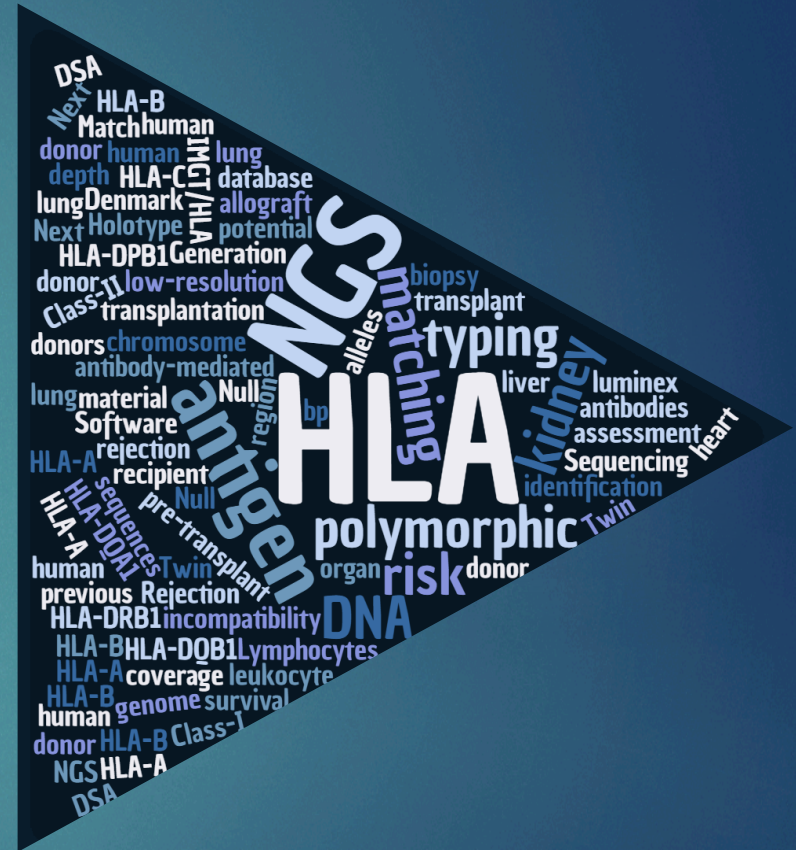
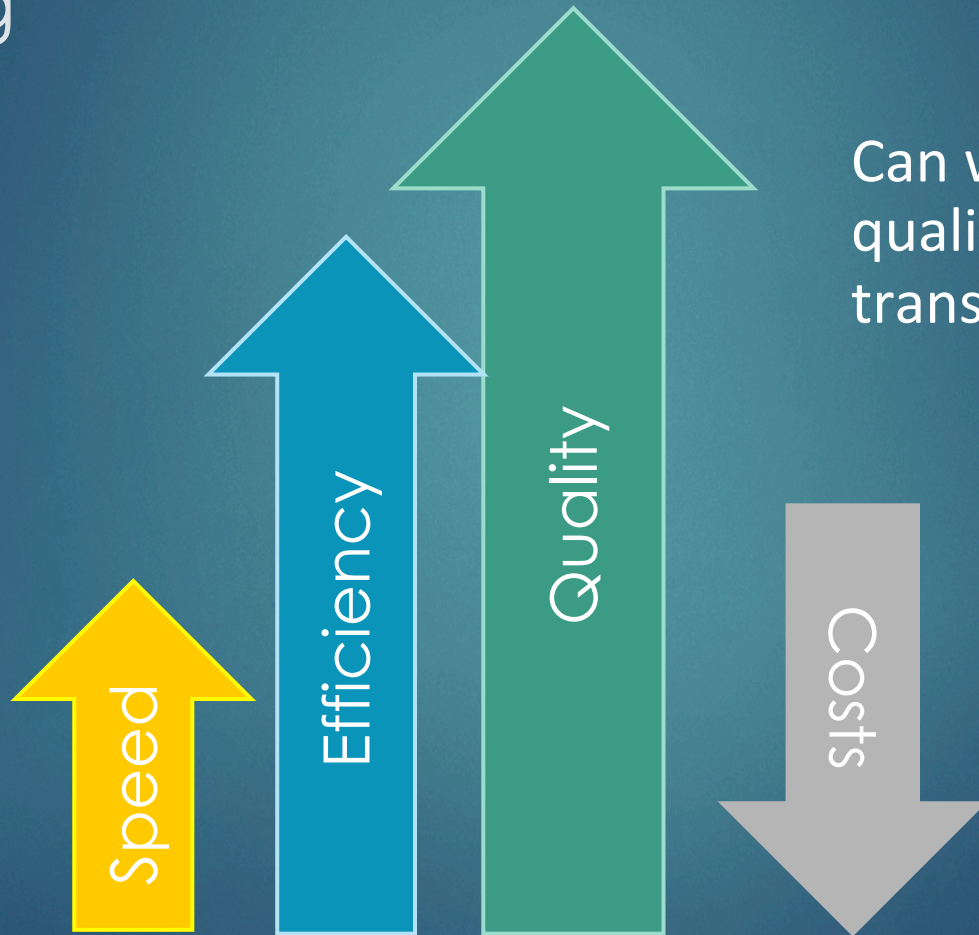


