AST | AMERICAN SOCIETY OF TRANSPLANTATION

The Barriers and Opportunities for Personalized Transplant Care

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CEOT CUTTING EDGE of TRANSPLANTATION

TRANSPLANT SUMMIT 2019

NO SIZE FITS ALL: *Uncovering the Potential of Personalized Transplantation*

FEBRUARY 21–23, 2019 • ARIZONA BILTMORE • PHOENIX, AZ

Disclosure

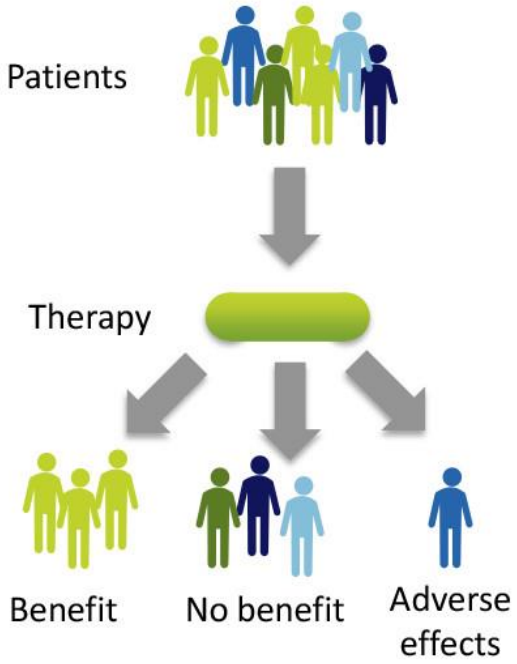
None

Learning Objectives

Provide the information informing the application of personalized medicine to transplant care.

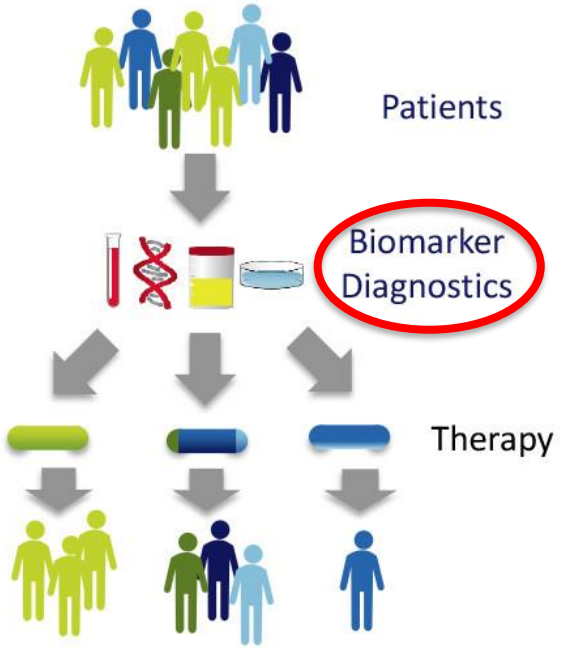
Without Personalized Medicine:

Some Benefit, Some Do Not

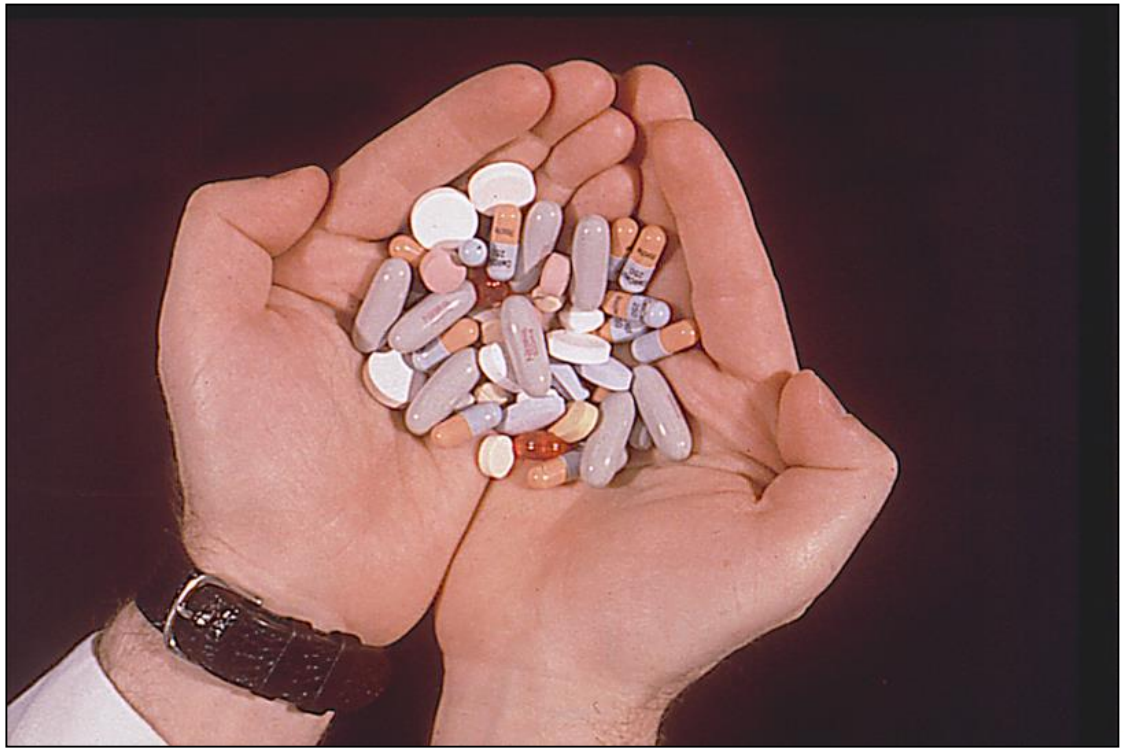


With Personalized Medicine:

Each Patient Receives the Right Medicine For Them



Each Patient Benefits From



Who am I?

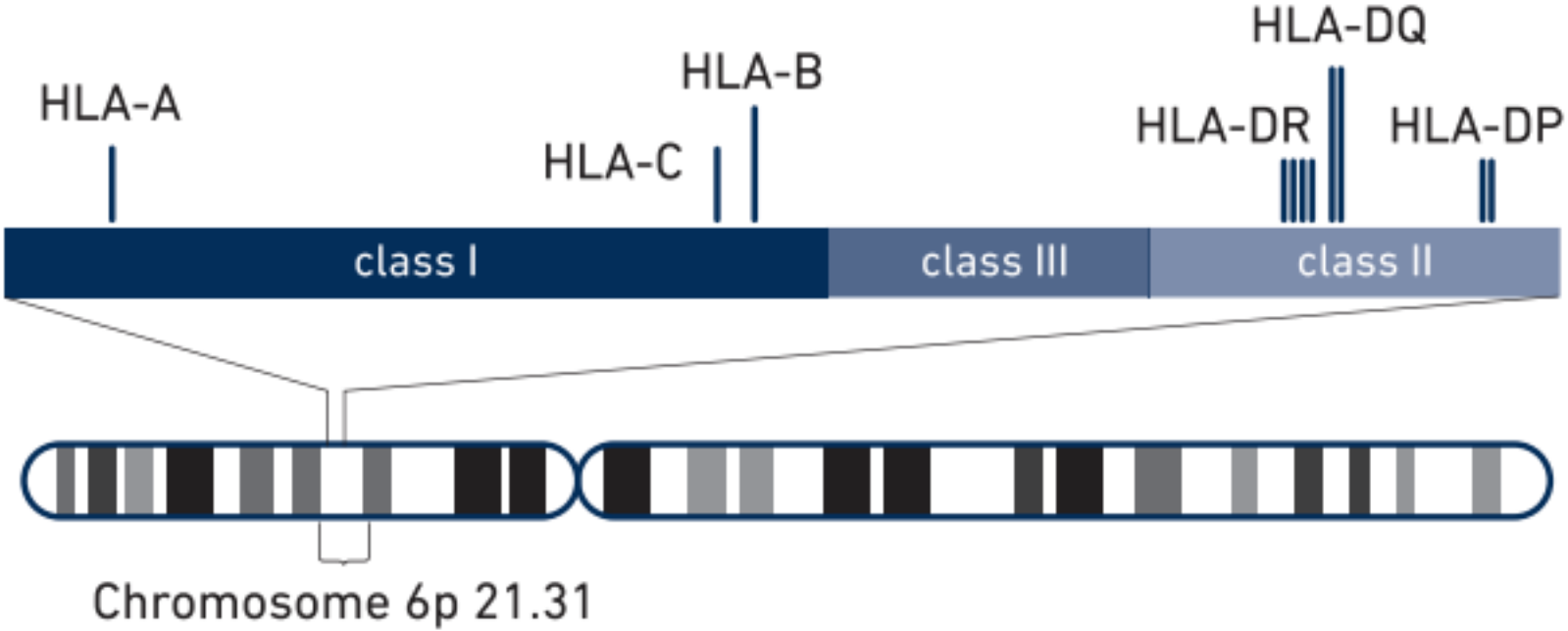

HLA-A
HLA-C
HLA-B
HLA-DR
HLA-DQ
HLA-DP
class I
class III
class II
Chromosome 6p 21.31

Table 1 Some major aims and results from the IHWSs[a]

WS number	Date	Place	Chairman	Some important aims and results	Reference
1	June 1964	Durham, NC, USA	D. Bernard Amos	Comparison of different typing techniques Results: very little consistency!	64
2	August 1965	Leiden, Holland	Jon J. van Rood	Comparison of different 'local' specificities Results: strong correlations between several	65
3	June 1967	Turin, Italy	Ruggero Ceppellini	Establish the genetics of leucocyte antigens Results: strong correlations between more 'local' specificities; most are encoded by genes at one chromosomal region; HLA	66
4	January 1970	Los Angeles, CA, USA	Paul I. Terasaki	Further definition of HLA specificities Eleven HLA specificities accepted	67
5	May 1972	Evian, France	Jean Dausset	Use of HLA in anthropology Established HLA frequencies in different populations	68
6	June 1975	Aarhus, Denmark	Flemming Kissmeyer-Nielsen	Focus on HLA LD antigens by exchange of homozygous typing cells. HLA-Dw1-6 accepted More HLA-A and -B antigens and five -Cw antigens accepted	69
7	September 1977	Oxford, UK	Julia and Walter F. Bodmer	Focus on antigens expressed on B cells HLA-DRw1-7 accepted, strong correlations to corresponding HLA-Dw antigens	70
8	February 1980	Los Angeles, CA, USA	Paul I. Terasaki	Focus on applications A possible beneficial effect of HLA matching in renal transplantation from unrelated donors	71

From Thorsby. Tissue Antigens 2009

The New England
Journal of Medicine

Volume 280 APRIL 3, 1969 Number 14

SIGNIFICANCE OF THE POSITIVE CROSSMATCH TEST IN KIDNEY TRANSPLANTATION*

RAMON PATEL, M.R.C.P., AND PAUL I. TERASAKI, PH.D.

