

Significance of donor H&I and impact on organ recipients

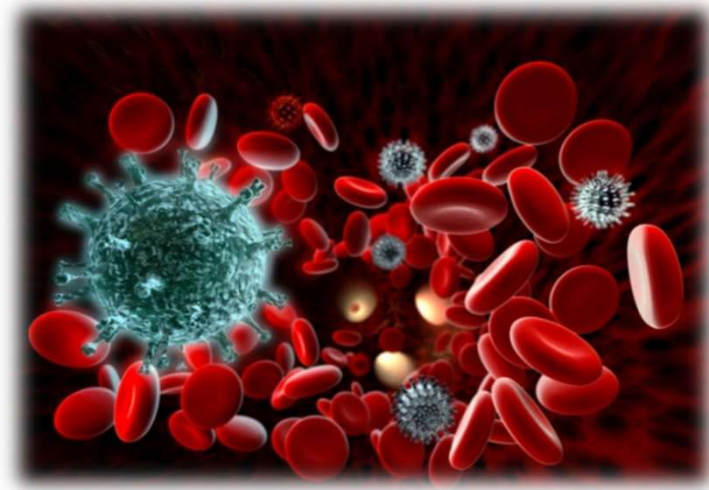
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Outline

- What is HLA?
- Why is it important in transplantation?
 - HLA matching
 - Sensitisation to HLA
 - Donor and recipient crossmatching

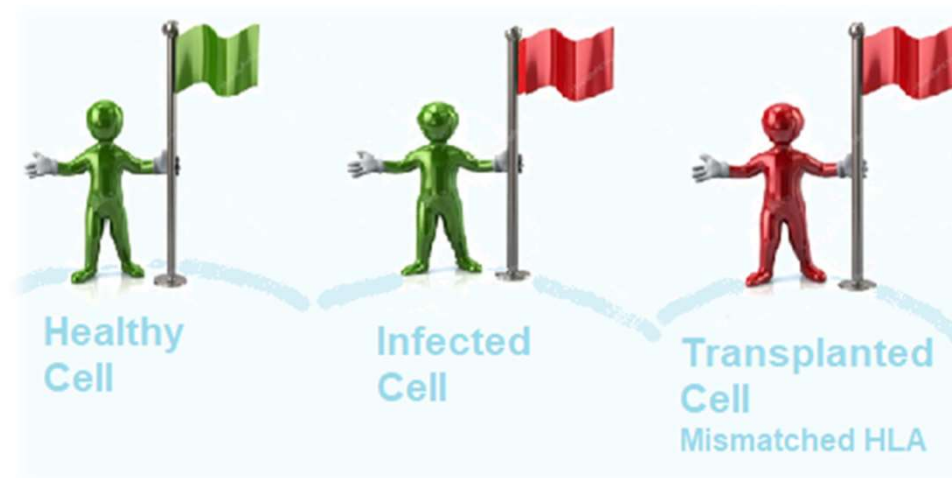
What are HLA types?

- HLA types are structures (antigens) found on almost all cells of the body
- Includes cells that make up your tissues and organs
- In blood they are found on white blood cells and platelets, but not on red blood cells
- Play an important role in the immune system



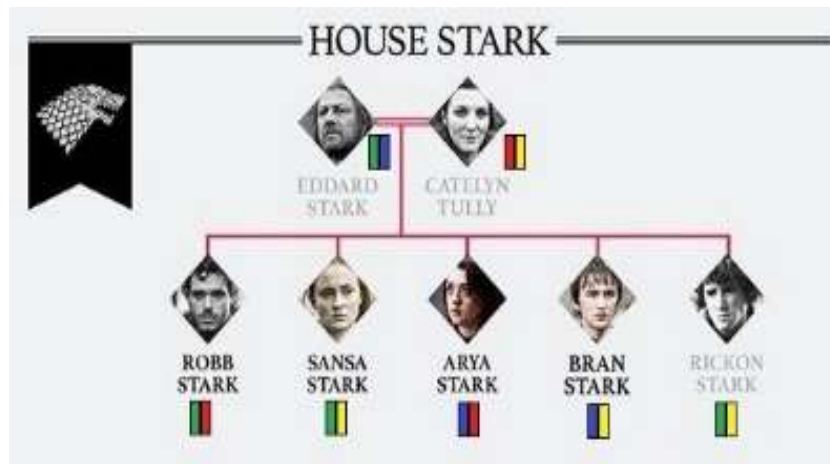
What are HLA types?

