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Probing expert opinions on the future of kidney replacement therapies

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Abstract

Patients with kidney failure can only survive with some form of kidney replacement (transplant or dialysis). Unfortunately, innovations in kidney replacement therapy lag behind many other medical fields. This study compiles expert opinions on candidate technologies for future kidney replacement therapies. A worldwide web-based survey was conducted with 1566 responding experts, identified from scientific publications on kidney (renal) replacement therapy, indexed in the Web of Science Core Collection (period 2014-2019). Candidate innovative approaches were categorized in line with the Kidney Health Initiative roadmap for innovative kidney replacement therapies. Most respondents expected a revolution in kidney replacement therapies: 68.59% before 2040 and 24.85% after 2040, while 6.56% expected none. Approaches anticipated as most likely were implantable artificial kidneys (38.6%) and wearable artificial kidneys (32.4%). A majority of experts expect that kidney replacement therapies can be significantly improved by innovative technologies.

KEYWORDS

innovation, kidney replacement therapies, roadmapping, survey, technology foresight

1 | INTRODUCTION

Kidney disease is a highly relevant public health problem worldwide and has been described as "the most neglected chronic disease".[1] Recent data suggest that, in 2017, 1.2 million people died from chronic kidney disease (CKD) globally.[2] CKD has been segmented into five stages of progressive severity with increasing morbidity and mortality,[3] but unfortunately, most cases are diagnosed relatively late (typically in CKD stage 3) when considerable kidney damage already has accumulated. CKD stage 5 is also known as kidney failure (also known as end-stage kidney disease—ESKD) where the kidneys function too poorly to sustain life, thereby necessitating the need for kidney replacement therapy (KRT, also known as renal replacement therapy—RRT). The presently available KRT choices are receiving a kidney transplant or frequent dialysis treatments. Transplantation forms the best presently available KRT option, but there is a chronic shortage of suitable kidneys to transplant. In fact, in the United States alone, each day 12 patients die waiting for a kidney transplant. Thus, the majority of patients with failing kidneys is deemed to survive on lifestyle- and life-limiting dialysis treatments, the side effects of which often leave them feeling sick and longing for a better quality of life.[4]

While the passage of CKD toward kidney failure can be slow in some patients, the nature of the underlying cause of kidney disease as well as associated conditions, such as hypertension and diabetes, can hasten this progression. Also, an episode of acute kidney injury (AKI), especially if it occurs in an individual with CKD, can greatly enhance the progression of CKD over time. In this light, and amidst the ongoing coronavirus disease 2019 (COVID-19) pandemic, it is concerning that severe COVID-19 disease is associated with a high incidence of kidney disease, with clinical presentation ranging from mild proteinuria to progressive AKI, often necessitating KRT.[5]

Kidney diseases generate very high costs for health systems.[6,7] Many developed nations spend large amounts of their annual healthcare budget to provide treatment for their kidney failure patients while these represent approximately just 0.02%-0.03% of their total population. In the United States, more than 7% of all Medicare costs are spent on KRT alone, with the vast majority for individuals on dialysis.[7]

Given the relevance of this public health problem, innovations are essential for improving the quality of life of patients, reducing costs, and decreasing the mortality rate. Unfortunately, KRT innovation has stagnated in relation to other technological developments in medicine. Incremental changes have been made to dialysis equipment and transplantation techniques since 1945 (first successful human dialysis treatment) and in the 1960s–1980s dialysis formed a frontier in medical technological innovation.[8] However, since then the pace of innovation slowed down to more or less crystallize in the 1990s, and demand for more innovation has been present for some decades now.[9] In general, literature points to the fact dialysis and transplantation therapeutic breakthroughs are needed to lessen the burden of kidney diseases in the near future.[7]