Donor Selection for Solid Organ Transplantation Guided by NGS High Resolution HLA Typing in Combination with PIRCHE

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The immediate benefits of changed workflow from only low resolution HLA typing to high resolution NGS based typing



Can we use the higher quality in solid organ transplantation?



Benefits from high-resolution HLA in organ transplantation

Risk assessment - allele specific antibodies

Detection of novel and rare null alleles

Selecting the best donor/recipient pair



Finding the immunologically best donor-recipient pair

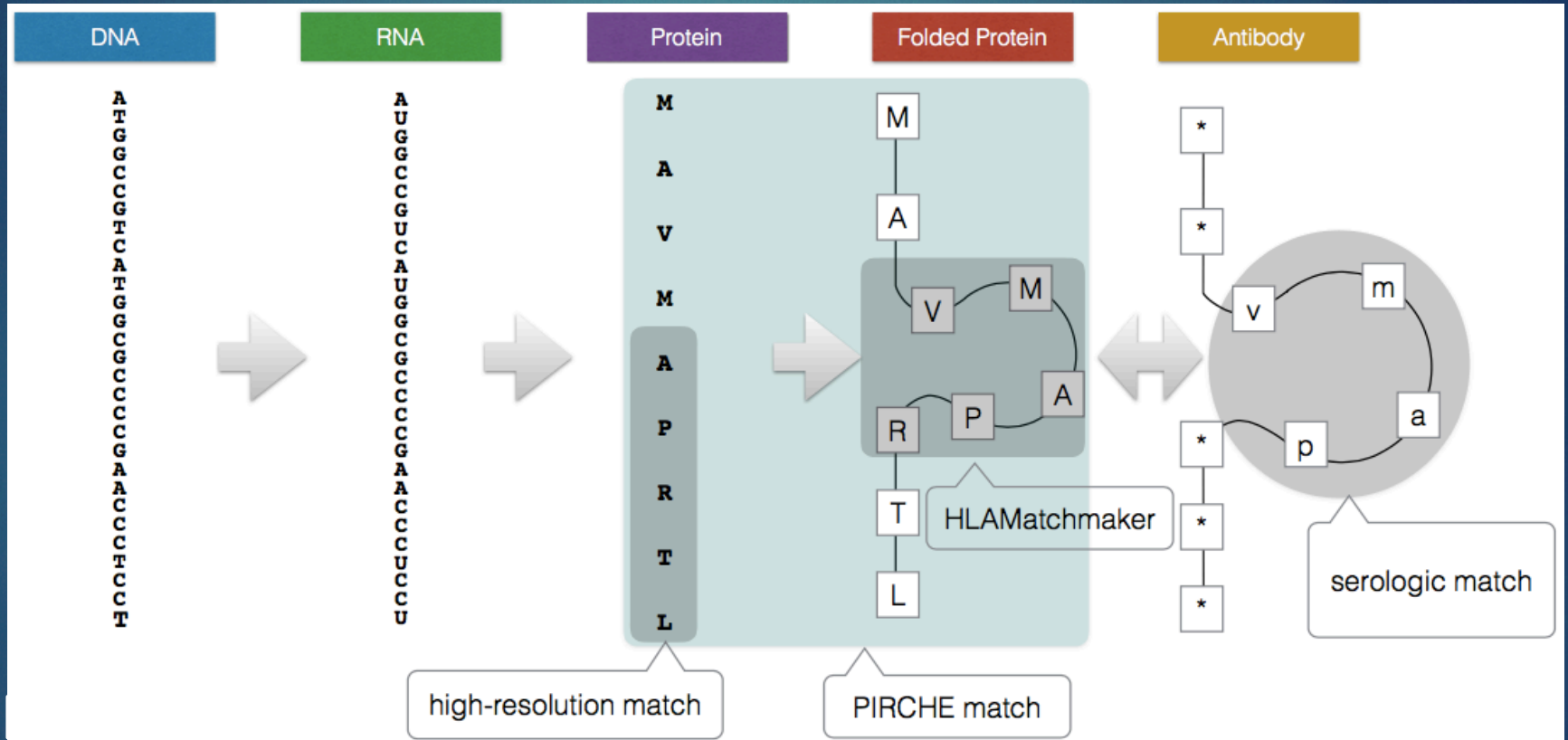
- ▶ HLA antigen Mismatches
- ▶ Select the donor/ recipient pair with fewest mismatches
- ▶ Does not take into account
 - ▶ How different the HLA antigens are
 - ▶ Which / how many immunologically relevant epitopes the recipient might encounter



