IL TRAPIANTO CROSS-OVER

Kidney Paired Donation(KPD)

Antonina Piazza

Winter School AIBT

Ravascletto (Udine) 3-5 Dicembre 2015

C.N.R., IFT UOS di Roma S. Camillo - Centro Regionale Trapianti Lazio

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- ✓ **Il trapianto di rene rappresenta la terapia d'elezione per il trattamento dell'insufficienza renale allo stadio finale.**
- ✓ **A causa della carenza di organi da donatore cadavere è auspicabile un incremento del trapianto da donatore vivente.**
- ✓ **Il trapianto da donatore vivente presenta, rispetto a quello da donatore cadavere i seguenti vantaggi:**
  - minor tempo d'attesa;
  - minore "delayed graft function";
  - migliore "graft survival";
- ✓ **Solitamente circa il 50% delle potenziali coppie donatore/ricevente non arrivano al trapianto per problematiche immunologiche (incompatibilità ABO o presenza di anti-HLA DSA).**
- ✓ **Le incompatibilità immunologiche possono essere, in alcuni casi, superate/mitigate mediante trattamenti desensibilizzanti che esitano in:**
  - buoni risultati in caso di incompatibilità ABO (soprattutto se il titolo delle isoagglutinine non è troppo elevato);
  - scarsi o nulli risultati in presenza di anti-HLA DSA (soprattutto se i DSA presentano elevati valori di MFI).

Nephrol Dial Transplant (2015) 30: 1276–1285

Kidney paired donation: principles, protocols and programs

Paolo Ferrari[1,2,3]*, WillemWeimar[4,5], Rachel J. Johnson[6], Wai H. Lim[2,7] and Kathryn J. Tinckam [8,9]

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KPD, FROM CONCEPT TO REALITY

Rapaport [10] first introduced the concept of KPD almost 30 years ago. South Korea, a nation with limited access to deceased donors where the majority of transplants are reliant on live-donor source, was the first country to report the establishment of a KPD program in 1991 [15]. Following the Korean experience a number of single-center, regional and national KPD registries have been established. Single-center KPD transplants have been reported from several countries including Romania [16], Turkey [17] and India [18]. Multicenter, integrated, national registries have been reported to date from four countries: the Netherlands [11, 19, 20], UK [21], Canada [22] and Australia [23–26]. In the USA, although there is a federal government-funded KPD registry managed by UNOS many organizations have established independent multicenter or hospital-based KPD programs, most notably the National Kidney Registry [27], the New England Kidney Exchange program [28], the Alliance for Paired Donation [29, 30], the Johns Hopkins Hospital incompatible kidney transplant program [31, 32] and the Methodist Hospital KPD program in San Antonio, Texas [33]. Commonalities and differences of the multiple US programs have been reviewed in detail elsewhere [27, 28, 33–35].

American Journal of Transplantation 2013; 13: 851–860

Dynamic Challenges Inhibiting Optimal Adoption of Kidney Paired Donation: Findings of a Consensus Conference

M. L. Melcher[a], C. D. Blosser[b], L. A. Baxter-Lowe[c], F. L. Delmonico[d,e], S. E. Gentry[f], R. Leishman[g], G. A. Knoll[h], M. S. Leffell[i], A. B. Leichtman[j], D. A. Mast[k], P. W. Nickerson[l], E. F. Reed[m], M. A. Rees[n], J. R. Rodrigue[o], D. L. Segev[p], D. Serur[q], S. G. Tullius[r], E. Y. Zavala[s] and S. Feng[c,*]

[a]*Department of Surgery, Stanford University, Stanford, CA;* [b]*Department of Internal Medicine, University of Iowa,Iowa City, IA;* [c]*Department of Surgery, UCSF, San Francisco, CA;* [d]*Department of Surgery, Massachusetts General Hospital, Boston, MA;* [e]*New England Organ Bank, Boston, MA;* [f]*Department of Mathematics, U.S. Naval Academy, Annapolis, MD;* [g]*United Network of Organ Sharing, Richmond, VA;* [h]*Department of Medicine, Ottawa Hospital, Ottawa, ON;* [i]*Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD;* [j]*Department of Internal Medicine, University of Michigan, Ann Arbor, MI;* [k]*Stanford Hospital and Clinics, Palo Alto, CA;* [l]*Department of Internal Medicine, University of Manitoba,Winnipeg, MB;* [m]*Department of Pathology, University of California Los Angeles, Los Angeles, CA;* [n]*Department of Urology & Pathology, University of Toledo Medical Center, Toledo, OH;* [o]*Transplant Institute, Beth Israel Deaconess Medical School, Boston, MA;* [p]*Department of Surgery, Johns Hopkins University,Baltimore, MD;* [q]*Department of Surgery, Cornell University, New York, NY;* [r]*Department of Surgery, Brigham & Women's Hospital Harvard University, Boston, MA;* [s]*Department of Surgery, Vanderbilt University Medical Center, Nashville, TN.*

