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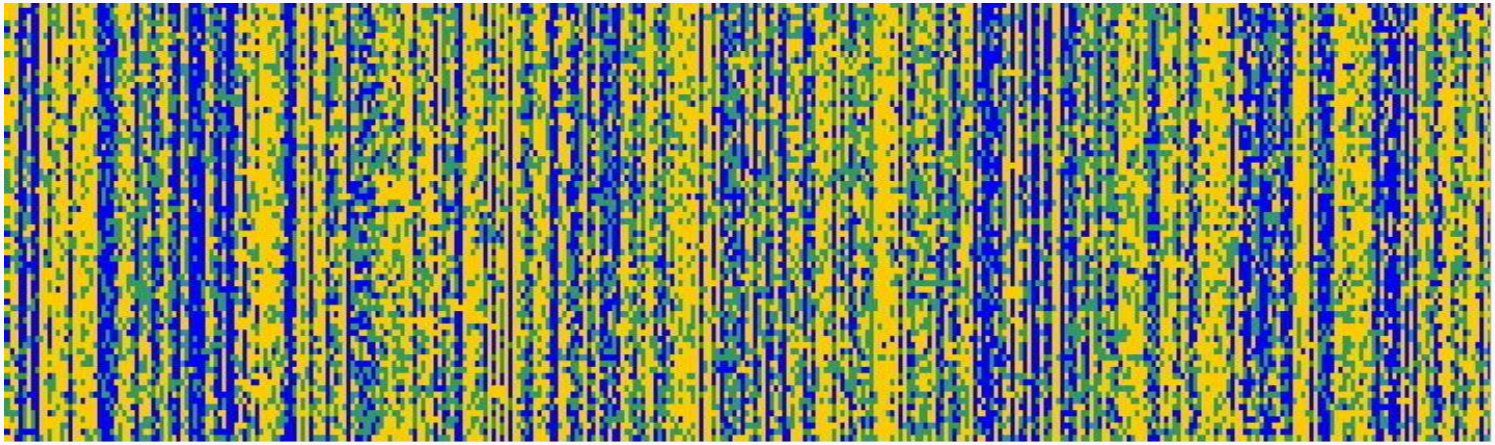
Pharmacogenomics of CV drugs in Admixed Caribbean Hispanics



Jorge Duconge, PhD, MSc, BSc Pharm
Professor
School of Pharmacy,
University of Puerto Rico
San Juan, 00936-5067 USA.

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Biographical

Institutional Position: Professor of Pharmacokinetics and Pharmacogenomics. Department of Pharmaceutical Sciences, University of Puerto Rico School of Pharmacy, Medical Sciences Campus

Education: BSc Pharm (1995, *Summa Cum Laude,* Gold Medal Honors List); MSc in Experimental Pharmacology (1997); and a PhD degree (1999, Best Thesis in Pharmaceutical Sciences, National Council of Scientific Degrees) from the School of Pharmacy University of Havana. Fellow of the advanced residency program in Pharmacokinetics/ Pharmacodynamics (Cambridge University, UK, 1998); trained in NONMEM Population Pharmacokinetics (SUNY at Buffalo, 2006). I spent a mini-sabbatical at the Genetics Research Center of Hartford Hospital and Genomas Laboratory of Personalized Health, CT (2007), receiving hands-on training on pharmacogenetics and personalized medicine. Genetic Analysis for Admixture and Epidemiology Studies in Latin American Populations, University of California at San Francisco (UCSF, 2010) and Next Generation Sequencing, University of Pittsburgh (2013)

Research Experience: From 1999 to 2004, performed over 30 research projects (mostly in pharmacokinetics) and received 4 research grants. Since 2005 to date, I have been working on the pharmacogenomic assessment of Puerto Ricans in order to infer their population structure and admixture pattern, by using physiogenomic markers (PG-array). My group has completed various analyses to ascertain frequency distribution of multiple pharmacogenes in Caribbean Hispanics and also conducted pharmacogenetic association studies of cardiovascular drugs and developed a Puerto Rican-oriented DNA-guided algorithm for optimal warfarin dosing in Puerto Ricans. Since 2011, I have served as Key Activity Leader of the RCMI Center for Genomics in Health Disparities and Rare Diseases. I am a member of the RTRN Translational Research Network-Cardiovascular Cluster Scientists (2010-present) and the RIBEF project (2014).

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Biographical

Number of Publications/ Presentations: I am the author of over 50 scientific publications including reviews, book chapter and research articles in peer-reviewed journals. My work has been presented in more than 45 national and international scientific meetings.

Funding Sources: National Heart, Lung and Blood Institute (NHLBI)/ NIH Grants# HL123911 and HL110393; NICHD/ NIH Grant# 5G11HDO46326 EARDA Program; CRC infrastructure initiative Pilot Projects Award (RCRII) Grant# 5P20RR011126, Research Center in Minority Institutions (RCMI) grants from the National Center for Research Resources (2G12-RR003051) and the National Institute on Minority Health and Health Disparities (8G12-MD007600); RCMI Mentorship awards; the Puerto Rico Newborn Screening Program (PRNSP), Hartford Hospital grant #123260 and Genomas internal research and development funds.

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Pharmacogenomics in Hispanics

Overall Research Goal/ Interest

To gain a better understanding of the genetic basis for observed variability in response to cardiovascular medications in admixed Caribbean Hispanics and advance the adoption of a pharmacogenetic-guided personalized healthcare paradigm in this medically underserved Latino population. Such translational studies will pursue the interest of leapfrogging current healthcare standards in this population as well as a reduction of disparities of health in Hispanics.

