جامعة قطر
QATAR UNIVERSITY

9. National
Congress of Turkish Transplantation Immunology and Genetics Society
18-21 April 2024

Precision Transplant Immunosuppression: The Coming Age of Pharmacogenomics

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Director of Clinical Services, Be The Match / National Marrow Donor Program (NMDP)

Outline

- Pharmacogenomics (PGx) as a tool for precision medicine (PM) in solid organ
- PGx in hematopoietic cell transplantation
- Barriers & strategies in implementing PGx testing

Problem Statement

- Medication efficacy rates vary considerably
- Millions of adverse drug reactions occur in the United States annually

Problem Statement

In inpatient settings, ADEs:

- Account for an estimated 1 in 3 of all hospital adverse events
- Affect about 2 million hospital stays each year
- Prolong hospital stays by 1.7 to 4.6 days

Problem Statement

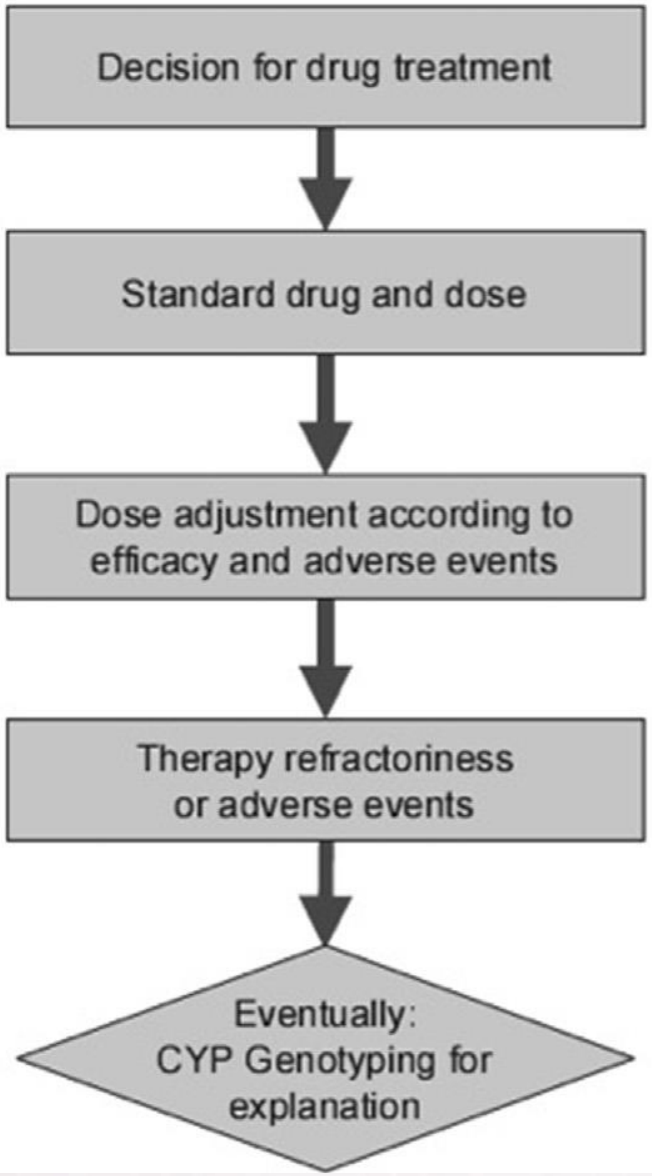
Each year, ADEs in outpatient settings account for:

- Over 3.5 million physician office visits
- An estimated 1 million emergency department visits
- Approximately 125,000 hospital admissions

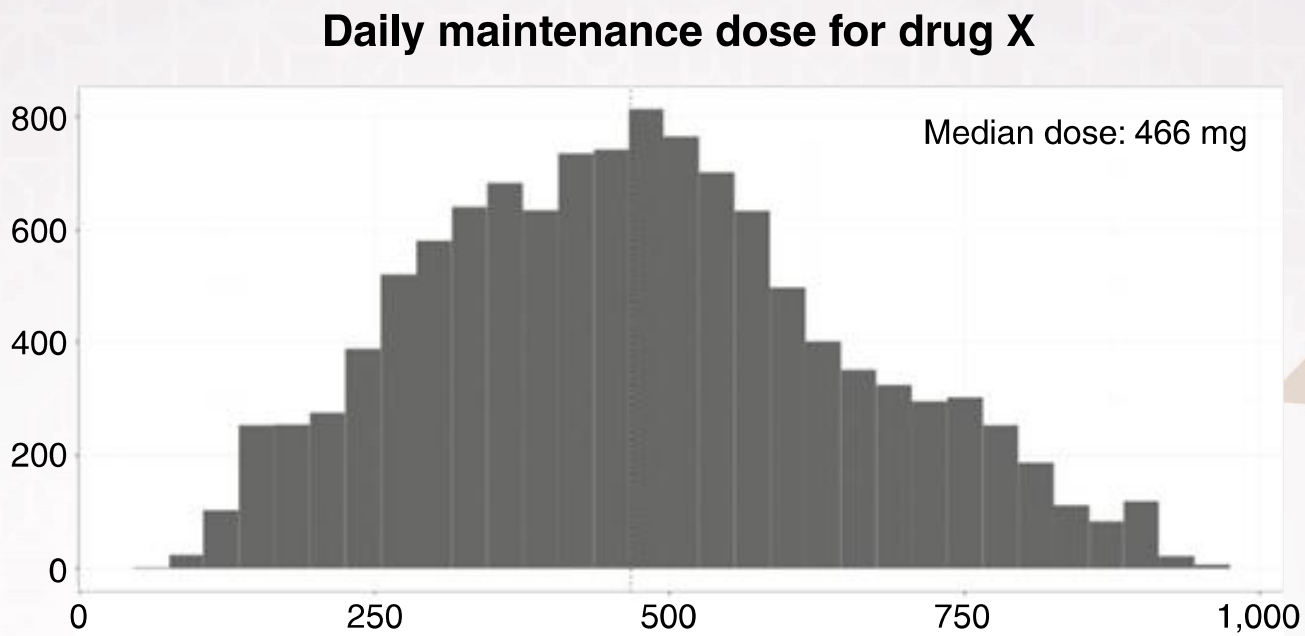
Consequences

- Frequent dose monitoring and titration for drug with narrow TI
- Iteration among medications
- Significant burdens on the patient, the provider, and the health care system as a whole

The explanatory (old) role of pharmacogenetics:



A



B

Adams et al, 2018

PGx in Solid Organ Tx

http://www.phaeurope.org/

Transplant International

ORIGINAL ARTICLE

Higher calcineurin inhibitor levels predict better kidney graft survival in patients with *de novo* donor-specific anti-HLA antibodies: a cohort study

Marc-Antoine Béland[1], Isabelle Lapointe[1], Réal Noël[1], Isabelle Côté[1], Eric Wagner[2], Julie Riopel[3], Eva Latulippe[3], Olivier Désy[1], Stéphanie Béland[1], Ciara N. Magee[4], Isabelle Houde[1] & Sacha A. De Serres[1]

Transplant International 2017; 30: 502–509

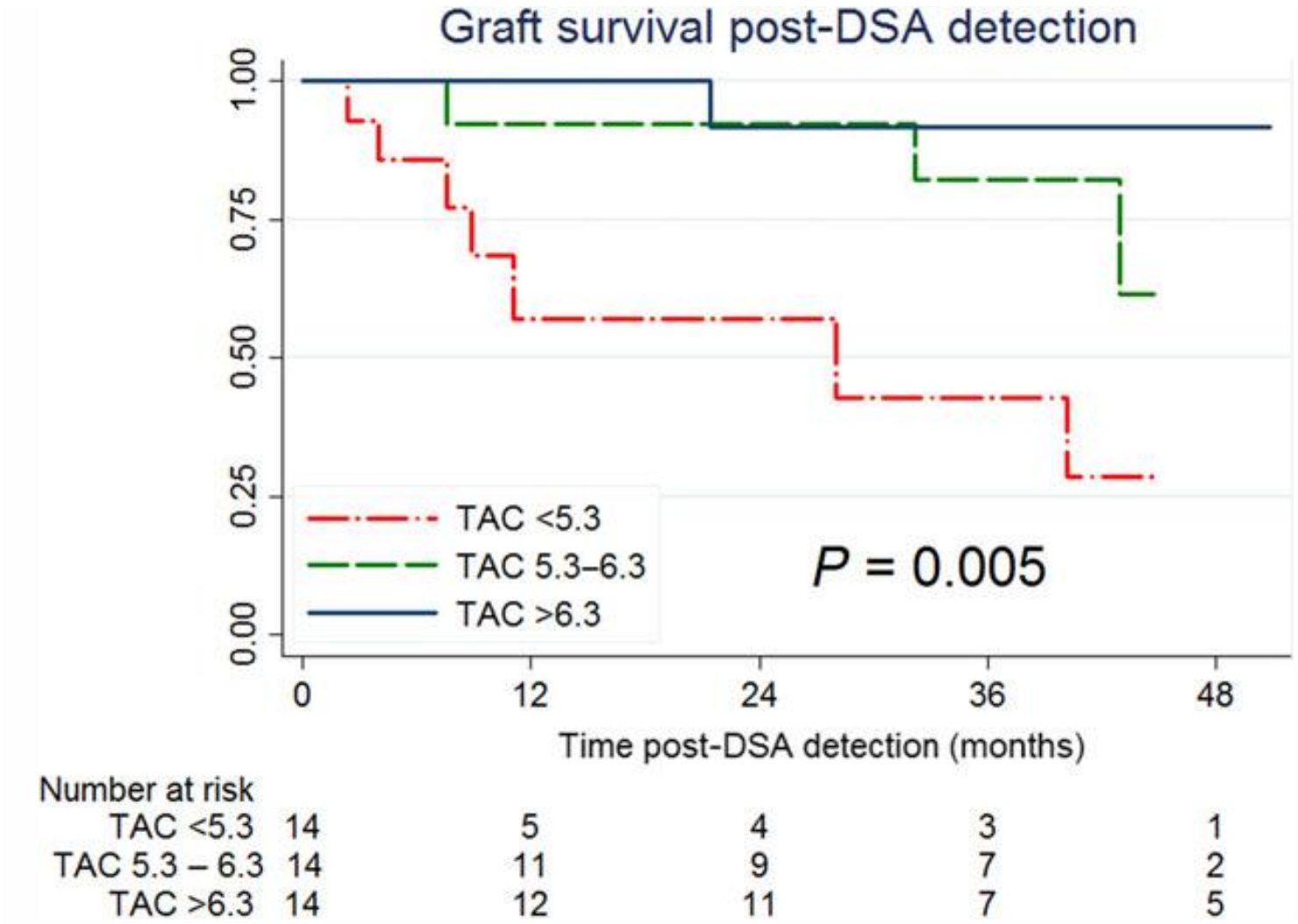


Figure 2 Kaplan–Meier plots for graft loss by tertile of mean tacrolimus levels post-dnDSA development. Comparison was assessed using log-rank test.

