How to overcome ABO and HLA barrier in living donor kidney transplantation

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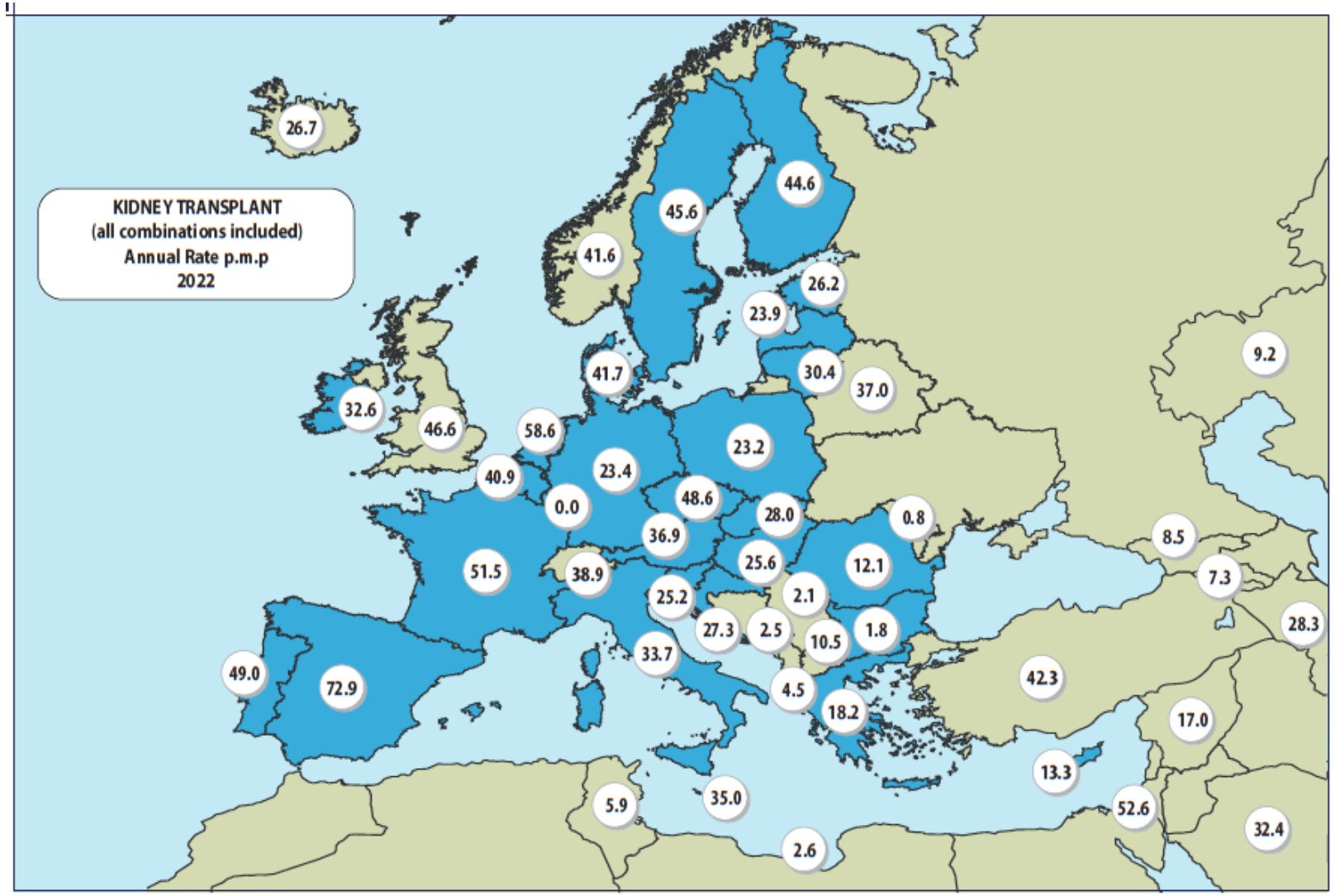
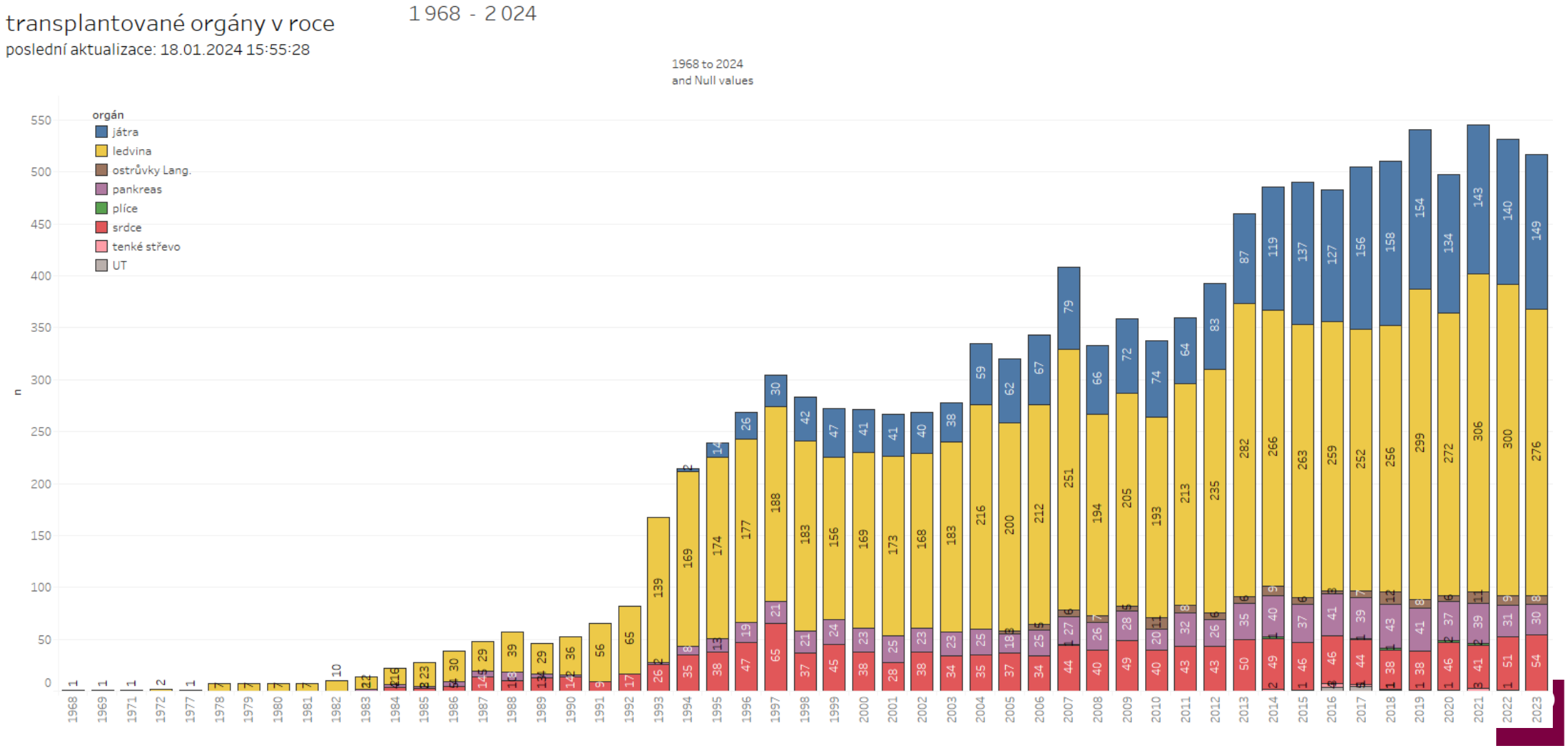
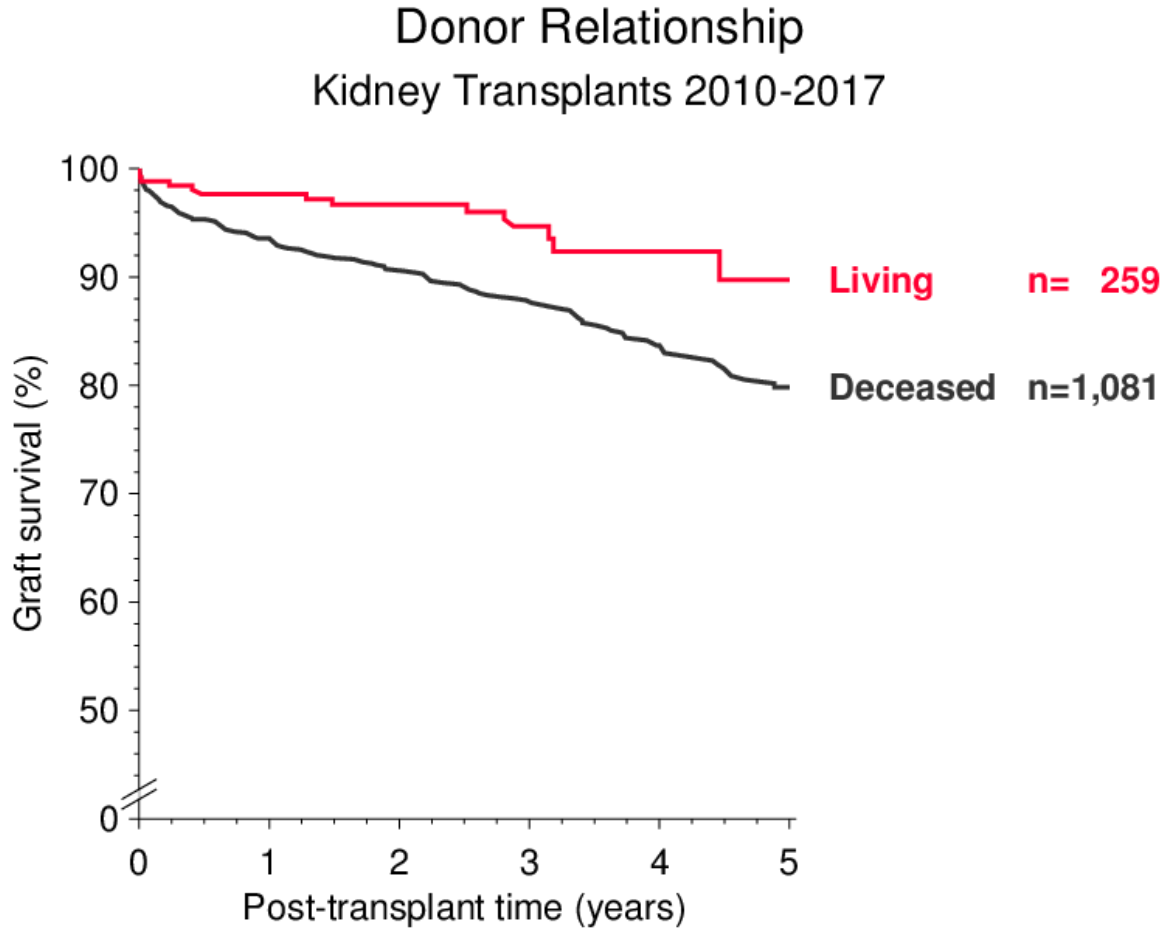
Kidney transplantation in Europe 2022



