THE PRESENT AND FUTURE OF UNRELATED STEM CELL DONOR REGISTRIES

Marrow Donor Program Belgium
ALEJANDRO MADRIGAL
Nov 2017

ANTHONY NOLAN
saving the lives of people with blood cancer

Registry of Unrelated Donors: Main Changes Over the Last 10 Years

- Number of unrelated bone marrow donors
- Number of Registries around the word
- Number of HLA alleles described
- Increased resolution of typing techniques
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>32 million unrelated donors

>1 million transplants

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WHO WAS ANTHONY NOLAN?

- Anthony was born in 1971 with Wiskott-Aldrich syndrome
- A bone marrow transplant was the only known cure but there was no system or process to find a match
- In 1974 his mother, Shirley, started the world's first bone marrow register
- Anthony died in 1979 but the register continues to grow

ANTHONY NOLAN

saving the lives of people with blood cancer

(LON-11)LONDON. Dec.20(AP)Mrs. Nolan, right, of Australia,campaigning with friends in Downing Street here today just before the arrival of Australian Prime Minister Gough Whitlam. She is trying to get British and Australian Government aid to help cure her son,Anthony, who is suffering from a rare bone disease. Mrs. Nolan has also started an Anthony Nolan Appeal Fund to assist Westm inster Hospital to treat all child sufferers of blood and bone marrow diseases. (AP CABLEPHOTO)

ANTHONY NOLAN

1971	-	Anthony Nolan was born suffering from Wiskott-Aldrich Syndrome	
1974	-	Donor recruitment commenced to establish a panel of donors	
1979	-	Anthony died without receiving a transplant	
2017	-	Number of donors on Register UK	= >1000,000
2017	-	Number of donors provided for transplant	= 15,000

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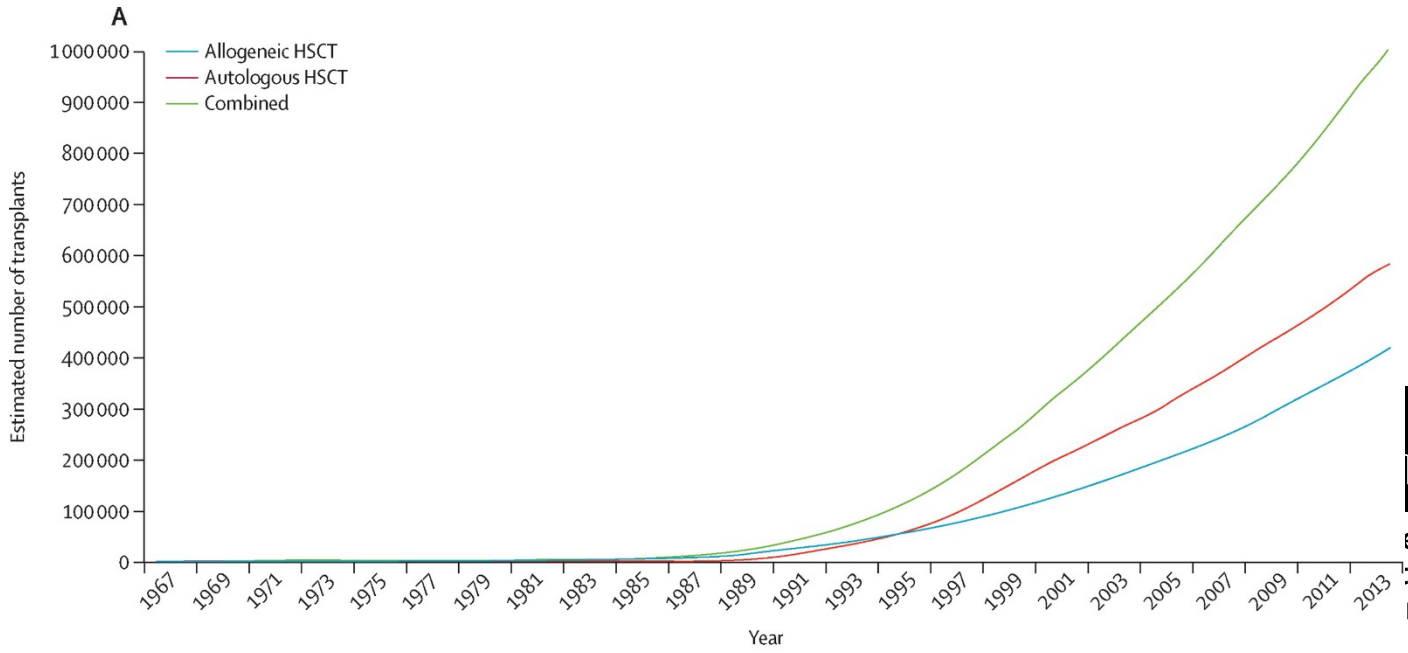
One million haemopoietic stem-cell transplants: a retrospective observational study

Alois Gratwohl, Marcelo C Pasquini, Mahmoud Aljurf, Yoshiko Atsuta, Helen Baldomero, Lydia Foeken, Michael Gratwohl, Luis Fernando Bouzas, Dennis Confer, Karl Frauendorfer, Eliane Gluckman, Hildegard Greinix, Mary Horowitz, Minako Iida, Jeff Lipton, Alejandro Madrigal, Mohamad Mohty, Luc Noel, Nicolas Novitzky, José Nunez, Machteld Oudshoorn, Jakob Passweg, Jon van Rood, Jeff Szer, Karl Blume†, Frederic R Appelbaum, Yoshihisa Kodera, Dietqer Niederwieser, for the Worldwide Network for Blood and Marrow Transplantation (WBMT)



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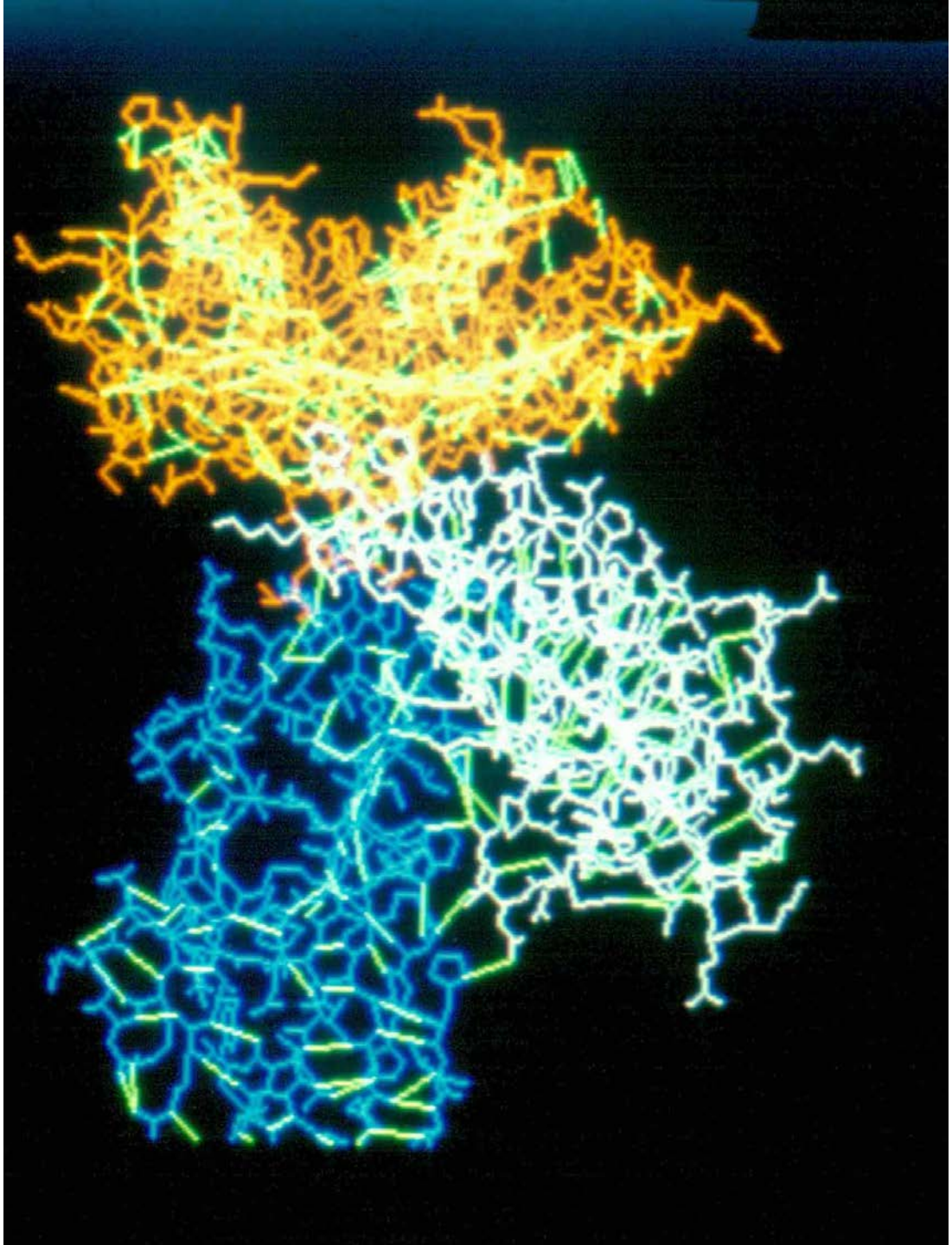

THE NUMBER OF RECOGNISED ALLELES AT EACH HLA LOCUS March/97

HLA-CLASS I

HLA-A	HLA-B	HLA-C
85	188	44

HLA- CLASS II

HLA-DRB	HLA-DQB1	HLA-DP
221	32	76

THE NUMBER OF RECOGNISED ALLELES AT EACH HLA LOCUS March/2007

HLA-CLASS I

HLA-A	HLA-B	HLA-C
485	816	262

HLA- CLASS II

HLA-DRB	HLA-DQB1	HLA-DP
543	75	125

THE NUMBER OF RECOGNISED ALLELES AT EACH HLA LOCUS Oct/2016

HLA-CLASS I

HLA-A	HLA-B	HLA-C
>3,500	>4,400	>3,100

HLA- CLASS II

HLA-DRB	HLA-DQB1	HLA-DP
>2,100	>950	>670

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HLA Typing Techniques

Serology

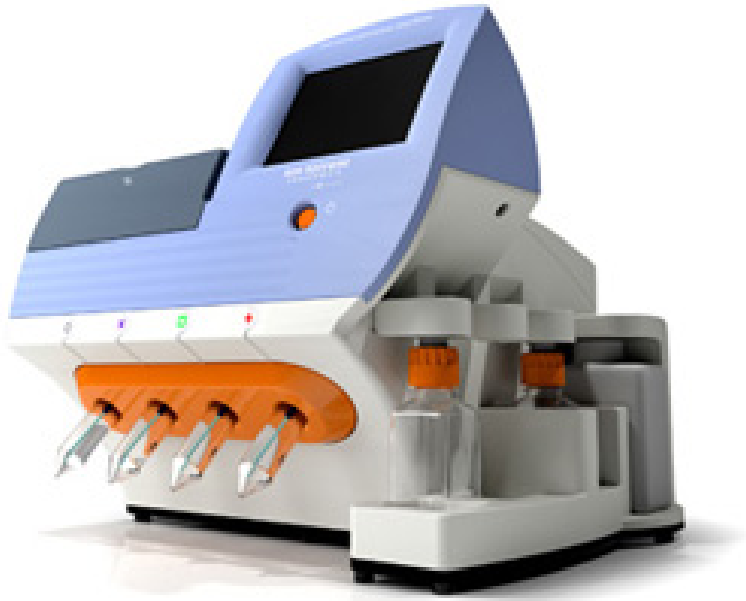
Uses antibodies to type for HLA molecules on viable cells

DNA based

- Sequence Specific Oligonucleotide Probing (SSOP)
- Sequence Specific Priming (SSP)
- **Sequencing Based Typing (SBT)**
- **Next Generation Sequencing (NGS)**
- **Third Generation Sequencing (TGS)**

