

THE EUROPEAN KIDNEY HEALTH ALLIANCE (EKHA) AND THE DECADE OF THE KIDNEY™

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ABSTRACT

The European Kidney Health Alliance (EKHA) is an advocacy organization that defends the case of the kidney patients and the nephrological community at the level of the European Union (EU), and from there, top to bottom, also at the national level of the EU member states and the EU-associated countries. The Decade of the Kidney™ is a global initiative launched by the American Association of Kidney Patients (AAKP) to create greater awareness and organize patient demands for long overdue innovation in kidney care. This article describes the medical and patient burden of kidney disease, the history of EKHA, its major activities and tools for policy action and the need for innovation. We then describe the Decade of the Kidney™ initiative, the rationale why EKHA joined this activity to emanate parallel action at the European side, the novel professionalized structure of EKHA, and its immediate targets. The final aim is to align all major stakeholders for an action plan on kidney disease comparable to Europe's successful Beating Cancer Plan, with the additional intent that the EKHA model is applied also by the respective national kidney-related societies to create a broad mobilization at all levels. The ultimate aims are that the EU considers chronic kidney disease (CKD) as a major health and health-economic problem, to consequently have CKD included as a key health research target by the European Commission, and to improve quality of life and outcomes for all kidney patients.

Keywords: advocacy, decade of the kidney, European commission, patient-oriented outcomes, policy

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INTRODUCTION

Despite its considerable burden for patients and society¹, kidney disease does not receive the attention it deserves. This is attributable to difficulties explaining kidney functioning, limited patient empowerment, and several obstinate misunderstandings: CKD is conceived as limited to dialysis and transplantation, and to be solved by these strategies. Also, CKD is not seen as a separate entity needing specific approaches, but merely as an appendix of other diseases, mainly diabetes and cardiovascular disease.

Of note, in the most recent annual report of the ERA registry, only 31% of kidney failure patients were attributed to cardiovascular disease or diabetes². Even if prevention of cardiovascular disease and diabetes would entirely forestall those pathways leading to kidney failure, which is unlikely, the remaining causes (acute kidney injury [AKI], nephrotoxic agents, hereditary and auto-immune disorders, infections, pollution, global warming, long-term consequences of cancer treatment) will grow in importance. The impact of COVID-19 is still uncertain, but in view of the many cases of kidney damage in hospitalized cases³, it is likely that it also will be substantial. In addition, an outcome and health-economic effect by prevention of the causes will be seen only 20 or more years from now. Meanwhile, the burden will continue to rise if no specific measures are taken without delay. This is why a specific approach for CKD is needed, and not only indirect action via a few of multiple causes.

At this moment kidney disease is not listed by the European Union (EU) as one of the main health focus points for research and innovation⁴. Neither is it included in the top five of non-communicable diseases (NCD's) to be tackled by a new strategic health plan of the European Commission, Healthier Together. This carries the risk of substandard research investment, and insufficient response to the continuing increase in mortality and cost of CKD¹.

This publication describes the efforts of the European Kidney Health Alliance (EKHA) to generate public awareness about kidney disease and the rationale why EKHA joined the Decade of the Kidney™ initiative.

THE MEDICAL BURDEN OF KIDNEY DISEASE

Around 100 million Europeans of which more than 50 million citizens in EU-27 suffer from chronic kidney disease (CKD)⁵. Many of those affected remain unaware of their condition⁶,

which precludes preventing progression and complications. Without adequate treatment, CKD culminates in advanced kidney failure with the need for kidney replacement therapies (KRTs), i.e. transplantation or dialysis. The number of affected individuals will continue to increase, because of ageing, unhealthy nutrition, lifestyle and environment, and as prolonged survival of underlying comorbidities will allow more CKD to manifest⁷.

Annual mortality of CKD in Europe is approximately 130,000⁵. Worldwide, CKD will become the fifth leading cause of death by 2040, above all cancer types, Alzheimer, diabetes, HIV and tuberculosis⁸. Over the last 20 years, mortality has not improved, in contrast to most other chronic diseases⁵. CKD also accelerates dismal outcomes of its comorbidities⁹. Premature death is mainly due to cardio-vascular disease, cancer and infection¹⁰⁻¹², but general awareness of this is very low. Those reaching KRT have worse survival chances than people diagnosed with cancer¹.

Especially dialysis comes at a high societal cost and the share of global healthcare expenditure of KRT is proportionally 10-20 times higher than the number of patients treated¹³. Annual reimbursement for in-center hemodialysis reaches up to 80,000 €/patient¹⁴. Although in countries with a lower gross domestic product (GDP), dialysis consumes less in absolute amounts, a larger percentage of their general health care budget is spent¹⁴, likely at the expense of other, more cost-effective health investments like screening and prevention¹⁵.

Individuals with CKD who are not on KRT also represent a substantial source of expenditures¹⁶. Overall annual costs of CKD in Europe are higher than those of other major NCDs like cancer and diabetes¹.