The Kidney Health Initiative (KHI)—a public-private partnership between the American Society of Nephrology (ASN), the US Food & Drug Administration (FDA) and over 100 other organizations and companies—in October 2018 published a roadmap to spur innovation, particularly disruptive innovation, in KRT.[4] In 2019 a patient-friendly summary of the KHI roadmap followed.[10] The KHI innovation roadmap[7] has been leveraged by subsequent publications.[11] The KHI roadmap was extended by a KHI report on fluid management innovation in 2019[12] and in 2020, a publication with recommendations for an updated version of the KHI roadmap appeared.[13]

In this study, we report the results of a worldwide web-based survey carried out with 1,566 responding KRT specialists to questions relating to their perceptions of the future of kidney replacement therapies. We focused our survey questions on four broad approaches to replacing kidney functions, as categorized within the KHI innovation roadmap, namely: (a) enhanced dialysis, (b) portable/wearable devices, (c) biohybrid/implantable kidneys, and (d) regenerated kidneys. Within these four main categories (approaches), between three and five specific KRT subcategories (technologies) were distinguished. We probed the expectations of the included KRT researchers regarding the future development of these approaches and technologies within the next 20 years.

2 | MATERIALS AND METHODS

A literature review was conducted to identify technologies that might be relevant for KRT in the future. A survey questionnaire was then created (note that when we developed our questionnaire, the term RRT was still dominantly used over KRT, which recently has been recommended as the preferred term[14]). The publications used for this purpose were identified in Web os Science (WoS), which provides internet access to multiple databases with academic data for different disciplines. The following search strategy was used:

> ts = ((kidney* OR renal) NEAR/1 (therap* OR replacement* OR substitut* OR disease* OR chronic* OR insufficienc*)) and ts = (future* or foresight* or forthcoming* or prospective* or imminent*)
>
> AND DOCUMENT TYPES: (News Item OR Review OR Editorial Material)
>
> Indexes = SCI-EXPANDED
> Timespan = 2014-2019

The search strategy combined thesaurus terms related to KRT/RRT from the Medical Subject Headings (MeSH) of the US National Library of Medicine (ncbi.nlm.nih.gov/mesh) and free text words for terms related to the future. It was applied to the WoS advanced search mode using the tag Topic (ts), which covers the fields title, abstract, and keywords. We used the Science Citation Index Expanded (SCI-EXPANDED) to retrieve publications related to the natural sciences and the time period was set to the last 5 years to collect recent information on KRT-related emerging technologies.

An initial search for relevant publications was performed in September 2019, which retrieved 105 publications, that were imported to the data/text mining software VantagePoint 11.0 for analysis. A preliminary selection of 45 was then made by reading their titles and abstracts, selecting the ones that mentioned future alternatives for KRT. These publications were then imported into the reference management software, Citavi 6.1, where we read the full texts to select the 25 that formed the basis of the literature review and survey questionnaire.

The respondents of this survey are authors of recent KRT-related scientific publications indexed in the WoS (published between 2014 and October 2019). The publications from

TABLE 1 Content of the questionnaire

1) Please indicate your knowledge level on kidney replacement therapy

☐ I have good knowledge ☐ I have some knowledge ☐ I have no knowledge

2) Please indicate your expectations regarding the following statement about the future:

"Kidney replacement therapy will radically change due to innovations"

☐ Likely, before 2040 ☐ Likely, after 2040 ☐ Unlikely

3) In the next twenty years, which of those broad approaches do you consider most likely to succeed as a kidney replacement therapy?

- ☐ Enhanced dialysis (incremental improvements to existing therapies)
- ☐ Portable/wearable devices (alternatives to stationary treatment)
- ☐ Biohybrid/implantable kidney (mimic normal physiology, bioengineered kidney, Xenotransplantation)
- ☐ Regenerated kidney (restore endogenous biological kidney function)

4) In the next twenty years, which enhanced dialysis technologies do you consider most likely to succeed as a kidney replacement therapy?

- ☐ Human acellular vessel (HAV)
- ☐ Human Nephron Filter (HNF)
- ☐ Membrane-free dialysis
- ☐ Home-based dialysis (eg, Quantas's SC+, NxStage's System One, etc)
- ☐ Other [input text window provided]

5) In the next twenty years, which portable/wearable device do you consider most likely to succeed as a kidney replacement therapy?