The future of HLA typing

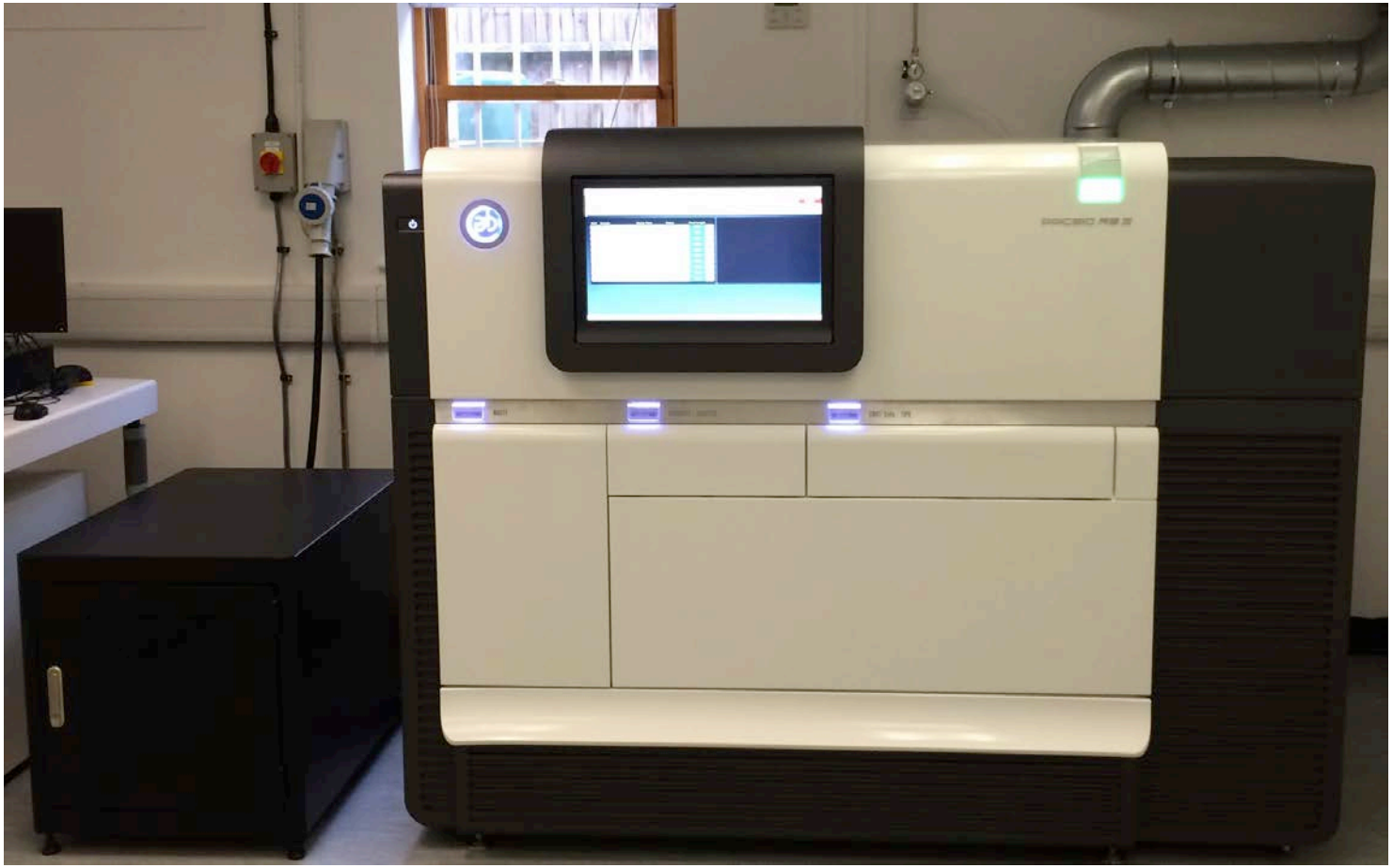
Illumina Mi-Seq



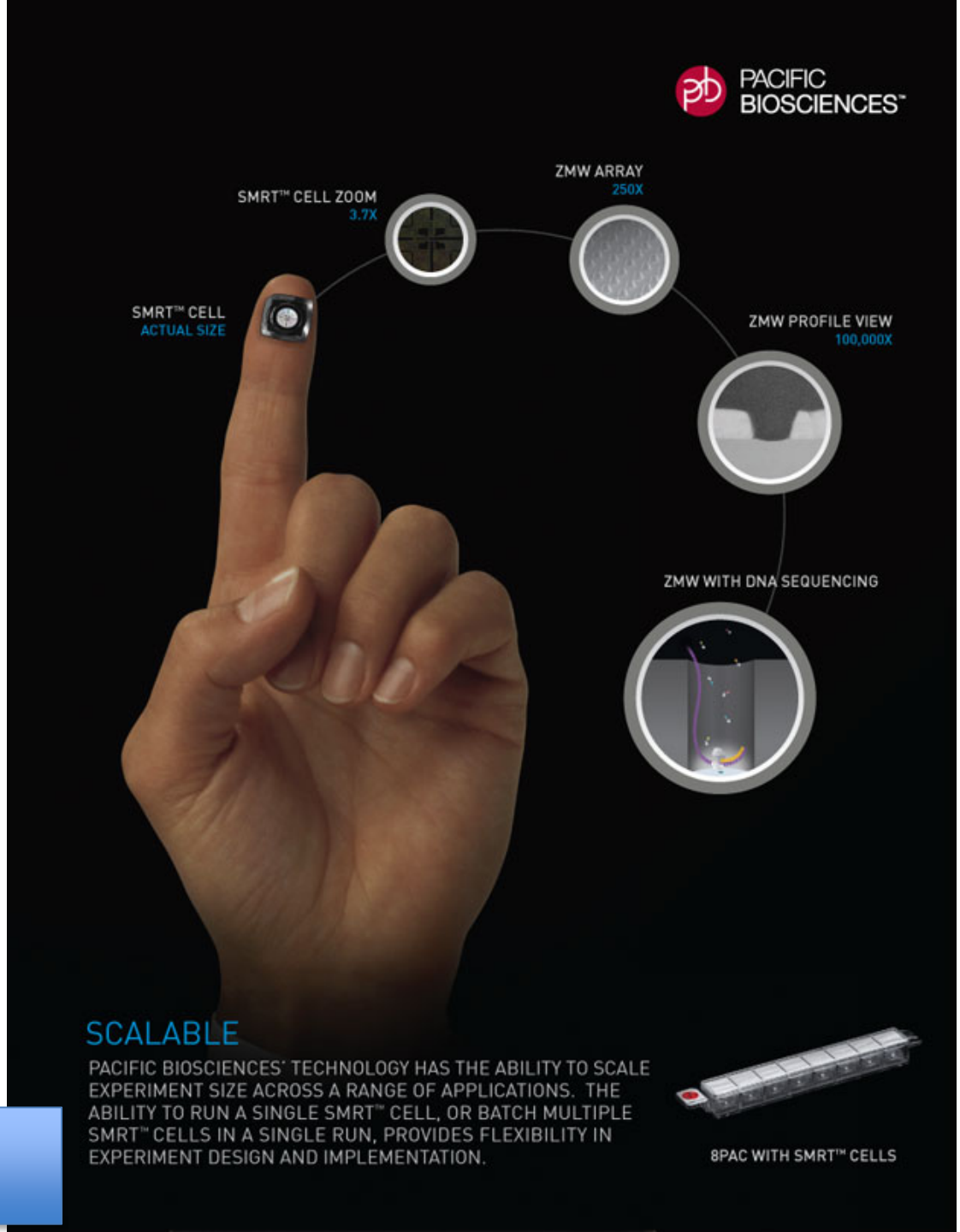
Life-Technologies
Ion-Torrent

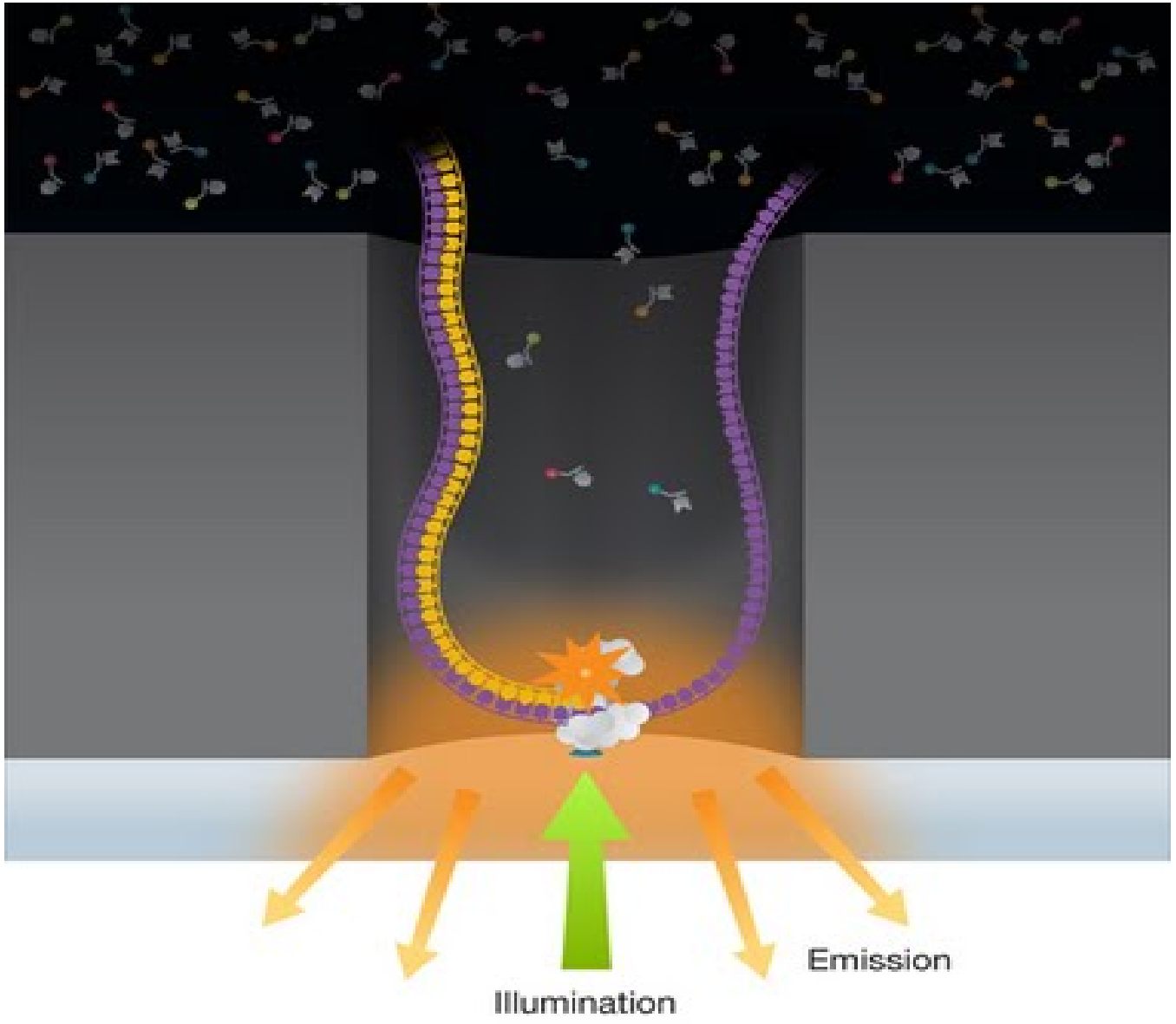
Roche GS Junior system
454 Technology

The PacBio Machine




SMRT™Cell


PACIFIC BIOSCIENCES™
SMRT™ CELL ZOOM
3.7X
ZMW ARRAY
250X
SMRT™ CELL
ACTUAL SIZE
ZMW PROFILE VIEW
100,000X
ZMW WITH DNA SEQUENCING
SCALABLE
PACIFIC BIOSCIENCES' TECHNOLOGY HAS THE ABILITY TO SCALE EXPERIMENT SIZE ACROSS A RANGE OF APPLICATIONS. THE ABILITY TO RUN A SINGLE SMRT™ CELL, OR BATCH MULTIPLE SMRT™ CELLS IN A SINGLE RUN, PROVIDES FLEXIBILITY IN EXPERIMENT DESIGN AND IMPLEMENTATION.
8PAC WITH SMRT™ CELLS


Emission
Illumination

An Example of Allele Level HLA data generated by Third Generation Sequencing

Sample ID	Barcode	Number of Reads	Predicted Accuracy	QV	Gene	Allele_Result
1	004F--004R	365	0.99994	42.00	HLA-A	A*02:01:01:01
1	004F--004R	177	0.99994	42.00	HLA-B	B*39:01:01:03
1	004F--004R	359	0.99994	42.00	HLA-C	C*07:02:01:01
2	014F--014R	150	0.99994	42.00	HLA-A	A*02:01:01:01
2	014F--014R	131	0.99994	42.00	HLA-A	A*31:01:02:01
2	014F--014R	319	0.99994	42.00	HLA-B	B*40:01:02
2	014F--014R	244	0.99994	42.00	HLA-B	B*15:01:01:01
2	014F--014R	452	0.99994	42.00	HLA-C	C*03:04:01:01
3						
3	018F--018R	175	0.99994	42.00	HLA-A	A*29:02:01:01
3	018F--018R	161	0.99994	42.00	HLA-A	A*02:01:01:01
3	018F--018R	118	0.99992	41.99	HLA-B	B*08:01:01
3	018F--018R	105	0.99994	42.00	HLA-B	B*44:03:01
3	018F--018R	236	0.99994	42.00	HLA-C	C*16:01:01
3	018F--018R	181	0.99994	42.00	HLA-C	C*07:01:01:01
4	021F--021R	500	0.99994	42.00	HLA-A	A*01:01:01:01
4	021F--021R	189	0.99994	42.00	HLA-B	B*44:02:01:01
4	021F--021R	140	0.99993	41.99	HLA-B	B*08:01:01
4	021F--021R	182	0.99994	42.00	HLA-C	C*07:01:01:01
4	021F--021R	158	0.99994	42.00	HLA-C	C*05:01:01:02
5	023F--023R	136	0.99994	42.00	HLA-A	A*01:01:01:01
5	023F--023R	107	0.99994	42.00	HLA-A	A*03:01:01:01
5	023F--023R	150	0.99965	41.98	HLA-B	B*52:01:01:02
5	023F--023R	132	0.99973	41.98	HLA-B	B*35:01:01:02
5	023F--023R	291	0.99994	42.00	HLA-C	C*04:01:01:05
5	023F--023R	249	0.99994	42.00	HLA-C	C*12:02:02

HLA typing for the next generation

Mayor NP, Robinson J, McWhinnie AJM,et all
PLoS ONE. (2015) **10(5)**:e0127153.

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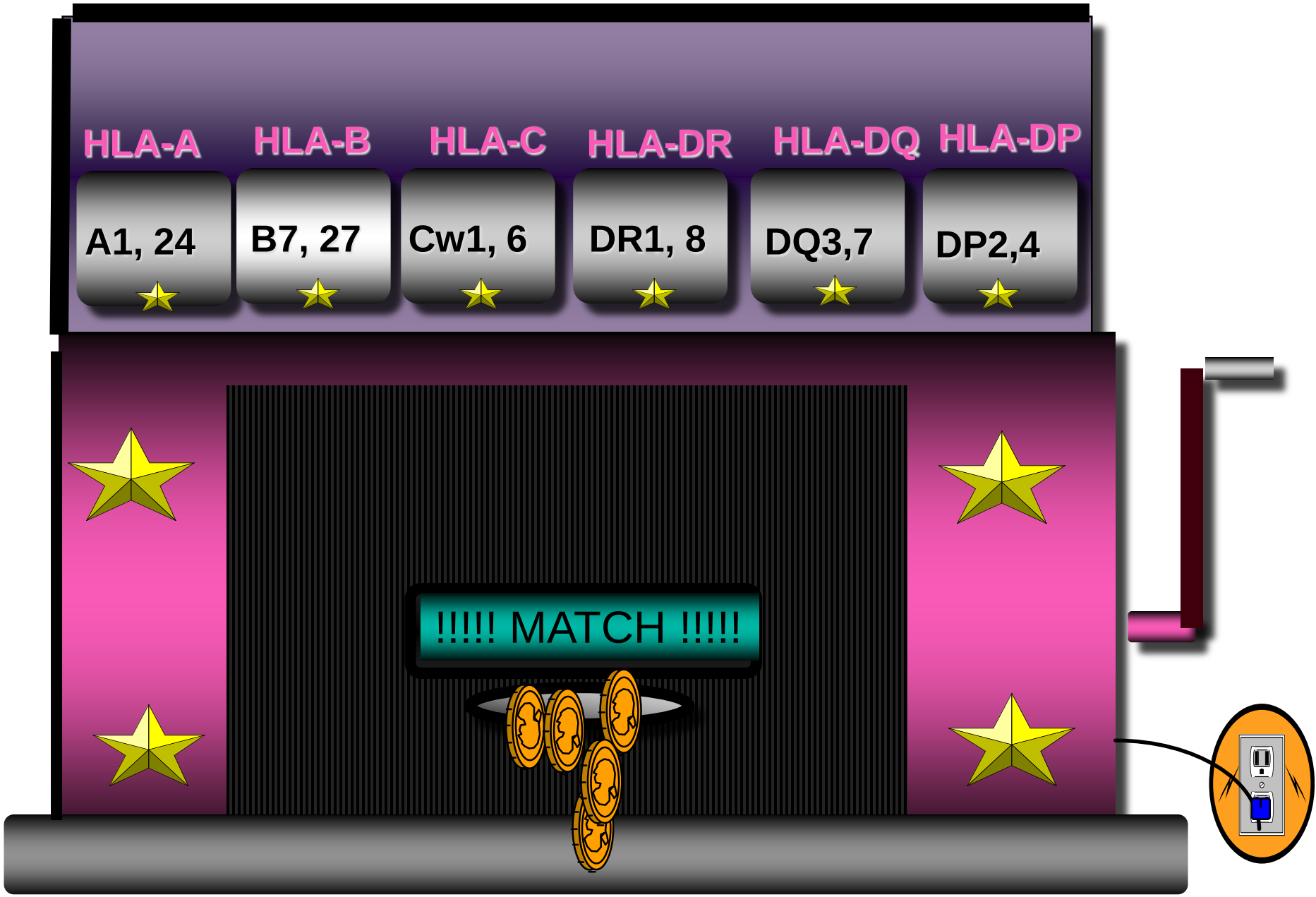
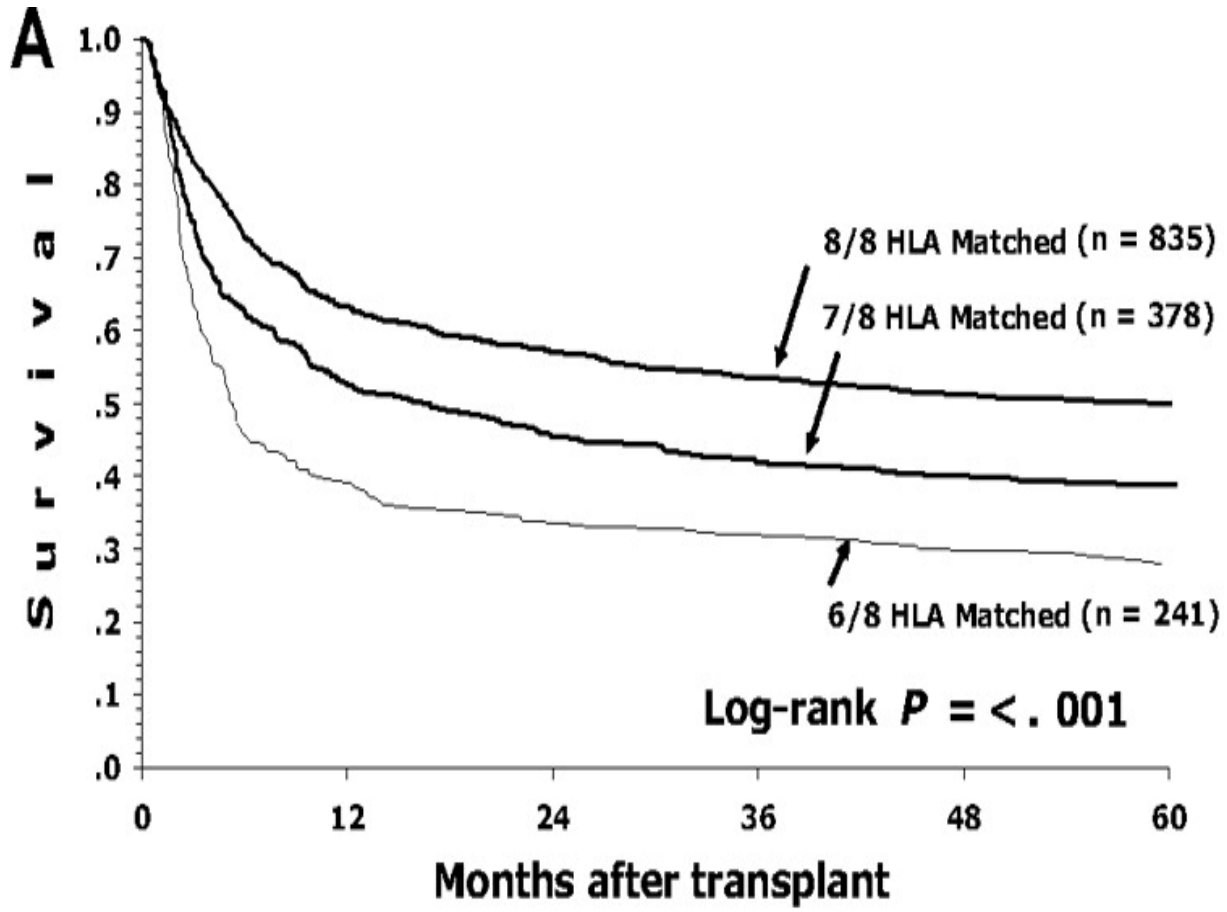