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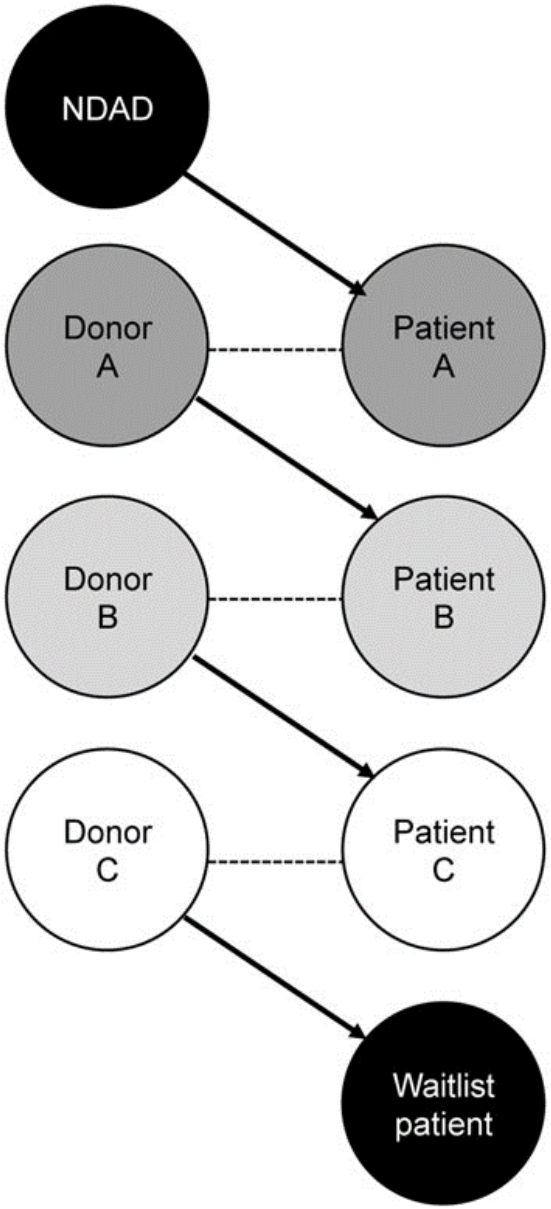
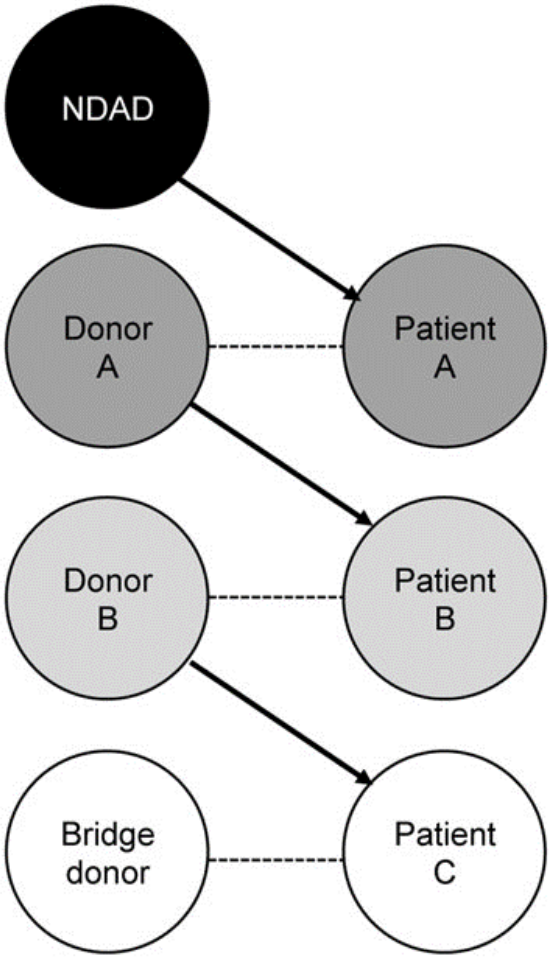
Table 1: Glossary

Batch matching: Identifies best matches among currently available participants
Bridge donor: A donor whose intended recipient has already received a kidney from another incompatible paired donor and waits to donate to a suitable recipient at a later date
Chain of custody principle in KPD: Precise and detailed documentation of the kidney's location and the responsible parties (name and contact information) for the donor kidney from its recovery until its delivery
Closed chain: A KPD chain that ends in the transplant of patient on the waitlist
Dynamic optimization: Identifies best matches among currently available participants but with consideration of and accommodation for (near) future match opportunities
Hierarchical matching: A matching strategy that orders potential match solutions based on based on a specific order of operations such as the most number of sensitized patients, the longest chains, etc.
Interactive matching: A matching strategy that generates multiple potential match solutions, and incorporates human judgment to choose among them
Kidney paired donation (KPD): Process in which two or more candidates with willing and healthy, but incompatible donors can exchange donor grafts such that two or more compatible transplants can occur simultaneously or in sequence. Also known as kidney paired exchanges
KPD champion: A person at a transplant center who advocates for KPD as a transplant option and identifies patients that may benefit from KPD
Lifeguard status: "A term attached to an airliner's radio call sign when the aircraft is transporting time sensitive medical materials" (38)
Nondirected Donor (NDD): An individual who donates a kidney to a recipient with whom they have no emotional or genetic relationship. Also known as an altruistic or a Good Samaritan donor.
Nonsimultaneous extended altruistic donor (NEAD) chain: Clusters of chain transplantations, in which the donor at the end of each cluster served as a "bridge donor", thus extending the interrupted chain at a later time
Open chain: A KPD chain that continues to be extended by donating to a recipient who offers an additional donor
Optimization matching algorithms: A matching strategy that identifies the solution with the largest number or best selection of transplants in the weighting system chosen, for example, priority points reflecting relative values for donor and recipient characteristics