Organ transplantation at IKEM



Better outcome of living donor kidney transplantation

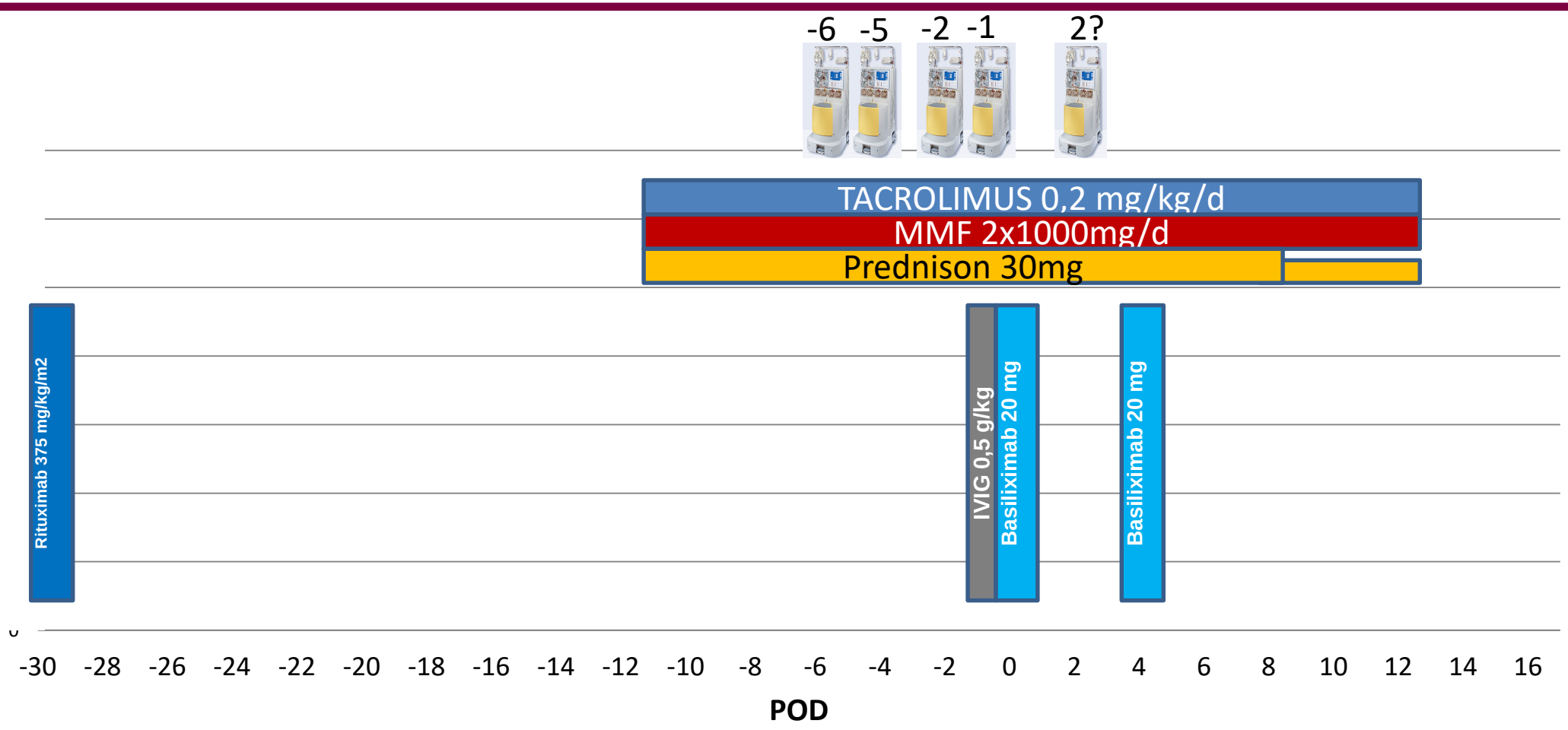


How to allow incompatible pairs transplantation?

- For AB0 incompatibility
  - Kidney paired donation (KPD)
  - AB0 incompatible transplantation
  - Deceased donor transplantation (waiting time?)

- For HLA incompatibility
  - Desensitization prior to living donor transplantation in some cases
  - Kidney paired donation (KPD) in some cases
  - Acceptable mismatch program for deceased donor transplantation

AB0i kidney transplantation at IKEM: protocol



Outcomes of AB0i kidney transplantation

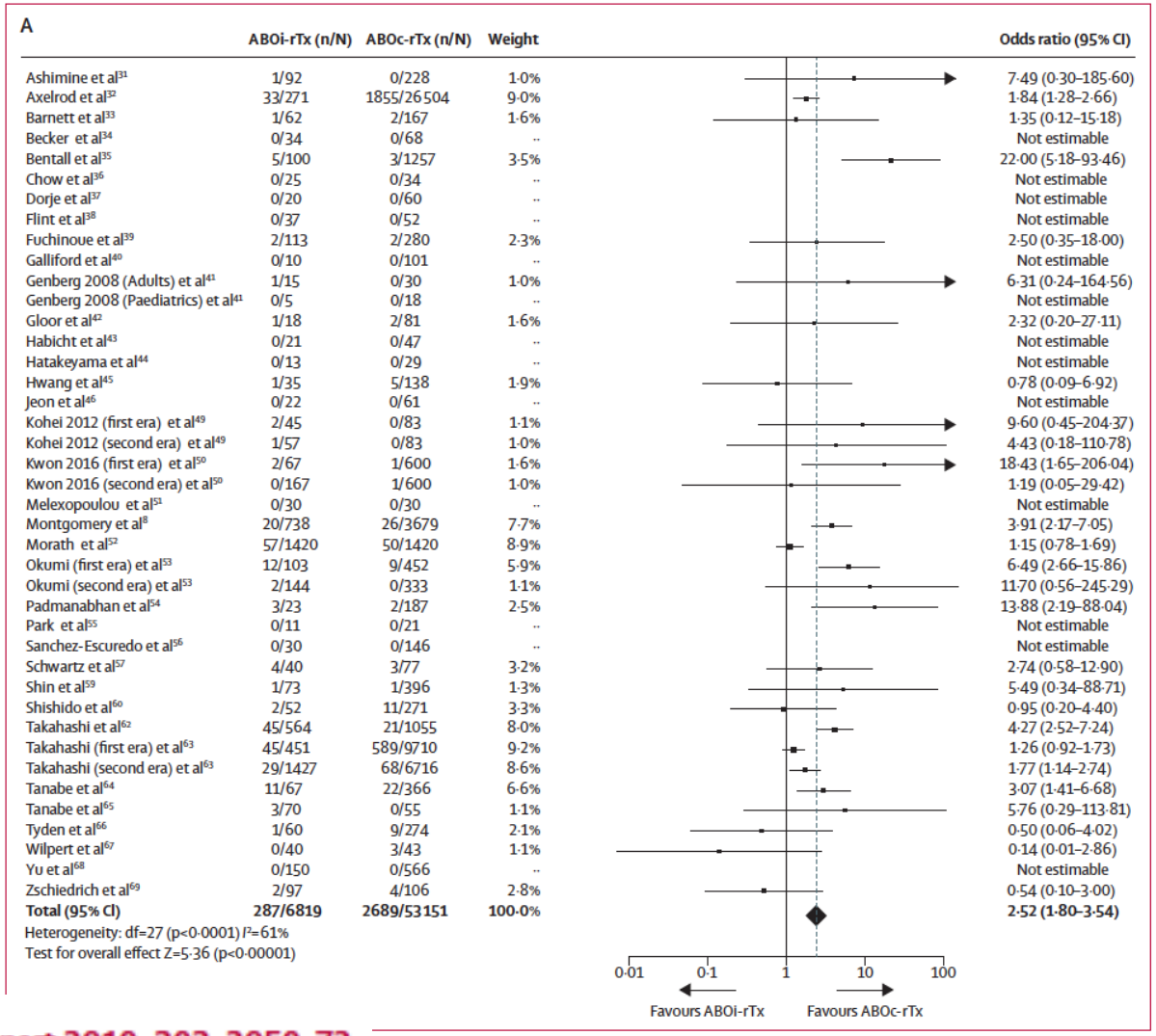
TABLE 4. Patient and graft survival among 60 ABOi kidney transplant recipients transplanted at the Johns Hopkins Hospital between 1999 and 2007

	ABOi cohort	
Years posttransplant	Graft survival[a] (%)	Patient survival[b] (%)
1 yr	98.3	96.3
3 yr	92.9	96.3
5 yr	88.7	89.4

Montgomery, Transplantation 2009; 87: 1246-1255

IK+E M

Higher risk of graft loss after AB0i kidney transplantation at 12 months: Lancet meta-analysis



A

	ABOi-rTx (n/N)	ABOc-rTx (n/N)	Weight	Odds ratio (95% CI)
Ashimine et al[31]	1/92	0/228	1·0%	7·49 (0·30–185·60)
Axelrod et al[32]	33/271	1855/26 504	9·0%	1·84 (1·28–2·66)
Barnett et al[33]	1/62	2/167	1·6%	1·35 (0·12–15·18)
Becker et al[34]	0/34	0/68	..	Not estimable
Bentall et al[35]	5/100	3/1257	3·5%	22·00 (5·18–93·46)
Chow et al[36]	0/25	0/34	..	Not estimable
Dorje et al[37]	0/20	0/60	..	Not estimable
Flint et al[38]	0/37	0/52	..	Not estimable
Fuchinoue et al[39]	2/113	2/280	2·3%	2·50 (0·35–18·00)
Galliford et al[40]	0/10	0/101	..	Not estimable
Genberg 2008 (Adults) et al[41]	1/15	0/30	1·0%	6·31 (0·24–164·56)
Genberg 2008 (Paediatrics) et al[41]	0/5	0/18	..	Not estimable
Gloor et al[42]	1/18	2/81	1·6%	2·32 (0·20–27·11)
Habicht et al[43]	0/21	0/47	..	Not estimable
Hatakeyama et al[44]	0/13	0/29	..	Not estimable
Hwang et al[45]	1/35	5/138	1·9%	0·78 (0·09–6·92)
Jeon et al[46]	0/22	0/61	..	Not estimable
Kohei 2012 (first era) et al[49]	2/45	0/83	1·1%	9·60 (0·45–204·37)
Kohei 2012 (second era) et al[49]	1/57	0/83	1·0%	4·43 (0·18–110·78)
Kwon 2016 (first era) et al[50]	2/67	1/600	1·6%	18·43 (1·65–206·04)
Kwon 2016 (second era) et al[50]	0/167	1/600	1·0%	1·19 (0·05–29·42)
Melexopoulou et al[51]	0/30	0/30	..	Not estimable
Montgomery et al[8]	20/738	26/3679	7·7%	3·91 (2·17–7·05)
Morath et al[52]	57/1420	50/1420	8·9%	1·15 (0·78–1·69)
Okumi (first era) et al[53]	12/103	9/452	5·9%	6·49 (2·66–15·86)
Okumi (second era) et al[53]	2/144	0/333	1·1%	11·70 (0·56–245·29)
Padmanabhan et al[54]	3/23	2/187	2·5%	13·88 (2·19–88·04)
Park et al[55]	0/11	0/21	..	Not estimable
Sanchez-Escuredo et al[56]	0/30	0/146	..	Not estimable
Schwartz et al[57]	4/40	3/77	3·2%	2·74 (0·58–12·90)
Shin et al[59]	1/73	1/396	1·3%	5·49 (0·34–88·71)
Shishido et al[60]	2/52	11/271	3·3%	0·95 (0·20–4·40)
Takahashi et al[62]	45/564	21/1055	8·0%	4·27 (2·52–7·24)
Takahashi (first era) et al[63]	45/451	589/9710	9·2%	1·26 (0·92–1·73)
Takahashi (second era) et al[63]	29/1427	68/6716	8·6%	1·77 (1·14–2·74)
Tanabe et al[64]	11/67	22/366	6·6%	3·07 (1·41–6·68)
Tanabe et al[65]	3/70	0/55	1·1%	5·76 (0·29–113·81)
Tyden et al[66]	1/60	9/274	2·1%	0·50 (0·06–4·02)
Wilpert et al[67]	0/40	3/43	1·1%	0·14 (0·01–2·86)
Yu et al[68]	0/150	0/566	..	Not estimable
Zschiedrich et al[69]	2/97	4/106	2·8%	0·54 (0·10–3·00)
Total (95% CI)	**287/6819**	**2689/53151**	**100·0%**	**2·52 (1·80–3·54)**