Finding the immunologically best donor-recipient pair using Predicted Indirectly Recognizable HLA Epitopes

- ▶ Prediction of T cell related immune responses against HLA derived peptides after transplantation
- ▶ Provides the number of donor- mismatched peptides, which may be detected by the patients' T cells.
- ▶ Selecting kidney donors with a lower PIRCHE-II score reduces immunological risk after transplantation.

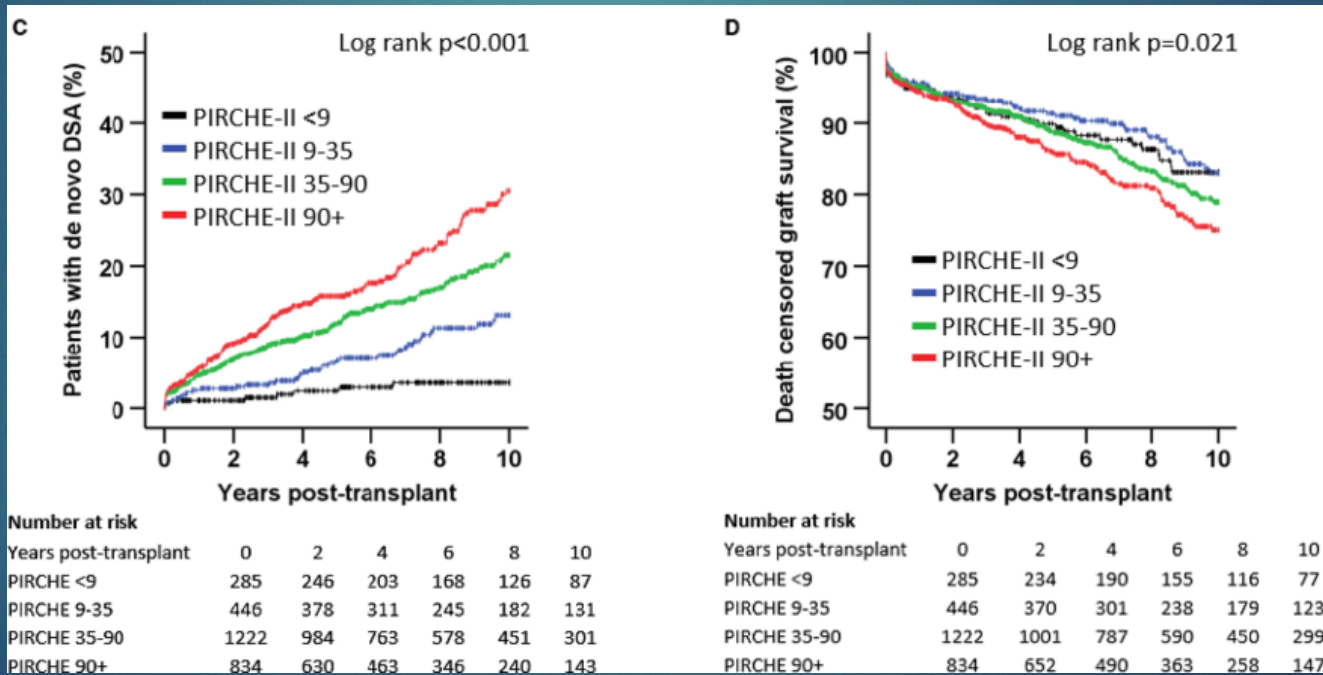
Different matching strategies





Kidney transplant study, Germany

- Retrospective single-center study, n=2787
- PIRCHE-II correlates with de novo DSA and graft survival



Retrospective analysis of kidney transplants with multiple donors

HOW CAN WE
EXPLOIT THE
FULL
POTENTIAL OF
HIGH
RESOLUTION
HLA DATA
WITH THE HELP
OF PIRCHE



Direct link to PIRCHE in HLA Twin Case I – 10 year old patient with 5 related donors

Genotyping sample result

Sample: 600441702411-20171009G-MQMA-30_S6_L001_R1_001_2017-10-12_08-52-00 Application version: 2.2.0
Application build id: 0ab65432ef1f2fb267cab0ba2e3679ef9e02fbcd