Research Focus

- Cardiovascular Drugs
- Pharmacogenomics
- Admixture
- Caribbean Hispanics

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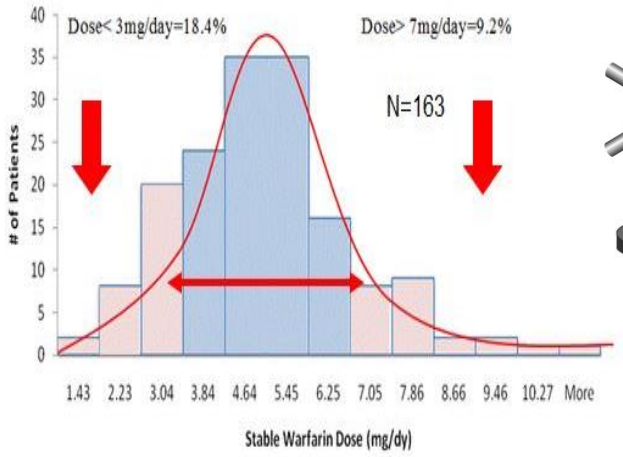
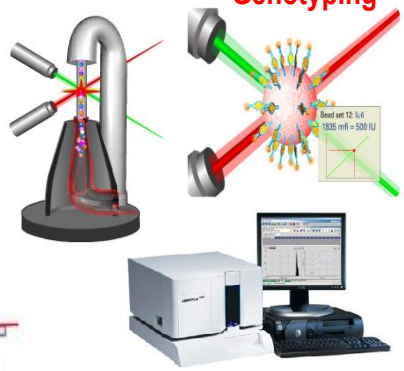
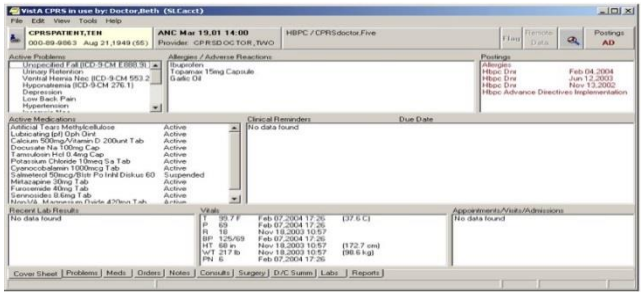
Pharmacogenomics in Hispanics:
PGt-guided Warfarin Dosing Algorithm (PGt Model) and Clinical Implementation (portal-driven)



Genotyping





Computerized Patient Record System (CPRS)

Web-based ThromboNet Tool

Dosing Algorithm for Puerto Ricans

$$\log(Dose, mg/day) = \exp\left[\begin{array}{l} 2.602 - \left(0.569 \times \frac{INR}{Dose}\right) - (0.463 \times VKORC1\,AA) - (0.153 \times VKORC1\,GA) - (0.174 \times CYP2C9) \\ - (0.272 \times PE) - (0.276 \times Amiodarone) - (0.0086 \times Age) \end{array}\right]$$

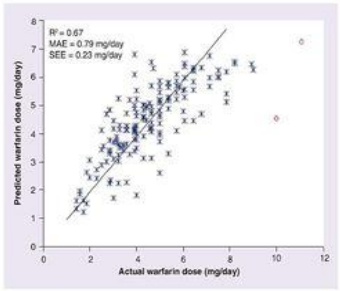
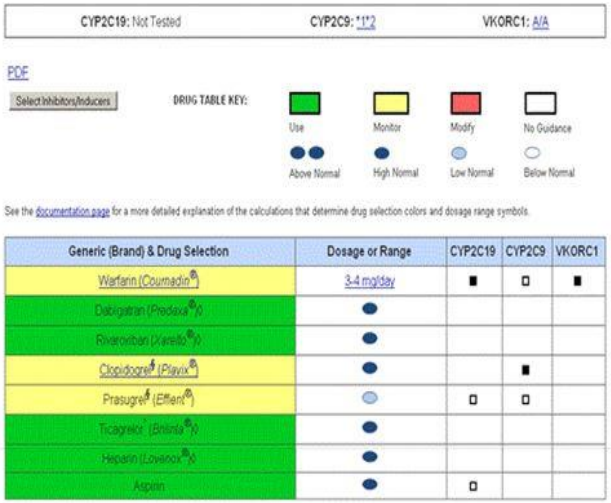
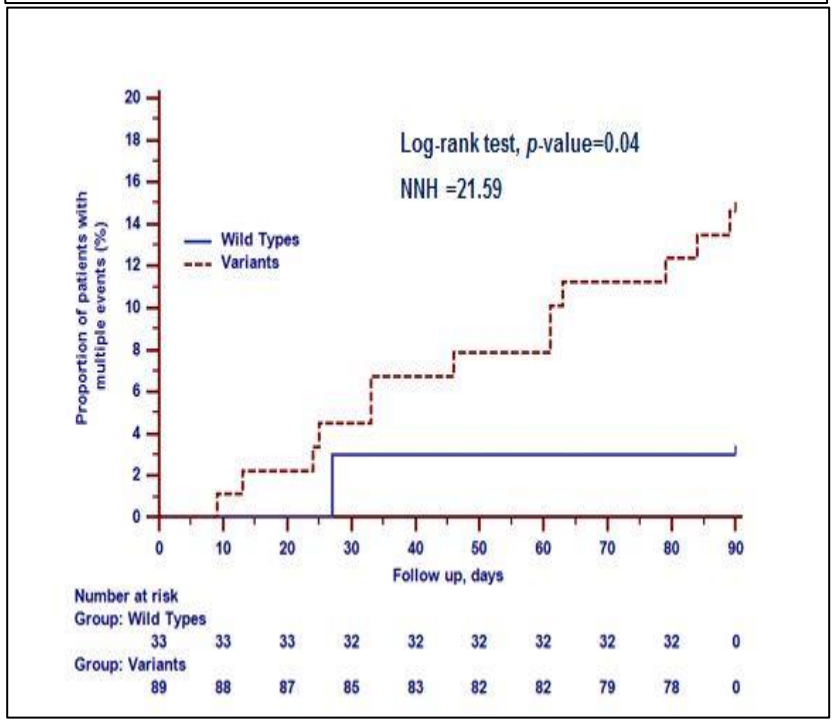


Figure 1. DNA-guided warfarin dosing algorithm in Puerto Rican patients (Veterans Affairs Caribbean Healthcare System model)