©Alejandro Madrigal 2015

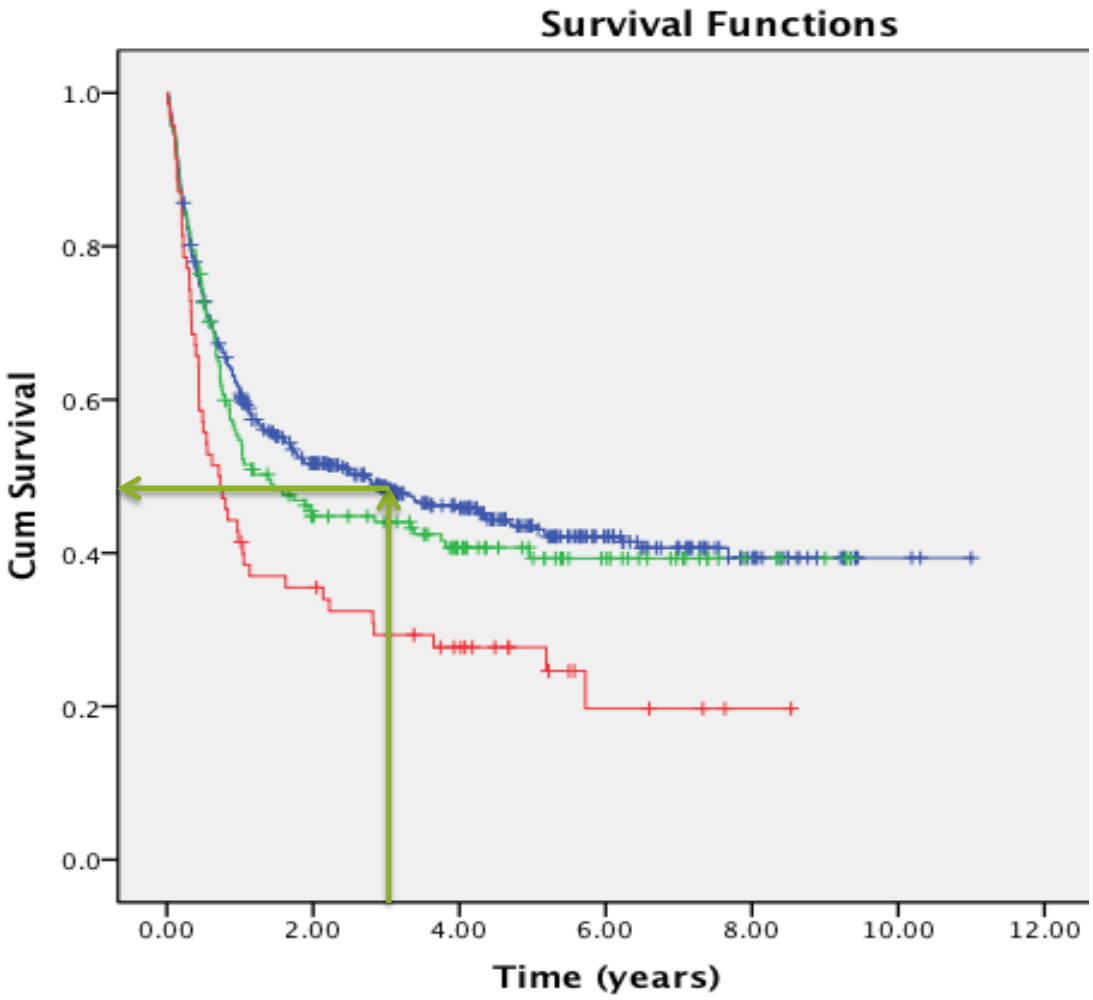
HLA allele matching on overall survival



Lee SJ *et al*. Blood (2007) **110** 4576-4583

UK DATA: 1996 - 2006

488 UD recipients



3 year overall survival for 10/10 match = 51%

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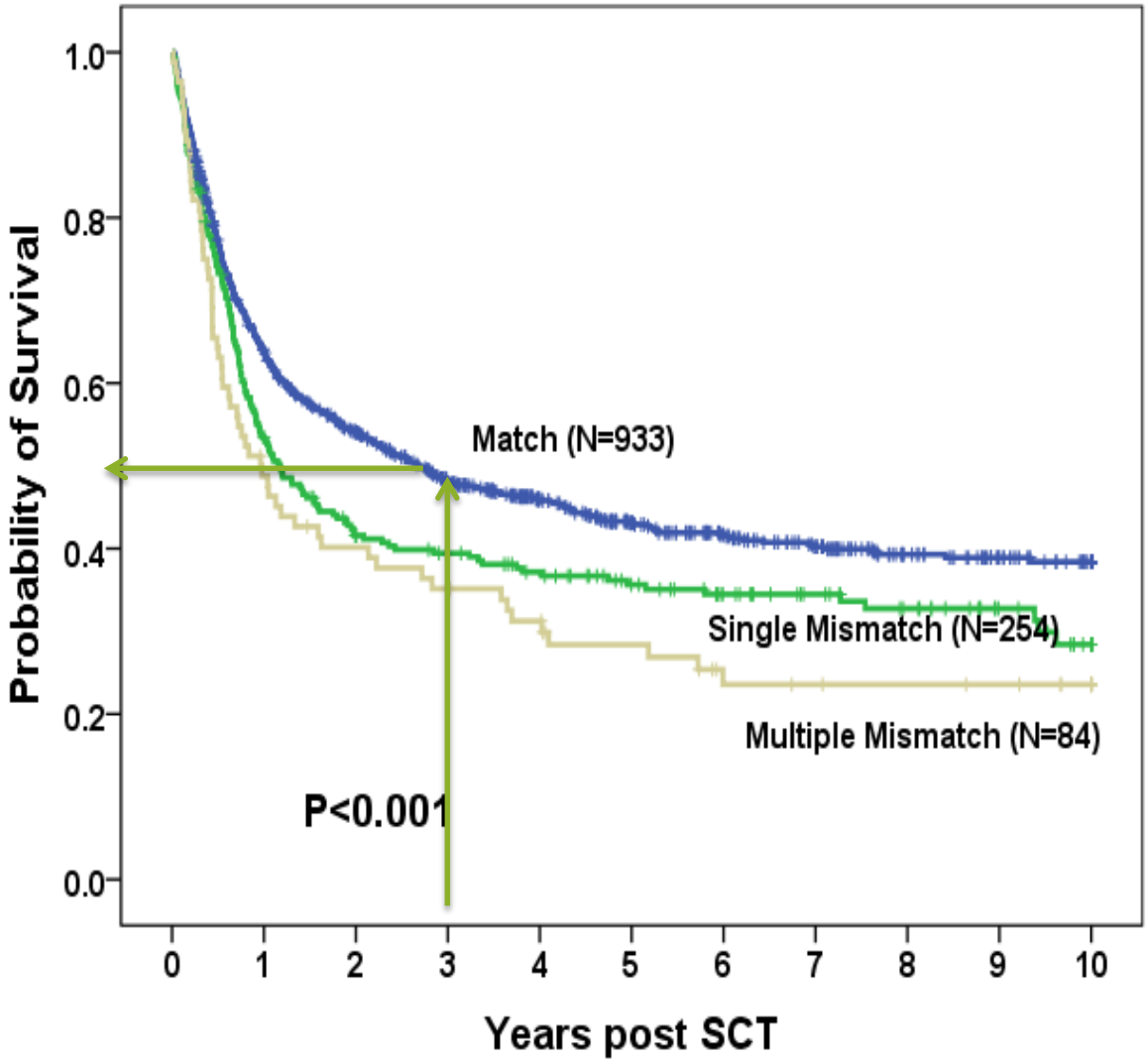
UK DATA: 1996 -2014

1271 UD recipients



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Diverging effects of HLA-DPB1 matching status on outcome following unrelated donor transplantation depending on disease stage and the degree of matching for other HLA alleles. Shaw BE, Mayor NP, Russell NH, Apperley JF, Clark RE, Cornish J, et al**. Leukemia 2010;24(1):58-65.**

Permissive HLA-DPB1 mismatching compared to a non-permissive mismatching significantly improves overall survival following allogeneic transplantation in patients with both 10/10 and 9/10 matched unrelated donors B E Shaw, K Fleischhauer, M Malkki, T Gooley, E Zino, S Spellman, Y Morishima, A Velardi, P Bardy, J Bignon, J A Madrigal, E W Petersdorf ***on behalf of the International Histocompatibility Working Group in Hematopoietic Ce***//

Fleischhauer K, Shaw BE, Gooley T, Malkki M, Bardy P, Bignon J-D, et al. Effect of T-cell-epitope matching at HLA-DPB1 in recipients of unrelated-donor haemopoietic-cell transplantation: a retrospective study. **The lancet oncology. 2012;13(4):366-74.**

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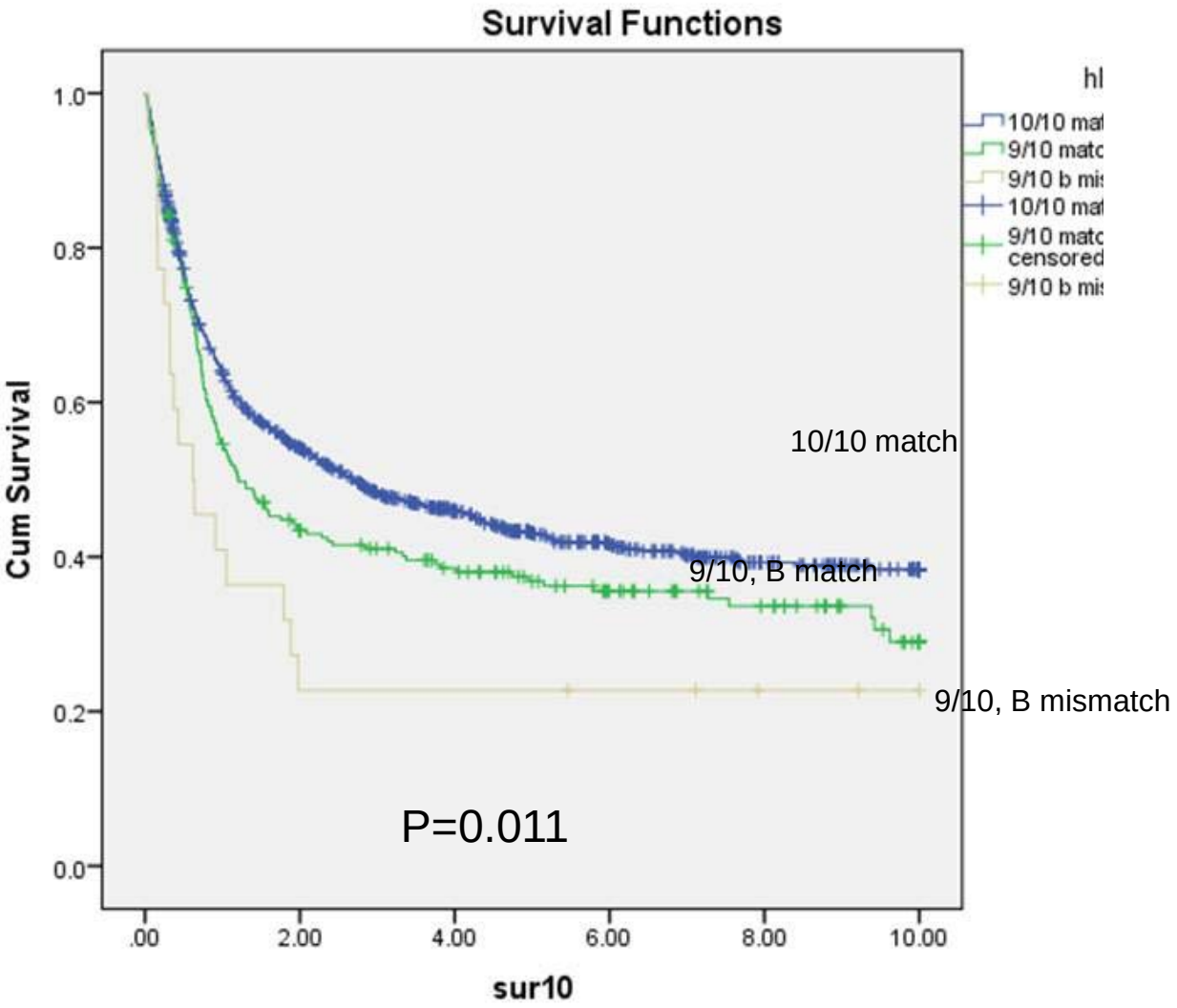
Impact of HLA-B matching on overall survival



