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Modelling and optimisation in European Kidney Exchange Programmes

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ABSTRACT

The complex multi-criteria optimisation problems arising in Kidney Exchange Programmes have received considerable attention both in practice and in the scientific literature. Whereas theoretical advancements are well reviewed and synthesised, this is not the case for practice. We present a synthesis of models and methods applied in present European Kidney Exchange Programmes, which is based on detailed descriptions we created for this purpose. Most descriptions address national programmes, yet we also present findings on emerging cross-national programmes. The synthesis provides a systematic and detailed description of the models and methods the programmes use, revealing important commonalities as well as considerable variation among them. Rather than distilling a single best practice from these results, we find that the variation in models and methods arises because of variation in country characteristics, policies, and ethics. The synthesised state of the art may benefit future national and cross-national initiatives and direct future theoretical contributions within and across the boundaries of the Operations Research discipline.

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1. Introduction

Since the seminal work of Rapaport (1986), the problems occurring in living donor kidney exchange programmes (KEPs) have received considerable attention in the fields of medicine, health

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policy, economics, computer science, mathematics, and in the Operations Research literature. This scientific activity advanced as existing KEPs developed and new KEPs emerged. It focused on the complex and multi-faceted dilemmas which present themselves when deciding which patients will receive a kidney - and may improve their health and longevity - and which patients will not, as yet. Should a first aim be to help as many patients as possible? Should longest waiting patients take preference? Or the sickest, the youngest? These are just a few of the ethical questions that KEPs raise and are being considered across scientific disciplines. Moreover, these complex delicate questions arise in practice where the answers provided have far reaching consequences.

In view of the sensitivity of these questions and the impact of the decisions for the individuals involved, operations researchers and other scientists have treated the resulting allocation problems with the greatest care. This placed new demands on their craftsmanship when developing models and solution methods. Often, such scientific advancement occurred in the relative safety of purely advancing theory. Glorie, Haase-Kromwijk, van de Klundert, Wagelmans, and Weimar (2014a) and Mak-Hau (2017) provide overviews of such primarily theory oriented models and solution methods.

While the theoretical advances are thus well synthesised, this is less true of the practical advances in modelling and solving KEPs. Practical advances often differ from the theory development as not all theoretical advances in modelling and solution methods are suitable in practice. Conversely, practical models and methods have been influenced by medical and policy developments, not all of which have reached the theoretical discourse. The recently emerging cross-national KEPs and the policy dilemmas they present illustrate such disconnects. Our research aim is to extend the policy oriented overview of national and cross-national European KEP practices by Biró et al. (2019) into the operations research domain. To this purpose, we present a review and synthesis of all models (including objectives and constraints) and solution methods (including algorithmic techniques) actively practiced in European KEPs, as surveyed via a questionnaire that was jointly developed for this purpose (original data are reported in Andersson, Biró, & et al., 2019).

For a number of reasons, European KEPs are of particular relevance. Many European countries have advanced transplantation programmes and have existing or newly developing KEPs. While these KEPs follow common regulations (see European Committee on Organ Transplantation (CD-P-TO) of the Council of Europe, 2018) each one is also clearly developed within a different national context and with different norms and values. An overview of models and methods practiced in European KEPs therefore provides a rich impression of related yet varied state of the art programmes. Moreover, we describe and discuss the most recent advancements in cross-national KEPs as they arise in Europe. The overview may inform theoretical research, as well as practices in other countries, European or not, who are developing (joint) programmes, models, and methods.

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2. Background

2.1. Context and principles for KEPs

The 2016 Global Burden of Disease Study identifies chronic kidney disease (CKD) as the 11th most common cause of death globally, accounting for almost 1.2 million deaths worldwide (2.17%)

(Institute for Health Metrics & Evaluation, 2018). In Europe, Chronic Kidney Disease accounts for 1.52% of all deaths. The number of deaths resulting from CKD grows both in absolute and in relative terms, and has almost doubled globally since 1990 (Institute for Health Metrics & Evaluation, 2018).

No cure exists at present for Chronic Kidney Disease. It may progress over several stages, the last one of which is called End Stage Renal Disease (ESRD). The most common treatment for ESRD is dialysis, which is costly. Recent UK evidence estimates yearly costs per patient at 15,000 to 35,000 GBP (Baboolal et al., 2008).

Compared to dialysis, the alternative of transplantation offers longer life expectancy, better quality of life, and lower average treatment costs (Axelrod et al., 2018; Haller, Gutjahr, Kramar, Harnoncourt, & Oberbauer, 2011; Sánchez-Escuredo et al., 2015; Wolfe, Roys, & Merion, 2010). Hence, transplantation is preferred as a treatment across Europe.

In Europe, transplantation treatments are often provided through dedicated and well organised transplantation programmes. Initially these programmes were set up to transplant kidneys from deceased kidney donors (DKD). At present, most European countries operate nationally organised DKD programmes through which the majority of transplants are conducted. There is a great variation in the volumes of DKD programmes across Europe, depending on ethical and legal regulations, as well as on the operational effectiveness of the programmes and the healthcare systems in general (European Directorate for the Quality of Medicines, 2017). By way of illustration, the Spanish DKD programme has the highest deceased donor kidney transplantation rate at 57.6 per million in 2016. Germany, on the other hand, has a deceased donation rate of 27.4 per million. From an operational perspective, variation is more limited, as many national programmes follow international protocols and standards, and collaborate across national borders to improve effectiveness. The organisations Eurotransplant and Scandiatransplant manage such international DKD programmes in Europe.

In many European countries, the demand for kidney transplants increasingly exceeds the supply of kidneys retrieved from deceased donors. Hence, DKD programmes have waiting lists. Recently reported waiting list lengths are for instance 2208 patients in Scandinavia (January 2018) and 5033 patients in the UK (March 2018). Both of these numbers considerably exceed the yearly number of transplants performed in these countries, and the same applies across Europe and beyond (European Directorate for the Quality of Medicines, 2017). Patients on the waiting lists are typically on dialysis, and it is not uncommon for patients to become too ill to transplant or to die while on the waiting list, as witnessed by the death rates presented above.