- Acts like a flag on the cell surface
 - Indicate to the immune system whether a response is needed
- Healthy cell - No response
- Infected cell – Immune Response
- Transplanted Cell - Rejection



What are HLA types?

- Everyone has two sets of HLA types
- Inherit 1 set from each parent
- Only a 1 in 4 chance of siblings being matched



What are HLA types?



- HLA types can be defined at different levels
 - Resolution
- Dog
- Spaniel
- Cocker Spaniel
- Blue Roan

HLA Types

Broad Specificity- Dog

HLA-A2, A3; B5, B15; Cw1, Cw3; DR6, - DR52, -; DQ1,

Split Specificity - Spaniel

HLA-A2, A3; B51, B62; Cw1, Cw10; DR13; DR52, -; DQ6,

Allele - Cocker Spaniel

HLA-A*02:01, A*03:01; B*15:01, B*51:01; C*01:02, C*03:04;
DRB1*13:01, DRB1*13:02; DRB3:03:01, - DQA1* 01:02
DQA1*01:03;DQB1*06:04, DQB1*06:03 DPA1*01:03
DPA1*02:01;DPB1*04:02 DPB1:02:01



There are many different forms of HLA Types

Gene	Alleles (Cocker)	Split Antigens (Spaniel)	Broad Antigens (Dog)
HLA-A	6,192	28	11
HLA-B	7,431	60	30
HLA-C	6,067	18	16
HLA-DRB1	3,391	20	11
HLA-DQB1	1,232	9	4