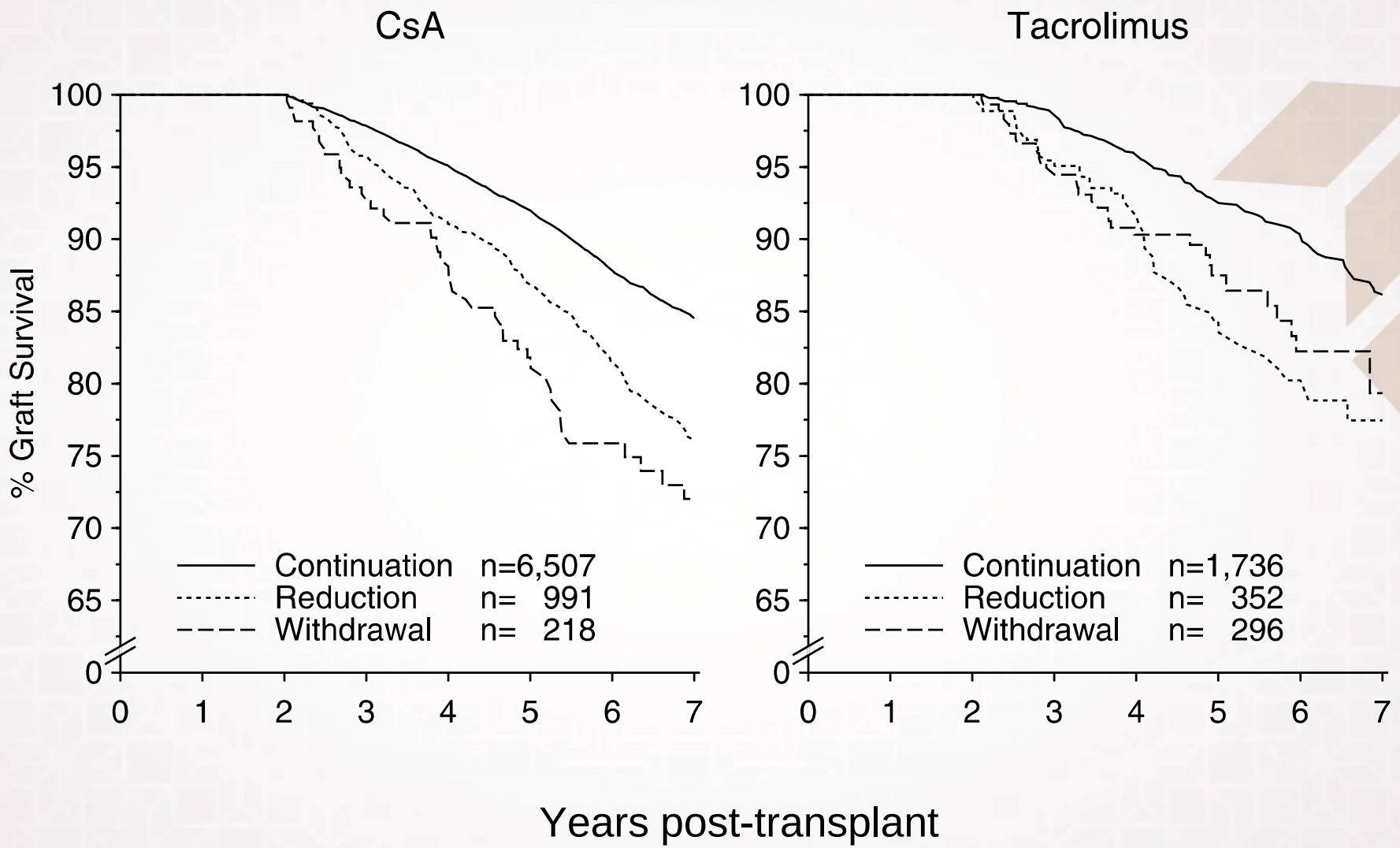
Béland et al, 2017

SPECIAL FEATURE

Effect on Kidney Graft Survival of Reducing or Discontinuing Maintenance Immunosuppression After the First Year Posttransplant

Gerhard Opelz and Bernd Döhler

Transplantation • Volume 86, Number 3, August 15, 2008



Opelz and Döhler, 2008

Higher Initial Tacrolimus Blood Levels and Concentration-Dose Ratios in Kidney Transplant Recipients Who Develop Diabetes Mellitus

E. Rodrigo, M.A. de Cos, G. Fernández-Fresnedo, B. Sánchez, J.C. Ruiz, C. Piñera, R. Palomar, J.G. Cotorruelo, C. Gómez-Alamillo, S. Sanz de Castro, A.L.M. de Francisco, and M. Arias

Transplantation Proceedings, 37, 3819–3820 (2005)

Functional Status	Alleles
Normal function[1]	*1
No function	*3, *6, *7
Unknown/limited data	*2,*4, *5, *8, *9

Assignment of Likely Metabolism Phenotypes Based on CYP3A5 Diplotypes:

Likely phenotype	Genotypes	Examples of diplotypes
Extensive metabolizer (CYP3A5 expresser)	An individual carrying two functional alleles	*1/*1
Intermediate metabolizer (CYP3A5 expresser)	An individual carrying one functional allele and one nonfunctional allele	*1/*3, *1/*6, *1/*7
Poor metabolizer (CYP3A5 nonexpresser)	An individual carrying two nonfunctional alleles	*3/*3, *6/*6, *7/*7, *3/*6, *3/*7, *6/*7

Frequencies of *CYP3A5* alleles in major race/ethnic groups [6].

Ethnicity	Frequencies of Alleles			
	*1	*3	*6	*7
African	0.558	0.298	0.172	0.077
African American	0.605	0.316	0.111	0.120
South East African	0.744	0.157	0.194	0.142
Asian	0.258	0.742	0.001	0.000
Southwest Asian	0.342	0.659	0.000	NA
Caucasian	0.078	0.921	0.001	0.000
Middle Eastern	0.105	0.881	0.019	0.002
Latin American	0.202	0.765	0.037	0.025

Zhang et al, 2018

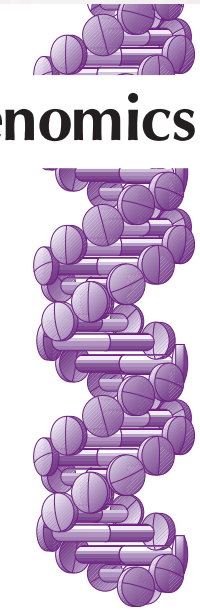
Table 2 Frequency of CYPA5 alleles in different ethnic populations

	Frequency of CYP3A5 allelei		
Ethnic population	**CYP3A5 *1/*1 (%)**	**CYP3A5 *1/*3 (%)**	**CYP3A5 *3/*3 (%)**
Caucasian	1	13–17	82–86
Black	37–45	40–54	9–15
Indian	2.5–11	38–57	32–60
Chinese	7.7	44.8	47.4

Chen & Prasad, 2018

Research Article

Pharmacogenomics



Pharmacogenetic-based strategy using *de novo* tacrolimus once daily after kidney transplantation: prospective pilot study

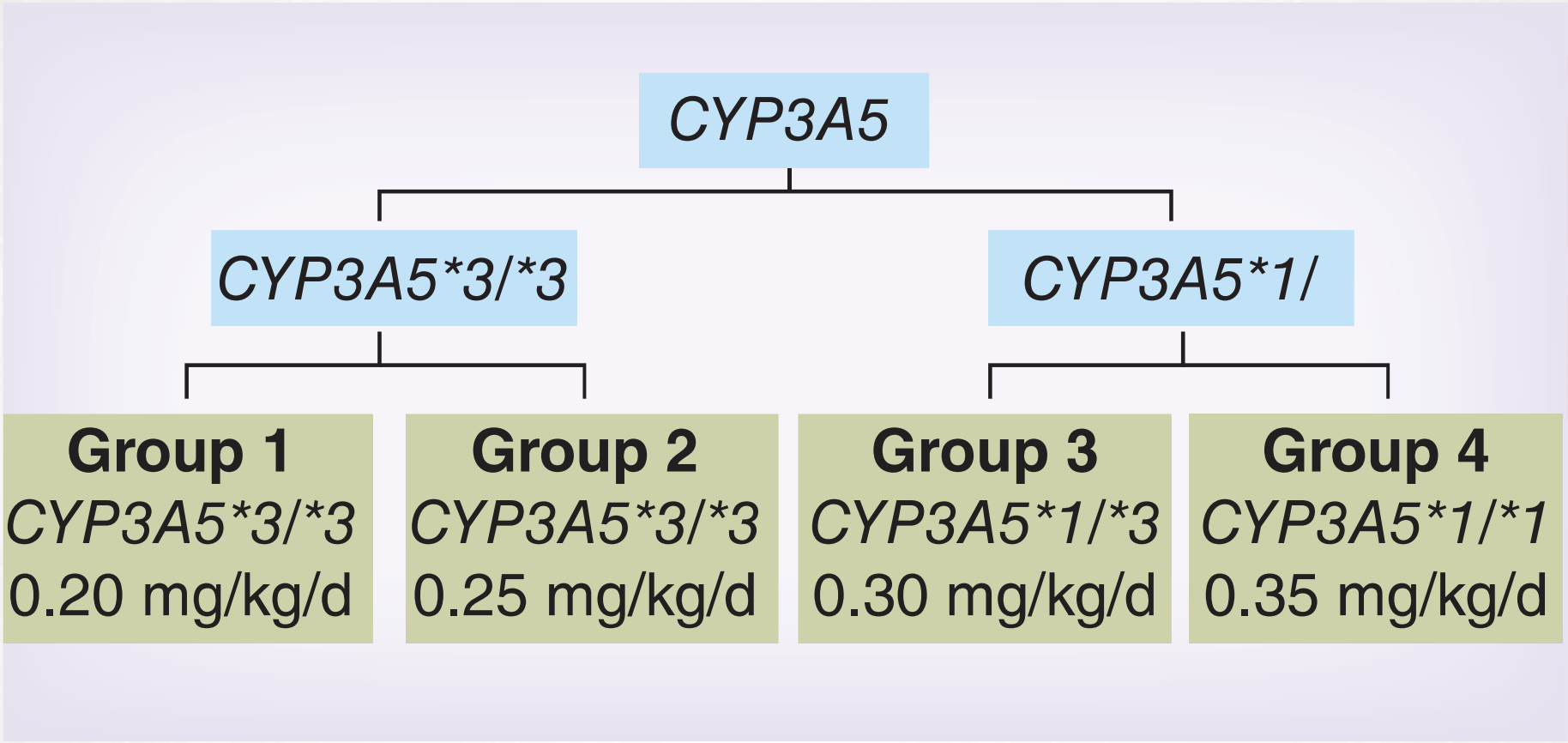
Pharmacogenomics (2016) 17(9), 1019–1027

Table 1. Population characteristics.