PATIENT BURDEN

CKD has a heavy impact on the lives of affected people, families and their financial stability. Despite its mortality and growing evidence of its epidemiologic and economic impact, the global response to CKD remains inadequate and the therapeutic options are far from satisfactory from a patient's viewpoint. Especially in lower income countries, access to dialysis is limited with even less likelihood for transplantation.

Hemodialysis patients must regularly connect to their dialysis machine and peritoneal dialysis requires recurrent performance of exchange procedures, both of which preclude

other activities and social life. Patients who want to be transplanted, often must wait for a suitable graft, requiring an unpredictable period of dialysis, due to a persistent shortage of donor organs. In addition, not everyone is transplantable. After transplantation, immunosuppression needed to prevent rejection, sometimes generates disturbing side-effects like changes in physiognomy, cancer, infections or reduced response to vaccination.

All people with CKD, irrespective of whether they are on dialysis, transplanted or not yet in need of KRT, have a high medication burden. They struggle with fatigue, uncertainty about the future, sexuality disorders, emotional stress, mental health problems, pain and discomfort¹. Moreover, CKD also impacts quality of life, daily life activities, employment and participation in social life of their partners, families and caregivers.

Incorporating patient reported outcome measures (PROMs) and patient reported experience measures (PREMs) could help to raise quality of life and lower the burden of kidney disease^{17,18}, but their wider adoption requires a shift in mindset and wider incorporation of patient-oriented science.

A more concerted, strategic, and multisectoral policy approach collaborating with kidney patients, underpinned by solid research and innovation, is essential to help reverse the negative trends in incidence, prevalence and outcomes of CKD.

EUROPEAN KIDNEY HEALTH ALLIANCE

EKHA was founded in 2007 to increase awareness on kidney disease in the European Union (EU) and the EU Member States. The first years were demanding since health was not a EU priority. From 2012 on, EKHA gathered momentum with several initiatives, culminating in the publication in 2015 of the Recommendations for Sustainable Kidney Care¹⁹.

EKHA is supported by five large European or international nephrology societies and nineteen national or smaller international societies (see acknowledgements) representing patients, physicians, researchers, nurses and kidney foundations from 12 EU and 5 non-EU countries (figure 1).

Building on the 2015 Recommendations¹⁹, several initiatives elaborated on EKHA's main focus points, using various tools to reach EKHA's aims (table 1). Each year, EKHA organizes a well-attended Kidney Forum in Brussels on one of its focus points. This activity usually takes

place in the European Parliament, but was organized digitally over the last two years due to COVID-19. The 2021 meeting on inequalities in nephrology attracted 184 participants. EKHA also participates with presentations in nephrology meetings and publishes advocacy documents in scientific journals, e.g. on containing the cost of kidney care¹³, increasing European transplantation activity²⁰, the burden of kidney disease¹, green nephrology, and recently, in the context of the Russian-Ukrainian conflict, on the need to specifically consider kidney patients in war rescue activities²¹.

Awareness on kidney disease could still be improved at policy level, and EKHA reaches out to EU policy makers and their administrations by regular meetings, white papers, open letters and position statements (figure 2, table 2). In February 2021, EKHA met with European Commissioner for Health and Food Safety, Stella Kyriakides, who fully endorsed EKHA's action points. Similarly, EKHA collaborates with consecutive Presidencies of the European Council, especially Croatia (2020), Portugal (2021) and France (2022). EKHA is also supported by a group of 23 Members of European Parliament (MEPs) representing 13 Member States.

EKHA's advocacy actions for the time being culminated in a campaign on World Kidney Day (WKD) 2022 (March 10) with video and written messages by patients, EKHA members, MEPs and the French Minister of Health. The same day, for the first time ever, also a plenary session was devoted to CKD in the European Parliament in Strasbourg, France.

EKHA obtained EU financing by the EU of EDITH²², to analyze country differences in uptake of kidney replacement therapies²³⁻²⁵. EKHA was also commissioned by the EU to develop a Thematic Network and Joint Statement on ways to promote organ donation and transplantation in the EU^{20,26}.

Finally, EKHA chairs the European Chronic Disease Alliance (ECDA)²⁷, joining twelve major non-communicable disease organizations.

All these actions were facilitated by a change of approach by the EU in the aftermath of COVID-19 to prioritize healthcare, emanating in supportive or financing programs such as the Beating Cancer plan (cancer and related chronic diseases) and EU4Health (healthcare adaptation to the evolving world), but also the Green Deal (environment) and Farm to Fork (sustainable food production programs).

EUROPEAN KIDNEY PATIENTS' FEDERATION (EKPF)

The European Kidney Patients' Federation (EKPF) is the oldest and largest kidney patient advocacy organization in Europe²⁸, representing close to 100 million of people with kidney health conditions. Created in 1980 and with headquarters based in Vienna (Austria), its membership consists of 27 national kidney patient societies from 26 European countries. The majority of the EKPF membership are patients on dialysis treatment and kidney transplant recipients, but EKPF also represents patients with CKD not on KRT, especially those with advanced stages.

