



LEIDS UNIVERSITAIR MEDISCH CENTRUM

The Acceptable Mismatch program of Eurotransplant.

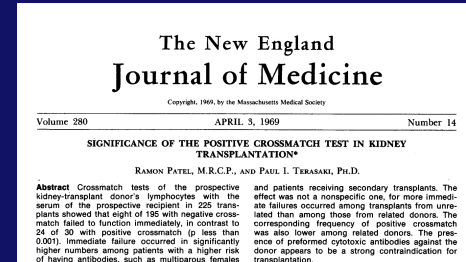
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Hinterzarten , December 7, 2013

Main problem of the sensitized patient: preformed donor specific HLA antibodies lead to hyperacute rejection



Patel & Terasaki (1969): 24/30 patients with donor specific antibodies experienced hyperacute rejection.



The introduction of a serological crossmatch and exclusion of donors toward which the patient has preformed antibodies, will prevent hyperacute rejection.

Highly sensitized patients often have positive crossmatches

Therefore highly sensitized patients accumulate on the waiting list .

Definition of a highly sensitized patient within Eurotransplant:

patient with antibodies against the HLA antigens of more than 85% of the donor population.

Not based anymore on % PRA in the antibody screening but on the specificity of the HLA antibodies in relation to the frequency of the target antigens in the organ donor population: virtual PRA.

Donor reactive antibody calculator on the Eurotransplant website based on the HLA types of 30,000 actual organ donors: uniform definition of a highly sensitized patient in the different centers.

Virtual PRA calculation

[Information](#)

Which Population	<input type="radio"/> Austria <input type="radio"/> Belgium <input type="radio"/> Germany <input type="radio"/> The Netherlands <input checked="" type="radio"/> All ET	
Give Antibodies/Specificities	<i>Example: A1,A2, B7,</i> <input type="text" value="A1,A2,A3,B7,B8,B22,B27,B35,B60,B41,B42,B46,CW6,CW15,DR8,DQ7,DQ4,"/>	
<input type="button" value="Calculate % PRA"/>		
Positive	<input type="text" value="3666"/>	
Persons	<input type="text" value="3760"/>	
PRA	<input type="text" value="97.50"/>	

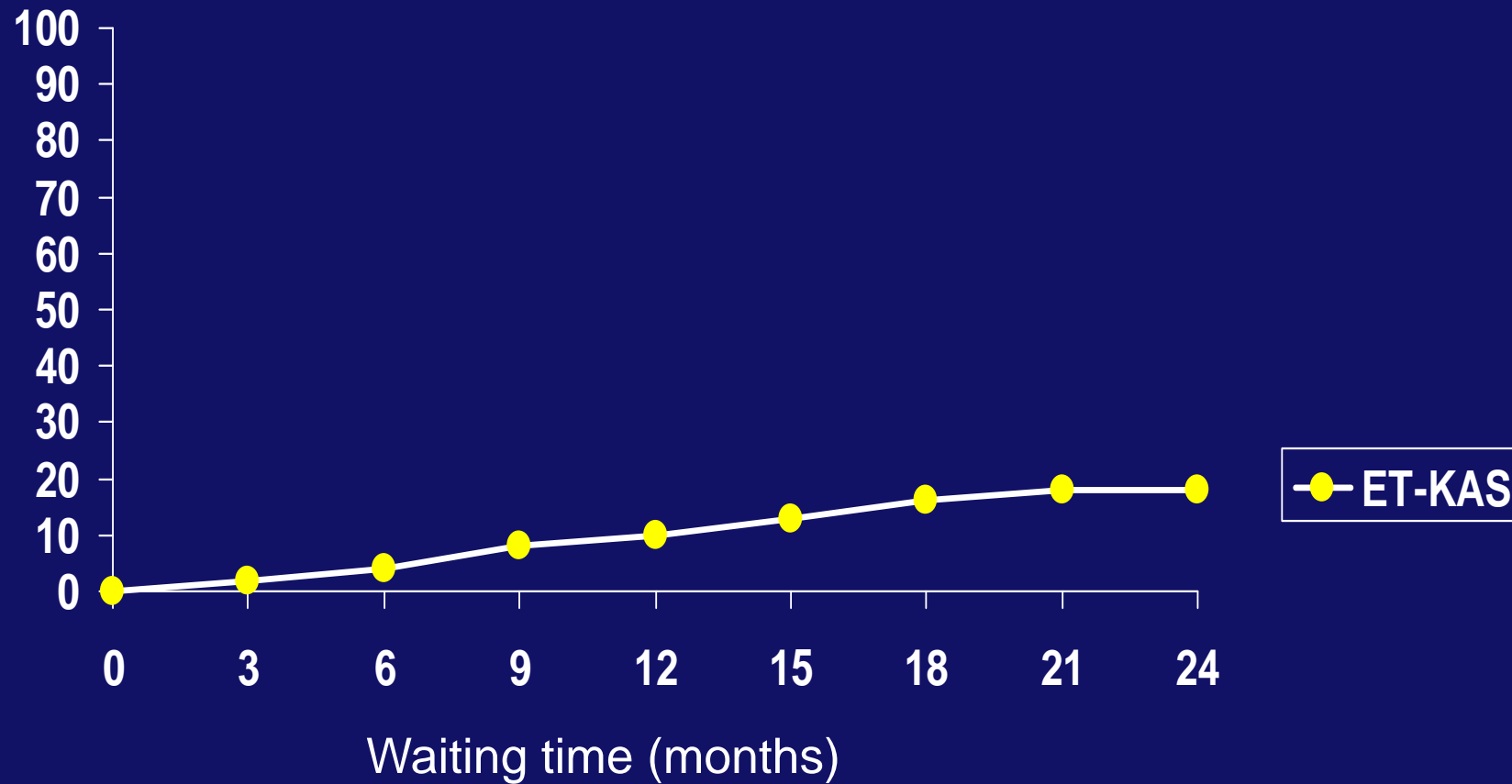
Eurotransplant Kidney Allocation System gives priority to highly sensitized patients.