Database version: 3.28.0
Displaying 7 loci out of ...
Displaying best matches of ...

Tools: Browse Alignment, Browse Allele 1, Browse Allele 2, Genotype Details, Show Mismatches, Show Novelties, Setup Loci, Setup Filters, Best Matches Only, Assignment State, Genotype Precision, Assignment, Comments, Send For Approval, Approve Result, Reject/Revoke Approval, Export Result, Turn LD on/off, **Show details**, Send to Pirche

State	Allele	HLA-A	HLA-B	HLA-C	HLA-DPB1	HLA-DQA1	HLA-DQB1	HLA-DRB1
Progress	Allele 1	✓ HLA-A*02:01:01:02L ✓ HLA-A*02:01:01:16 ✓ HLA-A*02:01:01:01	✓ HLA-B*07:02:01:03 ✓ HLA-B*07:02:01:01	✓ HLA-C*03:04:01:02 ✓ HLA-C*03:04:01:01	✓ HLA-DPB1*04:01:01:01	✓ HLA-DQA1*01:02:01:01	✓ HLA-DQB1*03:02:01:01	✓ HLA-DRB1*04:04:01
Progress	Allele 2	✓ HLA-A*31:01:02:01	✓ HLA-B*40:01:02:02 ✓ HLA-B*40:01:02:01 ✓ HLA-B*40:01:02:04	✓ HLA-C*07:02:01:09 ✓ HLA-C*07:02:01:10 ✓ HLA-C*07:02:01:11	✓ HLA-DPB1*05:01:01:01 ✓ HLA-DPB1*05:01:01:02	✓ HLA-DQA1*03:01:01	✓ HLA-DQB1*06:02:01:01	✓ HLA-DRB1*15:01:01:03 ✓ HLA-DRB1*15:01:01:04

