SOCIETAT CATALANA DE TRASPLANTAMENT

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Current strategies to kidney allocation

agence de la biomédecine

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Direction Prélèvement Greffe organes - tissus

From organ sharing to organ allocation optimization
Center or Patient based approach ?

Center based approach or so-called "local" priority

- Intuitive, natural, practical way to deal with organ allocation
- It preserves individual medical decision
- Links the level of transplantation activity to the level of dead donors procurement in a given area
  - Inequity in access to transplantation between patients from the same country
- Deals with to few prevalent patients on the waiting list a given day
  - Non optimal graft and patient survival because of bad recipient-donor age or HLA matching

Patient based approach

- To use organs with the highest possible relevance
- To allocate vital organs "just in time"
- To optimize donor-recipient matching on multivariate criteria
- Based on a scoring function taking into account multiple allocation criteria
- Implies acceptance of a supra-center computerized decision rule
- Has to be supported by a powerful Information System
- Requires to deal with logistical issues related to the transportation of organs

Patients with the highest score will receive the kidney

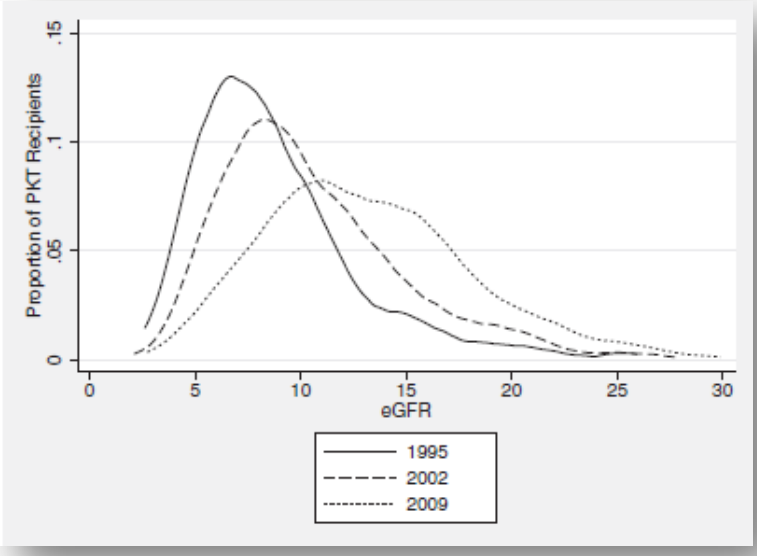
Which criteria for a fair kidney allocation ?

Equity ?

Efficiency?

Waiting time ? An increasing proportion of preemptive transplant recipients

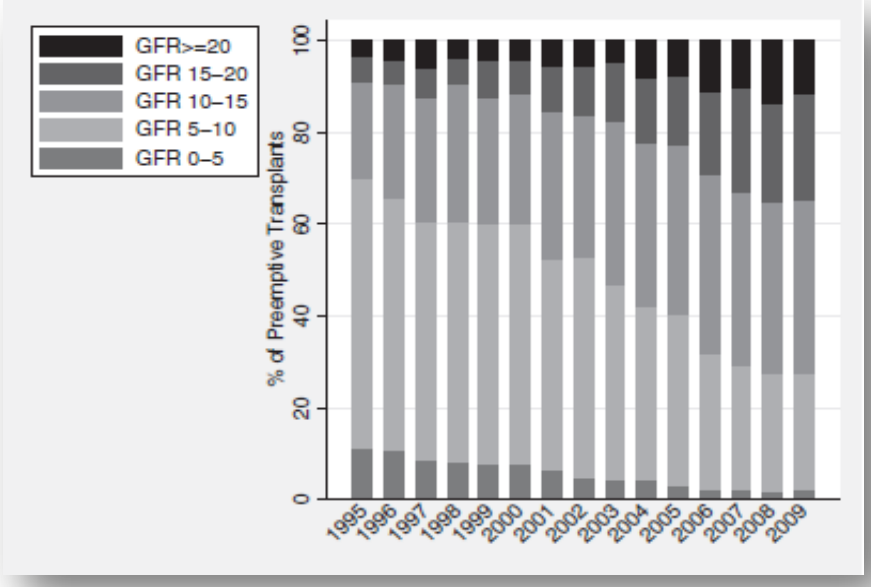
- No guidelines for the timing of registration during CKD progression



- Mean eGFR : 9.2 in 1995 to 13.8 ml/min/1.73m^2 in 2009 (P < 0.001)
- eGFR >15 ml/min/1.73m^2 : 9% in 1995 to 35% in 2009

Trends in the Timing of Pre-emptive Kidney Transplantation

Grams, J Am Soc Nephrol, 2011



UNOS database. 1995-2009, end point 31/12/2007, Deceased and living donors; 1st adult KTR

Absence of benefit to a too early transplantation

Trends in the Timing of Pre-emptive Kidney Transplantation

May subject patients to premature operative and imunosuppressive risk and waste the native kidney function of recipients

Grams, J Am Soc Nephrol, 2011

Table 2. PKT recipient and graft survival associated with pretransplant eGFR*

eGFR at PKT	Adjusted HR of Death	Adjusted HR of Death-Censored Graft Loss
eGFR<10	reference	reference
eGFR 10–15	1.10 (95% CI 0.99–1.21, $P = 0.07$)	0.97 (95% CI 0.88–1.08, $P = 0.6$)
eGFR 15–20	1.16 (95% CI 1.00–1.34, $P = 0.05$)	0.95 (95% CI 0.81–1.11, $P = 0.5$)
eGFR≥20	1.12 (95% CI 0.93–1.34, $P = 0.2$)	0.94 (95% CI 0.77–1.15, $P = 0.5$)

*Propensity score-adjusted.

Earlier Is Not Necessarily Better in Preemptive Kidney Transplantation

Akkina, AJT 2008

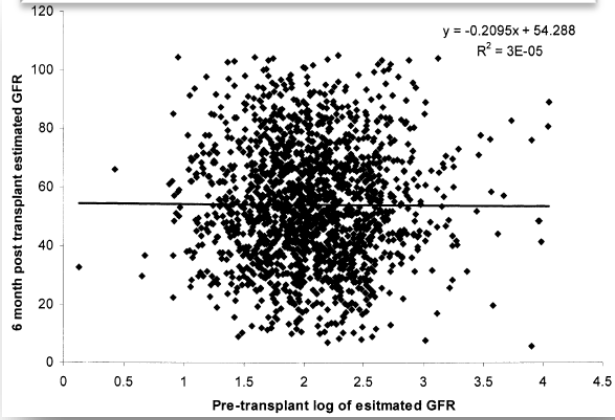
No improvement of graft survival after preemptive KTR with lower pretransplant eGFR

The Impact of Residual Renal Function on Graft and Patient Survival Rates in Recipients of Preemptive Renal Transplants

"No relationship between pre-Tx eGFR and 6-month eGFR, suggesting that post-Tx renal function is independent of the level of pre-Tx renal function. These data suggest that preemptive kidney transplantation should be delayed as long as possible",

Ishani, AJKD, 2003

Linear regression of 6-month eGFR on pretransplant eGFR.



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But a real negative impact of time dialysis on graft survival and patient survival !