- ☐ Wearable Artificial Kidney (WAK)
- ☐ Automated Wearable Artificial Kidney Peritoneal Dialysis System (AWAK PD)
- ☐ Vicenza Wearable Artificial Kidney (ViWAK PD)
- ☐ Nanodialysis (NaNo)
- ☐ Carry Life Renal
- ☐ Other [input text window provided]

6) In the next twenty years, which biohybrid/implantable kidney technology do you consider most likely to succeed as a kidney replacement therapy?

- ☐ Implanted artificial kidney
- ☐ Xenotransplanted or chimeric kidneys
- ☐ Bioartificial renal epithelial cell system (BRECS)
- ☐ 3D/4D bioprinting (including proximal tubules, vasculatures or whole kidney)
- ☐ Other [input text window provided]

7) In the next twenty years, which regenerated kidney technology do you consider most likely to succeed as a kidney replacement therapy?

- ☐ Stem cells
- ☐ Gene therapy
- ☐ Bioengineering through decellularization
- ☐ Other [input text window provided]

8) Considering the four broad approaches, please select which kidney function they are most likely to mimic/replace:

	Blood filtration	Fluid regulation	Electrolyte homeostasis	Toxin removal/secretion	Filtrate transport and drainage
Enhanced dialysis	☐	☐	☐	☐	☐
Portable/wearable devices	☐	☐	☐	☐	☐
Biohybrid/implantable kidney technologies	☐	☐	☐	☐	☐
Regenerated kidney technologies	☐	☐	☐	☐	☐

9) Would you like to share anything else with us? [input text window provided]

which the authors were selected were identified by using the following query:

> ts = ((kidney* OR renal) NEAR/1 (therap* OR replacement* OR substitut* OR disease* OR chronic* OR insufficienc*))
>
> Indexes = SCI-EXPANDED
> Timespan = 2014-2019

The main search for relevant publications took place in October 2019, which yielded 68 650 records of scientific publications (all document types). We imported these records into

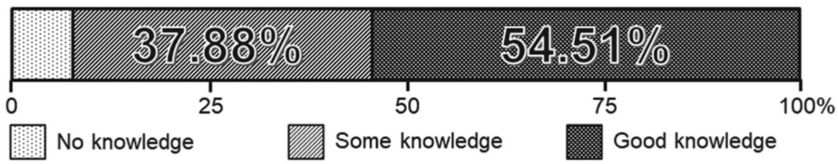

FIGURE 1 Knowledge of KRT among respondents (n = 1695). Only the 1566 respondents (92.39%) that declared to have some or good knowledge accessed the rest of the questions

VantagePoint 10.0, where we retrieved 46 592 authors' email addresses. Then, we linked 37 968 (81.5%) of these email addresses to the names of their owners using an internally developed Python code. To send personalized invitations and reminders to the authors, we opted to use only email addresses from authors that had their names reliably linked to an e-mail address through our Python code. Python is a programming language that allowed us to create a computer program to associate names and emails of respondents. The response rate can be expected to be considerably higher when the query e-mail contains the name of the potential respondent.[15] The list of authors and their e-mail addresses was then imported to the online survey platform SurveyMonkey (surveymonkey.com/), where we built the questionnaire and conducted the survey. After uploading, the number of emails was further reduced to 37 833 due to previous opted-out contacts in the SurveyMonkey's database and bounced emails. Other works that use a similar strategy have found satisfactory results.[16]

The questionnaire (Table 1) considered a future horizon of 20 years (2020-2040) and was structured in four parts. The first part informed the respondents about the purpose of the survey, data collection, confidentiality, privacy, and consent. In the second part, we asked about the respondents' knowledge of kidney replacement therapy. Respondents who indicated they had no knowledge were disqualified from the survey and did not answer the questionnaire. The third section asked the respondents to indicate their expectations on the likelihood that KRT will undergo major structural changes over the next 20 years due to innovations. An option was also provided for those who believed in major structural changes to come, but later than 2040. The final part was designed to gather the respondents' expectations on four broad KRT approaches, categorized according to the KHI roadmap:

1. Enhanced dialysis,
2. Portable/wearable devices,
3. Biohybrid/implanted kidneys,
4. Regenerated kidney

For these categories, we asked which approach was most likely to succeed as a kidney replacement therapy (eg, regenerated kidney) and then which sub-category (technology) within this approach was regarded as the most promising (eg, stem cells therapy, gene therapy, or bioengineering through decellularization). Respondents could only choose among the technologies within the approach they selected before. Considering the complexity of kidney functions, we also asked which of the four approaches would most likely mimic/replace five critical kidney functions: (a) blood filtration, (b) fluid regulation, (c) electrolytic homeostasis, (d) toxin removal, and (e) drainage, transport, and filtration.

Before the formal study, the questionnaire was validated through a pilot study with a random sample of 379 (1%) researchers. This pilot study yielded 12 respondents, and none of them suggested any changes to the questionnaire. Hence, neither the questionnaire nor the study protocol was furthermore modified and the collected pilot study data were included in the overall analysis. The pilot and the formal study were conducted between November and December 2019. The questionnaire was available for 1 week after the invitation email was sent, and up to three reminders were sent to nonresponders during this period. All those emailed were informed about the study both in the email invitation and reminders as well as in the first part of the questionnaire. Those who agreed to participate in the study gave their consent to use the collected data for research purposes (personal data were not requested) and voluntarily answered the questionnaire.

3 | RESULTS

From 37 833 invitations, we received 1695 responses from KRT-related researchers, of which 1566 were valid (129 responses from individuals who indicated they had "no knowledge" were excluded). Of these 1285 (82.05%) were fully answered questionnaires, which corresponds to a representative sample with a 99% level of confidence and a 4% margin of error. Figure 1 shows that most respondents self-reported good (54.51%) or some (37.88%) knowledge of kidney replacement therapy. To simplify the graphs and the description of the results, we combined the answers of these two groups of respondents. Statistically significant differences between them are reported in the text when appropriate.

Figure 2 shows what the researchers believe about the likelihood of radically new KRT therapies having a significant impact in the next 20 years. Almost 69% believed KRT will dramatically change *within* the next two decades due to innovations, while almost 25% believed such innovations will come, but only *after* 2040. Only slightly more than 6% regarded it unlikely that there will be radical innovative changes in current KRT technologies at *any* given time in the future.

The literature review identified four main approaches to KRT, mainly based on the KHI roadmap[4] and Bonventre et al.[7] For each of these, between three and five emerging technologies were found. Table 2 presents the four main approaches to KRT and their respective technologies as subcategories, sorted from the least scientifically complex to the most scientifically complex.

Considering the approaches and technologies, respondents were initially asked which main approach would be the most likely to succeed as kidney replacement therapy in the future. Then, they were asked to pick the most promising technology within the selected approach. Figure 3 shows the results. The most promising approach, as reflected by the highest percentage of respondents, was the biohybrid/

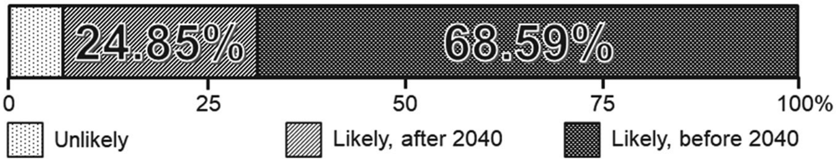

FIGURE 2 Response regarding the likelihood that kidney replacement therapy will change dramatically due to innovations over the next 20 years (n = 1493; this question was not answered by 73 of the knowledgeable respondents)

TABLE 2 Main KRT approaches, the different technologies distinguished within the main approaches, and the applied definitions of these various composing technologies

