CONGRESO ALAG 2019

FARMACOGENÓMICA CARDIOVASCULAR: EXPERIENCIAS EN TERAPIA ANTICOAGULANTE

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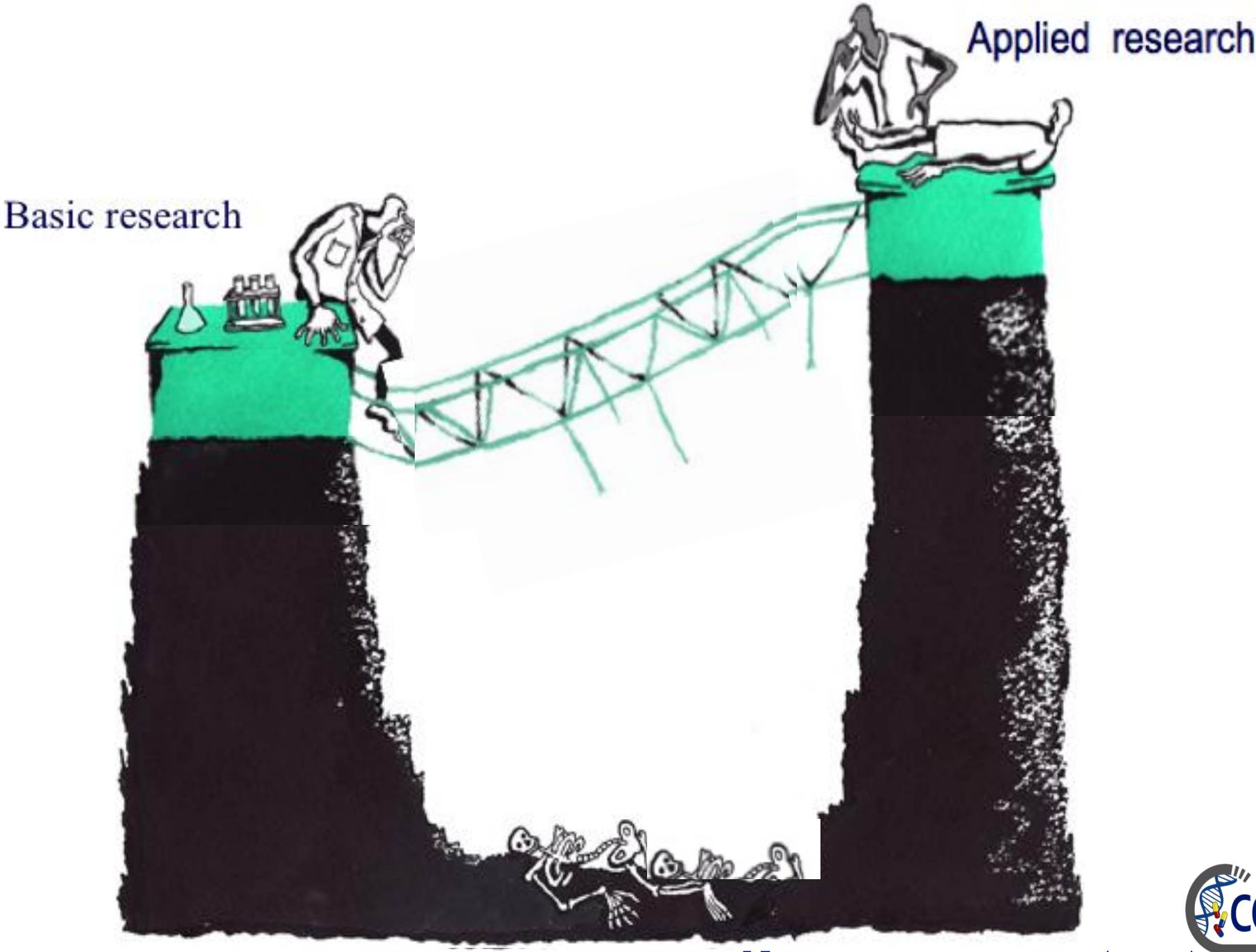
Ex - Presidente SOLFAGEM
Coordinador RED RELIVAF-CYTED

Mendoza, 08 de Octubre de 2019

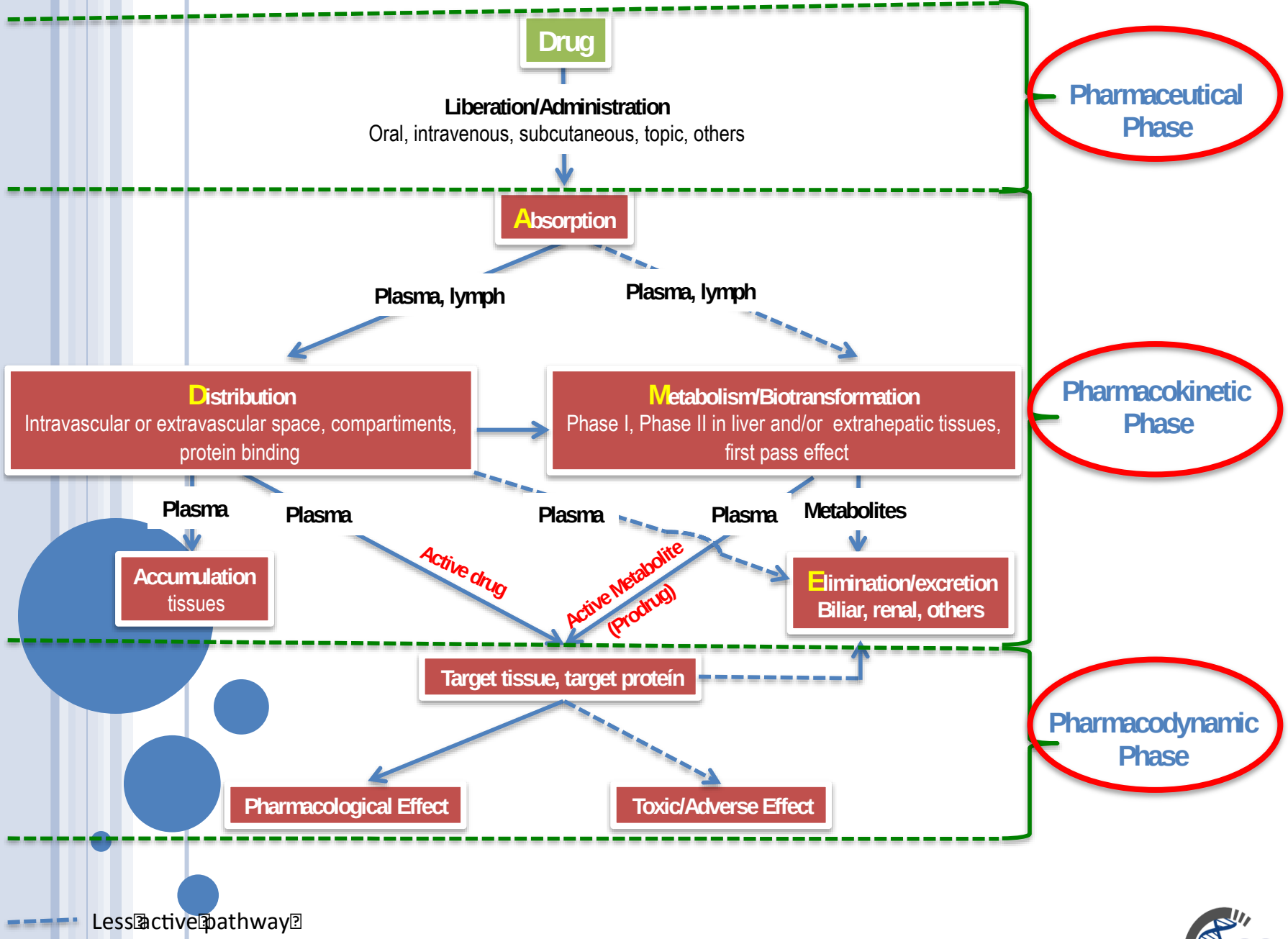
MEDICINA PERSONALIZADA/PRECISIÓN

- ¿Por qué alguien necesita el doble de la dosis estándar de un fármaco para que éste sea efectivo?.
- ¿Por qué esta droga funciona para ti pero no para mí?
- ¿Por qué tengo efectos secundarios y tú no?.
- ¿Por qué algunas personas contraen cáncer y otras no?

Como enfrentar apropiadamente esta "Odisea Terapéutica"?