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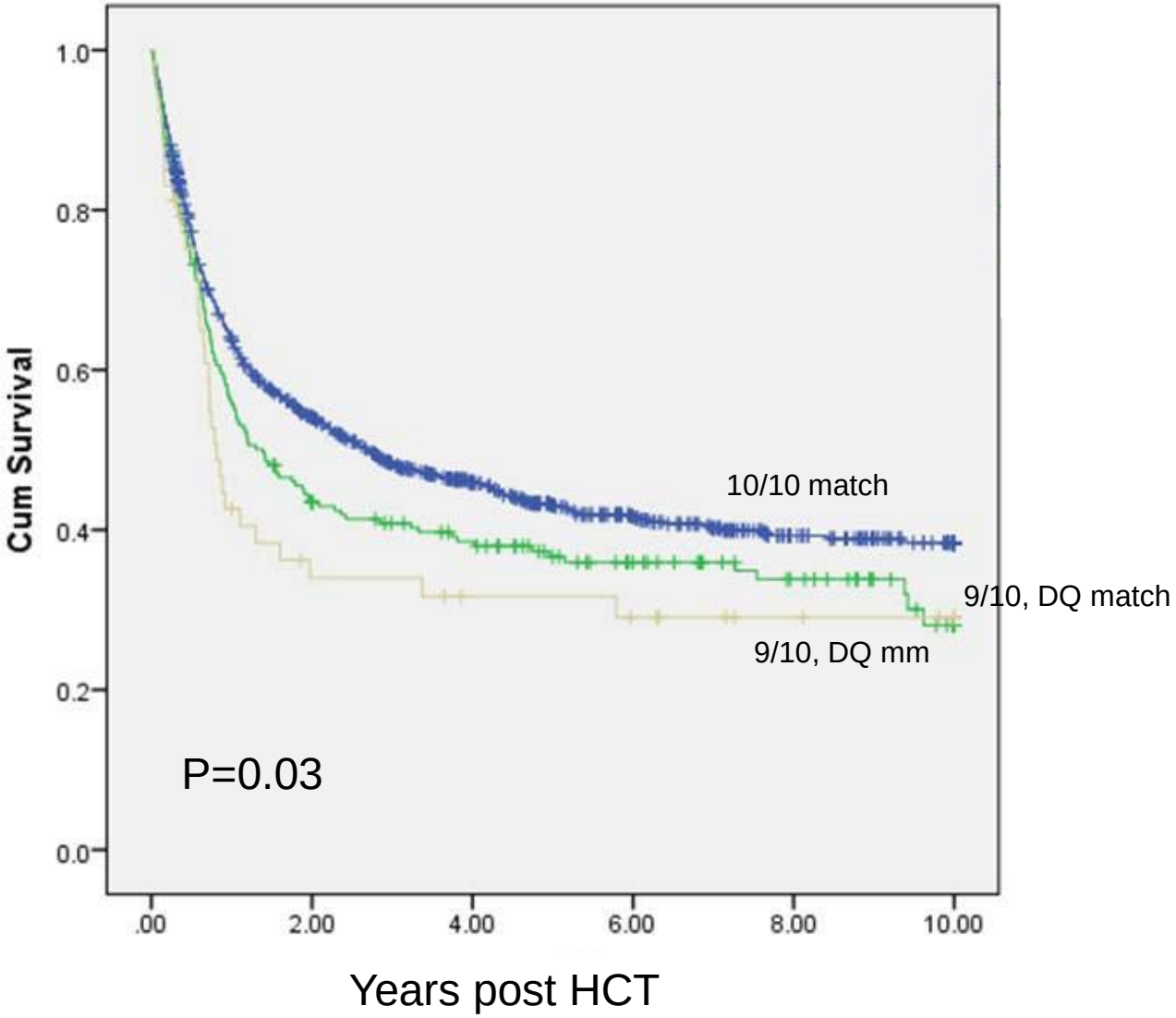
Impact of HLA-DQB1 matching on overall survival



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Impact of HLA mismatching at individual loci on overall survival

	OVERALL SURVIVAL			NRM AT 1 YEAR	
	N	Median Survival (y)	p-value	1 year NRM	p-value
HLA match status					
10/10	933	2.68		23.8	
1 mm	254	1.18	0.001	32.0	0.004
>1 mm	84	0.96		38.9	
HLA A					
10/10	933	2.68		23.8	
9/10 A match	194	1.18	0.17	32.1	0.063
9/10 A mm	60	1.10		31.4	
HLA B					
10/10	933	2.68		23.8	
9/10 B match	232	1.21	0.011	30.5	0.026
9/10 B mm	22	1.10		47.2	
HLA C					
10/10	933	2.68		23.8	
9/10 C match	143	0.91	0.28	36.9	0.026
9/10 C mm	111	1.47		25.8	
HLA DR					
10/10	933	2.68		23.8	
9/10 DR match	246	1.10	0.75	32.7	0.036
9/10 DR mm	8	2.08		12.5	
HLA DQ					
10/10	933	2.68		23.8	
9/10 DQ match	201	1.39	0.03	29.2	0.024
9/10 DQ mm	53	0.82		44.0	

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Number of HLA alleles, March 2016

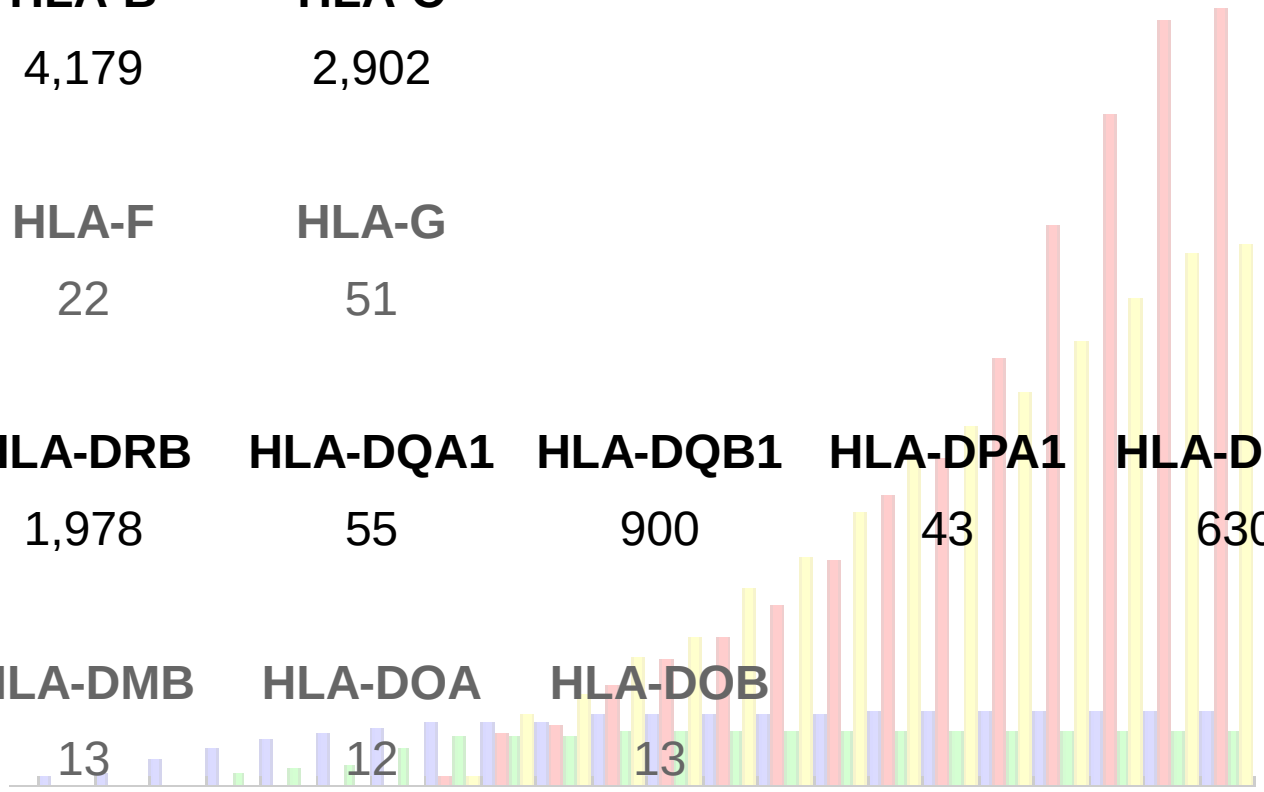
HLA-A	HLA-B	HLA-C
3,356	4,179	2,902

HLA-E	HLA-F	HLA-G
18	22	51

HLA-DRA	HLA-DRB	HLA-DQA1	HLA-DQB1	HLA-DPA1	HLA-DPB1
7	1,978	55	900	43	630

HLA-DMA	HLA-DMB	HLA-DOA	HLA-DOB
7	13	12	13

MICA	MICB	TAP1	TAP2	HFE
105	42	12	12	6



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Factors that influence the outcome of HSCT

- **HLA matching of donor and recipient**
- CMV status of donor and recipient
- Gender of donor and patient
- Allo-immunisation of the patient
- Age of the patient/donor
- Type and stage of the disease
- Conditioning and immunosupressive regimen
- PBSC vs Bone Marrow

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Factors that influence the outcome of HSCT

Recipient/Donor CMV matching may offset the survival disadvantage of an HLA mismatch in recipients of unrelated donor transplants

Bronwen E Shaw, Neema P Mayor, Richard M Szydlo, Will P Bultitude, Chloe Anthias, Keiren Kirkland, Julia Perry, Andrew Clark, Stephen Mackinnon, David I Marks, Antonio Pagliuca, Michael N Potter, Nigel H Russell, Kirsty Thomson, J Alejandro Madrigal, Steven G E Marsh

Bone Marrow Transplantation (2017) 52, 717–725

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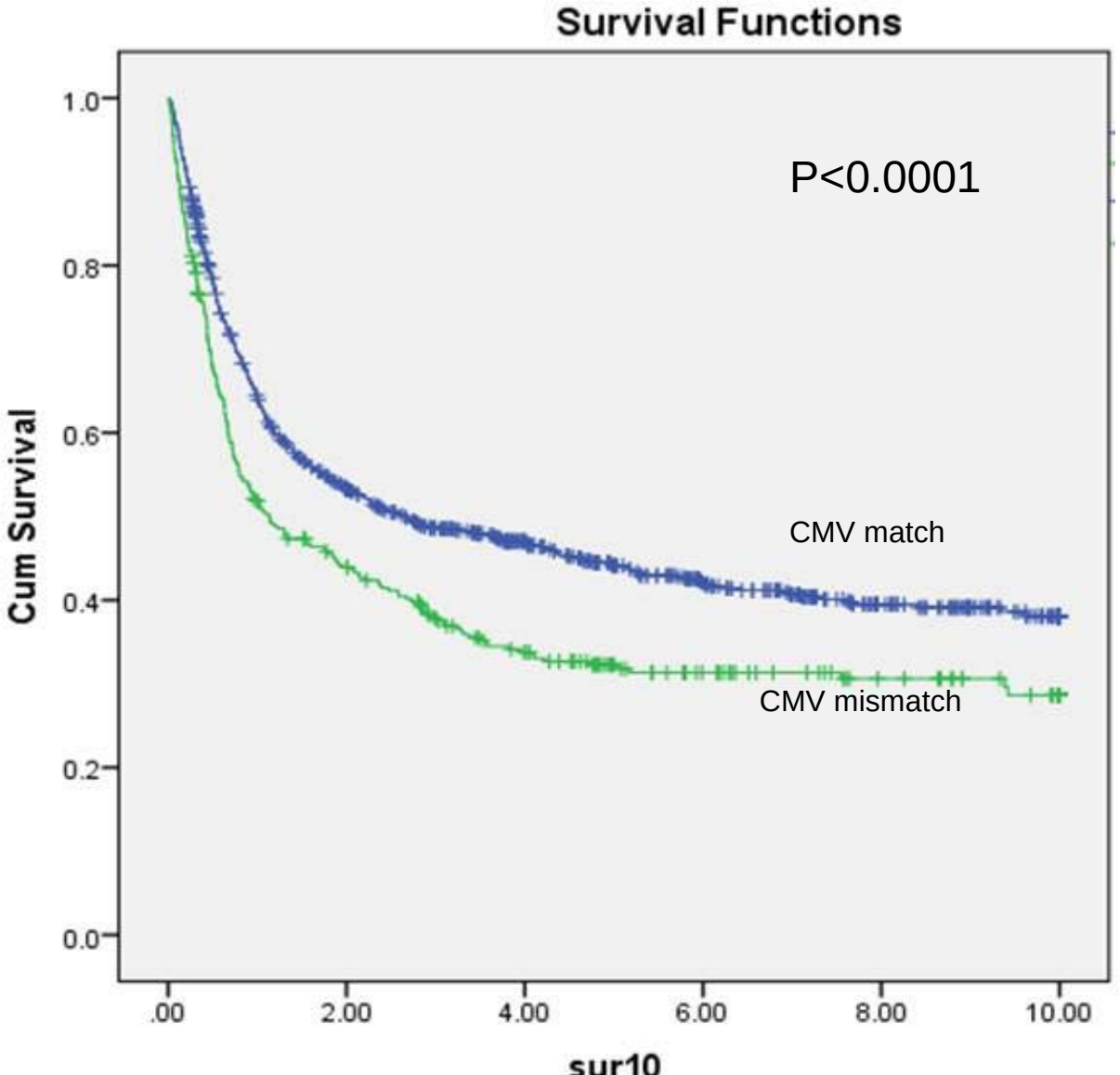
CMV MATCHING IMPROVES SURVIVAL IN TCD ALLOGRAFTS