Heterogeneity: df=27 (p<0·0001) I^2=61%

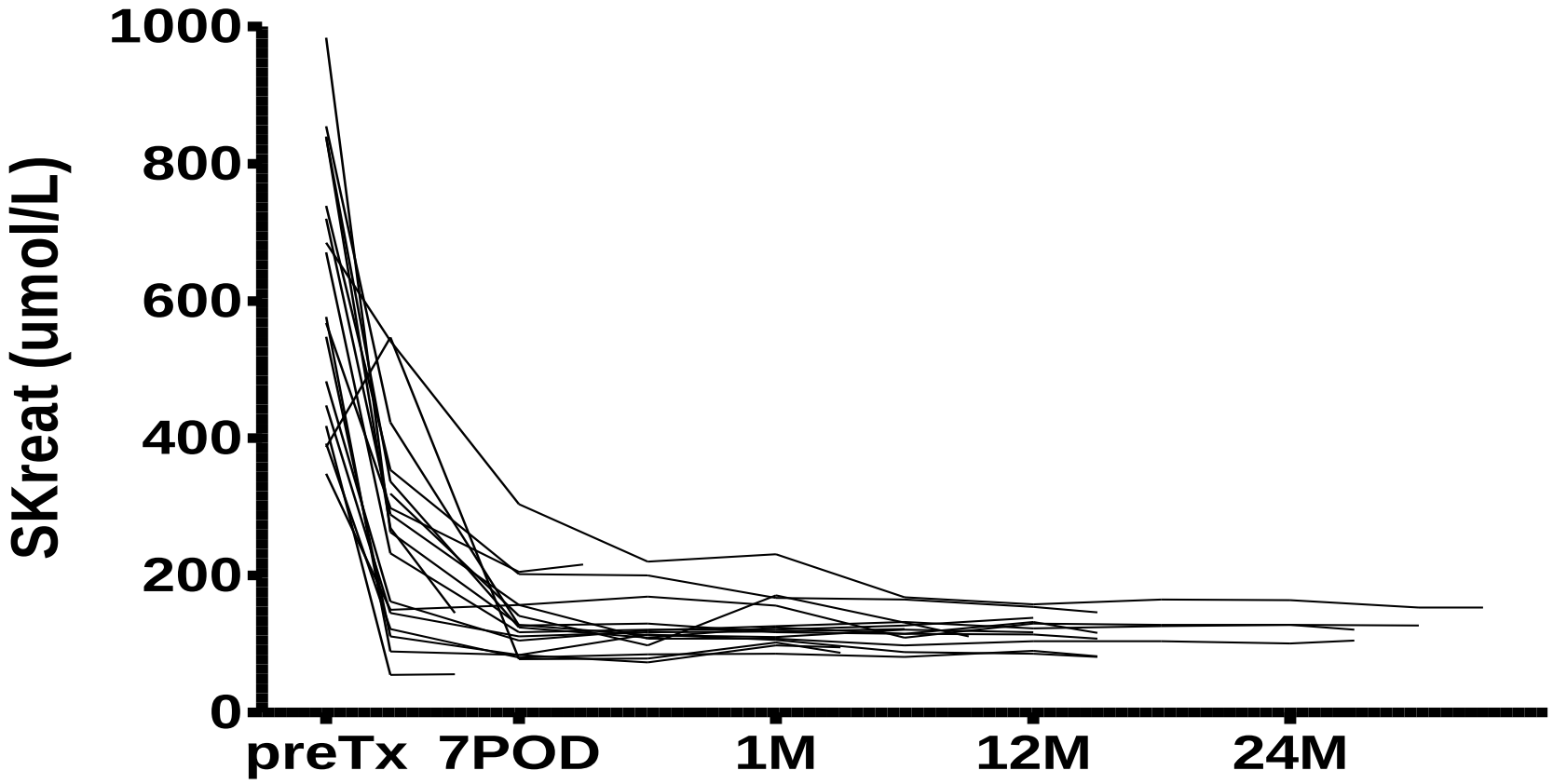
Test for overall effect Z=5·36 (p<0·00001)

Lancet 2019; 393: 2059–72

Clinical outcomes after ABO-incompatible renal transplantation: a systematic review and meta-analysis

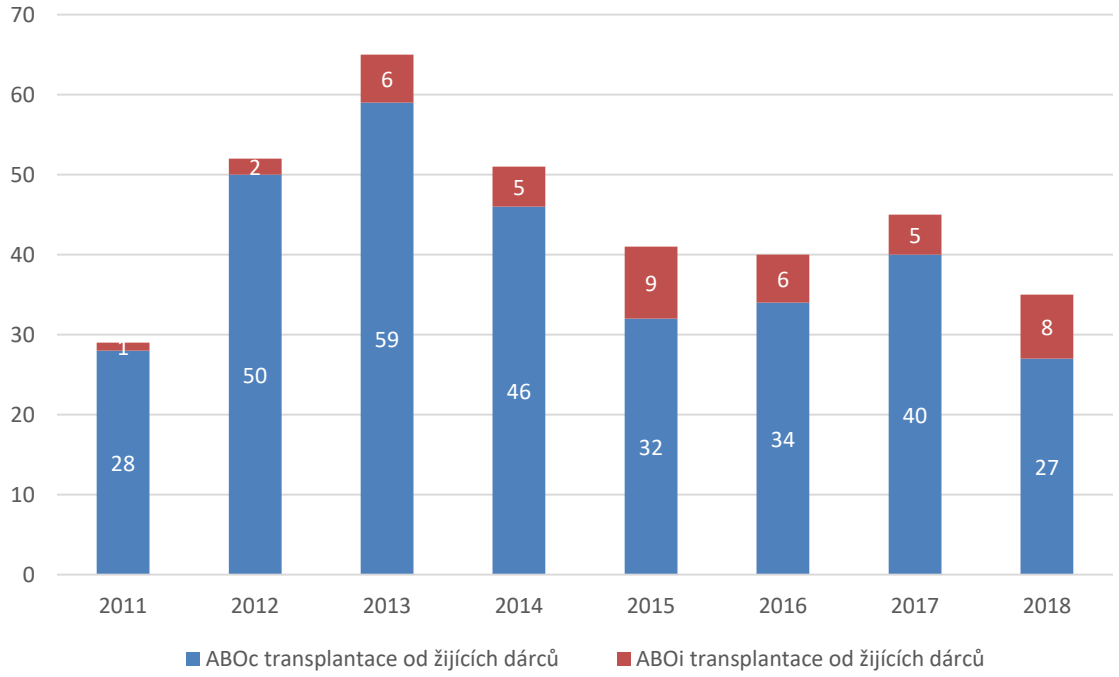
Florian G Scurt, Lara Ewert, Peter R Mertens, Hermann Haller, Bernhard M W Schmidt, Christos Chatzikyrkou

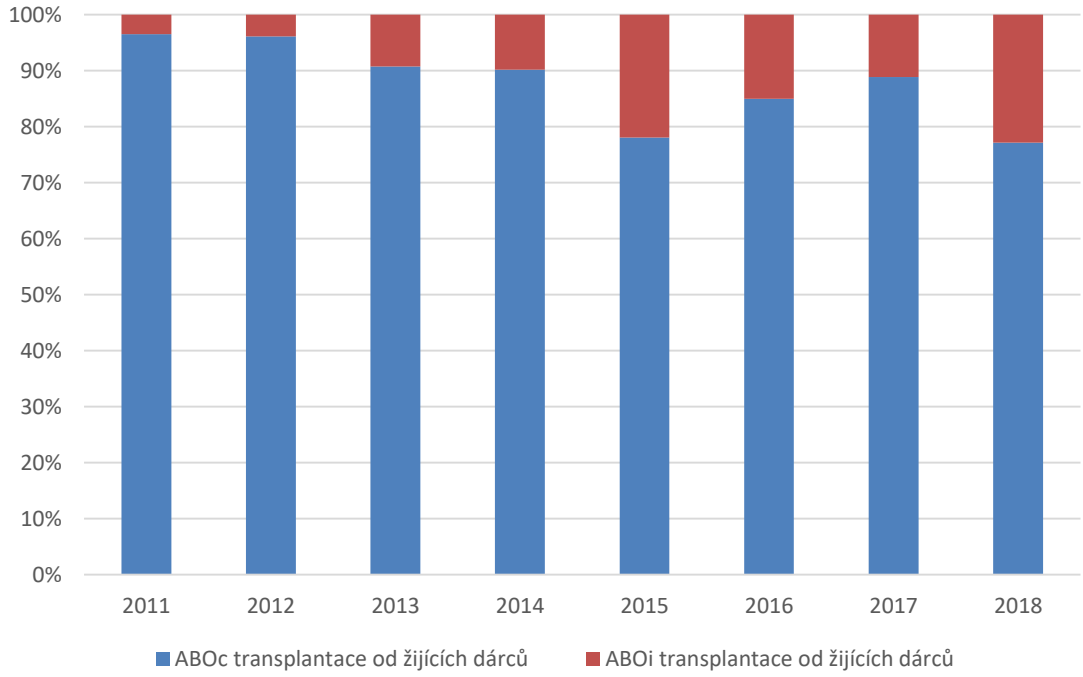
Initial experiences with AB0i kidney transplantation at IKEM



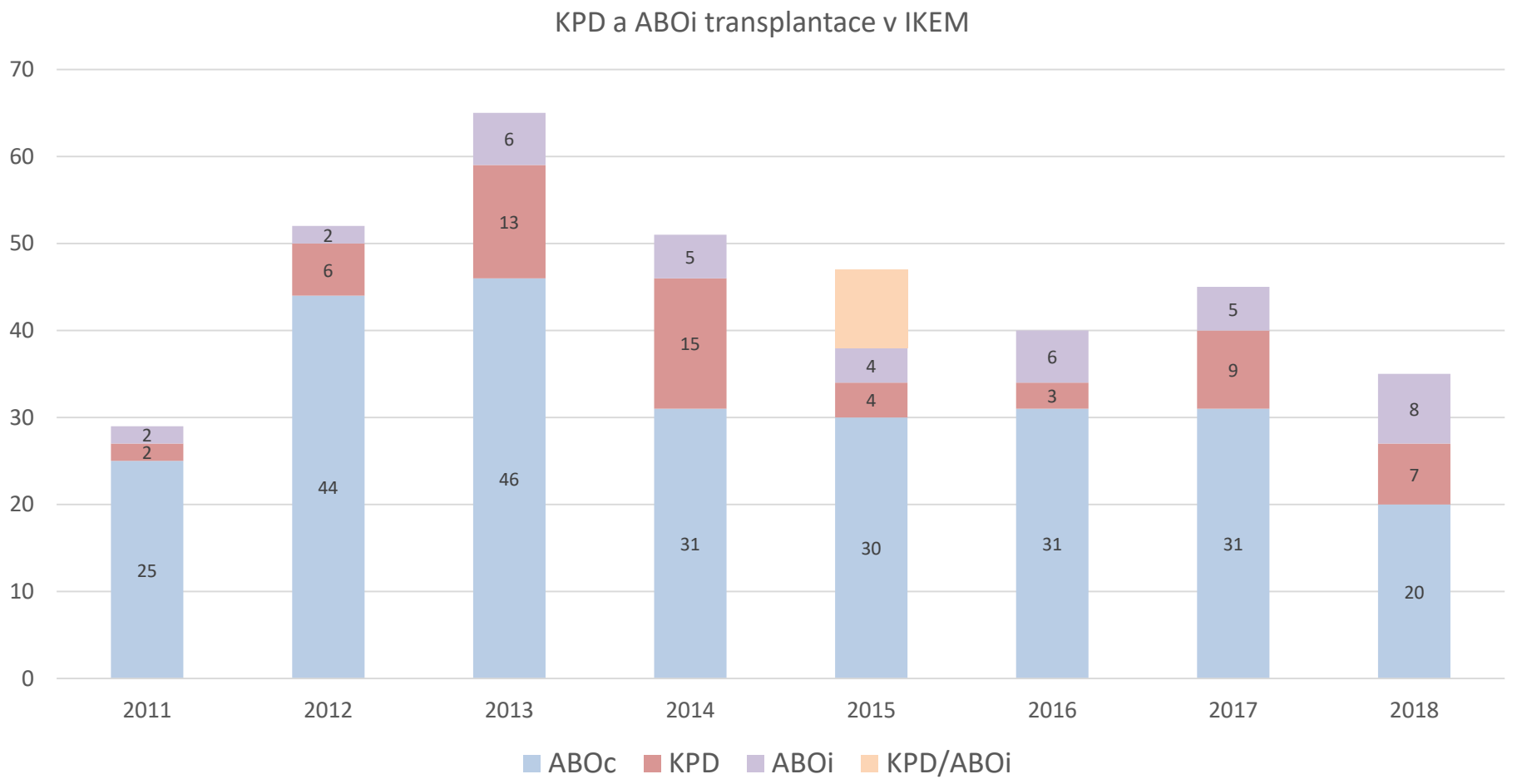
Viklicky O. et al., Vnitřní lékařství 2017