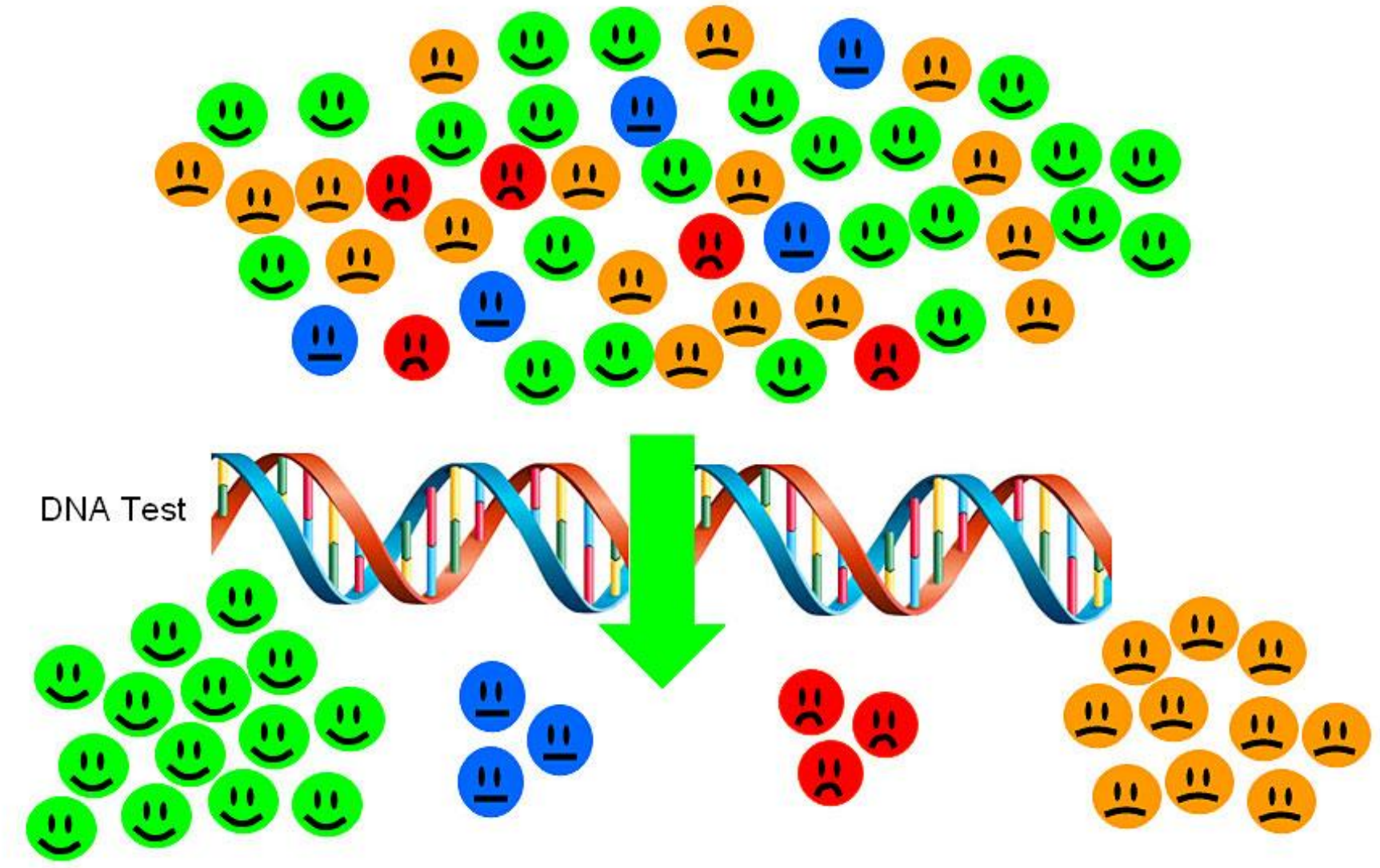


Nature **453**, 840-842 (2008)



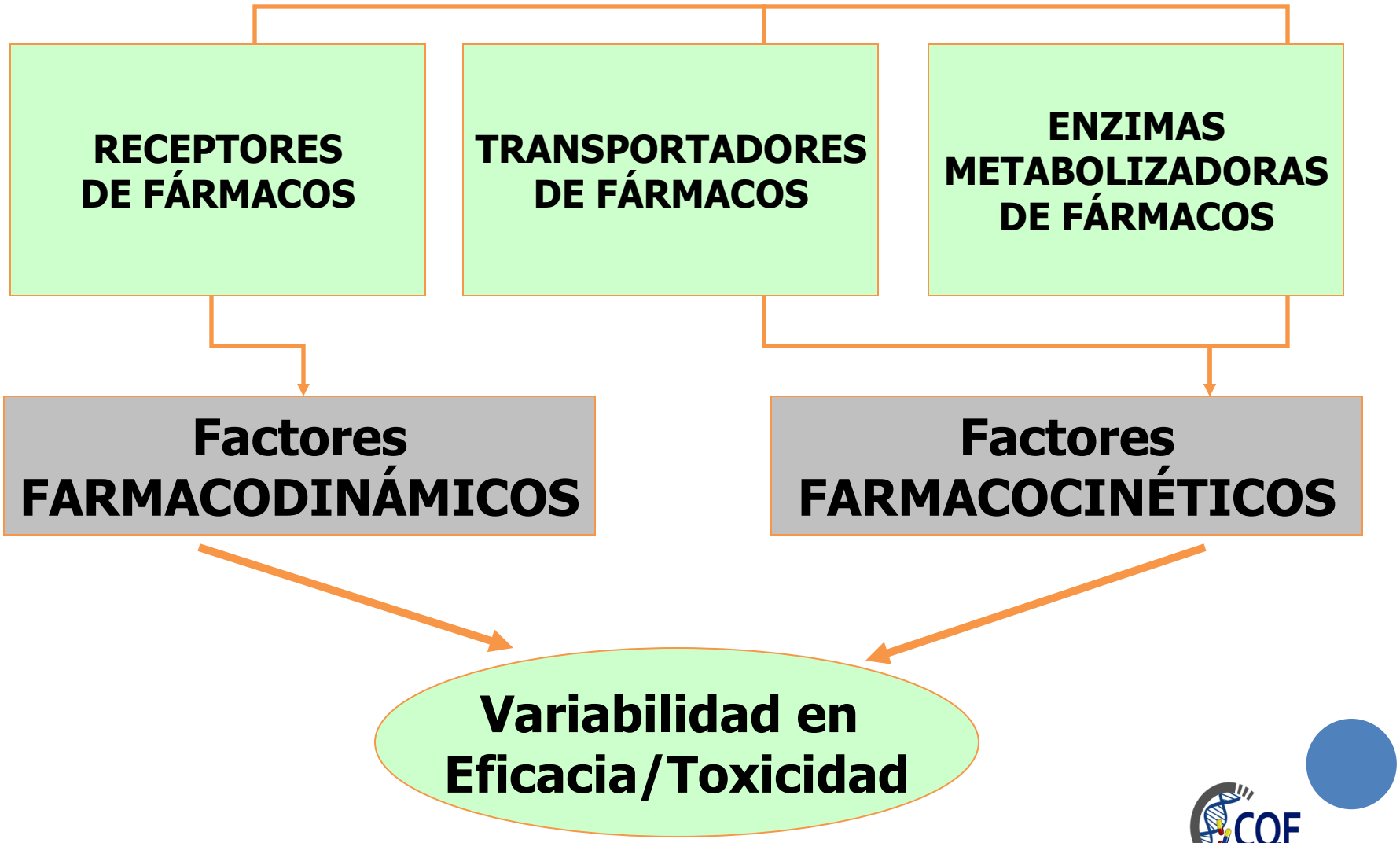
Relationship between pharmacokinetics and pharmacogenomics, and its impact on drug choice and dose regimens. *Matías F. Martínez, Luis A. Quiñones. In In: ADME processes and their impact on pharmaceutical sciences, Ed. López-Cortés A., Ed. Springer Nature, 2018.*