NDAD-chain ending with donation to waitlist patient



NDAD-chain ending with bridge donor



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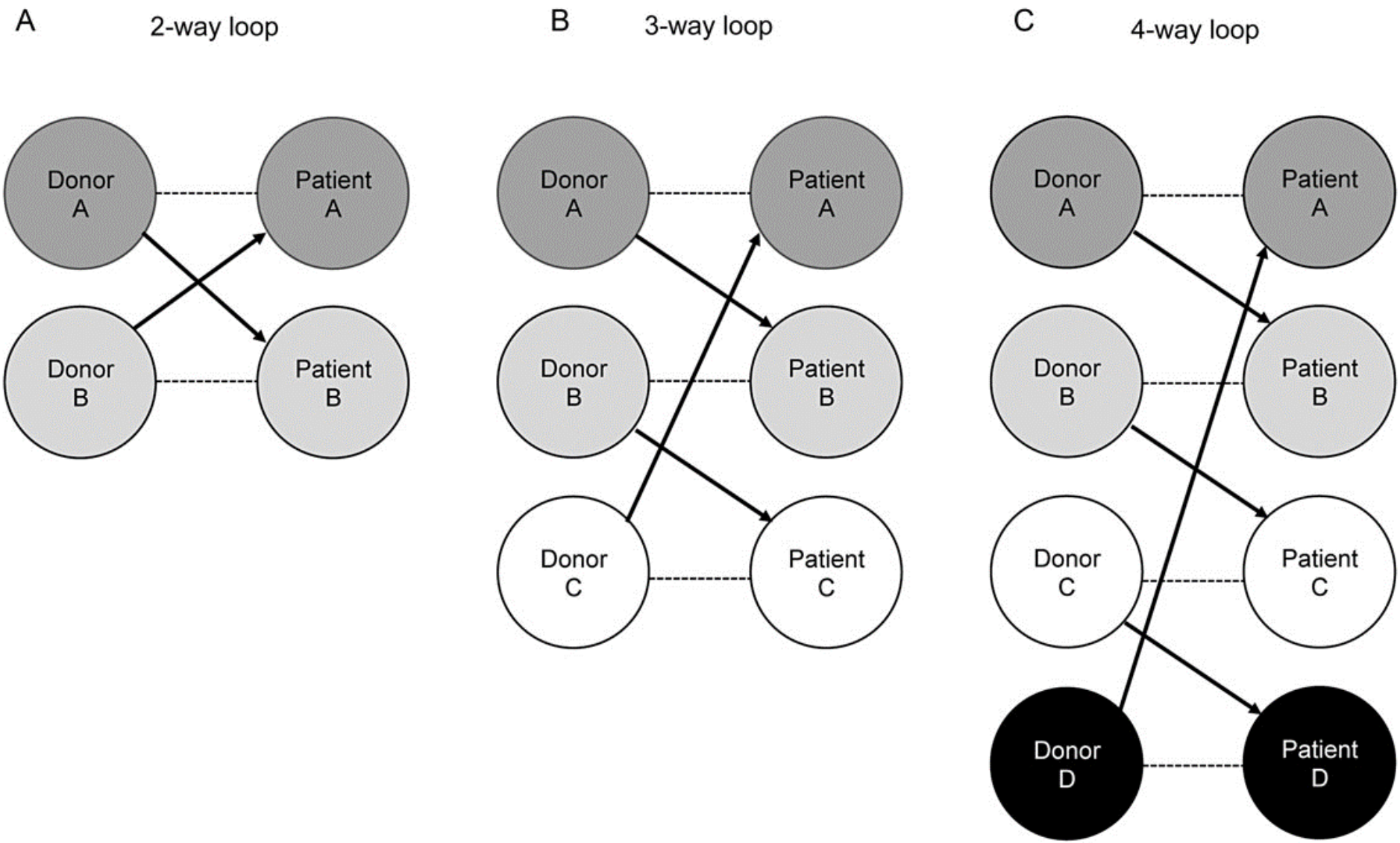

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Overcoming Geographic Barriers to KPD

Table 4: Recommended policies to overcoming geographic barriers to KPD

• Donors should have the option to travel to the recipient center and to choose to where they are willing to travel. Donors should never be required to travel
• KPD centers should be willing to transport kidneys, both to and from the center
• A standard format for sharing patient information and medical records should be defined
• Payers should cover donor travel and lodging costs when a donor travels for KPD.
• Packaging, labeling and transportation may benefit from OPO support or guidance
• Direct surgeon-to-surgeon communication is recommended prior to and immediately after KPD donor nephrectomy
• All kidney transport should follow chain-of-custody principles
• When traveling by commercial plane, all flights should be designated lifeguard. Kidneys on nonstop routes should be accompanied by a tracking device. Kidneys on routes involving any layovers should be accompanied by a courier

Outcomes of Kidney Paired Donation Transplants in Relation to Shipping and Cold Ischaemia Time