HLA-A
HLA-B
HLA-C
HLA-DPB1
HLA-DQA1
HLA-DQB1
HLA-DRB1

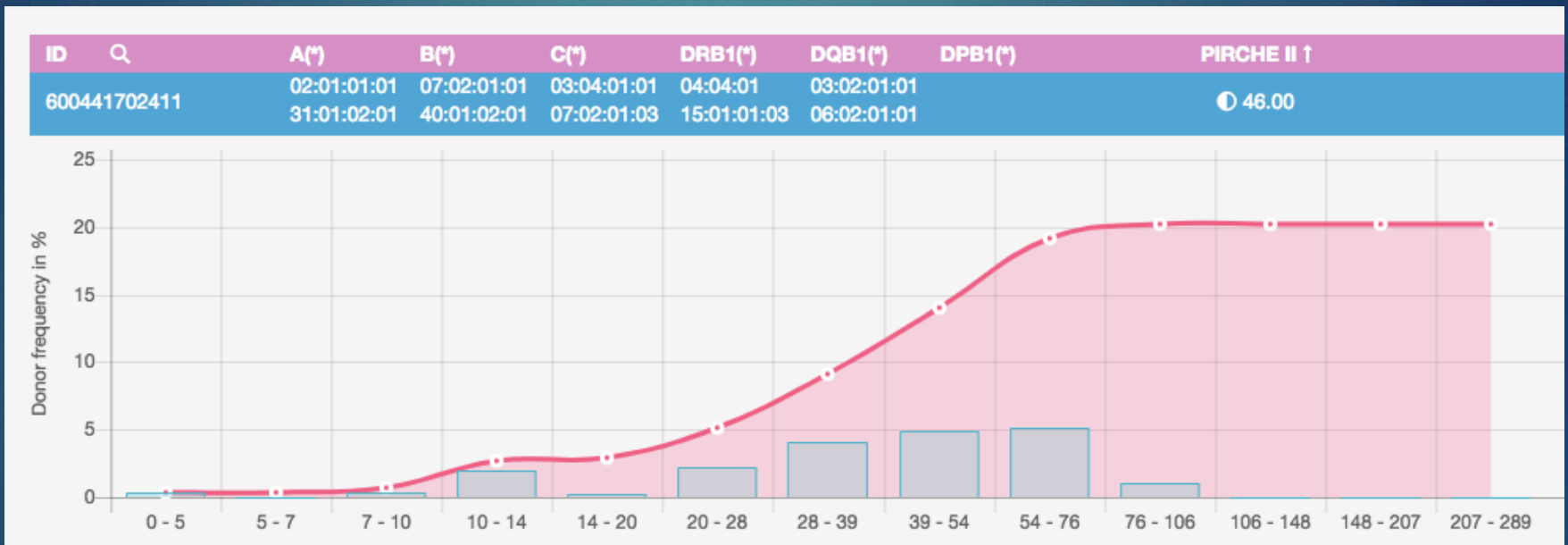
Genotype Quality control Data statistics

- ✓ HLA-DPB1*04:01P + HLA-DPB1*05:01P
 - ✓ HLA-DPB1*04:01:01G + HLA-DPB1*05:01:01G
 - #1 ✓ HLA-DPB1*04:01:01:01 + HLA-DPB1*05:01:01:01 Exon mismatches 0/0 Non-exon mismatches 0/0 Total mismatches 0/0
 - #2 ✓ HLA-DPB1*04:01:01:01 + HLA-DPB1*05:01:01:02 Exon mismatches 0/0 Non-exon mismatches 0/0 Total mismatches 0/0

