

Global kidney chains

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Kidney failure is a worldwide scourge, made more lethal by the shortage of transplants. We propose a way to organize kidney exchange chains internationally between middle-income countries with financial barriers to transplantation and high-income countries with many hard to match patients and patient-donor pairs facing lengthy dialysis. The proposal involves chains of exchange that begin in the middle-income country and end in the high-income country. We also propose a way of financing such chains using savings to US health care payers.

kidney exchange | transplantation | market design | global kidney exchange | chains

Transplantation is the treatment of choice for kidney failure, but many barriers prevent transplantation. The barriers in economically developed countries differ from those in developing countries, but transplantation is woefully undersupplied relative to the incidence of kidney failure in both richer and poorer nations.

In much of the developing world, transplantation or other treatment such as dialysis is largely unavailable due to financial constraints, and kidney failure is a death sentence (1–4). In the developed world, many people struggle on dialysis, a temporary treatment, while enduring long waits for transplantation, with many thousands dying each year while waiting due to the shortage of transplantable organs.*

This paper considers how these two problems—lack of access to transplantation or dialysis and the shortage of transplantable organs—each can help to alleviate the other.

Kidney exchange, which has become a standard form of transplantation in the United States and is growing elsewhere, can increase the number of transplants available from willing living donors who are otherwise unable to achieve their wish to donate a kidney by arranging exchanges in which the patient in each patient-donor pair receives a compatible kidney from another patient's donor (e.g., refs. 5-7). The capacity of kidney exchanges has steadily increased as exchange design has grown from simple exchanges between pairs to include larger cycles of exchange (8, 9) and transplant chains begun by a nondirected donor (e.g., refs. 10-15; the dynamics of chains are studied in refs. 16-18). Chains can include many patient-donor pairs. Two factors limiting the growth of kidney exchange in the United States, Europe, and elsewhere are a shortage of blood-type O donors and that many patients are highly sensitized (i.e., they have developed antibodies to many human proteins-so they need a very large kidney exchange pool to have a good chance of finding a pair with whom they can exchange a compatible kidney).

A recent proposal, called global kidney exchange (GKE), has US health organizations inviting foreign patients with financial restrictions who have willing donors to participate in the American kidney exchange, just as American patients do, for free (19, 20). Patient–donor pairs whose barrier to transplantation is financial may not themselves be difficult to match, which means that they can more easily match hard to match pairs who otherwise have difficulty finding a match (21). The medical treatment (including all pre- and postsurgical care of the foreign patient and donor) can be financed by the savings to the American health care system when a patient is transplanted and (thus)

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taken off dialysis, a much more expensive treatment. (That dialysis is much more expensive than transplantation is the key to the viability of GKE, in which the savings from reduced dialysis for American patients who would otherwise face long dialysis can pay for the care of foreign patient–donor pairs with whom they match.)

Although GKE has generated considerable support (22–24), it has also generated critics and rebuttals to those (e.g., refs. 25–32). One early criticism was that GKE somehow violated the laws against paying donors for their kidneys. This line of argument has been effectively rebutted by, among others, the European Society of Transplantation's Committee on Ethical, Legal, and Psychosocial Aspects of Transplantation (24), which observed that the payments in GKE are essentially no different from those in domestic kidney exchange. In each case, payments flow from health care payers to hospitals for medical services, while each patient–donor pair donates a kidney without financial compensation.[†]

Two criticisms have not so far been directly addressed through the design of global exchanges (compare ref. 34). The first is that transplanting foreign patients in the United States does not increase the number of transplants carried out by hospitals in their home countries. The second related criticism is that

Significance

Kidney failure is among the leading causes of death worldwide, and the best treatment is transplantation. However, transplants are in short supply because of shortfalls of transplantable organs and of finances. In the United States and some other countries, kidney exchange chains have emerged as a way to increase the number of transplants; patients who have a willing donor but cannot receive that donor's kidney can each receive a compatible kidney from another patient's intended donor. Such programs are much better developed within the borders of wealthy countries, which is of little help to patients in countries with limited kidney transplantation or exchange. This paper proposes and analyzes a way to extend kidney exchange chains to share the benefits globally.