AB0i kidney transplantation at IKEM 2011-2018: 42 *(13,7%)*





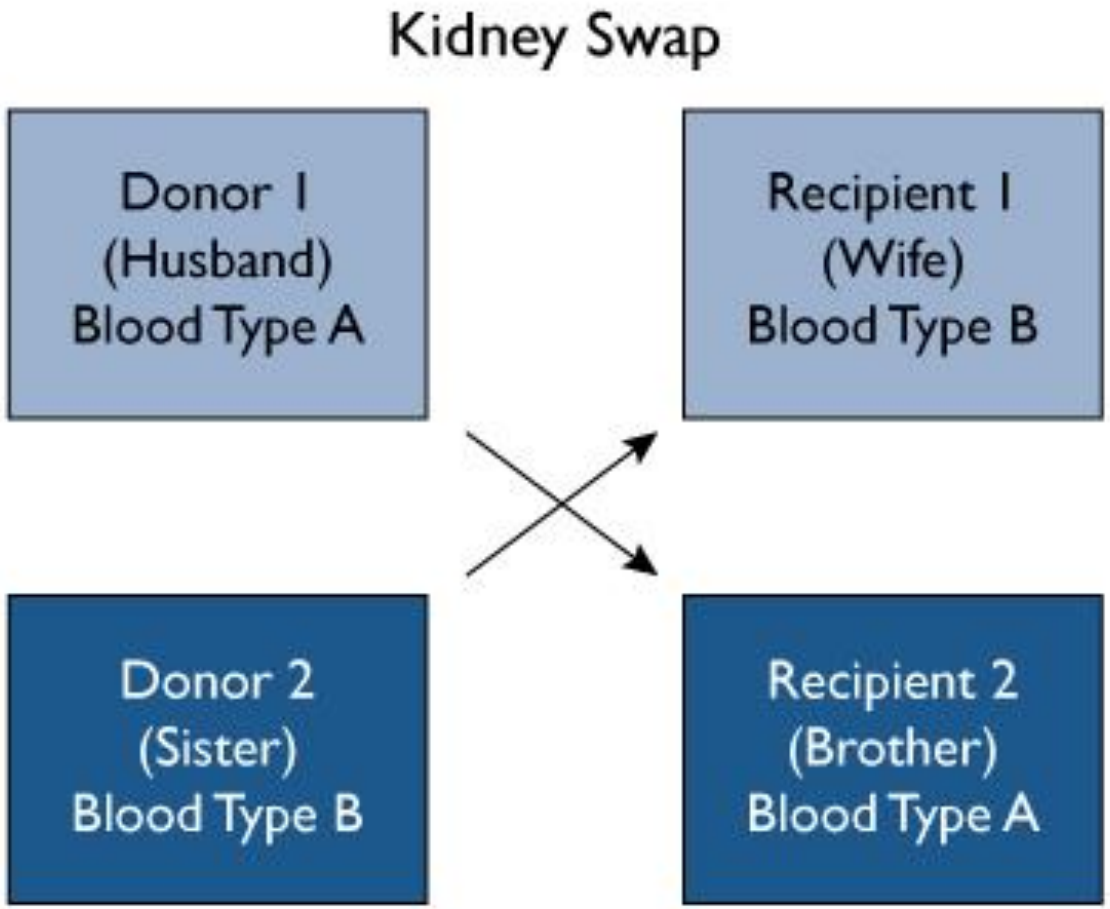
KPD/AB0i TX represent some 30-40% of living donor kidney transplant program



Kidney paired donation (KPD)

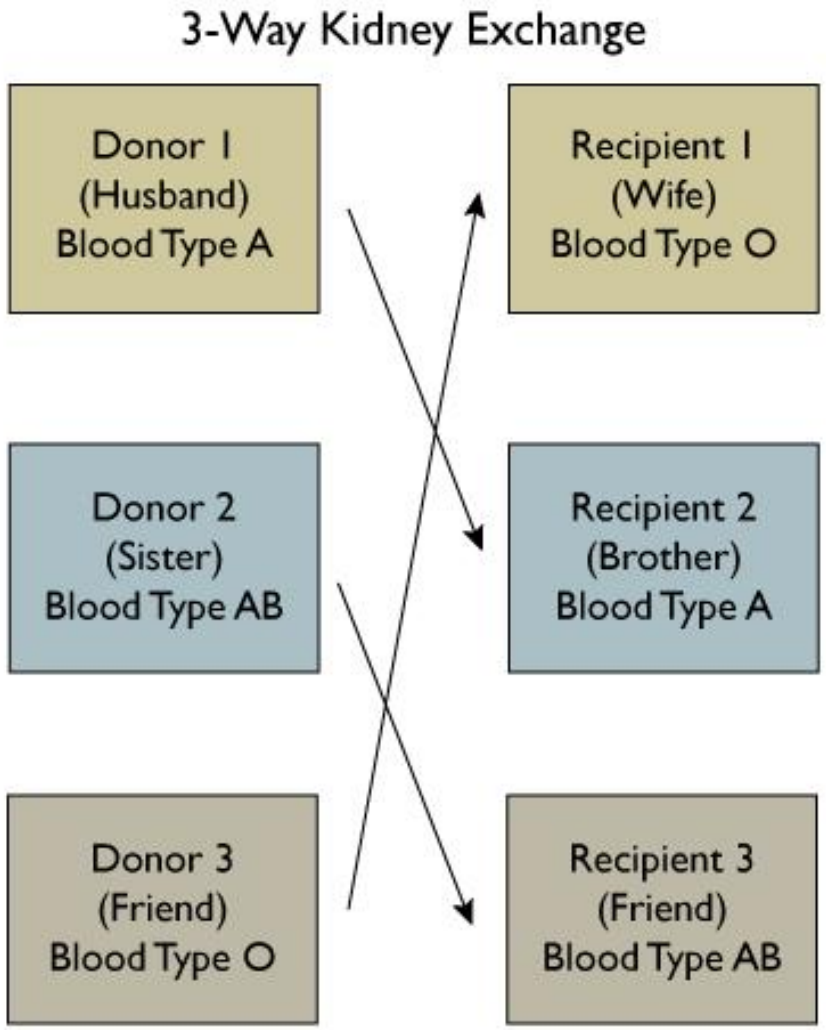
- 1986
  - Rapaport first proposes KPD to overcome immunologic incompatibility with live kidney donors
- 1991
  - Establishment of KPD program at Yonsei Univ in S. Korea
- 1998
  - Successful use of Plasmapheresis/IVIg to overcome immunologic incompatibility – Johns Hopkins Univ. – February
  - First international presentation of Korean PKE Program – ASTP - May
- 2001
  - First KPD Johns Hopkins U – Legal Dept. requirement to anesthetize donors simultaneously
- 2003
  - Establishment of Dutch "Crossover Transplantation Program"
- 2007
  - Rees removes logistical constraint of simultaneous operations with Nonsimultaneous, Extended, Altruistic-Donor Chain
  - Utilization of compatible donor/recipient pairs to facilitate KPD for incompatible donor/recipient pairs
- 2008
  - National Kidney Registry established
- 2010
  - UNOS KPD program

Paired exchange



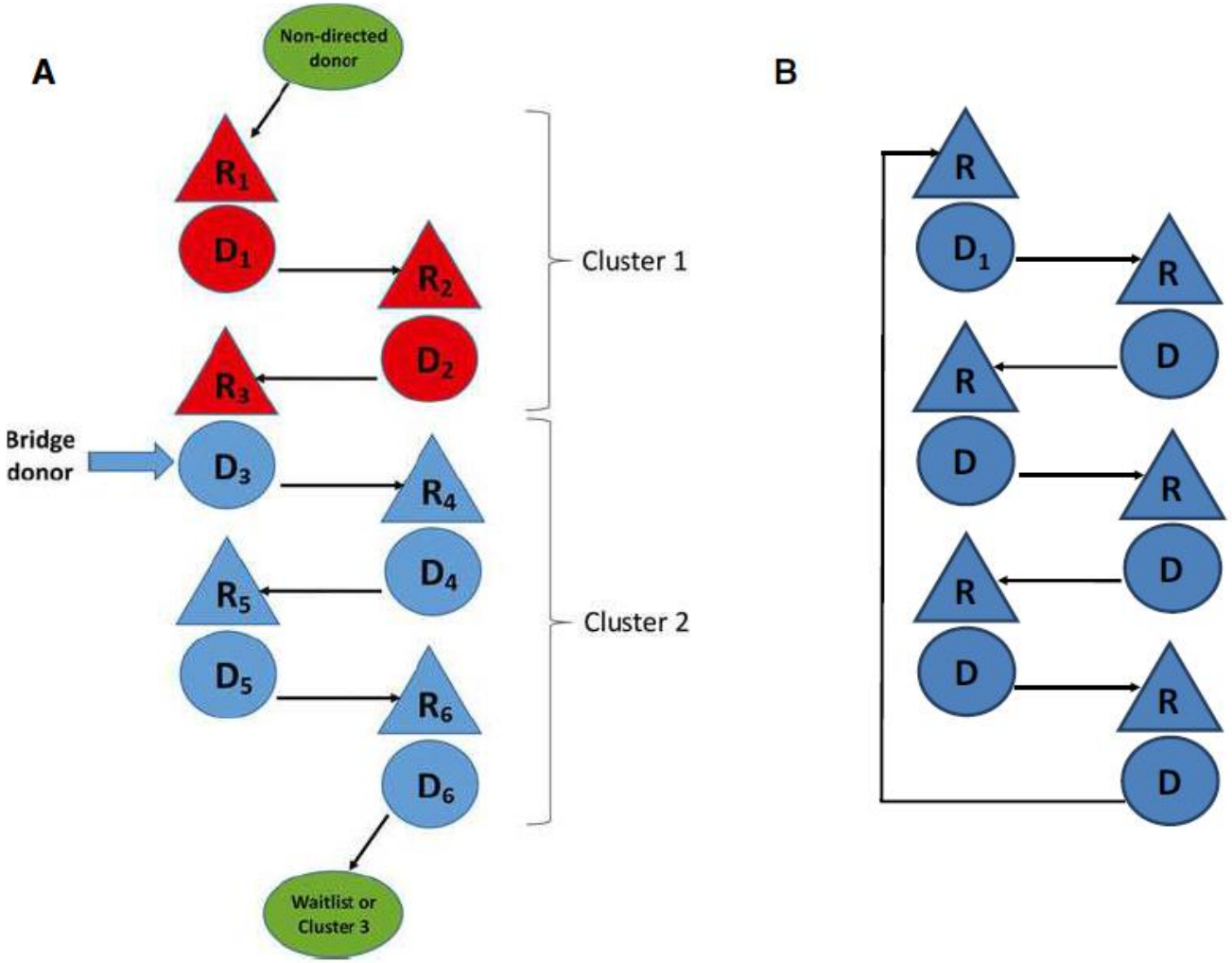
http://www.hopkinsmedicine.org/transplant

3-Way Kidney Exchange



http://www.hopkinsmedicine.org/transplant

Examples of chains with bridging donors and loop



American Journal of Transplantation 2017; 17: 2451–2457

Estimated number of match runs needed to have a 95% probability of finding acceptable donor based on cPRA

cPRA, %	Theoretical number of match runs to have a 95% chance of finding an acceptable donor
10	2
20	
30	
	59
	300
99.5	600
99.9	3000
99.99	30,000
99.999	300,000

Not realistic for any system…
Desensitization or implementation of AM necessary

Keith and Vranic. Clin J Am Soc Nephrol 11: 684–693, 2016.