Abstract Crossmatch tests of the prospective kidney-transplant donor's lymphocytes with the serum of the prospective recipient in 225 transplants showed that eight of 195 with negative crossmatch failed to function immediately, in contrast to 24 of 30 with positive crossmatch (p less than 0.001). Immediate failure occurred in significantly higher numbers among patients with a higher risk of having antibodies, such as multiparous females and patients receiving secondary transplants. The effect was not a nonspecific one, for more immediate failures occurred among transplants from unrelated than among those from related donors. The corresponding frequency of positive crossmatch was also lower among related donors. The presence of preformed cytotoxic antibodies against the donor appears to be a strong contraindication for transplantation.

PREFORMED allogeneic antibodies present in a recipient were first postulated as being responsible for immediate failure of a kidney transplant in 1964.[1] At that time it was suggested that a crossmatch test of the prospective recipient's serum against the donor's cells could be of importance. In the intervening four years, additional evidence[2-5] has confirmed the dramatic destruction of kidney grafts in recipients who have preformed antibodies. Immediate failure has also been observed when cytotoxic antibodies were not present,[4] and a case in which failure did not occur in spite of a positive crossmatch has been reported.[2]

Because prospective kidney-transplant patients are often sensitized, it is of critical importance to determine the clinical outcome when a sufficiently large number of these patients have received transplants. With the help of many transplant centers over the past four years, we have accumulated the results of 248 kidney transplants performed in 63 patients with preformed cytotoxic antibodies and 163 without. It is the purpose of this communication to document the high risk of immediate failure (43 per cent) when kidneys are transplanted into recipients with preformed antibodies and an even greater risk (80 per cent) when a direct positive crossmatch can be demonstrated.

*From the Department of Surgery, University of California, Los Angeles, School of Medicine (address reprint requests to Dr. Patel at the Department of Surgery, University of California Center for the Health Sciences, Los Angeles, Cal. 90024).

Supported in part by research grants (AM 02375, AM 07513 and AI 04444) from the National Institutes of Health, United States Public Health Service, and by a contract (PH 43 65 994) with the National Institute of Allergy and Infectious Diseases (computing assistance obtained from the Health Sciences Computing Facility, UCLA, sponsored by NIH Grant FR-3).

MATERIAL AND METHODS

The 226 kidney-transplant recipients were bled before transplantation, and the serums tested against lymphocytes of 10 to 40 randomly selected persons.[6] On the basis of these reactions, serums were divided into three groups: positive (those reacting with 20 per cent or more of cell samples of random persons); negative (those reacting with less than 10 per cent of cell samples of random persons); and doubtful (those reacting with 10 to 20 per cent of cell samples of random persons). Whether the antibodies detected against random lymphocytes were specific to the donor's lymphocytes was determined by crossmatching of the recipient's serum in three different volumes of 0.0005, 0.0015 and 0.0045 ml against the donor's lymphocytes. Clinical data pertaining to the patients were kindly supplied by the transplant centers concerned.

RESULTS

Occurrence of Preformed Cytotoxins

Preformed cytotoxic antibodies against lymphocytes of random persons were present in 131 serum samples among 681 prospective recipients of first kidney transplants – a figure of 19.2 per cent (Table 1). This proportion is somewhat lower than that previously reported from our laboratory in 218 recipients[2] and could reflect improvements in typing technics.

The female recipients had a significantly higher

Crossmatch	Graft Rejection	Functioning Graft
Positive	24	6
Negative	8	187

Paradigm: Transplantation is limited by individual immune incompatibility that gives rise to an immune response, which can be measured.

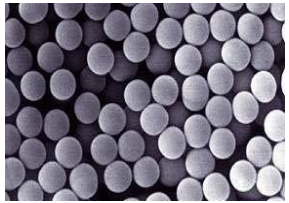
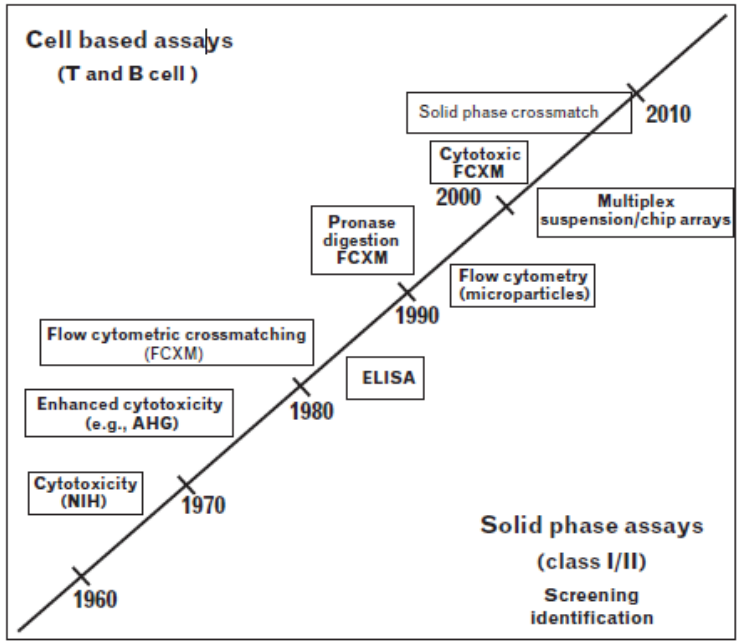


Figure 1 Evolution of human leukocyte antigen antibody testing



Gebel and Bray, Curr Opin Neph Hypertension. 2010.

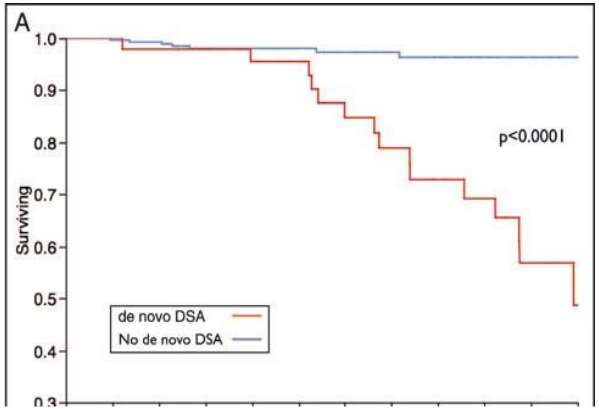
American Journal of Transplantation
Wiley Periodicals Inc.

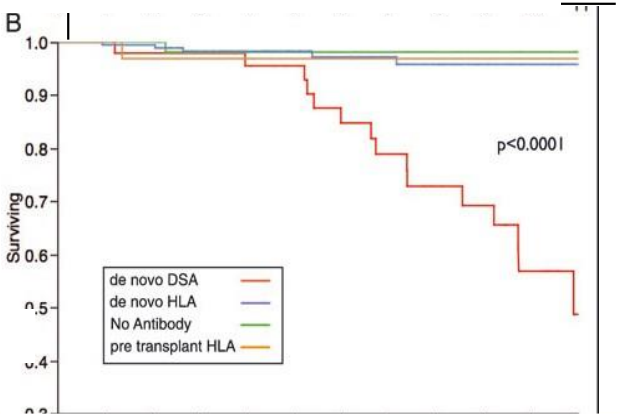
doi: 10.1111/j.1600-6143.2012.04013.x

Evolution and Clinical Pathologic Correlations of *De Novo* Donor-Specific HLA Antibody Post Kidney Transplant

C. Wiebe[a,†], I. W. Gibson[b,c,†], T. D. Blydt-Hansen[d], M. Karpinski[e], J. Ho[e], L. J. Storsley[e], A. Goldberg[d], P. E. Birk[d], D. N. Rush[e] and P. W. Nickerson[a,c,*]

Received 12 October 2011, revised 29 November 2011 and accepted for publication 22 December 2011





Alloantibody Measurement

- Pre-formed DSA is a clearly established risk factor for graft loss.
- De novo DSA is a clearly established risk factor for graft loss, and a likely biomarker for non-adherence.
- Modern immunosuppression, when used well, is good at preventing DSA formation.
- The cost effectiveness of serial DSA monitoring is not well established and protocols for DSA monitoring are not standardized.

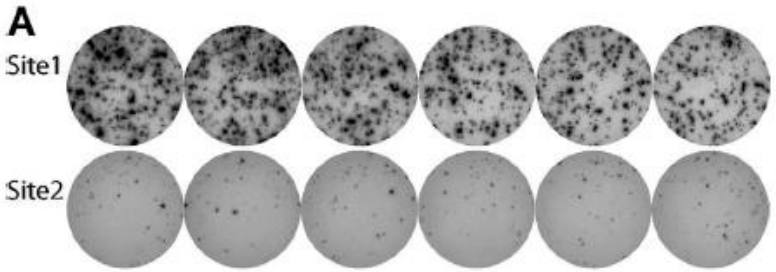
American Journal of Transplantation 2013; 13: 1871–1879
Wiley Periodicals Inc.