The mission of EKPF is to improve patient voice, engagement, safety, and autonomy, to address the humanistic burden and dismal quality of life of kidney disease, to promote prevention, early detection and therapeutic innovation, and to optimize life conditions for the family members and caregivers of CKD patients.

To reach these aims, kidney patients must be actively involved in kidney health policy and be made effective partners in the determination of their care, which is the only way to improve quality of health care for all without inequality among social groups or countries.

A NEED FOR INNOVATION

A Focal Issue of Nature Reviews Nephrology²⁹ illustrates in detail that kidney disease needs more attention for prevention and better and affordable therapies, and includes lists of current innovative actions. Compared to cancer or diabetes^{30,31}, the investment in innovation for CKD is low, despite its exponentially growing burden and cost.

Although the lack of innovation is most strongly perceived for dialysis, it is present at all stages of CKD. Inefficient screening results in too late diagnosis and inadequate prevention. After the detection of the Renin-Angiotensin-Aldosterone System (RAAS) inhibitors around the midst of last century, only the recent development of a series of novel antidiabetics provided for the first time an additional option to slow down kidney disease progression³². Although rare kidney diseases affect at least 10% of patients with kidney failure³³, specific therapies are largely missing. Also, for AKI, there have been virtually no therapeutic

innovations with clinical impact. The shortage of donor kidneys makes that many transplantation candidates die on the waiting list³⁴.

The basic principle of dialysis (a solute shift between plasma and dialysis water through a semipermeable membrane, based on a concentration gradient) remained unmodified since Willem Kolff applied in 1945 the first successful (hemo)dialysis³⁴. Whereas many other areas in technology, like telephony or computing, became mobile due to conceptual changes and miniaturization, both hemodialysis and peritoneal dialysis remained bulky and dependent on specific times and fixed locations. In addition, dialysis has also remained extremely un-ecological, with substantial energy consumption and waste production, including massive amounts of water that are simply discarded via the drain³⁵.

Most CKD patients die from cardiovascular disease but, whereas overall cardiovascular mortality decreases, mortality of CKD still increases⁸. A novel conceptual model should be developed to improve these dismal outcomes. If not, it is likely that current efforts to further improve cardiovascular outcomes, will largely be neutralized by the growth of CKD. Such an adaptation should also consider quality of life. Finally, societal cost grows exponentially and should be diminished.

Structural screening, early detection, prevention and self-care programs are needed, including education at all levels with specific approaches for health illiteracy. In addition, more granular approaches should be sought to prevent kidney disease progression. The potential of stem cells for kidney repair should be further explored.

Bionic artificial kidneys conform with a novel more flexible concept of dialysis. With the portable artificial kidney (PAK) and the wearable artificial kidney (WAK) as landmarks^{36,37}, presently more advanced portable and wearable dialysis devices are developed³⁸. The Implantable Artificial Kidney (IAK) will be the ultimate disruptive innovation. Silicon wafer-based manufacturing of nanopore membranes presently forms the cutting edge of this frontier³⁹. These advanced concepts may also partly solve the ecologic problem by reducing dialysis water consumption, although additional conceptual changes are needed to make dialysis energy neutral and circular. They may also make dialysis cheaper and more flexible, thus enabling its use in lower income regions and in precarious circumstances like disasters

and wars. Of note, portable therapeutic concepts are among the focus points of the 2021 Work Program of the European Innovation Council (EIC)⁴⁰.

For transplantation, more specific direct therapies to prevent immune damage and rejection, and approaches to increase transplantation rate and improve kidney preservation are needed²⁰. After years of stagnation, xenotransplantation recently underwent a breakthrough allowing implantation of kidneys from genetically modified pigs into a brain-dead person⁴¹. Further away on the horizon, stem cells from the donor might help to grow implantable bioengineered kidneys without risk of rejection⁴².

The role of the intestine as a source of toxic metabolites and inorganic compounds led to the development of oral sorbent mixtures to remove some of these compounds. Up to now, however, sorbent technology did not result in significant improvements of outcomes in controlled studies⁴³. Alternatively, xenobiotics (prebiotics, probiotics, symbiotics), also could decrease uremic toxin concentration⁴⁴ and might at the same time, more than other removal strategies, restore the balance between noxious and beneficial compounds generated by the intestinal microbiome⁴⁵.

The most important bottlenecks for progress are research and development funding and cooperation/coordination between parties. The current increased consideration of kidney disease by the European Commission should be an opportunity to obtain more support for kidney-related innovation and projects.