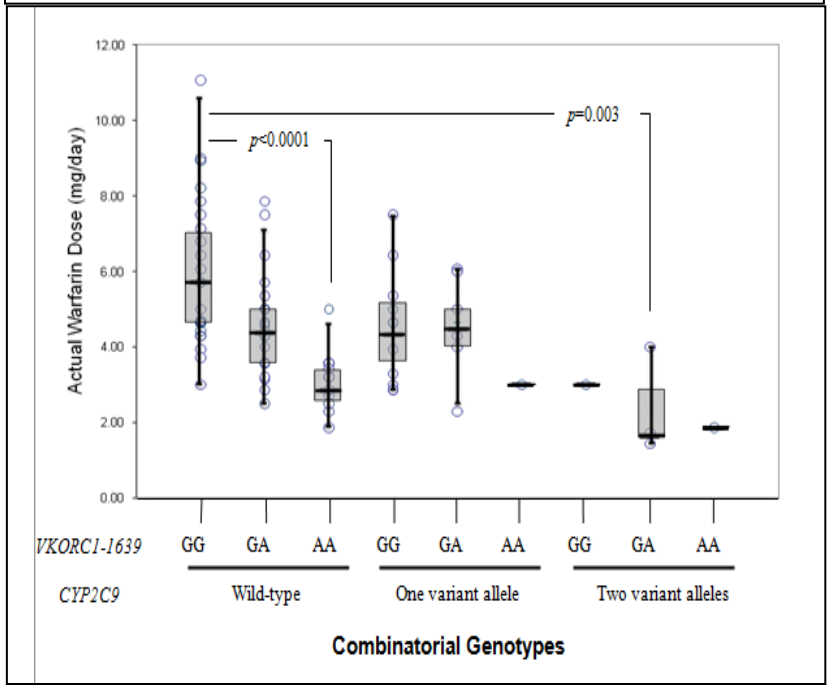


Pharmacogenomics in Hispanics:
Phenotype-Genotype Association Analysis

Survival Analysis: Safety endpoints-GNT Association in Puerto Ricans



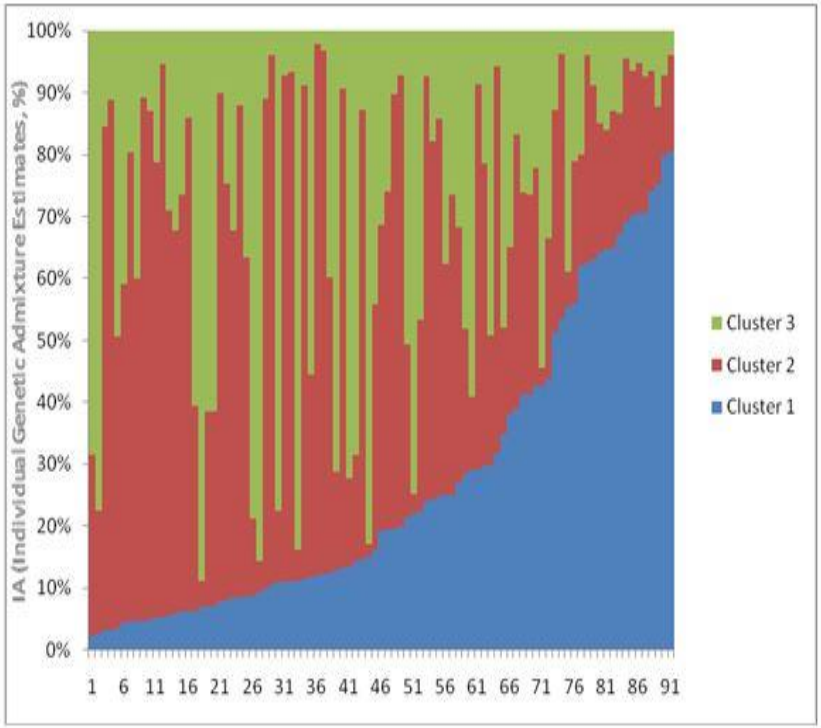
Dose-GNT Association in Puerto Ricans



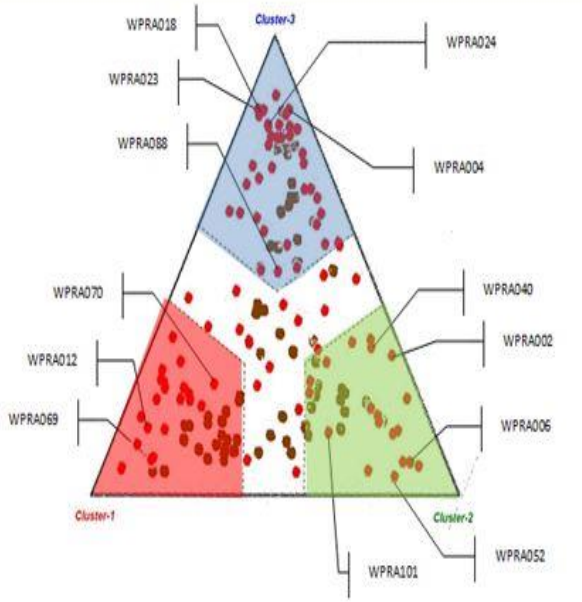
Associations between clinical outcomes and warfarin genotypes have been found in Puerto Rican Hispanics.

Pharmacogenomics in Hispanics:
A Case for Admixture-matching in Clinical PGt Studies

Degree of Genetic Admixture at Individual Level
PR Patients-Derivation Cohort



STRUCTURE-based clustering analysis



Green: Amerindians; Red: Africans; Blue: Europeans

Association between degree of Amerindian ancestry and low warfarin dose requirement: the Amerindian sector in the right-most vertex of the SRUCTURE triangle (green) showed a relatively higher proportion of patients with low-dose requirements (<3 mg/day) than the rest of the clusters (i.e., 33% vs. 19%, p<0.01).