KRT approach	Technologies composing approach	Definitions & sources of cited definitions
Enhanced dialysis	1 – Home-based dialysis	Group of distinct technologies that allows dialysis to be performed at home[17]
	2 –Human nephron filter (HNF)	Continuously functioning dialysis system[21]
	3 – Membrane-free dialysis	Micro-fluidics technology that may allow miniaturization of dialysis process[18]
	4 – Human acellular vessel (HAV)	Bioengineered human acellular vessel for dialysis access[22]
Portable wearable devices	1 –Wearable artificial kidney (WAK)	Wearable blood-based renal replacement device[23]
	2 –Automated Wearable Artificial Kidney Peritoneal Dialysis System (AWAK PD)	Tidal peritoneal dialysis-based artificial kidney that uses dialysate regeneration to minimize fluid requirements[23]
	3 – Nanodialysis	Miniature artificial kidney for peritoneal dialysis (PD), that recirculates the peritoneal dialysate via a tidal mode using a single lumen peritoneal catheter[24]
	4 –Vicenza Wearable Artificial Kidney (ViWAK PD)	Another system for continuous flow peritoneal dialysis[25]
	5 – Carry Life Renal	Wearable peritoneal dialysis that incorporates lower glucose levels, reducing the osmotic stress on the peritoneum[24]
Biohybrid implantable kidney	1 – Implanted artificial kidney	Combining artificial filters and living cells currently in preclinical testing[23]
	2 – Xenotransplanted or Chimeric kidneys	Transplantation of kidney living cells or tissue from one species to another or tissue deriving from donor and recipient[26]
	3 – 3D/4D bioprinting	Utilization of 3D/4D printing–like techniques to combine cells, growth factors, and biomaterials to fabricate whole kidney or parts of it[27]
	4 – Bioartificial renal epithelial cell system (BRECS)	First all-in-one culture vessel, cryostorage device, and cell therapy delivery system for renal cell therapy[28]
Regenerated kidney	1 – Stem cells	Cells that have a potential for tissue regeneration[18]
	2 – Bioengineering through decellularization	Decellularized scaffold derived from a whole organ, providing structural integrity of tissue[29]
	3 – Gene therapy	Introduction of a new gene into the body to help fight kidney diseases[30]