Transparent point system based on different parameters:

- HLA match
- Match prognostic index
 - extra points for patients with rare HLA phenotypes and for sensitized patients.
- Waiting time
- Regional donor (cold ischemia time)
- Country balance.

Despite this priority there is only a low chance that a highly sensitized patient will be transplanted.

% patients transplanted

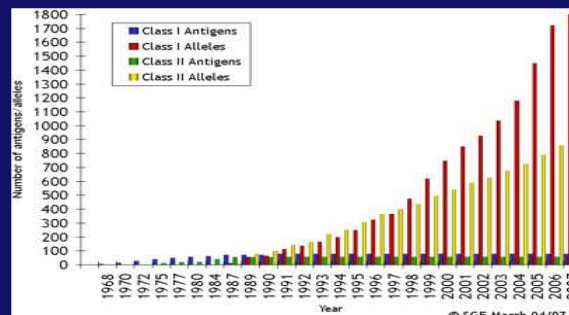


Need for an alternative approach

- Standard policy within Eurotransplant is registration of the non-acceptable HLA mismatches to prevent allocation of donor kidneys to patients with donor specific antibodies.

Aim: prevention of a **positive CDC crossmatch**

- Problem: there are too many HLA antigens: impossible to register all antibody specificities in case of highly sensitized patients.



Acceptable Mismatch Program

- **Basis:** definition of those HLA antigens toward which the patient never formed antibodies and use this knowledge for donor selection.
- **Aim:** prediction of a **negative CDC crossmatch**
- **Method:**

Extensive antibody screening in the recipient center to define HLA antigens, which do not react with the antibodies of the patient.

Validation of the results by the Eurotransplant Reference Laboratory.

- Consider HLA types of negative panel donors in CDC antibody screening.
- No reactivity against single antigen expressing cell lines (SALs) or single antigen beads
- A computer algorithm HLAMatchmaker is used routinely to facilitate identification of acceptable mismatches.

The acceptable HLA mismatches are included in the HLA phenotype of the patient used for allocation.

Assumption: any donor with a HLA type which is a combination of the patients' HLA and AM will have a negative crossmatch.

HLA patient: A24, A31, B27, B51, DR4

AM: A25, A26, B44

HLA phenotype
used for allocation

Suitable kidney donors: A25, A31; B27, B51; DR4
A26, A31; B27, B51; DR4
A24, A25; B27, B51; DR4
A24, A26; B27, B51; DR4
A24, A31; B44, B51; DR4
A24, A31; B27, B44; DR4
A25, A31; B44, B51; DR4
A26, A31; B44, B51; DR4
A25, A31; B27, B44; DR4
A26, A31; B27, B44; DR4
A24, A25; B44, B51; DR4
A24, A26; B44, B51; DR4
A25, A31; B27, B44; DR4 etc.

A donor kidney with a HLA type which is a combination of a patients' HLA and AM must be allocated to this patient.