Pharmacogenomics in Hispanics:
A Case for Admixture-matching in Clinical PGt Studies

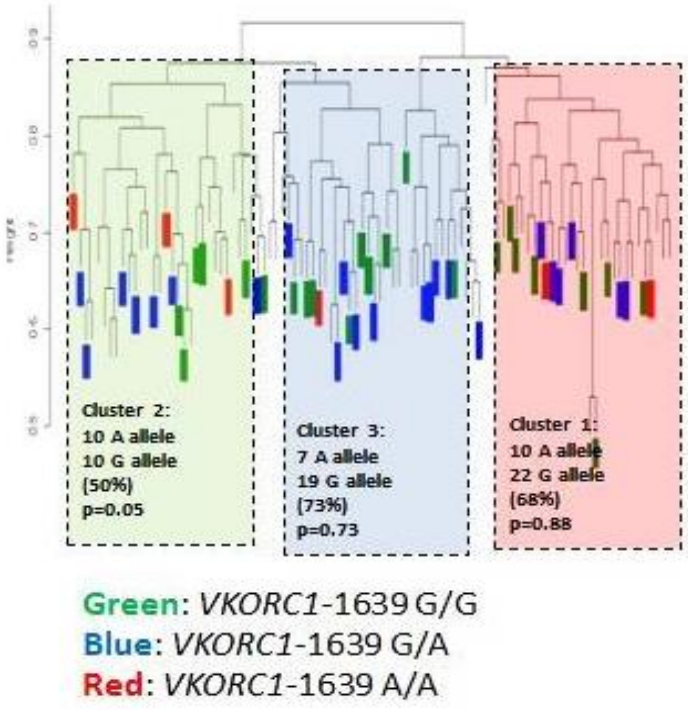


Figure 1. Individual *VKORC1* 1639 G→A genotypes, overlaid on the genetic distance dendrogram for the samples from the Puerto Rican population. Green color represents G/G genotype; whereas, blue and red colors are for the G/A and A/A genotypes, respectively. P-values were calculated by a χ2 test comparing observed allele frequencies with expected frequencies given the overall allelic ratios. The *VKORC1* SNP 1639 G→A is in high linkage disequilibrium with haplotype A , which has been associated with a significant decrease in the warfarin dose per allele.

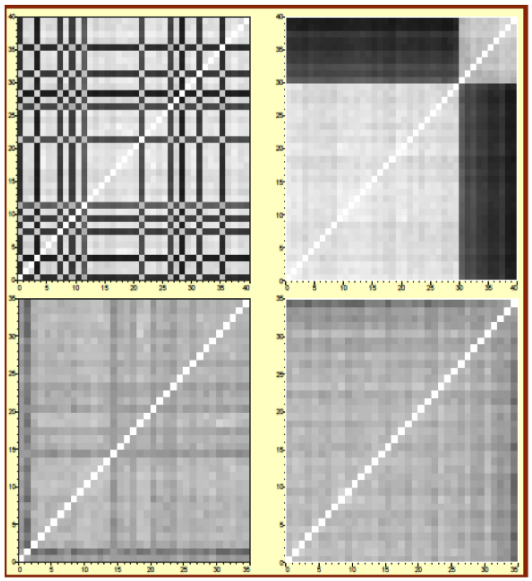
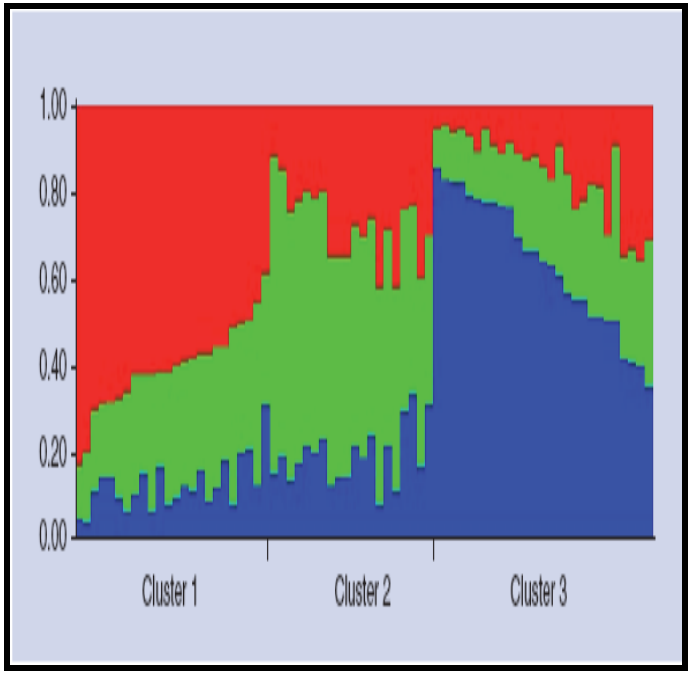


Figure 2. Genome-wide allelic dissimilarity and genomic admixture of a Puerto Rican population (n=35), as compared to a reference population from Kentucky (n=40, including European and African Americans). Plot depicts allelic dissimilarities as a distance matrix for reference (top) and Puerto Ricans (bottom). Each square represents a pair of individuals. Data are shown with samples reordered according to nearest neighbor clustering (right panels) and random order (left panels). The darker the spot, the more genetically distant the individuals are.