Approximated figures

HLA Matching/ Mismatching

HLA-A,B,DR
Mismatch grade

Donor

HLA-A1, A2, B7, B8, DR3, DR4

Recipient

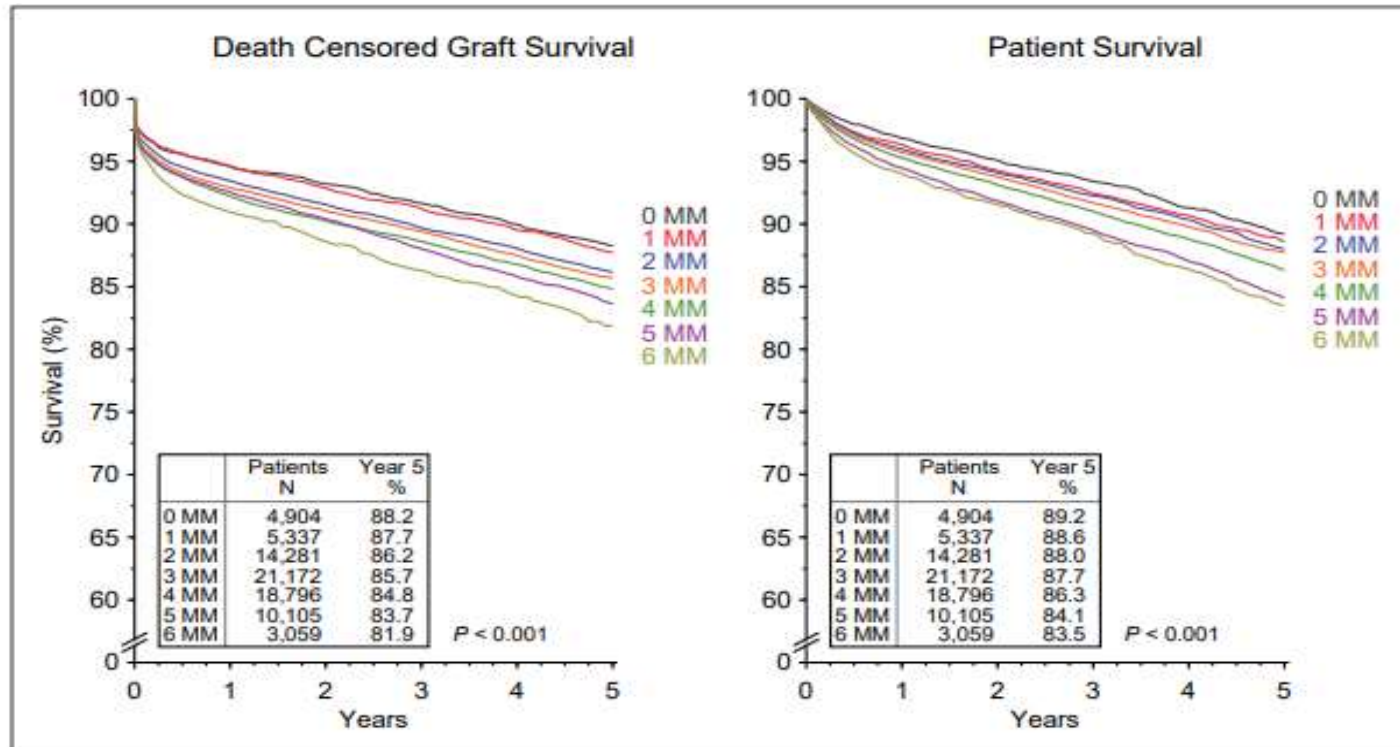
A HLA-A1, A2, B7, B8, DR3, DR4 000

B HLA-A1, A3, B7, B8, DR3, DR4 100

C HLA-A1, A9, B5, B8, DR3, DR4 110

D HLA-A3, A9, B5, B8, DR3, DR7 211

Collaborative Transplant Study Data –HLA matching 2005-2014



We observed a 71 % increase in death censored graft failures from 0 to 6 HLA mismatches and Cox multivariate analysis showed a mean hazard ratio of 1.09 per HLA mismatch (95% CI 1.07–1.10, *P* < 0.001). The corresponding hazard ratio for patient survival was 1.04 (95% CI 1.03–1.06, *P* < 0.001).

Why do we HLA type

Assess matching and likelihood of receiving a well matched graft

Matchability is a measure of how difficult it is to match a patient with an organ donor in the UK.

This score takes into account a patient's blood type, HLA type and unacceptable antigens.

A patient with a score = 1 is defined as easy to match and a score = 10 as difficult to match.

Predict graft survival

Prevent sensitisation (antibody production)

poorly matched graft = high sensitisation

high frequency single mismatch e.g. HLA-A2

Assist donor selection e.g. in living donor transplant

HLA Types

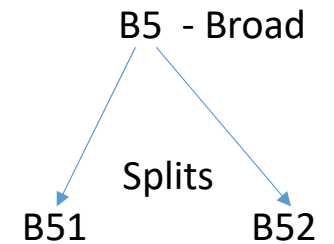
Broad Specificity Used for offering/assigning mismatch grades 000,110,222 etc.

HLA-A2, A3; B5, B15; DR6, DR7;

Deceased donor typing is at this level -

HLA-A*02, A*03; B*15:01 (62), B*51; C*01, C*03; DRB1*13, DRB1*07; DRB3:03 (52), DRB4*01; DQA1* 01:02, DQA1*01:03; DQB1*06, DQB1*02; DPB1*04:02, DPB1:02:01

Enables consideration of recipients antibodies (unacceptable antigens)



Antibodies

- Antibodies play a crucial role in our immune system
 - Bind to target
 - Neutralise
 - Recruit other cells to engulf target
 - Start chemical cascade which will kill the target
- Help to destroy bacteria and viruses
- HLA Antibodies are very significant in transplantation
- Antibodies can cause rejection
- In worst case can cause irreversible damage to the transplant