Population		Expressors		Non-expressors	Total
CYP3A5		**1/*1*	**1/*3*	**3/*3*	–
	n	7	16	128	151
Recipients	Mean age ± SD (y)	48 ± 14*	45 ± 12*	50 ± 13*	49 ± 12
	Sex (F/M)	4/3	9/7	43/85	56/95
Donors	Deceased	5	10	101	116 (77%)
	Living	2	6	27	35 (23%)
Mismatch	Median	3	3	3	3
	Range	2–5	0–6	0-6	0-6
Transplantation rank	First	6	16	123	145
	Second	1	0	5	6
Primary kidney disease	Glomerulonephritis	1	5	20	26
	Interstitial nephritis	0	3	17	20
	APKD	0	2	37	39
	Hereditary disease	1	1	12	14
	Systemic disease	0	2	12	14
	Vascular disease	1	0	6	7
	Diabetes	0	1	5	6
	Unknown	4	2	19	25

*$p > 0.1$.
APKD: Autosomal dominant polycystic kidney disease; F: Female; M: Male; SD: Standard deviation.

Byun et al, 2016



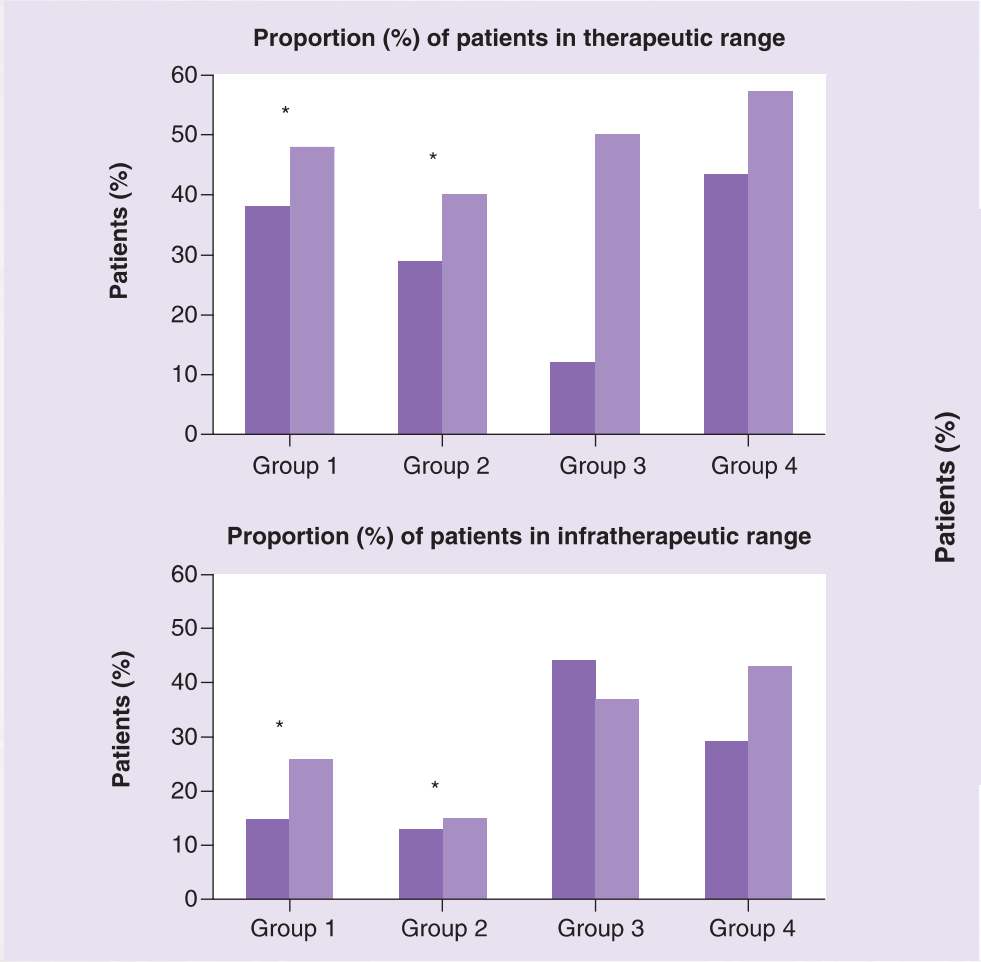
Byun et al, 2016

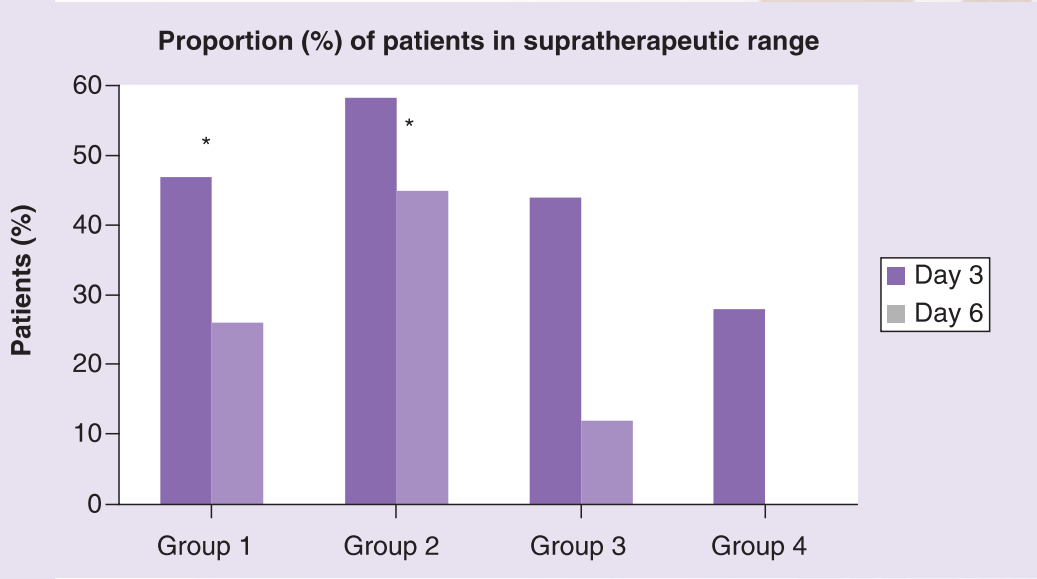
Table 4. Tacrolimus doses-adjusted blood concentrations according to study groups.

Patient groups	Dose-adjusted Tac C_{min} ($ng.ml^{-1}/mg/kg$ b.w.)						
	Day 3	Day 6	Day 14	Month 1	Month 3	Month 6	Month 12
Group 1	72.6 (29.1–162.3)†, n = 66	70.0 (24.8–161.5)†, n = 66	65.8 (23.5–212.8)†, n = 66	85.1 (21.2–293.8)†, n = 64	97.3 (29.2–372.3)†, n = 66	110.7 (26.8–327.4)†, n = 64	122.6 (19.5–270.0)†, n = 50
Group 2	65.5 (23.8–124.5)†, n = 62	65.9 (21.6–312.0)†, n = 62	58.2 (21.2–285.6)†, n = 61	67.9 (18.1–214.1)†, n = 61	88.0 (25.2–263.5)†, n = 62	97.1 (21.3–292.4)†, n = 62	103.7 (33.3–360.8)†, n = 60
Group 3	45.6 (15.6–95.1)‡, n = 16	37.3 (10.8–83.1)‡, n = 15	34.3 (11.7–90.0)‡, n = 15	38.4 (14.9–118.4)‡, n = 16	43.8 (13.5–70.0)‡, n = 16	38.0 (17.8–118.8)‡, n = 16	38.1 (21.3–103.7)‡, n = 14
Group 4	37.7 (23.9–51.8)‡, n = 7	22.3 (12.8–36.7)‡, n = 7	21.3 (17.0–34.5)‡, n = 7	27.8 (20.9–33.3)‡, n = 7	30.0 (18.1–46.3)‡, n = 7	25.1 (20.6–37.0)‡, n = 7	32.9 (13.7–40.9)‡, n = 6
Kruskal–Wallis test	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$

Values are expressed as median (range [Kruskal–Wallis test]).
†,‡Values with the same superscript letter do not differ significantly from each other, according to *post-hoc* analysis.