Meier-Kriesche HU *et al.* Transplantation 2002; 74(10): 1377

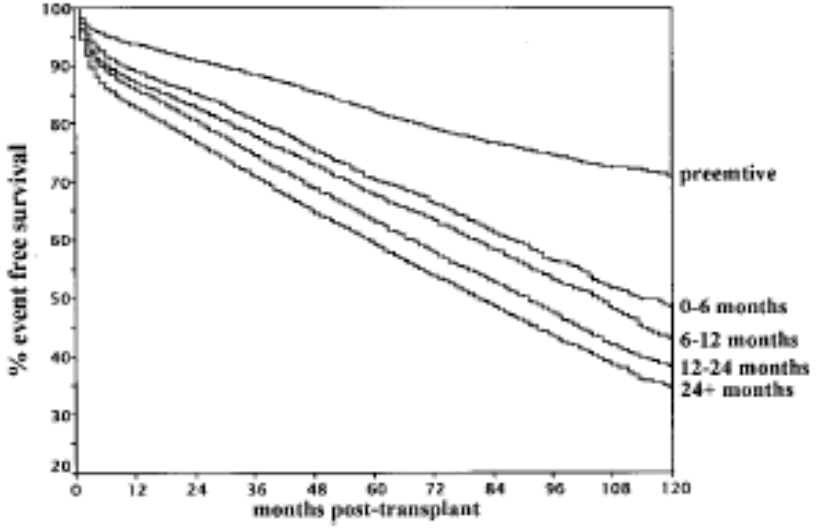
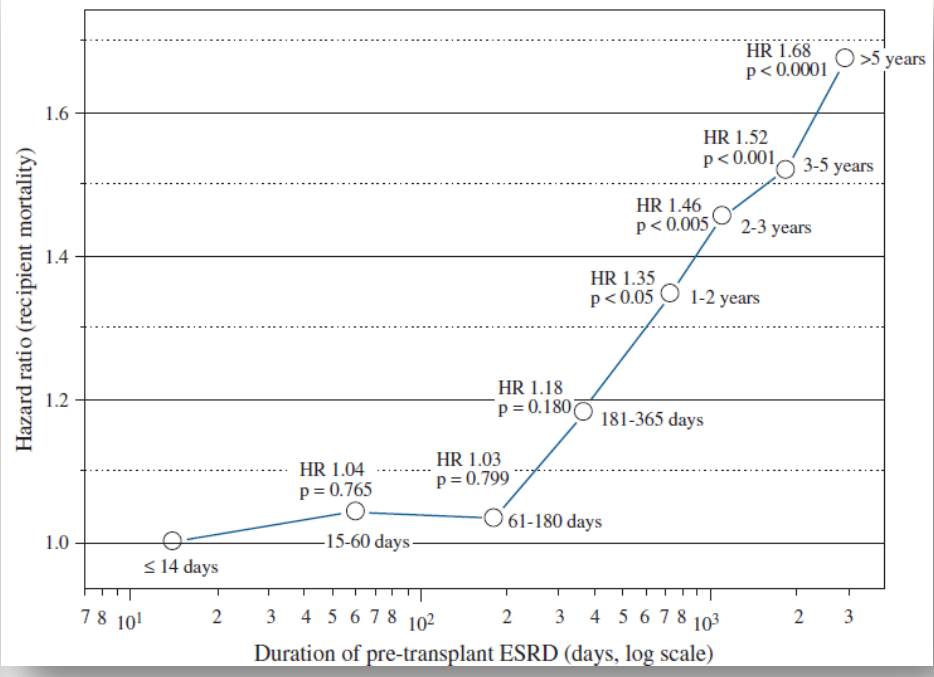


FIGURE 2. Unadjusted graft survival in 56,587 recipients of cadaveric transplants by length of dialysis treatment before transplant.

Goldfarb-Rumyantzev Nephrol Dial Transplant (2005)



"ESRD time is arguably the strongest independent modifiable risk factor for renal transplant outcomes".

USRDS database.1988-1998, paired cadaveric kidney primary adult,single-organ,renal transplant recipients

"The duration of ESRD was a significant risk for recipient death (HR 1.04 per year, p<0.001)"

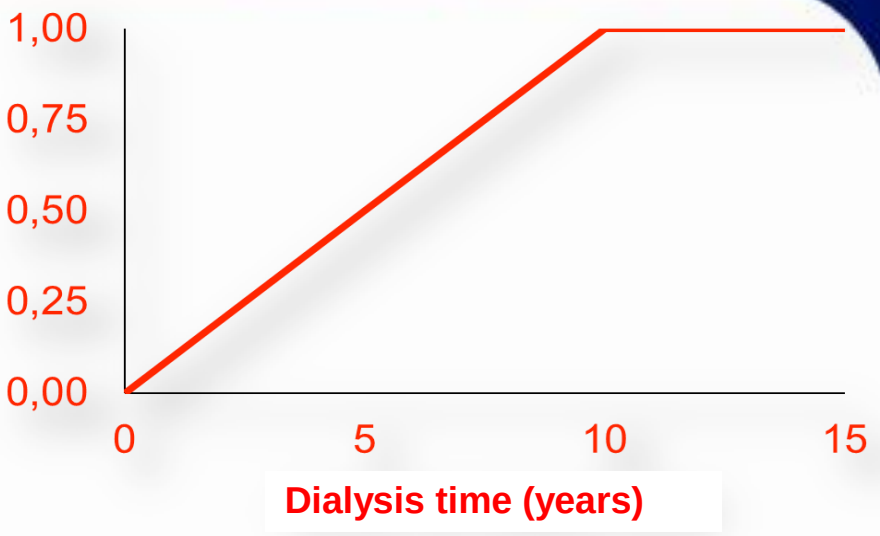
USRDS database. 1990-1999, only primary kidney transplantation

In France, Waiting Time and Dialysis time as equity criteria

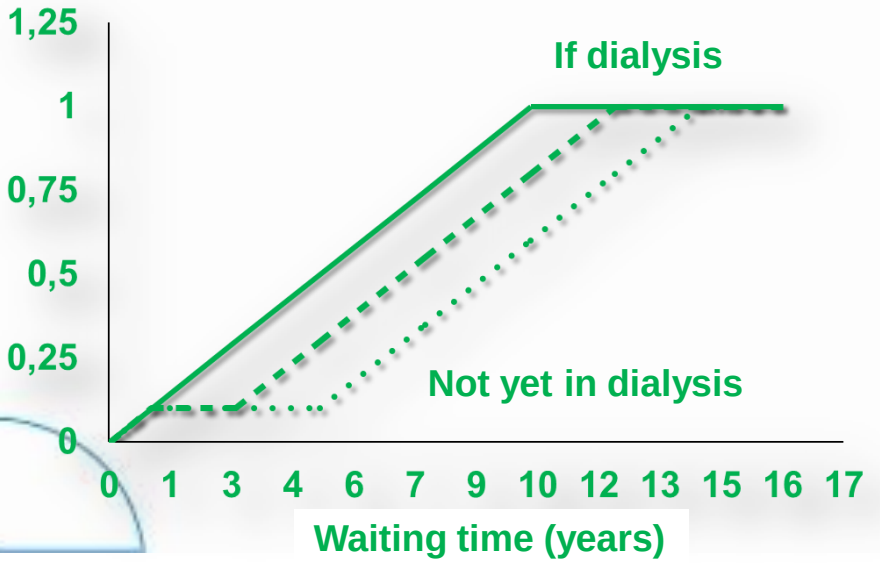
ScoreHΔage [0 - 1050] =

100 x $\mathbf{f_1}$(**DD**) + 200 x $\mathbf{f_2}$(**DA**, **Dial**)