Pharmacogenomics in Hispanics:
Admixture as a covariate in the PGt Model



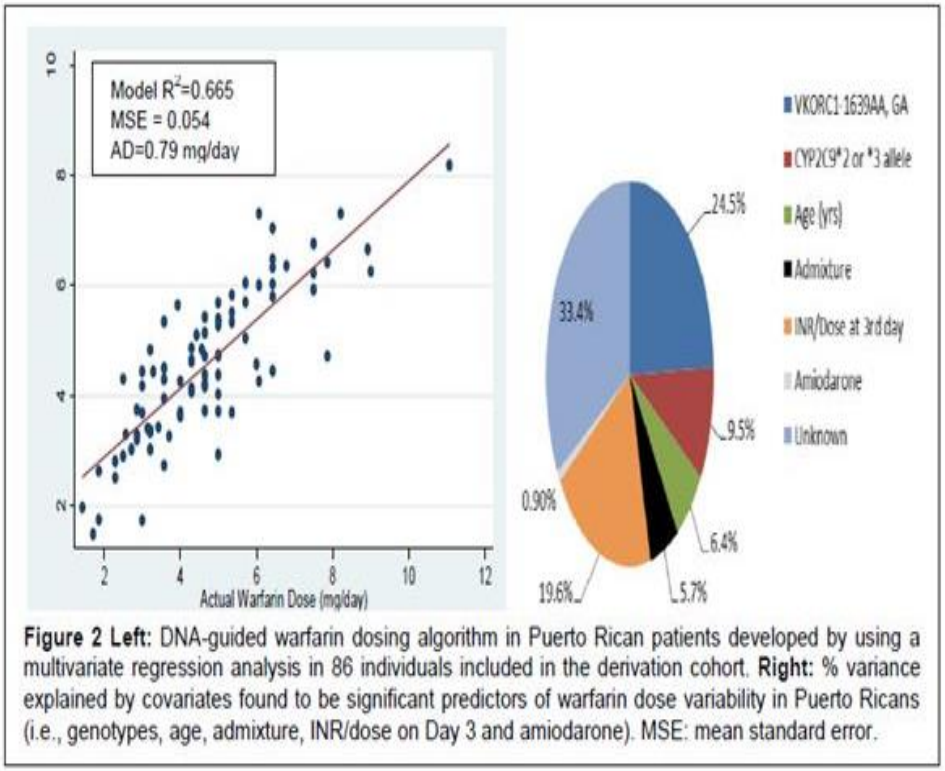


Figure 2 Left: DNA-guided warfarin dosing algorithm in Puerto Rican patients developed by using a multivariate regression analysis in 86 individuals included in the derivation cohort. **Right:** % variance explained by covariates found to be significant predictors of warfarin dose variability in Puerto Ricans (i.e., genotypes, age, admixture, INR/dose on Day 3 and amiodarone). MSE: mean standard error.

Pharmacogenomics in Hispanics:
PK-PD analysis to validate the PGt Model

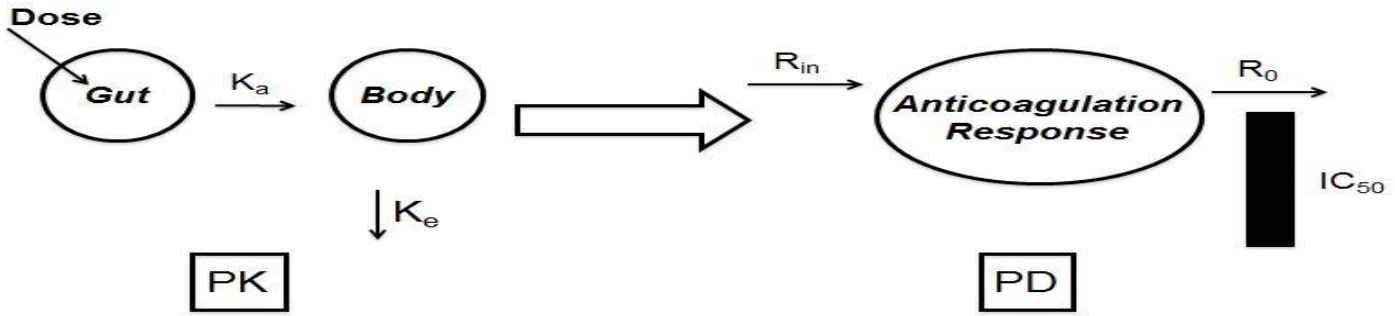


Figure 1: Schematic representation of the indirect pharmacokinetic-pharmacodynamic (PK-PD) model to be employed.
Parameter values used for simulation of warfarin levels and INR response time course during model development are the following; Ka=Absorption rate constant (1.17), Ke=Elimination rate constant (*1/*1=0.0189, *1/*2= 0.0158, *1/*n=0.0132, *2/*2=0.0130, *2/n=0.009, n/n=0.0075;where n= *3, *5 or *6) R_{in}=Input Rate (1.5), R_0=Rate of elimination (2.5), IC_{50}=half maximal inhibitory concentration (1.5), PK=Pharmacokinetic, PD=Pharmacodynamic.

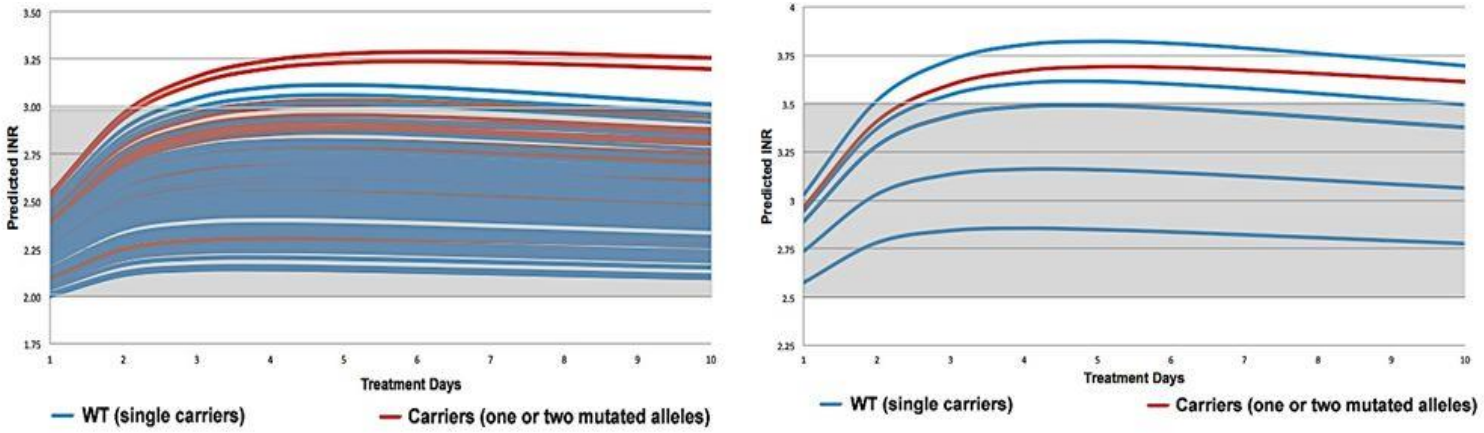


Figure 2 & 3: PK-PD simulations with WinNonlin® software to predict INR response in patients with therapy range of 2-3 (n=114) & 2.5-3.5 (n=7).