In addition to deceased donation, kidneys can be donated by living donors, as the human body has two kidneys, while commonly one suffices. Compared to DKD, living donor kidney donation (LKD) has better long-term patient and transplant outcomes (Hart et al., 2017; MacNeill, Casula, Shaw, & Castledine, 2016; Wolfe et al., 2010) (we refer to Reese, Boudville, & Garg, 2015 for a discussion of donor outcomes). This, in combination with the relatively poor outcomes of dialysis and the shortage of deceased donor organs, led to the establishment of LKD programmes in Europe, to complement existing DKD programmes. In 2017, the number of transplants resulting from LKD as a percentage of the total number of transplant in Europe were for instance, 5 % in Germany, 10% in Spain, 26.4% in Scandinavia, 30% in the UK, and slightly over 50% in the Netherlands (European Directorate for the Quality of Medicines, 2017).

The default procedure to enable LKD is for a patient to find a living person willing to donate a kidney, and receive a kidney from this *specified donor*. In the remainder we will refer to such a pa-

tient and donor as a *pair* and also refer to the patient as a *recipient*, or as the *specified recipient* of the donor.

Even when a patient finds a specified donor, however, transplantation of the kidney from this donor to the patient may be unfeasible because the patient (recipient) and donor are not *medically compatible* (are *incompatible*). Below we explain the forms and definitions of compatibility, while noting already that these have changed over time. (The reader may further note that they also apply in case of DKD.) Compatibility may take into account:

- *ABO-Compatibility* refers to the blood types, A, B, AB, and O. Type O donors can donate to all recipients. Type A donors can donate to Type A and Type AB recipients. Type B donors can donate to Type B and Type AB recipients. Type AB donors can only donate to Type AB recipients. A donor and recipient are said to be ABO-compatible if the blood type of the donor and recipient are such that the donor can donate to the recipient.
- *HLA-Match*, which refers to the extent to which the *Human Leukocyte Antigens* of the recipient and the donor are alike. The more they are alike, the more compatible from a viewpoint of HLA matching. When fully alike (e.g. for identical twins) we speak of a perfect HLA match (Fuller et al., 2004; Terasaki, Cecka, Gjertson, & Takemoto, 1995).
- *HLA-Crossmatch* refers to the test to decide whether a recipient has antibodies to the HLA of the donor (in significantly high concentration). If this is indeed the case, one speaks of a *positive crossmatch* which is seen as an indication that the transplantation will not be successful. A positive crossmatch is only possible when the HLA match is not perfect. (Below we also elaborate on virtual cross matches.)

Originally, recipients and donors were only considered compatible when they were ABO-compatible, and there was a perfect HLA match (and hence the crossmatch is negative). The development of immunosuppressant drugs made donation possible in case of less than perfect HLA-match. Recent advancements with so called *desensitisation* also make ABO-incompatible and HLA-incompatible transplants possible (Halloran, 2004). These dynamics have led to the definition of *half-compatibility* (Andersson & Kratz, 2016). A recipient-donor pair is said to be half-compatible when the crossmatch is negative and transplantation between donor and recipient requires desensitisation to overcome ABO-incompatibility. Recent meta analyses conclude that outcomes of state of the art desensitisation treatment results are good but some are significantly worse than outcomes of ABO-compatible transplants (De Weerd & Betjes, 2018; Scurt et al., 2019).

Highly sensitised patients are less likely to find compatible donors due to the presence of high titres of HLA antibodies in their blood. Different KEPs use different parameters to characterise (high) sensitisation. Some KEPs give highly sensitised patients priority to improve their chances of receiving a transplant.

Other factors that influence transplantation outcomes, in particular graft survival, relate to the quality of the kidney - which is for instance correlated with donor age - and the health of the recipient - which in turn is correlated with recipient age and time on dialysis.

With these reflections on outcomes and definitions of compatibility at hand, we can now consider the purpose of KEPs. Originally, KEPs were initiated to provide recipients who do not match with their specified donor access to a compatible donor by exchange of donors between recipients. In later years, the scope of KEPs has been extended. Because of advances in immunosuppression and desensitisation, recipient-donor pairs that are (half-)compatible might still choose to participate to find a more compatible donor. Furthermore, *altruistic donors*, i.e. donors without an intended recipient, may volunteer to participate. Fourth, some

KEPs integrate their LKD programme with the DKD programme, e.g. by starting chains with deceased donors. All of these extensions are further covered below.

2.2. KEP design variations

Below we synthesise the variations in the design of KEPs as identified from the detailed data collected for the purpose of our research by existing European KEPs (Andersson et al., 2019). Detailed country level comparisons can be found in Table 1 of Biró et al. (2019) and in Fig. 1 below. KEPs register a set $P = \{p_1, p_2, \dots, p_n\}$ of recipient-donor pairs $p_i = (r_i, d_i)$, $i = 1, \dots, n$ where r_i denotes the recipient and d_i the donor of pair p_i .

- *Exchange cycles*: Initially KEPs sought to match recipient-donor pairs together. More precisely, they sought to identify two pairs $p_i = (r_i, d_i)$ and $p_j = (r_j, d_j)$ such that recipient r_i is compatible with donor d_j and - vice versa - recipient r_j is compatible with donor d_i . Such exchanges are called *pairwise exchanges*. The KEPs of some European countries, such as France, are based on pairwise exchanges. Other countries with larger programmes (UK, Spain, the Netherlands) also prioritise pairwise exchanges (see below).

