rigatto C, Tangri N, et al. Evaluating the implementation strategy for estimated glomerular filtration rate reporting in Manitoba: the effect on referral numbers, wait times, and appropriateness of consults. Can J Kidney Health Dis. 2014; 1: 9.
73) Bahiense-Oliveira M, Duarte D, Meira GG, de Codes JJ, Ribeiro MZ. Referral to the nephrology outpatient clinic: inappropriate referral to the nephrologist. J Bras Nefrol. 2010; 32: 145-8.
74) Schulz C, Messikh Z, Reboul P, Cariou S, Ahmadpoor P, Pambrun E, et al. Characteristics of outpatients referred for a first consultation with a nephrologist: impact of different guidelines. J Nephrol. 2022; 35: 1375–85.
75) Kiel S, Weckmann G, Chenot JF, Stracke S, Spallek J, Angelow A. Referral criteria for chronic kidney disease: implications for disease management and healthcare expenditure-analysis of a population-based sample. BMC Nephrol. 2022; 23: 225.
76) Wright J, Glenister KM, Thwaites R, Terry D. The importance of adequate referrals for chronic kidney disease. Aust J Gen Pract. 2018; 47: 58-62.
77) Oliva-Damaso N, Oliva-Damaso E, Rivas-Ruiz F, Lopez F, Castilla MDM, Baamonde-Laborda E, et al. Impact of a phone app on nephrology referral. Clinical Kidney Journal. 2019; 12: 427-32.
78) https://www.hrh.ca/wp-content/uploads/2018/10/2MCKCReferralFormFeb282018.pdf
79) https://www.sahealth.sa.gov.au/wps/wcm/connect/23e2ee0046acf62eb255b22195233e2a/Outpatient+GP+Referral+Guidelines+Nephrology+SALHN.pdf?MOD=AJPERES&CACHEID=ROOTWORKSPACE-23e2ee0046acf62eb255b22195233e2a-nzLdZ.o