Byun et al, 2016





Byun et al, 2016

Accepted: 15 November 2017

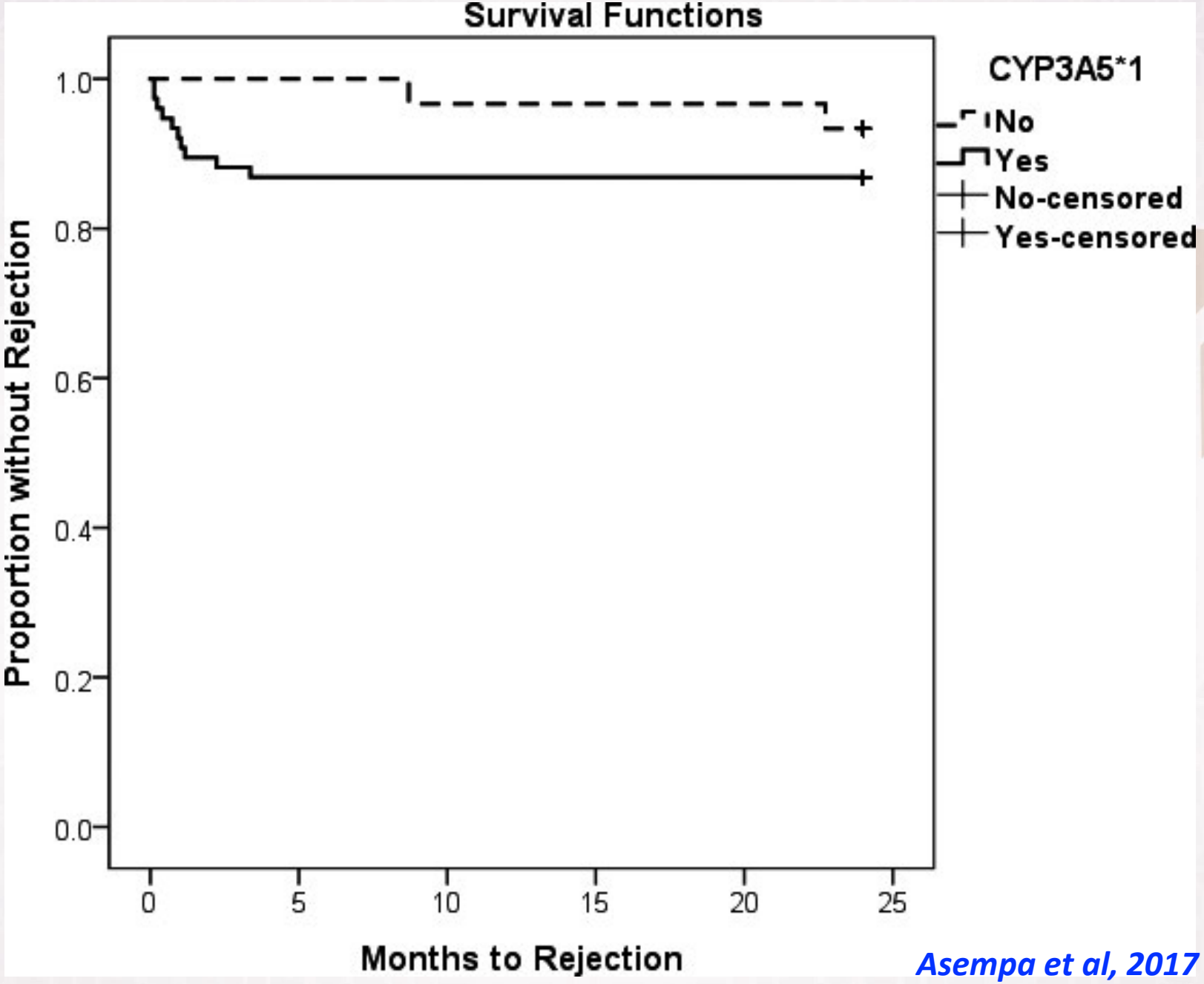
DOI: 10.1111/ctr.13162

ORIGINAL ARTICLE

WILEY Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research

Impact of CYP3A5 genomic variances on clinical outcomes among African American kidney transplant recipients

Tomefa E. Asempa[1] | Lorita M. Rebellato[2] | Suzanne Hudson[3] | Kimberly Briley[2] | Angela Q. Maldonado[4]



Asempa et al, 2017

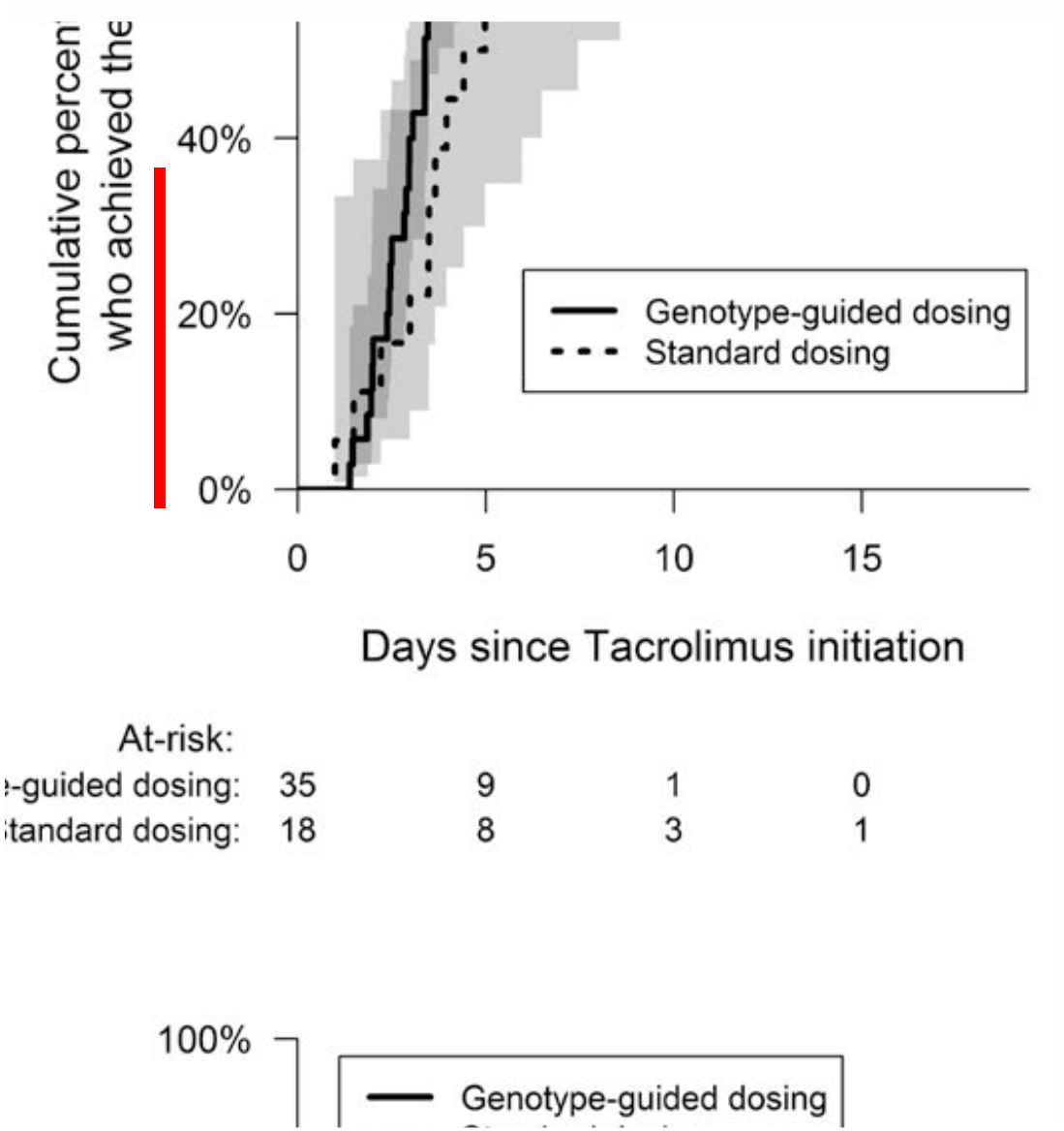
[redacted]

ORIGINAL ARTICLE

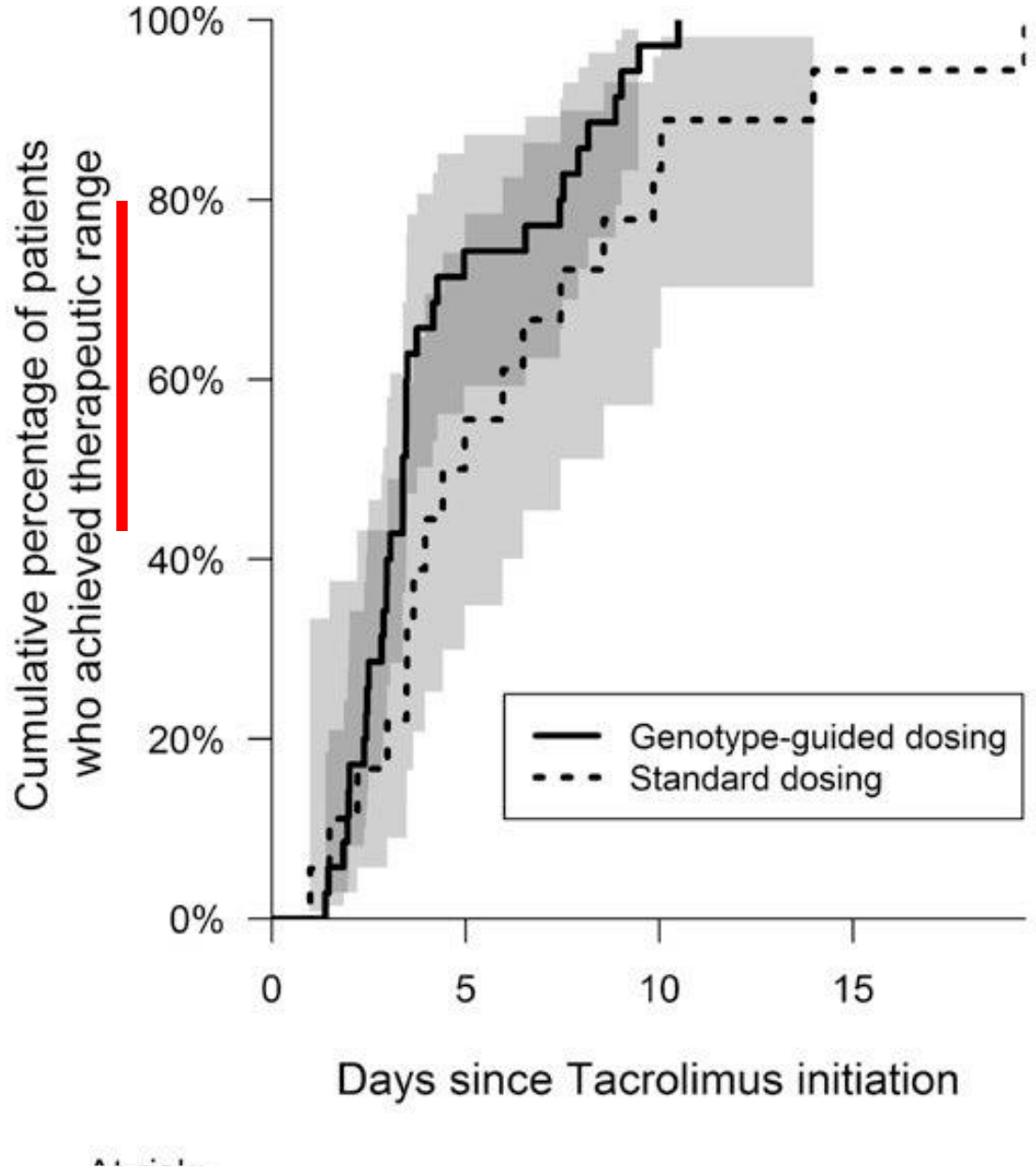
WILEY

A randomized clinical trial of age and genotype-guided tacrolimus dosing after pediatric solid organ transplantation