Most of the European KEPs have advanced beyond pairwise exchanges, or are preparing to do so. As pairwise exchanges can be viewed as forming a cycle of length two, between pairs i and j , a natural extension is to cycles of length three, also known as *three-way exchanges*. In a three-way exchange, there are three pairs, $p_i = (r_i, d_i)$, $p_j = (r_j, d_j)$ and $p_k = (r_k, d_k)$, and r_i is matched with d_j , r_j with d_k , and r_k with d_i . At present, the Spanish and the UK KEPs only consider pairwise and three-way exchanges (for reasons explained below). Four-way exchanges are allowed in the Netherlands. Within Europe, longer exchanges are allowed in several countries (such as Belgium and Portugal), yet so far they have only been conducted in the Czech Republic.

- *Altruistic chains*: Altruistic donation is allowed in some European countries. It is legally forbidden in France, Poland and Portugal. Where allowed, it can take the form of donating to a recipient in the DKD programme (by default in Belgium, but occasionally also in other countries). the Netherlands, Spain, and the UK explicitly incorporated altruistic donation in their KEPs. An altruistic donor then donates to a (first) patient, whose specified donor can then donate to a (second) patient and so on, with the last kidney donated to the waiting list. Thus, altruistic donors may initiate an exchange involving multiple pairs, which form a *chain*. As was the case for cycles, KEPs may impose limits on the maximum number of pairs involved in chains. Such limitations vary across European KEPs, roughly following the limitations on cycle length described above.

Alternatively, donation by the last donor may be postponed to continue the chain at a later moment. The last donor is then called *bridge donor*. Bridge donors can make chains longer or even *never ending*. European KEPs have no explicit arrangements yet for never ending chains.

- *Timing of match runs*: A match run is the process of constructing cycles and chains among donors and recipients participating in a KEP. Many European KEPs organise their match runs periodically. Poland organises a match run every month; the Netherlands, Portugal, and the UK have match runs every three months; whilst Spain has match runs every four months. Spain also organises match runs whenever a new altruistic donor arrives. Other countries also choose to organise their match runs on occasion, rather than following

	Belgium	Czech Rep. (& Austria)	Netherlands	Poland	Portugal	Spain (& Italy)	Sweden	United Kingdom
max size of solution	1	1	1	1	1	1	1	2
min lengths of the cycles	-	-	4	-	-	-	-	-
max # cycles selected	-	2	-	-	-	2	-	3
max # back-arcs	-	-	-	-	-	3	-	4
max # 2-cycles and 3-cycles with embedded 2-cycles	-	-	-	-	-	-	-	1
min# desensitisations	-	w	-	-	-	-	3	-
max HLA-matching	-	w	-	w	-	-	-	w
max DR-antigen matching in particular	-	w	-	-	-	-	-	-
min age-differences between the donors and patients	5	-	-	w	-	w	-	-
priority for paediatric patient	-	-	-	-	-	w	-	-
priority for patients not yet on dialysis	-	-	-	w	-	-	-	-
priority for highly sensitive patients	-	-	-	w	-	4	-	w
priority for O patients	-	-	-	w	-	-	-	-
priority for hard-to-match patients	3	-	3	w	w	w	2	-
priority for waiting time in KEP	-	-	-	-	-	w	-	w
priority for time on dialysis	4	-	6	-	w	w	-	-
priority for same blood-group transplants	2	-	2	-	w	w	-	-
priority for pairs with AB-donors	-	-	-	-	-	w	-	-
max # of transplant centres in (long) cycles	-	-	5	-	-	-	-	-
priority for donor-patients in the same region	-	-	-	-	-	w	-	-
min the donor-donor age differences	-	-	-	w	w	-	-	w
Constraints on length of exchanges	no	no	4	3	no	3	2	3
(Longest exchange already conducted)	3	7	4	3	3	3	n.a.	3
Constraints on length of chains	n.a.	no	4	n.a.	n.a.	no	n.a.	3
(Longest chain already conducted)	n.a.	6	4	n.a.	n.a.	6	n.a.	3
providing strictly better donors for compatible pairs	n.a.	yes	yes	n.a.	n.a.	yes	yes	yes
providing strictly better donors for half-compatible pairs	n.a.	yes	n.a.	n.a.	n.a.	n.a.	yes	n.a.
altruistic chain ends in the same region where started	-	-	yes	-	-	yes	-	-

Fig. 1. Objectives and constraints in European KEPs. Numbers reflect hierarchy level, w denotes the criterion is weighed against other criteria at the lowest level.

periodic patterns. For instance, in Belgium the match runs are organised when requested by a transplant centre.

- *Relationships with DKD:* As it avoids health risks for donors, deceased donation is often considered the default treatment. Patients registered in a KEP therefore may also register for the DKD waiting list.

Some countries allow and utilise interaction with the DKD programme in the form of deceased chains, when one recipient in the KEP receives a kidney from a deceased donor and then his/her donor starts a chain (as in the case of an altruistic chain) with the last donor donating to a recipient in the DKD programme. Three such chains were started in Italy in the summer of 2018. The most common modality for interaction with the DKD programme is through altruistic chains, as described above.

- *Inclusion of compatible pairs:* Some European KEPs explicitly restrict registration to incompatible pairs, e.g., Belgium, France and Portugal. Other countries allow or even encourage compatible pairs to participate, to improve outcomes for themselves and/or for other recipients. KEPs that enable such participation often provide additional arrangements to ensure that corresponding patients are matched to a donor

who is at least as good (to be defined below) as their specified donor. The KEPs of the Czech Republic, Scandinavia and Spain have explicit arrangements for this purpose. Notice that these KEPs may end up simply matching such recipients to their specified donors.

- *Desensitisation as an alternative of KEP:* For ABO-incompatible pairs transplantation from the specified donor to his/her recipient is possible with desensitisation. Hence, these pairs do not need to register in a KEP and be transplanted through an exchange. The recommended pathway for such pairs differs across Europe depending on healthcare systems, traditions and also the size and effectiveness of their KEPs. If the default treatment is desensitisation and, as a consequence, the KEP pool is small, then this gives another reason for the patients not to register in the KEP due to the relatively limited chance of finding exchange partners. This is the case in France and Italy, for example. In the countries with the longest standing KEPs (the Netherlands, UK, and Spain) the policy is to prefer exchange over desensitisation. As a result, these countries have larger pools which increases match probabilities and reduces waiting times for patients (Biró et al., 2019). In these programmes,

the ABO-incompatible pairs which are not matched within a reasonable period of time (e.g. two match runs) are advised to consider desensitisation.