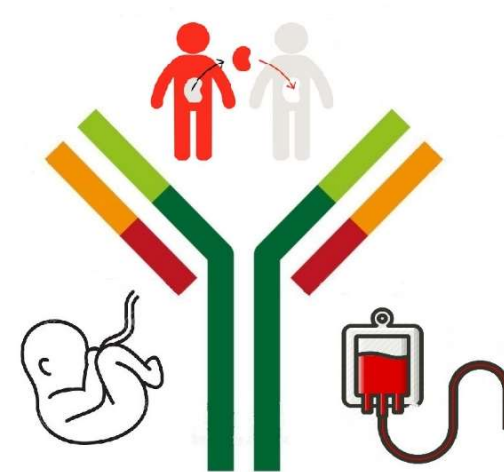
NHS

Blood and Transplant



HLA antibodies

- Patients can make HLA-antibodies in different ways
 - Pregnancy
 - Transplantation
 - Transfusion
- Patients with antibodies are “sensitised”
- If a patient is highly sensitised they become very difficult to transplant
- Calculated Reaction Frequency (cRF) – percentage of donors in pool of 10,000 with whom the donor is antibody incompatible



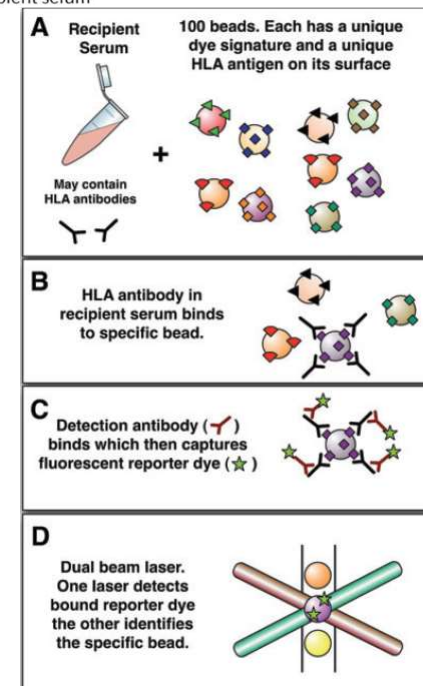
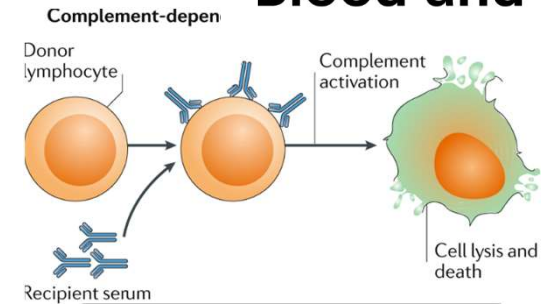
Laboratory Testing