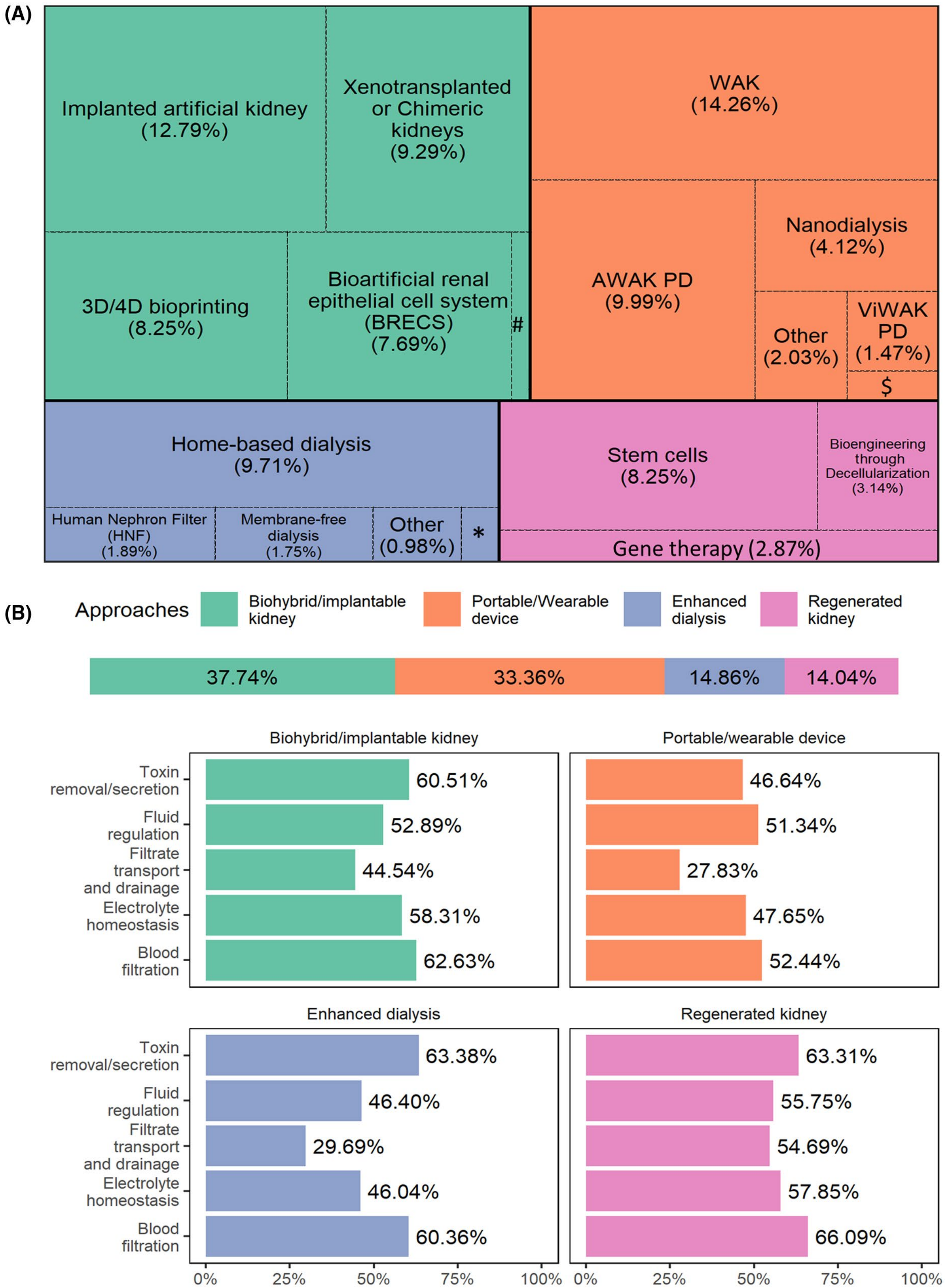

FIGURE 3 Top: Ranking of four kidney replacement therapy main approaches (color-coded) with their sub-categories of technologies perceived most likely to be effective in managing advanced kidney diseases in the next 20 years. $, Carry Life Renal (0.56%); #, Other biohybrid/implantable kidney technologies (0.56%); *, Human acellular vessel (HAV) (0.42%). A, Scored *absolute* percentages for the four main KRT approaches and color codes legend (n = 1460). B, Individual *relative* distributions of the four main approaches' functional performances (n = 1235) [Color figure can be viewed at wileyonlinelibrary.com]

implantable kidney (37.74%), followed by portable/wearable devices (33.36%). Enhanced dialysis and regenerated kidney were the approaches chosen by, respectively, 14.86% and 14.04% of the respondents. Considering individual technologies, regardless of approaches, the wearable artificial kidney (WAK) was leading according to 14.26% of the respondents, followed by the implanted artificial kidney (12.79%). It is thus important to distinguish between individual technologies and approaches (which are groups of technologies).

The last part of the questionnaire asked respondents to select which approach was the most promising to mimic or replace five listed kidney functions. Respondents could choose one or more approach(es) for each kidney function. Thus here, the sum of results could surpass 100%. While being the approach perceived to be most difficult to realize, regenerated kidney technologies were also considered the most likely to mimic or replace three of five functions, namely: (a) fluid regulation, (b) filtrate transport & drainage, and (c) blood filtration. This approach was (if once realized) also considered the second most likely to mimic or replace the other two kidney functions (electrolyte homeostasis and toxin removal/secretion) by a small margin.