80) https://www.cdha.nshealth.ca/.../nsha-nephrology-referral-form.pdf
81) https://www.niddk.nih.gov/.../Nephrology_Referral_Form_508.pdf
82) Brimble KS, Boll P, Grill AK, Molnar A, Nash DM, Garg A, et al. Impact of the KidneyWise toolkit on chronic kidney disease referral practices in Ontario primary care: A prospective evaluation. BMJ Open. 2020; 10: e032838.
83) Singh K, Waikar SS, Samal L. Evaluating the feasibility of the KDIGO CKD referral recommendations. BMC Nephrol. 2017; 18: 223.
84) Duggal V, Montez-Rath ME, Thomas IC, Goldstein MK, Tamura MK. Nephrology Referral Based on Laboratory Values, Kidney Failure Risk, or Both: A Study Using Veterans Affairs Health System Data. Am J Kidney Dis. 2022; 79: 347-53.
85) Tangri N, Stevens LA, Griffith J, Tighiouart H, Djurdjev O, Naimark D, et al. A predictive model for progression of chronic kidney disease to kidney failure. JAMA. 2011; 305: 1553-9.
86) Tangri N, Grams ME, Levey AS, Coresh J, Appel LJ, Astor BC, et al. for the CKD Prognosis Consortium. Multinational Assessment of Accuracy of Equations for Predicting Risk of Kidney Failure: A Meta-analysis. JAMA. 2016; 315: 164-74.
87) Bhachu HK, Cockwell P, Subramanian A, Adderley NJ, Gokhale K, Fenton A, et al. Impact of using risk-based stratification on referral of patients with chronic kidney disease from primary care to specialist care in the United Kingdom. Kidney Int Rep. 2021; 6: 2189-99.
88) Sullivan MK, Jani BD, Rutherford E, Welsh P, McConnachie A, Major R, et al. Potential impact of NICE guidelines on referrals from primary care to nephrology. Br J Gen Pract. 2022; BJGP.2022.0145. DOI: 10.3399/BJGP.2022.0145
89) Stevenson JK, Campbell ZC, Webster AC, Chow CK, Tong A, Craig JC, et al. eHealth interventions for people with chronic kidney disease. Cochrane Database of Systematic Reviews 2019, Issue 8. Art. No.: CD012379.
90) Kim LG, Cleary F, Wheeler DC, Caplin B, Nitsch D, Hull SA; UK National Chronic Kidney Disease Audit. How do primary care doctors in England and Wales code and manage people with chronic kidney disease? Results from the National Chronic Kidney Disease Audit. Nephrol Dial Transplant. 2018; 33: 1373-9.
91) Major RW, Shepherd D, Medcalf JF, Xu G, Gray LJ, Brunskill NJ. The Kidney Failure Risk Equation for prediction of end stage renal disease in UK primary care: An external validation and clinical impact projection cohort study. PLoS Med. 2019; 16(11): e1002955.
92) Stoves J, Connolly J, Cheung CK, Grange A, Rhodes P, O'Donoghue D, Wright J. Electronic consultation as an alternative to hospital referral for patients with chronic kidney disease: a novel application for networked electronic health records to improve the accessibility and efficiency of healthcare. Qual Saf Health Care. 2010; 19(5): e54. doi: 10.1136/qshc.2009.038984.
93) Keely E, Li J, Magner P, Afkham A, Liddy C. Nephrology eConsults for Primary Care Providers: Original Investigation. Can J Kidney Health Dis. 2018; 5:2054358117753619.
94) Scherpbier-de Haan ND, van Gelder VA, Van Weel C, Vervoort GM, Wetzels JF, de Grauw WJ. Initial implementation of a web-based consultation process for patients with chronic kidney disease. Ann Fam Med. 2013; 11: 151-6.
95) van Gelder VA, Scherpbier-de Haan ND, van Berkel S, Akkermans RP, de Grauw IS, Adang EM, et al. Web-based consultation between general practitioners and nephrologists: a cluster randomized controlled trial. Fam Pract. 2017; 34: 430-436.