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Pharmacogenomics in Hispanics: Future Work> Sequencing

Goal: To identify and characterize missed and novel variants on the *CYP2C9* and *VKORC1* loci in warfarin-treated high-risk Puerto Rican patients.

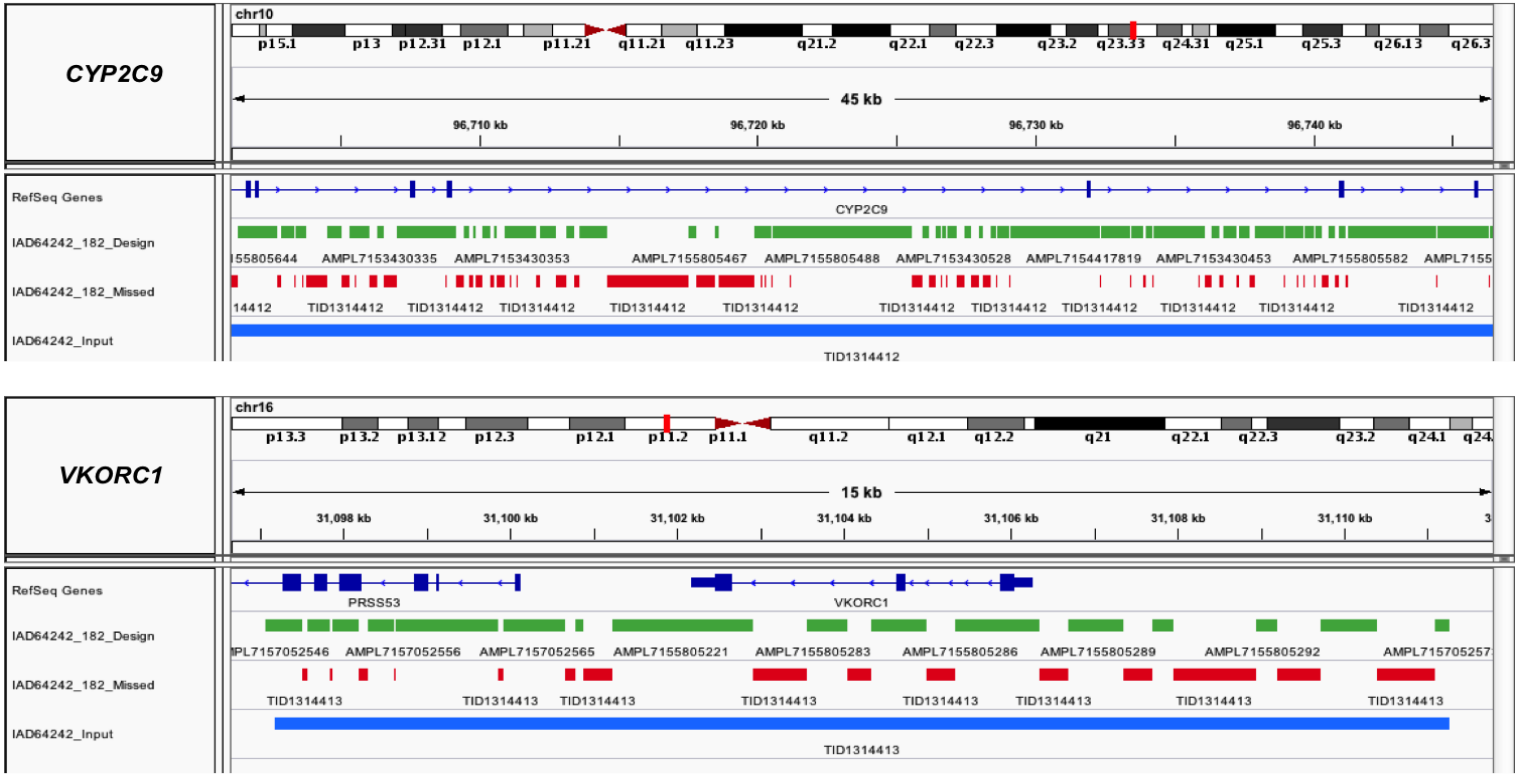

Figure 4. Illustration of the Ampliseq design in the IGV viewer for *CYP2C9* (top panel) and *VKORC1* (lower panel) and flanking regions. From top to bottom each panel shows the chromosome location (top), the gene of interest (dark blue), regions targeted by primers designed by Ampliseq Designer (green bands), missed regions (red bands) and input region (light blue continuous bands).

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Pharmacogenomics in Hispanics: Future Work> Other Goals

- Replication cohorts & mining multiple databases
- Identify informative markers that best represent the Native American (Taino)–ancestry contribution to Caribbean Hispanics
- Locus-specific ancestry (admixture) analysis
- Other Cardiovascular and Neuroendocrine conditions/drugs (Plavix, Statins, AAP-induced adverse events, etc.)

Partners in PGx Research

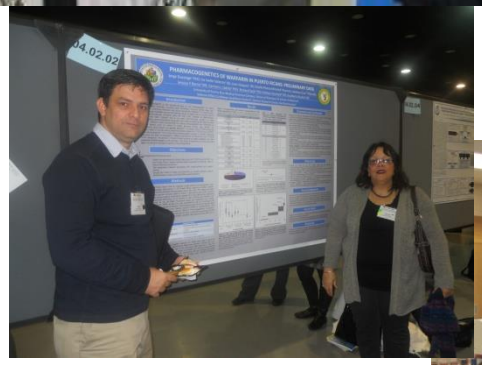
Hartford, CT
Dr. Gualberto Ruaño (GRC, Hartford)
Dr. Andreas Windemuth (GRC, Hartford)
Dr. Richard Seip (GRC, Hartford)
Dr. Hongyu Zhao (Yale University)
Mohan Kocherla (GRC, Hartford)
Krystyna Gorowski (GRC, Hartford)