Problems of small volume paired exchange program

- „0“ recipients hardly find a matched donor
- Poorer HLA match than in deceased donor program > cause sensitization
- Sensitized patients hardly find a matched HLA compatible donor

Shipping of living donor kidneys is associated with some CIT

N=1267 shipped kidneys, distance 1,5-2717 miles

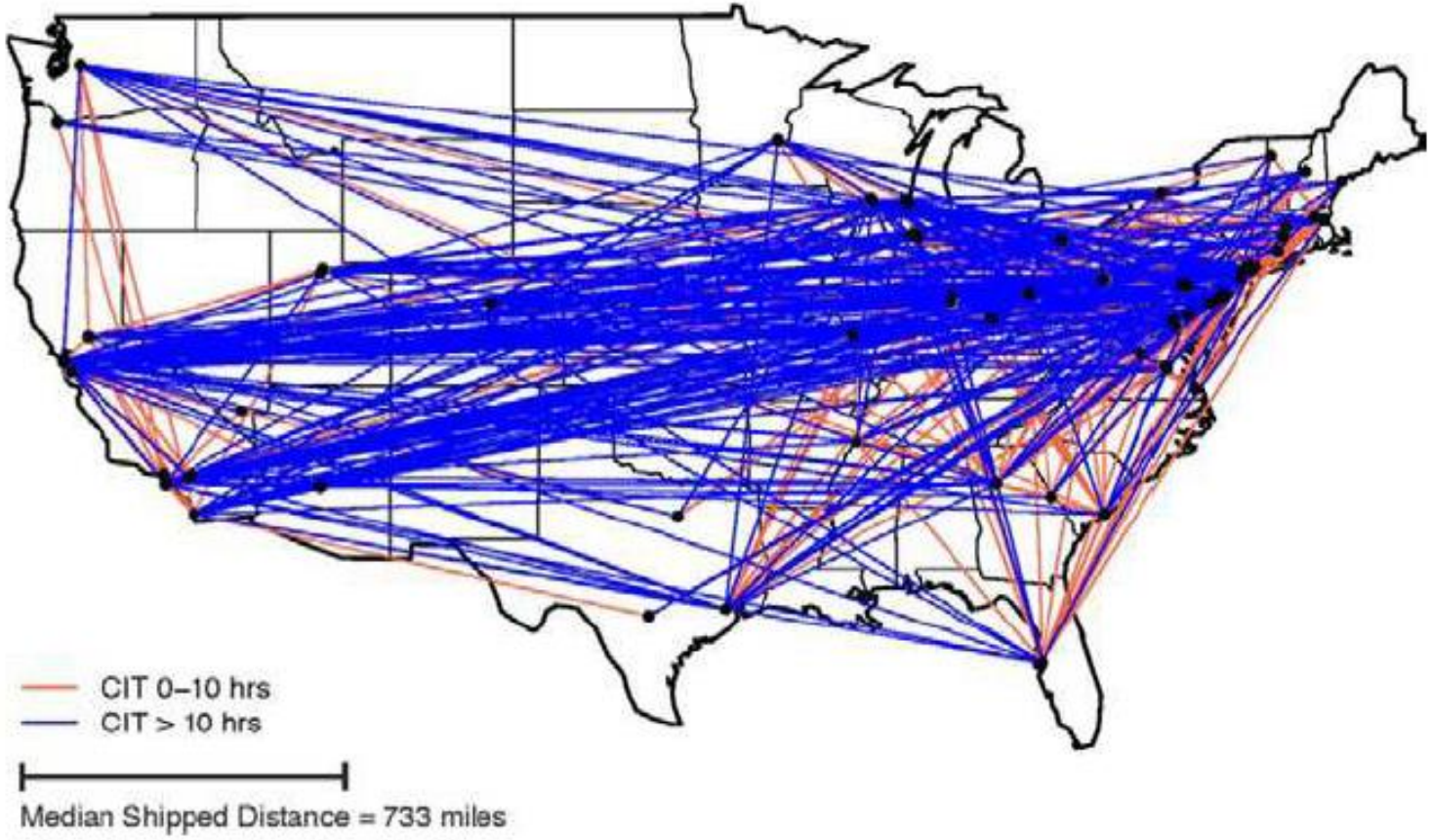
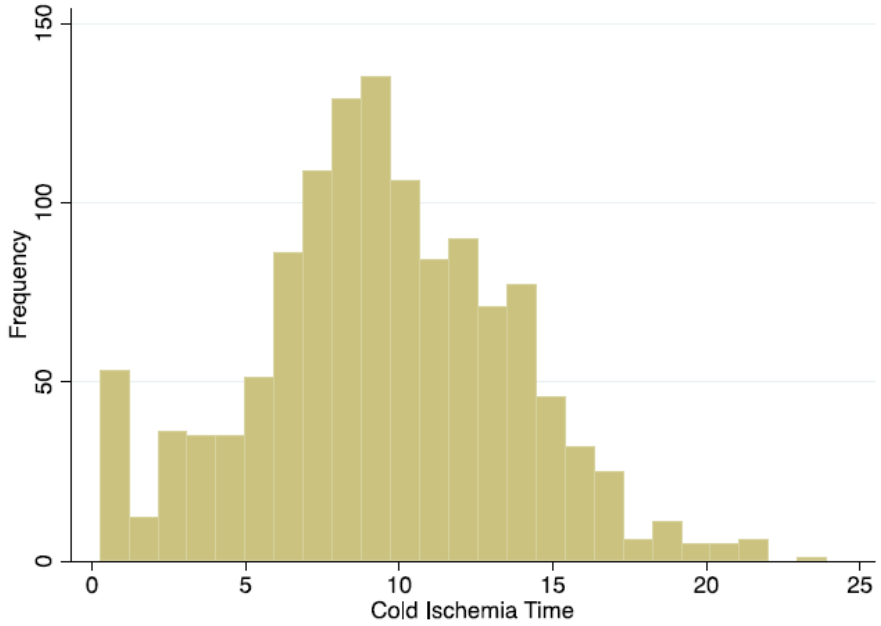
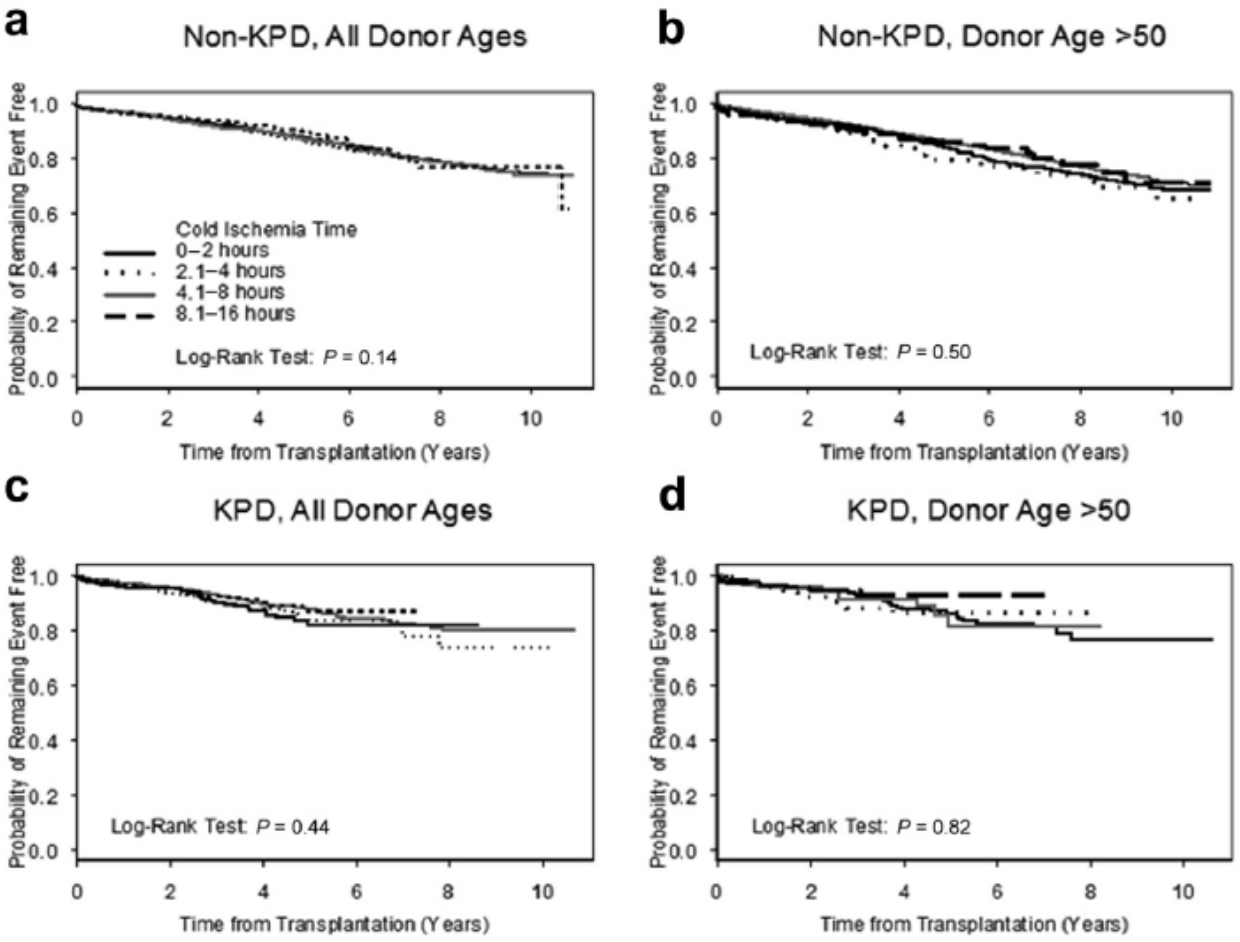


FIGURE 2 (A) Cold ischemia time of shipped kidney paired donation transplants. (B) Cold ischemia time of in-center kidney



Am J Transplant. 2018;18:632–641.