Sandar Min[1] | Tanya Papaz[1] | Myriam Lafreniere-Roula[1] | Nadya Nalli[2] | Hartmut Grasemann[1] | Steven M. Schwartz[3] | Binita M. Kamath[1] | Vicky Ng[4] | Rulan S. Parekh[1,5,6] | Cedric Manlhiot[7] | Seema Mital[1]



Min et al, 2018



Min et al, 2018

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for *CYP3A5* Genotype and Tacrolimus Dosing

KA Birdwell[1,2], B Decker[3], JM Barbarino[4], JF Peterson[2,5], CM Stein[2,6], W Sadee[7], D Wang[7], AA Vinks[8,9], Y He[10], JJ Swen[11], JS Leeder[12], RHN van Schaik[13], KE Thummel[14], TE Klein[4], KE Caudle[15] and IAM MacPhee[16]

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 98 NUMBER 1 | JULY 2015

Table 2 Dosing recommendations for tacrolimus based on *CYP3A5* phenotype

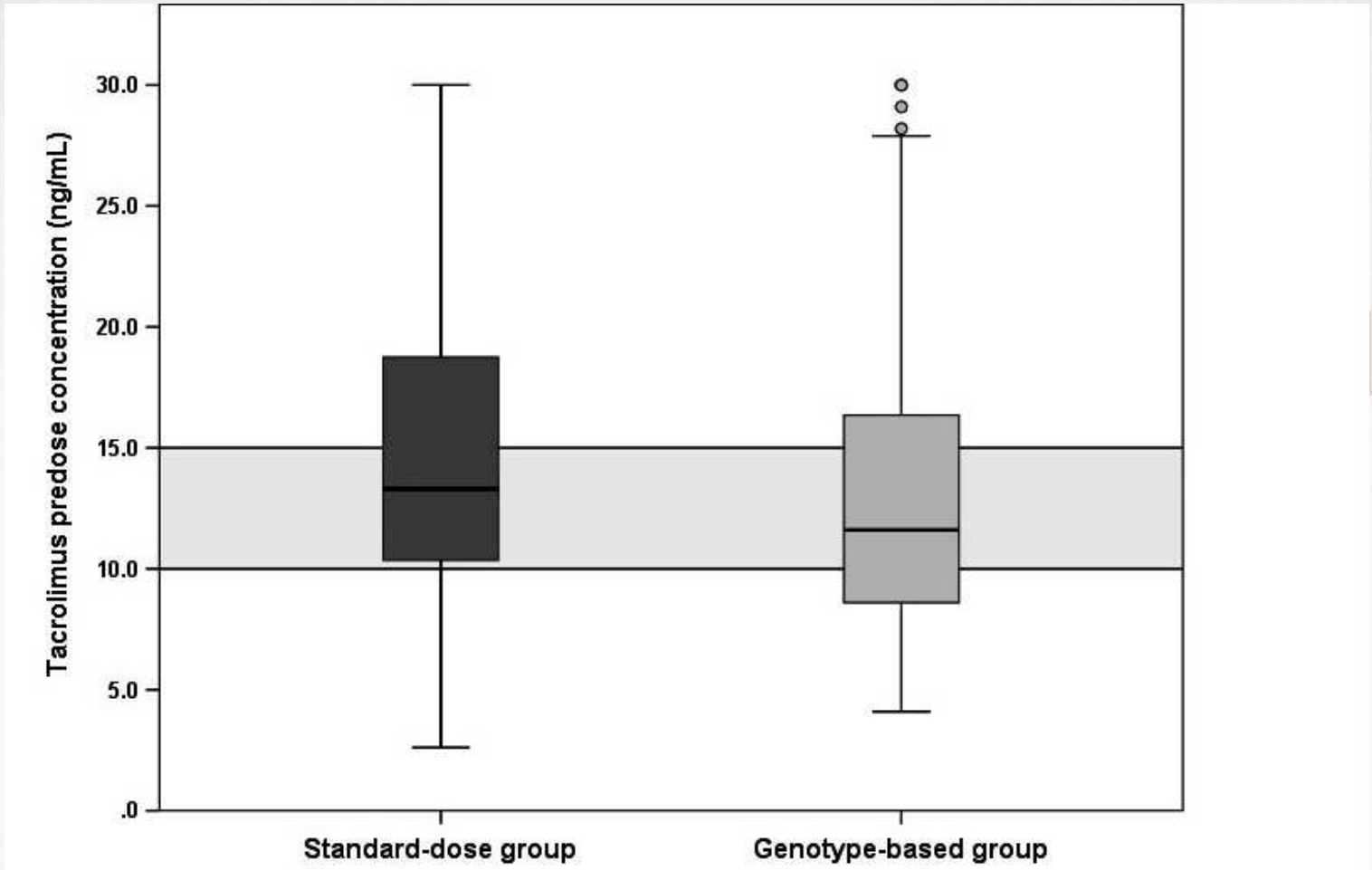
CYP3A5 phenotype[a]	Implications for tacrolimus pharmacologic measures	Therapeutic recommendations[b]	Classification of recommendations[c]
Extensive metabolizer (CYP3A5 expresser)	Lower dose-adjusted trough concentrations of tacrolimus and decreased chance of achieving target tacrolimus concentrations.	Increase starting dose 1.5–2 times recommended starting dose.[d] Total starting dose should not exceed 0.3 mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments.	Strong
Intermediate metabolizer (CYP3A5 expresser)	Lower dose-adjusted trough concentrations of tacrolimus and decreased chance of achieving target tacrolimus concentrations.	Increase starting dose 1.5–2 times recommended starting dose.[a] Total starting dose should not exceed 0.3 mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments.	Strong
Poor metabolizer (CYP3A5 nonexpresser)	Higher ("normal") dose-adjusted trough concentrations of tacrolimus and increased chance of achieving target tacrolimus concentrations.	Initiate therapy with standard recommended dose. Use therapeutic drug monitoring to guide dose adjustments.	Strong

American Journal of Transplantation 2016; 16: 2085–2096
Wiley Periodicals Inc.

doi: 10.1111/ajt.13691

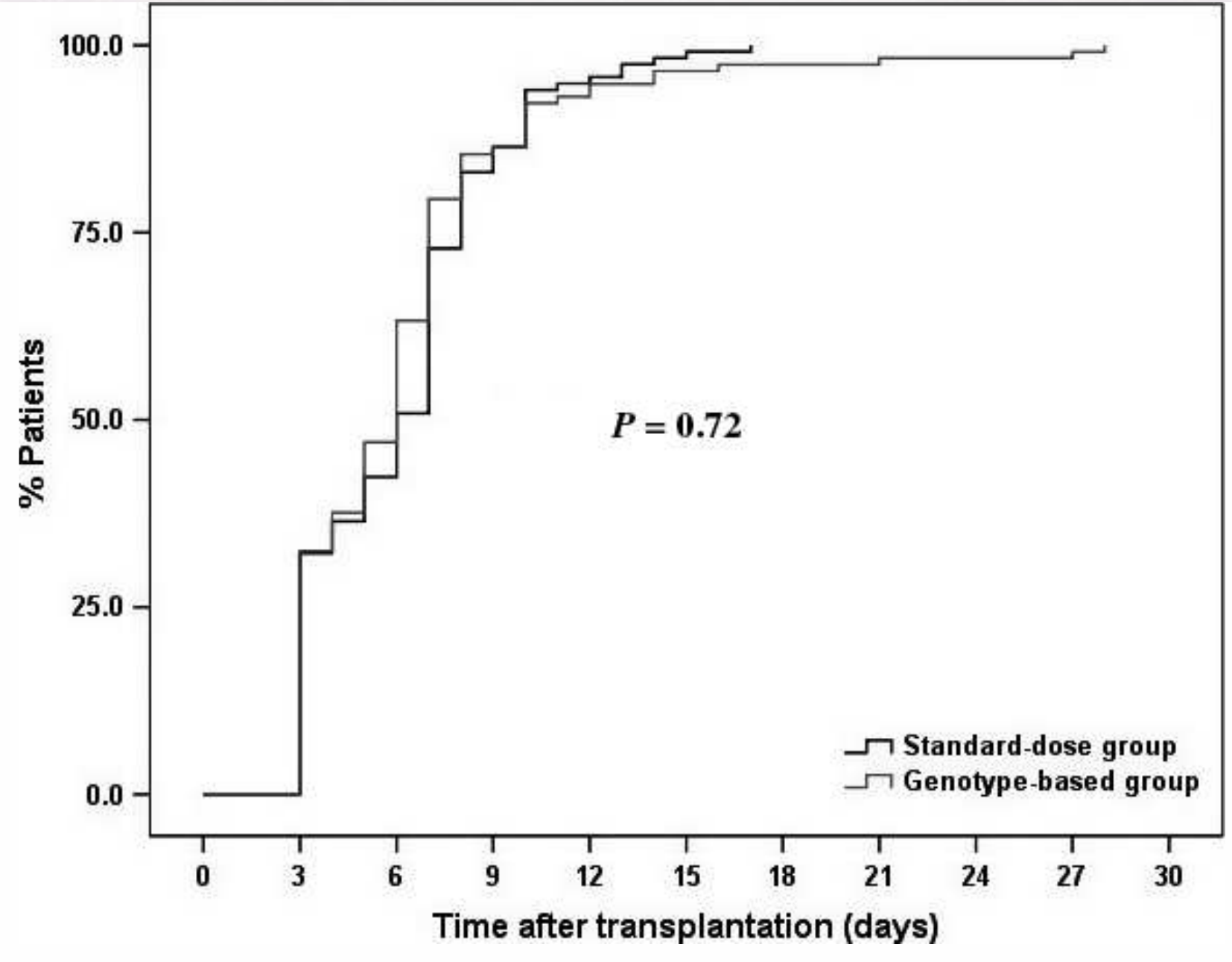
A Randomized Controlled Trial Comparing the Efficacy of *Cyp3a5* Genotype-Based With Body-Weight-Based Tacrolimus Dosing After Living Donor Kidney Transplantation