EL DNA AFECTA LA RESPUESTA A FÁRMACOS

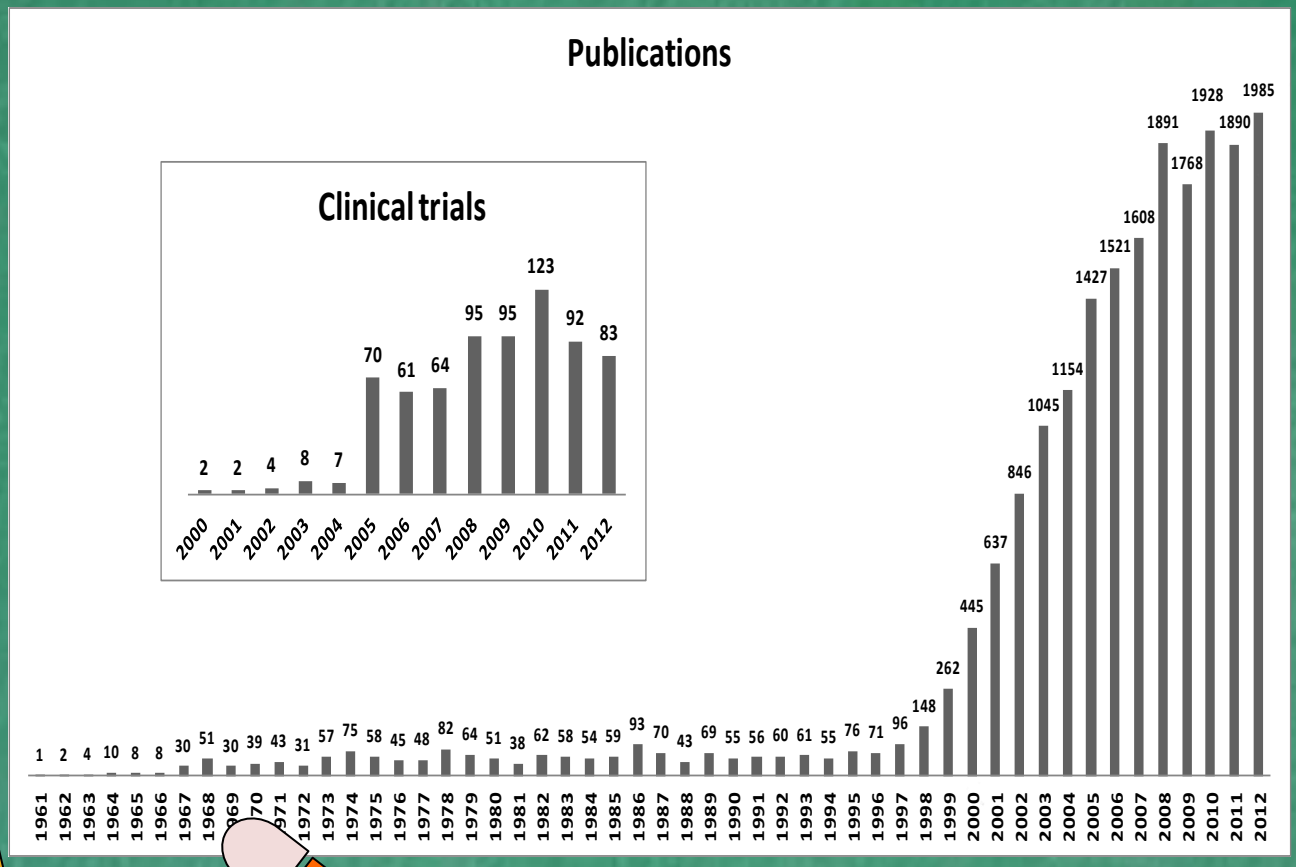


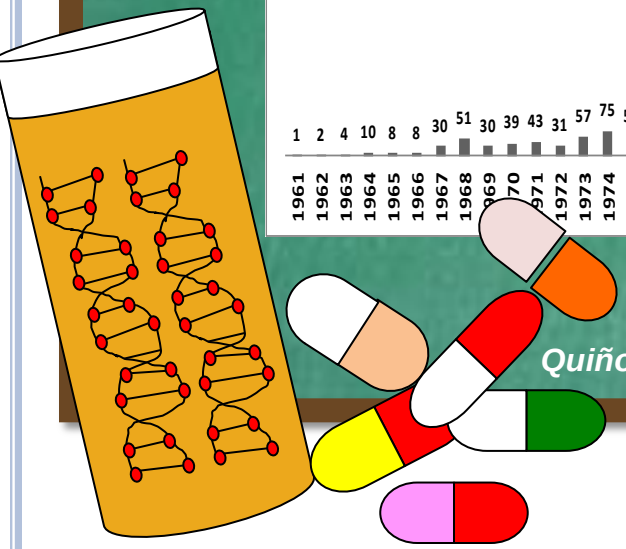
Farmacogenómica

Estudio del total de genes que influencian la respuesta farmacológica y la visión global del genoma.



FARMACOGENOMICA





Quiñones et al, Current Drug Metabolism 15(2):202-8 (2014)

PATOLOGÍA CARDIOVASCULAR

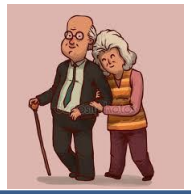
EPIDEMIOLOGÍA

17,5 millones de muertes → 2030 → 23,6 millones de muertes

FUENTE: OMS

EXPECTATIVA DE VIDA




1960 1970 1980 1990 2000 2010 2017

57,4 años | 63,3 años | 67,4 años | 72,3 años | 76,8 años | 78,5 años | 79,7 años

Pacientes con Terapia Anticoagulante (TACO)

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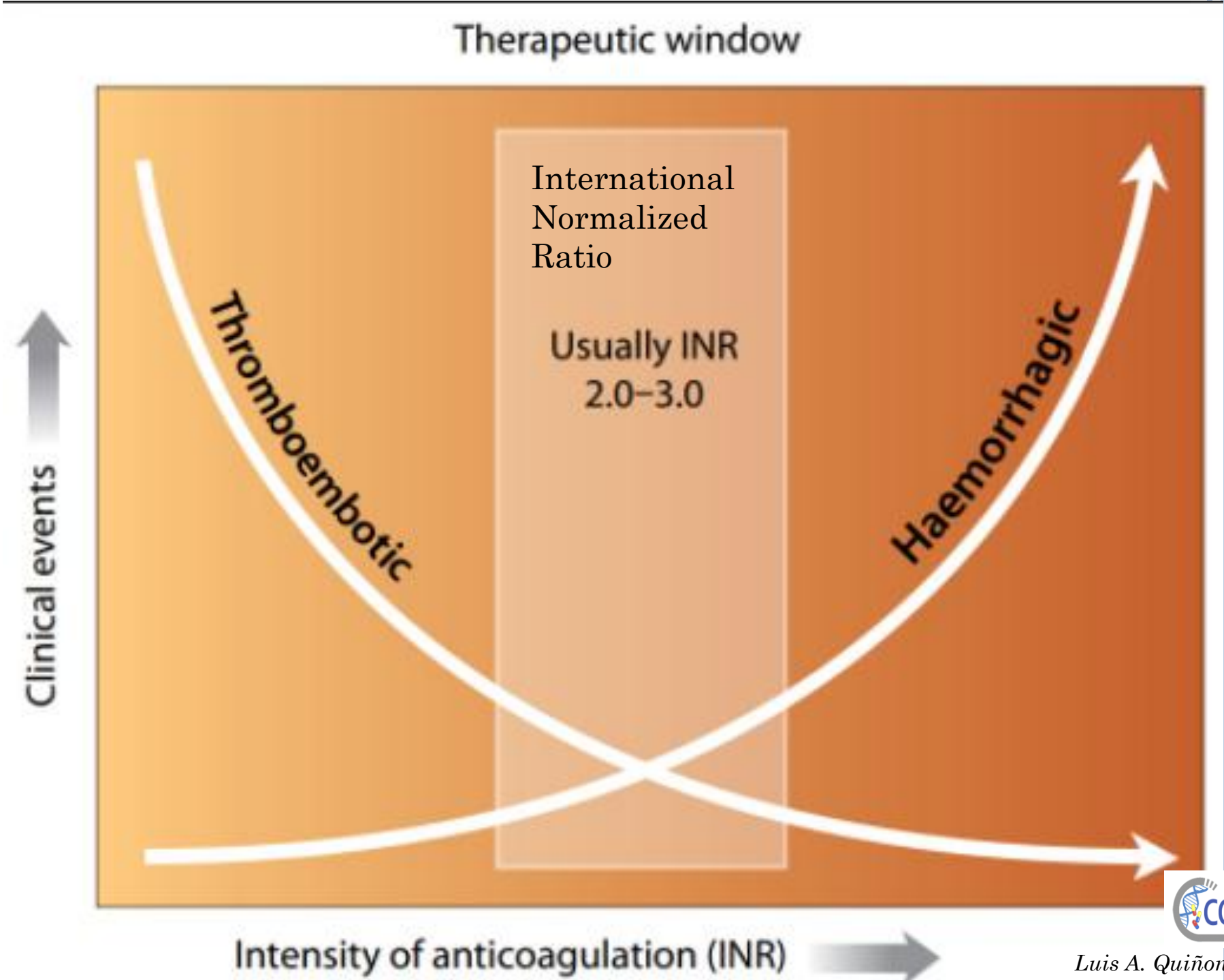

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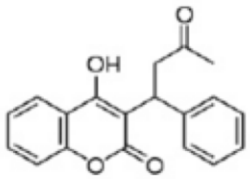
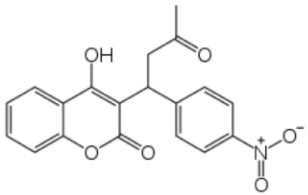
Características Farmacocinéticas y Farmacodinámicas de Cumarinas

Fármaco		Warfarina		Acenocumarol
Estructura química				
Presentación		2,5 y 5 mg		1 y 4 mg
Dosis de Inicio		5-7,5 mg		8-12 mg
Tiempo de vida media		30-40 horas		5-9 horas
Unión a proteínas (%)		97		97
Diana terapéutica		VKORC1		VKORC1
Frecuencia de administración		Una vez al día		Una vez al día
Monitorización		INR-ajustado		INR-ajustado
Metabolismo	**R(+)**	CYP2C9, CYP1A2, CYP1A1, CYP2C8, CYP2C19 y CYP3A4		CYP2C9 CYP1A2 CYP2C19
	S(-)	CYP2C9		CYP2C19

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¿Qué se observa en la práctica clínica en pacientes con TACO?