Dialysis time (DIAL) from the date of dialysis start



Waiting time from the date of registration according to dialysis (DA,Dial)



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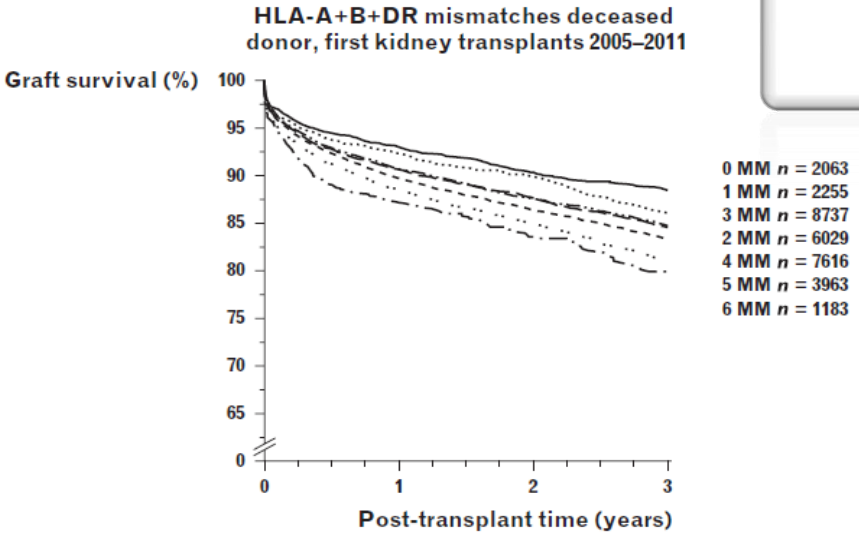
Why to optimize HLA matching ?

- To improve graft survival



CURRENT OPINION

Current role of human leukocyte antigen matching in kidney transplantation

Caner Süsal and Gerhard Opelz 2013

"better HLA matching is associated not only with better graft survival, but also with the administration of lower dosages of immunosuppressive agents, a lower incidence of side-effects of immunosuppression such as non-Hodgkin lymphoma, hip fractures, and death from infection"

- To decrease the risk of allosensitization
  - Following failure of a first renal TR
  - Incrementally with the number of mismatches at all HLA A,B,DR,DQ loci
  - For all recipients ?

HLA matching : a solution to preserve immunological capital

Impact of donor mismatches at individual HLA-A, -B, -C, -DR, and -DQ loci on the development of HLA-specific antibodies in patients listed for repeat renal transplantation

Kosmoliaptsis, Kidney International 2014

Table 2 | Influence of HLA mismatches on the likelihood of developing HLA-specific allosensitization after re-listing for repeat transplantation

	Likelihood of developing sensitization to individual HLA loci per mismatch		Likelihood of increasing cRF for individual HLA loci per mismatch	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
HLA-A	3.2 (2.0, 4.7)	<0.001	1.4 (1.2, 1.8)	0.002
HLA-B	3.4 (2.2, 4.9)	<0.001	1.3 (1.1, 1.6)	0.006
HLA-C	2.5 (1.5, 3.5)	<0.001	1.2 (1.0, 1.5)	0.074
HLA-DRB1	3.5 (2.3, 5.5)	<0.001	1.3 (1.0, 1.6)	0.015
HLA-DRB3/4/5	3.9 (2.4, 7.8)	<0.001	1.3 (1.1, 1.7)	0.011
HLA-DQ	3.0 (2.0, 4.3)	<0.001	1.4 (1.1, 1.8)	0.003

A Lifetime Versus a Graft Life Approach Redefines the Importance of HLA Matching in Kidney Transplant Patients

Meier-Kriesche, Transplantation 2009

"negative impact from poor HLA matching of their first kidney transplant ..// …particularly important in patients with a long life expectancy because of the high likelihood of needing a second transplant during their lifetime"

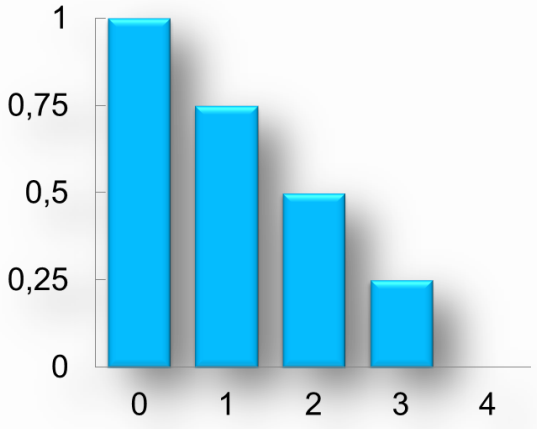
The Impact of Human Leukocyte Antigen Mismatching on Sensitization Rates and Subsequent Retransplantation After First Graft Failure in Pediatric Renal Transplant Recipients

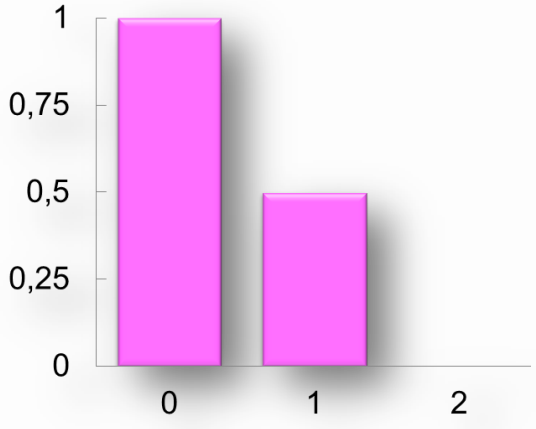
Gralla J et al, Transplantation 2013,

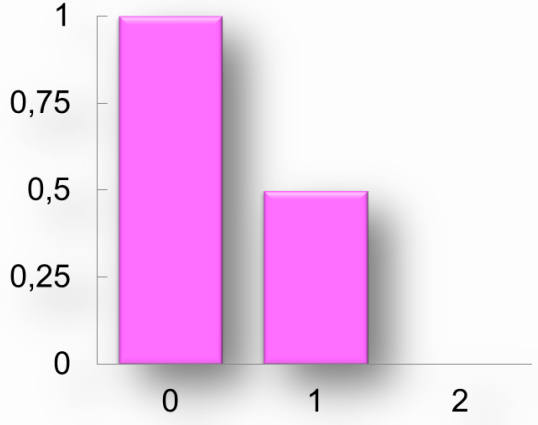
"DR mismatching at the time of first transplant results in higher degrees of sensitization, reduced retransplant rates, and longer time to transplant if retransplant is achieved".