N. Shuker[1,2,*,†], R. Bouamar[2,†], R. H. N. van Schaik[3], M. C. Clahsen-van Groningen[4], J. Damman[5], C. C. Baan[1], J. van de Wetering[1], A. T. Rowshani[1], W. Weimar[1], T. van Gelder[1,2] and D. A. Hesselink[1]



	Standard-dose group	Genotype-based group	*p*
	n = 99	n = 104	
Supra-therapeutic concentration	39 (39.4%)	31 (29.8%)	0.20
Therapeutic concentration	37 (37.4%)	37 (35.6%)	0.79
Sub-therapeutic concentration	23 (23.2%)	36 (34.6%)	0.10

Shuker et al, 2017



Shuker et al, 2017

Table 1: Baseline characteristics

	Standard-dose group	Genotype-based group	p
Recipient gender			
Male/female	73 (61.3%)/46 (38.7%)	75 (63.6%)/43 (36.4%)	0.73
Age of recipient (years)	57 (19–79)	55 (19–79)	0.55
Ethnicity			0.89
White	93 (78.2%)	93 (78.8%)	
Asian	13 (10.9%)	10 (8.5%)	
Black	11 (9.2%)	12 (10.2%)	
Other	2 (1.7%)	3 (2.5%)	

Shuker et al, 2017

ATC2024
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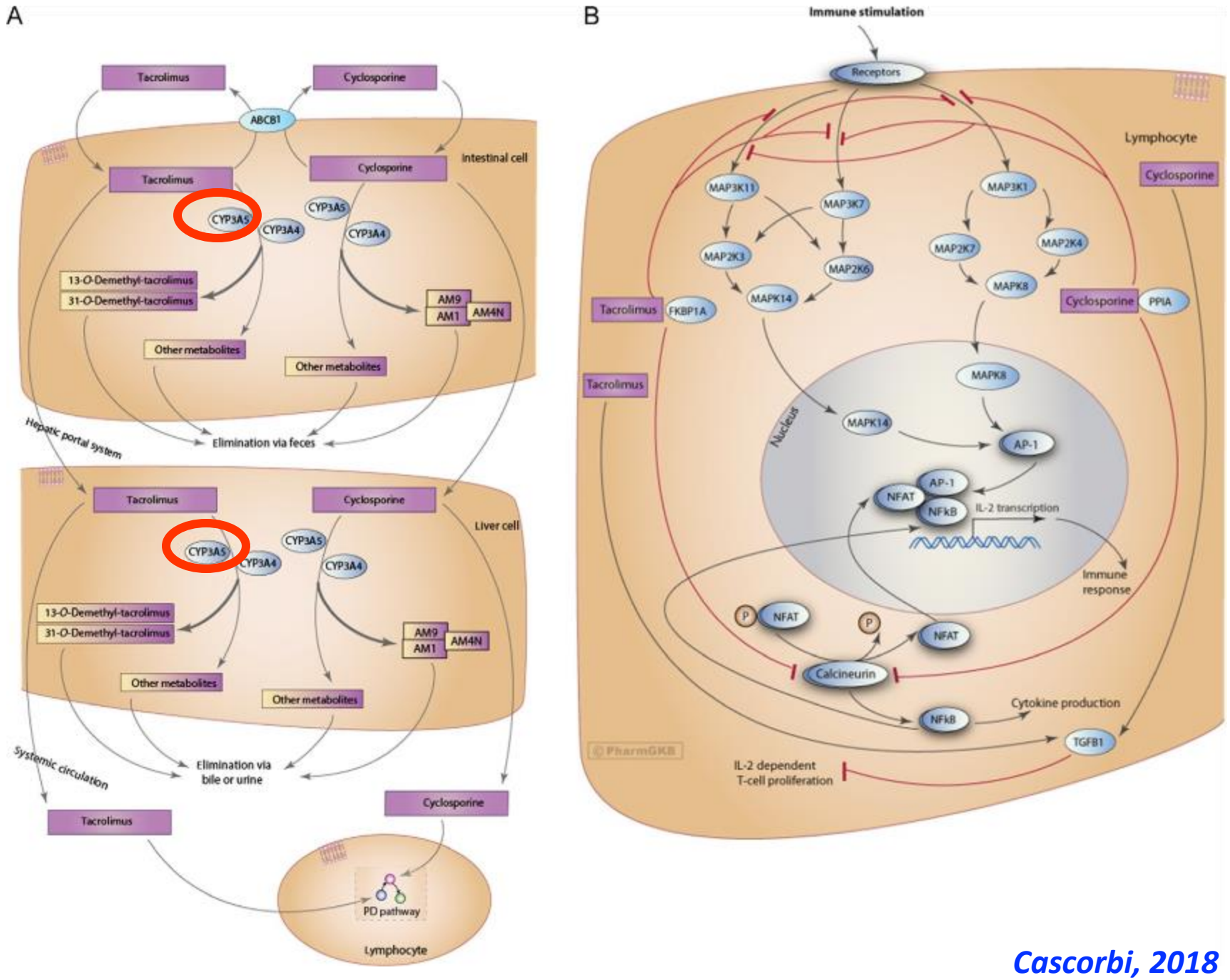
PHILADELPHIA, PA • JUNE 1-5

Prospective CYP3A5 Genotyping Is Associated with Significantly Lower ACR ≥2R in Heart Transplant Recipients

Wilson NK[1,2], Van Zyl J[1,2], Kataria AD[1,2], Patel R, Sam T[1,2], Hall SA[1,2], Askar M[1,2,3]

Table: Comparison of Outcomes between Patients retrospectively vs. prospectively assessed with CYP3A5 genotyping.

Baseline Characteristics	Overall (n=158)	Retrospective (n=55)	Prospective (n=103)	P-value
Age (years)	59.8 [54.5, 65.3]	59.5 [53.9, 64.6]	60.2 [55.4, 65.8]	0.31
Sex, male	116 (73%)	39 (71%)	77 (75%)	0.74
Diabetes	64 (41%)	23 (42%)	41 (40%)	0.94
Ischemic Cardiomyopathy	55 (35%)	19 (35%)	36 (35%)	1.00
CYP3A5 Genetic Polymorphism				0.56
*1/*1	11 (7%)	5 (9%)	6 (6%)	
*1/*3	33 (21%)	9 (16%)	24 (23%)	
*1/*other	8 (5%)	1 (2%)	7 (7%)	
*3/*3	95 (60%)	36 (65%)	59 (57%)	
*3/Other	9 (6%)	3 (5%)	6 (6%)	
Other	2 (1%)	1 (2%)	1 (1%)	
Induction				**0.02**
None	134 (85%)	43 (78%)	91 (88%)	
Simulect (basiliximab)	17 (11%)	11 (20%)	6 (6%)	
Antithymocyte globulin (Thymo, rATG)	7 (4%)	1 (2%)	6 (6%)	
Outcomes				
FK Coefficient of Variation (%)	27.3 [22.4, 34.2]	27.1 [20.7, 34]	27.3 [23.9, 34.4]	0.15
FK Mean (ng/mL)	10.2 [9.3, 11.1]	10.4 [9.4, 11.1]	10.1 [9.3, 11.1]	0.36
FK SD (ng/mL)	2.8 [2.3, 3.4]	2.7 [2.1, 3.5]	2.8 [2.4, 3.4]	0.30
Time to stable therapeutic levels (days)	11 [8, 18]	11 [8, 20.5]	10 [7, 17]	0.11
Time to therapeutic levels (days)	7 [6, 10]	8 [5, 10]	7 [6, 9]	0.79
ACR≥2R	12 (8%)	11 (20%)	1 (1%)	**<0.001**
pAMR≥1	8 (5%)	0 (0%)	8 (8%)	0.05
Death 1-year	1 (1%)	0 (0%)	1 (1%)	1
Death 2-year	7 (4%)	2 (4%)	5 (5%)	1
Positive DSA	59 (37%)	21 (38%)	38 (37%)	1
Positive De Novo DSA	56 (35%)	21 (38%)	35 (34%)	0.72



Cascorbi, 2018

Covariate	Coefficient[a] (S.E.)	P value
*CYP3A5*3*	0.54 (0.044)	7.15×10^{-29}
Albumin[b] (x)	−0.17 (0.04)	2.07×10^{-5}
(x')	0.12 (0.04)	0.005
Age	0.007 (0.002)	1.80×10^{-5}
Weight[b] (x)	−0.007 (0.002)	3.24×10^{-4}
(x')	0.006 (0.002)	0.004
Hemoglobin	0.015 (0.006)	0.012
Days post transplant[b] (x)	0.0004 (6.2×10^{-5})	2.97×10^{-9}
(x')	−0.0012 (2.5×10^{-4})	2.44×10^{-6}
Sex (Male vs. Female)	0.034 (0.043)	0.431

Birdwell et al, 2012

frontiers in Genetics

Beyond Single Nucleotide Polymorphisms: *CYP3A5*3*6*7* Composite and *ABCB1* Haplotype Associations to Tacrolimus Pharmacokinetics in Black and White Renal Transplant Recipients

Daniel A. Brazeau[1], Kristopher Attwood[2], Calvin J. Meaney[3,4], Gregory E. Wilding[2], Joseph D. Consiglio[2], Shirley S. Chang[5,6], Aijaz Gundroo[5,6], Rocco C. Venuto[5,6†], Louise Cooper[3,4] and Kathleen M. Tornatore[3,4,5]*

August 2020 | Volume 11 | Article 889

British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2019) **85** 601–615 601

ORIGINAL ARTICLE

A population pharmacokinetic model to predict the individual starting dose of tacrolimus in adult renal transplant recipients

L. M. Andrews[1], D. A. Hesselink[2,3,*], R. H. N. van Schaik[4], T. van Gelder[1,2,3], J. W. de Fijter[5], N. Lloberas[6], L. Elens[7], D. J. A. R. Moes[8] and B. C. M. de Winter[1]

L. M. Andrews et al.

$$\text{Dose (mg)} = 222\ \text{ng h ml}^{-1} * 22.5\ \text{l h}^{-1} * [(1.0, \text{if CYP3A5} * 3/*3) \text{ or } (1.62, \text{if CYP3A5} * 1/*3 \text{ or CYP3A5} * 1/*1)] * [(1.0, \text{if CYP3A4} * 1 \text{ or unknown}) \text{ or } (0.814, \text{if CYP3A4} * 22)] * \left(\frac{\text{Age}}{56}\right)^{-0.50} * \left(\frac{\text{BSA}}{1.93}\right)^{0.72} / 1000$$

- For a good prediction of tacrolimus pharmacokinetics, age, BSA, CYP3A4 and CYP3A5 genotype are important covariates.