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- *In the United States, there are over 90,000 people officially registered on the waiting list for a deceased donor kidney transplant. In 2019, there were only 16,534 deceased donor transplants; 3,811 patients on the waiting list died while waiting, while another 3,814 were removed from the list when they became too sick to transplant (https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/).
- [†]GKE previously received support from the American Society of Transplant Surgeons (https://asts.org/about-asts/position-statements#.X8g-GshKg2w), and surveys indicate public support (33).

when foreign patient-donor pairs participate in American kidney exchange chains, more American than foreign patients are transplanted, and this can appear inequitable (and perceived inequity can contribute to the perceived repugnance of a transaction [compare ref. 35]).

This paper proposes a design, global kidney chains (GKCs), which would address these criticisms by building kidney exchange chains that originate in a country with modern transplant capabilities but with financial barriers to transplantation. A foreign nondirected donor could start a kidney exchange chain in the foreign country (that could not otherwise be financed), with the donor of the last pair in the foreign chain (the bridge donor) donating to an American. The costs needed to cover the foreign patients and donors (at home and in the United States) would be paid by the savings to the American health care system from transplanting American patients who would otherwise have remained on dialysis.

In practice, several foreign transplants could be funded by starting a long chain of transplants with a nondirected donor in the foreign location, with a bridge donor traveling to the United States to continue a chain that would include several hard to match American patients and conclude with donation to a patient on the American deceased donor waiting list.

Some financial engineering is needed to make this program self-financing. The money saved by transplanting an American (or citizen of another high-income country) is saved on dialysis, while the additional costs will be incurred at transplant centers in the foreign country and (for the donor who travels) in the United States (in countries with single-payer health care, this may be feasible more simply than in the United States as long as the savings exceed the costs that would otherwise be incurred since savings and costs come from the same budget). Since such a program will decrease time spent waiting for a transplant, it will also decrease dialysis costs, and we need to show that the US savings on dialysis remain sufficient to finance the additional foreign transplants even when the program operates on a very large scale, as many patients and patient-donor pairs in high- and middle-income countries gain access.

A concern for the American health care system is that it would require legislative changes to enable Medicare (which pays a very large share of dialysis costs) to finance transplantation of foreign patients, despite the savings that would accrue to Medicare through earlier transplantation of Americans. Fundamental legislative changes are relatively easy to imagine and advocate for, but they are difficult to implement.[‡]

Instead, we propose here a financial design that could be implemented in the United States without further legislation. Private insurers in the United States are responsible for paying for the first 33 mo of their patients' dialysis, with Medicare activated only after that (https://www.medicarerights.org/guestposts/2016/09/27/blog-kidney-failure-medicare-know). Since transplantation is considerably cheaper than 33 mo of dialysis (and average dialysis times are considerably longer),[§] insurance companies and self-insuring American companies also experience savings from prompt transplantation, sufficient to pay for additional transplants. We propose that the costs for foreign patients be paid from this pool of savings.

These savings are greatest for patients who have been on dialysis for the shortest time, and so, a final part in the design we propose is that the queue for these American patients to receive a living donor kidney transplant from the bridge donor will have an approximate last in, first out (LIFO) queue discipline. This will be important in allowing the savings to remain large even when GKC operates on a scale that substantially reduces average time on dialysis.[¶]

GKCs thus involve three unconventional design features: kidney exchange chains that cross borders, financing by private payers (such as consortia of self-insured companies), and an approximately LIFO queue discipline.

Note that it has been the policy of organizations like the World Health Organization to recommend that countries build self-sufficiency in transplantation. However, no country has yet done so; even the wealthiest countries have more patients in need of transplants than they have transplantable organs. Additionally, for middle-income countries that cannot finance transplantation for all their citizens who need it, this recommendation of self-sufficiency is simply the advice to wait until the country becomes wealthy, which is an effective death sentence for their contemporary patients who cannot be treated. This paper, instead, considers how we might seek to ameliorate this global health problem with a global solution.

The Model with Short Chains

The model that we will present is intended to represent a simple minimal realization of GKC, with the shortest possible US side chain involving a single US transplant—and hence, the smallest US savings. Specifically, a kidney exchange chain begins in the foreign location. The donor from the last patient–donor pair (i.e., the bridge donor) travels to the United States and immediately donates to an American in a pool of patients expecting long dialysis, ending the chain. This allows our estimated cost savings to be conservative and avoids the need to model explicitly the uncertainties associated with assembling a longer American chain initiated by the foreign bridge donor.[#]

We consider a population of domestic (American) patients with a long expected duration of dialysis who are covered by private insurance for the first 33 mo of dialysis and who might receive a kidney from a foreign bridge donor who is part of the last patient–donor pair in a chain of transplants conducted in the foreign country.

To build intuition, we start by considering as an example a (too) simple deterministic model.