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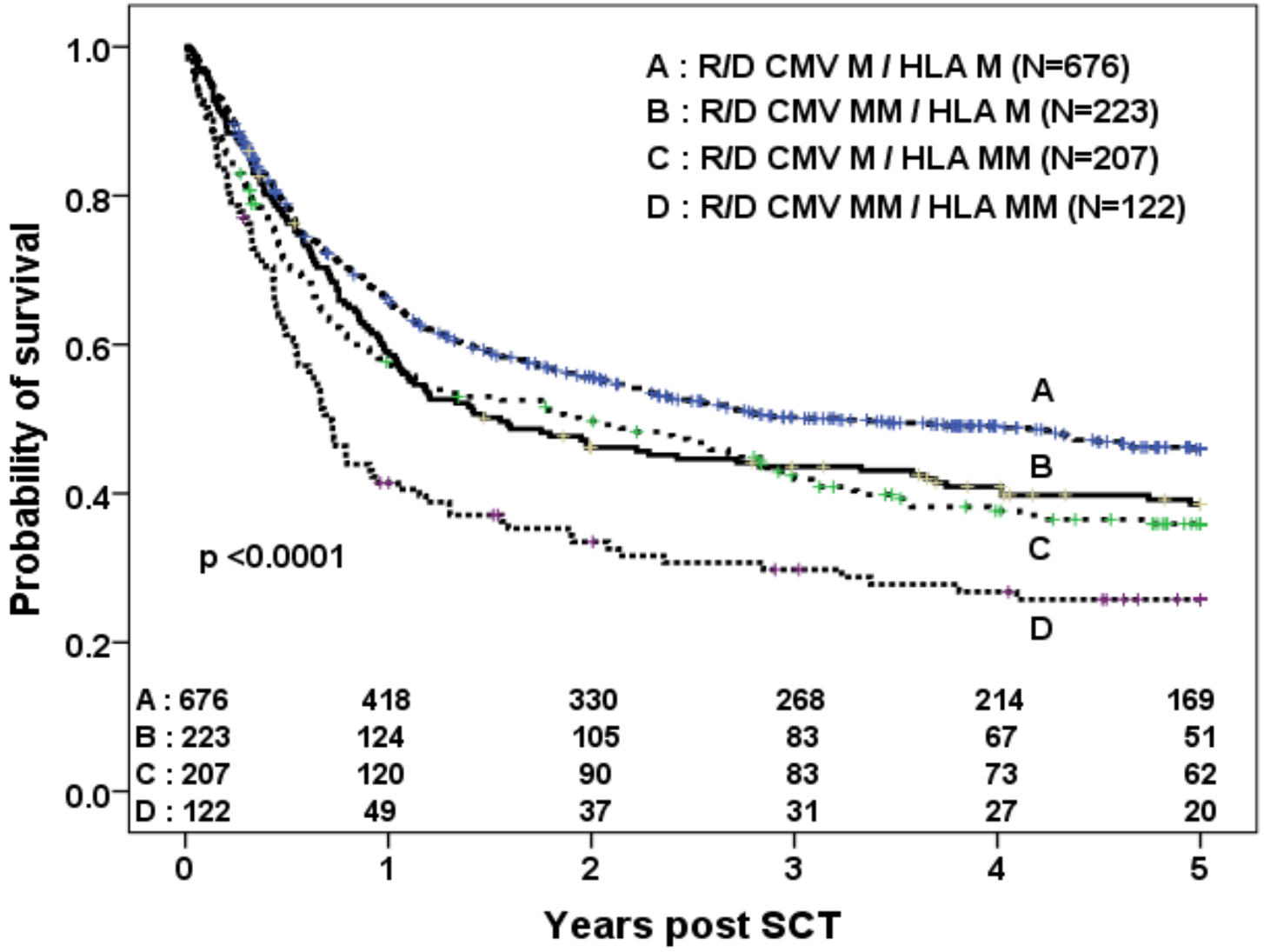
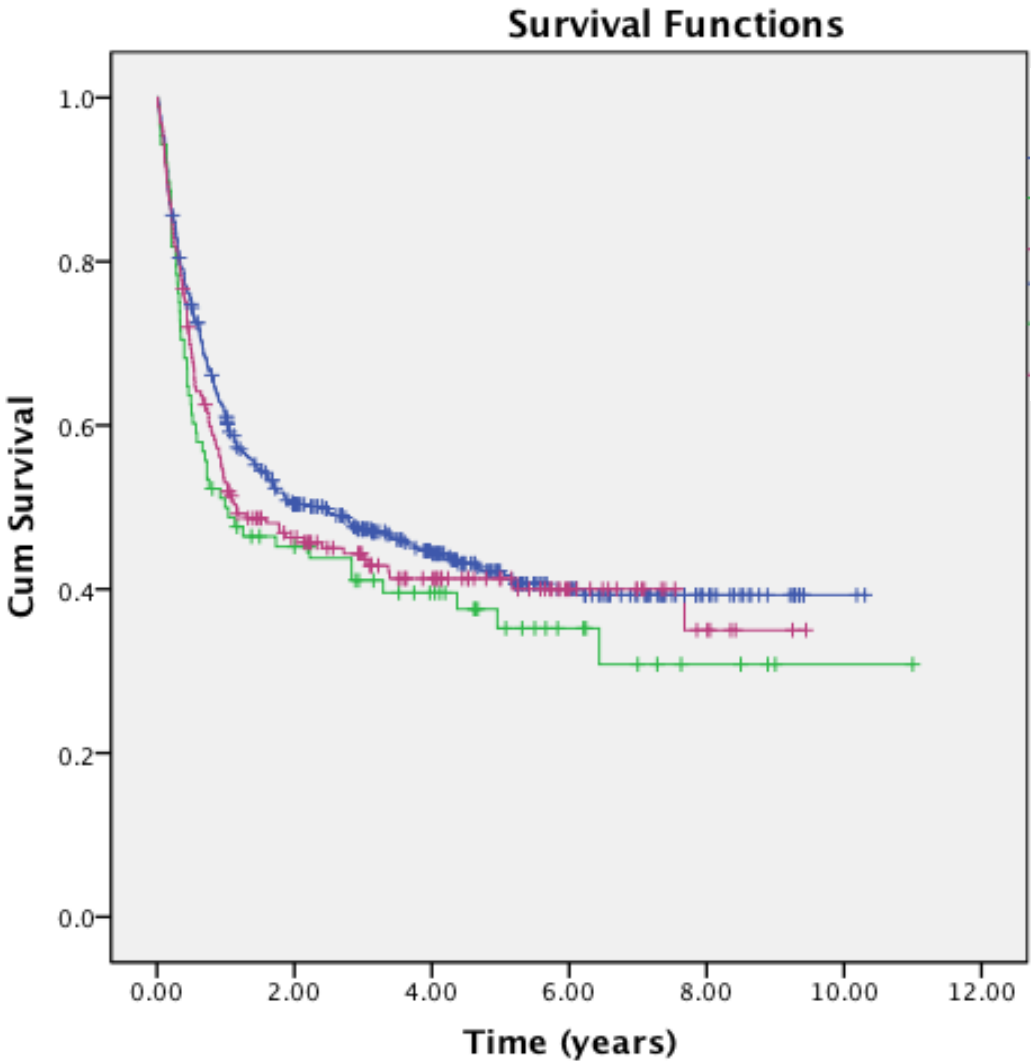
COMBINED IMPACT OF HLA MATCHING AND CMV SEROSTATUS



Survival dependent on donor sex



Sex Match
Male Donor Female Recipient
Female Donor Male Recipient

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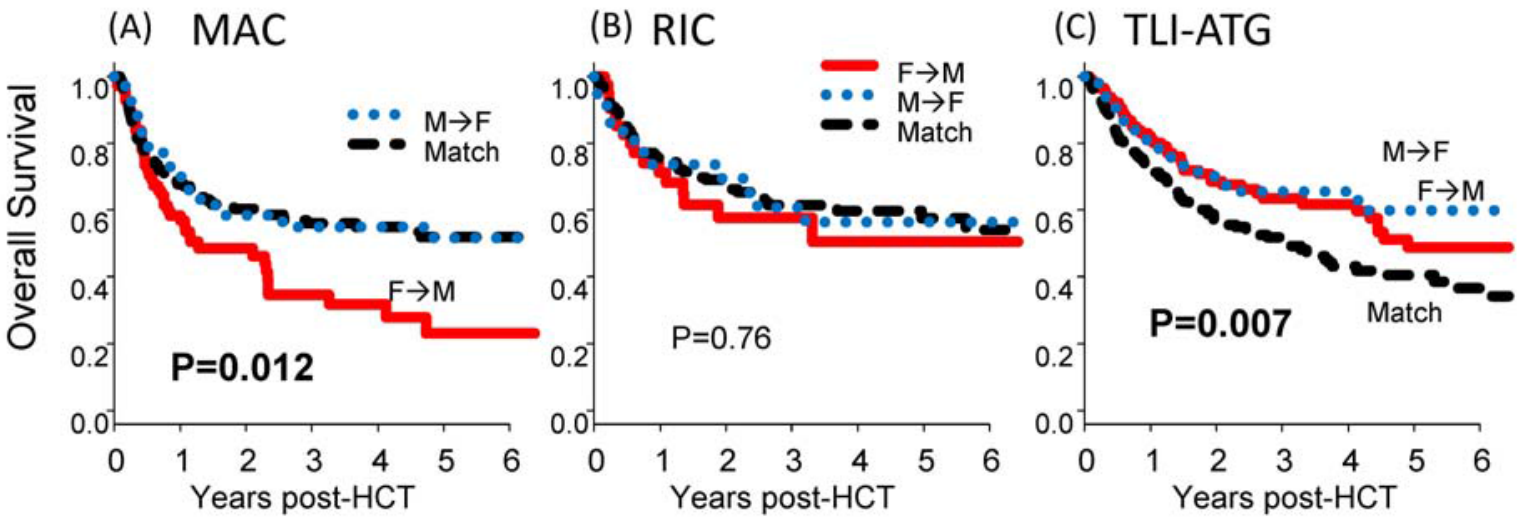
Gender of donor and recipient

Figure 1



Risks and Benefits of Sex-mismatched Hematopoietic Cell Transplantation Differ by Conditioning Strategies
by Hideki Nakasone, Mats Remberger, Lu Tian, Petter Brodin, Bita Sahaf, Fang Wu, Jonas Mattsson, Robert Lowsky, Robert Negrin, David B. Miklos, and Everett Meyer
HAEMOTOLOGICA 06/215

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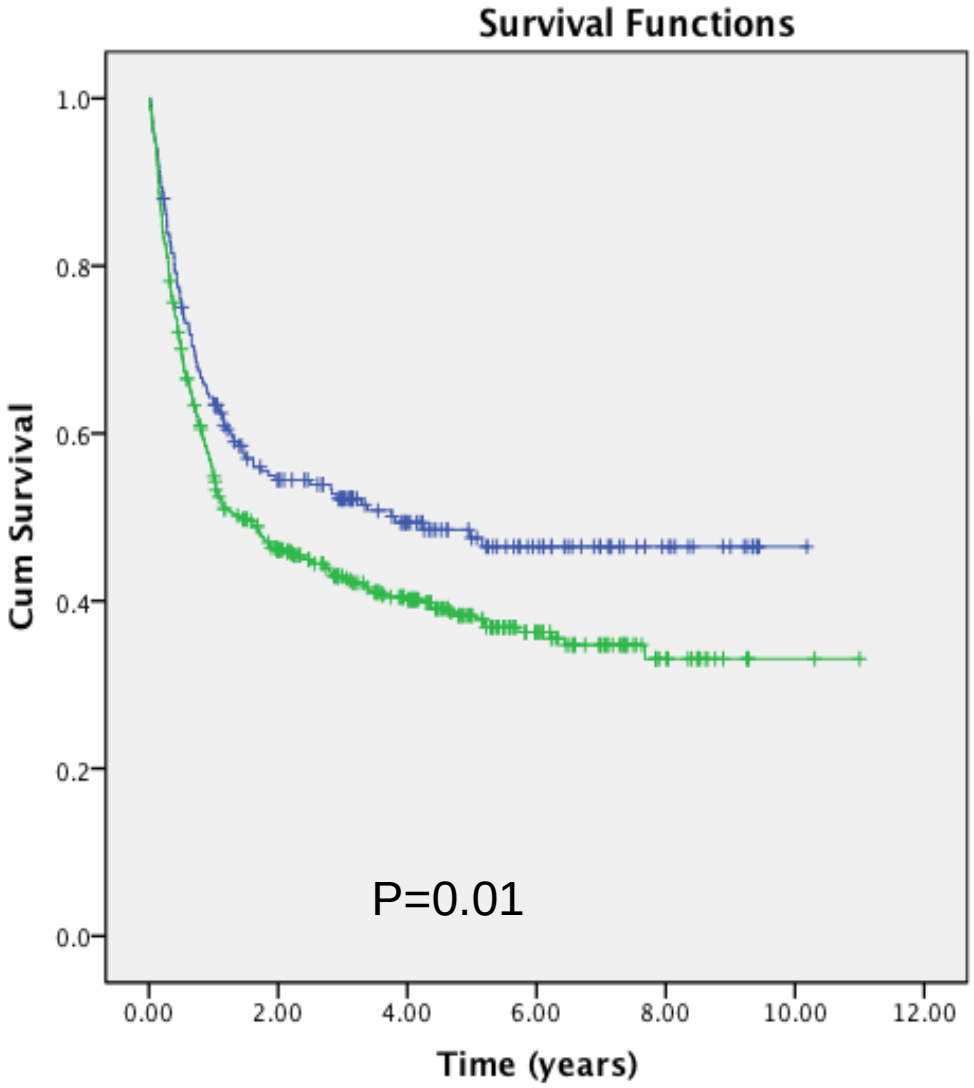
Donor Age



Donor Under 30

Donor Over 30

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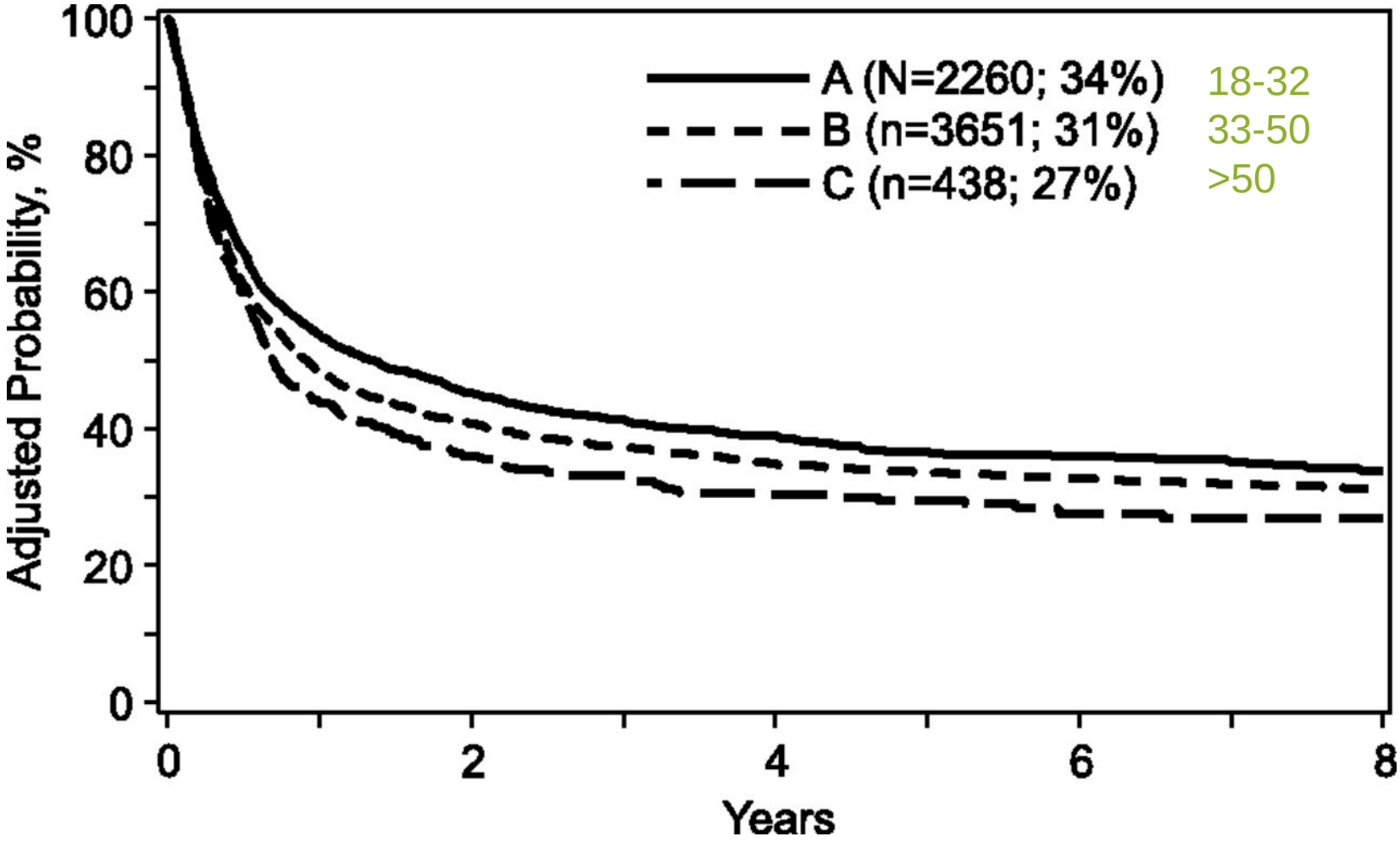
MORTALITY INCREASES WITH DONOR AGE