CIT up to 16 hours has no effect on living donor kidney graft survival



clinical investigation www.kidney-international.org

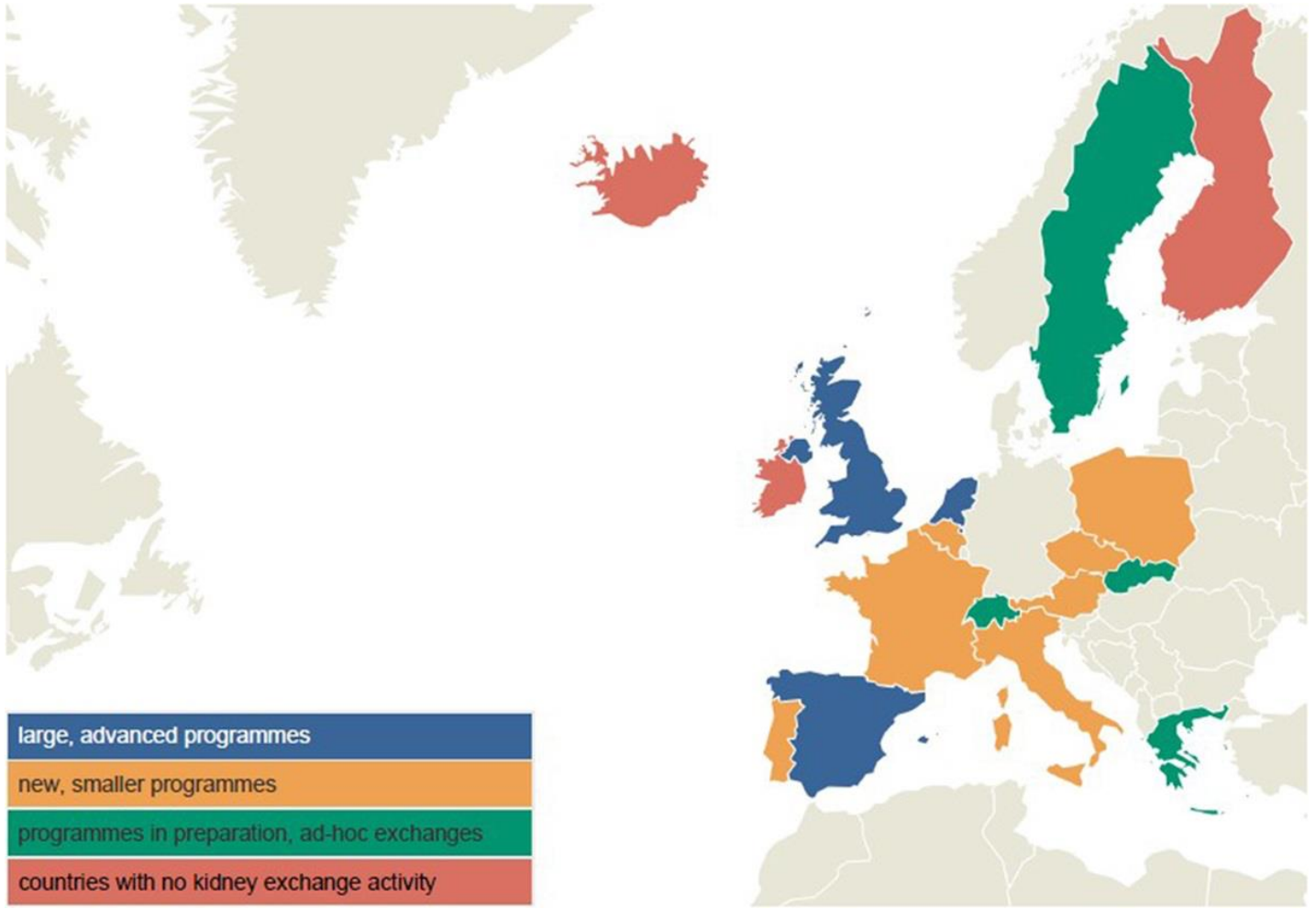
Cold ischemia time up to 16 hours has little impact on living donor kidney transplant outcomes in the era of kidney paired donation

Jagbir Gill[1,2], Caren Rose[1,2], Yayuk Joffres[1], Matthew Kadatz[1] and John Gill[1,2,3]

[1]Division of Nephrology, University of British Columbia, Vancouver, British Columbia, Canada; [2]Center for Health Evaluation and Outcomes Sciences, Vancouver, British Columbia, Canada; and [3]Tufts–New England Medical Center, Boston, Massachusetts, USA

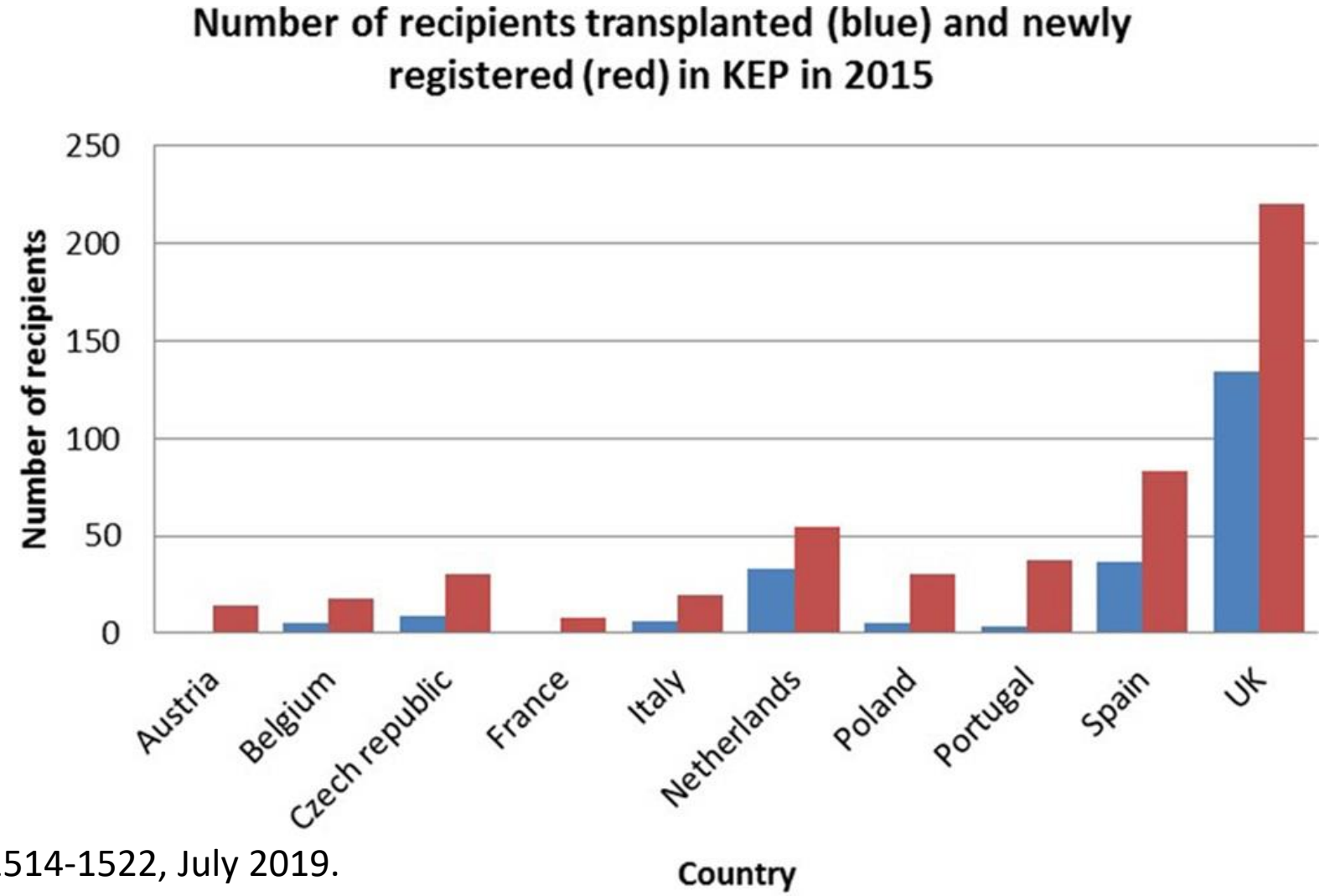
Kidney International (2017) **92,** 490–496

Developments of KPD programs in Europe

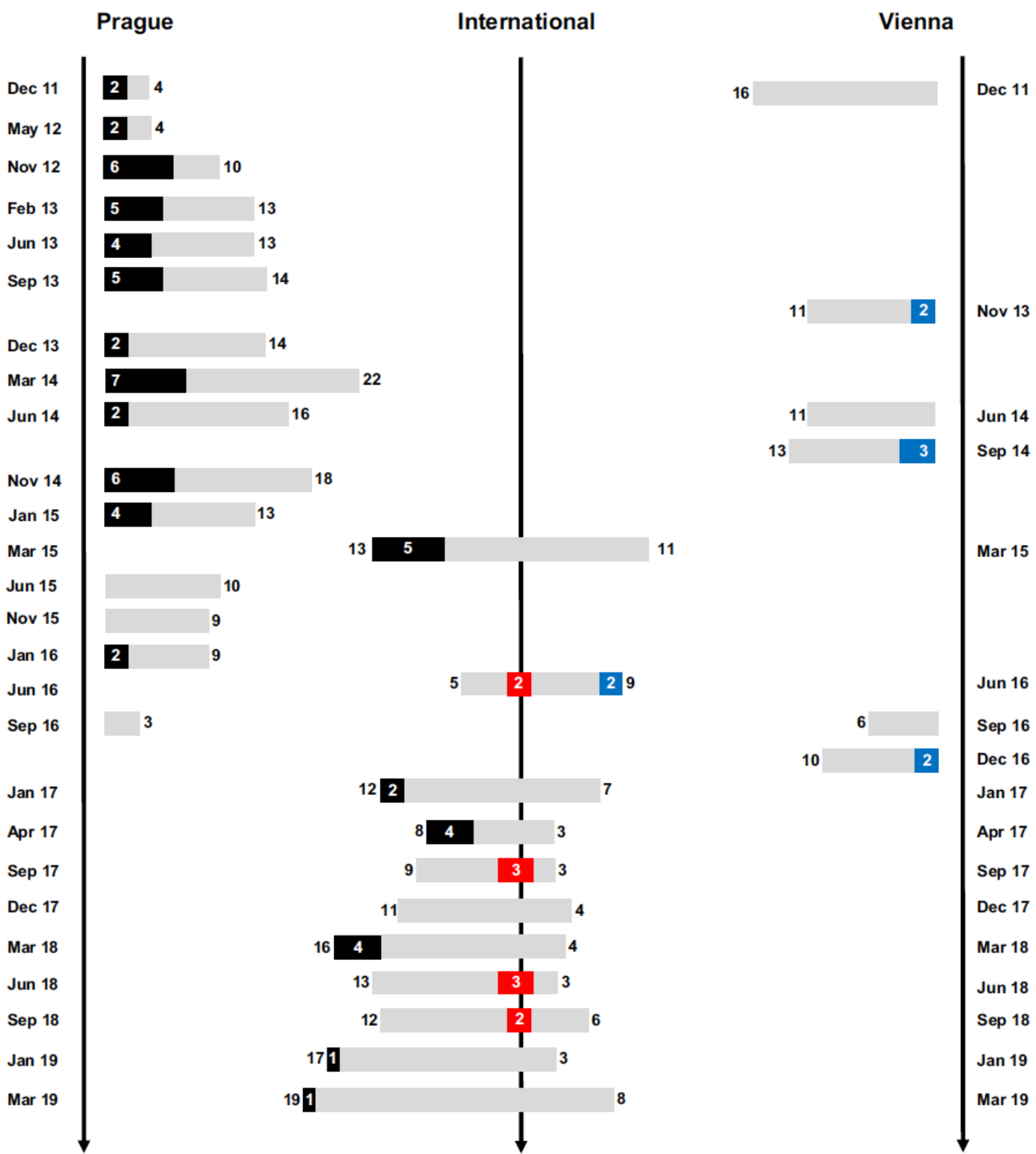


Transplantation103(7):1514-1522, July 2019.

KPD programs in Europe



Transplantation103(7):1514-1522, July 2019.