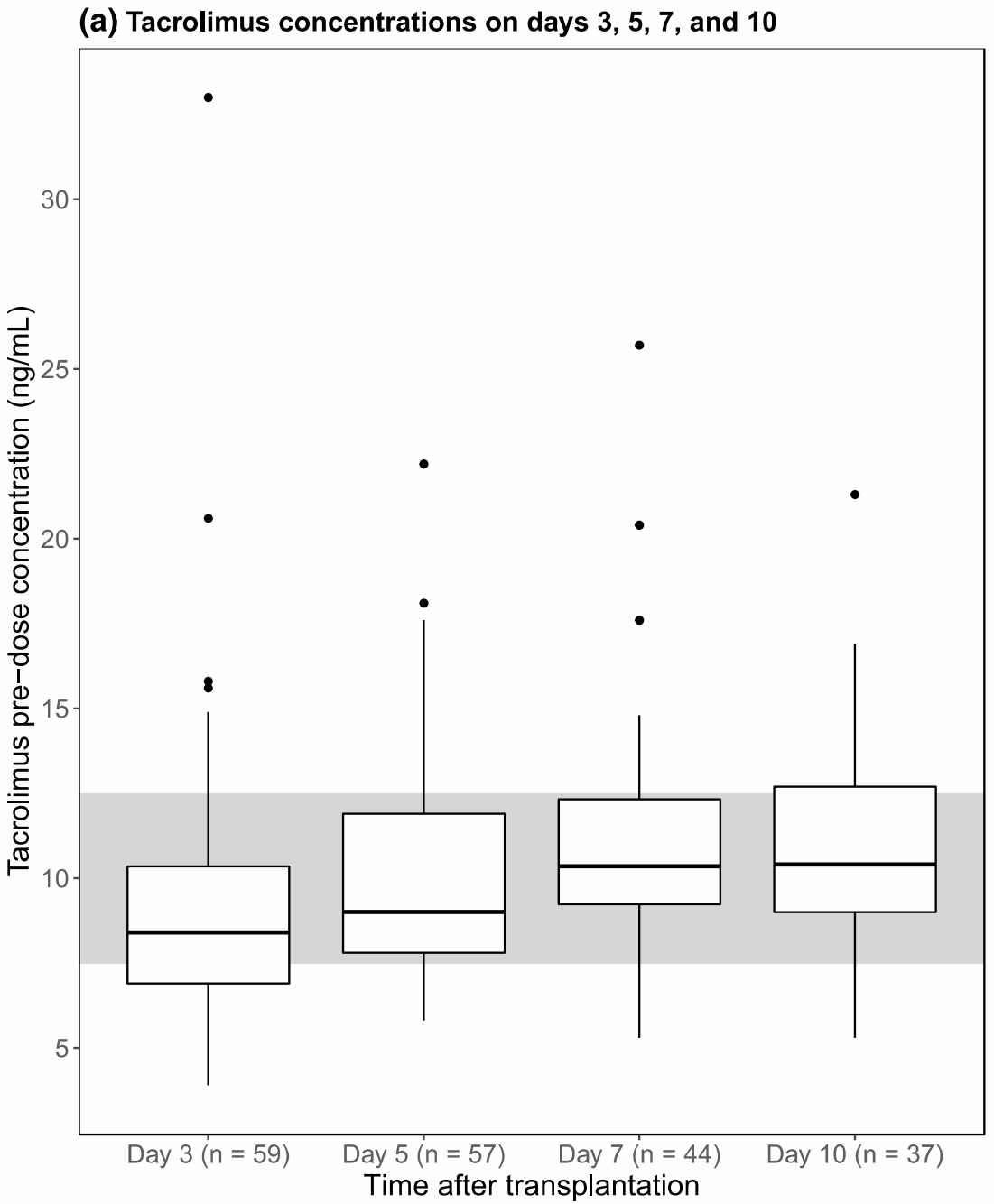
- The model proved effective in calculating the optimal tacrolimus dose based on these parameters and can be used to individualize the tacrolimus dose in the early period after transplantation.

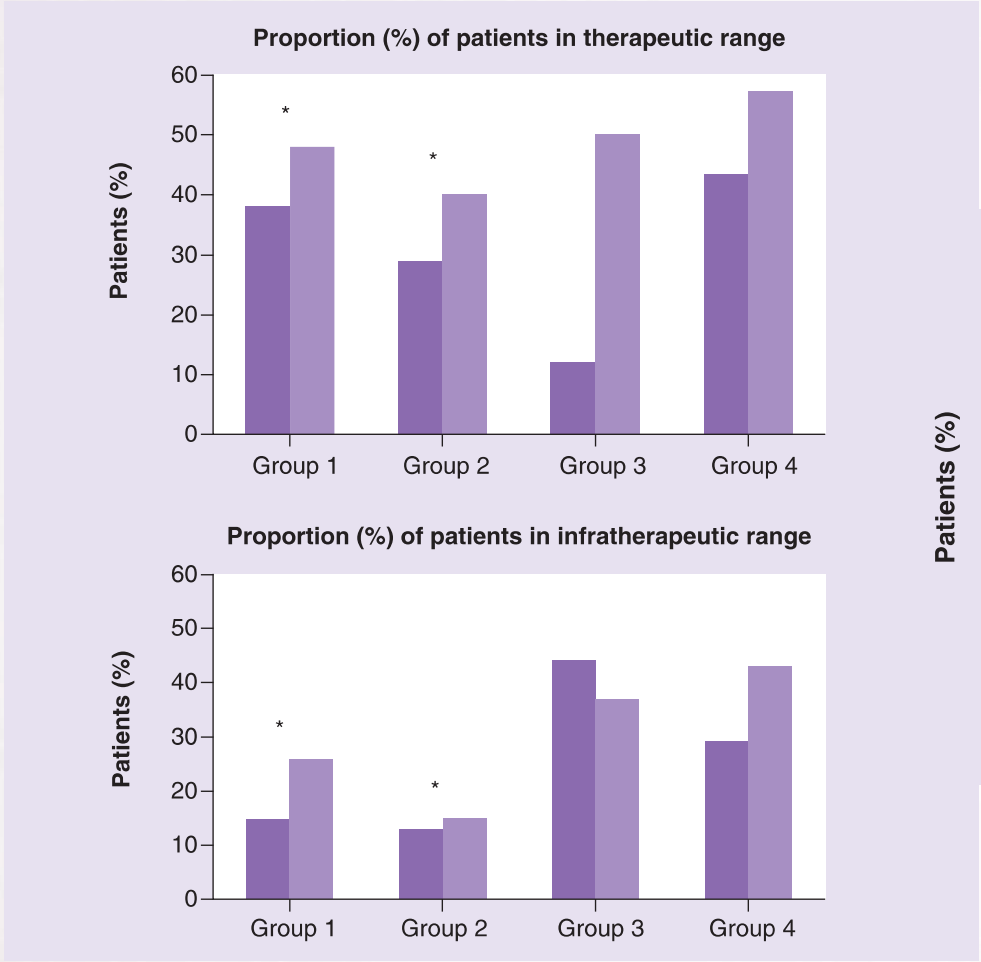
ARTICLE

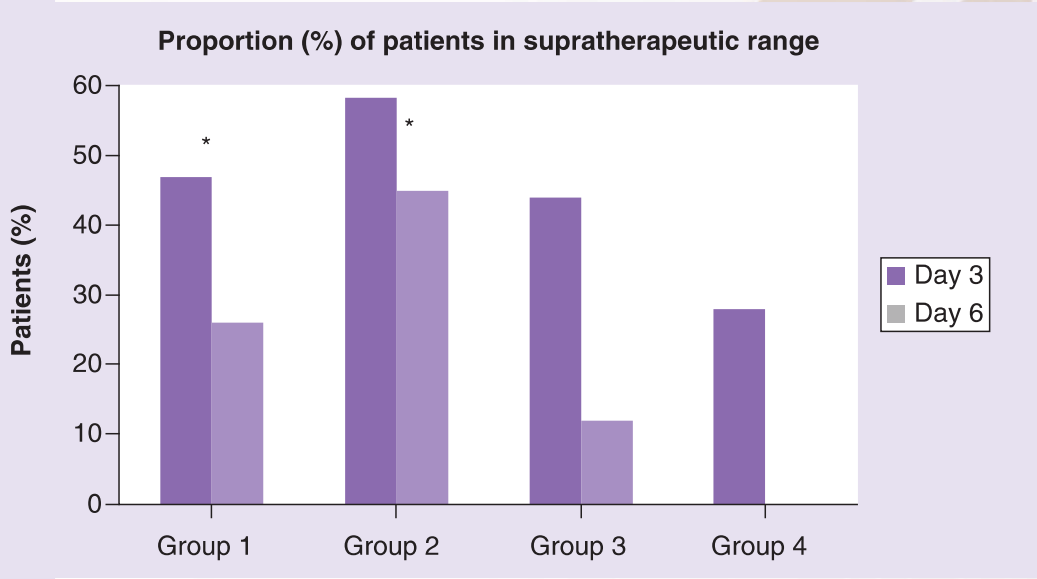
Avoiding Tacrolimus Underexposure and Overexposure with a Dosing Algorithm for Renal Transplant Recipients: A Single Arm Prospective Intervention Trial