Example: Suppose that one domestic patient arrives to the pool every day. A patient departs the pool if she is not matched (i.e., has not received a transplant) after 33 mo. Patients undergo dialysis while waiting in the pool, which costs D per patient per day, incurred by the private payer. A foreign bridge donor arrives to the pool every n days, starting at time 0, where n > 1 is an integer. Any donor is compatible with every patient and hence, can

⁴ Even simple legislative anomalies have remained despite attempts over many years to fix them. For example, Medicare pays for both dialysis and transplantation for endstage renal disease (ESRD) patients, but for decades for some patients, it paid only for 3 y of immunosuppressive drugs following transplantation, despite the cost savings that accrue from helping patients avoid rejection and having to resume dialysis (which Medicare then paid for). This was resolved only in 2020 by new federal legislation: H.R.5534—Comprehensive Immunosuppressive Drug Coverage for Kidney Transplant Patients Act of 2020, 116th Congress (2019 to 2020).

[§]In 2018, more than 60% of deceased donor kidney recipients had waited on dialysis for more than 3 y (and more than 40% had waited more than 5 y; details are at https://srtr.transplant.hrsa.gov/annual_reports/2018/Kidney.aspx#KI_9_char_adult_tx_clin in Table KI 9. Clinical characteristics of adult kidney transplant recipients, 2018).

[¶]Note the contrast with how deceased donor organs are traditionally allocated, in which at least tie-breaking priority is given to those who have been waiting the longest. The LIFO priority proposed here is a possible source of repugnance, but given the large potential gains in transplants, both domestic and (particularly) foreign, and consequent reduction in disease burden and inequality, we anticipate this will not be a critical barrier. Additionally, we will show that the system we propose remains viable even when strict LIFO is somewhat relaxed.

[#]Another simplification we make is to ignore the possibility that one of the patients expecting long dialysis might unexpectedly receive a deceased donor kidney. It will become clear later why this should not materially change the results.

According to the LIFO allocation policy, an arriving foreign bridge donor is matched to the compatible patient with the most recent arrival time present in the pool. Thus, under the LIFO policy, every donor is matched upon arrival to a patient who arrived at the same time and thus, has waiting time 0. Therefore, decreasing n (i.e., increasing the arrival rate of foreign bridge donors) reduces the average waiting time for domestic patients under the LIFO policy by increasing the proportion of patients who have zero waiting time. Hence, when S is sufficiently small relative to D, reducing n decreases the total cost incurred by the private payer per unit of time under the LIFO policy.

In contrast, under the first in, first out (FIFO) allocation policy, a foreign bridge donor is matched to the patient with the earliest time of arrival present in the pool. So, in the steady state under the FIFO policy, every donor is matched upon arrival to a patient who arrived 33 mo earlier. Therefore, decreasing n(i.e., increasing the arrival rate of foreign bridge donors) does not change the average waiting time under the FIFO policy, as long as n > 1. Hence, reducing n increases the cost under the FIFO policy, as it adds surgery costs but does not subtract any dialysis costs.^{||}

This simple example shows that GKC has the capacity to be self-financing on a scale approaching that of the arrival rate of domestic patients who can expect dialysis throughout the time they are covered by private insurance. It also shows the importance of the LIFO policy vs. the FIFO policy; the savings on dialysis are realized under the LIFO policy but not under the FIFO policy. This is because, as long as the arrival rate of donors is smaller than that of patients, there will always be patients who are supported by the private payer for the full first 33 mo of dialysis, so that the FIFO policy, while transplanting the same number of patients as the LIFO policy (and incurring the same additional costs for surgeries), does not reduce the payer's dialysis costs.

This simple example does not consider the essential stochastic nature of arrivals, departures, lengths of foreign chains, etc. We next consider a formal model with which we can show that the intuition obtained from the example is robust to these features.

A Formal Model. Domestic patients arrive according to a Poisson process with rate m. Each patient stays in the pool for $\zeta > 0$ units of time and then departs. The foreign bridge donors arrive according to a Poisson process with rate λm , where λ is the policy parameter to be set. We suppose that a bridge donor b is the last donor in a chain involving l_b foreign patients. The random variable l_b is drawn independently for every bridge donor b from a distribution F with mean μ . We suppose that each bridge donor is compatible to each patient independently with probability r > 0.