THE KIDNEY HEALTH INITIATIVE (KHI) AND DECADE OF THE KIDNEY™

The need for innovation in the kidney field is also recognized in the US. In 2012, the Food and Drug Administration (FDA) and the American Society of Nephrology (ASN) jointly launched the Kidney Health Initiative (KHI), engaging over 100 stakeholders. KHI developed a Roadmap for innovative, patient-centered and more affordable KRTs. EKHA and many other organizations worldwide support this Roadmap. As a next step, an even broader collaboration involving non-kidney innovation leaders is needed to realize this Roadmap.

Figure 3 highlights this multistakeholder approach but also the importance of the patient voice. In 2019, the American Association of Kidney Patients (AAKP) launched the Decade of the Kidney™ (2020-2030), a global, mobilization to advocate vis-à-vis governments for breakthrough innovations, reminiscent of US President John F. Kennedy's 1962 Rice

University “moonshot speech” communicating his vision to land a man on the moon before 1970. Similarly, AAKP’s initiative aims at breakthrough innovations for kidney diseases within a 10-year timespan.. Encouraged by the US Congressional Kidney Caucus, in 2018, the US Department of Health and Human Services (HHS) and the ASN established KidneyX as a public-private partnership for funding innovative solutions^{46,47}. The KHI Roadmap served to define the target technical milestones. Additionally, an explicit US presidential Executive Order signed in 2019 boosted kidney-related innovations⁴⁸.

In parallel, on the European side, the European Parliament and Commission have been made aware of this need and are discussing possible solutions with EKHA. Individual countries already made a start: the Netherlands and the Region of Flanders, Belgium, jointly funded Regenerative Medicine Crossing Borders (RegMedXB) for three “moonshots”, one of which targeting kidney failure. Kidney disease also profits indirectly from EU projects targeted at other NCDs that are linked to CKD, and other projects target specific kidney problems, but the perception is that kidney disease still receives less attention than for other disease areas. Like for Beating Cancer, a more holistic, focused, and structured action plan should be developed, targeting kidney disease and its entire metabolic spectrum (diabetes, the brain-heart-liver-intestine-kidney axis), while covering screening, prevention, artificial kidney and transplantation.

STRUCTURAL REORGANIZATION AND CURRENT ACTIVITIES OF EKHA

The above description illustrates how efforts to develop innovative therapies are not always aligned to public health and health systems’ needs. More should be done to develop drugs that can treat progressive kidney damage as well as devices that replace the function of the kidney more effectively, at lower cost, and with less impact on the patients’ well-being. In absence of this investment, burden and cost will grow exponentially. Therefore, EKHA organizes structured actions under the label of the Decade of the Kidney™ (2020-2030). During this period, EKHA wants that real advancements occur for people with kidney disease, while contributing to a sustainable and resilient health system. In this decade, EKHA will advocate to achieve several goals through a wide range of activities, to raise awareness of the unmet needs in kidney disease.

The Board of Directors of EKHA accordingly decided to restructure and professionalize EKHA (figure 4). The somewhat monolithic concept of a Board of Directors supported by a few

professionals for a wide array of functions was replaced by a more granular concept, in which, the Board of Directors still plays a central role in defining future activities, but supported by three work groups (on screening and prevention, disease management, and breakthrough innovation), a supporting group of kidney-related industries (see acknowledgements), and an extended group of professionals with various competences (management, EU policy, advocacy, finance, event organization).

EKHA TARGETS FOR THE IMMEDIATE FUTURE

The intention is to implement a stepwise progressive approach, compared to climbing a mountain (figure 5), with four immediate goals (see below), emanating at the end of the Decade of the Kidney™ in 2030 in attention at EU level for kidney disease in proportion to its burden, and a broad set of innovative therapies with major impact on cost, prognosis, quality of life and lifestyle.

Goal 1: Structural Acknowledgement of CKD in EU programs and strategies

Although frequently associated with other comorbidities, CKD is a specific entity and accelerator of other diseases with its own pathophysiology and need for specific therapeutic approaches. EKHA desires to have this acknowledged by the European Commission.

The French government, the current President of the European Council (first semester of 2022), embraced EKHA's message into its communications in their briefing on the European Health Union, recognizing for the first time the impact of CKD in an official EU document.

Goal 2: Development of an EU Code for prevention and screening of CKD

To increase awareness of risk factors that can lead to CKD and to detect CKD as early as possible, EKHA plans to design a Kidney Prevention & Screening Code. This code aims to inform people about actions they can take to reduce their risk of kidney diseases and on the other hand, to detect kidney dysfunction early and to prevent further deterioration via screening protocols.

Goal 3: Improve disease management

This goal aspires to develop a self-management tool that helps people with kidney disease (all stages) to better manage their disease. Using this tool should make it easier for patients

to adhere to healthy lifestyle and therapy resulting in better quality of life and retarding disease progression.

Goal 4: Promotion of transplantation & home therapies

Transplantation is currently the optimal therapeutic solution for kidney failure²⁰. Home dialysis reduces in-hospital infection risk and need to travel⁴⁹. Both options improve quality of life, capacity for part-time or full-time work, and, additionally, transplantation offers better survival.