- *Allowing ABOi transplants in exchanges:* When a recipient is not even half-compatible with the specified donor, KEPs may consider matching with half-compatible donors through donor exchange. The Czech, Scandinavian, Spanish, and UK KEPs presently facilitate such matches.
- *Multiple donors registering for one recipient:* This is allowed in most KEPs but not yet in Belgium, France and Netherlands. It likely increases the chances of the recipient to be matched. When the recipient is matched, only one of the corresponding specified donors donates to another recipient.

2.3. Logistics and organisation

Most KEPs require transplantations for all donors and pairs in a same cycle to occur simultaneously to avoid withdrawal of donors after their specified recipients have received kidneys but before donating themselves (see e.g. Cowan, Gritsch, Nassiri, Sina-core, & Veale, 2019). The Czech Republic and Poland do not enforce simultaneity in cycles and have successfully conducted non-simultaneous exchanges (such as a 7-way exchange conducted in the Czech Republic). As parallel transplantation may bring capacity and logistics challenges, a simultaneity requirement poses restrictions on exchange cycle length.

In the case of altruistic donation, simultaneity may be less of a strict requirement, as recipients can receive kidneys before their specified donor donates, thus avoiding the risk of leaving a recipient unmatched and without donor. Thus, the maximum length KEPs allow for chains may exceed the maximum length for cycles. In fact, when the last donor repeatedly initiates a new chain in the next match run, the chain can become never ending. We refer to Fig. 1 for an overview of chain and cycle length limitations implemented by European KEPs.

KEPs admitting longer cycles for which they perform all transplants simultaneously may need or prefer to spread these transplants across multiple centres because of capacity limitations, as is the case for the Dutch programme.

Anonymity may form another reason to involve multiple centres. Several European countries (e.g. the Netherlands, Spain, UK) require anonymity, either legally or by protocol. Anonymity is difficult to ensure when performing surgeries for multiple pairs involved in an exchange in the same hospital or when the donor travels to the hospital of the patient for the transplant.

Large travel distances for donors or kidneys can be considered undesirable. Spain for example, prefers to match recipients to donors from the same region.

2.4. HLA-testing and re-optimisation

Before a transplant is conducted, laboratory tests for HLA matching and cross matching must be done. Depending on the lab results, the transplant can be considered infeasible, or requiring immunosuppression and/or desensitisation. The European KEPs vary considerably in their organisations of the lab testing and the integration of the lab tests with the match runs.

HLA matching requires the HLA profile of each recipient and each donor to be determined. HLA matches can subsequently be determined by comparing the HLA profiles of donors and recipients. HLA cross matching requires to determine whether a recipient has antibodies against the specific HLA of a donor. The compatibility check of a pair is done first via so-called *virtual crossmatch* tests by comparing the ABO types and the HLA data of the patient and donor. For pairs that are matched and estimated to be compatible, a laboratory crossmatch test must subsequently

be done before transplantation is approved. The timing of the lab crossmatch tests differ across countries, as these can be costly or time consuming, especially if multiple HLA labs are involved in the testing.

For KEPs with smaller numbers of participating pairs and in smaller countries it may be feasible to conduct all the lab crossmatch tests prior to executing the match run. Poland and Portugal have adopted this practice. For larger KEPs, complete a-priori crossmatching is often considered undesirable. The lab crossmatch testing is then done after the match run on the virtual crossmatch input has resulted in a set of cycles (and chains) to consider for transplantation. Now, any cycle or chain can only be executed if all transplants implied by the cycle (or chain) are between a recipient and donor for which the lab crossmatch is negative.

European KEPs have different procedures to advance in case there are positive crossmatches for one or more transplants in the proposed exchanges. Three examples for crossmatch testing and re-optimisation strategies in large KEPs are:

- UK: The UK KEP uses multiple HLA-labs and considers only one solution per periodic match run. To improve the likelihood that all transplants in a cycle will proceed the UK KEP only allows pairwise and three way exchanges to minimise the risk of immunological, clinical or logistical reasons preventing transplants proceeding to plan. Moreover, it prefers three-way exchanges that contain embedded pairwise exchanges, such that an embedded pairwise exchange can go ahead if the three-way exchange cannot proceed (Manlove & O'Malley, article 2.6, 21pp, 2014). After the crossmatch results have been obtained, the KEP performs as many transplants as possible from the match run solution.
- Spain: There are multiple HLA labs and two rounds of testing. In the first round an optimal solution is tested and in the second round an alternative solution, where the cancelled cycles are intended to be repaired.
- Netherlands: One central HLA lab is responsible for the HLA testing and the crossmatch tests. If a positive crossmatch is found the match run will be repeated by the coordinators to find a next-best solution, until the crossmatch tests are negative.

2.5. KEPs as dynamic systems and their long term performance

After each match run, some recipients may have received a transplant, and hence these pairs and some or all of the altruistic donors leave the KEP. Over time, new recipient-donor pairs arrive and register. Additionally, pairs may leave, for example as a result of receiving a transplant from the DKD programme, finding a (half-)compatible donor, preferring a donation involving desensitisation (i.e. the presence of high titres of HLA antibodies in their blood) or becoming too sick to be transplanted.

From the above it is evident that the effectiveness of a KEP is not determined by the quality of the solution found for a single match run, but by its contribution to address the long-term health problems of the recipients registering over a period of time, and in relation to alternative solutions, such as the DKD programme and desensitisation programmes. When assessing the ways KEPs are organised and exchanges are identified at match runs, it is therefore appropriate to take a longer term perspective. This holds particularly true when including altruistic chains that span multiple match runs.