Show details
Send to Pirche



Risk profile of patient



50% of the potential donors will have a PIRCHE II lower than 46

Calculated PIRCHE II values



PIRCHE® organ transplant report for patient ID: 600441702411

Created by mette.christiansen@rm.dk



Patient / Donor ID	A*	B*	C*	DRB1*	DQB1*	DPB1*	PIRCHE II
600441702411	02:01:01:01 31:01:02:01	07:02:01:01 40:01:02:01	03:04:01:01 07:02:01:03	04:04:01 15:01:01:03	03:02:01:01 06:02:01:01	04:01:01 05:01:01	
400441702415	03:01:01:01 31:01:02:01	07:02:01:01 40:01:02:01	03:04:01:01 07:02:01:03	04:04:01 12:01:01:01	03:01:01:05 03:02:01:01	04:01:01:01 04:01:01:01	40.00
500441702418	02:01:01:01 02:01:01:01	07:02:01:01 27:05:02:01	01:02:01:01 07:02:01:03	01:01:01 15:01:01:03	05:01:01:03 06:02:01:01	04:01:01:01 05:01:01:01	54.00
000441702413	02:01:01:01 31:01:02:01	07:02:01:01 51:01:01:01	07:02:01:03 15:02:01:01	04:07:01:01 15:01:01:03	03:01:01:01 06:02:01:01	03:01:01:01 05:01:01:01	55.00
100441702416	02:01:01:01 31:01:02:01	40:01:02:01 51:01:01:01	03:04:01:01 16:02:01	01:01:01 04:04:01	03:02:01:01 05:01:01:03	02:01:02:04 04:01:01:01	67.00
800441702417	02:01:01:01 03:01:01:01	07:02:01:01 51:01:01:01	07:02:01:03 16:02:01	01:01:01 12:01:01:03	03:01:01:05 05:01:01:03	02:01:02:01 04:01:01:04	106.00



However, donor selection is more than immunology...

A	B	C	DRB1	DQA1	DQB1	DPA1	DPB1
*02:01,*31:01	*07:02,*40:01	*03:04,*07:02	*04:04,*15:01	*01:02,*03:01	*03:02,*06:02		*04:01,*05:01
*02:01,*31:01	*07:02,*51:01	*07:02,*15:02	*04:07,*15:01	*01:02,*03:03	*03:01,*06:02		*03:01,*05:01
*03:01,*31:01	*07:02,*40:01	*03:04,*07:02	*04:04,*12:01:01G	*03:01,*05:05	*03:01,*03:02		*04:01
*02:01	*07:02,*27:05	*01:02,*07:02	*01:01,*15:01	*01:01,*01:02	*05:01,*06:02		*04:01,*05:01
*02:01,*31:01	*40:01,*51:01	*03:04,*16:02	*01:01,*04:04	*01:01,*03:01	*03:02,*05:01	*01	*02:01,*04:01
*02:01,*03:01	*07:02,*51:01	*07:02,*16:02	*01:01,*12:01:01G	*01:01,*05:05	*03:01,*05:01	*01	*02:01,*04:01

- ▶ All 5 donors can be used.
- ▶ Donor 1 (father) is immunologically the best suited donor and donor 5 (uncle) is immunologically the least preferable donor.
- ▶ The patient has weak DSA against all donors - flowcytometric crossmatch is needed.
- ▶ Patient can't wait for deceased donor.
- ▶ **Donor 5** is - despite all - selected due to health problems with the other donors.



Case with two previous transplants

PIRCHE® organ transplant report for patient ID: 700441702638

Created by mette.christiansen@rm.dk



Patient / Donor ID	A*	B*	C*	DRB1*	DQB1*	DPB1*	PIRCHE II
700441702638	01:01:01:01 03:01:01:01	08:01:01:01 08:01:01:01	07:01:01:01 07:01:01:01	03:01:01:01 03:01:01:01	02:01:01 02:01:01		
800441702587 RAT2	01:01:01:01 03:01:01:01	08:01:01:01 57:01:01	06:02:01:01 07:01:01:01	03:01:01:01 03:01:01:01	02:01:01 02:01:01		12.00
900441800826 RAT1	<u>02:01:01:08</u> 03:01:01:01	08:01:01:01 <u>15:01:01:01</u>	<u>03:03:01:01</u> 07:01:01:01	03:01:01:01 <u>11:03:01</u>	02:01:01 <u>03:01:01:03</u>		24.00

First transplantation with mother in 2000

Needs second transplantation

- no repeated mismatches, PIRCHE II is low but there is a weak DSA

Conclusions



We initiated high-resolution HLA typing of organ recipients and donors for practical reasons (to fill up the NGS run) – BUT we received more:

NGS is extremely beneficial in regard to DSA

NGS enables detection of novel and rare null alleles

High resolution typing can be exploited along with PIRCHE to help selecting the best matched donor – we aim to use this prospectively