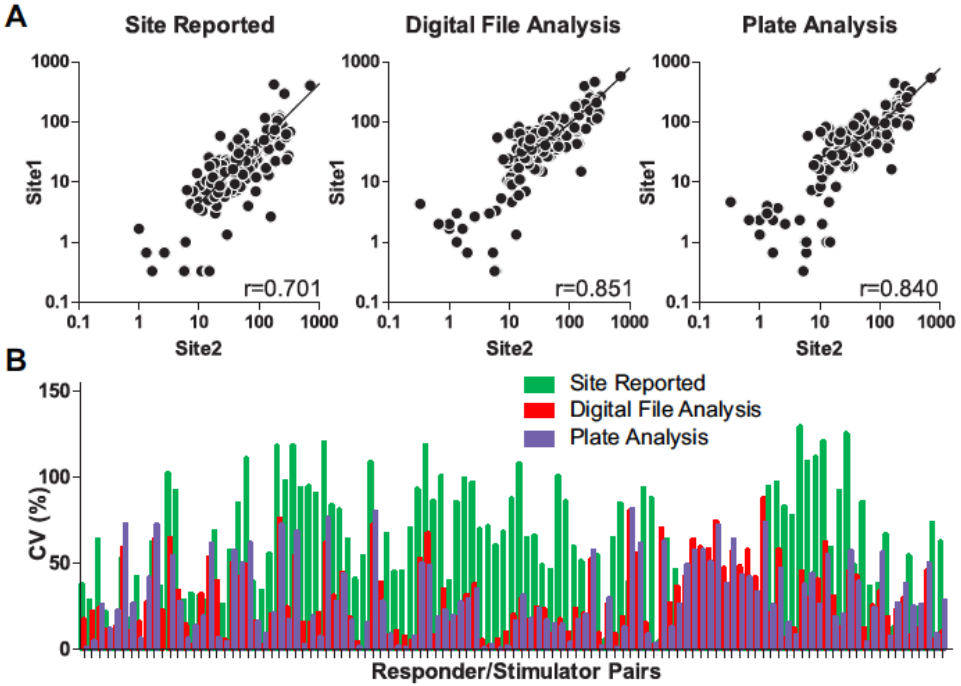
doi: 10.1002/ajt.12286

Brief Communication

Standardization and Cross Validation of Alloreactive IFNγ ELISPOT Assays Within the Clinical Trials in Organ Transplantation Consortium

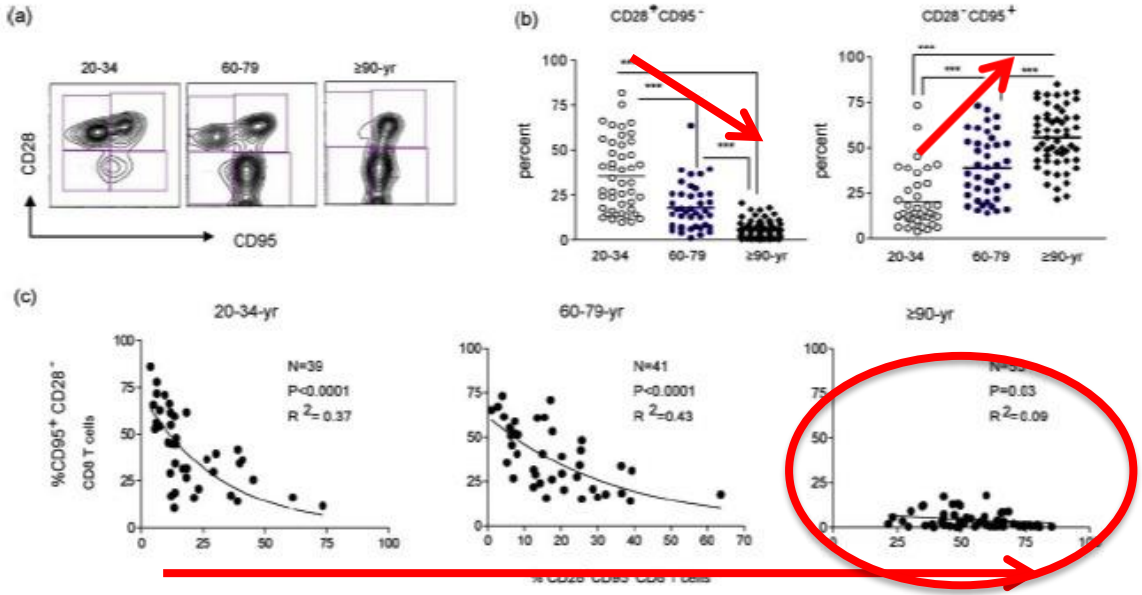
I. Ashoor[1], N. Najafian[1], Y. Korin[2], E. F. Reed[2], T. Mohanakumar[3], D. Iklé[4], P. S. Heeger[5] and M. Lin[5,*]





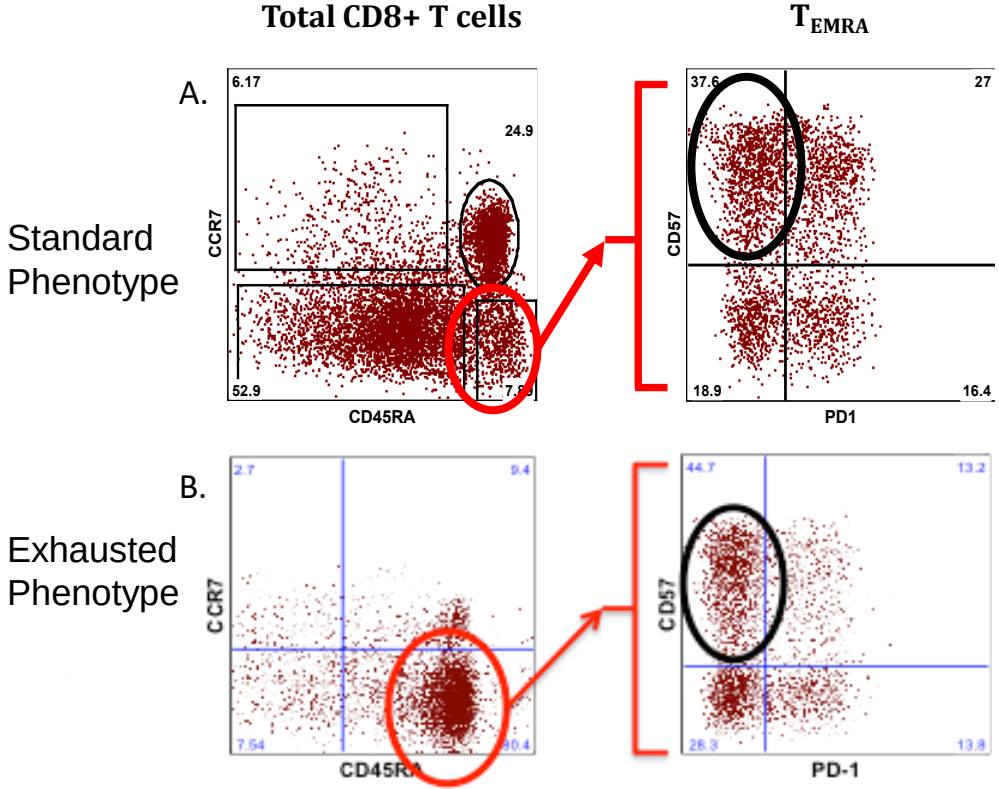
Changes T cell Phenotype with Age

Reduced thymus, increased reliance on homeostatic proliferation

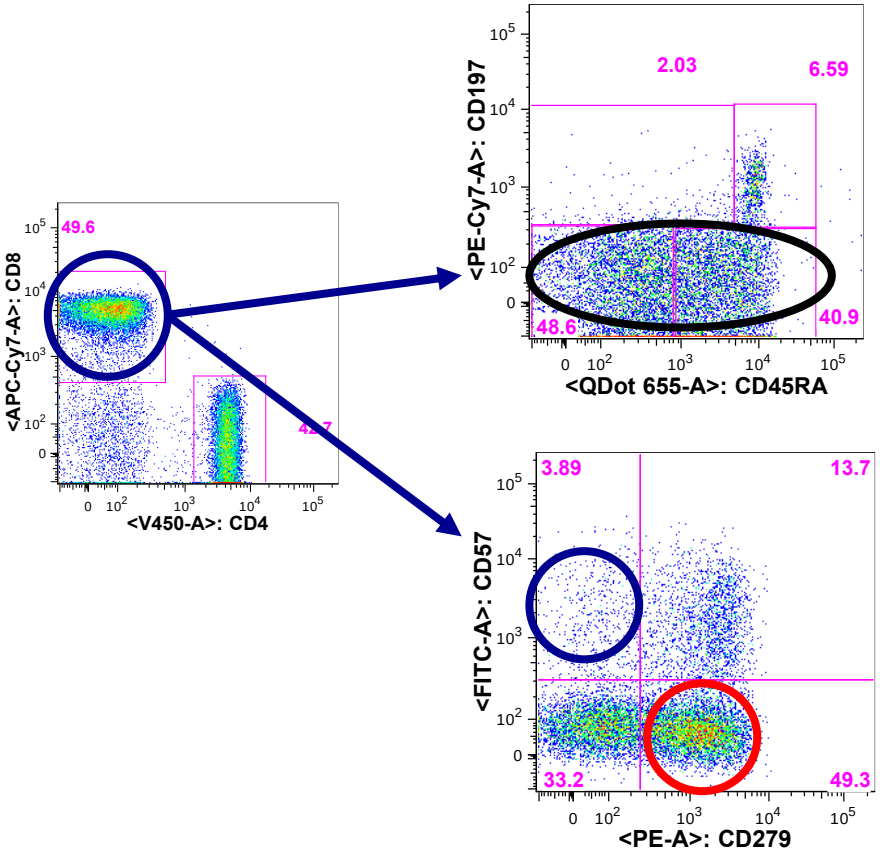


Chen, et al. Mech Aging Dev. 2010, 131:29-37.