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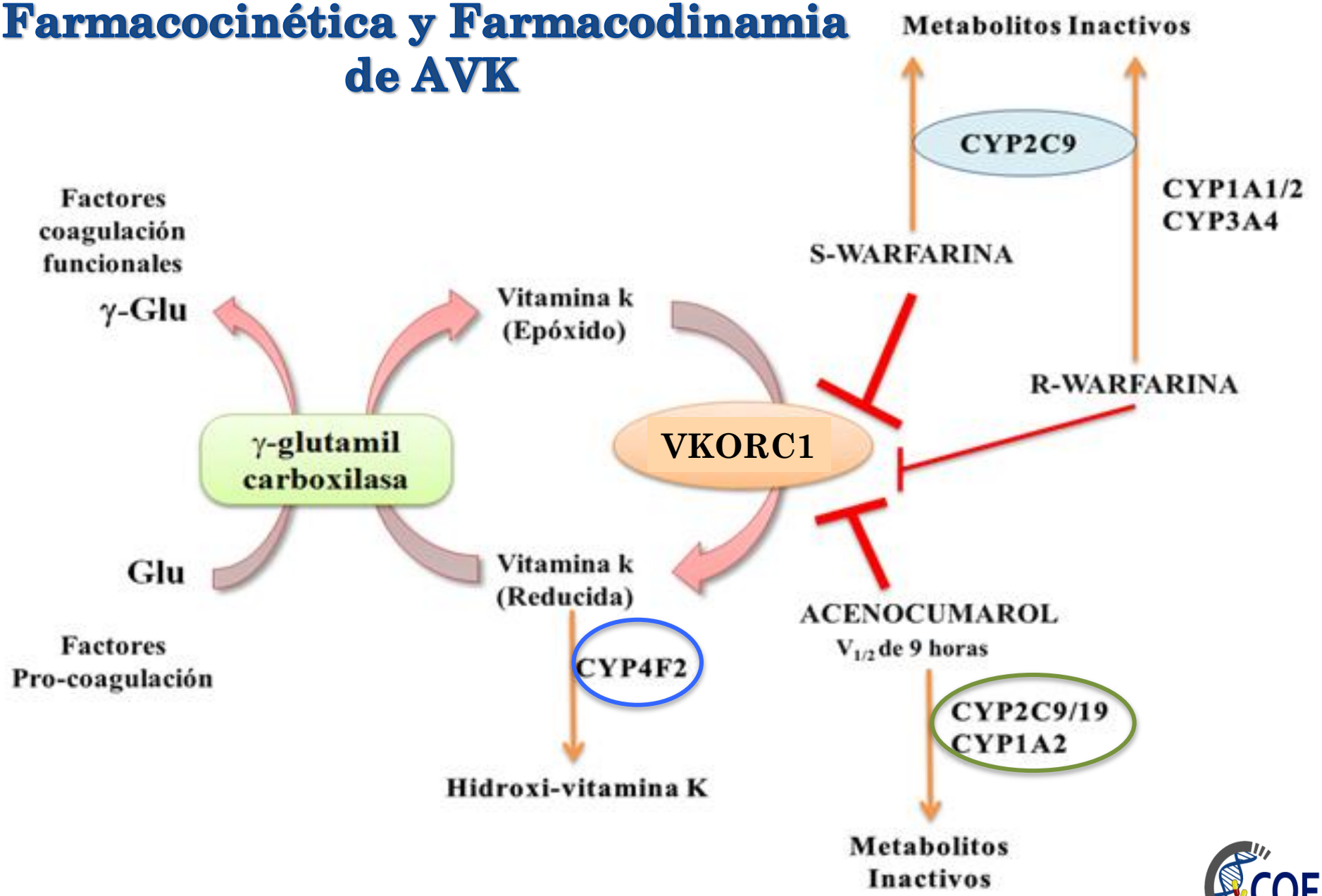
Dos pacientes con Trombosis venosa profunda (TVP) que deben estar anticoagulados INR: 2,0 – 3,0. Uno con dosis 55 mg semanales de Acenocumarol y otro con 3,5 mg semanales.

Lunes	Martes	Miercoles	Jueves	Viernes	Sabado	Domingo
		23/03/2016 Toma: 2	24/03/2016 Toma: 2	25/03/2016 Toma: 2	26/03/2016 Toma: 2	27/03/2016 Toma: 2
28/03/2016 Toma: 1+3/4	29/03/2016 Toma: 2	30/03/2016 Toma: 2	31/03/2016 Toma: 2	01/04/2016 Toma: 2	02/04/2016 Toma: 2	03/04/2016 Toma: 2
04/04/2016 Toma: 1+3/4	05/04/2016 Toma: 2	06/04/2016 Toma: 2	07/04/2016 Toma: 2	08/04/2016 Toma: 2	09/04/2016 Toma: 2	10/04/2016 Toma: 2
11/04/2016 Toma: 1+3/4	12/04/2016 Toma: 2	13/04/2016 Toma: 2	14/04/2016 Toma: 2	15/04/2016 Toma: 2	16/04/2016 Toma: 2	17/04/2016 Toma: 2
18/04/2016 Toma: 1+3/4	19/04/2016 Toma: 2	20/04/2016 Toma: 2	21/04/2016 CONTROL			

Lunes	Martes	Miercoles	Jueves	Viernes	Sabado	Domingo
	05/04/2016 Toma: 0 NO TOMAR	06/04/2016 Toma: 1/4	07/04/2016 Toma: 1/4	08/04/2016 Toma: 1/4	09/04/2016 Toma: 1/4	10/04/2016 Toma: 1/4
11/04/2016 Toma: 1/4	12/04/2016 Toma: 1/4	13/04/2016 Toma: 1/4	14/04/2016 Toma: 1/4	15/04/2016 Toma: 1/4	16/04/2016 Toma: 1/4	17/04/2016 Toma: 1/4
18/04/2016 Toma: 1/4	19/04/2016 Toma: 1/4	20/04/2016 Toma: 1/4	21/04/2016 Toma: 1/4	22/04/2016 Toma: 1/4	23/04/2016 Toma: 1/4	24/04/2016 Toma: 1/4
25/04/2016 Toma: 1/4	26/04/2016 CONTROL					

INR: International Normalized Ratio

Farmacocinética y Farmacodinamia de AVK



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Blood. 2008 Aug 15; 112(4): 1013–1021.

PMCID: PMC2515137

1521-0081/65/3/987–1009$25.00
PHARMACOLOGICAL REVIEWS

http://dx.doi.org/10.1124/pr.112.007252
Pharmacol Rev 65:987–1009, July 2013

ASSOCIATE EDITOR: RHIAN M. TOUYZ

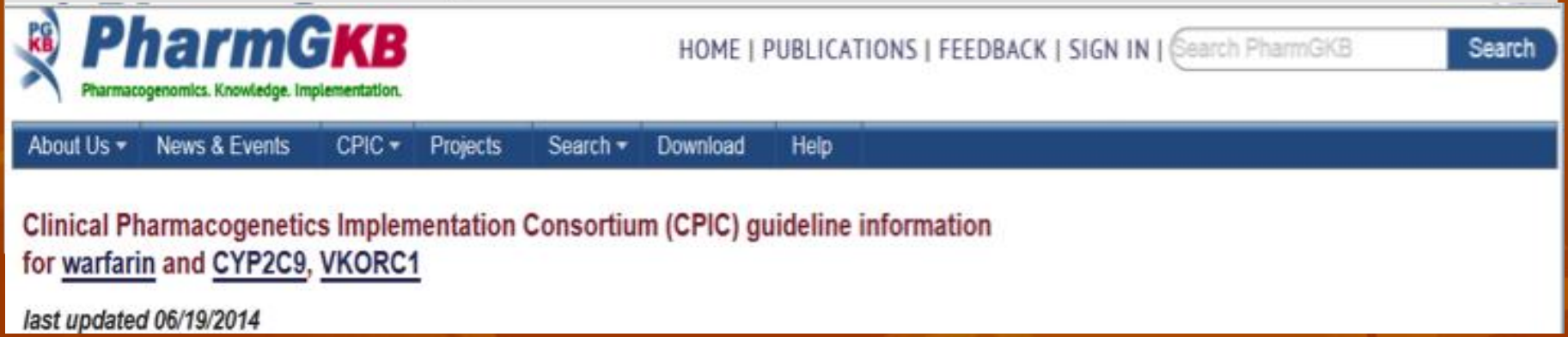
Pharmacogenetics and Cardiovascular Disease—Implications for Personalized Medicine