San Juan, PR
Dr. Carmen L Cadilla (UPR-MSC)
MSc. Jessica Y Renta (UPR-MSC)
Dr. Iadelisse Cruz (UPR-MSC)
Prof. Rafael Garcia (UPR-MSC)
MSc. Marco Felici (UPR-MSC)
MSc. Mariely Nieves (UPR-MSC)
Dr. Pedro J Santiago Borrero (UPR-MSC)

Dr. Giselle Rivera (VACHS-San Juan)
Dr. Juan F Feliu (VACHS-San Juan)

12 PharmD, 1 PhD, 6 BSc and 6 Graduate students





Grant# HL123911 and HL110393, National Heart, Lung and Blood Institute, National Institutes of Health; Research Centers in Minority Institutions Award, G12RR-03051, from the NCRR-NIH; a Clinical Research Center Infrastructure Initiative Pilot Projects Award (RCRII) Grant No. 5P20RR011126; EARDA-Puerto Rico Newborn Screening Program and Genomas internal research and development funds.

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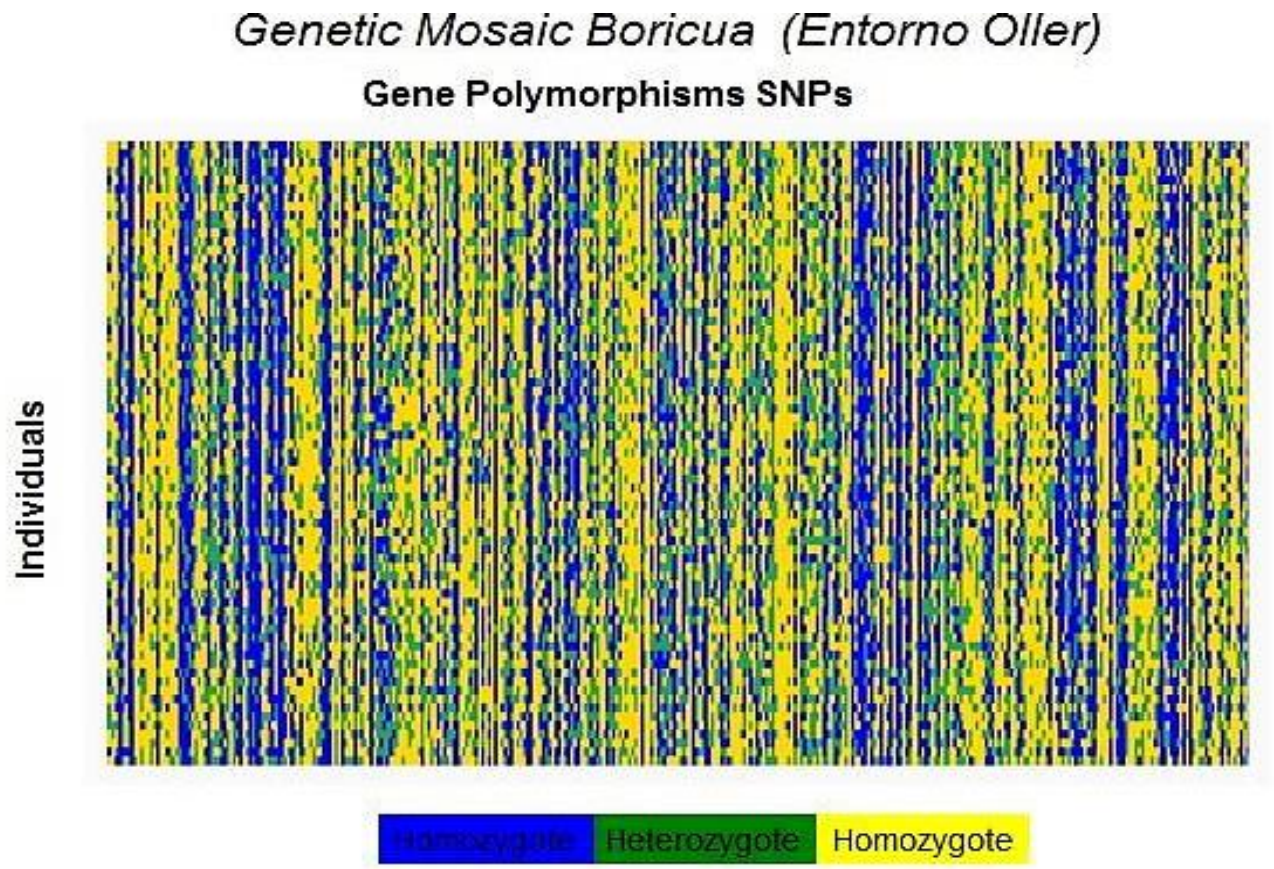
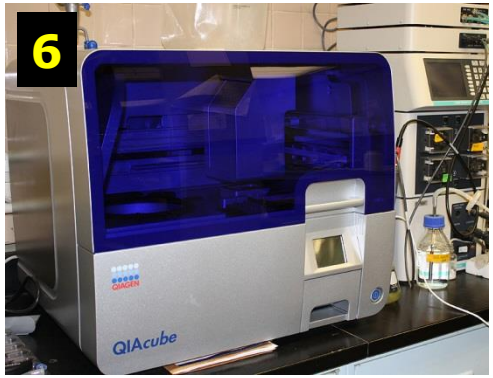
Pharmacogenomics in Hispanics: DNA Collage Puerto Ricans



Lab Instrumentation and Resources

Instruments for Genotyping and DNA Analysis

1) ABI Prism 3130 Genetic Analyzers; **2)** Affymetrix GeneChip Scanner 3000 7G systems & fluidic station; **3)** NanoDrop 8000 spectrophotometer; **4)** STEPOne™ thermo cycler & Veriti ABI Gradient Cyclers**;** **5)** Illumina BeadArray™ platform & workstation **;** **6**) Qiagen QIAcube System; **7)** FluoStar Optima Fluor-spectrophotometer, Bio Robot EZ1 workstation and Luminex 100 xMAP; **8)** Ion Torrent PGM semiconductor and Ion Proton sequencer systems