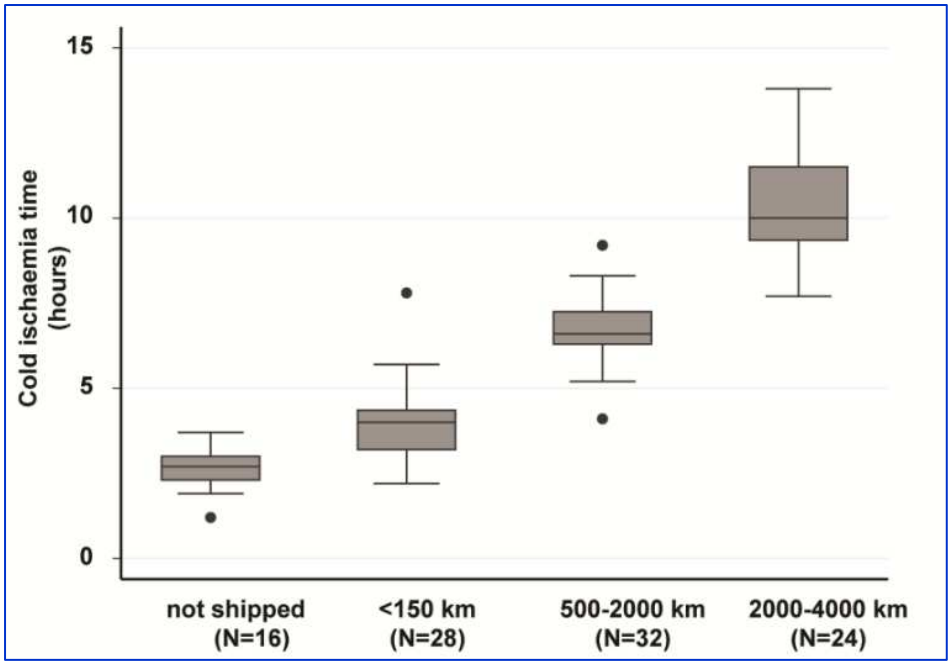
(Running Title: Kidney paired donation and organ transport)

Richard Allen[1,2], Henry Pleass[2,3], Phil A Clayton[4], Claudia Woodroffe[5], Paolo Ferrari

[1]Department of Surgery, Royal Prince Alfred Hospital, Camperdown, Sydney, NSW, Australia, [2]Discipline of Surgery, Sydney Medical School, University of Sydney, NSW, Australia, [3]Department of Surgery, Westmead Hospital, Westmead, Sydney, [4]Australia and New Zealand Dialysis and Transplant Registry, University of Adelaide at Central Northern Adelaide Renal & Transplant Services, Adelaide, South Australia, [5]Department of Nephrology and Transplantation, Prince of Wales Hospital, [6]Clinical School, University of New South Wales, Sydney, Australia

Transpl Int. 2015 Nov 17. doi: 10.1111/tri.12719. [Epub ahead of print]

Figure 1: Cold ischaemia time in relation to shipping distance.



Transpl Int. 2015 Nov 17. doi: 10.1111/tri.12719. [Epub ahead of print]

Figure 2: Initial function of AKX kidneys by shipping distance.

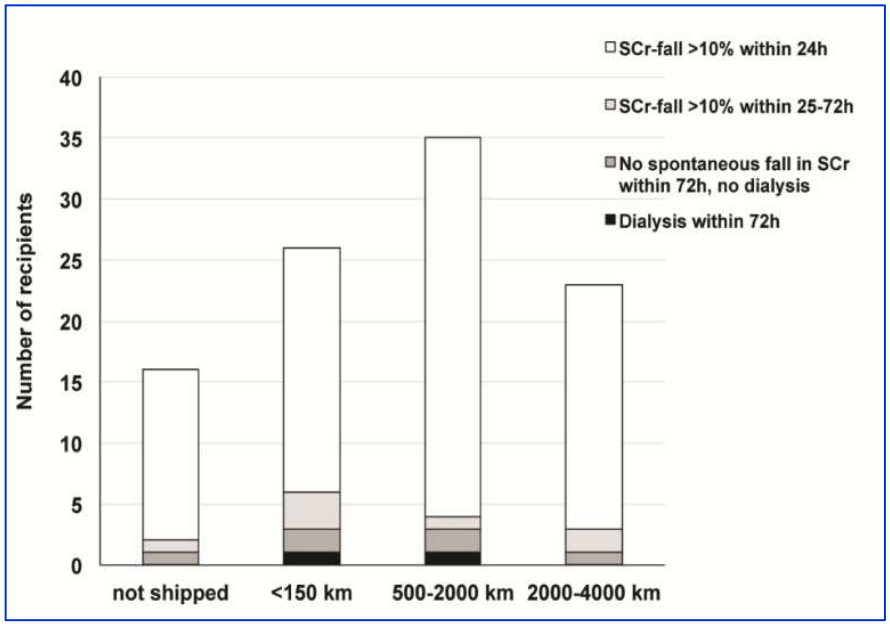


Figure 3: Serum creatinine at 1 month in recipients of AKX kidneys in relation to shipping distance.