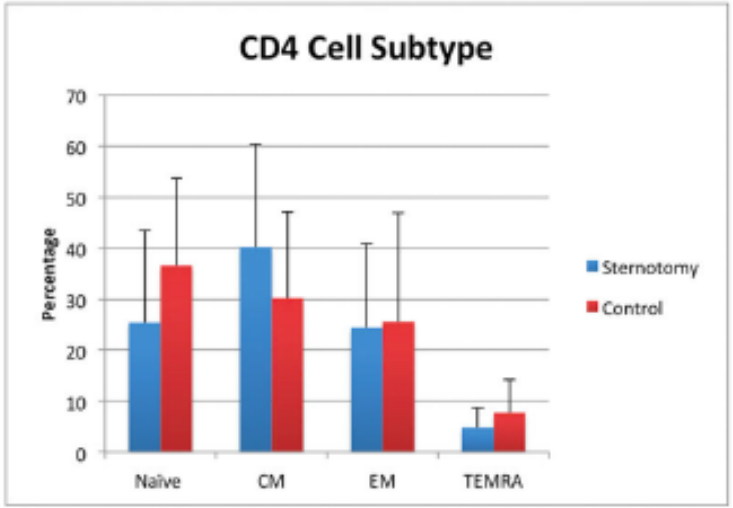
Variable Exhaustion/Senescence Profiles at Presentation for Transplant

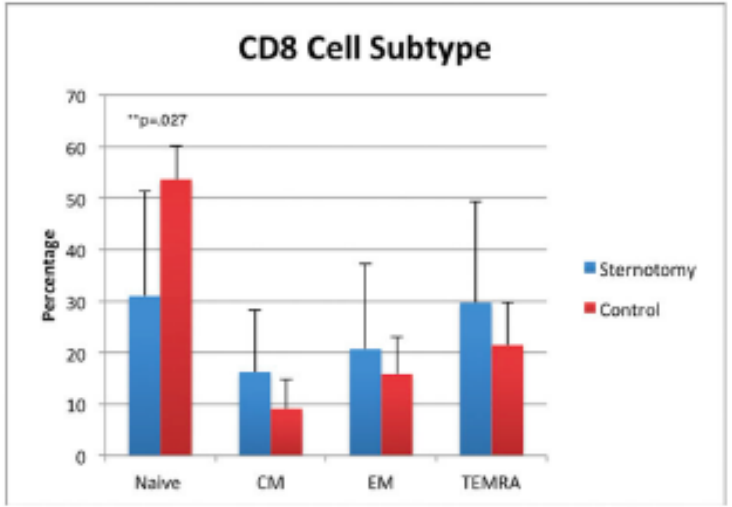


Advanced Exhaustion post Thymectomy



Thymectomy and Immune Exhaustion





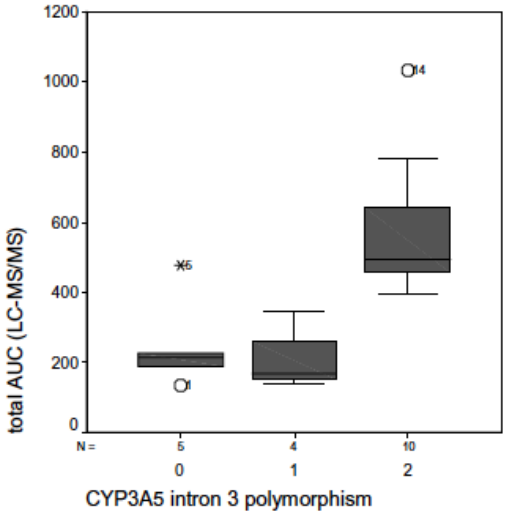
Pediatr Cardiol. 2015 Oct;36(7):1411-6.

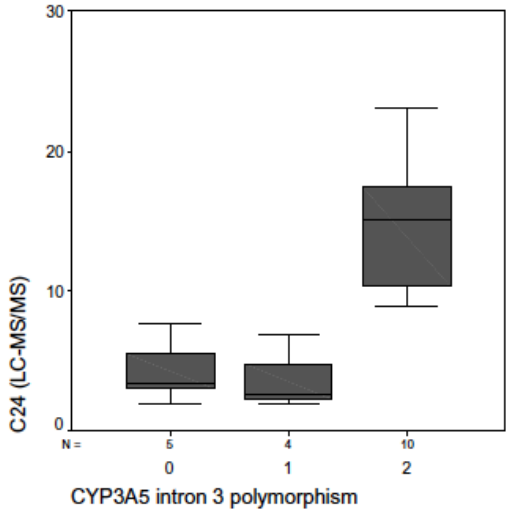
American Journal of Transplantation 2006; 6: 2706–2713
Blackwell Munksgaard

doi: 10.1111/j.1600-6143.2006.01518.x

CYP3A5 and *ABCB1* Polymorphisms and Tacrolimus Pharmacokinetics in Renal Transplant Candidates: Guidelines from an Experimental Study

V. Haufroid[a,b,*], P. Wallemacq[b], V. VanKerckhove[a], L. Elens[a], M. De Meyer[c], D. C. Eddour[c], J. Malaise[c], D. Lison[a] and M. Mourad[c]





Tacrolimus AUC

Abbreviated tacrolimus area-under-the-curve monitoring for renal transplant recipients.
Wong KM, Shek CC, Chau KF, Li CS.
Am J Kidney Dis. 2000 Apr;35(4):660-6.

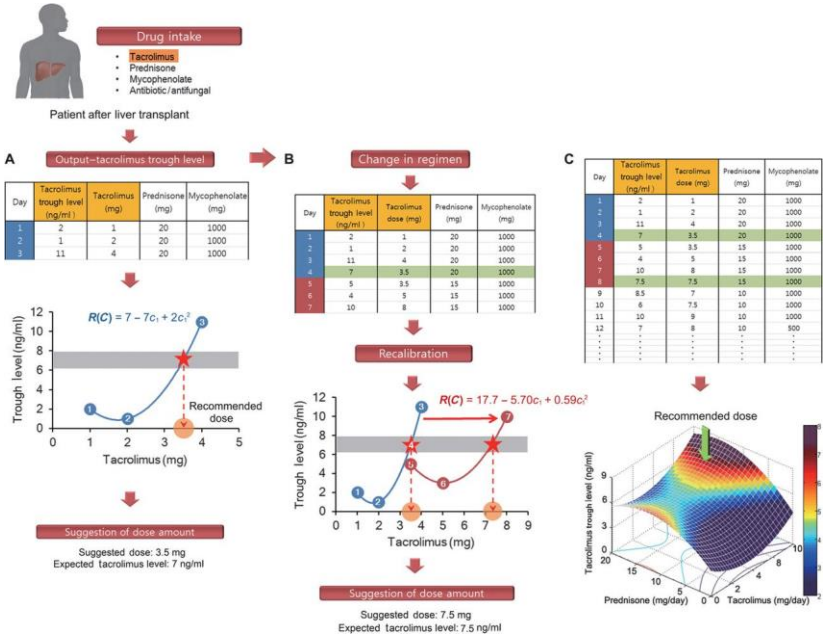
10+1.4*0h +0.8*1h+1.6*2h+5.5*4h

Universal approach to pharmacokinetic monitoring of immunosuppressive agents in children.
Filler G, Feber J, Lepage N, Weiler G, Mai I.
Pediatr Transplant. 2002 Oct;6(5):411-8.

4.2+3.2*0h +1.3*1h+0.8*2h+5.5*4h

Target 80-120

Phenotypic Personalized Medicine



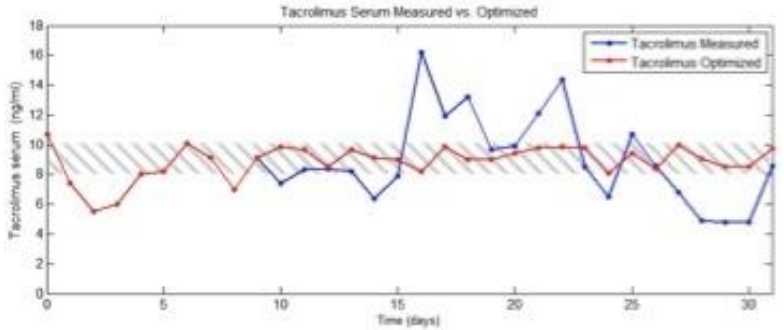
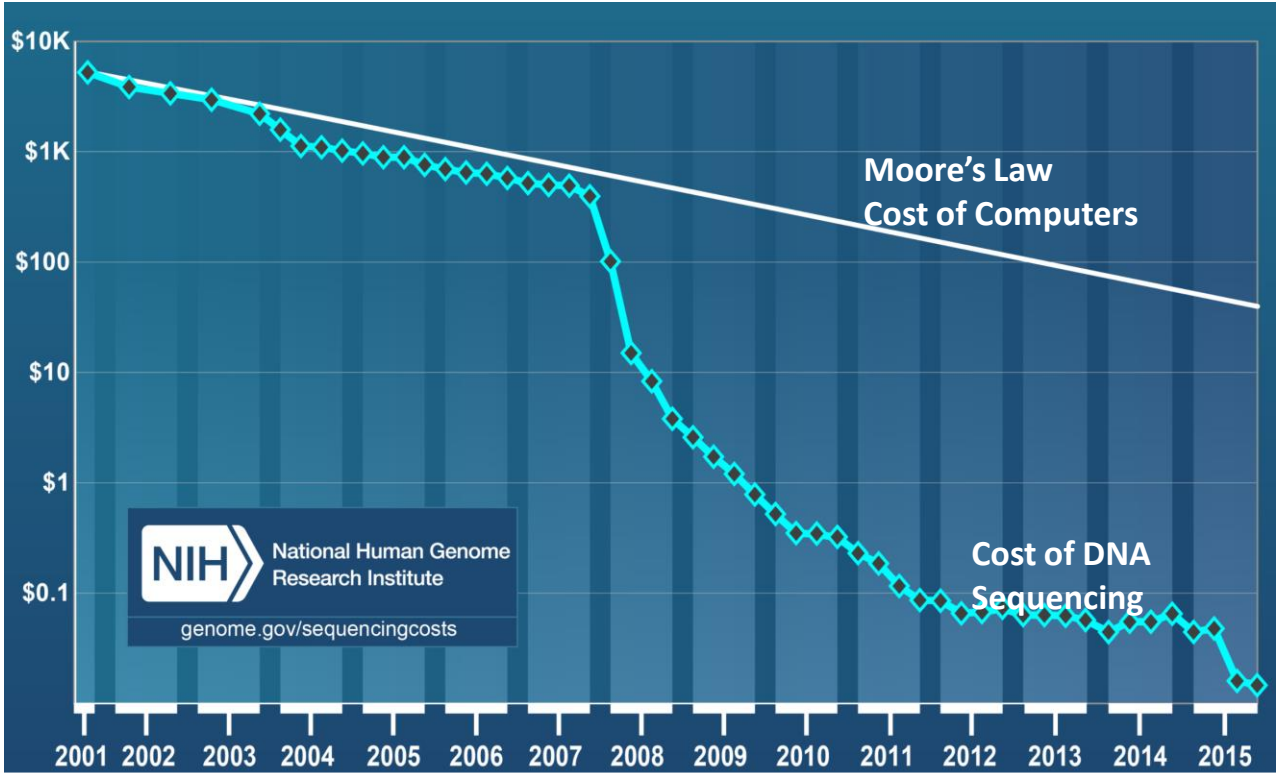