Julie A. Johnson and Larisa H. Cavallari

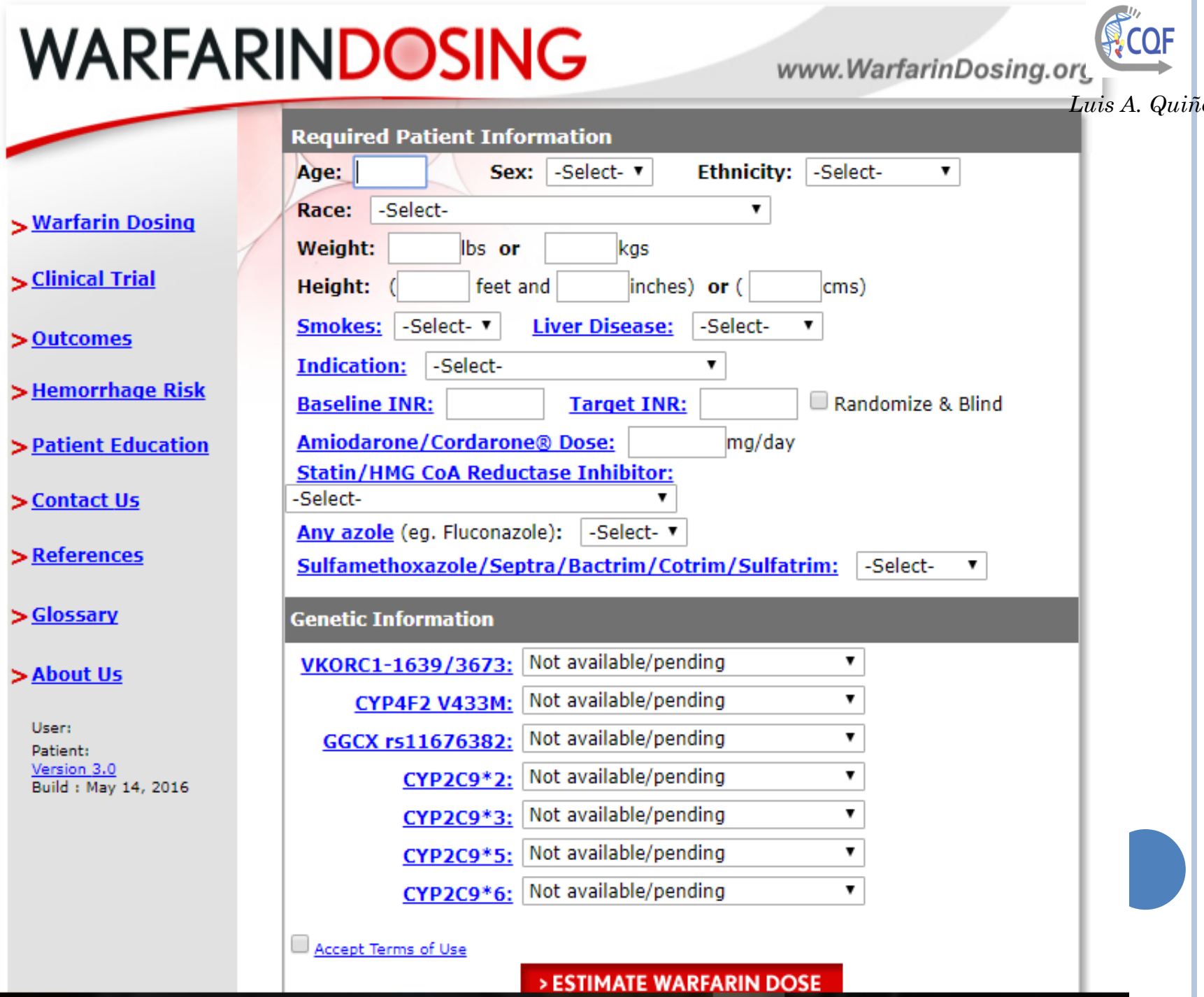
Center for Pharmacogenomics, Department of Pharmacotherapy and Translational Research and Department of Medicine, Colleges of Pharmacy and Medicine, University of Florida, Gainesville, Florida (J.A.J.); and the Department of Pharmacy Practice, College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois (L.H.C.)

DOSING ALGORITHM 2006 PROPOSED

Predictor(s)	Regression Equation	Model P-value	R^2
Age	log(D) = 2.870 – 0.020 (Age)	0.0003	0.18
Sex	log(D) = 1.276 + 0.415 (Sex)	0.0024	0.13
Weight	log(D) = 0.298 + 0.006 (Weight)	< 0.0001	0.28
VK3673	log(D) = 1.349 – 0.426 (VK3673-M) + 0.426 (VK3673-W)	0.0001	0.27
2C9*	log(D) = 1.659 – 0.248 (2C9*2) – 0.625 (2C9*3)	0.0003	0.22



Linder MW Ph.D. DABCC, Manage the "Over-steer" in warfarin dose titration.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www.WarfarinDosing.org
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> Warfarin Dosing
> Clinical Trial
> Outcomes
> Hemorrhage Risk
> Patient Education
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> References
> Glossary
> About Us
User:
Patient:
Version 3.0
Build : May 14, 2016
Required Patient Information
Age:
Sex: -Select-
Ethnicity: -Select-
Race: -Select-
Weight: lbs or kgs
Height: (feet and inches) or (cms)
Smokes: -Select-
Liver Disease: -Select-
Indication: -Select-
Baseline INR:
Target INR:
Randomize & Blind
Amiodarone/Cordarone® Dose: mg/day
Statin/HMG CoA Reductase Inhibitor:
-Select-
Any azole (eg. Fluconazole): -Select-
Sulfamethoxazole/Septra/Bactrim/Cotrim/Sulfatrim: -Select-
Genetic Information
VKORC1-1639/3673: Not available/pending
CYP4F2 V433M: Not available/pending
GGCX rs11676382: Not available/pending
CYP2C9*2: Not available/pending
CYP2C9*3: Not available/pending
CYP2C9*5: Not available/pending
CYP2C9*6: Not available/pending
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> ESTIMATE WARFARIN DOSE

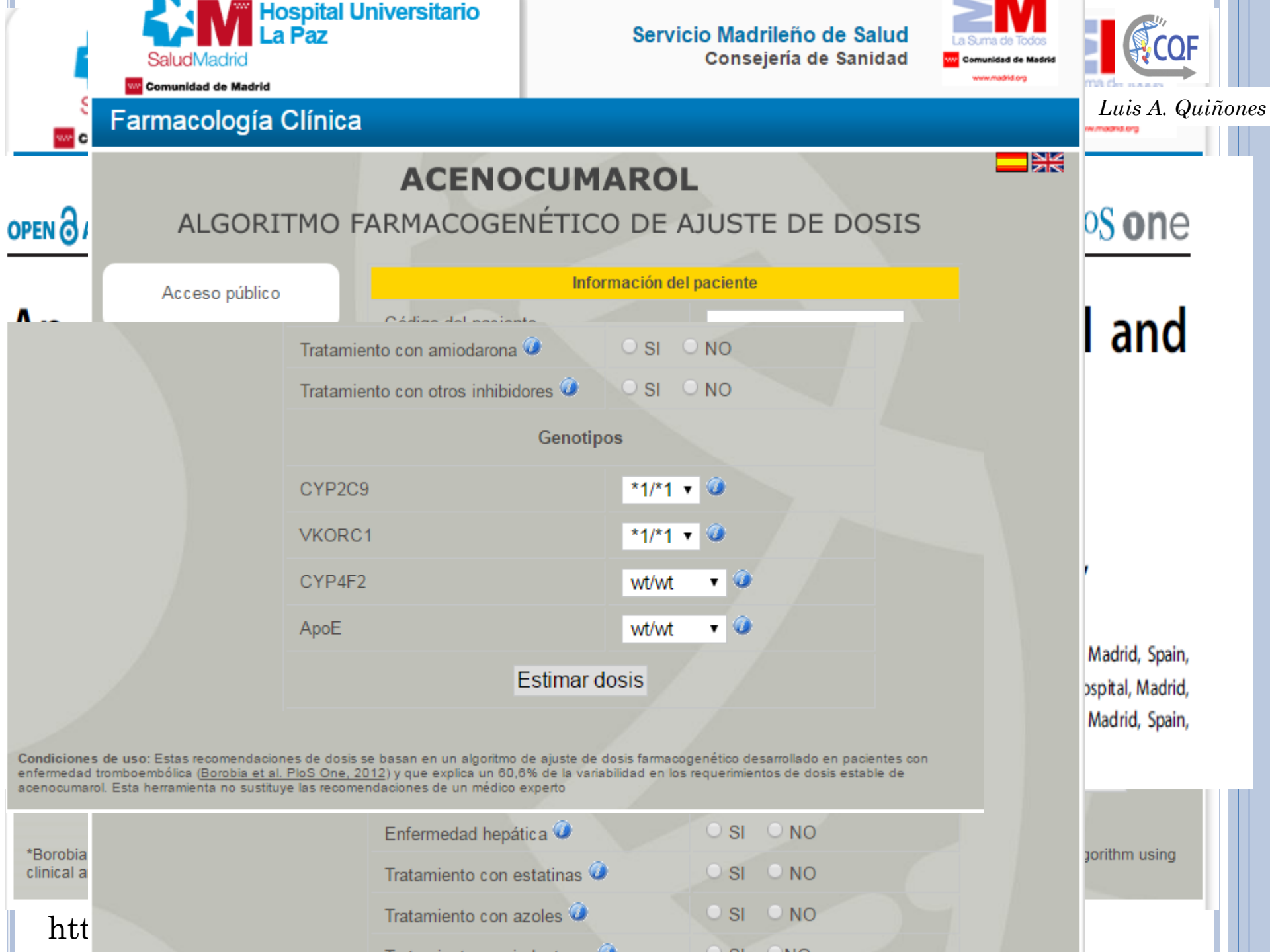
Rango de dosis de Warfarina basado en genotipos de *CYP2C9* y *VKORC1*