- HLA antibody Detection and Definition

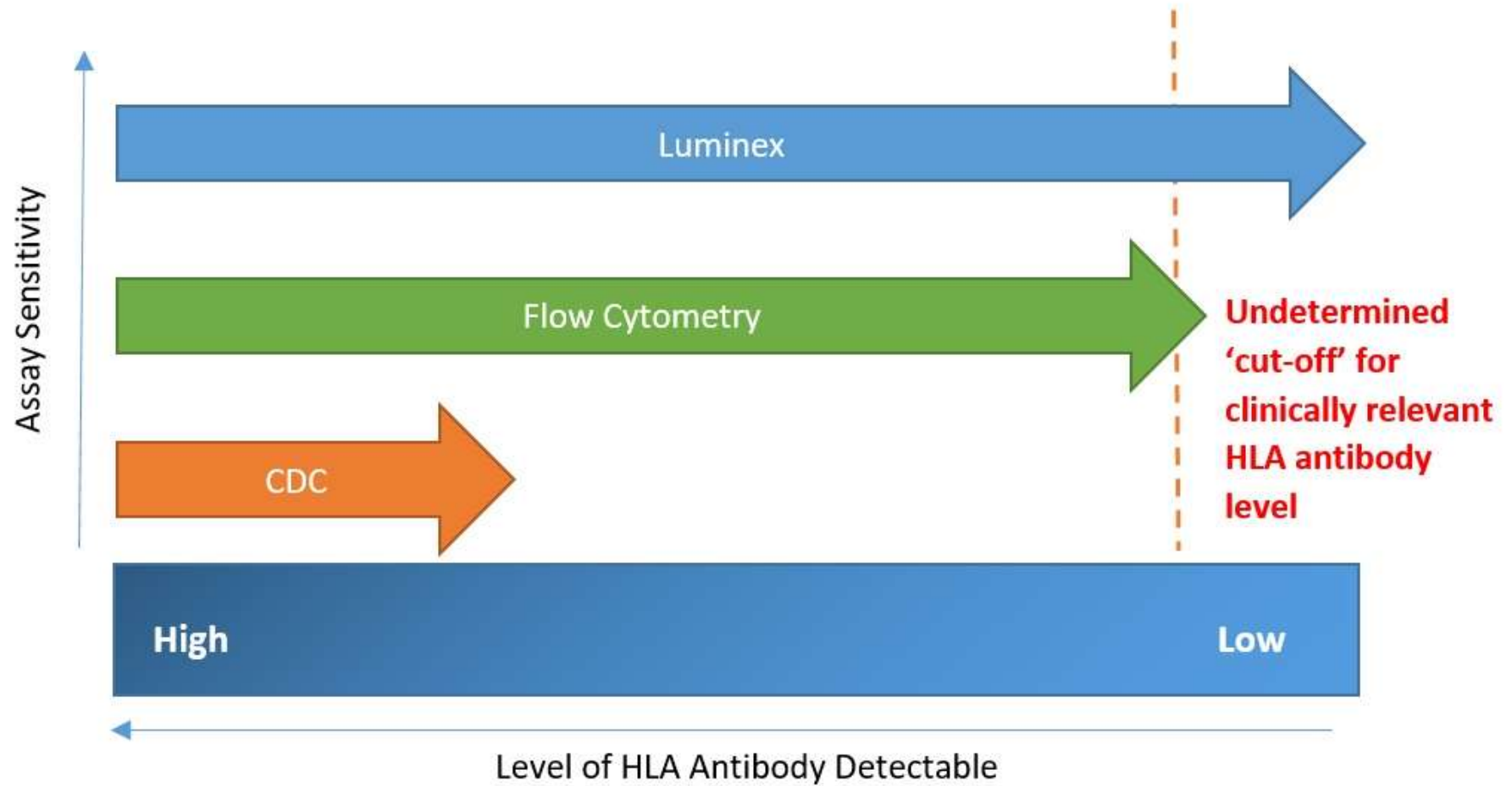
2 techniques

- CDC
 - detects “strong” antibodies which would cause instant rejection
- Luminex
 - Sensitive technique
 - Detects “weak” and “strong” antibodies
 - “Weak” antibodies increase risk of transplant but it may still be possible to transplant

Blood and Transplant



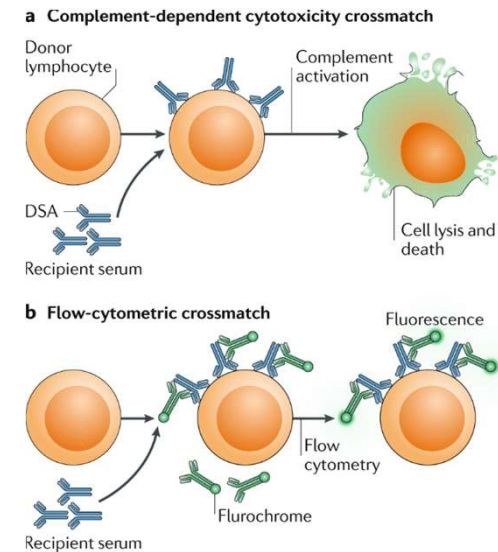
Antibody Testing – Techniques and Sensitivity