It is worth mentioning that some individual technologies got statistically different responses from respondents with different self-reported knowledge levels. Within the portable/wearable device approach, the WAK presented a significantly higher percentage of responses (almost two times) for respondents with "high knowledge" whereas AWAK PD was significantly higher for respondents with "some knowledge." Within the biohybrid/implantable approach, xenotransplanted or chimeric kidneys were chosen by a significantly greater group for respondents with "high knowledge."

As for question 9, which offered a free text field for feedback, 102 individual texts were received. We highlight a few topics that were mentioned by two or more different respondents. The need to also put effort in preventive aspects and trying to delay the progression of CKD was most named (n = 18). Financial aspects (costs of devices, affordability for low-income countries, hurdles to raise funding for development) were also repeatedly pronounced (n = 7). Stem cell technologies, and particularly using autologous stem cells from urine, was named (n = 4). Informatics & Computer Technology (ICT) plus Artificial Intelligence (AI) were also mentioned (n = 3) in various ways: as enablers to enhance existing dialysis technologies, as stimuli for more home dialysis, as well as facilitators for the management of implantable devices with embedded sensors.

Overall, respondents from over 100 countries replied to the questionnaire. Figure 4 shows the respondents' locations. The questionnaire did not ask participants from which country they were. Instead, Figure 4 is drawn using proxy information derived from the respondents' internet protocol (IP) addresses.

4 | DISCUSSION

The KHI roadmap[4] and a connected extensive review of Bonventre et al[7] formed key references in our study. Yet, there are also other relevant contributions to the discussion of the future of KRT worth highlighting here, including a report

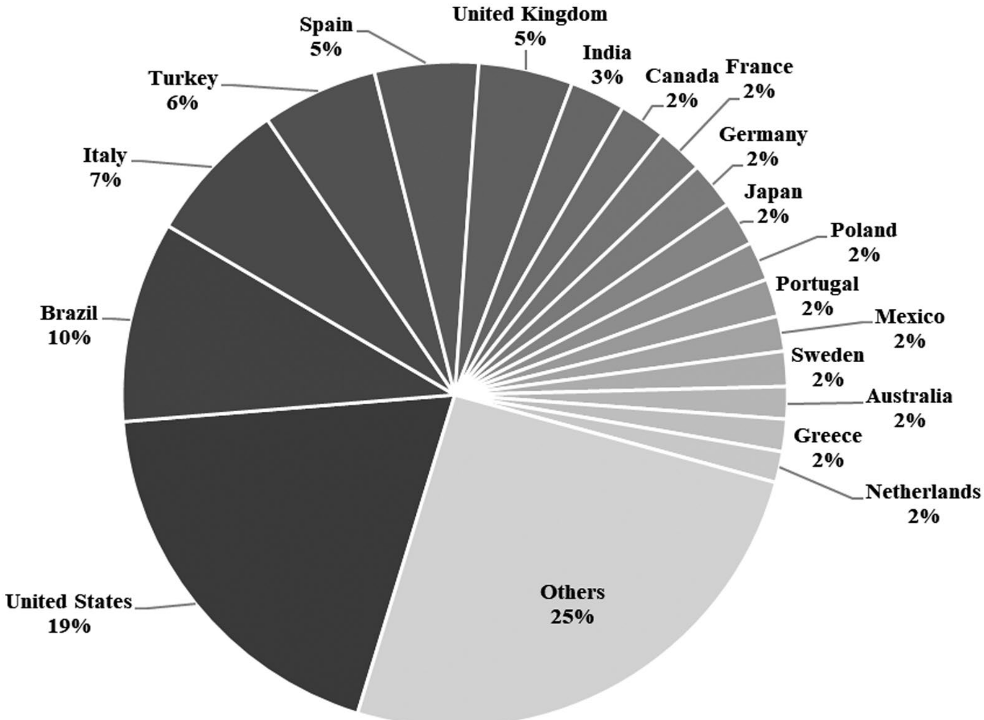

FIGURE 4 Respondent's locations, groups representing less than 2% are combined into "Others"

prepared by Ernst and Young,[17] which also identifies emerging technologies in this area. Other publications, focused on the future of kidney care were also deemed highly relevant.[18-20] Our study differs from all these by investigating the individual expectations of many KRT researchers from around the world regarding the future of these technologies in the next 20 years.