Craig Kollman et al. Blood 2016;127:260-267

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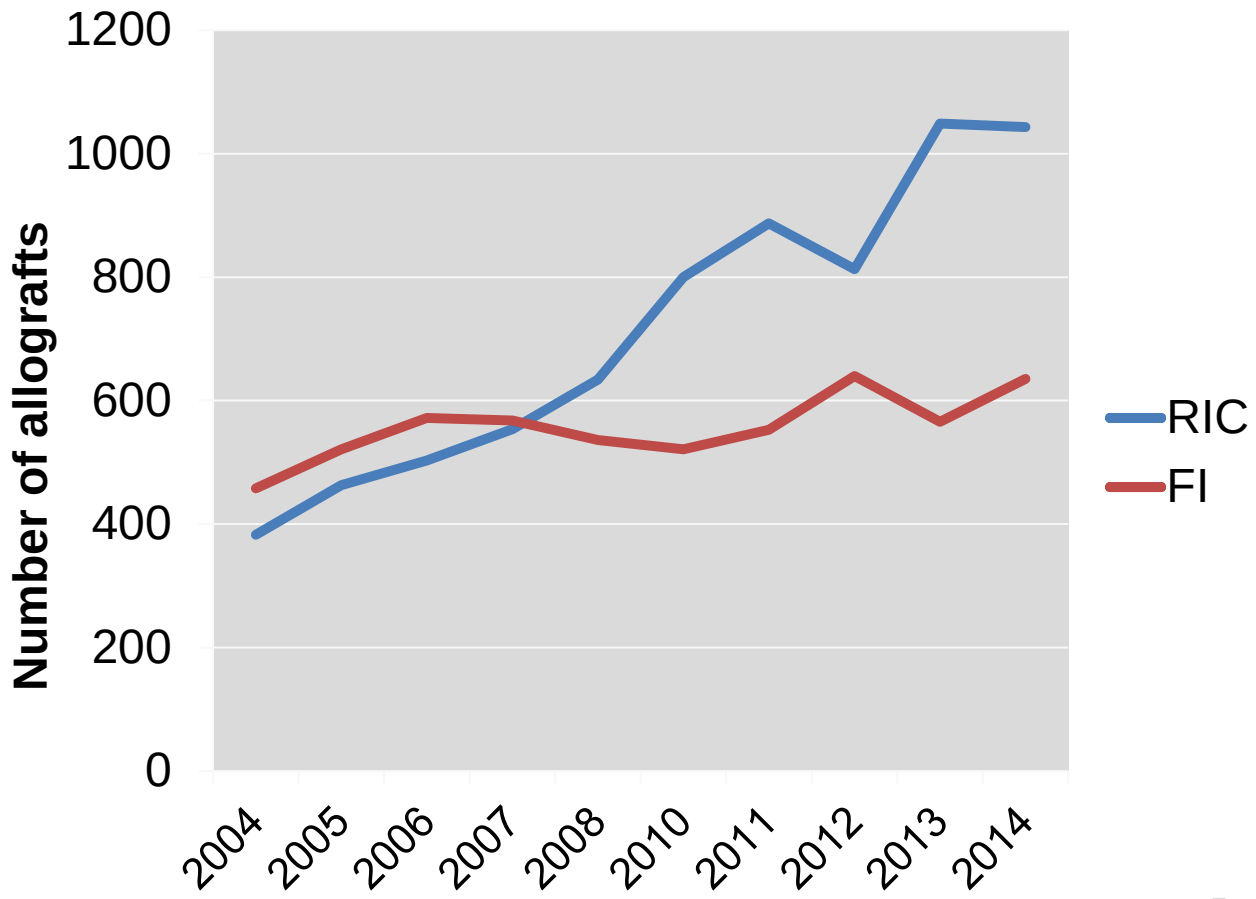
WE ARE TRANSPLANTING A DIFFERENT PATIENT POPULATION



BSBMT activity data

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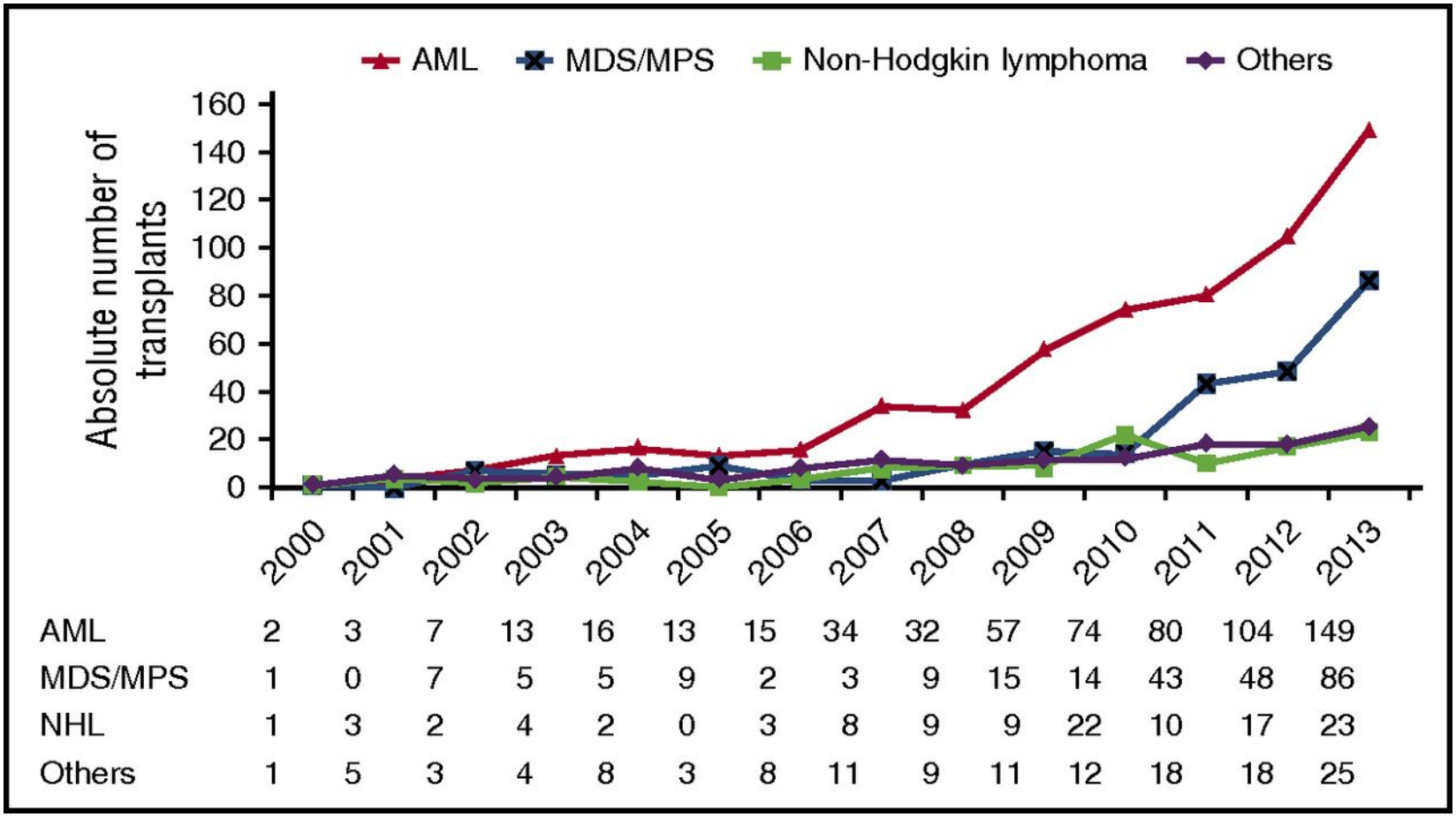
ANNUAL NUMBER OF HSCTs IN PATIENTS OVER 70 BY DISEASE INDICATION



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
AML	2	3	7	13	16	13	15	34	32	57	74	80	104	149
MDS/MPS	1	0	7	5	5	9	2	3	9	15	14	43	48	86
NHL	1	3	2	4	2	0	3	8	9	9	22	10	17	23
Others	1	5	3	4	8	3	8	11	9	11	12	18	18	25

Lori Muffly et al. Blood 2017;130:1156-1164

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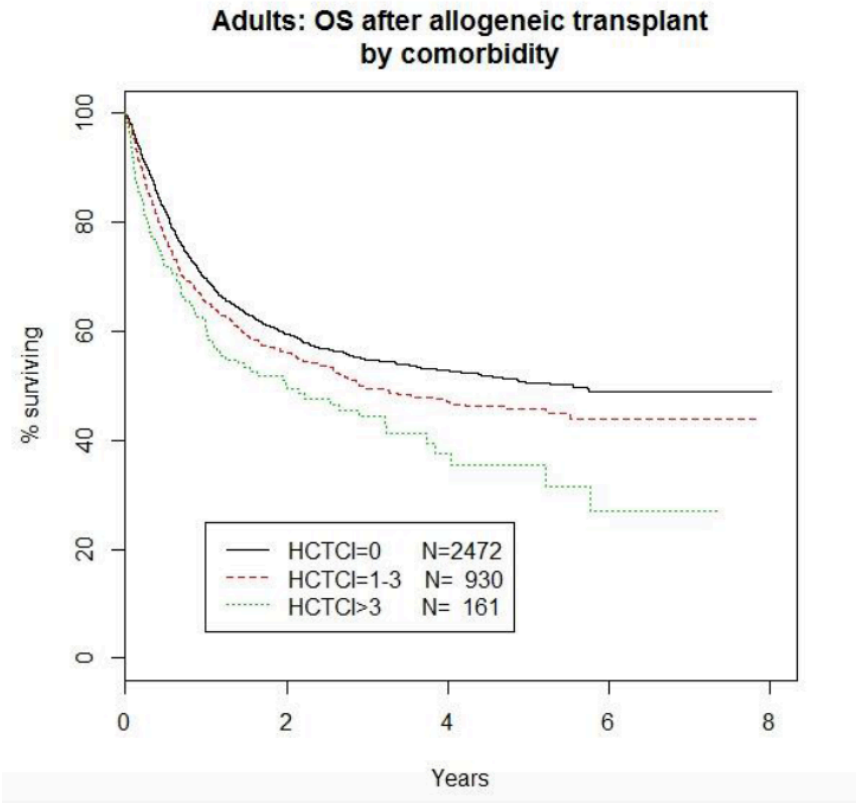
OLDER PATIENTS HAVE MORE COMORBIDITIES WHICH INFLUENCES TRANSPLANT OUTCOME



BSBMT commissioners report 2016

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NOVEL ANTI-CANCER TREATMENTS

- ….mean that some patients will no longer need a transplant
- ….but other patients with higher risk disease are now surviving to receive a transplant
- For some diseases (eg lymphoma) we are now transplanting higher risk patients
- More patients with pre-existing treatment toxicities are undergoing allograft

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Registry of Unrelated Donors: Main Changes Over the Last 10 Years

- Number of unrelated bone marrow donors
- Number of Registries around the word
- Number of HLA alleles described
- Increased resolution of typing techniques
- Number of HLA genes needed to be matched
- Matching for non-HLA genes
- Understanding other factors that impact on the outcome of HSCT
- Changes in the demographic composition of UD Registries
- Contribution of UD Registries in the improvement of the outcome of HSCT

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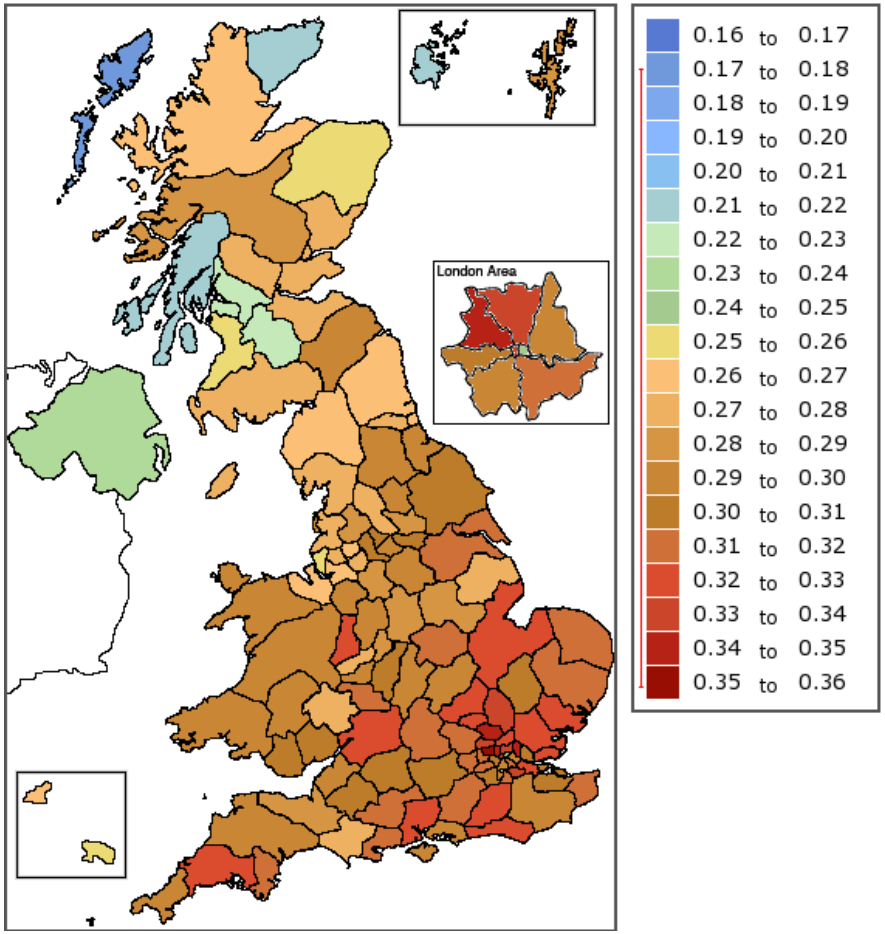
Phenotypic Diversity



Area	Expected	Observed
NW - Northwest London	35.42%	38.09%
N - North London	34.25%	35.20%
IP - Ipswich	31.61%	32.20%
NR - Norwich	31.98%	35.91%
BT - Belfast	24.06%	22.65%
G - Glasgow	22.38%	21.24%