Figure 1. Optimized Serum Tacrolimus Levels

Zarrinpar, et al. *Sci Trans Med.* 2016; 8: 333ra49

Cost DNA Sequencing vs. Moore's Law



Project Baseline HOME THE STUDY THE TEAM LOGIN APPLY English

WE'VE MAPPED THE WORLD.
NOW LET'S MAP HUMAN HEALTH.

American Journal of Transplantation 2017; 17: 2851–2862
Wiley Periodicals Inc.

doi: 10.1111/ajt.14329

Real Time Central Assessment of Kidney Transplant Indication Biopsies by Microarrays: The INTERCOMEX Study

P. F. Halloran[1,2]*, J. Reeve[1], E. Akalin[3], O. Aubert[4], G. A. Bohmig[5], D. Brennan[6], J. Bromberg[7], G. Einecke[8], F. Eskandary[5], C. Gosset[4,9], J.-P. Duong Van Huyen[4], G. Gupta[10], C. Lefaucheur[4,9], A. Malone[6], R. B. Mannon[11], D. Seron[12], J. Sellares[12], M. Weir[7] and A. Loupy[4,13]


ATAGC

Alberta Transplant Applied Genomics Centre
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Edmonton, AB T6G 2S2, ph. 780-407-8980, fax 780-407-8817

INTERCOM Study: Molecular Diagnostic Report

General

Patient ID	-
Biopsy Site ID	-
INTERCOM Study ID	-
Attending Physician	-
Date Reported (Y-M-D)	-
Date Received (Y-M-D)	-
Date of Transplant (Y-M-D)	-
Date of Biopsy (Y-M-D)	-

Name:
-
DOB (Y-M-D):
-
Age at Bx:
-

Clinical Information

Time of Biopsy Post-Tx	1.9 years	Biopsy Indication	-
Primary Disease	-	Transplant Type	-
GFR (CG) at Biopsy	-	To before Biopsy	-
Proteinuria	-	DSA Status at Biopsy	-
Hematuria	-	PRA Status at Biopsy	-

Local Histopathology Phenotype: the Banff System

Inflammation/TCMR Lesions		ABMR Lesions		Atrophy/Scarring		Other	
i	-	g(c)	-	ci	-	BK	-
t	-	g	-	ct	-		
v	-	cg	-	cv	-		
total i	-	C4d	-	ah	-		
		mm	-				
Banff Diagnosis 1		-		Banff Diagnosis 2		-	

Molecular Phenotype: the Edmonton Molecular Microscope System

Classifier/PHT	Biopsy Score	Range in Reference Set	Percentile compared to Reference Set	Interpretation
Global Disturbance Score	0.81	0.0 -> 3.10	All:81.2 Late:80.1	High
Acute Kidney Injury (AKI) Score	0.86	-0.92 -> 1.98	All:91 Late:97.9	Moderate
Atrophy-Fibrosis Score	0.83	0.0 -> 1.4	All:93.2 Late:92	Moderate
Rejection Score	0.77	0.0 -> 1.0	All:80.6 Late:88.7	High
TCMR Score	0.00	0.0 -> 1.0	All:52.8 Late:81.7	Low
ABMR Score	0.94	0.0 -> 1.4	All:99.6 Late:99.1	Very High

Pure molecular interpretation

Severe ABMR with g, ptc and cg molecular features. No TCMR. Extensive inflammation with associated AKI and moderate atrophy-fibrosis.

Clinical Notes

Integrated interpretation incorporating histo-clinical variables as available

Legend: NA = not available, ABMR = antibody-mediated rejection, TCMR = T cell-mediated rejection

DRAFT: FOR RESEARCH PURPOSES ONLY


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INTERCOM Study: Molecular Diagnostic Report

Classifier/PHT	Biopsy Score	Range in Reference Set	Percentile Compared to Reference Set	Interpretation
TCMR				
TCMR I	0.00	0.0 -> 1.0	All:42.6 Late:46.7	Low
TCMR II/III	0.00	0.0 -> 1.0	All:46.7 Late:36	Low
Mean of 2 TCMR classifiers	0.00	0.0 -> 1.0	All:44.5 Late:58.3	Low
DNR related				
Rejection	0.77	0.0 -> 1.0	All:89.6 Late:88.7	High
Rejection(bk)	0.66	0.0 -> 1.0	All:87.2 Late:84.1	High
Mean of 2 Rejection classifiers	0.81	0.0 -> 1.0	All:89.2 Late:89.4	Moderate
Others not in rej related				
AKI score	0.44	-0.43 -> 1.98	All:93 Late:97.9	Moderate
ptc	-0.91	-2.84 -> 8.18	All:2.6 Late:21.6	Moderate
cg(c)	0.35	0.0 -> 1.0	All:95.3 Late:85	Moderate
ABMR related				
cbx(c) (abc only)	1.31	-4.36 -> 1.12	All:99.6 Late:99.1	High
ABMRptm	0.50	0.0 -> 1.0	All:99.6 Late:99.3	Very High
ABMRptm(bk)	0.97	0.0 -> 1.0	All:98.2 Late:99.7	Very High
ABMRptm	0.95	0.0 -> 1.0	All:97.1 Late:93	Very High
Mean of 3 ABMR classifiers	0.97	0.0 -> 1.0	All:99.1 Late:98.3	Very High
ABMRtx	0.11	0.0 -> 1.0	All:31.8 Late:39.8	Low
ABMRtx(mc)	0.11	0.0 -> 1.0	All:31.9 Late:44.8	Low

g > 0 prob	0.99	t>i > 0 prob	0.35
cg > 0 prob	0.97	t>i > 1 prob	0.53
ptc > 1 prob	0.89	ah > 2 prob	0.69
DSA+ prob	0.96	ah > 0 prob	0.75
i > 1 prob	0.18	v > 0 prob	0.87
t > 1 prob	0.06	Prot+ prob	0.61
		BM < 30 prob	0.15

For classifiers:
t = TCMR, b= Borderline, k=BK virus, x=Mixed, p=DSA+, n=C4d, [ ] = corners of square bracket) left out.
E.g. TCMR(abc) is a classifier comparing TCMR with everything else, with borderline, BK virus, and Mixed left out.

Legend: NA = not available, ABMR = antibody-mediated rejection, TCMR = T cell-mediated rejection

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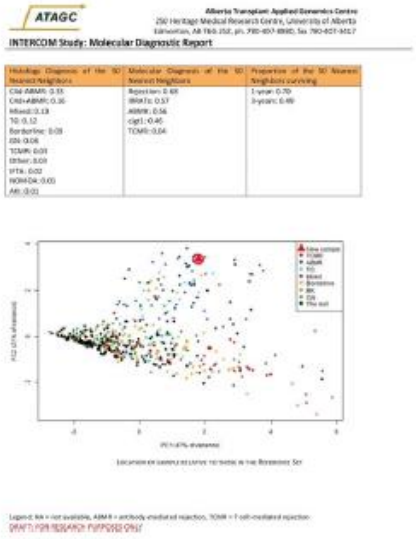
ATAGC

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Edmonton, AB T6G 2S2, ph. 780-407-8980, fax 780-407-8817

INTERCOM Study: Molecular Diagnostic Report

Histologic Diagnosis of the 50 Nearest Neighbors	Molecular Diagnosis of the 50 Nearest Neighbors	Proportion of the 50 Nearest Neighbors surviving
Cld-ABMR: 0.55 CNI+ABMR: 0.16 Mixed: 0.13 TCMR: 0.12 Borderline: 0.03 IDN: 0.01 TCMR: 0.01 Other: 0.01 VITA: 0.02 NONE DX: 0.01 Alb: 0.01	Rejection: 0.48 IBMR Tx: 0.37 ABMR: 0.06 cg(c): 0.46 TCMR: 0.04	1-year: 0.70 3-years: 0.49

Legend: NA = not available, ABMR = antibody-mediated rejection, TCMR = T cell-mediated rejection

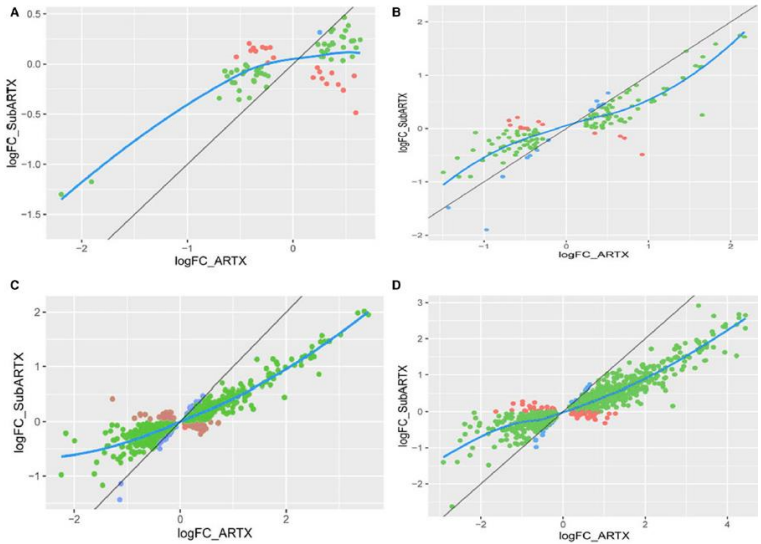
DRAFT: FOR RESEARCH PURPOSES ONLY

American Journal of Transplantation 2017; 17: 2103–2116
Wiley Periodicals Inc.