Recent/Relevant Publications

1. Valentin I, Rivera G, Nieves-Plaza M, Cruz I, Renta JY, Cadilla CL, Feliu JF, Seip RL, Ruaño G, Duconge J. Pharmacogenetic Association Study of Warfarin Safety Endpoints in Caribbean Hispanics. PR Health Sci. Journal 2014; 33:97-104. PMCID: PMC4196861
2. Duconge J, Cadilla CL. CYP2D6's functional status associated with the length of hospitalization stay in psychiatric patients: a twist in the tale or evidence that matters? Biomark Med. 2013 Dec; 7(6):913-4.
3. Orengo-Mercado C, Nieves B, Lopez L, Valles-Ortiz N, Renta Y, Santiago PJ, Cadilla CL and Duconge J. Frequencies of Functional Polymorphisms in Three Pharmacokinetic Genes of Clinical Interest within the Admixed Puerto Rican Population. J Pharmacogenom Pharmacoproteomics 2013; (4)1:113. PMCID: PMC3769800
4. Ramos AS, Seip R, Rivera G, Felici M, Alejandro-Cowan Y, Garcia R, Kocherla M, Renta J, Cruz I, Feliu JF, Cadilla CL, Gorowski K, Vergara C, Ruaño G, and Duconge J. Development of a Pharmacogenetic-guided Warfarin Dosing Algorithm for Puerto Rican Patients. Pharmacogenomics 2012; 13(16): 1937-50. PMCID: PMC3538136 [recipient of the ASHP Foundation Literature Awards]
5. Duconge J, Ruaño G. 'Generic to genetic' transition in cardiovascular and neuropsychiatric drugs: opportunity for personalized medicine. Pharmacogenomics 2012; 13(10): 1097–1100. PMCID: PMC3505752
6. Valentin II, Vazquez J, Rivera-Miranda G, Seip RL, Velez M, Kocherla M, Bogaard K, Cruz-Gonzalez I, Cadilla CL, Renta JY, Feliu JF, Ramos AS, Alejandro-Cowan Y, Gorowski K, Ruaño G, and Duconge J. Prediction of Warfarin Dose Reductions in Puerto Rican Patients based on Combinatorial CYP2C9 and VKORC1 Genotypes. The Annals of Pharmacotherapy. 2012; 46(2): 208-18. PMCID: PMC3378722

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Recent/Relevant Publications

7. Duconge J, Ruaño G. Emerging Role of Admixture in the Pharmacogenetics of Puerto Rican Hispanics. J Pharmacogenom Pharmacoproteomics 2010; (4)1:101. PMCID: PMC3515058
8. Rodriguez-Velez R, Ortiz-Rivera OJ, Bower B, Gorowski K, Windemuth A, Villagra D, Kocherla M, Seip RL, D'Agostino D, Ruaño G, and Duconge J. Exposure to Non-Therapeutic INR in a High Risk Cardiovascular Patient: Potential Hazard Reduction with Genotype-Guided Warfarin (Coumadin®) Dosing. PR Health Sci J. 2010; 29(4): 402-408. PMCID: PMC3679530
9. Duconge J, Villagra D, Windemuth A, Cadilla CL, Kocherla M, Gorowski K, Bogaard K, Renta JY, Cruz IA, Mirabal S, Seip RL, Ruaño G. CYP2C9 and VKORC1 Genotypes in Puerto Ricans: A Case for Admixture-Matching in Clinical Pharmacogenetic Studies. Clinica Chimica Acta 2010; 411:1306-1311. PMCID: PMC2903218.
10. Seip RL, Duconge J, Ruaño G. Implementing Genotype-guided Antithrombotic Therapy. Future Cardiology 2010; 6(3): 409-424. PMCID: PMC2903229
11. Duconge J, Cadilla CL, Windemuth A, Kocherla M, Gorowski K, Seip RL, Bogaard K, Renta J, Paola Piovanetti P, D'Agostino D, Santiago-Borrero PJ, Ruaño G. Prevalence of combinatorial CYP2C9 and VKORC1 genotypes in Puerto Ricans: Implications for Warfarin Management in Hispanics. Ethnicity & Disease 2009; 19(4): 390-395. PMCID: PMC2903231
12. Ruaño G, Duconge J, Windemuth A, Cadilla CL, Kocherla M, Renta J, Seip R, Santiago-Borrero PJ. Physiogenomic Analysis of the Puerto Rican population. Pharmacogenomics 2009; 10(4):565-77. PMCID: PMC2846824

Recent/Relevant Publications

13. Duconge J, Escalera O, Korchela M, Ruaño G. (2012). Clinical Implications of Genetic Admixture in Hispanic Puerto Ricans: Impact on the Pharmacogenetics of CYP2C19 and PON1, Chapter 7, In: Clinical Applications of Pharmacogenetics, Dr. Despina Sanoudou (Ed.), ISBN: 978-953-51-0389-9, InTech, March 21: pp. 151-164. DOI: 10.5772/28567
Available from: http://www.intechopen.com/books/clinical-applications-of-pharmacogenetics/clinical-implications-of-genetic-admixture-in-hispanic-puerto-ricans-impact-on-the-pharmacogenetics-
14. Seip RL, Duconge J, Ruaño G. Genotype-Guided Statin Therapy. In: Pharmacogenomic Testing in Current Clinical Practice: Implementation in the Clinical Laboratory. A.H.B. Wu and K.T.J. Yeo (eds.), Molecular and Translational Medicine series. Springer Science & Business Media (Humana Press), LLC, 2011; 1st edition, Chapter 10; pp. 155-174. doi: 10.1007/978-1-60761-283-4

Pharmacogenomics & Pharmacoproteomics Related Journals

- Journal of Molecular and Genetic Medicine
- Journal of Data Mining in Genomics & Proteomics
- Journal of Proteomics & Bioinformatics

Pharmacogenomics & Pharmacoproteomics Related Conferences

- 2nd International Conference on Predictive, Preventive and Personalized Medicine & Molecular Diagnostics
- 4th International Conference on Proteomics & Bioinformatics
- 2nd International Conference on Genomics & Pharmacogenomics

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