The planner adopts a LIFO allocation policy. When a foreign bridge donor arrives, he or she is matched to the compatible patient with the latest time of arrival. In case no patient is in the pool, the donor departs immediately. (This simplifying assumption can be understood as having the bridge donor continue the chain in the home country, perhaps ending it by donating to someone on the home country deceased donor waiting list.) Let *D* denote the domestic cost of dialysis per patient per unit of time. Also, let S_d and S_f denote the costs per domestic and foreign kidney transplant, respectively. Define $C(m, \lambda)$ to be the average, per domestic patient per unit of time, of total health care costs when the policy parameter is λ . Note that $C(m, \lambda)$ accounts for all the costs of foreign patients as well. Define $C(\lambda) = \lim_{m\to\infty} C(m, \lambda)$. The next result computes the derivative of the average health care costs with respect to λ and shows that, in a large market, increasing λ reduces the total health care cost. (Note that ζD is the dialysis cost for a patient who does not receive a transplant.)

Theorem 2.1. Under the LIFO policy, for any $\lambda \in (0, 1)$, $\mathbf{C}'(\lambda) = S_d + \mu S_f - \zeta D$.

The proof of the theorem also leads to a counterpart result in finite markets. This result, stated in the next theorem, shows that for every finite m, increasing λ by any positive $\epsilon < 1 - \lambda$ that is not "too small" reduces $\mathbf{C}(m, \lambda)$ if $\zeta D > S_d + \mu S_f$.

Theorem 2.2. Suppose that $\zeta D > S_d + \mu S_f$. Then, for any fixed m, increasing λ by any positive $\epsilon < 1 - \lambda$ decreases $\mathbf{C}(m, \lambda)$ if $\epsilon > \gamma \cdot \frac{\zeta D}{\zeta D - S_d - \mu S_f}$, where $\gamma \leq \frac{2}{\zeta m} + \frac{1+r}{r} \cdot \frac{\log(\zeta m \lambda + 1)}{\zeta m}$. This theorem requires ϵ to be not too small. The right-hand

This theorem requires ϵ to be not too small. The right-hand side of the constraint that ensures ϵ is not too small is the parameter γ multiplied by a constant independent of m.** Observe that γ approaches zero with rate $\frac{\log m}{m}$ as m grows large. Hence, as m grows large, the lower bound on ϵ becomes essentially nonbinding.

A back-of-the-envelope account of these theorems goes as follows. Whenever a patient is about to enter the system under the LIFO policy, she is matched with probability close to λ . Thus, an increase in λ by ϵ reduces her expected dialysis cost approximately by $\epsilon \zeta D$ and increases the expected transplant costs by $\epsilon(S_d + \mu S_f)$, incurred by her own transplant and the preceding chain. Thus, $\mathbf{C}'(\lambda) = S_d + \mu S_f - \zeta D$.

For the average health care costs to decrease with the arrival rate of bridge donors, both of the theorems above require $\zeta D > S_d + \mu S_f$. We next evaluate this condition using estimated values for its parameters (36). In the United States, dialysis costs about \$250,000 per patient year for a commercial payer, and a transplant costs about \$100,000 followed by the cost of immunosuppressive medications and follow-up care, which is about \$30,000 per year. We account for 10 y of immunosuppressives and follow-up care and hence, set $S_d = $400,000$. We account for the transplant cost of a foreign patient, using the Philippines for our example, by a \$12,000 surgery cost plus 10 y of immunosuppressive medications and follow-up care costing about \$6,000 per year. Hence, we set $S_f = $72,000$.^{††} For these parameter values, the condition $\zeta D > S_d + \mu S_f$ is satisfied if $\mu \leq 3.99$.

Nikzad et al.

Global kidney chains

Note that if we had added deceased donation to the model, some domestic patients would have received a deceased donor kidney under the national FIFO policy. These would also be patients who had waited the longest and for whom there would be little or no savings on dialysis.

^{**}The lower bound required on ϵ is due to a limitation of our proof approach, and we conjecture that this lower bound is dismissible. To provide bounds on the additional dialysis costs incurred for increasing λ by ϵ , we track how this can change the average pool size. To do this, we bound the average pool size for any λ from below and above by $\zeta m(1 - \lambda)$ and $\zeta m(1 - \lambda + \overline{\gamma})$, respectively, where $\overline{\gamma} = \frac{2}{\zeta m} + \frac{1+r}{r} \cdot \frac{\log(\zeta \lambda m+1)}{\zeta m}$. These bounds can guarantee that the average pool size does not increase after increasing λ only if ϵ is sufficiently large.