doi: 10.1111/ajt.14224

Orthogonal Comparison of Molecular Signatures of Kidney Transplants With Subclinical and Clinical Acute Rejection: Equivalent Performance Is Agnostic to Both Technology and Platform

S. M. Kurian[1,*,†], E. Velazquez[1,†], R. Thompson[1], T. Whisenant[1], S. Rose[2], N. Riley[1], F. Harrison[1], T. Gelbart[1], J. J. Friedewald[3], j. charette[3], S. Brietigam[3], J. Peysakhovich[3], M. R. First[2,3], M. M. Abecassis[3] and D. R. Salomon[1]



Comparison	cAR vs. TX	subAR vs. TX	Overlap (%)
Microarrays - Blood	2287	720	73 (3.2%*, 10.1%^)
NGS - Blood	2566	1647	143 (5.6%*, 8.7%^)
Microarrays - Biopsies	7376	2931	937 (12.7%*, 32.0%^)
NGS - Biopsies	8922	2565	1188 (13.3%*, 46.3%^)

* - Overlap compared to cAR vs. TX
^ - Overlap compared to subAR vs. TX

Research article Related Commentary, page 1803

Identification of a B cell signature associated with renal transplant tolerance in humans

Kenneth A. Newell,[1] Adam Asare,[2,3] Allan D. Kirk,[1] Trang D. Gisler,[2,3] Kasia Bourcier,[2,3] Manikkam Suthanthiran,[4] William J. Burlingham,[5] William H. Marks,[6] Ignacio Sanz,[7] Robert I. Lechler,[8,9] Maria P. Hernandez-Fuentes,[8,9] Laurence A. Turka,[3,10] and Vicki L. Seyfert-Margolis,[3,11] for the Immune Tolerance Network ST507 Study Group

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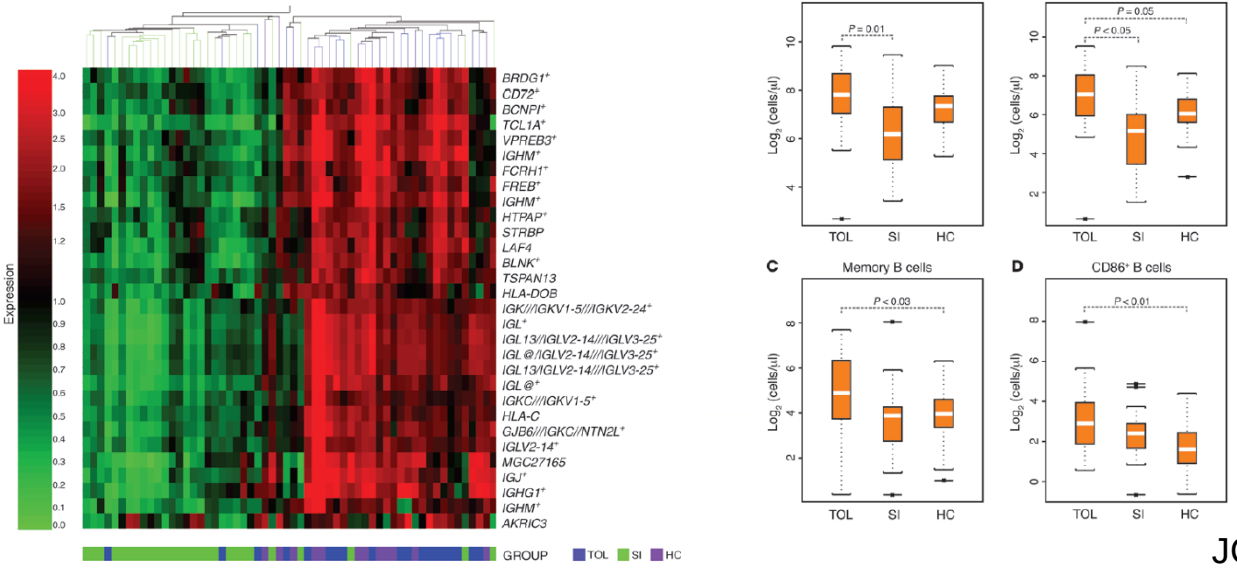

JCI 2010; 120:1836-47.

American Journal of Transplantation 2017; 17: 2627–2639
Wiley Periodicals Inc.

doi: 10.1111/ajt.14283

B Cell Receptor Genes Associated With Tolerance Identify a Cohort of Immunosuppressed Patients With Improved Renal Allograft Graft Function

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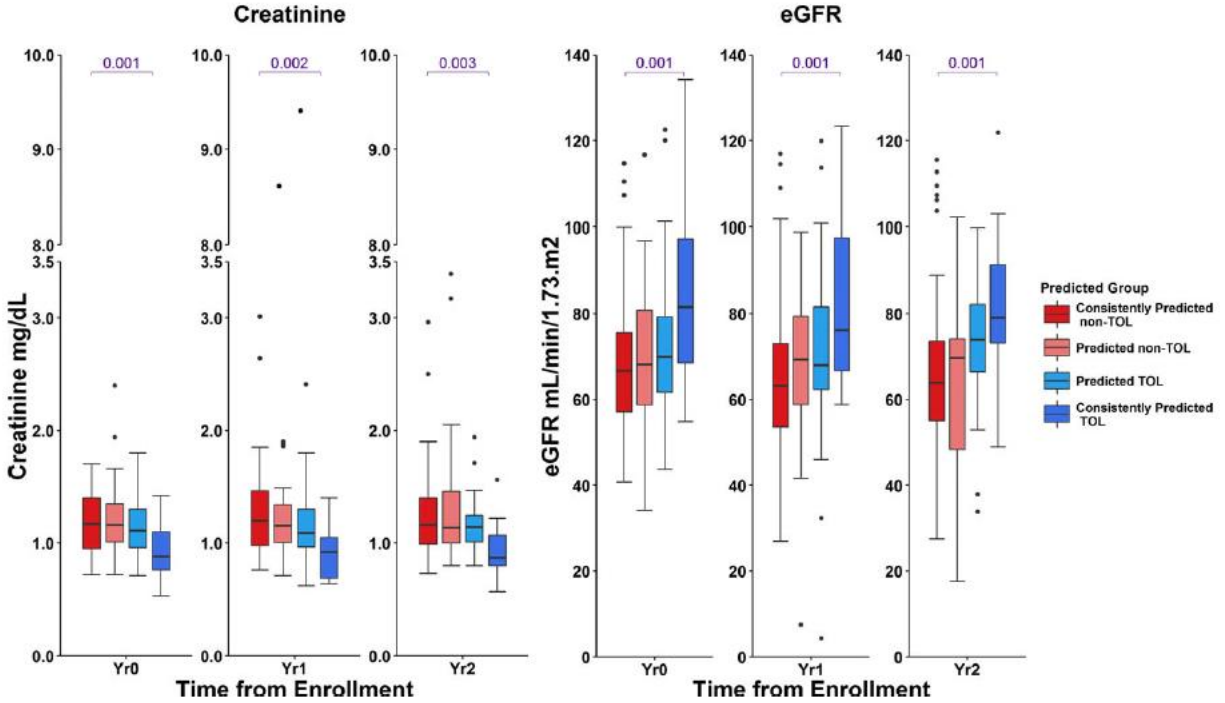


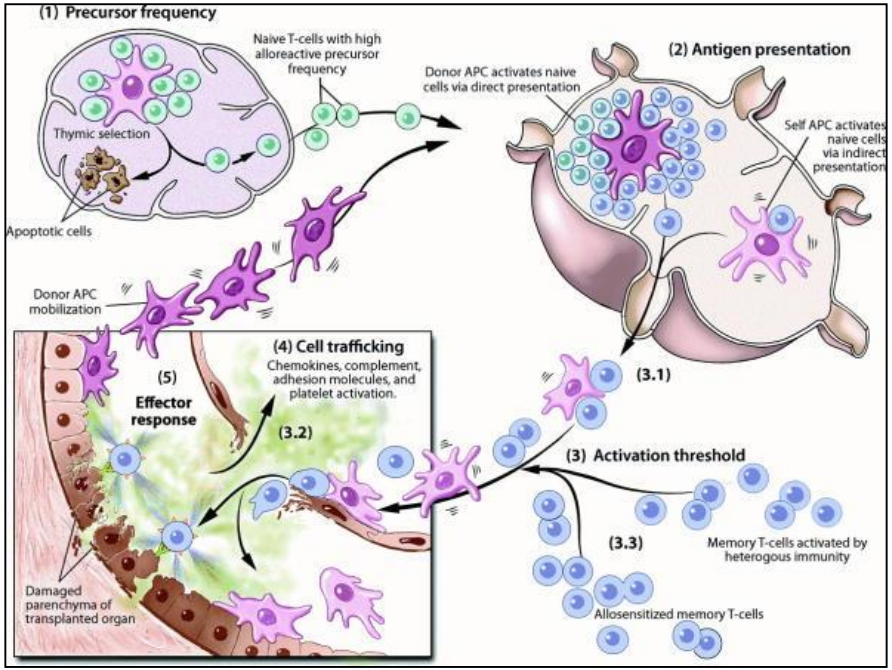
Mechanisms of Allograft Rejection

Thymic Selection

Precursor Frequency

DAMPs

Effector Molecules/ Antibody



Direct and Indirect Antigen Presentation

T/B cell Activation

T cell Trafficking

Transplantation 2006; 82(5):593-602

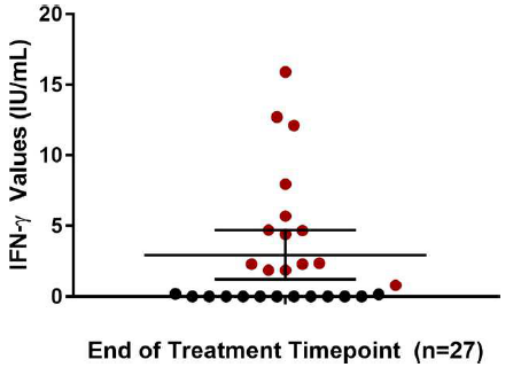
American Journal of Transplantation 2017; 17: 2468–2473
Wiley Periodicals Inc.