Longer-term performance criteria considered by European KEPs are: total number of transplants performed, percentage of recipients in the KEP who have received a transplant, average waiting time until being matched, quality of life for recipients and donors after transplant, graft survival times, recipient survival rates, and

donor survival rates (Andersson et al., 2019). Moreover, these outcomes are considered over various recipient sub-populations, e.g., per blood type, or with regard to highly sensitised patients, to also assess equity and fairness considerations.

2.6. International collaborations

As described above, international collaboration is common practice for DKD programmes and increasingly practised by KEPs. Such collaboration can result in finding better matches and in matching more recipients. The resulting international KEPs typically align with national KEPs already in place, rather than replacing them. We categorise the possible cooperations as follows:

- *Merged pools* In the most advanced mode of cooperation, the pools are merged and a solution is found for a match run involving the merged set of pairs. In this variant, there are no national match runs. Still, the countries involved may have different constraints and objectives. An example of this approach is STEP organised by Scandiatransplant, which started in Sweden and now includes Denmark and Norway. The same approach is used in the cooperation between Austria and Czech Republic since 2016 (Böhmi et al., 2017).
- *Consecutive runs* In the cooperation of Portugal, Spain and Italy each country first conducts its national matching run, after which the remaining patient-donor pairs participate in an international match run.
- *Outside registrations* A (large) country may extend registration of pairs to its KEPs to pairs from another country. Such arrangements exist between the UK and Ireland, and between France and Switzerland (where the pairs from the latter countries join the KEPs of the former).

3. Matching models

This section presents the models and methods used to find a solution for a single match run of a KEP. The objectives and constraints in the models, as well as the design of the solution methods are closely based on the contextual considerations described in the previous section.

Before going into the details of the models and optimisation methods however, let us mention that most European KEPs have adopted procedures through which in the end clinicians decide on the actual matching. This is done with the purpose of taking all relevant medical considerations into account, as well as to have feasibility explicitly checked by all centres involved. As a result, the technologies applied may not be optimisation methods in the classical sense. For instance, the methods practised by the Czech, Polish and Portuguese KEPs deliver a ranked list of solutions, from which clinicians choose. In Spain, once a solution is obtained and the centres are informed, those centres share clinical information and coordinate the crossmatch tests. They inform the Spanish KEP whether they advance with the transplantations resulting from the match run. In the Netherlands the donor is assessed in the recipient centre which ultimately decides on the suitability of the donor for the patient (sometimes crossmatches tests are therefore repeated in the recipient centre).

There are two broad classes of models used to describe the problem of finding an optimal set of exchanges for a match run. The first class encompasses graph models, which are intuitive and insightful. A second class is formed from integer programming formulations. These formulations have been particularly helpful to advance solution methods. Both classes, and the corresponding models and methods are considered in more detail below.

The classical model that is used to formulate the problem of finding solutions for a match run that take compatibility into account is the so-called *compatibility graph*. It is a directed graph $D(N,$

$A)$, in which there is a node $n_i \in N$ for each recipient-donor pair for $i = 1, \dots, n$. There is an arc (i, j) from node $n_i \in N$ to node $n_j \in N$ if the donor of pair n_i is compatible with the patient of pair n_j . If ABOi transplants are also considered, we may distinguish a special set of arcs $A' \subseteq A$ representing half-compatible donor-patient pairs. A self loop, i.e. an arc (i, i) where $n_i \in N$, emanates from each (half-) compatible recipient donor pair. The compatibility graph is called *virtual compatibility graph* if the compatibilities and weights are estimated based on virtual crossmatch test results.

Multiple donors may also be registered for one patient, in which case we have an arc (i, j) if some of the donors of pair n_i is compatible with the patient of n_j .

We may distinguish a special class of nodes $N^a \subseteq N$ to represent altruistic donors. A possible way of simplifying the modelling is to assume that altruistic donors have specified dummy recipients who are compatible with all donors, except for altruistic donors. Hence the altruistic donor nodes $n_i \in N^a$ have incoming arcs from every node $n_j \in N \setminus N^a$. Any chain emanating from an altruistic donor node can now be trivially extended to form a cycle by adding an arc from the last node on the chain to the altruistic donor node.

After the modification of $D(N, A)$ for altruistic donor nodes, a match run solution consists of a set of cycles in $D(N, A)$. As each donor and recipient can participate in at most one transplant, the problem of finding a match run solution can now be interpreted as a node-disjoint cycle packing problem. Moreover, a maximum cardinality cycle packing in $D(N, A)$ now refers to a match run solution with the highest possible number of transplants.

Each arc (i, j) , can have a weight $w_{i,j}$ to represent the utility of matching the donor from pair $n_i \in N$ with the recipient of pair $n_j \in N$. This value can include clinical considerations as well as other priority-based contributions, such as matching type O donors to type O patients. Moreover, nodes $n_i \in N$ can have weights to distinguish priorities among recipients, for instance depending on waiting time or sensitisation. Further, cycles can have cycle weights, for instance according to cycle length or to the structure of the subgraph induced by the nodes included in the cycle. An example of such a subgraph property is the number of pairwise exchanges in the induced subgraph of a three-way exchange (also referred to as the number of *back-arcs* in a three-way exchange). All such weights enable solutions to be distinguished based on performance criteria for the KEPs and subsequently per match run.

As is common, the graph model presented above can be formulated as an integer program. Here we present two basic formulations, referred to as the arc formulation and the cycle formulation (Abraham, Blum, & Sandholm, 2007).