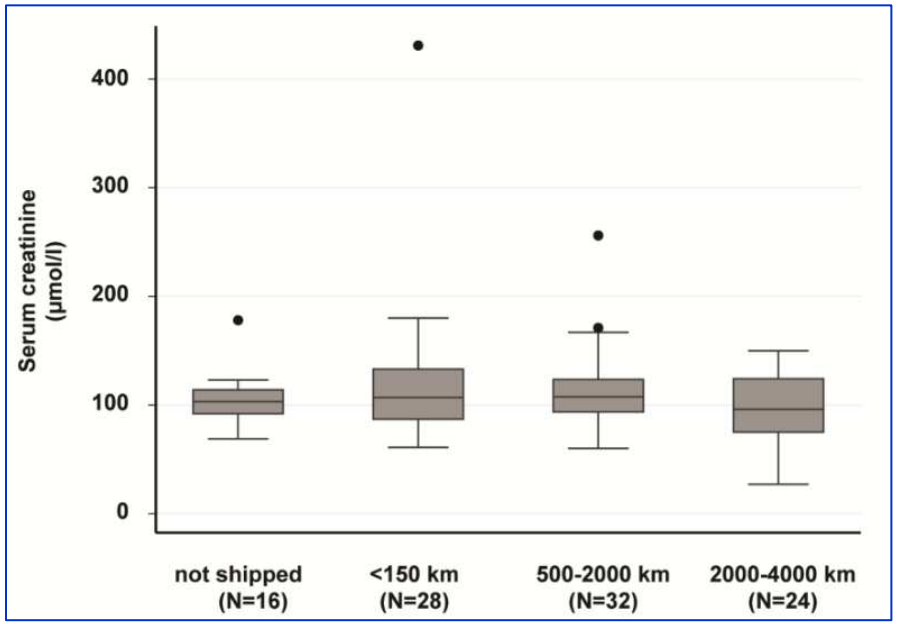


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Table 1. Key ingredients of four national kidney paired donation registries

Country	The Netherlands	UK	Canada	Australia
Year established	2004	2007	2009	2010
Name of program	Living Donor Exchange Programme	National Living Donor Kidney Sharing Scheme (NLDKSS)	Canadian Blood Services Kidney Paired Donation Program (CBS-KPD)	Australian paired Kidney eXchange Program (AKX)
Dedicated central support staff	Yes	Yes	Yes	Yes
HLA laboratories involved	Single	Multiple	Multiple	Multiple
Types of exchanges considered	Multiway and domino	Multiway and domino	Multiway and domino	Multiway and domino
Accepts ABO-incompatible donor matching	No	Yes	No	Yes
Donor travel or organ transport	Donor travel	Organ transport	Donor travel (rarely organ transport)	Organ transport
Frequency of match cycles	Every 3 months	Every 3 months	Every 4 months	Every 3 months
Donor allocation algorithm	Virtual cross-match	Virtual cross-match	Virtual cross-match	Virtual cross-match
Primary allocation criteria	Unacceptable antigens based on recipient's serological DSA for HLA-A, B, Bw, DR, DQ	Negative virtual cross-match at HLA-A, B, C, DRB1, DRB345, DQB1, DPB1	Negative virtual cross-match at HLA-A, B, C, DRB1, DRB345, DQA1, DQB1, DPA1, DPB1	Negative virtual cross-match at HLA-A, B, C, DRB1, DRB345, DQA1, DQB1, DPA1, DPB1

Table 3: Recommended guidelines for KPD histocompatibility testing

• **HLA typing:** Should be DNA based for HLA-A,-B, -C, -DRB1, -DRB3–5, -DQA1, -DQB1, -DPB1 loci and inclusive of certain specific alleles and common null alleles, as needed. Extended donor typing may be required depending upon antibody specificities.

• **Antibody testing:** Two methods should be used, at least one being a solid phase immunoassay. Antibody specificity should be confirmed by a single antigen assay. Assay limitations should be recognized and considered in interpretation. Antibody testing should be performed at least quarterly and after any proinflammatory/sensitizing event.

• **Unacceptable antigens:** Unacceptable antigens should be assigned based on the transplant center's crossmatch acceptance criteria and should be updated whenever antibody tests indicate a change. There should be two levels of unacceptable antigens, high and low risk; possible listing of antigen combinations to address multiple, weak antibodies. Definition of sensitization should be based on the calculated panel reactive antibody.

• **Virtual crossmatching:** Correlation of antibody assays with transplant center risk criteria is essential. Labs should achieve 95% accuracy in crossmatch prediction. Labs should try to identify combinations of multiple, weak antibodies that could yield a positive crossmatch when a donor has all of the corresponding antigens.

• **Crossmatching:** Flow cytometric crossmatches are recommended for sensitized patients. Unexpected positive results should be resolved and unacceptable antigens updated. Patients should be inactive until reasons for failed crossmatches have been resolved and unacceptable antigens are updated. Cryopreserved donor cells should be available for preacceptance, "exploratory" crossmatches.

• **Exchange of specimens and data:** There should be standardized practices for test requisitions, labeling, and shipment of shared samples. Data entry should be verified by two person audit, at least one of whom should have histocompatibility expertise.

• **Communication:** Histocompatibility Laboratory Directors should participate in the evaluation of proposed paired donation matches and be available to provide consultation. KPD programs should have a *Histocompatibility Advisory Committee* comprised of physicians, surgeons, coordinators and histocompatibility experts provide quality assurance review and facilitate logistical planning for testing KPD should include additional testing needed to monitor desensitization efficacy.

Rete Nazionale Trapianti

Centro Nazionale Trapianti

PROTOCOLLO PER LA REALIZZAZIONE DEL TRAPIANTO DI RENE DA VIVENTE IN MODALITA' INCROCIATA (cross-over).