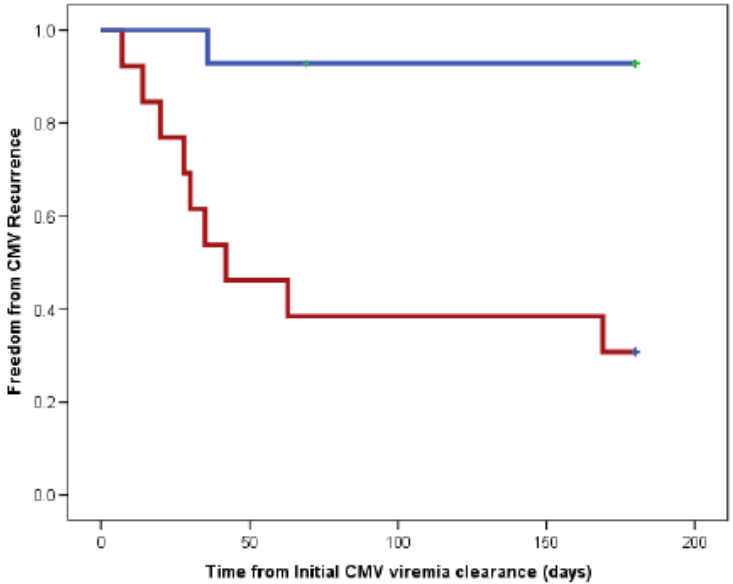
doi: 10.1111/ajt.14347

Brief Communication

An Interventional Study Using Cell-Mediated Immunity to Personalize Therapy for Cytomegalovirus Infection After Transplantation

D. Kumar*, M. Mian, L. Singer and A. Humar





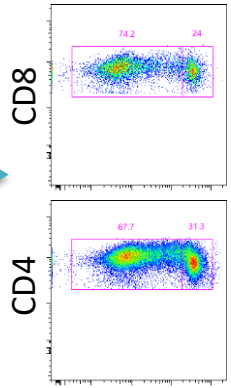
Strategy for Alloreactive TCR discovery

PBMC collection → PBMC culture with allo antigen(s) → FACS sorting for expanded T cell clones → TCR library construction → Deep sequencing → TCR repertoire analysis

PBMCs

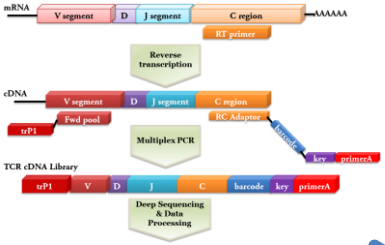
5 days

PBMCs stimulated by donor/third party mDCs

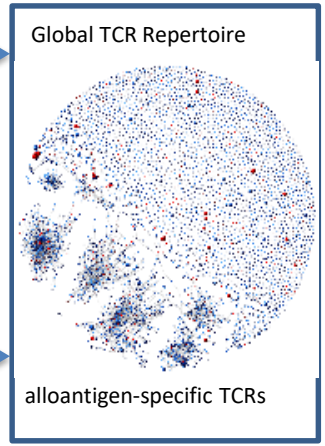


Sort cells

Direct ex vivo Repertoire Sequencing



Repertoire Sequencing for T cells after alloantigen-stimulated proliferation



Execution

Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research

Original Article

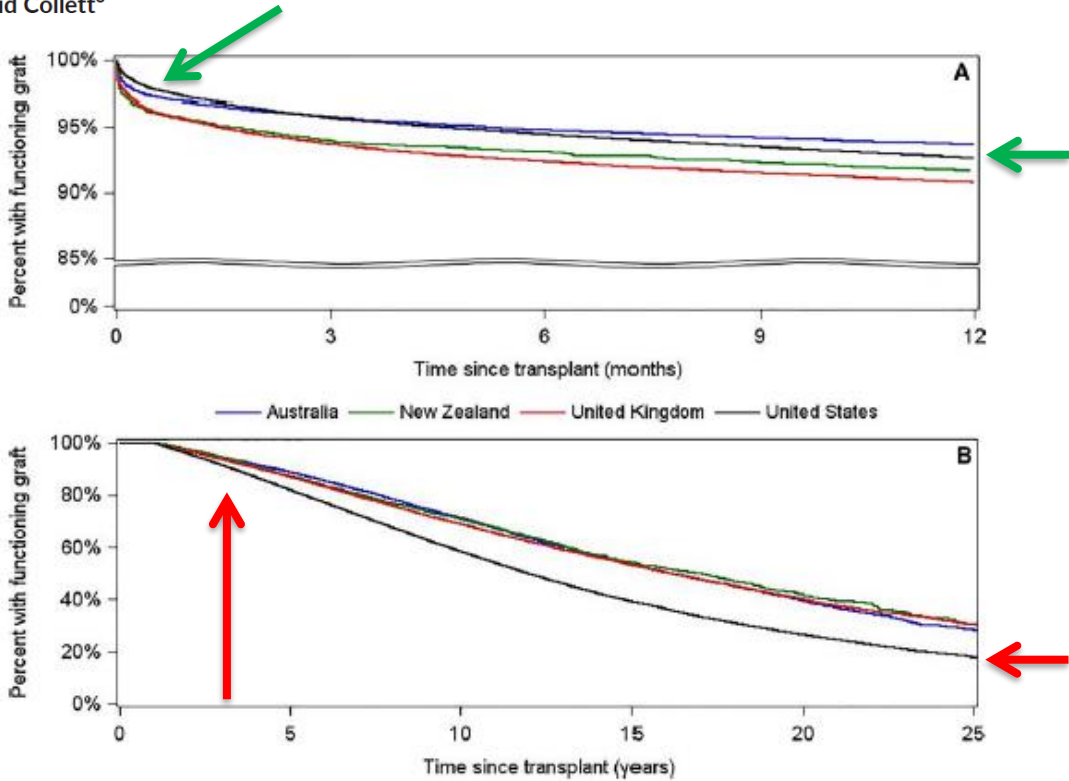
Medication understanding, non-adherence, and clinical outcomes among adult kidney transplant recipients

Patzer , et al

- patients took a mean of 10 medications
- 32% had a medication change within the last month.
- patients knew what 91% of their medications were and demonstrated proper dosing (via observed demonstration) for 83% of medications.
- 35% were non-adherent based on either self-report or tacrolimus level

Kidney transplant graft outcomes in 379 257 recipients on 3 continents

Robert M. Merion[1,2] | Nathan P. Goodrich[1] | Rachel J. Johnson[3] | Stephen P. McDonald[4,5] | Graeme R. Russ[4,5] | Brenda W. Gillespie[2] | David Collett[3]



Am J Transplant. 2018; 18:1914-1923

The association between loss of Medicare, immunosuppressive medication use, and kidney transplant outcomes

Allyson Hart, MD, MS,[1,2] Sally K. Gustafson, MS,[1] Andrew Wey, PhD,[1] Nicholas Salkowski, PhD,[1] Jon J. Snyder, PhD,[1,3] Bertram L. Kasiske, MD,[1,2] Ajay K. Israni, MD, MS[1,3]

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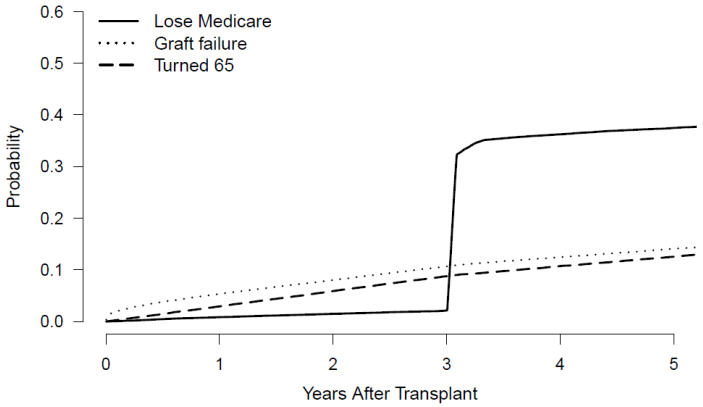
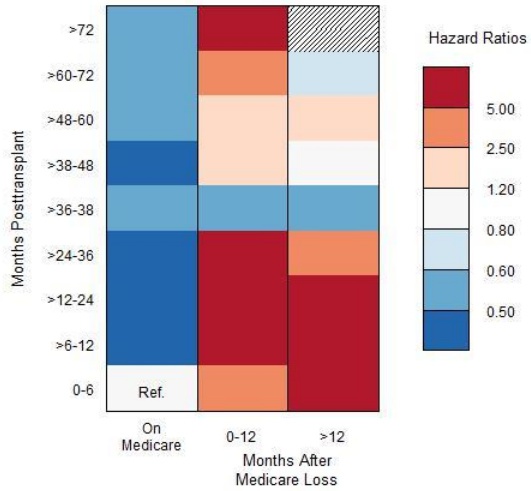


Still on Medicare	78861	61902	48284	36097	13961	8231
Lost Medicare	0	623	1022	1350	16734	17093
Graft Failure	275	4027	5711	7079	7794	8266
Turned 65	0	2150	4007	5489	6279	6796



Am J Transplant 2019 (in press)

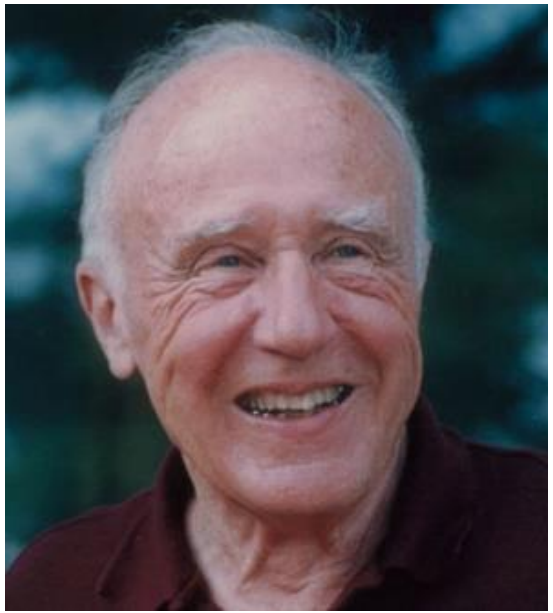
Personalized vs. Probabilistic

Who will be?