How to optimize immunological matching

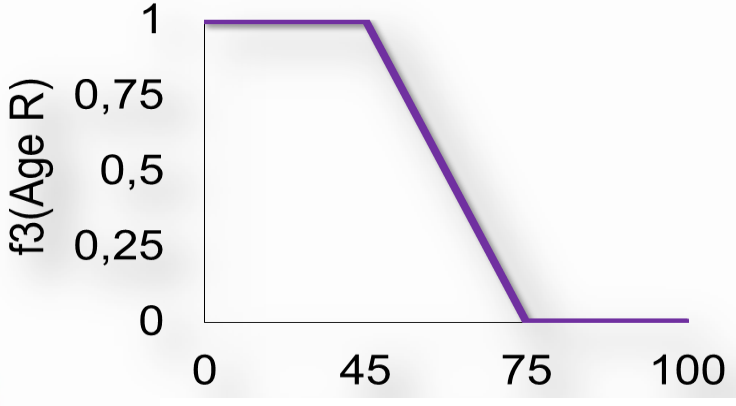
$$+ \left[100 \times f_3(AB) + 400 \times f_4(DR) + 100 \times f_4(DQ) + 150 \times f_7(FAGN)\right]$$







$$\times f_5(AgeR, 45, 75)$$



The young recipients obtain the maximum of points for HLA matching (class II especially)

It is decreasing as from 45 years, and no more taken into account beyond 75 years.

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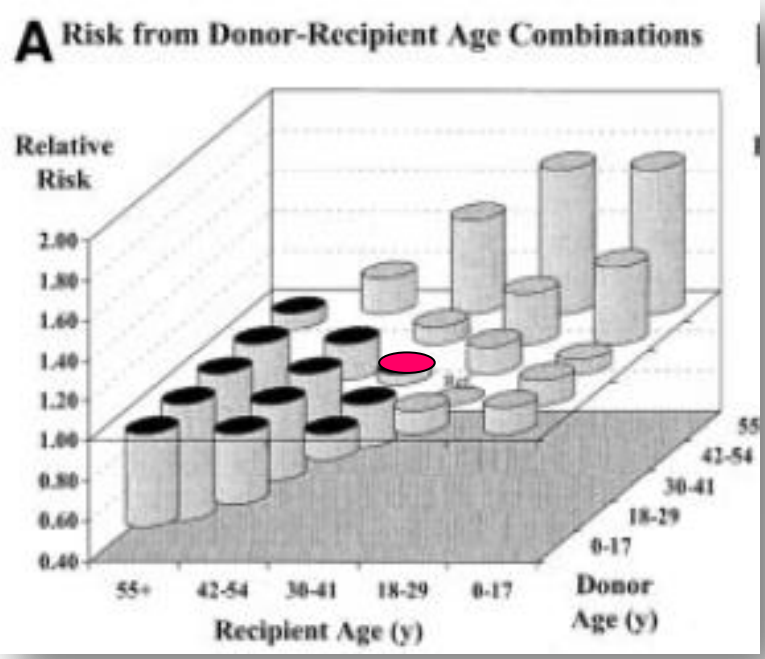
Age matching

Données UNOS, Kasiske , JASN, 2002

Meier-Kriesche, AJT, 2005

- Relative risk of graft loss (with death censure) regarding donor-recipient age combinaision
- Cox model
- Referent risk factor: R=D= age 18-29 y



- By excluding transplantation of younger kidneys to older recipients
- The overall projected improvement in graft survival: 3 years per transplant.
- Significant increase of the overall graft life, by a total 27 500 graft years, between 1990 and 2002

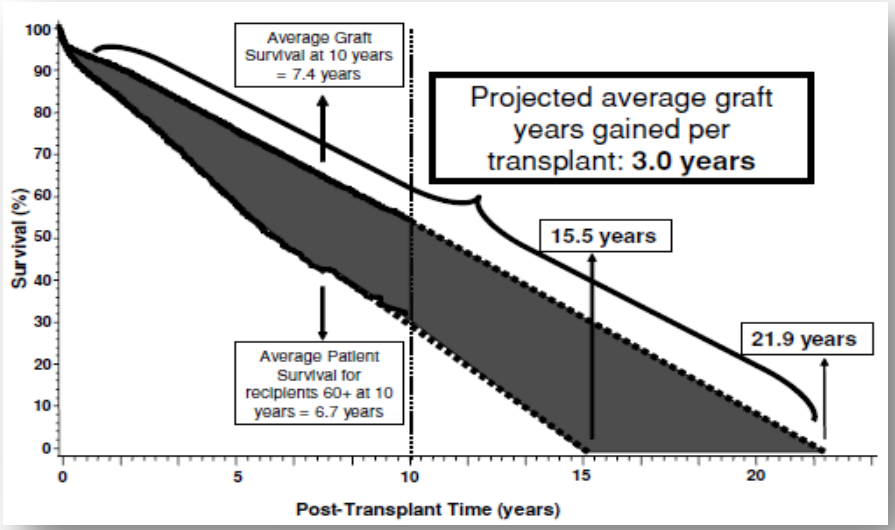
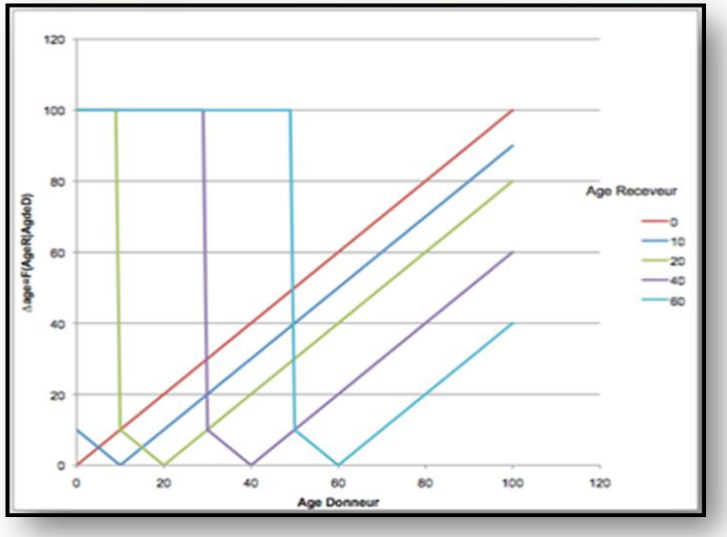


Figure 5: Projected graft years saved with allocation amendment.

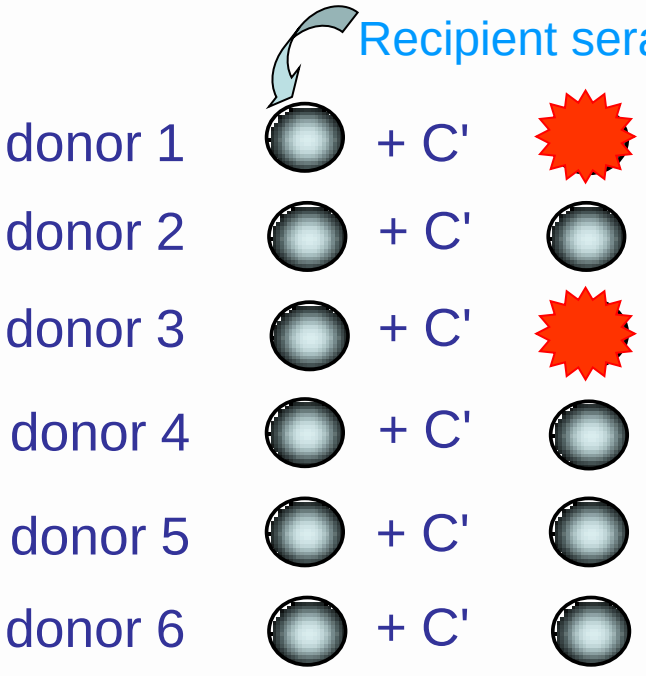
To optimize donor-recipient matching on multivariate criteria



- Age matching is a major allocation criteria
  - More efficient to allocate old grafts to older recipients who have shorter life expectancies and who need less nephronic mass
  - Not as a “cut-point” but redistribution of grafts towards recipients with same age or slightly younger.
- Eurotransplant Senior Program (ESP)
  - Availability of elderly donors doubled
  - Waiting time for ESP patients decreased
  - Local allocation led to shorter cold ischemia time and less DGF
  - Graft and patient survival were not negatively affected by the ESP allocation

How to define and measure sensitization ?