HLA patient: A24, A31, B27, B51, DR4

AM: A25, A26, B44

**HLA phenotype
used for allocation**

Suitable kidney donors: A25, A31; B27, B51; DR4

A26, A31; B27, B51; DR4

A24, A25; B27, B51; DR4

A24, A26; B27, B51; DR4

A24, A31; B44, B51; DR4

A24, A31; B27, B44; DR4

A25, A31; B44, B51; DR4

A26, A31; B44, B51; DR4

A25, A31; B27, B44; DR4

A26, A31; B27, B44; DR4

A24, A25; B44, B51; DR4

A24, A26; B44, B51; DR4

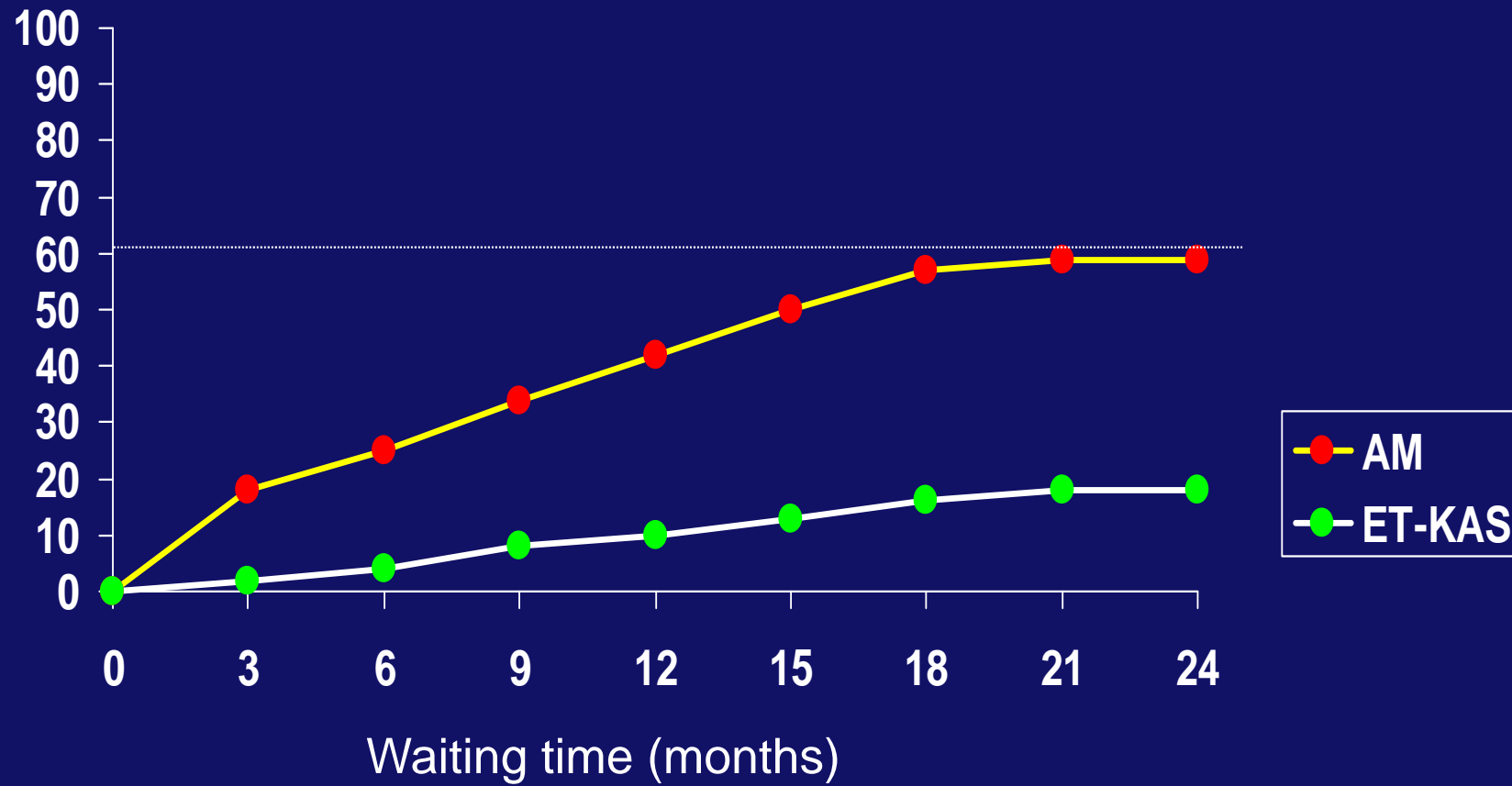
A25, A31; B27, B44; DR4 etc.

**If a compatible donor
becomes available within
Eurotransplant:
mandatory shipment of
the kidney to this highly
sensitized patient.**