96) Mendu ML, McMahon GM, Licurse A, Solomon S, Greenberg J, Waikar SS. Electronic Consultations in Nephrology: Pilot Implementation and Evaluation. Am J Kidney Dis. 2016; 68: 821-3.
97) Schettini P, Shah KP, O'Leary CP, Patel MP, Anderson JB, Cho AH, et al. Keeping care connected: e-Consultation program improves access to nephrology care. J Telemed Telecare. 2019; 25: 142-50.
98) Poyah PS, Quraishi TA. The Impact of a New Triage and Booking System on Renal Clinic Wait Times. Can J Kidney Health Dis. 2020; 7:2054358120924140.
99) Trnka P, White MM, Renton WD, McTaggart SJ, Burke JR, Smith AC. A retrospective review of telehealth services for children referred to a paediatric nephrologist. BMC Nephrol. 2015; 16: 125.
100) Liddy C, Drosinis P, Deri Armstrong C, McKellips F, Afkham A, Keely E. What are the cost savings associated with providing access to specialist care through the Champlain BASE eConsult service? A costing evaluation. BMJ Open. 2016; 6(6):e010920.
101) National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002; 39 (2 Suppl 1): S1-266.
102) Abdel-Kader K, Greer RC, Boulware LE, Unruh ML. Primary care physicians' familiarity, beliefs, and perceived barriers to practice guidelines in non-diabetic CKD: a survey study. BMC Nephrol. 2014; 15:64. doi: 10.1186/1471-2369-15-64.
103) Sperati CJ, Soman S, Agrawal V, Liu Y, Abdel-Kader K, Diamantidis CJ, et al.; National Kidney Foundation Education Committee. Primary care physicians' perceptions of barriers and facilitators to management of chronic kidney disease: A mixed methods study. PLoS One. 2019; 14(8): e0221325.
104) Chronic kidney disease guidelines. https://www.cariguidelines.org/guidelines/chronic-kidney-disease/early-chronic-kidney-disease/ Accessed 6 October 2021
105) Chronic kidney disease: assessment and management. https://www.nice.org.uk/guidance/ng203. Accessed 6 October 2021.
106) Alcázar R, Egocheaga MI, Orte L, Lobos JM, González Parra E, Alvarez Guisasola F, et al. Documento de consenso SEN-SEMFYC sobre la enfermedad renal crónica [SEN-SEMFYC consensus document on chronic kidney disease]. Nefrologia. 2008; 28: 273-82.
107) Coronado Daza J, Vernooij RWM, Salas K, Osorio D, Urrútia Cuchí G. Quality assessment of clinical practice guidelines for chronic kidney disease: a systematic review. BMC Nephrol. 2019; 20: 192. doi: 10.1186/s12882-019-1387-x.
108) Salvador-González B, Mestre-Ferrer J, Soler-Vila M, Pascual-Benito L, Alonso-Bes E, Cunillera-Puértolas O; en representación del grupo de investigación del proyecto MARREC-HTA. Chronic kidney disease in hypertensive subjects ≥60 years treated in Primary Care. Nefrologia. 2017; 37: 406-414.
109) Puchades MJ, Navarro J, Vivas D, Uso R, Sauri I, Diaz-Carnicero J, et al. Características basales del estudio RECODYS. Prevalencia de DM2 y realización de cribado para la enfermedad renal en el Departamento de Salud Valencia Clínico-La Malvarrosa. Nefrologia. 2020; 40 (Suppl 1): 6.
110) Bramlage P, Lanzinger S, Tittel SR, Hess E, Fahrner S, Heyer CHJ, et al. Guidelines adherence in the prevention and management of chronic kidney disease in patients with

diabetes mellitus on the background of recent European recommendations - a registry-based analysis. BMC Nephrol. 2021; 22(1):184. doi: 10.1186/s12882-021-02394-y.

111) Folkerts K, Petruski-Ivleva N, Comerford E, Blankenburg M, Evers T, Gay A, et al. Adherence to Chronic Kidney Disease Screening Guidelines Among Patients With Type 2 Diabetes in a US Administrative Claims Database. Mayo Clin Proc. 2021; 96: 975-986.

112) Bello AK, Ronksley PE, Tangri N, Kurzawa J, Osman MA, Singer A, et al. Quality of Chronic Kidney Disease Management in Canadian Primary Care. JAMA Netw Open. 2019; 2(9):e1910704.

113) Lu J, Zhao W, Chen T, Xu Z, Sun X, Xie H, et al. Influence of guideline adherence and parameter control on the clinical outcomes in patients with diabetic nephropathy. BMJ Open Diabetes Res Care. 2020; 8(1): e001166.

114) Peeters MJ, van Zuilen AD, van den Brand JA, Bots ML, van Buren M, Ten Dam MA, et al. Nurse practitioner care improves renal outcome in patients with CKD. J Am Soc Nephrol. 2014; 25: 390-8.

115) Stengel B, Muenz D, Tu C, Speyer E, Alencar de Pinho N, Combe C, et al.; CKDopps investigators. Adherence to the Kidney Disease: Improving Global Outcomes CKD Guideline in Nephrology Practice Across Countries. Kidney Int Rep. 2020; 6: 437-48.

116) Drawz PE, Miller RT, Singh S, Watts B, Kern E. Impact of a chronic kidney disease registry and provider education on guideline adherence--a cluster randomized controlled trial. BMC Med Inform Decis Mak. 2012; 12:62.

117) Ennis J, Gillen D, Rubenstein A, Worcester E, Brecher ME, Asplin J, et al. Clinical decision support improves physician guideline adherence for laboratory monitoring of chronic kidney disease: a matched cohort study. BMC Nephrol. 2015; 16:163.