^{1†} As noted in ref. 19, an escrow account of \$50,000 was established "for follow-up care for the Filipino donor and recipient, including assistance with immunosuppressive and other medications and treatment of potential complications." Here, we have modeled establishing an escrow account of \$6,000 per year for 10 y or \$60,000 for each foreign recipient. We anticipate that this fund will be treated as reserved capital for the cost of all recipients, understanding that some transplants will last less than 10 y, while others will exceed 10-y survival. Thus, the fund anticipates being able to pay for all recipients' transplantation-related postoperative care and immunosuppression, regardless of how long the kidney transplant lasts. We anticipate an average transplant survival of 10 y, but appropriate management of the reserve funds will allow some patients to have more than 10 y of coverage. In addition to funding the transplantation-related postoperative care and immunosuppression for recipients, the escrowed funds will also be used to finance donor follow-up and complications consistent with US policy.

Hence, according to the above estimates, the LIFO policy reduces the total health care costs when the average length of foreign chains is not larger than 3.99.

We note that a simple static back-of-the-envelope argument based on current dialysis and surgery costs is insufficient for establishing these results; such an argument ignores the counterfactual costs, which depend on the dynamics. For instance, suppose the planner switches to the FIFO policy. In that case, increasing λ by any $\epsilon < 1 - \lambda$ will increase total costs! That is, as long as the number of GKC bridge donors is below what would be needed to secure transplants for all domestic patients, under the FIFO policy all domestic patients will have a waiting time of ζ , whether they get transplanted or not. So, increasing λ would not affect the average dialysis costs paid by the private insurer, although it would add the transplant costs of the foreign patients. The next theorem captures this effect.

Theorem 2.3. Under the FIFO policy, for any $\lambda \in (0, 1)$, $\mathbf{C}'(\lambda) > 0$.

Hence, the cost-benefit analysis crucially depends on market dynamics.

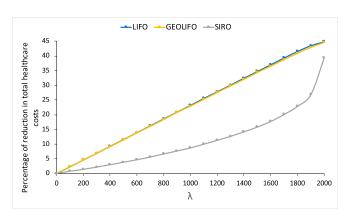
Sensitivity Analysis of LIFO Policy: Simulations

In this section, we use simulations to give some indication of how total costs $C(m, \lambda)$ vary under LIFO and two related allocation policies as a function of λ , the rate at which foreign bridge donors arrive. LIFO can be somewhat modified without much reduction in cost savings, but attention to dialysis months saved does remain important until the arrival rate of foreign donors becomes comparable with the arrival rate of hard to match domestic patients.

For the base setting, we assume m = 2,000 and adopt the same estimates for the parameters ζ , D, S_d , and S_f as in the previous section. We also assume that r = 1. The qualitative findings are not sensitive to the choice of r.

In the first simulation, we consider the base case parameters and investigate how increasing λ from zero to *m* changes the total health care costs under the LIFO policy. Fig. 1 plots the percentage of reduction in total health care costs [i.e., $\frac{C(m,0)-C(m,\lambda)}{C(m,0)} \times 100$] as a function of λ .

The second simulation is the same as the first simulation but for the LIFO policy being replaced with the geometric last in, first out (GEOLIFO) policy. According to this policy, an arriving foreign donor is matched to the latest arriving compatible patient with a fixed probability p_0 . With probability $1 - p_0$, the match is not made, and the donor is matched to the next latest





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arriving patient independently with probability p_0 and so on. We assume that $p_0 = \frac{1}{10}$ and plot the reduction in total health care costs while varying λ in Fig. 1. As in the base setting, increasing λ reduces the total health care costs for all λ considered in the simulation. However, note that the two curves are almost on top of one another; GEOLIFO saves virtually as many months of dialysis as LIFO does.

The third simulation is the same as the first one, except that the allocation policy changes from LIFO to selection in random order (SIRO). This policy matches a bridge donor to a domestic patient chosen uniformly at random from the set of all compatible patients in the pool. Again, increasing λ reduces total health care costs, but now, we see that unless the number of foreign donors approaches the number of domestic patients, the cost savings are much reduced.

Operational Matters

Although the focus of this paper has been on long-run feasibility, it is worth pausing to consider some essential operational matters. For example, while GKE involves establishing cooperation with foreign transplant centers, GKC involve establishing cooperation with foreign kidney exchange programs. In many cases, this will involve helping to establish those programs by providing advice on best practices, software, etc. (see ref. 15), so that kidney exchange programs can be established at existing transplant centers.