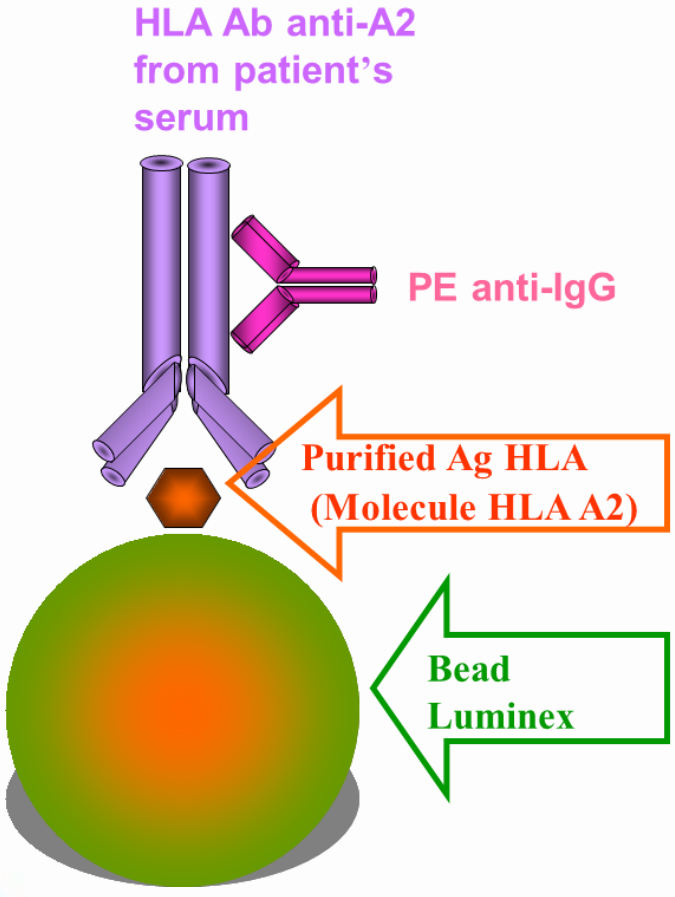
Complement dependent cytotoxicity



PRA : 30/100 = 33%

Date	T	B	specificity
24/2/09	12/40	2/10	anti-A2

Solid-phase assays



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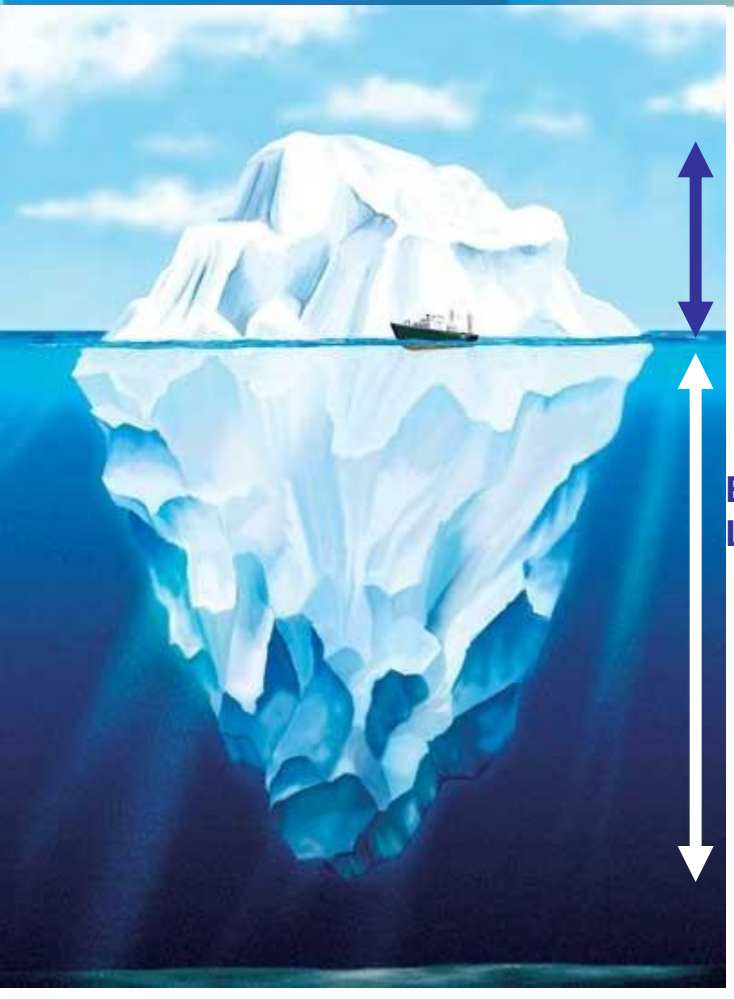
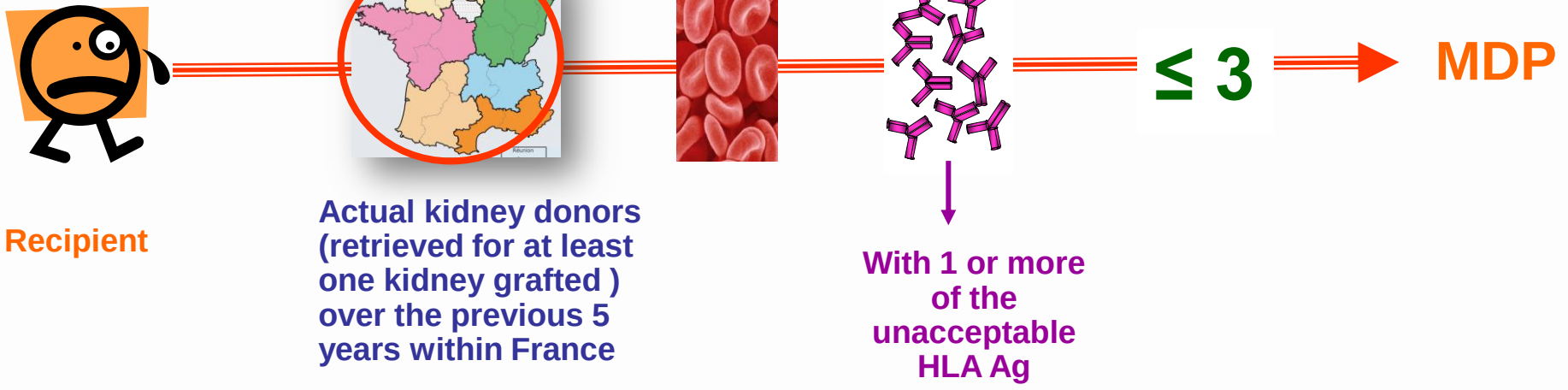
The solid-phase techniques :