Unfortunately, home-based therapies are underused and underappreciated, with only 12% of European kidney patients undergoing treatment at home and less than half of KRT patients being transplanted²⁴. To promote these two options, and to improve their outcomes, structural promotional and policy measures should be developed. This includes support for telemedicine and restriction of hospital-based approaches to cases where they are really needed, conform the learnings of the COVID-19 pandemic⁵⁰.

CONCLUSIONS

For the time being, EKHA is primarily focusing on creating awareness on EU level on the heavy burden of kidney disease. This includes focusing on the recognition of CKD as a specific disorder deserving specific attention, regarding burden on outcomes, quality of life and the health-economic and general economic impact. This should result in a structured transnational approach and investment in research aimed at reducing this burden, comparable to the effort developed by the European Commission in the Beating Cancer Plan. More than an exemplary effort from EKHA and our US counterparts alone, this should be paralleled by activities at the national level of the EU member states and affiliated countries, resulting in both efforts cross-fertilizing each other.

ACKNOWLEDGEMENTS

European Kidney Health Alliance network

- Member societies
 - o Large international organizations (full members)
 - Dutch Kidney Foundation (DKF)
 - European Dialysis and Transplant Nurses Association – European Renal Care Association (EDTNA-ERCA)
 - European Kidney Patient Federation (EKPF)
 - European Renal Association (ERA)
 - International Society of Nephrology (ISN)
 - o National or smaller international organizations* (affiliated members)
 - Belgian Society of Nephrology
 - Croatian Society of Nephrology
 - Dialysis, Nephrology and Kidney Transplantation Union of Georgia
 - Dutch Kidney Patient Society
 - Estonian Society of Nephrology
 - French Society of Nephrology, Dialysis and Transplantation
 - Federation of European Patient Groups affected by rare and/or Genetic Kidney Diseases (FEDERG)
 - German Society of Nephrology
 - Italian Society of Nephrology
 - Lithuanian Society of Nephrology
 - Polish Society of Nephrology
 - Portuguese Society of Nephrology
 - Russian Dialysis Society
 - Slovenian Society of Nephrology
 - Society of Nephrology, Dialysis and Transplantation of Bosnia Herzegovina
 - Spanish Dialysis Foundation
 - Spanish Society of Nephrology
 - Turkish Society of Nephrology
 - United Kingdom National Kidney Federation (NKF)
- Industry support
 - o AstraZeneca
 - o Hansa Biopharma
 - o Baxter
 - o BBraun Avitum
 - o Fresenius KABI
 - o Fresenius Medical Care
 - o Vifor Pharma
 - o Medtronic
 - o Novartis

*: English translation of the genuine names (in that case no acronym)

CONFLICT OF INTEREST STATEMENT

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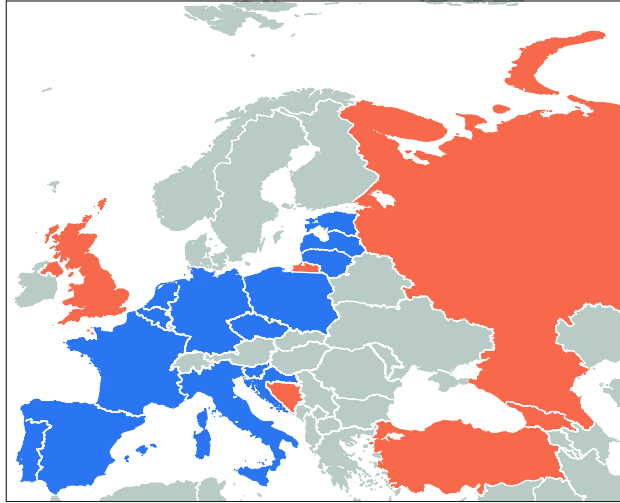


Figure 1: Countries represented as affiliated members of EKHA. EU countries: Belgium, Croatia, Estonia, France, Germany, Italy, Lithuania, the Netherlands, Poland, Portugal, Slovenia, Spain. Non-EU countries: Bosnia and Herzegovina, Georgia, Russian Federation, Turkey, United Kingdom.