Care will have to be taken to make sure that donors in a global chain are qualified under the laws of both countries (e.g., that they are healthy donors able to give noncoerced informed consent). The status of the donors may require more care to establish than in domestic kidney exchange in the United States.

It may be prudent to conduct initial global chains so that all surgeries take place simultaneously, as kidney exchange chains used to be conducted in the United States before substantial successful experience with nonsimultaneous chains was accumulated. After reliable procedures are established, we anticipate that global chains too may be conducted nonsimultaneously.

Among the costs that will have to be covered by a kidney exchange program will be costs for examining potential donors (many of whom would not become actual donors), as is presently the case in the US kidney exchange. If these costs cannot be covered by the foreign kidney exchange program, they may become part of the overhead to be covered by global exchange.

Concluding Remarks

Since the beginning of the twenty-first century, kidney exchange at scale has developed from a largely academic idea initially implemented at a small scale (5, 37) to a standard mode of transplantation in the United States (with well over 1,000 exchange transplants in 2019) and in several other countries. This has been an important development, with many milestones along the way including, crucially, developments in the design and implementation of kidney exchange chains. However, these accomplishments have been victories in a war that we are losing. At the turn of the century, there were in the neighborhood of 40,000 patients on the US waitlist for deceased donor organs, and today, there are close to 100,000.^{‡‡} The situation is similar elsewhere in the wealthy world. Over the same period, there has been a growth of kidney disease as a cause of death around the world (as developing

4 of 6 | PNAS

^{‡‡}The increase in the number of patients on the waiting list is not entirely bad news related to the growing incidence of kidney disease; it also represents progress in keeping kidney patients alive longer before they receive a transplant. Additionally, it reflects increases in traffic safety, which reduces the number of deceased donor transplants from victims of automobile accidents.

countries have made progress in combating infectious disease), and there have begun to be high-quality transplant centers in middle-income as well as in rich countries, which nevertheless face obstacles—including important financial obstacles to increasing the number of transplants they are able to deliver.^{§§}

Before the development of kidney exchange, the organization of transplantation developed largely within the national boundaries of wealthy countries. It was primarily focused on deceased donor transplants, and the scarcity of organs meant that the concentration of effort within single countries did not have a large impact on the total number of transplants achieved. (There are well-established efforts to share deceased donor kidneys across national borders in limited circumstances.) With the growth of kidney exchange, there are now some preliminary explorations of coordinating across borders between countries with existing kidney exchange programs, primarily concentrating on looking for exchanges between hard to match pairs who have been left unmatched in the within-country kidney exchange. GKE opens up this possibility to a much larger part of the world, including countries in which unmatched patient-donor pairs may have had financial rather than immunological barriers, and so, may be easier to match with hard to match pairs. Additionally, because kidney exchange chains have amplified kidney exchange wherever they have been implemented, global exchange chains offer a way to bring these advantages to a much larger group of patients and donors. ¶¶

While Medicare aims to insure all Americans against kidney disease, the same cost savings described here could be employed to fund care for foreign patients who are uninsured, including those who are undocumented immigrants who may not have

- J. Coresh, T. H. Jafar, Disparities in worldwide treatment of kidney failure. *Lancet* 385, 1926–1928 (2015).
- T. Liyanage et al., Worldwide access to treatment for end-stage kidney disease: A systematic review. Lancet 385, 1975–1982 (2015).
- D. C. H. Harris, S. J. Davies, F. O. Finkelstein, V. Jha, The second Global Kidney Health Summit outputs: Developing a strategic plan to increase access to integrated end-stage kidney disease care worldwide. *Kidney Int Suppl (2011)* 10, e1–e2 (2020).
- International Society of Nephrology, CKD early identification & intervention toolkit. https://www.theisn.org/initiatives/ckd-early-screening-intervention/. Accessed 9 August 2021.
- A. E. Roth, T. Sönmez, M. U. Ünver, Kidney exchange. Q. J. Econ. 119, 457–488 (2004).
 C. B. Wallis, K. P. Samy, A. E. Roth, M. A. Rees, Kidney paired donation. Nephrol. Dial. Transplant. 26, 2091–2099 (2011).