118) Carroll JK, Pulver G, Dickinson LM, Pace WD, Vassalotti JA, Kimminau KS, et al. Effect of 2 Clinical Decision Support Strategies on Chronic Kidney Disease Outcomes in Primary Care: A Cluster Randomized Trial. JAMA Netw Open. 2018; 1(6):e183377.

119) Donald M, Smekal MD, Elliott MJ, McBrien K, Weaver RG, Manns BJ, et al. Online clinical pathway for chronic kidney disease management in primary care: a retrospective cohort study. BMC Nephrol. 2021; 22: 332.

120) Nickolas TL, Frisch GD, Opotowsky AR, Arons R, Radhakrishnan J. Awareness of kidney disease in the US population: findings from the National Health and Nutrition Examination Survey (NHANES) 1999 to 2000. Am J Kidney Dis. 2004; 44: 185-97.

121) Plantinga LC, Boulware LE, Coresh J, Stevens LA, Miller ER 3rd, Saran R, et al. Patient awareness of chronic kidney disease: trends and predictors. Arch Intern Med. 2008; 168: 2268-75.

122) Gray NA, Kapojos JJ, Burke MT, Sammartino C, Clark CJ. Patient kidney disease knowledge remains inadequate with standard nephrology outpatient care. Clin Kidney J. 2016; 9: 113-8.

123) Rudd RE. Improving Americans' health literacy. N Engl J Med. 2010; 363: 2283-5.

124) Kaesler N, Baid-Agrawal S, Grams S, Nadal J, Schmid M, Schneider MP, et al. Low adherence to CKD-specific dietary recommendations associates with impaired kidney function, dyslipidemia, and inflammation. Eur J Clin Nutr. 2021; 75: 1389-97.

125) Fernandes AS, Ramos CI, Nerbass FB, Cuppari L. Diet Quality of Chronic Kidney Disease Patients and the Impact of Nutritional Counseling. J Ren Nutr. 2018; 28: 403-10.

126) Peng S, He J, Huang J, Lun L, Zeng J, Zeng S, Zhang L, et al. Self-management interventions for chronic kidney disease: a systematic review and meta-analysis. BMC Nephrol. 2019 ; 20(1): 142.

127) https://www2.deloitte.com/es/es/pages/technology-media-and-telecommunications/articles/Nota-prensa-consumo-medios-espana.html. [accessed 2022-05-28].

128) WHO 139th Executive Board, 2016; Geneva, Switzerland.

129) https://buildfire.com/app-statistics/. [accessed 2022-05-29].

130) ©Research2Guidance 2017 – mHealth Economics 2017/2018 – www.research2guidance.com

131) U.S. Department of Health and Human Services, Office of Disease. Prevention and Health Promotion. (2010). Health literacy online: A guide to writing and designing easy-to-use health Web sites. Washington, DC.

132) Patient Adoption of mHealth. Report by the IMS Institute for Healthcare Informatics. https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/patient-adoption-of-mhealth.pdf. [accessed 2022-05-30].

133) Singh K, Diamantidis CJ, Ramani S, Bhavsar NA, Mara P, Warner J, et al. Patients' and Nephrologists' Evaluation of Patient-Facing Smartphone Apps for CKD. Clin J Am Soc Nephrol. 2019; 14: 523-9.

134) Ong SW, Jassal SV, Miller JA, Porter EC, Cafazzo JA, Seto E, et al. Integrating a Smartphone-Based Self-Management System into Usual Care of Advanced CKD. Clin J Am Soc Nephrol. 2016; 11: 1054-62.

12. Annexes

Annex 1a. Consens català sobre atenció a la malaltia renal crónica. https://www.socane.cat/pdfs/document_de_consens1.pdf

Annex 1b. Documento de consenso sobre atención a la enfermedad renal crónica (Hipertens riesgo vasc. 2013; 30: 107-14.)