(Centro Nazionale Trapianti - revisione 2015)

Per trapianto incrociato di rene da donatore vivente (cross-over) si intende *"l'evento in cui il donatore e il ricevente non sono compatibili per la presenza di anticorpi anti HLA o anti- ABO o per altri motivi di incompatibilità ed è preclusa la procedura standard di trapianto da donatore vivente"*. In tal caso, e in presenza di almeno un'altra coppia in situazione analoga, i donatori e i riceventi, se biologicamente compatibili, si "incrociano",nella consapevolezza che gli esiti per i riceventi possano differire in termini di successo, e che la cessione dopo il trapianto sia definitiva ed irrevocabile

2.2 Il trapianto di rene da donatore vivente in modalità incrociata è consentito quando donatore e ricevente *non sono compatibili per la presenza di anticorpi anti HLA o anti- ABO o per altri motivi di incompatibilità ed è preclusa la procedura standard di trapianto da donatore vivente.*

3.2 L'identificazione delle nuove coppie donatore/ricevente da trapiantare in modalità crociata deve rispondere ai seguenti criteri:

- compatibilità di gruppo sanguigno (ABO)
- Negatività del cross match eseguito con tecnica di linfocitotossicità complemento-mediata e/o con tecnica citofluorimetrica

3.3 L'abbinamento delle varie coppie tiene inoltre conto dei seguenti parametri di scelta:

a) criterio geografico (a parità di condizioni di cui al punto 3.2 tra più possibili abbinamenti si privilegia la coppia geograficamente più vicina)

b) fasce di età

c) disparità di peso corporeo (Body Mass Index)

d) mismatch HLA.

3.5 Sia prima che dopo aver completato l'iter valutativo, i centri confronteranno tutti gli elementi clinici raccolti e si accorderanno per i futuri step organizzativi. I Centri concorderanno la data dei trapianti e tutti i dettagli organizzativi ,tenendo conto che la contemporaneità appare condizione auspicabile per garantire ad ogni soggetto coinvolto il completamento della procedura di prelievo e trapianto.

Il trapianto secondo modalità crociata tra due o più coppie di soggetti dovrà essere effettuato, sempre ed esclusivamente in strutture autorizzate al trapianto da donatore vivente. Nel caso in cui uno dei due trapianti non venisse effettuato, al ricevente non trapiantato verrà data una priorità, nella lista d'attesa nazionale d'urgenza e/o PNI come da nuovi criteri di assegnazione, già approvati dal Centro Nazionale Trapianti.

A.Trasmissione al Centro Nazionale Trapianti della seguente documentazione, possibilmente mediante posta certificata .....

Tipizzazione HLA del DONATORE e del RICEVENTE per i loci HLA-A, -B, -C, -DR, -DQ eseguita con tecnica genomica a bassa risoluzione. La tipizzazione tuttavia deve essere informativa per eventuali alleli corrispondenti a split sierologici

- % PRA di classe I e II del RICEVENTE, sia quello massimo che quello dell'ultimo siero;

- Specificità degli anticorpi anti-HLA presenti nel siero, identificate con tecnica Luminex-Single Antigen Beads di classe I e/o II. Vicino ad ogni specificità occorre riportare l'intensità di fluorescenza espressa in MFI

- referto di eventuale cross match eseguito sulla coppia

Tutti i referti devono essere inviati in copia conforme all'originale

B. Iscrizione nel registro unico nazionale gestito dal Centro Nazionale Trapianti e verifica dello stesso dei requisiti di ammissione