The responding researchers all had to self-indicate their level of expertise. While this is not a very objective indicator, the inclusion of only peer-reviewed publications to identify survey participants provides some protection against including respondents who have no knowledge of KRT. Another potential weakness is that researchers that are investigating therapeutic approaches are likely to have a positive bias toward the effect of research in their area. Yet, they also are the most suitable candidates to judge the hurdles and milestones on the road toward solutions. In an absolute sense, the time scale on which the anticipated change is expected to come may be too optimistic. But in a relative sense, the collected distribution of expert expectations does form a meaningful indication of where KRT will likely be heading toward in the coming decades.

When looking at the expected functional performances of the various approaches, we see that the regenerated kidney received the highest overall score. This is logical, given that it is conceived to most closely mimic nature, this approach can indeed be expected to come closest to the original natural kidney functionalities. But it is also expected to be one of the most difficult approaches to succeed within 20 years. With the present average survival time on dialysis being 5 to 6 years, it is clear that improvements are needed quickly, which makes it logical to also include shorter term step-wise innovations. Our questionnaire reveals the complexity of trade-offs between achieving progress within a reasonable time-frame versus achieving the best obtainable performance in the long run.

It should also be noted that 6.56% of the responding experts regarded changes due to radical innovations in KRT *unlikely*, even after 2040. Of those, nearly two-thirds were self-reported to be highly knowledgeable. Although this is by far a minority opinion, it seems to indicate that the challenges for successful innovation are large (and they are not only technological & biological, but also financial and regulatory).

5 | CONCLUSION

We present the results of a web-based survey with 1,566 responding researchers from over 100 countries with at least one peer-reviewed scientific publication related to kidney replacement therapy in the period from 2014 to 2019. The results suggest that most KRT researchers expect an important positive change after decades of stagnation in technological development for KRT.[4,7] About 93.44% of them expected a revolution in kidney replacement therapies: 68.59% before 2040 and 24.85% after 2040. In this relatively optimistic scenario, most respondents perceived portable/wearable devices and biohybrid/implanted kidneys as the most likely approaches toward successful products. The wearable artificial kidney was regarded as the most promising technology among those listed in the portable/wearable devices approach, while the implanted artificial kidney was regarded as the most promising technology in the biohybrid/implanted kidney approach. This study might form a useful input to a version 2.0 of the KHI roadmap for innovation in KRT, possibly in conjunction with other suggestions to help in focusing the efforts of the community toward technologies that are most likely to help our patients in a reasonable amount of time.[13]

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DISCLOSURES

Dr Bonventre reports serving as a consultant for, Aldeyra, Astellas, Biomarin, Boehringer Ingelheim, Catabasis, Cerespir, Eleven, Eli Lilly, Eloxx, Medimmune, Merck, Mitobridge, and PTC. Dr Bonventre also reports ownership equity in Dicerna, DXNow, Goldfinch, Goldilocks, Innoviva, Medibeacon, Medssenger, Rubius, Sensor-Kinesis, Sentien, Theravance, and Verinano; he also reports prior grant funding from Astellas and Boehringer Ingelheim and current funding from the National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases and National Center for Advancing Translational Science (R37 DK39773, RO1 DK072381, UG TR002155). In addition, Dr Bonventre is a coinventor on KIM-1 and human kidney organoid patents assigned to Partners Healthcare. Dr Wieringa reports serving as a consultant for the Dutch Kidney Foundation & Neokidney initiative. Dr Pereira Cabral and Dr Mota have nothing to disclose.

AUTHOR CONTRIBUTIONS

All authors read and approved the final version of the manuscript.
Conception: Pereira Cabral, Mota
Data collection and data analysis: Pereira Cabral
Drafting and critical revision of the article: Pereira Cabral, Bonventre, Wieringa, Mota

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