VKORC1	CYP2C9					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0,5-2 mg
AG	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0,5-2 mg	0,5-2 mg
AA	3-5 mg	3-4 mg	0,5-2 mg	0,5-2 mg	0,5-2 mg	0,5-2 mg

Johnson et al., 2011

Pharmacogenomic Biomarkers in Drug Labeling

Drug	Therapeutic Area*	Biomarker†	Referenced Subgroup‡	Labeling Sections
Warfarin (4)	Cardiology, Hematology	PROC	Protein C deficient	Warnings and Precautions
Warfarin (3)	Cardiology, Hematology	PROS	Protein S deficient	Warnings and Precautions
Warfarin (2)	Cardiology or Hematology	VKORC1	VKORC1 A allele carriers	Dosage and Administration, Clinical Pharmacology
Warfarin (1)	Cardiology or Hematology	CYP2C9	CYP2C9 intermediate or poor metabolizers	Dosage and Administration, Drug Interactions, Clinical Pharmacology
Vortioxetine	Neurology	CYP2D6	CYP2D6 poor metabolizers	Dosage and Administration, Clinical Pharmacology
Voriconazole	Infectious Diseases	CYP2C19	CYP2C19 intermediate or poor metabolizers	Clinical Pharmacology
Venlafaxine	Psychiatry	CYP2D6	CYP2D6 poor metabolizers	Precautions
Valproic Acid (2)	Neurology	NAGS, CPS1,	Urea cycle enzyme deficient	Contraindications, Warnings and Precautions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Farmacología Clínica
ACENOCUMAROL
ALGORITMO FARMACOGENÉTICO DE AJUSTE DE DOSIS
Acceso público
Información del paciente
Tratamiento con amiodarona
SI
NO
Tratamiento con otros inhibidores
SI
NO
Genotipos
CYP2C9
*1/*1
VKORC1
*1/*1
CYP4F2
wt/wt
ApoE
wt/wt
Estimar dosis
Condiciones de uso: Estas recomendaciones de dosis se basan en un algoritmo de ajuste de dosis farmacogenético desarrollado en pacientes con enfermedad tromboembólica (Borobia et al. PloS One, 2012) y que explica un 60,6% de la variabilidad en los requerimientos de dosis estable de acenocumarol. Esta herramienta no sustituye las recomendaciones de un médico experto
Enfermedad hepática
SI
NO
Tratamiento con estatinas
SI
NO
Tratamiento con azoles
SI
NO
OPEN
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Madrid, Spain,
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PROYECTO TERAPIA ANTICOAGULANTE (TACO) Y FARMACOGENOMICA

Servicio de Salud Metropolitano Occidente, Ministerio de Salud, Santiago, Chile
Hospital San Juan de Dios, Santiago, Chile.
Laboratorio de Carcinogénesis Química y Farmacogenética (CQF).

Elena Nieto, Angela Roco, Marcelo Suárez, Luis A. Quiñones.

OBJETIVO: GENERAR UN ALGORITMO DE DOSIFICACIÓN PARA PACIENTES CHILENOS EN TACO

Original Article

Anticoagulation Management With Coumarinic Drugs in Chilean Patients

Clinical and Applied Thrombosis/Hemostasis
Volume 25: 1-7
© The Author(s) 2019
DOI: 10.1177/1076029619834342
journals.sagepub.com/home/cat
SAGE

Elena Nieto, MD[1], Marcelo Suarez, MSc[2], Ángela Roco, PhD[2,3,4], Juan Carlos Rubilar, MSc[2], Francisca Tamayo, PCh[2], Mario Rojo, MSc[2], Gabriel Verón, MSc[2], Juliana Sepúlveda, MD[5], Fanny Mejías, MD[6], Patricio Salas, MD[7], María Góngora, MD[8], Patricio Andrade, MD[9], Alicia Canales, MD[7], Jorge Carabantes, MD[1], Daniela Cruz, MSc[1], Emma Contreras, MSc[5], Daniela Pavez, MSc[7], Paulina Charo, MSc[9], Gabriela Bravo, MSc[10], Juan Calderón, MSc[6], Carlos Gallardo, MD[3], Patricia Vega, MSc[3], and Luis A. Quiñones, PhD[2]

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Table 4. Results of the FIR and TTR Indicator in Patients Face-to-Face Care Versus Telemedicine Care of 2017.

		FIR			TTR		
Province	Quarters	Face to Face	Telemedicine	*P* Value[a]	Face to Face	Telemedicine	*P* Value[a]
Santiago	I	49.5	56.0	**.001**	40	63.3	**.016**
	II	48.2	53.3		40	50	
	III	49.5	56.8		50	63.3	
	IV	50.1	55.9		50	66.7	
Melipilla	I	46.6	44.2	.299	33	40	.554
	II	47.2	51.5		40	33	
	III	47.2	48.7		40	40	
	IV	45.9	51.1		40	50	
Talagante	I	44.1	44.9	.275	33	33	.356
	II	42.9	43.9		33	33	
	III	42.7	44.0		33	33	
	IV	45.3	49.2		33	50	

Abbreviations: FIR, percentage of the total INR readings that were in range for total of patient; INR, international normalized ratio; TTR, time in therapeutic range.
Significant values ($p<0.05$) are in bold.
[a]*P* value: student *t* test.

Table 5. Average Daily Dose in Patients With Oral Anticoagulant Treatment According to Ethnicity and Type of Coumarin.[7,20]

	Warfarin					Acenocoumarol	
	African American	Caucasian	Asian	Chile (This Study)	Spanish	Spanish	Chile (This Study)
Average dose (mg/d)	5.2 ± 1.7	4.3 ± 2.2	2.7 ± 1.1	4.3 ± 2.2	4.0 ± 1.1	2.0-3.0	1.9 ± 1.1

Acta Cardiol 2015; 70(5): 528-535 doi: 10.2143/AC.70.5.3110513

[Original article]

Prevalence of seven cardiovascular-related genetic polymorphisms in a Chilean mestizo healthy population

Angela ROCO[1,2,3], PhD; Luis A. QUIÑONES[1], PhD; Pablo SEPÚLVEDA[4], MD; Hernán DONOSO[4], MD; Carolina LAPOSTOL[4], RN; Romina ALARCÓN[5], MT; María E. TORRES[5], MT; Paulo C. VÉLIZ[6], MT; Guillermo ACUÑA[6], MT; Oscar WILKE[6], MT; Cristián ACEVEDO[1,7], MD

Table 1 Anthropometric and biochemical characteristics of the study population

CHARACTERISTICS	
Total (N)	146
Male (%)	98 (67.1%)
Female (%)	48 (32.9%)
Age (y) (mean ± SD)	35.7 ± 14.5
BMI ± SD (< 25 Kg/m^2)	24.5 ± 3.4
Cholesterol (mean ± SD) (RV: 50-200 mg/dL)	136 ± 47
Triglycerides (mean ± SD) (RV: 50-150 mg/dL)	96 ± 77
HDL-cholesterol (mean ± SD) (RV: 30-95 mg/dL)	35 ± 16
LDL-cholesterol (mean ± SD (RV: < 130 mg/dL)	81 ± 32
Cholesterol/HDL-cholesterol (mean ± SD (RV: < 5.0)	4.3 ± 1.7
LDL-cholesterol/ HDL-cholesterol (mean ± SD) (RV: < 2.0)	2.6 ± 1.2

SD: standard deviations, BMI: body mass index. RV: reference value.