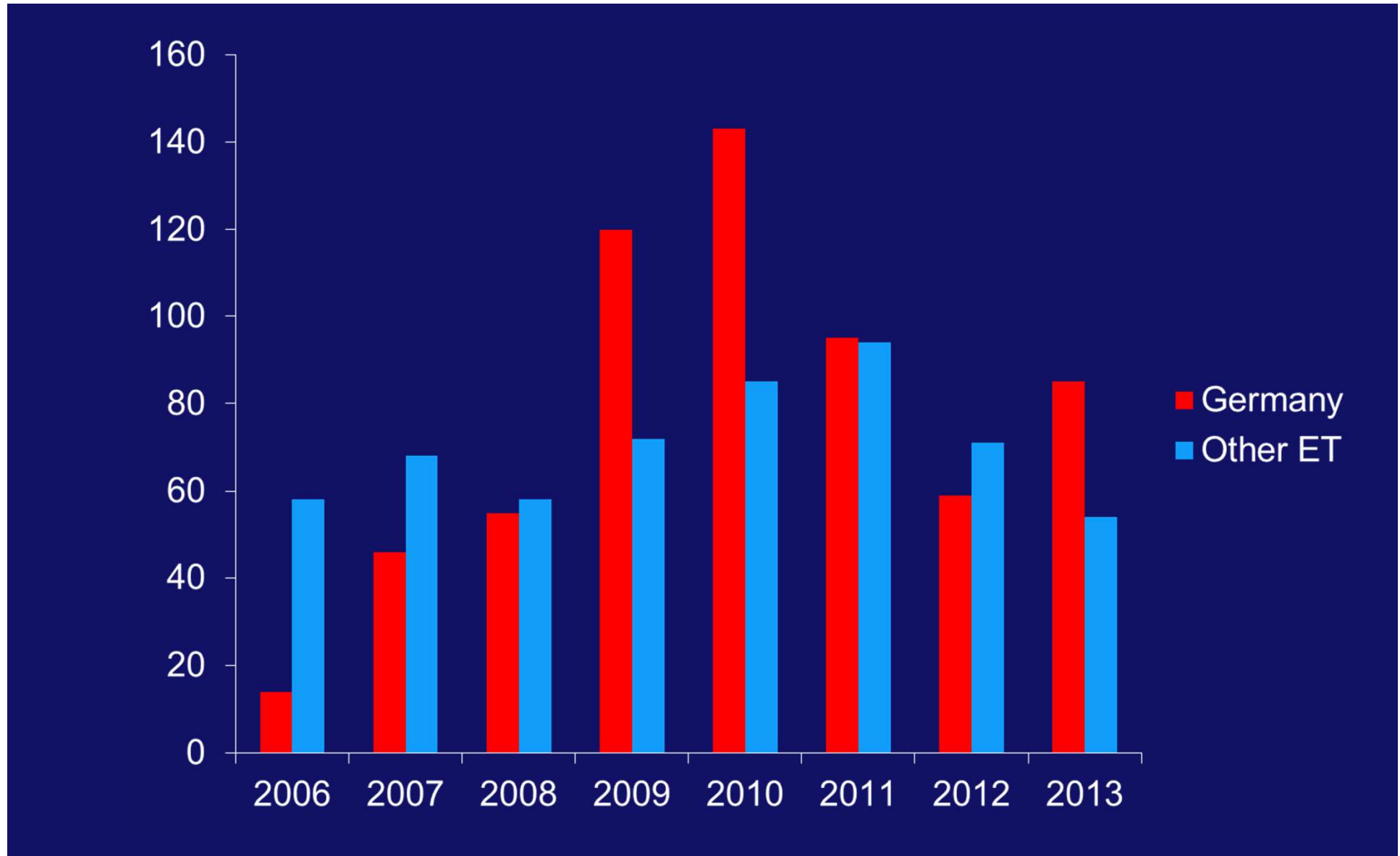
Crossmatch is performed
in the recipient center and
97% of them are negative.

Increased chance to receive a crossmatch negative organ.