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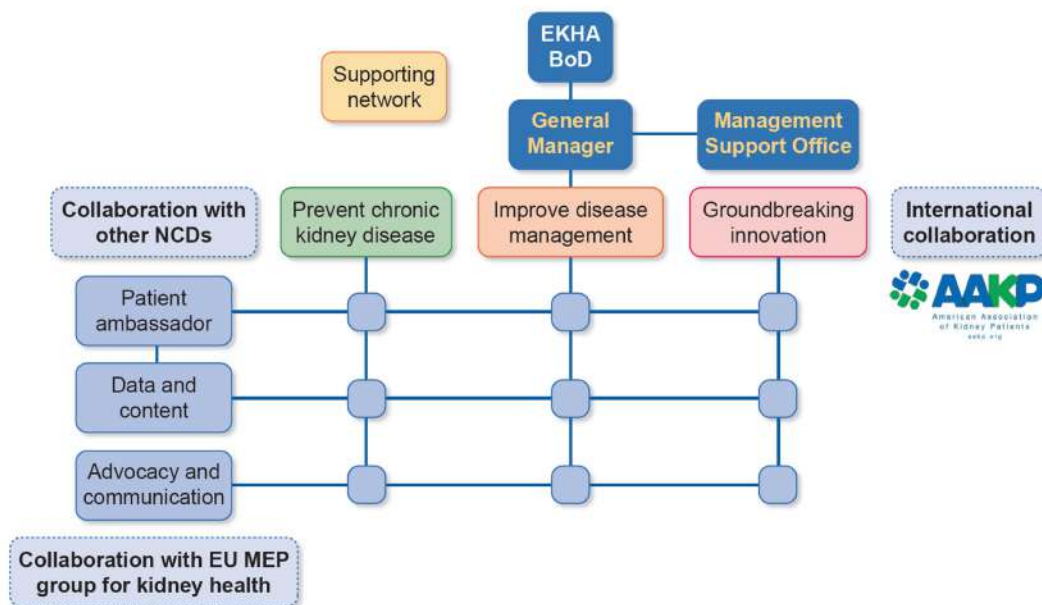


Figure 4: Corporate structure of EKHA: The Board of Directors drives a General Manager, assisted by a Support Office. The Supporting Network consists of Individuals and organizations assisting the Association by funding or in kind. Activities are backed by three Working Groups, on screening and prevention (green), disease management (orange) and innovation (red). Activities are based on patient engagement, data and content to emanate in advocacy and communication. Collaboration is sought with other non-communicable disease organizations, kidney organizations outside Europe (e.g. the US) and Members of European Parliament. Abbreviations: BoD: Board of Directors, EKHA: European Kidney Health Alliance; NCDs: non-communicable diseases; AAKP: American Association of Kidney Patients; MEPs: Members of European Parliament.

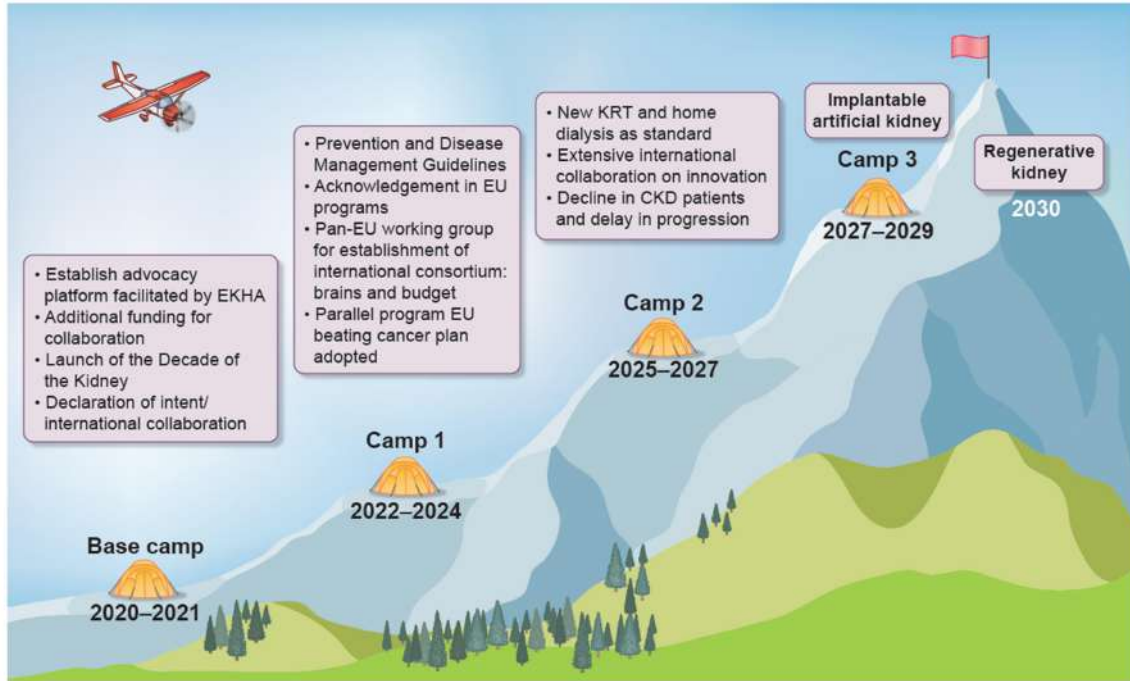


Figure 5: Progressive targets for the European Kidney Health Alliance during the Decade of the Kidney™, compared to climbing a mountain. The action aim is steady upward progression, although at some points it might be necessary to temporarily return to a lower level. The targets for 2020-2021 have all been reached. Abbreviations: EKHA: European Kidney Health Alliance; EU: European Union; KRT: Kidney Replacement Therapy; CKD: Chronic Kidney Disease.