The arc formulation has a binary variable $y_{i,j}$ for each arc (i, j) . Finding a maximum (value) solution with cycles and chains of length at most K can be solved through (1) – (4), where (4) ensures the arc formulation has a binary variable $y_{i,j}$ for each arc (i, j) . Finding a maximum (value) solution with cycles and chains of length at most K can be solved through (1) – (4), where (4) ensures that no cycle longer than K exists in the solution.

$$\max \sum_{i,j} w_{i,j} y_{i,j} \quad (1)$$

$$\text{s.t. } \sum_j y_{i,j} - \sum_j y_{j,i} = 0, \quad \forall i \in V \quad (2)$$

$$\sum_j y_{i,j} \leq 1, \quad \forall i \in V \quad (3)$$

$$y_{i_1,i_2} + y_{i_2,i_3} + \dots + y_{i_{k-1},i_k} \leq K - 1, \quad \text{for each directed chain of length } K \quad (4)$$

The cycle formulation uses a binary variable x_c for each cycle (and chain, see above) c of length at most K . We denote this set

of cycles by c^K . The weight of a cycle c is denoted by w_c , which can be taken as the sum of the edge-weights in the cycle, or can be defined differently as mentioned above. Finding all cycles in the graph can be done using e.g. Johnson's algorithm.

$$\max \sum_{c \in c^K} w_c x_c \quad (5)$$

$$\text{s.t.} \quad \sum_{c \in c^K, i \in c} x_c \leq 1 \quad \forall i \in V \quad (6)$$

As not all of the listed objectives can be expressed using the edge-formulation, the cycle-formulation appears more robust. For instance, objectives 2.-5. that prioritise shorter cycles or cycles with more back-arcs require a cycle formulation. However, the edge-formulation can have additional value, for instance to find long (never-ending) chains, sometimes in combination with cycle-variables. We refer to Anderson, Ashlagi, Gamarnik, and Roth (2015) and Dickerson, Manlove, Plaut, Sandholm, and Trimble (2016) for recent related results. Refinements for the case where a KEP applies different upper bounds for chains and cycles are presented (Anderson et al., 2015; Dickerson et al., 2016; Glorie, van de Klundert, & Wagelmans, 2014b).

3.1. Data and parameters

Most data required to solve actual match runs can be collected from medical records of recipients and donors. These records need to include the ABO types and HLA profiles as obtained from the lab test. The individual lab tests will also provide the data needed for virtual crossmatch tests. These lab tests can be done according to different methods and with different degrees of accuracy and hence the correctness of the virtual crossmatch tests may vary among KEPs. They may even vary within KEPs in case multiple labs are involved, as is particularly relevant for international KEPs.

The policy related parameters may be set implicitly, as is for instance the case when restricting the matching to pairwise exchanges or to pairwise and three-way exchanges (Scandinavia, Spain, and the UK). Other KEPs may fix these parameters explicitly in policies or leave them to be set manually (as in Poland and Portugal). Obviously, other constraint parameters and objective functions coefficients must also be set. With few exceptions, these parameters are fixed as they are set in legislative frameworks or formalised policies.

3.2. Objectives

Below, we synthesise model variations among European KEPs. Objective functions are presented first, after which constraints follow. The performance measures, or criteria, considered in the objective function can often also be modelled in constraints and vice versa. For example, age differences may be weighed as an objective function component or bounded via a constraint. The synthesis groups the criteria thematically. Where helpful, brief motivations and interpretations provide further clarification. Between brackets we list the countries that include the objective criterion or constraint. We also include a short explanation of a sample implementation of each criterion for a cycle formulation.

All European KEPs have formulated multiple-criteria objective functions. In fact, many adopt a hierarchical objective function. For instance, the Czech KEP prioritises to maximise the number of transplants, and within all such matchings, chooses one that maximises the number of cycles, constituting a hierarchy of two criteria. As hierarchical objective functions can be reformulated as weighted objective functions, we may consider all objective functions as weighted. However, as the hierarchies are often distinguished in the solution methods, the hierarchical models are also explicitly presented as such. Fig. 1 summarises the findings.

Optimising number of actual transplants to perform:

1. Maximising the number of transplants (All).
This can be implemented with the objective function $\max \sum w_c x_c$ where w_c is the length of cycle c .
2. Minimising the length of the longest selected cycle, as longer cycles are more likely to result in positive cross-matches, and thus in transplants that will not be performed. Selecting shorter cycles is also important for logistical reasons (NL, UK).
Mathematically, this is formulated as $\min \max w_c x_c$ where w_c is the length of cycle c . This can be implemented in an ILP by adding a variable m_i for each $i \in \{1, \dots, L\}$ where L is the length of the longest cycle. Constraints will ensure that m_i will take the value 1 if and only if a cycle of length $\geq i$ is selected. These constraints are implemented by first letting C_i be the set of cycles with lengths at most i (so C_3 is the set of all cycles of length 2 or 3), and then adding the constraints

$$m_i \geq \frac{\sum_{c \in C_i} x_c}{|C_i|}$$
 for each $i \in \{1, \dots, L\}$. We can then minimise the function $\sum m_i$ to minimise the length of the longest cycle.
3. Maximising the number of cycles selected, (which in turn reduces the average lengths of the cycles) (CZ, ES, UK).
This can be implemented with the objective function $\max \sum x_c$.
4. Maximising the number of pairwise exchanges in the sub-graphs induced by three-way exchanges, i.e. the number of back-arcs, in order to improve the number of matches remaining after deleting positive crossmatches from the solution, and also for logistical reasons. (ES, UK).
This can be implemented by the objective function $\max \sum w_c x_c$ where w_c is the number of back-arcs in cycle c .
5. Maximising the number of pairwise exchanges and three-way exchanges with embedded two-way exchanges (UK).
This can be implemented with the objective function $\max \sum w_c x_c$ where $w_c = 1$ if and only if cycle c is a pairwise exchange or a three-way exchange with an embedded two-way exchange.
Improving the overall quality of the transplants:
6. Minimising the number of implied desensitisations in KEPs that allow ABO_i and/or HLA_i transplants (CZ, SE).
This can be implemented with the objective function $\min \sum w_c x_c$ where w_c is the number of implied desensitisations in cycle c .
7. Maximising the (weighted) sum of the HLA-matching scores (CZ, PL, UK) with focusing on DR-antigen in particular (CZ).
This can be implemented with the objective function $\max \sum w_c x_c$ where w_c is the weighted sum of HLA-matching scores across all transplants in cycle c .
8. Minimising age differences between the donors and patients (BE, PL, ES).
This can be implemented with the objective function $\min \sum w_c x_c$ where w_c is the sum of the age differences between donors and patients in transplants in cycle c .
9. Prioritising paediatric patients (ES).
This can be implemented with the objective function $\max \sum w_c x_c$ where w_c is the number of paediatric patients involved in the cycle.
10. Prioritising patients that have not started dialysis yet (BE, PL).
This can be implemented with the objective function $\max \sum w_c x_c$ where $w_c = 1$ if and only if the patient has not started dialysis.