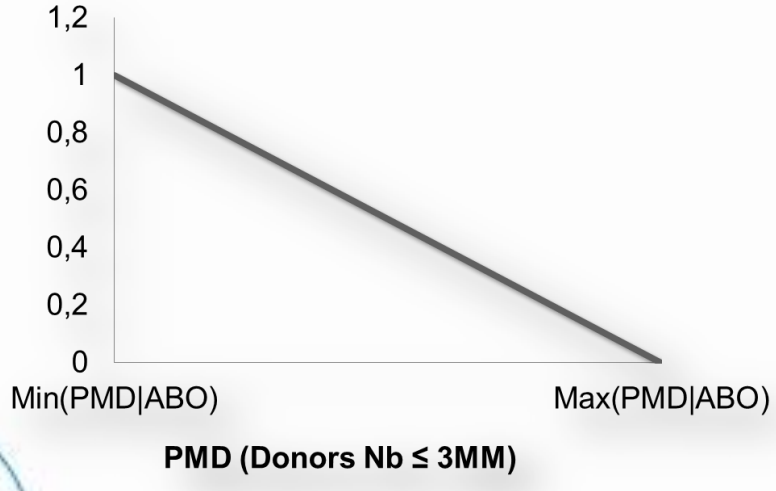
- Accurate definition of a patient sensitization profile
  - More (too?) sensitive, rapid and reproducible **(…but MFI variation !!)** inter and intra laboratories *Reed AJT 2013*
- exclusively HLA class I or class II Ag
  - Exclude non HLA Ag recognition
- Tracks of HLA Ab deleterious to the graft not revealed by cells phase assay
- Permits precise identification of the unacceptable HLA Ags even in broadly sensitized patients
- More unacceptable HLA Ags are identified, leading to exclude more potential donors
- cPRA (2009)

Match donor potentiel : extra points for patients with a low Transplant accessibility



Match Donor Potentiel :

Number of donors matching recipient blood group, retrieved during the 5 past years in France, without unacceptable HLA antigen, and with less than 3 HLA A, B and DR mismatches



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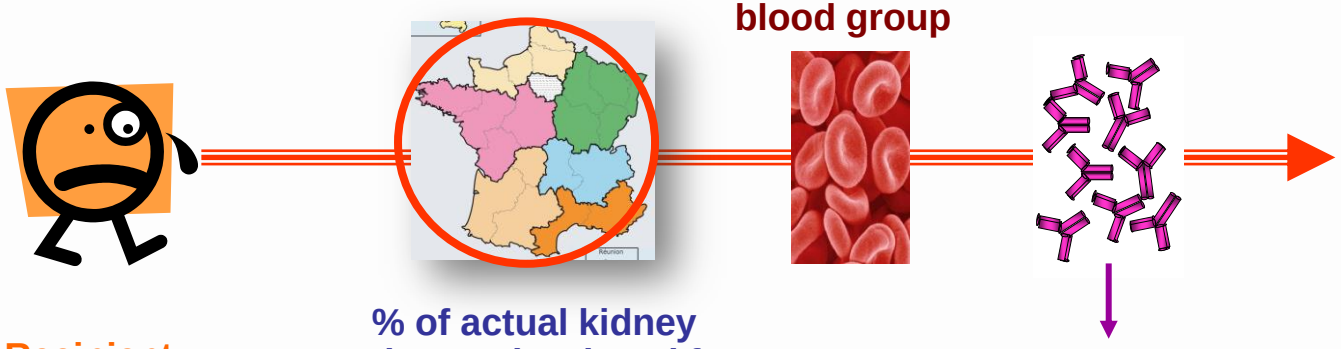
cPRA and national priorities

H3 program
If ≤ 1 HLA A B DR mismatch
Since 1996



Recipient

% of actual kidney donors (retrieved for at least one kidney grafted) over the previous 5 years within France

Matched for blood group

With 1 or more of the unacceptable HLA Ag

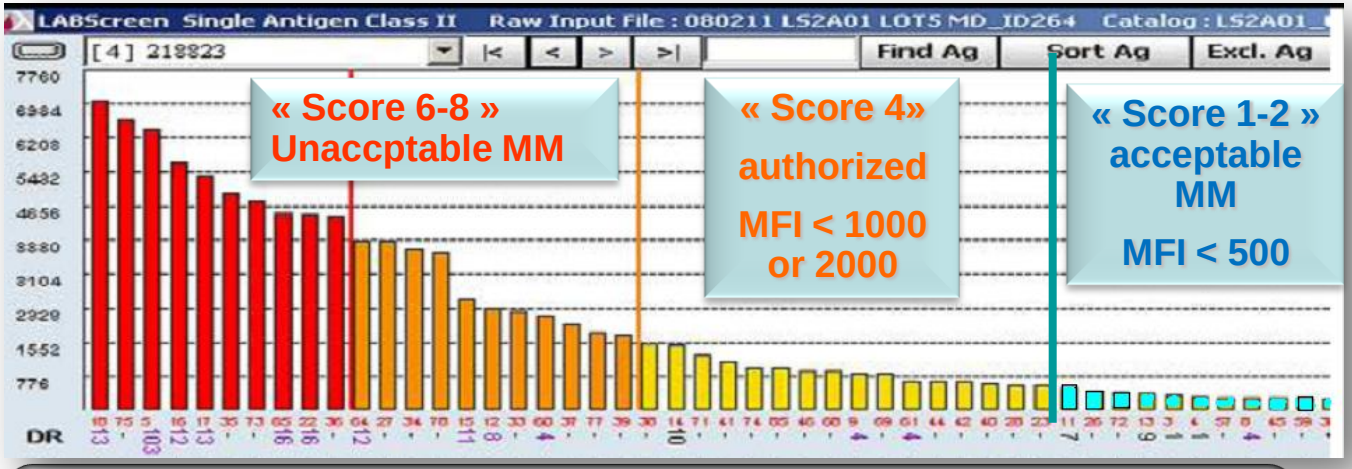
If cPRA ≥ 85%
→**National priority :**

National priority if ≤ 1 HLA A B DR MM with the donor

Election promise !!

Acceptable mismatch program (april 2005)

- Objective : to increase the number of HLA compatible donors without increasing the immunological risk of graft failure and without increasing the cold ischemia time
- How ? : By authorizing more than 1 mismatch under conditions that each mismatch corresponds to an acceptable Ag according to the national recommendations
- An Ag is considered as permissible when the highest bead bearing this Ag presents a normalized MFI <500 on historic and current sera (Single Ag assay exclusively)