Marith I. Francke[1,2,3,*], Louise M. Andrews[4,5], Hoang Lan Le[4], Jacqueline van de Wetering[1,2], Marian C. Clahsen-van Groningen[2,6], Teun van Gelder[7], Ron H. N. van Schaik[8], Bronno van der Holt[9], Brenda C. M. de Winter[2,4] and Dennis A. Hesselink[1,2]

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 0 NUMBER 0 | Month 2021


(a) Tacrolimus concentrations on days 3, 5, 7, and 10
Tacrolimus pre−dose concentration (ng/mL)
30
25
20
15
10
5
Day 3 (n = 59)
Day 5 (n = 57)
Day 7 (n = 44)
Day 10 (n = 37)
Time after transplantation

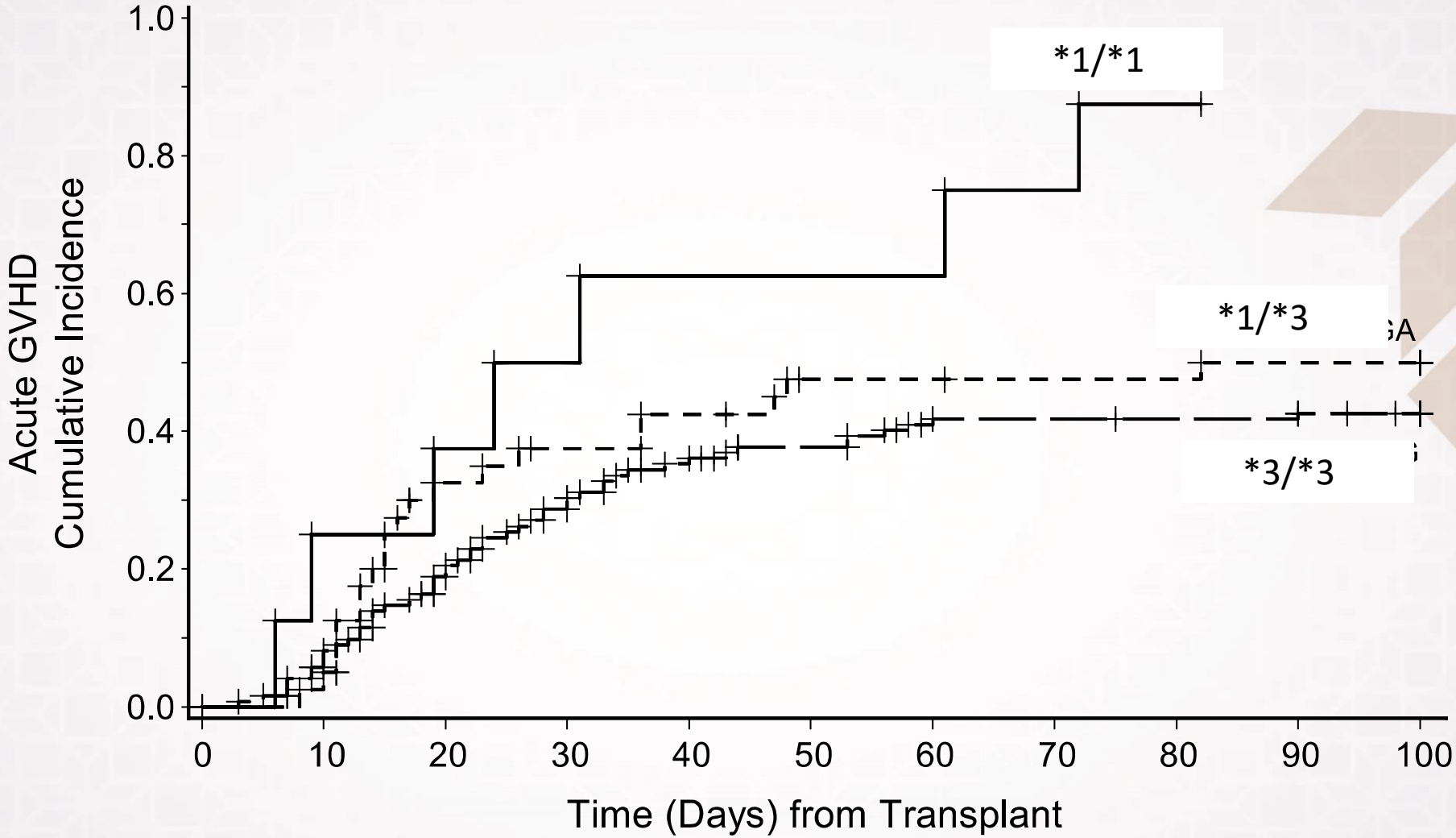




Byun et al, 2016

PGx in HCT

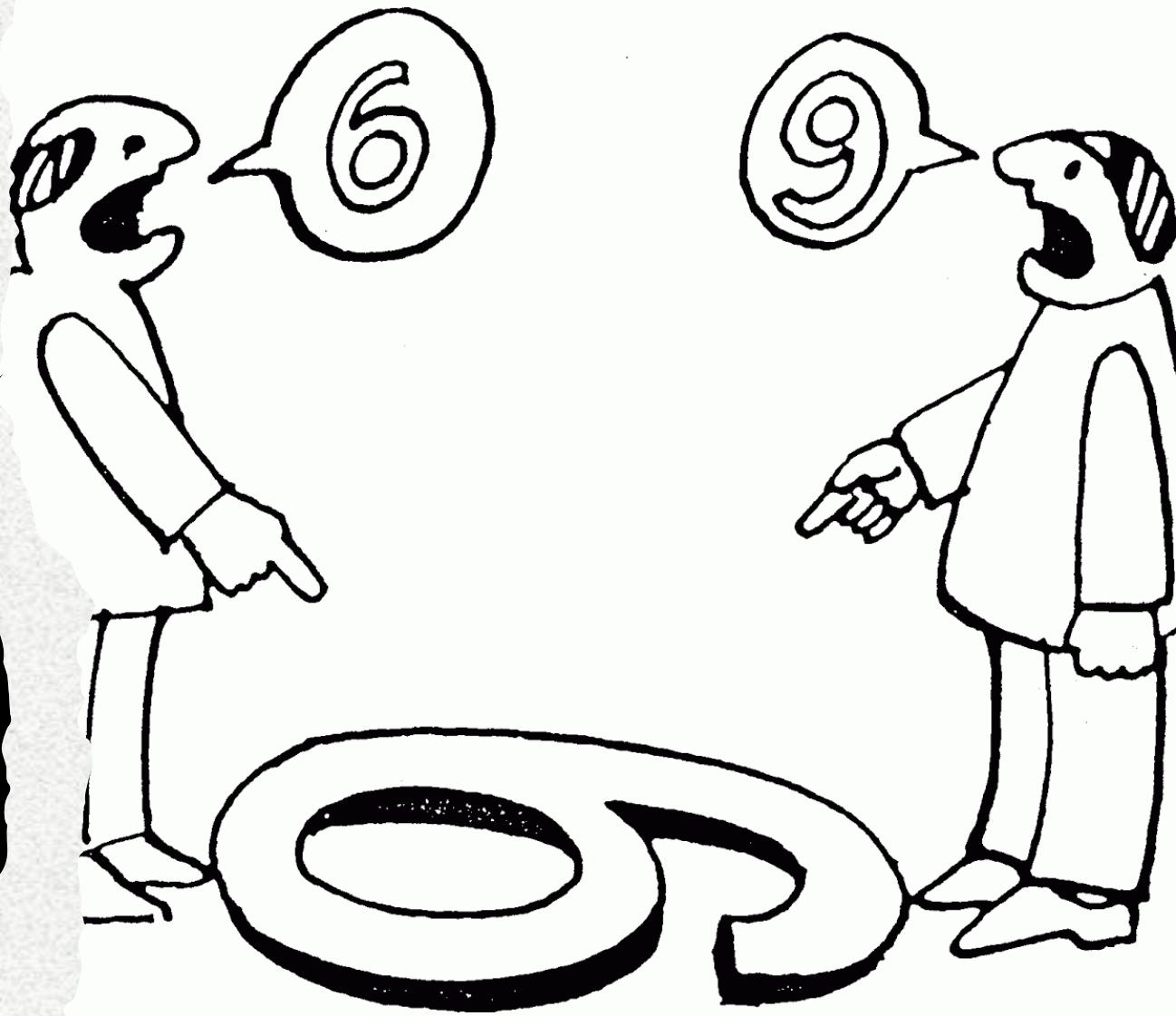
http://www.huffingtonpost.com



Khaled et al, 2016

Very Convincing!

Right?



Barriers

Testing

- Availability of testing
- Cost of testing
- Slow turnaround time for results
- Data management
- Testing reimbursement

Informatics

- Lack of standardization of terminology
- Poor interoperability of clinical informatics systems
- Inadequate decision support and point-of-care tools
- Few clinical genetic data storage solutions
- Few patient centered tools (e.g. apps)

Clinical

- Few drug or dose selection algorithms
- Lack of real-world or randomized controlled data on outcomes (clinical utility) and economic value
- Lack of medication use data
- Few patient return of results systems

Education

- Poor training of current and future health professionals in pharmacogenomics and pharmacogenomics communication
- No common point-of-care education resources
- Few patient education materials

ELSI

- Ethics (privacy, equity, incidental findings, decision making)
- Privacy issues (informed consent)
- Legal issues (discrimination, patents)
- Incomplete coverage of the Genetics Nondiscrimination Act (GINA)

Adams et al, 2018

Summary

- PGx testing yields clinically actionable results that are conducive to the practice of precision medicine
- Future models for prediction of optimal dosing will integrate PGx markers as well as biological attributes such as pharmacokinetics, age and BSA

Thank you

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