For the criteria below, prioritisation can be implemented by including an objective that maximises the total weight of the matching ($\max \sum w_c x_c$) and adding a suitable weight to a cycle for each transplant of the particular type. For instance, the Spanish system prioritises highly sensitised patients by adding 30 points to the weight of a cycle for each donor with less than a 26% chance of finding a compatible donor. Certain types of transplants (i.e., ones that require desensitisation) can be avoided by instead subtracting from the weight of a cycle.

For improving equal access in expectation:

11. Prioritise highly sensitised recipients (PL, ES, UK)
12. Prioritise blood-type-O recipients, for which the donor pool is the smallest (PL)
13. Prioritise recipients according to (low) matching probability [see e.g. Keizer et al. 2005] (BE, NL, PL, PT, ES, SE)
14. Prioritise recipients based on waiting time (in KEP / on dialysis) (ES, UK / NL, BE, PT, ES)
15. Prioritise identical blood-group transplants (BE, NL, PT, ES)
16. Prioritise pairs with type-AB donors (ES)

Logistical considerations: Besides prioritising shorter cycles and chains, the following objectives can be explained by logistical reasons:

17. Prioritise recipient-donor pairs from the same region (ES)
 18. Prioritise solutions that involve more transplant centres (NL)
- Fairness:*
19. Minimising age differences between donor and donor of the matched recipient (NL, PL, PT, UK)

3.3. Constraints

The list of potential constraints are as follows (see Fig. 1).

To avoid cancellation or for logistics reasons:

20. Upper bound on the length of cycles (PL, PT, SE, ES, UK)
21. Upper bound on the length of chains (NL, UK)

Upper bounds on the lengths of cycles (chains) are implemented by not creating variables for cycles (chains) that are too long.

Fairness considerations:

22. Providing strictly better donors for compatible pairs, where the definitions of 'better' vary per country and relate to one or more of the criteria mentioned above (CZ, NL, ES, SE, UK)
23. Providing strictly better donors for half-compatible pairs (CZ, SE)
24. Bound the donor-donor or donor-patient age differences (PL, PT, UK)
25. End the altruistic chain in the region where the donor registered (IT, NL, ES)

The above restrictions can be implemented by not considering cycles that break them. For instance, in the Italian system altruistic chains that would end in a different region to the one in which the altruistic donor registered would not be considered at all (no variable x_c would be created for such a chain).

3.4. Solution methods

The solution methods for the models formulated for each of the European KEPs are grouped and synthesised below.

- *Edmonds' algorithm.* It is well known that the version in which the maximum cycle length is bounded by two, i.e., only pairwise exchanges are allowed, reduces to finding a maximum (weight) matching in an undirected graph. This problem is solvable in polynomial time, e.g. through Edmonds' algorithm. The Scandinavian KEP relies on the application of Edmonds' algorithm, even though their model

is complicated by the introduction of half-compatibility (Andersson & Kratz, 2016). The UK KEP uses Edmonds' algorithm as a first step, to maximise the number of pairwise exchanges within the selected exchange.

- *Graph heuristics.* When allowing cycles (and chains) of bounded lengths greater than two, the resulting optimisation problems are known to be NP-hard (Abraham et al., 2007). The Spanish KEP employs a polynomial-time, yet heuristic solution method that searches for cycles of length two and three. The heuristic makes use of Edmonds' algorithm. For further details we refer to Bofil et al. (2017).
- *Exact methods using the arc formulation.* The Polish KEP uses the arc based integer programming formulation in the case that enumeration of all cycles results in too many cycles. The proposed approach for the arc formulation IP with cycle length constraint is as follows. The cycle length constraint is relaxed and the remaining IP is solved using standard software. If the solution satisfies the cycle length constraint it is optimal and is reported. Otherwise, constraints are added to eliminate the cycles included in the solution that are too long from the solution space, and the resulting IP is again solved using standard techniques. This process repeats until a feasible solution is obtained. Moreover, it is executed hierarchically to first obtain a maximum cardinality solution, and subsequently optimise a weighted objective function. The subsequent optimisation incorporates as a constraint that the matching found is of the previously determined maximum cardinality.
- *Exact methods using the cycle formulation.* The Portuguese KEP uses exact methods to solve the cycle-based integer programming formulation. The Polish KEP does likewise if the number of cycles is not too large. This is done hierarchically to first obtain a maximum cardinality solution, and subsequently optimise a weighted objective function. The UK KEP uses multiple hierarchical levels that are optimised sequentially (Manlove & O'Malley, article 2.6, 21pp, 2014). The first level is optimised using Edmonds' algorithm, while later levels use the cycle formulation to potentially select different exchanges that still contain the same number of pairwise exchanges as computed by Edmonds' algorithm. An important part of using the cycle formulation is generating all cycles within a graph. This can be done using e.g., Johnson's algorithm.
- *Enumerative methods.* The Dutch and Czech KEPs in principle enumerate all solutions. To reduce the search space, the Czech KEP firstly determines all strongly connected components of the compatibility graph (in polynomial time) and subsequently enumerates per component. Both KEPs subsequently present a sorted list of solutions. From this list, the computer program of the Dutch KEP only shows one optimal solution. The proposed exchanges in this solutions are tested and in the case of a positive crossmatch a new (next-best) solution is sought (and tested).