entered the country legally (but may nevertheless be long-term residents).^{##}

Notice that if an international exchange works perfectly-i.e., when all of the patients and donors involved have successful surgeries, have excellent follow-up care, and are restored to active, long-lasting good health-then it will be easy to see the exchange as just another example of the success of standard kidney exchange in which all patients are from the same country. However, if the pair from the developing country was to return home and have bad health outcomes, it would look a lot like badly arranged black market transactions, which are justly condemned. So, to make kidney exchange work between developed and developing countries, exceptional care will have to be delivered to the developing country donors and patients, particularly since patients in poor countries—like their compatriots who have never suffered from kidney disease-can be expected to have somewhat worse health outcomes than otherwise comparable people in rich countries, no matter what efforts are made to give them the best possible postoperative care. International exchange may also require increased vigilance, compared with domestic exchange, to ensure that donors are not coerced or otherwise exploited. Consequently, the first element of a successful design for GKC is the choice of reliable international partners able to provide excellent care for patients and donors, both prospectively and postoperatively.

The other three design elements proposed and explored in this paper involve starting a chain in a foreign country and having a bridge donor continue it in the United States; using a LIFO queue policy on the pool of patients assembled by, for example, a coalition of self-insured companies responsible for paying for their care; and having those savings finance the otherwise unfunded additional costs (compared with an entirely domestic chain) in both countries. As we have shown, such a program could operate at a significant scale, comparable with the number of domestic patients presently beginning lengthy dialysis annually. GKCs thus appear to present a scalable approach to cross-border kidney exchange and to increasing the availability of transplantation globally. They have the potential to become at least a first step toward providing a global solution to the global problem of kidney failure

Data Availability. There are no data underlying this work.

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- P. Biró et al., Kidney Exchange Practices in Europe. First Handbook of the COST Action CA15210: European Network for Collaboration on Kidney Exchange Programmes (ENCKEP, 2017).
- S. L. Saidman, A. E. Roth, T. Sönmez, M. U. Ünver, F. L. Delmonico, Increasing the opportunity of live kidney donation by matching for two- and three-way exchanges. *Transplantation* 81, 773–782 (2006).
- V. B. Kute et al., Non-simultaneous kidney exchange cycles in resource-restricted countries without non-directed donation - a prospective single-center cohort study. *Transpl. Int.* 34, 669–680 (2021).
- A. E. Roth, T. Sönmez, M. U. Ünver, F. L. Delmonico, S. L. Saidman, Utilizing list exchange and nondirected donation through 'chain' paired kidney donations. *Am.* J. Transplant. 6, 2694–2705 (2006).
- M. A. Rees et al., A nonsimultaneous, extended, altruistic-donor chain. N. Engl. J. Med. 360, 1096–1101 (2009).

Nikzad et al. Global kidney chains

on November 30.

^{§§}Harris et al. (3) write: "It is estimated that the number of people dying globally with ESRD for want of kidney replacement therapy is up to 3 times the number who receive it. Kidney transplantation meets only a small fraction of the therapeutic need. Finally, about 188 million people experience catastrophic health expenditure annually as a result of kidney diseases across low- and middle-income countries, the greatest of any disease group."

 $^{^{}m II}$ If our concern in this paper were only with American patients, GKCs, with their costs of care for international patients, would likely be more expensive per patient initially than other ways of increasing, on the margin, the number of donor kidneys available to Americans. (These avenues should also be, and are being pursued, of course.) Some of these-like increasing the number of deceased donor kidneysdo not have the potential to cover the full need for organs (because only a tiny fraction of deaths occur in a way that makes organs potentially recoverable for transplant), but each life saved is precious, and each viable organ is very valuable. Other avenues, like increasing the number of living donors by providing greater incentives to donate, may be repugnant and illegal under current law in the United States and elsewhere. It seems likely that financial disincentives to donation could be reduced under current law, however, and limited steps in this direction are included under the recent executive order (https://www.federalregister.gov/documents/2019/07/15/2019-15159/advancing-american-kidney-health). Each of these avenues is well worth exploring, and each has the prospect of saving lives and medical costs; however, none of them seem to offer a scale that could end the growth in the deceased donor waiting list, and none would offer the prospect of extending the benefits of transplantation to international patients while also furthering domestic American goals.

^{##}Regrettably, US health insurance nevertheless lets some people who should be insured fall through the cracks. The majority of people who are denied access to kidney transplantation for financial reasons in the United States are patients who cannot cover their Medicare or Medicaid copays. The obstacle to committing to covering this is that it may not only be 20% of a kidney transplant but 20% of all their copays because transplant teams do not want to leave a patient with a transplant without access to a cardiac bypass surgery if needed or care for a terrible trauma after a kidney transplant. So, covering such a financial risk is complicated for US patients because of the high cost of US medical care.