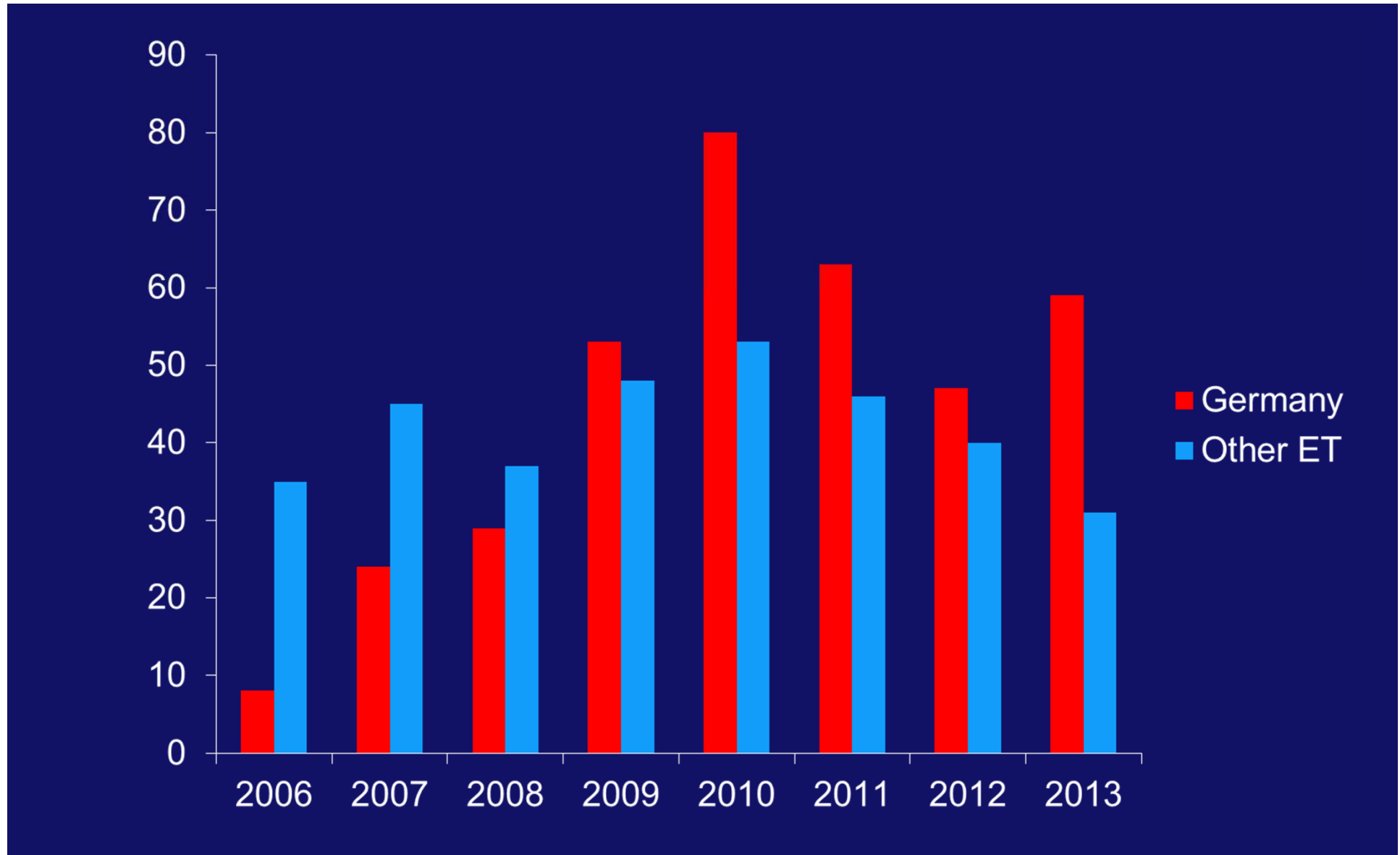
% patients transplanted



Patients included in the acceptable mismatch program

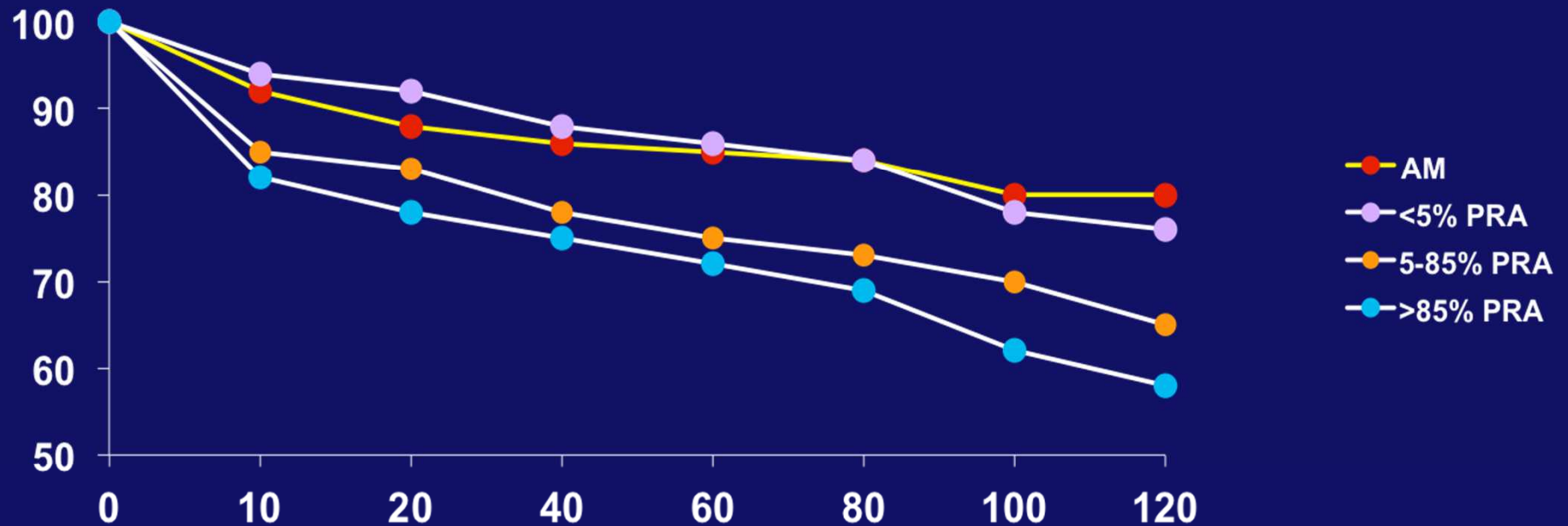


Patients transplanted via the acceptable mismatch program



Graft survival of AM patients is similar to that of non-sensitized patients.