Donor HLA typing
*HLA **A2** A29 **B7** B44*
DR4 DR17 DQ2 DQ4

Concept of virtual CXM
No DSA HLA A B DR DQ
Peak and current sera

Recipient HLA typing
*HLA **A2** A3 B51 **B7** **DR4** DR13 **DQ2** DQ6*

*A24 A25 **A29** A31*
*B8 **B44** B35 B61*
DR17 DQ4

without taking into account
Ab anti DP or CW

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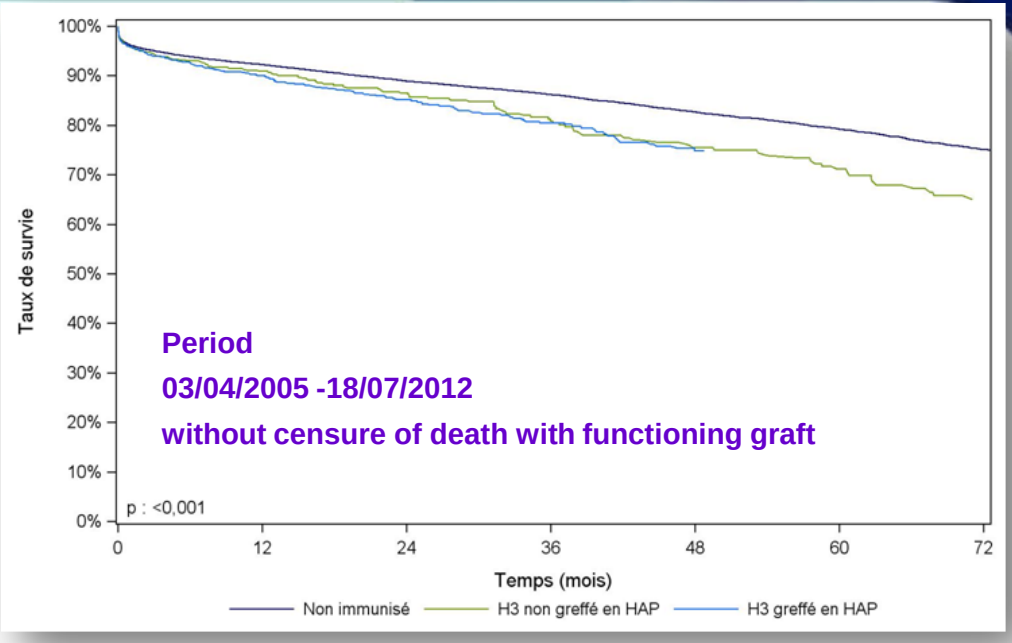
HAP results :graft survival

- An improved access to transplantation for hyper-immunized patients
  - 2 years access: from 42 to 51 %, in France in the same period.
  - Increase proportionally with the rate of recipients included in this program
- Efficient only on a large pool of donors (national priority)
- Good 2-years (86%) and 5-years graft survival
- Can we improve the acceptable mismatch concept
  - Better selection of eligible patients ?
  - How to determine more accurately HLA Ab specificities with clinical relevance ?
  - Problem of HLA DQ barriers and its effects on cPRA calculations



	N	1 months	1 year	5 years
Non immunized	13050	96,2% [95,9% - 96,5%]	92,3% [91,8% - 92,7%]	79,2% [78,4% - 80,0%]
number at risk*		12379	11308	4337
Hyperiimmunized exclude HAP	552	95,9% [93,8% - 97,3%]	90,9% [88,2% - 93,1%]	71,2% [65,5% - 76,1%]
number at risk*		509	439	122
Hyperimmunized and HAP	1082	95,9% [94,6% - 97,0%]	90,1% [88,1% - 91,7%]	NO
number at risk*		1006	841	117

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Adapted from the acceptable mismatch program of Eurotransplant
more than 450 Tx since may 1996

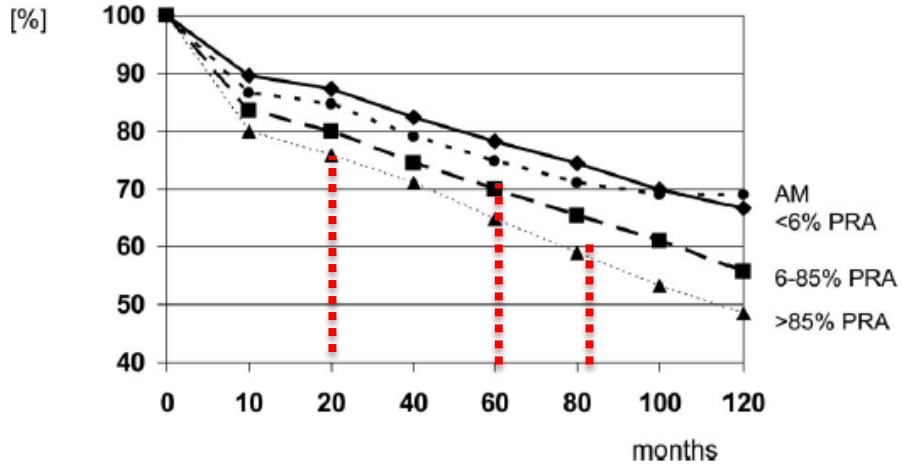


FIGURE 3. Long-term graft survival of patients transplanted via the AM program. **Claas, Tx, 2009**

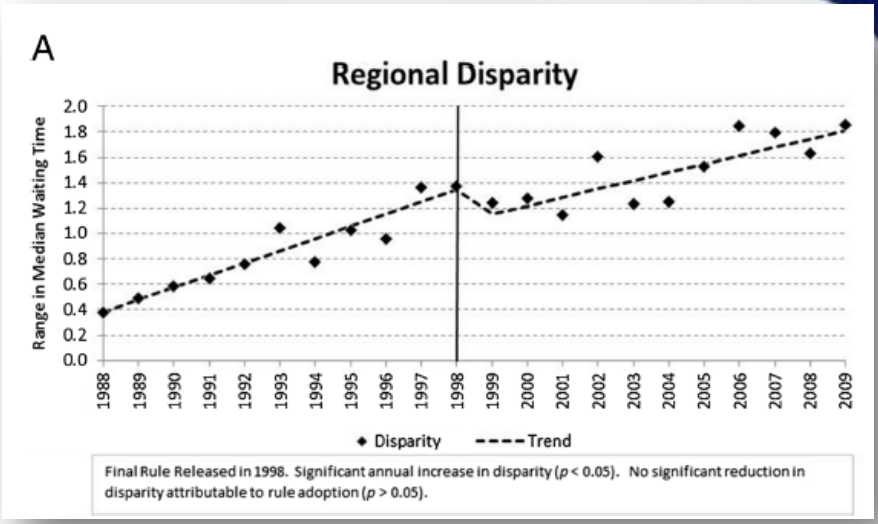
- Eurotransplant : 2% of hyper-immunized patients
- Improved access to transplantation : 17% to 60% after 2 years
- 4% of + CM
- Graft survival in « AM » patients is identical to that of non-sensitized recipients (87% at 2 years)

- Only one HLA referent center for Eurotransplant (Leiden) for inclusion
- Only patients with a virtual PRA more than 85% will be included in the AM program + waiting time > 1 year
  - Serum are screened in complement-dependent cytotoxicity (CDC), including HLA repeat mismatch with a previous Tx
  - Virtual PRA is mainly based on HLA-A, -B, and –DR Ab specificities (compared to a panel of donor HLA type from Eurotransplant)
  - HLAMatchmaker is used for the identification of potential acceptable HLA mismatches
- Final CDC crossmatch will only be performed in the recipient center (mostly current serum)