C. Individuazione delle coppie compatibili da parte del CNT

D. Esecuzione dei test di compatibilità presso il laboratorio di riferimento del programma

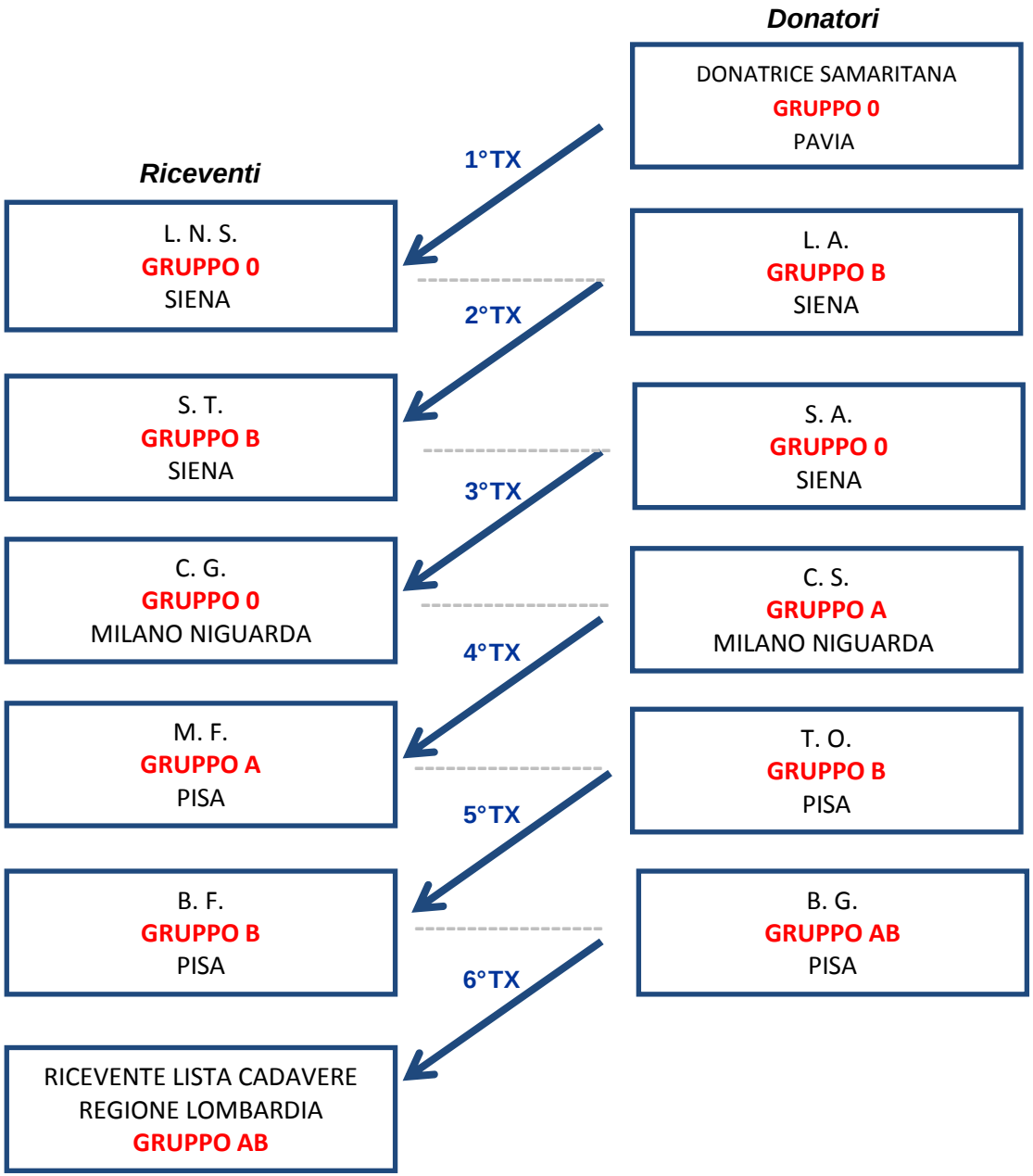
E. Valutazione delle nuove coppie da parte dei centri coinvolti

F. Accordo sulla data dei trapianti tra i centri coinvolti in modo da eseguirli in contemporaneità

G. inserimento nel registro unico nazionale degli atti, delle procedure seguite e dei follow-up dei donatori e dei riceventi.

NB *Una coppia potrà rifiutare le proposte che le saranno rivolte senza alcuna limitazione in relazione anche a scelte fiduciarie nei confronti dei centri proposti.*

Programma Nazionale Trapianto Cross-over



Cari Colleghi,
proviamo a programmare questa nuova lunga catena di trapianti con donatore samaritano.
Per esigenze di laboratorio, avrei pensato di scaglionare gli invii di cellule e sieri in due giornate:

1. Prima giornata: **Prelievo** il giorno **17/03** con **arrivo** nel nostro laboratorio **entro le ore 12.00** del giorno **18/03:**

- **NIT (Cardillo)**
1)Don. Samaritano (1a coppia della catena) = 20 ml di sangue periferico con anticoagulante (Eparina sodica o ACD);
2) Ric. C. G. (3a coppia della catena) = 1,5 ml di siero attuale (lo storico è già in nostro possesso);

- **Siena (Rombolà)**
3) Ric. L. N.S. (1a coppia della catena) = 1,5 ml di siero attuale (lo storico è già in nostro possesso);
4) Don. L. A. (2a coppia della catena) = 20 ml di sangue periferico con anticoagulante (Eparina sodica o ACD);
5) Ric. S. T. (2a coppia della catena) = 1,5 ml di siero attuale (lo storico è già in nostro possesso);
6) Don. S. A. (3a coppia della catena) = 20 ml di sangue periferico con anticoagulante (Eparina sodica o ACD);