KPD programs: Prague and Vienna

Transplant International

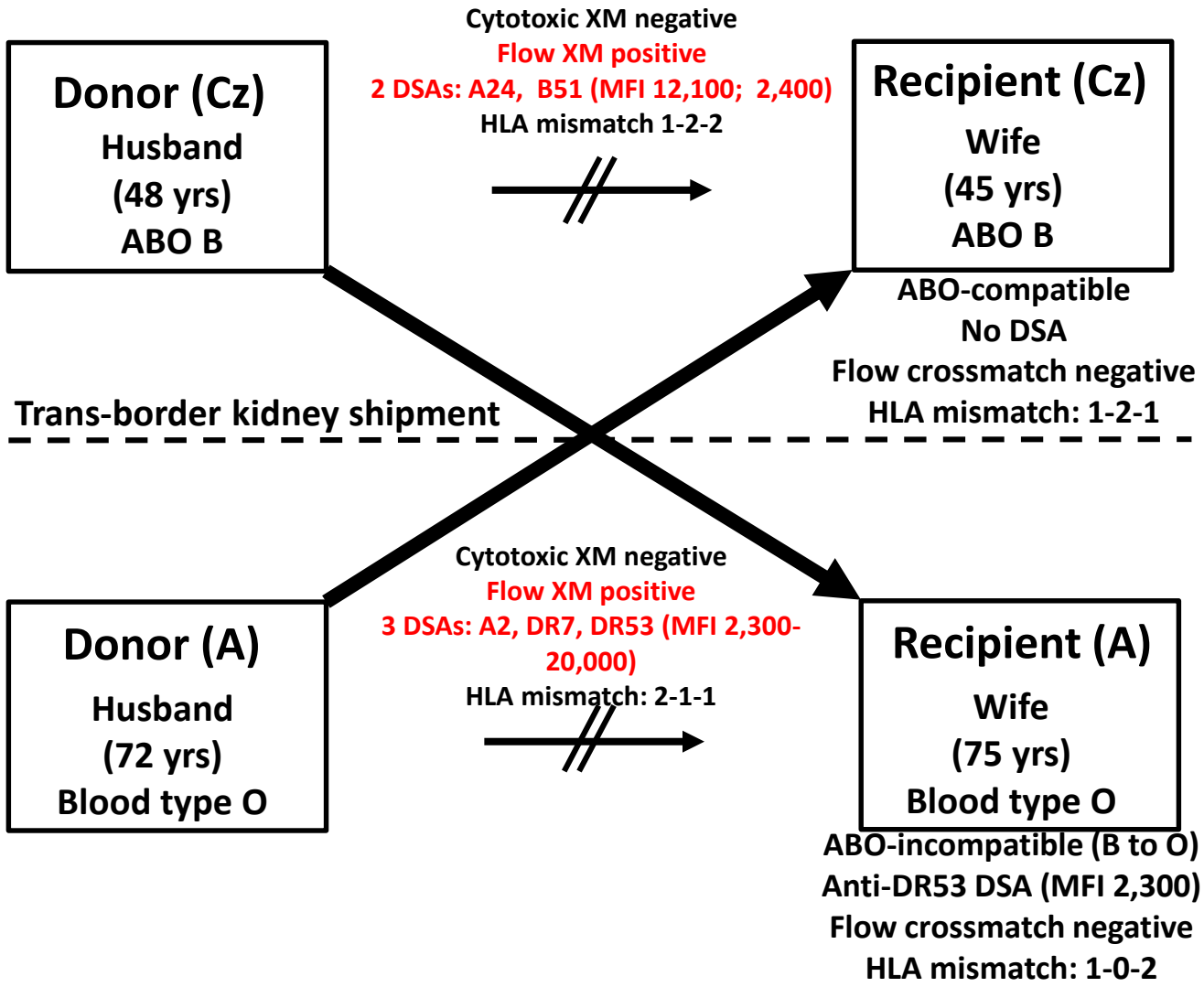
ORIGINAL ARTICLE

Crossing borders to facilitate live donor kidney transplantation: the Czech-Austrian kidney paired donation program – a retrospective study

Ondrej Viklicky[1], Sebastian Krivanec[2], Hana Vavrinova[1], Gabriela Berlakovich[3], Tomas Marada[4], Janka Slatinska[1], Tereza Neradova[4], Renata Zamecnikova[4], Andreas Salat[3], Michael Hofmann[3], Gottfried Fischer[5], Antonij Slavcev[6], Pavel Chromy[4], Rainer Oberbauer[2], Tomas Pantoflicek[4], Sabine Wenda[5], Elisabeth Lehner[2], Ingrid Fae[5], Paolo Ferrari[7,8,9], Jiri Fronek[4] & Georg A. Böhmig[2]

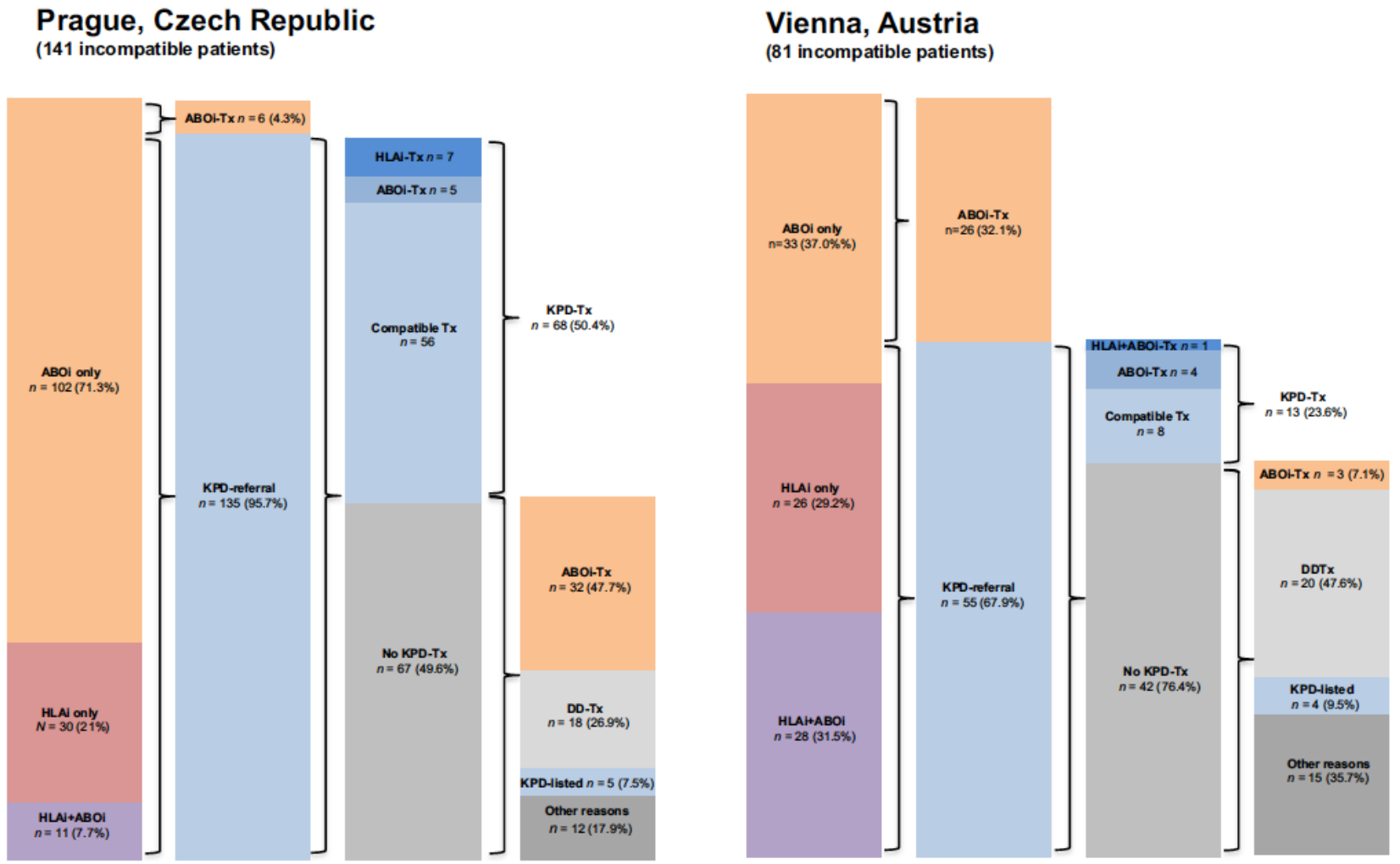
Viklicky & Böhmig et al: Transpl Int. 2020 Jun 3. doi: 10.1111/tri.13668.

International kidney exchange for KPD: Czech –Austrian experience



Böhmig G. et al. Transplant Int 2017

Recipients with incompatible donors in Prague and Vienna: Patients flow



Viklicky & Böhmig Transpl Int. 2020 Jun 3. doi: 10.1111/tri.13668.

Current Czech-Austrian KPD collaboration with Israel

2016

2019

Simultaneus surgery

CIT 5 hours

PRG

CIT 7 hours

TLV

Non Simultaneus surgery

IK+E M | Transplant Matching

CONFIGURATION

TXM event	**36-TXM-2022-01**
Solver	**Solver.ILPSolver**
Scorer	**Scorer.SplitScorer**
Forbidden crossmatch level	**BROAD**
Require compatible blood group	No
Require new donor having better CI match than original donor	No
Require new donor having better CI match than original donor or blood group match	**Yes**
Use binary scoring	No
Use high resolution	**Yes**
Manual donor recipient scores	**CZD9 -> P1113 : -1**

Maximum number of matchings	**5**
Minimum transplant score	**0**
Max countries in round	**3**
Max cycle length	**5**
Max sequence length	**5**
Compatible blood group bonus	**50**
Max kidney debt for one country	**0**
Max donor with blood group 0 debt for one country	**3**
Forbidden country combinations	
Required patient ids	

Matchings summaries

SELECTED: MATCHING #4

Score: **100.0** | Rounds: **1** | Transplants: **2** | 1/1 | 1/1

1B **CZD9 > W-80R** **W-80D1 > CZR27**

IK+E M

IK+E M | Transplant Matching

Score: 100.0 | Rounds: 1 | Transplants: 2 | 1/1 | 1/1

ROUND #1

BRIDGING DONOR

CZD9 > W-80R — 50.0

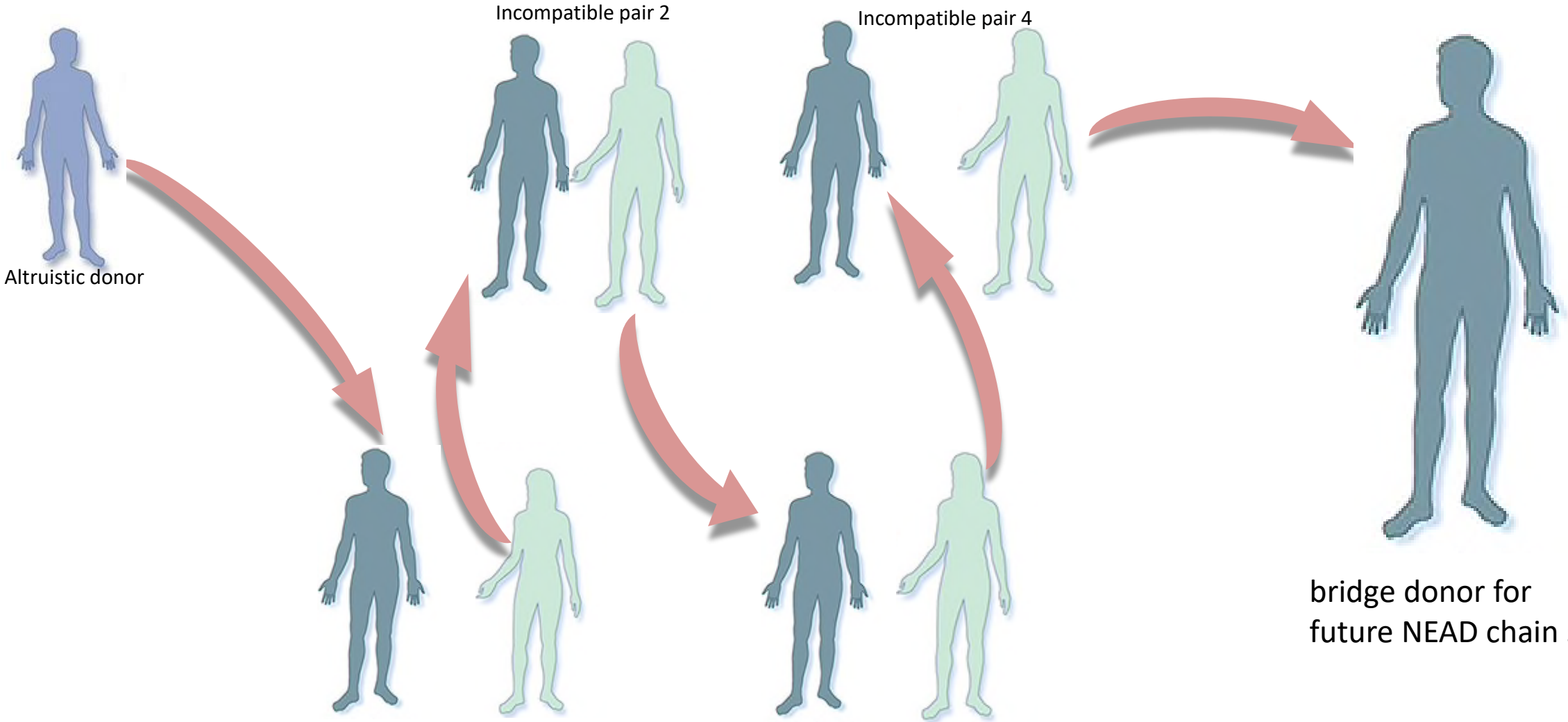
	CZD9 F - 1957	W-80R F - 1972		Score
Blood type	A	A Acceptable: A B 0 AB		-
	ANTIGENS	ANTIGENS	ANTIBODIES	
A	A*01:01 A*03:01	A*02:01 A*02:01	A*25:01	0.0
B	B*07:02 B*37:01	B*35:03 B*51:01	B*13:01 B*13:02	0.0
DRB1	DRB1*11:03 DRB1*15:01	DRB1*01:01 DRB1*08:02		0.0
Other	C*06:02 C*07:02 DPA1*01:03 DPB1*04:01 DQA1*01:02 DQA1*05:05 DQB1*03:01 DQB1*06:02 DRB3*02:02 DRB5*01:01	C*01:02 C*04:01 DPA1*01:03 DPA1*02:01 DPB1*01:01 DPB1*04:01 DQA1*01:01 DQA1*04:01 DQB1*04:02 DQB1*05:01	C*17:01 DQB1*06:03	-