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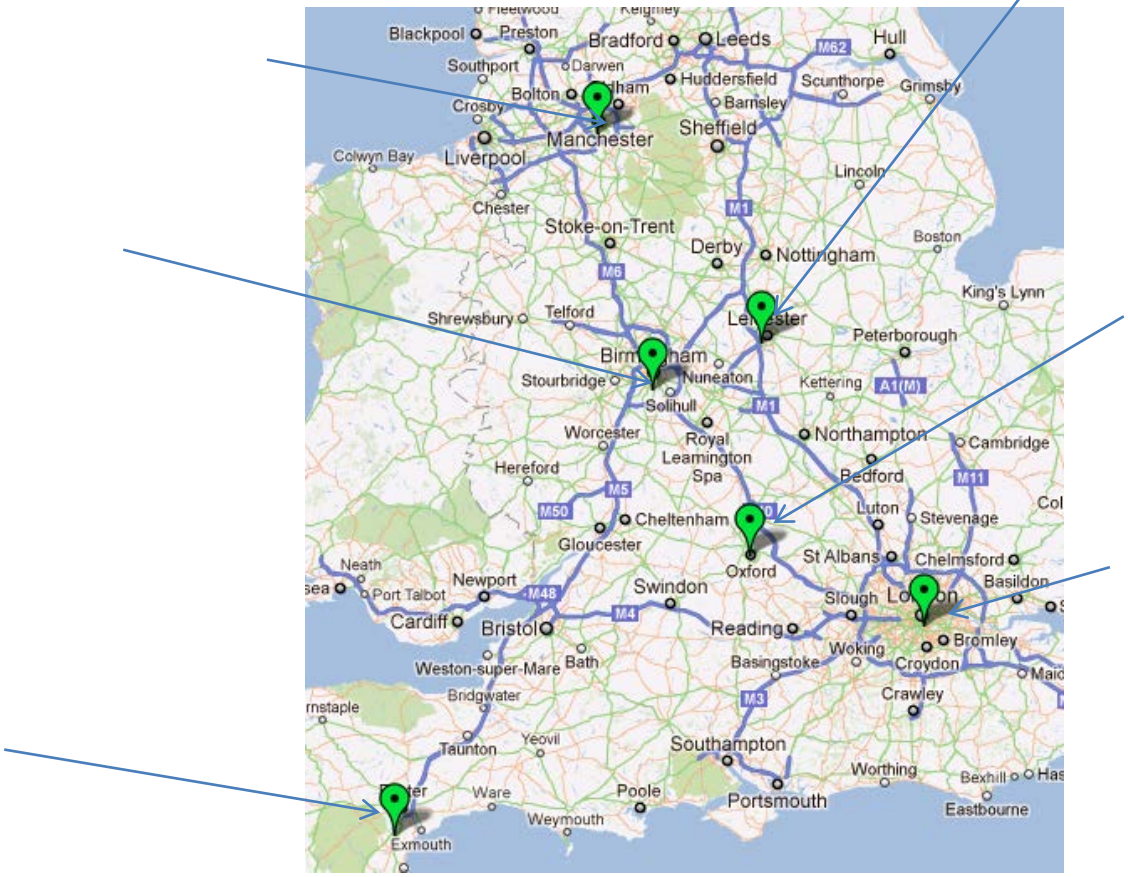
saving the lives of people with blood cancer

HOT SPOT ACTIVITY



All areas: Materials to Marrow groups and Army bases; encourage local sports teams to support Fit to Spit day; pitch articles with donors to local media; promote existing recruitment events; relevant case studies; Targeted FB ads; promoting offline recruitment events through relevant online channels (e.g. "local" Twitter profiles); trail targeting geographically for blog seeding,

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Our targeted recruitment strategy

- In 2012 we changed our joining age from 18-40 to 16-30
- We have a targeted recruitment strategy focussing on young men
- One of the ways we are trying to improve the chances for Black, Asian and Minority Ethnic communities in the UK is to target our recruitment in BAME communities
- According to UK census data 14% of the UK population are BAME and in 2015 19% of our register define themselves as BAME

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Estimate Likelihood of Successful Search Based on Genotype Frequency

Race/ ethnicity	Prob of one or more 8/8	Good search prognosis (>2 matched donors)
Caucasian	.72	**.58**
African	.30	**.08**
Hispanic	.44	**.16**
Asian/Pacific Islander	.46	**.31**

In a validation cohort, 42% of patients with Good, 10% with Fair and 4% with Poor search scores underwent a 10/10 HCT (Wadsworth, et al, BMT 2016)

Registry of Unrelated Donors: Main Changes Over the Last 10 Years

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- **The future potential role of UD Registries**

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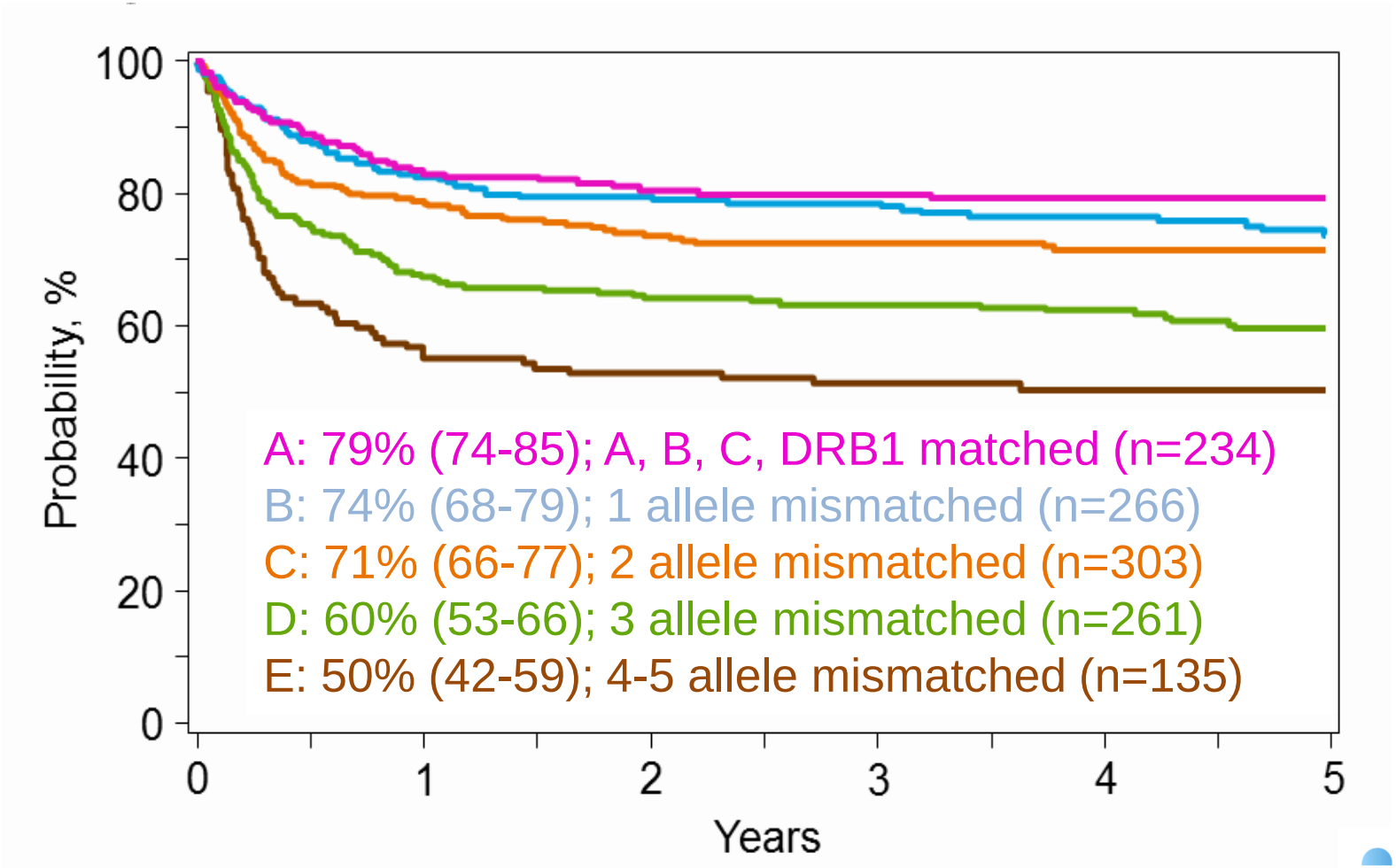
A DONOR FOR EVERYONE

- Related Donors
- Unrelated Donors
- Cord blood
- Haploidenticals
- +Cell therapy

Effect of Allele-level Matching at A, B, C, DRB1 on Survival after Cord Blood HCT for Non-malignant Disease in Children (Eapen, Lancet Haematology 2017))



eurocord

The NEW ENGLAND JOURNAL of MEDICINE

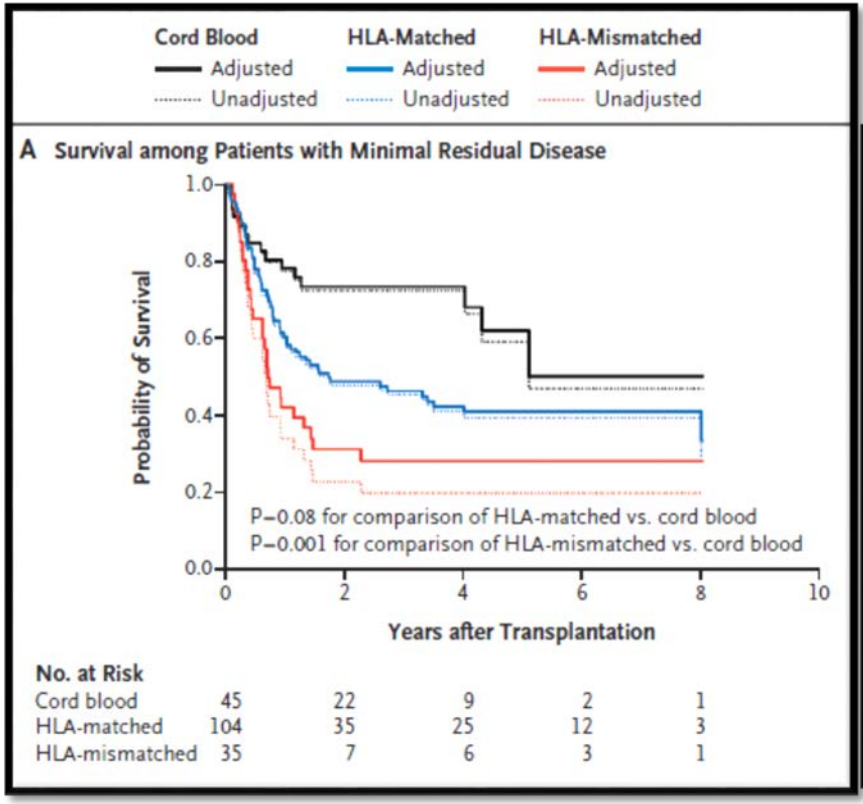
ORIGINAL ARTICLE

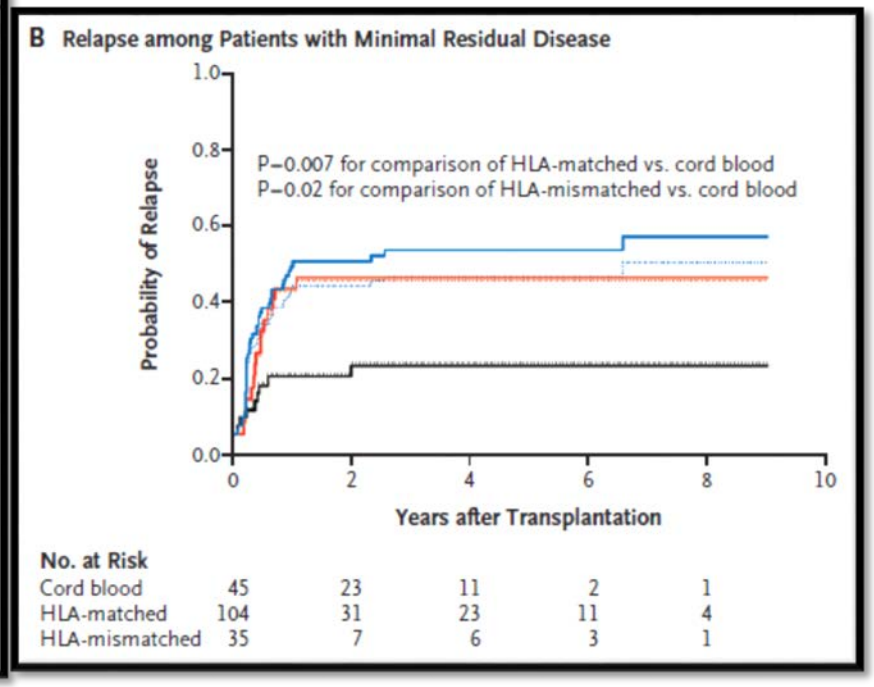
Cord-Blood Transplantation in Patients with Minimal Residual Disease

Filippo Milano, M.D., Ph.D., Ted Gooley, Ph.D., Brent Wood, M.D., Ann Woolfrey, M.D., Mary E. Flowers, M.D., Kristine Doney, M.D., Robert Witherspoon, M.D., Marco Mielcarek, M.D., Joachim H. Deeg, M.D., Mohamed Sorror, M.D., Ann Dahlberg, M.D., Brenda M. Sandmaier, M.D., Rachel Salit, M.D., Effie Petersdorf, M.D., Frederick R. Appelbaum, M.D., and Colleen Delaney, M.D.

"Among patients with pretransplantation minimal residual disease, the probability of overall survival after receipt of a transplant from a cord-blood donor was at least as favorable as that after receipt of a transplant from an HLAmatched unrelated donor and was significantly higher than the probability after receipt of a transplant from an HLA-mismatched unrelated donor.

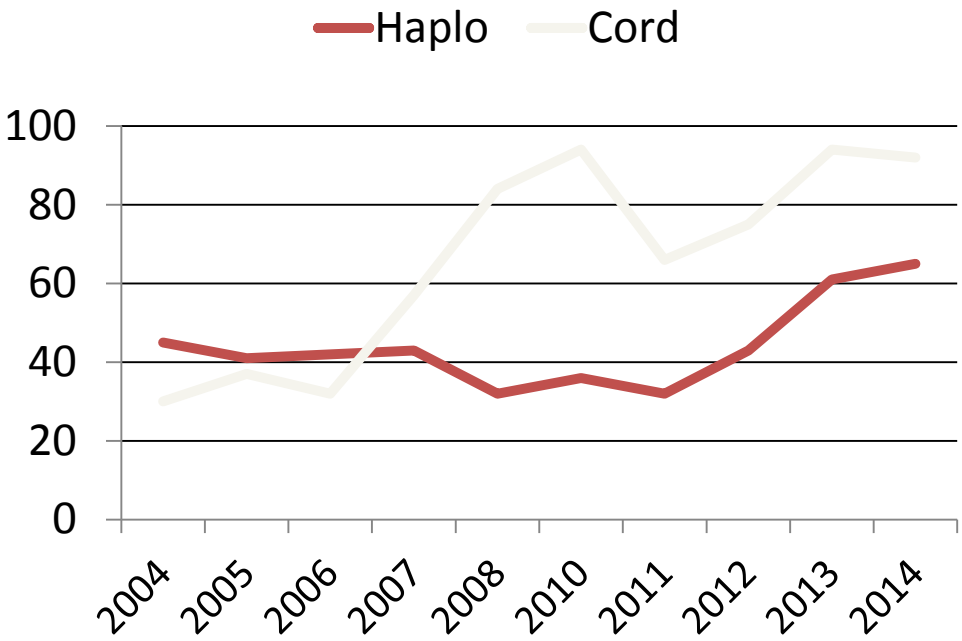
Furthermore, the probability of relapse was lower in the cord-blood group than in either of the other groups."