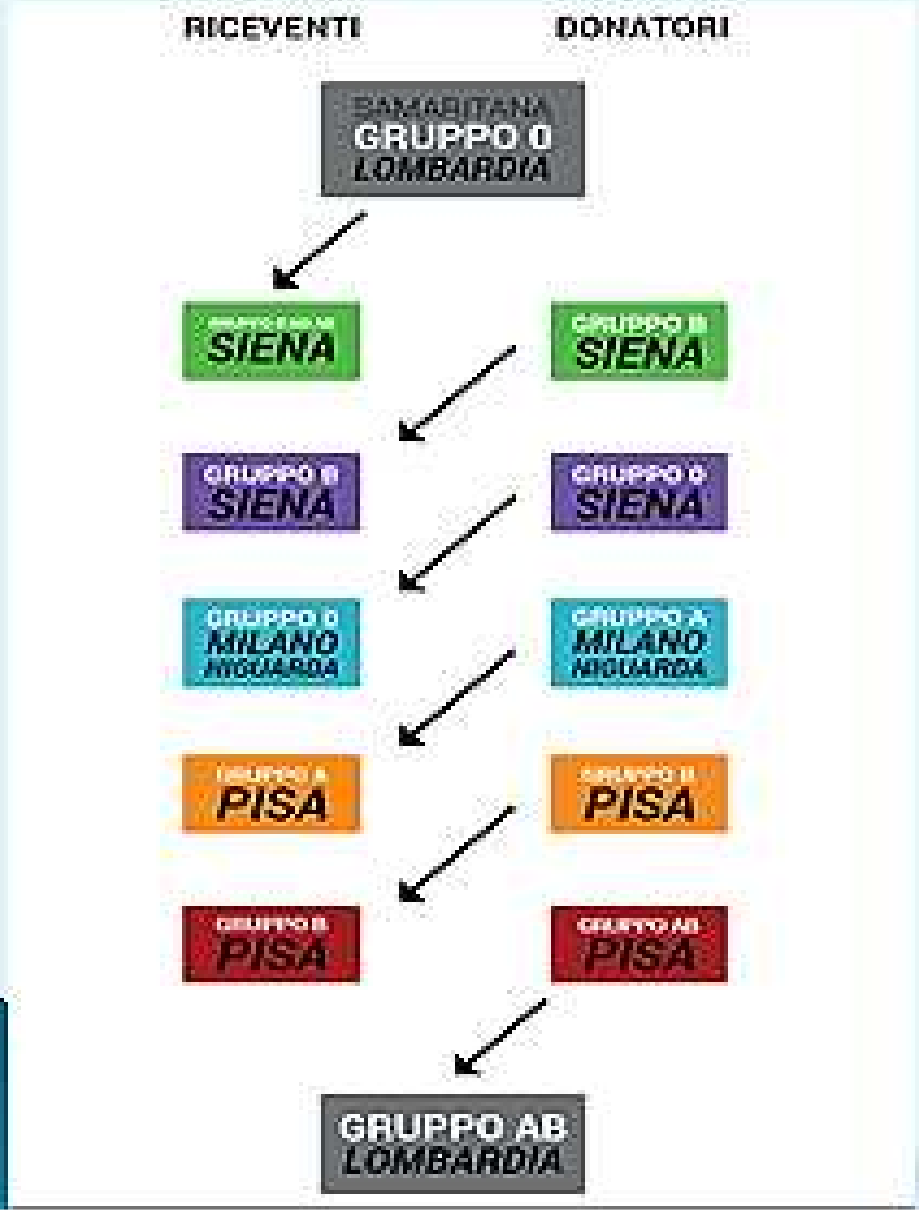
2. Seconda giornata: **Prelievo** il giorno **23/03** con **arrivo** nel nostro laboratorio **entro le ore 12.00** del giorno **24/03:**

- **NIT (Cardillo)**
1) Don. C. S. (4a coppia della catena) = 20 ml di sangue periferico con anticoagulante (Eparina sodica o ACD);
2) Ric. da lista cadavere gruppo AB (6a coppia della catena) = 1,5 ml di sieri (attuale e storico)

- **Pisa (Mariotti)**
1) Ric. M. F. (4a coppia della catena) = 1,5 ml di siero attuale (lo storico è già in nostro possesso);
2) Don. T. O. (5a coppia della catena) = 20 ml di sangue periferico con anticoagulante (Eparina sodica o ACD).
3) Ric. B. F. (5a coppia della catena) = 1,5 ml di sieri (attuale e storico);
4) Don. B. G. (6a coppia della catena) = 20 ml di sangue periferico con anticoagulante (Eparina sodica o ACD).

Grazie per la collaborazione,
Antonina Piazza

Centro Nazionale Trapianti



TEMPISTICA PER LA REALIZZAZIONE DELLA CATENA DI TRAPIANTI SECONDO MODALITÀ INCROCIATA PARTENDO DA UNA DONAZIONE SAMARITANA

Martedì 7 aprile 2015
Ore 8.00 Centro trapianti Lombardia: prelievo rene donatore samaritano.
Ore 11:30 Invio Rene a Siena
Ore 14:00 Centro trapianti Siena: trapianto rene ricevente prima coppia

Mercoledì 8 aprile 2015
Ore 8:30 Centro trapianti Siena: prelievo rene donatore prima coppia
Ore 12:00 Centro trapianti Siena: trapianto rene ricevente seconda coppia
Ore 14:00 Centro trapianti Siena: prelievo donatore seconda coppia
Ore 17:00 Invio rene a Milano
Ore 20:30 Centro trapianti Milano Niguarda: trapianto ricevente terza coppia

Giovedì 9 aprile 2015
Ore 9:00 centro trapianti Milano Niguarda: prelievo rene donatore terza coppia
Ore 11:30 Invio Rene a Pisa
Ore 14:00 Centro trapianti Pisa (sala 1): trapianto rene ricevente quarta coppia
Ore 14:00 Centro trapianti Pisa (sala 2): prelievo rene donatore quarta coppia
Ore 15:00 Centro trapianti Pisa (sala3): prelievo donatore quinta coppia
Ore 15:30 Centro trapianti Pisa (sala 4): trapianto ricevente quinta coppia
Ore 18:00 (da confermare) Invio Rene a Milano
Ore 21:00 (da confermare) Centro trapianti Policlinico Milano: trapianto ricevente iscritto nella lista da cadavere

Ore 1:00 La prima catena cross-over da donatore samaritano si chiude!


POLIZIA

Laboratorio di Tipizzazione Tissutale ed Immunologia dei Trapianti – CRT Lazio

<u>Analisi di Anticorpi</u> :

Elvira Poggi

Anna Rita Manfreda

Lucia Spano

Antonio Bianculli

Damiano Colasante

<u>Tipizzazione HLA</u>:

Giuseppina Ozzella

Silvia Sinopoli

Andrea Giaffreda

Maria Rosaria Fazio

Grazie