ORIGINAL UNEDITED MANUSCRIPT

20. Vanholder R, Dominguez-Gil B, Busic M, et al. Organ donation and transplantation: a multi-stakeholder call to action. *Nature reviews Nephrology* 2021; **17**(8): 554-68.
21. Vanholder R, Gallego D, Sever MS. Wars and kidney patients: a statement by the European Kidney Health Alliance related to the Russian-Ukrainian conflict. *Journal of nephrology* 2022; **35**(2): 377-80.
22. <https://edith-project.eu/>.
23. Jager KJ, Stel VS, Branger P, et al. The effect of differing kidney disease treatment modalities and organ donation and transplantation practices on health expenditure and patient outcomes. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association* 2017.
24. Stel VS, de Jong RW, Kramer A, et al. Supplemented ERA-EDTA Registry data evaluated the frequency of dialysis, kidney transplantation, and comprehensive conservative management for patients with kidney failure in Europe. *Kidney international* 2021; **100**(1): 182-95.
25. de Jong RW, Jager KJ, Vanholder RC, et al. Results of the European EDITH nephrologist survey on factors influencing treatment modality choice for end-stage kidney disease. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association* 2021; **37**(1): 126-38.
26. http://ekha.eu/wp-content/uploads/FINAL_Joint-Statement-of-the-Thematic-Network-on-Organ-Donation-and-Transplantation.pdf.
27. <https://alliancechronicdiseases.org/>.
28. <https://www.eu-patient.eu/Members/The-EPF-Members/Full-Membership/European-Kidney-Patients-Federation---CEAPIR/>.
29. <https://www.nature.com/collections/bjfibafbd>.
30. Nevala-Plagemann C, Hidalgo M, Garrido-Laguna I. From state-of-the-art treatments to novel therapies for advanced-stage pancreatic cancer. *Nat Rev Clin Oncol* 2020; **17**(2): 108-23.
31. Perreault L, Skyler JS, Rosenstock J. Novel therapies with precision mechanisms for type 2 diabetes mellitus. *Nat Rev Endocrinol* 2021; **17**(6): 364-77.
32. Wanner C, Marx N. SGLT2 inhibitors: the future for treatment of type 2 diabetes mellitus and other chronic diseases. *Diabetologia* 2018; **61**(10): 2134-9.
33. Devuyst O, Knoers NV, Remuzzi G, et al. Rare inherited kidney diseases: challenges, opportunities, and perspectives. *Lancet* 2014; **383**(9931): 1844-59.
34. Vanholder R, Argiles A, Jankowski J, European Uraemic Toxin Work G. A history of uraemic toxicity and of the European Uraemic Toxin Work Group (EUTox). *Clinical kidney journal* 2021; **14**(6): 1514-23.
35. Agar JW. Green dialysis: the environmental challenges ahead. *Seminars in dialysis* 2015; **28**(2): 186-92.
36. Savitz SR, Turkel EJ, Shen D, Friedman EA. A microcomputer based portable hemodialysis system. *The International journal of artificial organs* 1978; **1**(1): 9-13.
37. Gura V, Rivara MB, Bieber S, et al. A wearable artificial kidney for patients with end-stage renal disease. *JCI Insight* 2016; **1**(8).
38. Himmelfarb J, Vanholder R, Mehrotra R, Tonelli M. The current and future landscape of dialysis. *Nature reviews Nephrology* 2020; **16**(10): 573-85.
39. Kim S, Feinberg B, Kant R, et al. Diffusive Silicon Nanopore Membranes for Hemodialysis Applications. *PloS one* 2016; **11**(7): e0159526.
40. https://ec.europa.eu/info/funding-tenders/opportunities/docs/2021-2027/horizon/wp-call/2021/wp_horizon-eic-2021_en.pdf.
41. Porrett PM, Orandi BJ, Kumar V, et al. First clinical-grade porcine kidney xenotransplant using a human decedent model. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons* 2022.
42. Song JJ, Guyette JP, Gilpin SE, Gonzalez G, Vacanti JP, Ott HC. Regeneration and experimental orthotopic transplantation of a bioengineered kidney. *Nature medicine* 2013; **19**(5): 646-51.