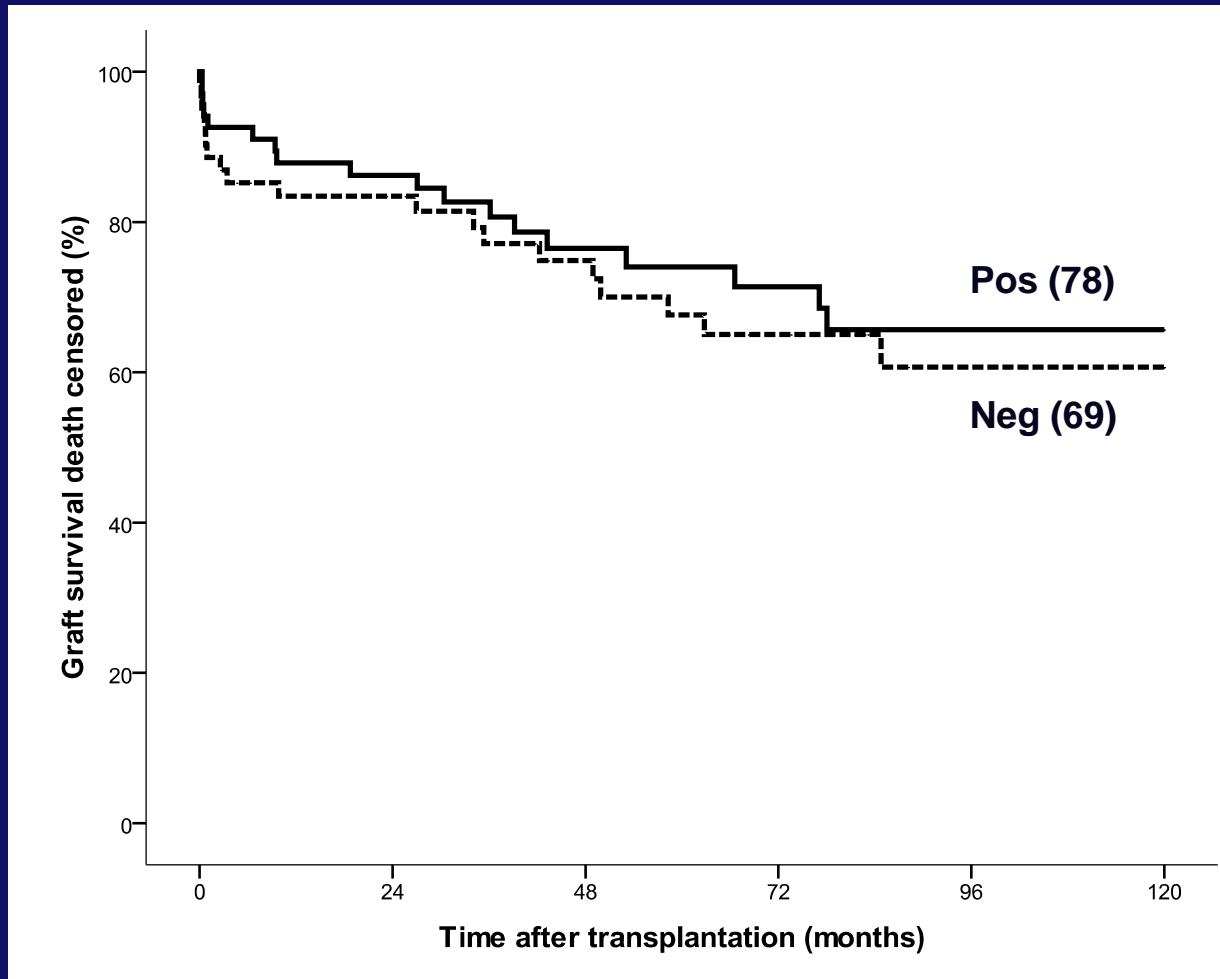
% graft survival



Months post transplantation.