For witch geographical level and matrix

Changes in Geographic Disparity in Kidney Transplantation Since the Final Rule

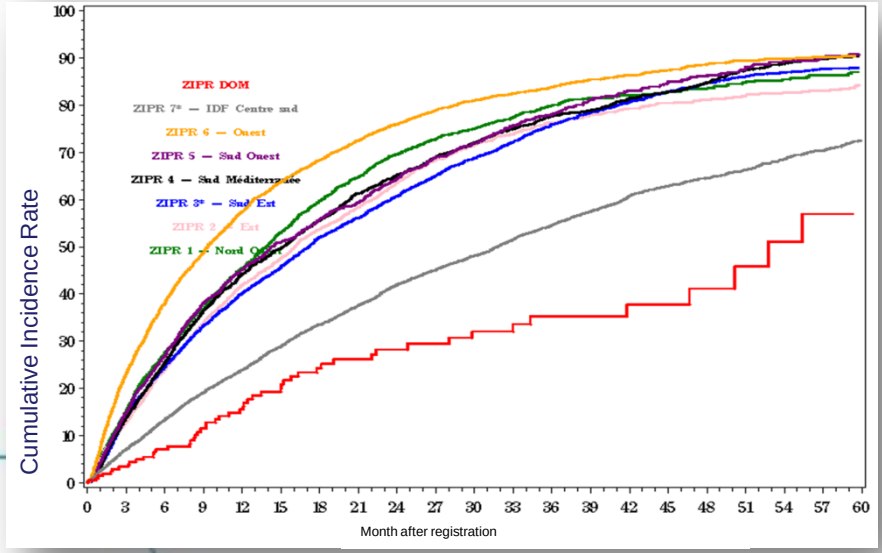
Davis Transplantation 2014



- USA : difference between the maximum and minimum median waiting times to transplantation each year across UNOS regions

- France : Transplant access kinetic according to area of registration

  Biomedecine Agency Datas



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Unique registration on the national waiting list
Donor-recipient ABO blood group identity

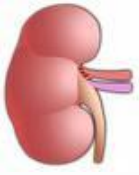
Nationwide allocation priorities

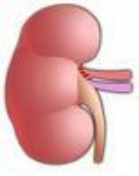
1. High emergency
2. Hypersensitized recipients
3. Children < 18 y if donor age < 18 y

Experts committee

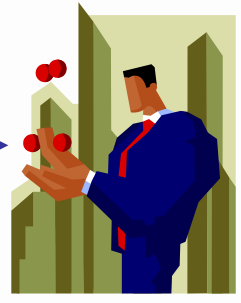
Regional priority

1. Emergency
2. Combined transplantation
3. Children (if donor age < 30y)





Absence of well age-matched recipient locally



Recipient

Local level
Patient based Allocation system

National level

-To a patient according to a score system
Taking into account proximity
Disappearance of geographical levels

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Allocation policy

- Requires a national waiting list : an efficient mean to support a transparent, traceable and auditable allocation system.
- Elaborated with all concerned parties
  - Heath care professionals
  - National health authority (public state agency : Agence de la biomédecine)
  - Patients and population representatives
- Applied by a public state agency, guarantee for a proper application of procedures
- An empirical compromise between equity, justice, efficacy, practicability, quality of post-transplant results and technical constraints related to organ retrieval and preservation
  - So difficult to simultaneously maximize utility, efficiency, equity and predictability
- Promoting as much as possible a patient-based allocation and not a center-based allocation system
- Remains a moving and open topic, needing periodic evaluations to exclude bias or side effects
  - Complete information for both health professionals and the general public
  - The interest of simulation tools
- Objective, official, clear, transparent and fair in order to obtain the general public trust and organ donation acceptance

gràcies per la seva atenció

La première égalité, c'est l'équité.

Victor Hugo « Les Misérables »

Unacceptable HLA Ag are registered on the National Transplant Database (CRISTAL)

Formation Cristal /receveurs

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Corinne ANTOINE (FT7R7)

Dossier

Aide Accueil Contacter l'administrateur Quitter

- Administration
  - Inscrire en attente
  - Tableau de bord
  - Liste de travail
  - Recherche patient
  - Patients à transférer
  - Indisponibilité des équipes
- Patient
  - Historique du patient
  - Historique des déménagements
- Dossier
  - Edition inscription
  - Déclarer un décès
  - Changer de centre
  - Contre-indication temporaire
  - Sortir de liste
  - Déclarer greffe
  - Historique dossier
  - Suivi avant greffe
  - Saisir le HLA

NEFG 157213 - **NATT** 188690 hyper-immunisé — Groupe sanguin : A +

> **Patient :** BREQE YQIHHI, Toghujy — > **Sexe :** M

> **Rein - FT7R7** — en attente de greffe

BREQE YQIHHI, Toghujy
Né le : 30/06/1954

Inscription | Immuno. | Coord. attente | Suivis | Observ.

HLA type

▸ **HLA**

A1	A2	B1	B2	DR1	DR2	DQ1	DQ2
2	32	53	0	8	11	7	0

Cw Cw DP DP
.. ..

▸ **Anticorps** - renseignés par Dominique MEUNIER

Taux IgG anti-Ly T ou totaux : 5%

Taux d'anticorps anti-HLA Classe 2 : 5%

PRA LCT

Taux de greffons incompatibles : 98% **Taux de greffons incompatibles historisé : 96%**

Pic cPRA ≥ 85%

Current cPRA > 70%

▸ **Date de dernière recherche Ac anti-HLA validée :** 02/11/2011

❖ **Données saisies par l'équipe (utilisées pour l'aide au choix)**

Transférer automatiquement les Ac de classe I et II saisies par le laboratoire vers les données cliniques : Oui

▸ **Spécificités des anticorps Classe 1**

A34 A66 A11 A3 A80 A23 A24 B44 B45 B13 B65 B62 B63 B76 B18 B54 B27 B37 B60 B61 B41 B42 B46 B47 B48 B7 B72 B73 B8 B81 B82

▸ **Spécificités des anticorps Classe 2**

DR4 DR7 DR9 DQ2 DQ8 DQ9 DQ4

▸ **Antigènes interdits**

Les mismatch du conjoint, ceux du ou des greffon (s) antérieur(s), les anti-CW et anti-DP

Non authoriezed mismatch

▸ **Spécificités des anticorps Classe 1**

A34 A66 A11 A3 A80 A23 A24 B44 B45 B13 B65 B62 B63 B76 B18 B54 B27 B37 B60 B61 B41 B42 B46 B47 B48 B7 B72 B73 B8 B81 B82

▸ **Spécificités des anticorps Classe 2**

DR4 DR7 DR9 DQ2 DQ8 DQ9 DQ4

▸ **Spécificités HLA de la zone grise (antigènes ni interdits ni permis)**

A1 A30 A33 A36 B75 B39 B55 B35 B67 DR1 DR10 DR95 DR2 DR15 DR16 DR17 DR18 DR12 DR13 DR1 DQ6

2 MM DQ low MFI authorized

▸ **Antigènes permis**

A25 A26 A29 A31 A32 A74 A2 A28 A68 A69 A43 B64 B77 B38 B17 B57 B58 B21 B49 B50 B56 B5 B51 B52 B53 B59 B71 B78 DR11 DR8 DQ5 DQ7

Acceptable mismatch

▸ **Commentaire**

HAP programm : DSA antiCw and anti DP authorized

❖ **Nombre d'incompatibilités acceptables**

A : **B :** **DR :** **Maximum :**

❖ **Accès à la greffe**

Potentiel match donor (with restriction in HLA MM (≤3 ABDR MM))

FAG : 6 **FAG A :** 3 **FAG B :** 0 **FAG AB :** 0 **FAG O :** 3

Version 3.2.0_1
COF5

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