43. Schulman G, Berl T, Beck GJ, et al. Randomized Placebo-Controlled EPPIC Trials of AST-120 in CKD. *Journal of the American Society of Nephrology : JASN* 2015; **26**(7): 1732-46.
44. Rossi M, Klein K, Johnson DW, Campbell KL. Pre-, pro-, and synbiotics: do they have a role in reducing uremic toxins? A systematic review and meta-analysis. *International journal of nephrology* 2012; **2012**: 673631.
45. Vanholder R, Nigam SK, Burtay S, Glorieux G. What If Not All Metabolites from the Uremic Toxin Generating Pathways Are Toxic? A Hypothesis. *Toxins* 2022; **14**(3).
46. <https://www.hhs.gov/cto/initiatives/kidneyx/index.html>.
47. Bonventre JV, Hurst FP, West M, Wu I, Roy-Chaudhury P, Sheldon M. A Technology Roadmap for Innovative Approaches to Kidney Replacement Therapies: A Catalyst for Change. *Clinical journal of the American Society of Nephrology : CJASN* 2019; **14**(10): 1539-47.
48. <https://www.whitehouse.gov/presidential-actions/executive-order-advancing-american-kidney-health/>.
49. Mendu ML, Divino-Filho JC, Vanholder R, et al. Expanding Utilization of Home Dialysis: An Action Agenda From the First International Home Dialysis Roundtable. *Kidney Med* 2021; **3**(4): 635-43.
50. Quintaliani G, Reboldi G, Di Napoli A, et al. Exposure to novel coronavirus in patients on renal replacement therapy during the exponential phase of COVID-19 pandemic: survey of the Italian Society of Nephrology. *Journal of nephrology* 2020; **33**(4): 725-36.

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Table 1: Main focus points of EKHA

- Screening and prevention
 - EU Screening and prevention code
 - Specific approaches for rare kidney diseases
- Home treatment
 - Home hemodialysis
 - Peritoneal dialysis
 - On-line consultation
 - Telemedicine
- Kidney transplantation
- Equality
 - Among EU and EU-affiliated countries
 - Among social classes within countries
- Education/information
 - General public
 - Children
 - Policy makers, administrators
 - Medical professionals
 - Students
 - Postgraduate
 - Special attention for health illiteracy
- Fair reimbursement
 - Global cost kidney care
 - Exuberant cost orphan drugs
 - Access to therapies for lower income countries
- Personalized medicine
- Regenerative medicine
- Patient empowerment
 - Patient reported outcome measures (PROMs)
 - Patient reported experience measures (PREMs)
- Links with other non-communicable diseases

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Table 2: Main advocacy achievements by EKHA

Accomplishment	Scope and outcome
Recommendations for Sustainable Kidney Care	Baseline document and roadmap for future actions by EKHA
International questionnaire on patient education and choice	Analysis on the lack of patient information in different European countries
Consolidation of EU support for the EDITH project (1,000,000 €)	Investment by EU in a study project to analyze trans-European differences in uptake of kidney replacement therapies
Roundtable in the European Parliament on improving Prevention and Health-literacy in CKD	Meeting to collect suggestions for improvements in prevention, especially regarding sodium intake
Thematic network on improving Organ Donation and Transplantation in the EU	Multidisciplinary stakeholder network coordinated by EKHA to prepare suggestions to the European Commission to increase transplantation rate
EKHA becoming a Legal Entity according to Belgian Law	More possibility to participate in projects and acquire funds
Joint Statement on improving Organ Donation and Transplantation in the EU	Written recommendations to the EU on how to improve transplantation in Europe, based on the conclusions of the Thematic Network
Support by the Croatian Presidency of the European Council for EKHA's transplantation plan	Positive response to EKHA's transplantation roadmap
Meeting with Portuguese Presidency of the European Council on the importance of promoting Transplantation	Positive response in favor of transplantation
Meeting with European Commissioner of Health and Food Safety, Stella Kyriakides	Meeting with the top level EU policy maker to convey to her the burden of kidney disease; obtaining full support of EKHA's endeavors
Interview with POLITICO on importance of kidney disease and its prevention	Statement on all problems related to kidney diseases coordinated by a major EU-linked media channel
Support by the French Presidency of the European Council on the Importance of Kidney Disease	Inclusion of reference to CKD in official document of the French Presidency on Health in EU Video message by French Minister of Health Olivier Véran for World Kidney Day
Input in Advisory Document from the Expert Panel on Effective Ways of Investing in Health	Input on impact of COVID-19 on the population with CKD
Input in Advisory Document on Sustainable Health Security Preparedness and Response	Focus on the need for prevention, screening and innovation for CKD
Open Letter to the European Commission on Organ Donation and Transplantation	Call for second EU Action Plan on Organ Donation and Transplantation
Open Letter to the European Commission with key recommendations on CKD	Call to improve Prevention, Treatment and Care of CKD
Contribution on Report of Friends of Europe on how to improve the Post-Pandemic EU Health System	Report focusing on integrated care, home therapy and telemedicine
Open letter to the European Commission on	Focus on the specific problems of kidney

Kidney Patient Care in the Ukrainian War	patients in wars
Plenary Debate in the European Parliament (Strasbourg) on CKD	Parliamentary questions on kidney disease in open debate with European Commissioner Stella Kyriakides

EKHA: European Kidney Health Alliance; EU: European Union; EDITH: Effect of Differing Kidney Disease Treatment Modalities and Organ Donation and Transplantation Practices on Health Expenditure and Patient Outcomes; CKD: Chronic Kidney Disease; DG Santé: General Directorate of Health of the European Commission

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