What is happening?

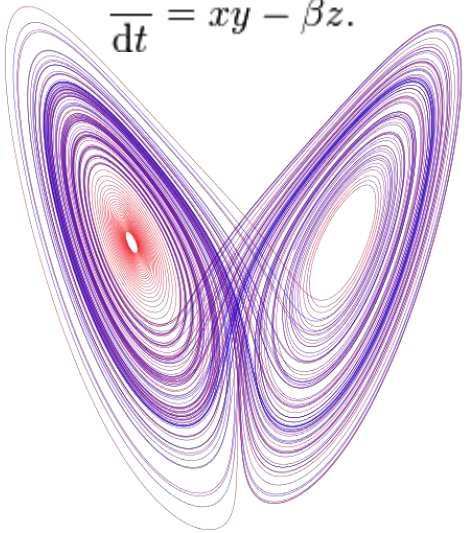
Chaos

Lorenz equations for atmospheric convection



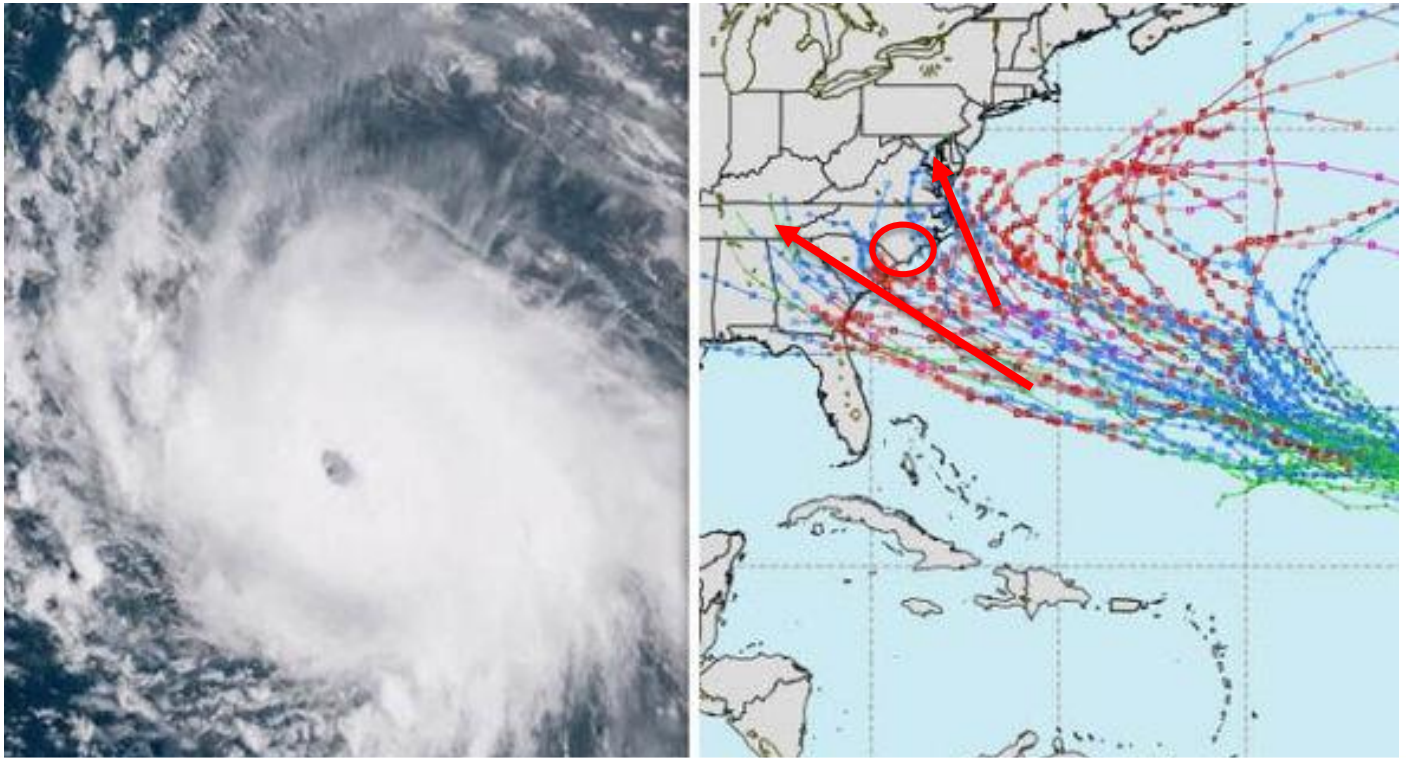
Edward N. Lorenz, 1963

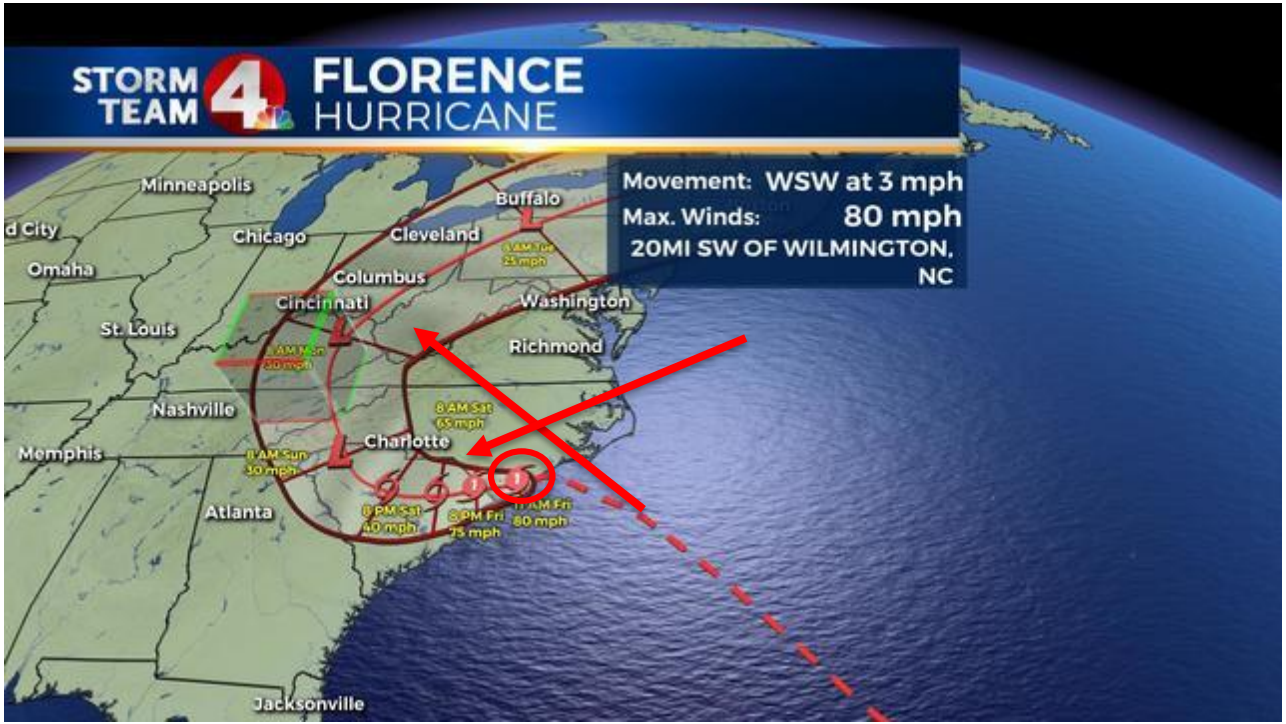
$$\frac{\mathrm{d}x}{\mathrm{d}t} = \sigma(y - x),$$
$$\frac{\mathrm{d}y}{\mathrm{d}t} = x(\rho - z) - y,$$
$$\frac{\mathrm{d}z}{\mathrm{d}t} = xy - \beta z.$$



"Two states differing by imperceptible amounts may eventually evolve into two considerably different states ... If, then, there is any error whatever in observing the present state — and in any real system such errors seem inevitable — an acceptable prediction of an instantaneous state in the distant future may well be impossible.... In view of the inevitable inaccuracy and incompleteness of weather observations, precise very-long-range forecasting would seem to be nonexistent."

Hurricane Florence




STORM TEAM 4
FLORENCE
HURRICANE
Movement: WSW at 3 mph
Max. Winds: 80 mph
20MI SW OF WILMINGTON, NC
Minneapolis
Chicago
Cleveland
Buffalo
Omaha
Columbus
Cincinnati
Washington
St. Louis
Richmond
Nashville
Charlotte
Memphis
Atlanta
Jacksonville
8 AM Sat
65 mph
8 PM Sat
40 mph
8 PM Fri
75 mph
80 mph

Summary

- Personalized medicine is increasingly possible, with numerous technologies informing the condition of transplant patients.
- Numerous biomarkers exist already and are underutilized.
- Our inability to execute on basic care delivery will obscure the impact of personalized care design.
- Definition of a current state does not establish grounds for prediction of a future state.

Thank you