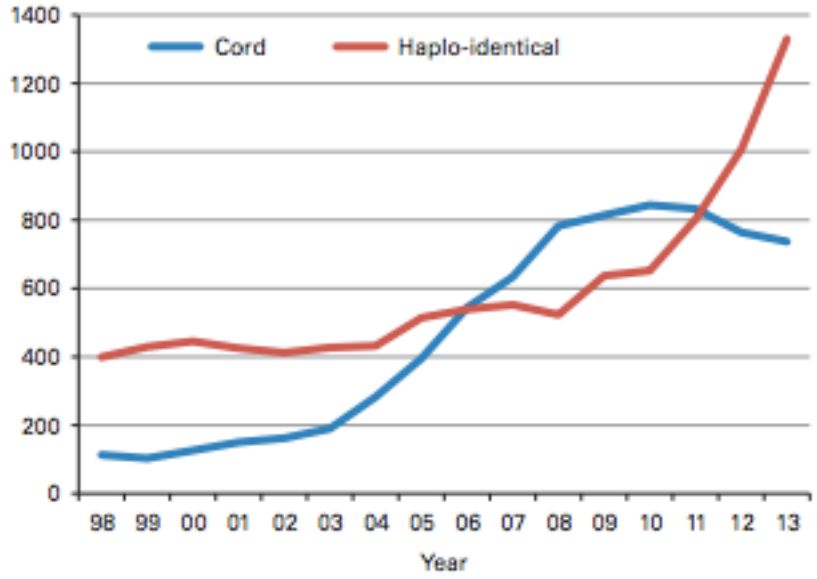


INCREASING ALTERNATIVE DONOR TRANSPLANTS IN UK AND EUROPE

UK



EBMT

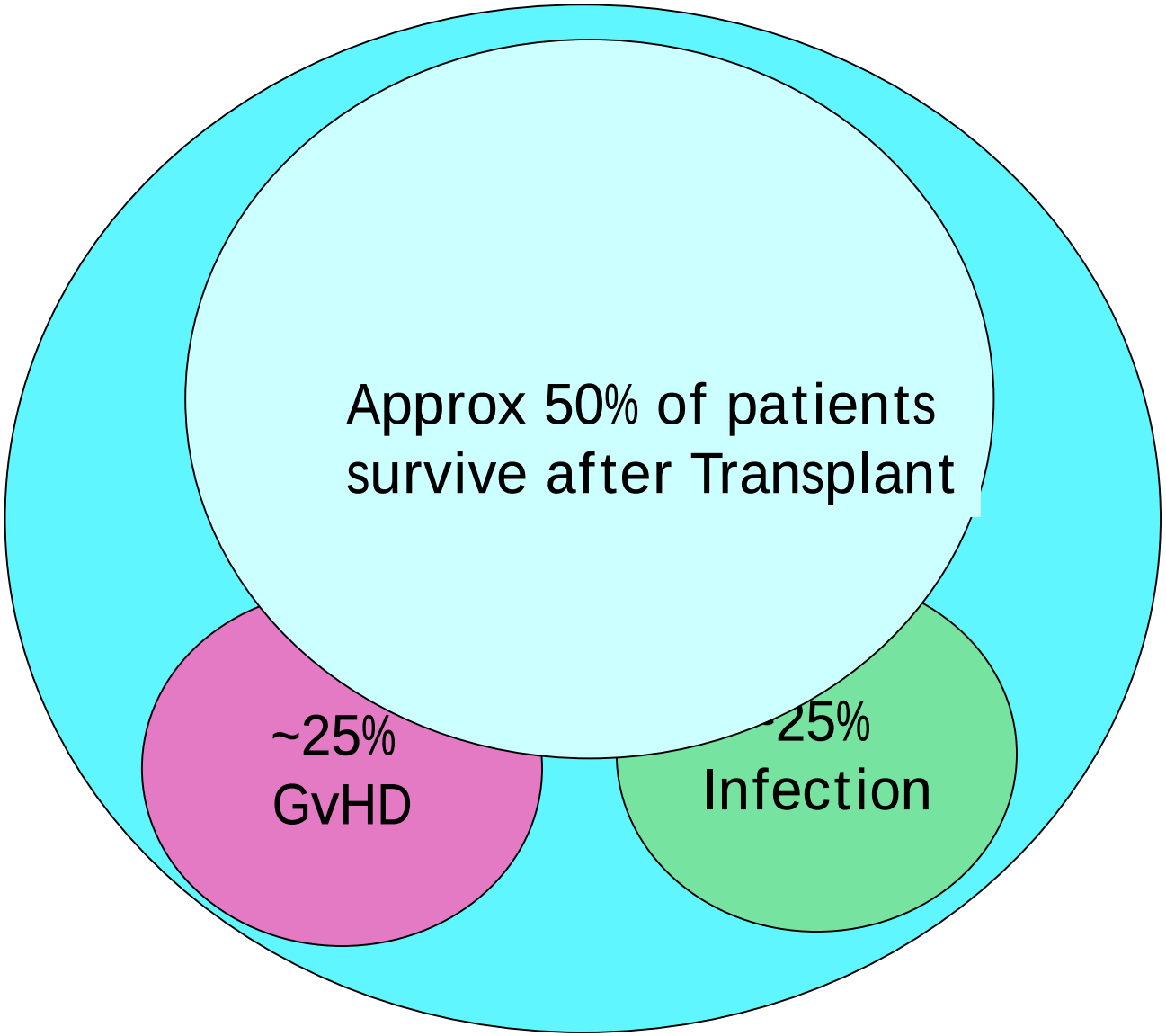


BSBMT and EBMT activity data 2014

CURRENT HAPLO TRANSPLANT PLATFORMS

- Post transplant cyclophosphamide
  - Reduced intensity, Baltimore
  - Myeloablative: Genoa group
- China: ATG based conditioning + aggressive IS with GCSF mobilised BM/PBSC
- Graft manipulation: Selective T cell (and B cell) depletion
- Manipulating conditioning
  - TBF- Primed BM- ATG + MTX + CSA + MMF+Basiliximab
  - TBF FluTBI- BM+ CSA + MMF+CTX (+3, +5)
  - TreoFlu- PBSC- ATG+MMF+Rapamycine

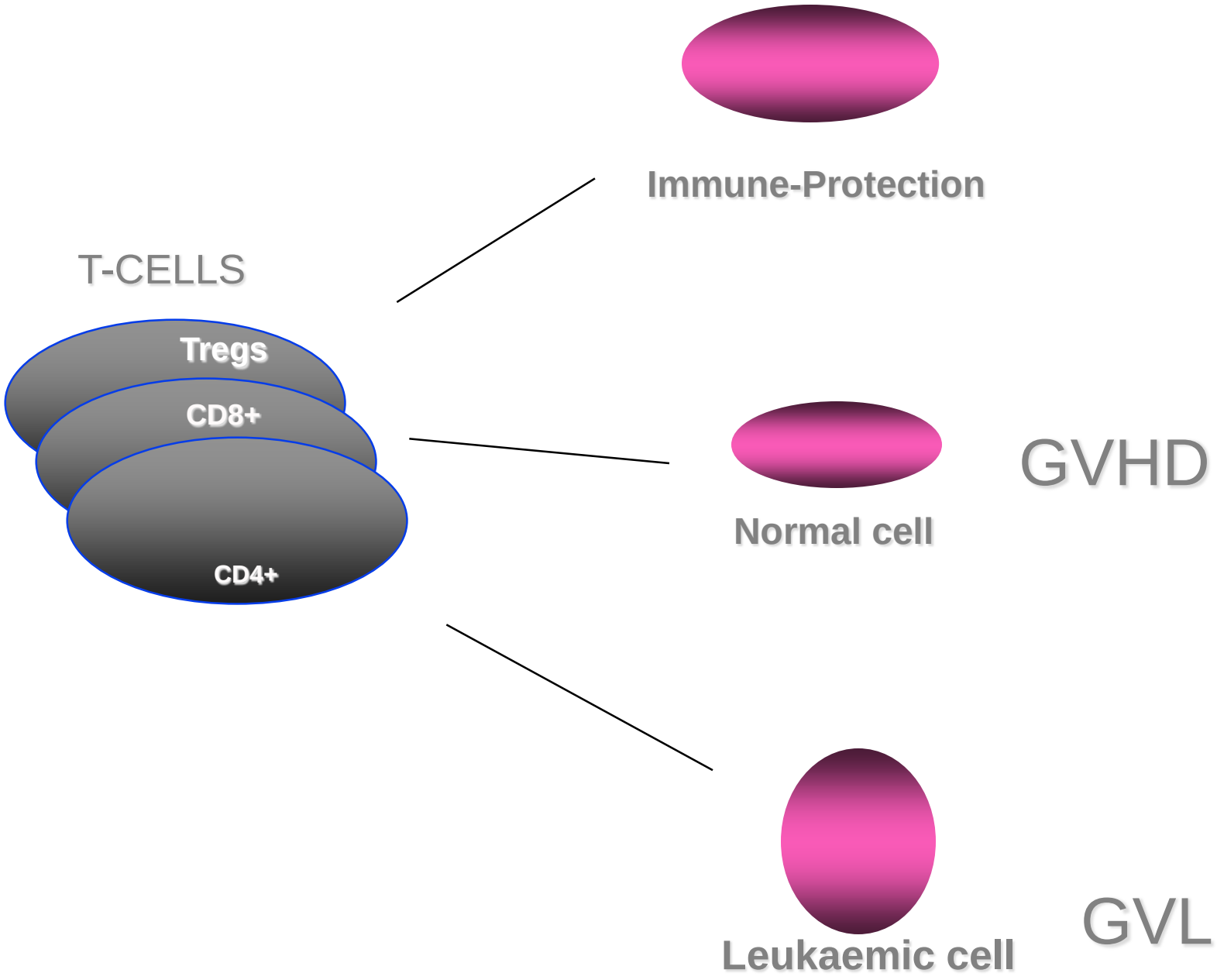
TRANSPLANTATION OUTCOME



Breakthrough of the Year 2013

1. Cancer Immunotherapy
2. CRISPR
3. CLARITY
4. Human Stem Cells from Cloning
5. Mini-Organs
6. Cosmic Particle Accelerators
7. Perovskites Solar Cells
8. Why We Sleep
9. Our Microbes, Our Health
10. In Vaccine Design, Looks Do Matter

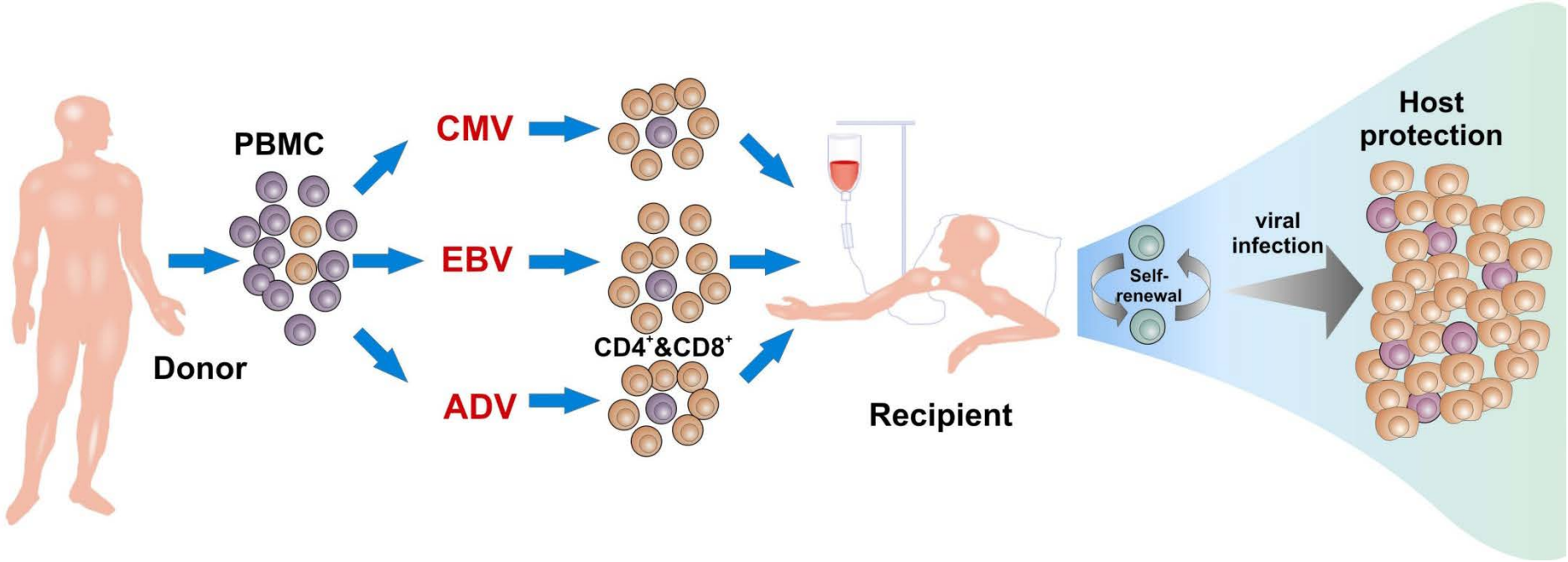
THE ANTHONY NOLAN RESEARCH INSTITUTE


Immune-Protection
T-CELLS
Tregs
CD8+
CD4+
Normal cell
GVHD
Leukaemic cell
GVL

IMMUNE CELL THERAPY

Strategy

Isolation of multipathogen-specific T-cells



adapted from Feuchtinger et al. *Leukemia & Lymphoma* 2006

SUMMARY

- There is now a donor for every patient who needs one
- Results of Cord and Haplo are approaching those of UD allografts and equal to MMUD in most diseases
- Expense and slow engraftment limit cord use
- Relapse remains an issue in haplo for acute leukaemia
- Need randomised comparison data!
- Cord blood expansion techniques and results of allelic level typed cord studies may improve outcomes

Our Future Task

- Continue to develop strategies to improve outcomes – decreasing both toxicity and relapse
- Understand who is the right donor for the right kind of transplant delivered at the right time to optimize survival and quality of life
- Ensure that all patients have access to the best therapy


Q&A


VIVALDOL


Q&A

Acknowledgements

The Anthony Nolan Research Inst:

- Steven Marsh
- Bronwen Shaw
- Richard Szydlo
- Chloe Anthias
- Neema Mayor

Robert Danby

WMDA

Lydia Foeken

BSBMT

Keiren Kirkland

Julia Perry

Nigel H Russell

Andrew Clark

Stephen Mackinnon

Charles Craddock

David I Marks

Antonio Pagliuca

Michael N Potter

Andy Peniket

Kirsty Thomson