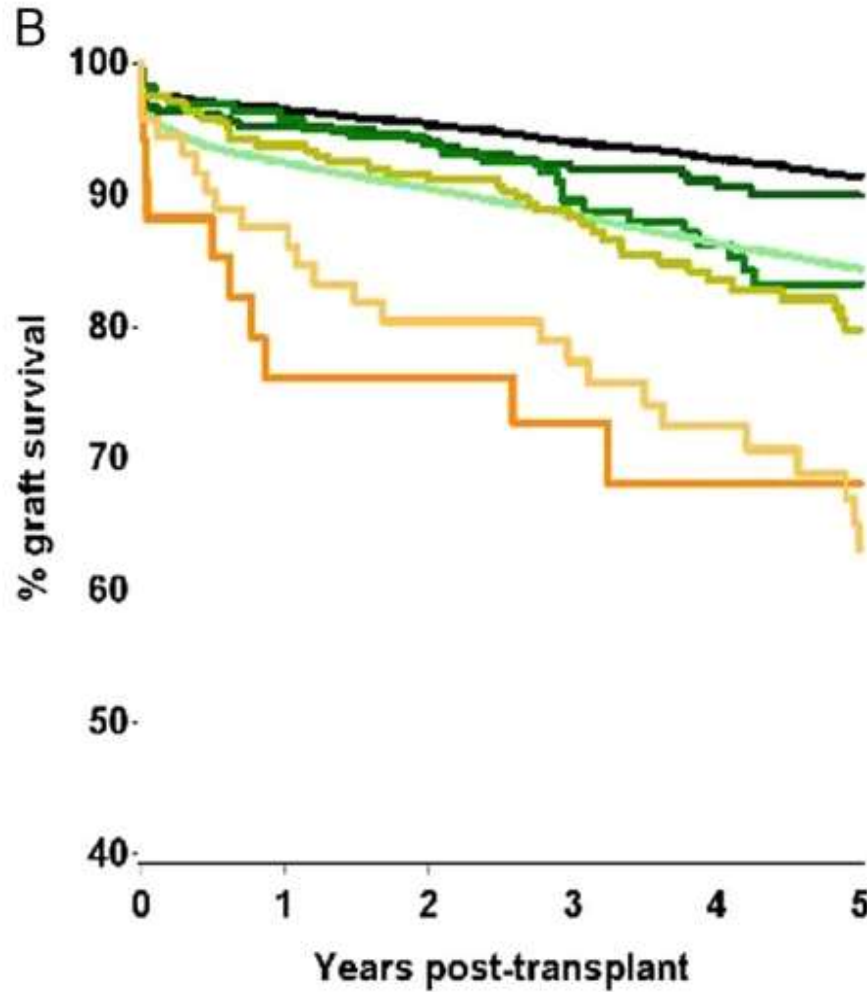
Laboratory Testing

Blood and Transplant

- Crossmatching
 - Specific test between a recipient and donor
 - Kidney and Pancreas patients
 - Used to determine risk of transplant
 - Decide whether the transplant can go ahead
- Virtual Crossmatch
 - Use donor HLA-type and recipient antibody profile to predict crossmatch result
 - Quicker results
 - Reduces cold ischaemic time
 - Reduces laboratory workload on-call
- Physical Laboratory Crossmatch
 - 2 different techniques
 - CDC XM
 - Detects strong antibodies
 - Flow Cytometry XM
 - Able to detect weak antibodies
 - Not HLA-specific