- I. Ashlagi, D. S. Gilchrist, A. E. Roth, M. A. Rees, Nonsimultaneous chains and dominos in kidney- paired donation-revisited. *Am. J. Transplant.* 11, 984–994 (2011).
- I. Ashlagi, D. S. Gilchrist, A. E. Roth, M. A. Rees, Nead chains in transplantation. Am. J. Transplant. 11, 2780–2781 (2011).
- R. Anderson, I. Ashlagi, D. Gamarnik, A. E. Roth, Finding long chains in kidney exchange using the traveling salesman problem. *Proc. Natl. Acad. Sci. U.S.A.* 112, 663–668 (2015).
- 15. I. Ashlagi, A. E. Roth, Kidney exchange: An operational perspective. Manage. Sci.
- I. Ashlagi, P. Jaillet, V. H. Manshadi, Kidney exchange in dynamic sparse heterogenous pools. arXiv [Preprint] (2013) https://arxiv.org/abs/1301.3509 (Accessed 9 August 2021).
- 17. I. Ashlagi et al., Effect of match-run frequencies on the number of transplants and waiting times in kidney exchange. Am. J. Transplant. 18, 1177–1186 (2018).
- I. Ashlagi, M. Burq, P. Jaillet, V. Manshadi, On matching and thickness in heterogeneous dynamic markets. Oper. Res. 67, 927–949 (2019).
- M. A. Rees et al., Kidney exchange to overcome financial barriers to kidney transplantation. Am. J. Transplant. 17, 782–790 (2017).
- D. N. Bozek *et al.*, Complete chain of the first global kidney exchange transplant and 3-yr follow-up. *Eur. Urol. Focus* 4, 190–197 (2018).
- L. E. Ratner et al., The altruistic unbalanced paired kidney exchange: Proof of concept and survey of potential donor and recipient attitudes. *Transplantation* 89, 15–22 (2010).
- F. Minerva, J. Savulescu, P. Singer, The ethics of the global kidney exchange programme. Lancet 394, 1775–1778 (2019).
- P. Singer, F. Minerva, J. Savulescu, The global kidney exchange programme–authors' reply. Lancet 395, 1485–1486 (2020).
- 24. F. Ambagtsheer et al., Global Kidney Exchange: Opportunity or exploitation? An ELPAT/ESOT appraisal. Transpl. Int. 33, 989–998 (2020).

- F. L. Delmonico, N. L. Ascher, Opposition to irresponsible global kidney exchange. Am. J. Transplant. 17, 2745–2746 (2017).
- M. A. Rees et al., Global kidney exchange: Financially incompatible pairs are not transplantable compatible pairs. Am. J. Transplant. 17, 2743–2744 (2017).
- I. R. Marino, A. E. Roth, M. A. Rees, C. Doria, Open dialogue between professionals with different opinions builds the best policy. *Am. J. Transplant.* 17, 2749–2749 (2017).
- A. E. Roth et al., People should not be banned from transplantation only because of their country of origin. Am. J. Transplant. 17, 2747–2748 (2017).
- A. E. Roth et al., Global kidney exchange should expand wisely. Transplant. Intl. 33, 985–988 (2020).
- M. López-Fraga, B. Domínguez-Gil, The global kidney exchange programme. Lancet 395, 1484 (2020).
- L. Valera, M. A. Carrasco, The global kidney exchange programme. *Lancet* 395, 1484– 1485 (2020).
- 32. G. M. Danovitch, The global kidney exchange programme. Lancet 395, 1485 (2020).
- A. E. Roth, S. W. Wang, Popular repugnance contrasts with legal bans on controversial markets. Proc. Natl. Acad. Sci. U.S.A. 117, 19792–19798 (2020).
- C. Ro, Why the global kidney exchange remains controversial. Forbes, 15 December 2019. https://www.forbes.com/sites/christinero/2019/12/15/why-the-globalkidney-exchange-remains-controversial/?sh=3c0932955bcc. Accessed 9 August 2021.
- 35. A. E. Roth, Repugnance as a constraint on markets. J. Econ. Perspect. 21, 37–58 (2007).
- P. J. Held, F. McCormick, A. Ojo, J. P. Roberts, A cost-benefit analysis of government compensation of kidney donors. *Am. J. Transplant.* 16, 877–885 (2016).
- A. E. Roth, T. Sönmez, M. U. Ünver, Pairwise kidney exchange. J. Econ. Theory 125, 151–188 (2005).