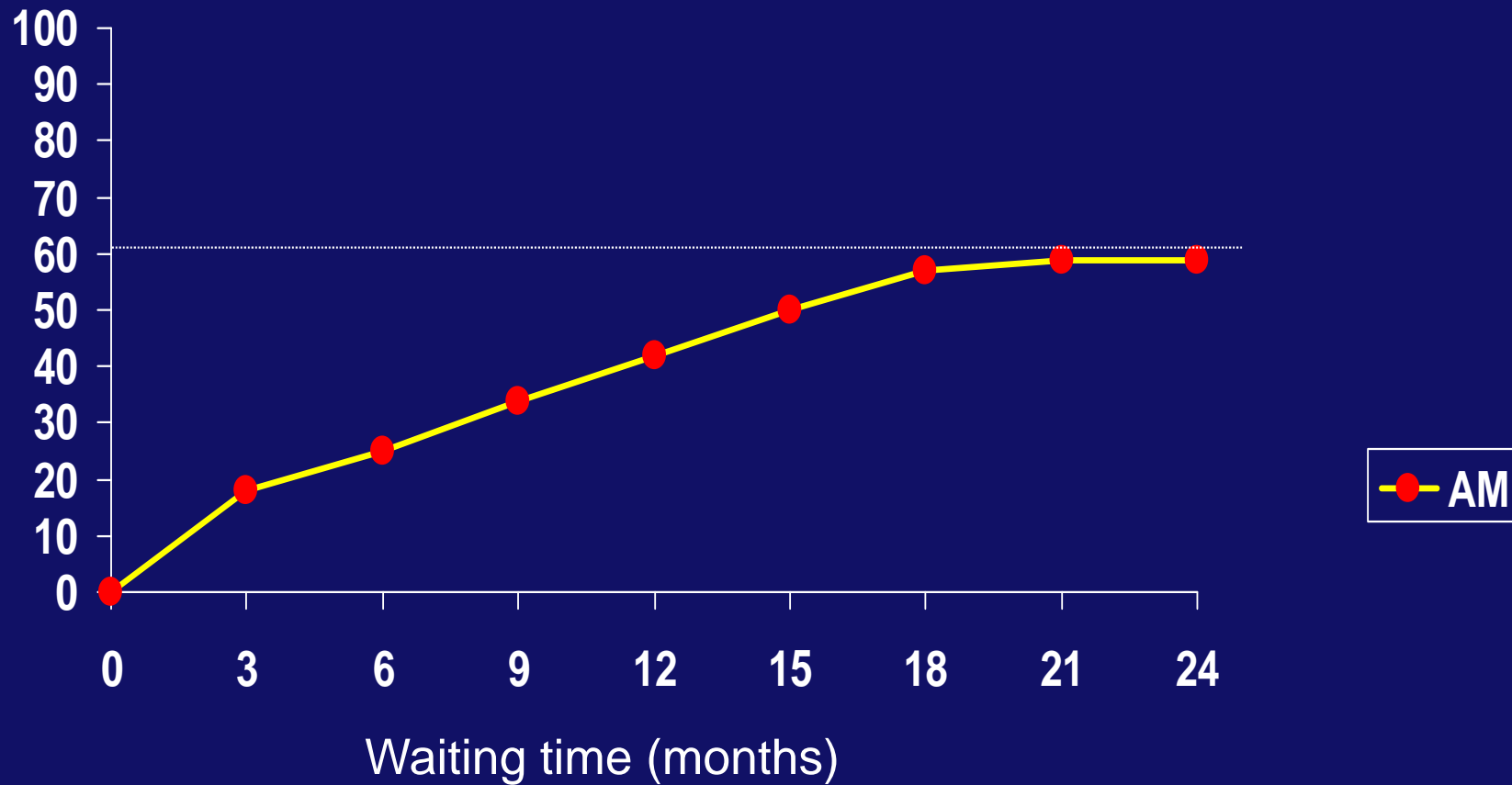
No difference in long term graft survival between highly sensitized patients transplanted with and without DSA in luminex

Patients from Leiden and Rotterdam transplanted via the AM program on basis of a negative CDC crossmatch



However, not all patients can be transplanted via the AM program

% patients transplanted



- Calculation of the expectation to find a compatible donor based on the HLA types of $\geq 30,000$ actual organ donors within Eurotransplant.
- Parameters: blood group compatibility and compatibility with the combination of the patients HLA, B, DR type and the defined acceptable mismatches.

The frequency calculator can also be used to further characterize antibody profile