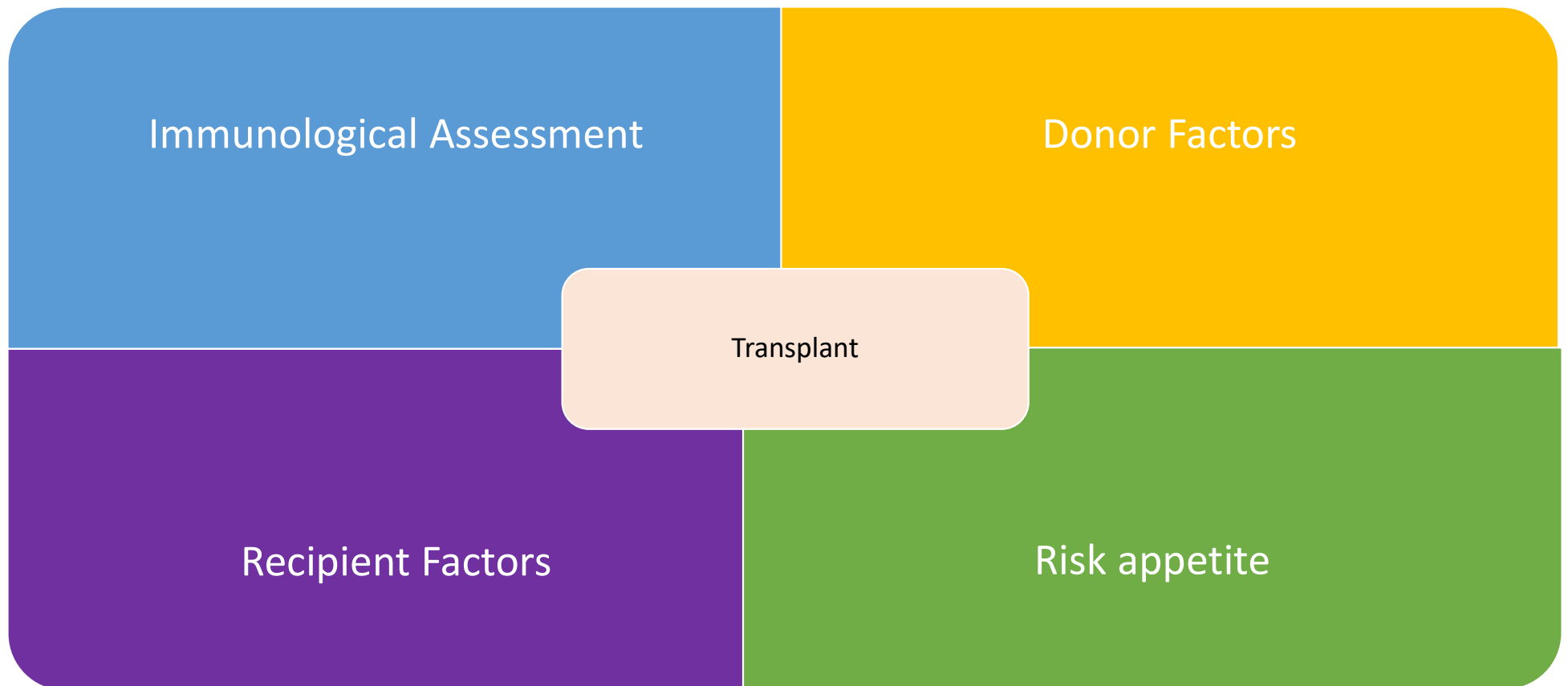


Blood and Transplant



	N	% Surv	95% CI
Compatible LD	7,822	91	91-92
ABO incompatible LD	357	90	86-93
Compatible DD	16,292	84	84-85
HLA I LD and DD CDC neg, Flow neg, DSA SPA pos	165	83	76-89
HLA I LD and DD CDC neg, Flow pos, DSA SPA pos	246	78	73-85
HLA I LD and DD: CDC not tested, Flow pos, DSA SPA pos	34	68	48-82
HLA I LD and DD CDC pos, Flow pos, DSA SPA pos	72	63	50-74

Assessing Risk



Why do we test for HLA antibodies

Define HLA antibodies and agree unacceptable antigen listing

Monitor every three months to check for increase or decrease

Check after sensitisation events e.g. transfusion, graft nephrectomy

Prevent hyperacute rejection

Avoid **unexpected** positive crossmatches

Determine cRF (calculated reaction frequency) – predict likelihood of receiving transplant