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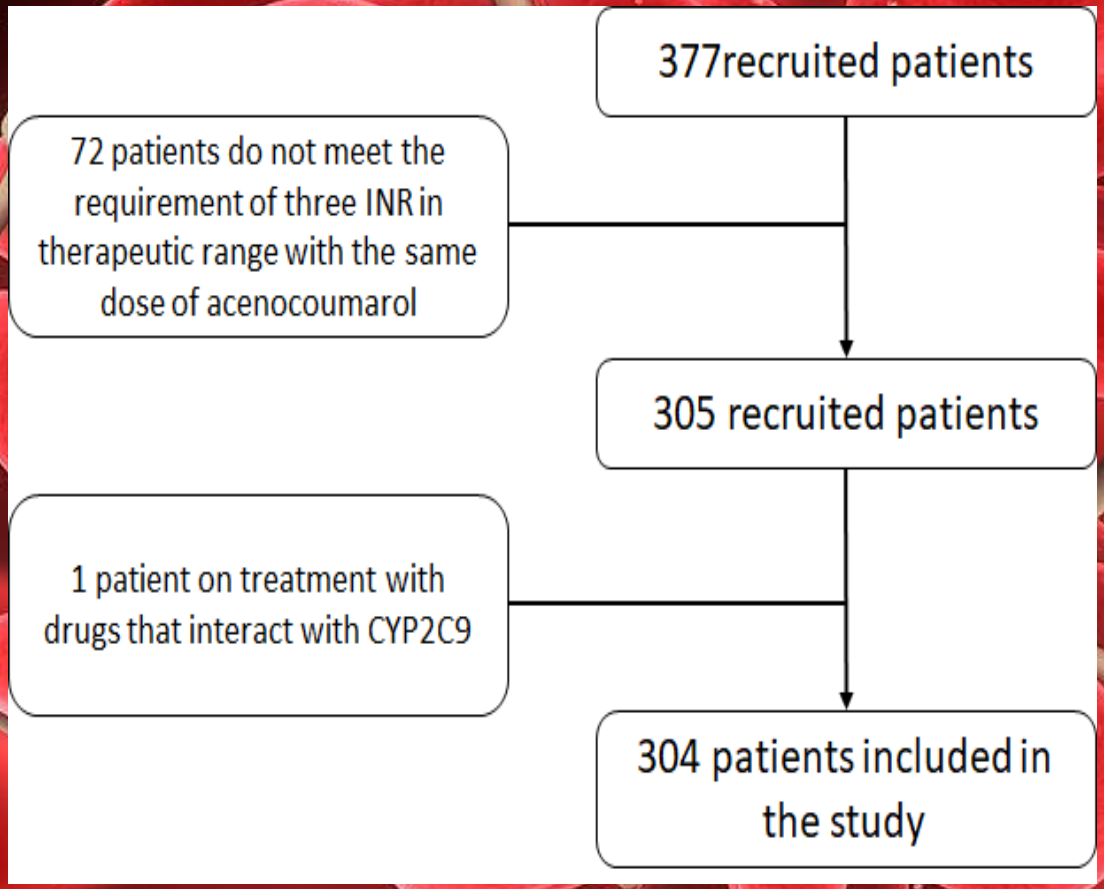
ESTUDIO DE ASOCIACIÓN ENTRE POLIMORFISMOS GENÉTICOS Y DOSIS DE ACENOCUMAROL EN PACIENTES TACO



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CARACTERÍSTICAS DEMOGRÁFICAS Y CLINICAS DE LOS PACIENTES

Characteristics	N (%)
Women	144 (47,4 %)
Men	160 (52,6 %)
Total	304 (100 %)
% Caucasian Aboriginal Mix	9,80%
Age +/- S.D (years)	65,01+/-13,99
Body Mass Index (BMI)(Kg/m^2) +/-S.D (Median)	29,2 +/- 5,7 (28,4)
Acenocoumarol	100 %
Therapeutic weekly dose of Acenocoumarol (mg/week) +/- S.D	14,6 +/- 2,2
Dosage range of Acenocoumarol mg / week (Median)	3,5 - 46 (13)
Average to reach therapeutic range (days) +/- S.D	308 +/- 343
Range of days to reach the therapeutic range (Median)	3 - 353 (206)
Primary diagnosis	**N (%)**
Rhythm disorders	156 (51,3 %)
Venous thrombosis with / without pulmonary thromboembolism	64 (21,1 %)
Occlusive Arterial Disease (ATE)	24 (7,9 %)
Stroke	17 (5,6 %)
Others	43 (14,1%)
Total	304 (100 %)
Secondary diagnosis	**N (%)**
Arterial hypertension	64 (25,6 %)
Diabetes mellitus	27 (10,8 %)
Cardiomyopathies	26 (10,4 %)
Others	88 (42,9 %)
Total	205 (100 %)

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SNPs Y SU EFECTO EN LA DOSIS DE VKA

Enzyme	Gen	SNP	Change	Effect on dose of VKA
MDR1	*ABCB1*	rs1045642	c.3435C>T, exon 26 p.Ile1145Ile silent	Decrease
CYP4F2	*CYP4F2*	rs2108622	c.1297 C>T, exon 11 missense p.Val433Met	Increase
CYP2C9	*CYP2C9*2*	rs1799853	c.3608C>T, exon 3 missense p.Arg144Cys	Decrease
	*CYP2C9*3*	rs1057910	c.42614 A>C, exon 7 Missense p.Ile359Leu	Decrease
GGCx	*GGCX*	rs11676382	c.2084+45 C>G Intron 14	Decrease
VKORC1	*VKORC1*	rs9923231	– 1639 G > A promotor	Decrease
	VKORC1	rs7294	3730 G > A 3'UTR	Increase
APO E	*ApoE*	rs7412	T>C, exon 4 p.Arg176Cys missense	Decrease
FVII	*FVII*	rs6046	c.10976 G>A exon 8 p.R353Q missense	Decrease

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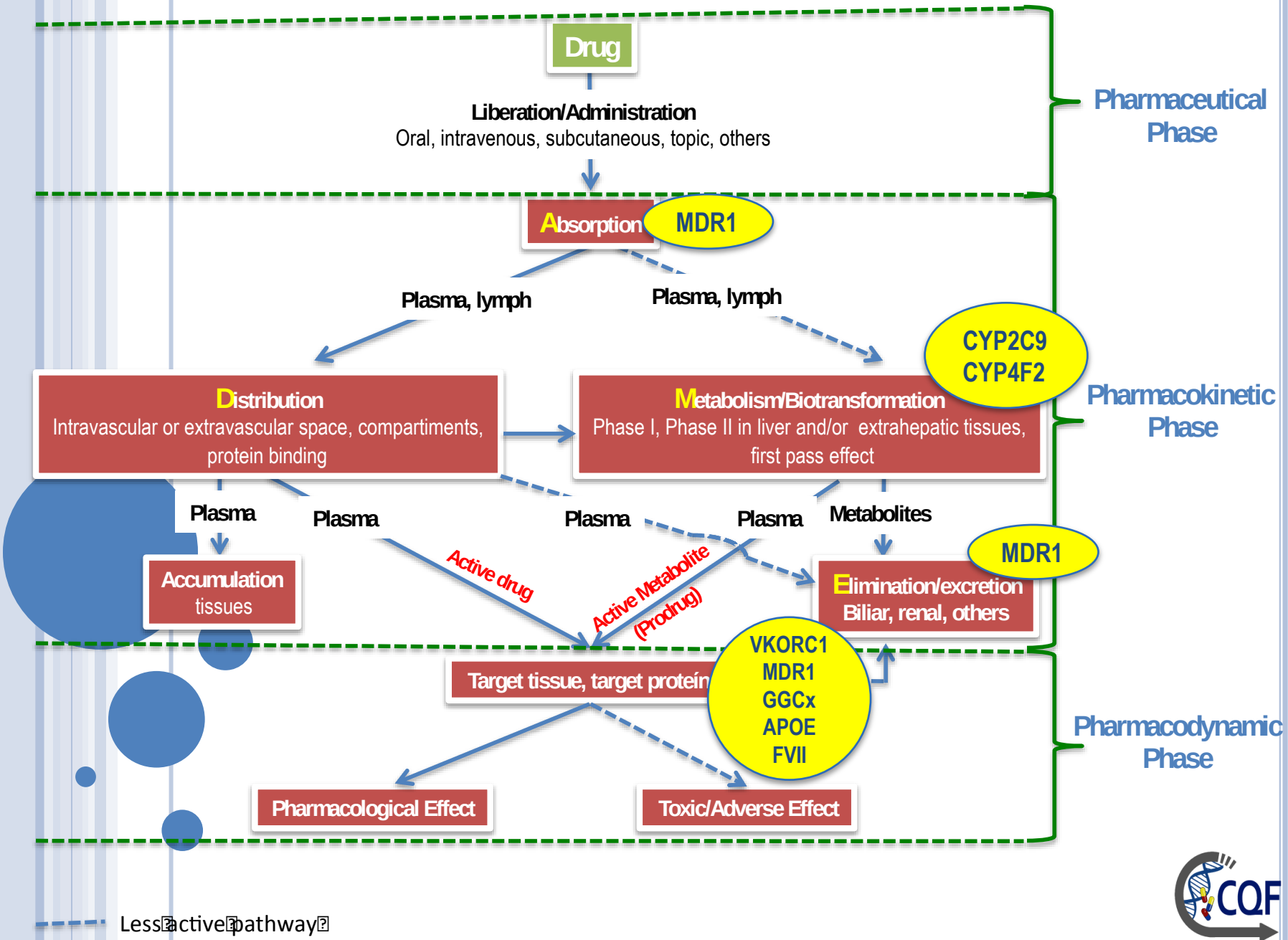

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TACO Patients

MSc Thesis:
Q.F. Marcelo Suárez M.