Donor Frequency Calculator 2.0

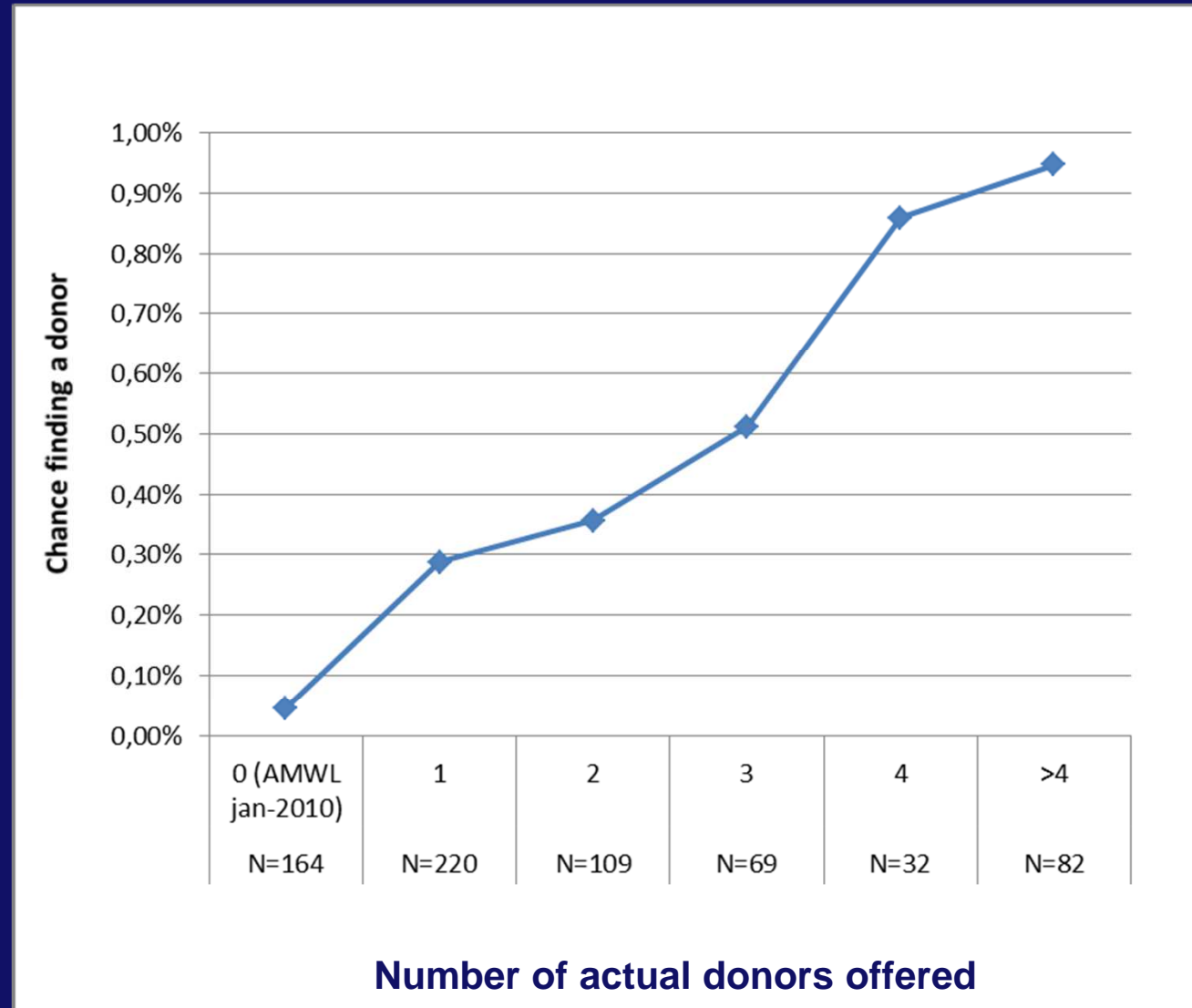
File Extra

Donor Frequency Calculator 2.0

		ABO Compatible	ABO Identical
<input type="button" value="Frequency"/>			
<input type="button" value="Clear"/>	Frequency with acceptables	0.104%	0.046%
<input type="button" value="Exit"/>	Frequency without unacceptables	3.701%	0.792%

<p>A_1 <input type="text" value="A29"/></p> <p>A_2 <input type="text" value="A68"/></p> <p>B_1 <input type="text" value="B44"/></p> <p>B_2 <input type="text" value="B51"/></p> <p>DR_1 <input type="text" value="DR7"/></p> <p>DR_2 <input type="text" value="DR13"/></p> <p>Blood <input type="text" value="B"/></p>	<p style="text-align: center;">Acceptable Antigens</p> <div style="border: 1px solid black; padding: 5px; min-height: 100px;"> <p>A23,A24,A25,A11,A31,A69,B52,B77,B38,B49,B53,B59,</p> </div> <p style="text-align: center;">Unacceptable Antigens</p> <div style="border: 1px solid black; padding: 5px; min-height: 100px;"> <p>A1,A2,A3,B7,B8,B22,B27,B35,B60,B41,B42,B46,CW6,CW15,DR8,D7,DQ4,</p> </div>
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Calculated chance to be transplanted is indeed predictive for the number of actual donors offered.



Current status

- The acceptable mismatch (AM) program is a well accepted tool to enhance transplantation of highly sensitized patients.
(>1000 patients transplanted).
- However, a subgroup of patients does not benefit from this program: especially patients with rare HLA phenotypes in relation to the donor population remain on the waiting list.
- For these patients, the options are:

Desensitization: removal of donor specific antibodies.

A larger donor pool : a Europe wide acceptable mismatch program

EUROSTAM: A **EURO**pe-wide **S**trategy to enhance **T**ransplantation of highly sensitized patients on basis of **A**cceptable HLA **M**ismatches .

- **Simulation studies on basis of the HLA phenotypes of the actual deceased kidney donor populations of the participating countries and organizations: Czech Republic, France, Greece, Spain, UK and Eurotransplant.**
- **Additional simulation studies on basis of the HLA phenotypes in different European countries.**
- **Transplantation of a number of patients in order to make an inventory of the logistic problems associated with a Europe wide AM program. (coordinated by Eurotransplant).**



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