W-80D1 > CZR27 — 50.0

	W-80D1	CZR27 M - 1972 - 176/-		Score
Blood type	B	B Acceptable: 0 A B AB		-
	ANTIGENS	ANTIGENS	ANTIBODIES	
A	A*02:01 A*11:01	A*03:01 A*03:01		0.0
B	B*51:01 B*51:01	B*07:02 B*07:02		0.0
DRB1	DRB1*13:03 DRB1*14:54	DRB1*04:01 DRB1*16:01		0.0
Other	C*03:03 C*16:02 DPA1*01:03 DPB1*04:01 DPB1*104:01 DQA1*01:04 DQA1*05:05 DQB1*03:01 DQB1*05:03 DRB3*01:01 DRB3*02:02	C*07:02 DPA1*01:03 DPB1*03:01 DPB1*04:01 DQA1*01:02 DQA1*03:03 DQB1*03:01 DQB1*05:02 DRB4*01:03 DRB5*02:02		-

IK+E M

Nonsimultaneous Extended Altruistic Donor chains (NEAD)



Ashlagi I. et al. Am J Transplant 2011;11:984-994

Altruistic donors at IKEM since 2012

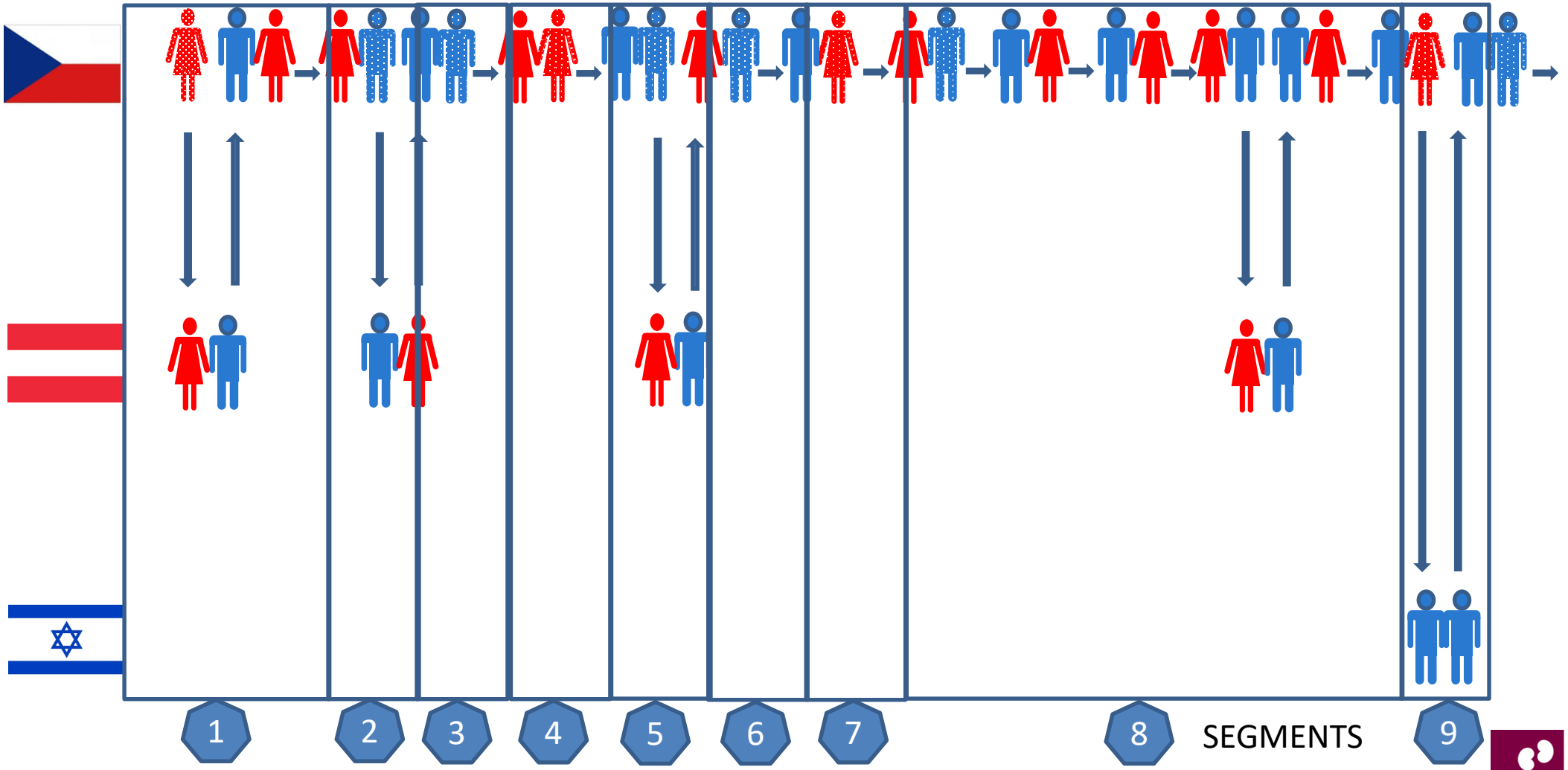
No	Donor	Age	Gender	Follow-up	Donor nephrectomy
1	JV	31	M	KI on psychological assessment	N
2	HR	63	F	accepted, initiated KPD	Y
3	TH	23	F	KI on young age	N
4	KD	19	F	KI on young age	N
5	VT	28	M	accepted, initiated KPD	Y
6	MM	30	M	accepted, initiated KPD, first contact 4 years ago	Y
7	ZS	22	M	KI on young age	N
8	FF	22	M	KI on young age, immature personality	N
9	JR	34	M	accepted 2015, than no contact	N
10	SP	22	M	KI on young age, immature personality	N
11	JK	34	F	accepted, initiated KPD which generated bridge donor	Y
12	OB	40	M	accepted, waiting for KPD	N

Much more contacts without visiting transplant team!!

IKEM

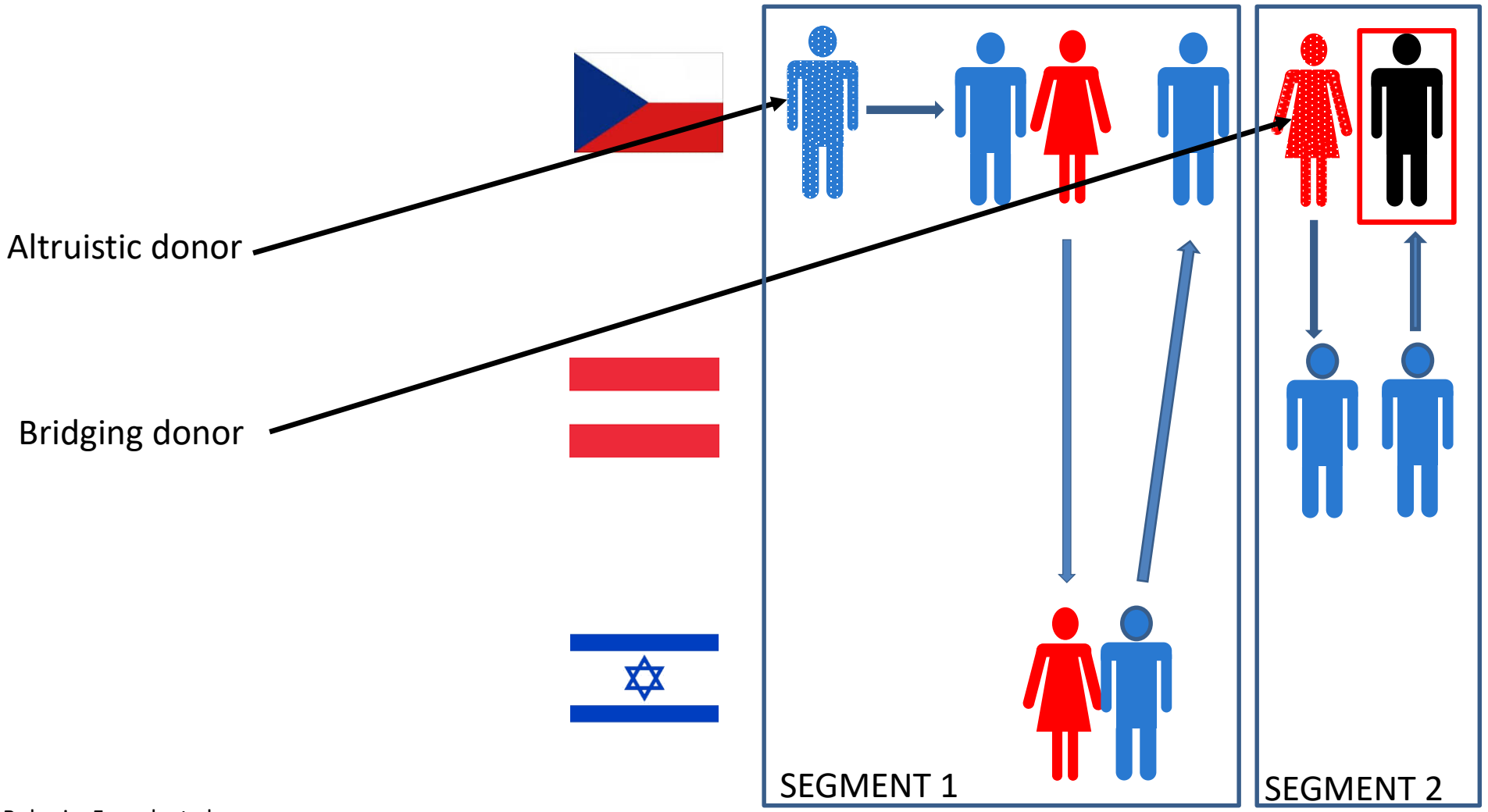
3-country-9-segments unterminated NEAD chain

since 2018: 19 kidney transplantations



Viklicky, Bohmig, Fronek et al.

3-country closed NEAD chain



Viklicky, Bohmig, Fronek et al.

Simultaneus vs. Non-simultaneus transplantation

Simultaneus

- Previously required by law or ethics
- Demanding on surgeons and facilities
- All recipients satisfied at once

Non-simultaneus

- Possible donor may refuse donation
- Allows kidney shipment or donor travel to other hospital
- Larger chains possible, international/intercontinental exchange…
- Bridge donor possible for future chains

Rees MA et al. N Eng J Med 2009;360:1096

IK+E M

Conclusion

- Higher rate of KPD referrals as primary option in Prague
- Higher rate of ABOi transplants as primary option in Vienna
- 30.8% KPD transplants in Vienna as results of international exchange
- International exchange offers chance for sensitized and blood group 0 recipients
- Organ shipment is not an issue: short CIT (5 hours in fact)
- More incompatible couples needed to improve HLA match
- Demanding logistics!

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