Patients
n = 304

Genotyping
- qPCR (*TaqMan®*)

CYP2C9
VKORC1
CYP4F2
GGCx
MDR1
APOE
FVII

PHARMACOGENOMIC ALGORITM

DOSAGE model

Clinical Files

INRs
TTR
RTRT

Demographic and Clinical Data

Multivariate Logistic Regression Analyses (p<0,05)

Stepwise Forward Procedure (cut-off p<0.2)

Univariate Logistic Regression Analyses (p<0,05)

CQF

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Relación genotipo dosis AVK

Dosis terapéutica semanal (DTS)

*CYP2C9*2*	rs1799853
***1/*1**	**DTS (mg)**
Promedio	**11,15**
D.E	**6,62**
***1/*2**	**DTS (mg)**
Promedio	**8,99**
D.E	**3,27**
***2/*2**	**DTS (mg)**
Promedio	**ND**
D.E	**ND**

*CYP2C9*3*	rs1799853
***1/*1**	**DTS (mg)**
Promedio	**11,21**
D.E	**6,21**
***1/*3**	**DTS (mg)**
Promedio	**7,85**
D.E	**2,12**
***3/*3**	**DTS (mg)**
Promedio	**6,50**
D.E	**0,71**

VKORC1	*rs9923231*
GG	**DTS (mg)**
Promedio	**12,91**
D.E	**6,76**
GA	**DTS (mg)**
Promedio	**11,35**
D.E	**6,45**
AA	**DTS (mg)**
Promedio	**6,78**
D.E	**2,25**

GGCx	rs11676382
CC	**DTS (mg)**
Promedio	**11,09**
D.E	**6,30**
CG	**DTS (mg)**
Promedio	**10,28**
D.E	**4,39**
GG	**DTS (mg)**
Promedio	ND
D.E	ND

REGRESIÓN LOGÍSTICA MULTIVARIADA

N obs	287
P model	0
R^2	0,5147
R^2-adjusted	0,4999

Variable	Coefficient	standard error	p-value	CI (95%)	
Sex (men)	0,1668786	0,0407027	0,000	0,0867528	0,2470045
Age	-0,008101	0,001472	0,000	-0,0109987	-0,0052034
INR initial	-0,0547186	0,0168253	0,001	-0,0878404	-0,0215969
BMI	0,0125554	0,0035861	0,001	0,0054959	0,0196149
*CYP2C9*2*					
**1/*2*	-0,1067491	0,0538426	0,048	-0,2127418	-0,0007565
*CYP2C9*3*					
**1/*3*	-0,3227895	0,0806461	0,000	-0,4815465	-0,1640324
**3/*3*	-0,7465348	0,2416193	0,002	-1,222178	-0,2708915
VKORC1 (rs9923231)					
G/A	-0,2704925	0,0479039	0,000	-0,3647945	-0,1761906
A/A	-0,7008277	0,0583063	0,000	-0,8156074	-0,586048
constant	3,080551	0,1622701	0,000	2,761112	3,33999

Luis A. Quiñones

ALGORITMO PROPUESTO PARA ACENOCUMAROL EN POBLACIÓN CHILENA

Log WTD = 3,081 + (0,167 x men) - (age x 0,081) - (initial INR x 0,055) + (BMI x 0,013) - (*CYP2C9*1/*2* x 0,107) - (*CYP2C9*1/*3* x 0,323) - (*CYP2C9*3/*3* x 0,746) – (*VKORC1 G/A* x 0,270) - (*VKORC1 A/A* x 0,701)

Luis A. Quiñones

ANÁLISIS COMPARATIVO DE ALGORITMOS DE AVK EN DIVERSAS POBLACIONES

Algorithms		Chile (this study)	CPIC	Puerto Rico	Brazil	Colombia	Spain
Drugs	VKA	Acenocoumarol	Warfarin	Warfarin	Warfarin	Warfarin	Acenocoumarol
Clinical variables	Age	X	X	X	X	X	X
	Sex	X			X		
	INR initial	X		X			
	Amiodarone		X	X	X	X	X
	Weight		X		X	X	
	Size		X			X	
	BMI*	X					X
	Inductors CYP2C9		X		X	X	X
	Race / color		X		X	X	
Genetic variables	*VKORC1 (rs9923231)*	X	X	X	X	X	X
	*CYP2C9*2 (rs1799853)*	X	X	X	X	X	X
	*CYP2C9*3 (rs1057910)*	X	X	X	X	X	X
	*CYP2C9*5 (rs28371686)*		Afro-American's	X			
	APO E (rs7412)						X
	CYP4F2 (rs2108622)		Optional				X
Explanation of variability of the VKA dose		**50 %**	**47%**	**51%**	**40%**	**45,9%**	**60,6%**

Luis A. Quiñones

“Aquí están mis genotipos..."

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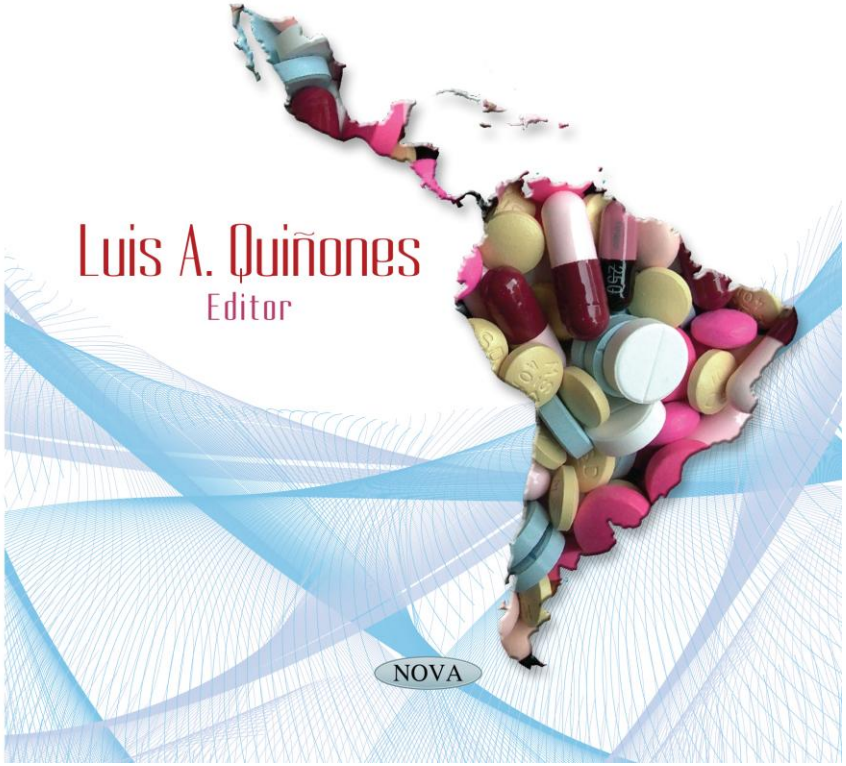
Pharmacogenomics in Latin America

Challenges and Opportunities



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Chapter 8

CARDIOVASCULAR PHARMACOGENOMICS: CLINICAL APPLICATIONS IN LATIN AMERICA

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ABSTRACT

Cardiovascular diseases (CVDs) are the number one cause of death globally. Most cardiovascular diseases can be prevented by addressing behavioral risk factors such as tobacco use, unhealthy diet and obesity, physical inactivity and harmful use of alcohol using population-wide strategies. Various factors help the occurrence of cardiovascular diseases. There are not-modifiable factors such as genetic inheritance and other modifiable such as smoking, alcohol intake, diet and physical activity risk factors. The overall level of risk of an individual is the one that determines the probability of cardiovascular disease, such as acute myocardial infarction, stroke, among others.

On the other hand, a number of medications, including: antiarrhythmics, anticoagulants, beta-blockers, calcium channel blockers, angiotensin receptor blockers, digitalis, diuretics, angiotensin converting enzyme (ACE) are the pharmacotherapeutic arsenal available. The drug of choice by the doctor must be in accordance with the characteristics of each patient and consider the recommendation of pharmacogenomic clinical guidelines.

Nowadays, the relationship between adverse reactions of drugs and genetically determined variations is a main focus of interest. Thus, pharmacogenomic studies are

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