4. Discussion and conclusion

Kidney Exchange Programmes are complex and dynamic healthcare system components addressing the needs of patients with ESRD. Variation among healthcare systems - for instance regarding the effectiveness of the deceased donation programme - subsequently translates into variation in purposes of KEPs. The detailed country descriptions which we composed and synthesised show that this translates into variation in KEP designs. The size of the country and the KEP pools, and the number of HLA labs involved in cross match testing also affect the KEP designs. Finally, KEP designs importantly vary with differences in ethical and legal frame-

works e.g. regarding the admission and integration of altruistic donation. A first conclusion is therefore that each of the European KEPs is designed to fit its particular context and should be assessed within this context. By consequence, an apparently advanced KEP that serves its own context well may be a poor match in another setting. For instance, while some countries have advanced to increase the effectiveness of altruistic donation, altruistic donation is considered unethical and forbidden by law in other (neighbouring) countries. Likewise, some countries prefer desensitisation as a treatment for a patient-donor pair over participating in a KEP, while other countries consider participating in the KEP preferable.

Still, KEPs can learn from each other and advance by adopting (and adapting) each other's practices. Below we synthesise commonly applicable advances as emerging from this study. Operations Research can contribute by providing such general advancements. In view of the conclusion above, however, we would caution against 'one size fits all' ambitions, or against claims that certain models and methods are better than others. Even presented empirical evidence should always be considered in context. Hence, Operations Research can also contribute by tailoring models and methods to the demands, norms and values of specific contexts.

Let us start with some general observations on the models and methods used in the European KEPs. Integer Programming models appear to be the most generic models in use. The UK, Portugal and Poland are robustly and effectively solving their match runs using Integer Programming-based solution methods. Other countries make use of enumerative solution methods or use heuristic approaches. Regardless of these methods, we notice that relatively few countries tend to directly implement the solutions provided by the optimisation methods. Many countries leave the decision making to a committee based on a (ranked) list of alternative solutions' to allow the committee to weigh in additional considerations.

A key aim of all European KEPs is to facilitate as many transplants as possible. Therefore, the primary goal of (most of) the models and methods proposed is to find maximum cardinality matchings. Yet, because of the risk of cancellations (e.g. due to positive crossmatches), the practical goal is to maximise the number of transplants that can actually be conducted. Countries have tailored a variety of approaches to reduce the gap between the cardinality of the maximum matching and the number of transplants that can actually be conducted.

A generic solution is to restrict the solution to only consist of short cycles, as cycles involving fewer pairs carry a lower risk of cancellation. Hence, many programmes put upper bounds on the cycle length (3 is a common bound) or prioritise shorter cycles. The usage of a single HLA-lab can also decrease cancellation risk, as it harmonises test procedures and enables quick re-optimisation. Countries with a central HLA lab (e.g. the Netherlands) may therefore allow longer cycles and need not consider minimising cycle length a high priority. Larger countries with multiple HLA labs can mitigate the failure risks by selecting solutions with back-up options, e.g., three-cycles with embedded two-cycles (UK and Spain).

Altruistic donation can also greatly benefit the number of transplants. A first main advantage of chains over cycles is that simultaneity is not considered to be required and thus chains can be longer than cycles. A second main advantage is that the last donor in the altruistic chain can be kept as a bridge donor for later, thus extending the advantages into the future.

HLA-matching and age difference between matched donors and patients are the two main factors influencing expected graft survival times. Hence, many countries maximise HLA-matchings and/or minimise age differences to improve the quality of the transplants. Some countries even include such quality considerations through hard constraints on HLA-matching or age differences.

For KEPs which allow ABO-incompatible transplantation, quality can also encompass the number of desensitisation transplants in

the optimisation objectives. Match quality is also a consideration to include compatible pairs. The patients from such pairs may find a better matched donor themselves and their participation may also be beneficial to other participating pairs. To encourage their participation, KEPs then may guarantee quality of matching for recipients from such pairs (as is the case in the UK).

In addition to maximising the number of transplants and their quality, equity is of explicit importance. For instance, many KEPs restrict type O donors to donate to type O patients to ensure an equitable transplant probability for type O patients. Similarly, several KEPs prioritise highly sensitised patients to improve their poor match probability. Following comparable fairness principles, some KEPs prioritise patients with long waiting times.

Ethical considerations are not limited to participants in single match runs. From a policy perspective, the effectiveness of KEPs is typically evaluated over time and hence for larger populations. The relationships between the complex optimisation models, methods and objectives employed for single match runs and the longer-term outcomes considered by policy makers is as yet not always well understood. This is certainly an area for further research where analysis on multiple, longitudinal, empirical data sets is called for.

Lastly, it is worth considering the emerging cross-national initiatives. Three collaborations have already started: between Austria and the Czech Republic, between Italy, Portugal and Spain, and between Sweden, Norway and Denmark. For now these cross-national KEPs have mainly considered patients left unmatched in the national KEPs. We may expect the cross-national KEPs to further expand their benefits in the near future when initiating to merge national patient pools and to optimise the resulting cross-national patient pool. This will bring about new challenges. Firstly, how to ensure that national regulations (constraints) and priorities (optimisation criteria) of each participating country are respected. Secondly, it should be noted that consideration of equity and fairness now not only apply to individual patients, but also to patient populations from multiple countries. Patients from one country might benefit more than patients from another country. Such equity considerations occurring among countries form a relatively unexplored area. The current European cross-national initiatives can play a guiding role in developing equitable cross-national KEPs and in the lively global scientific and policy discourses on this matter (Bozek et al., 2018; Delmonico & Ascher, 2017; European Union National Competent Authorities on Organ Donation & Transplantation, 2–18).

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Supplementary material

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