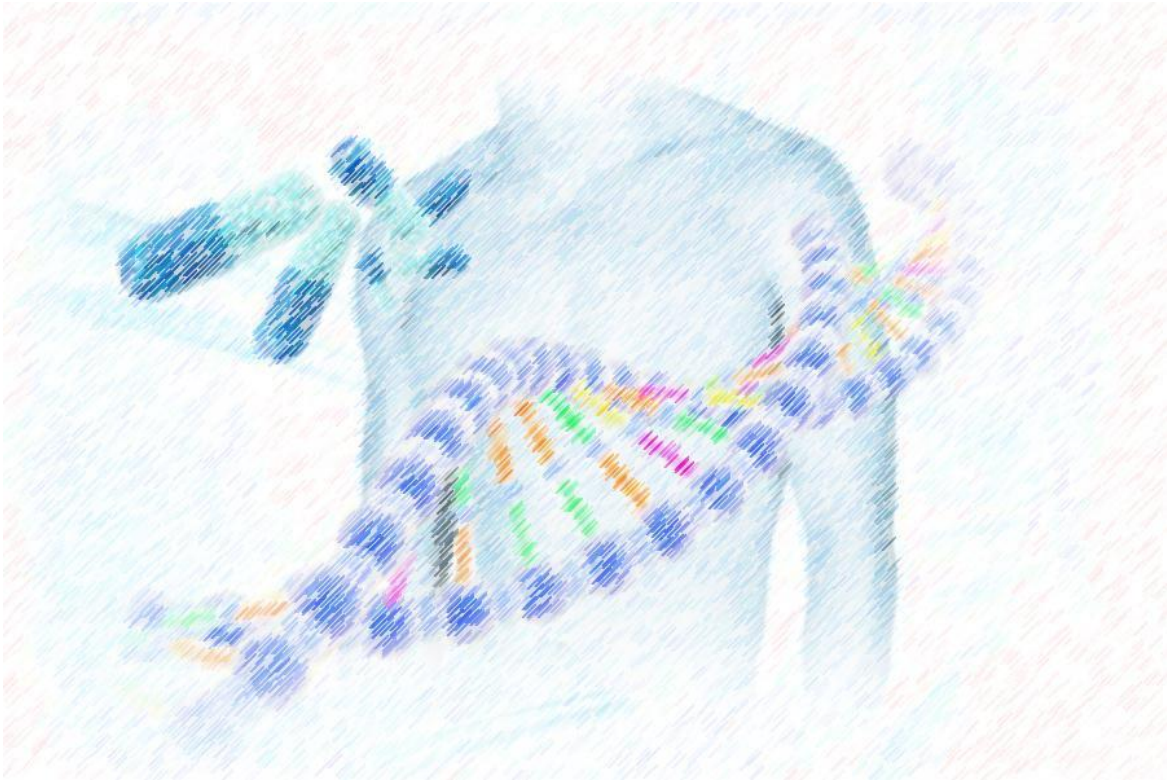
Instituto de Investigación Sanitaria La Fe



Plataforma de Farmacogenética

Dra. María José Herrero
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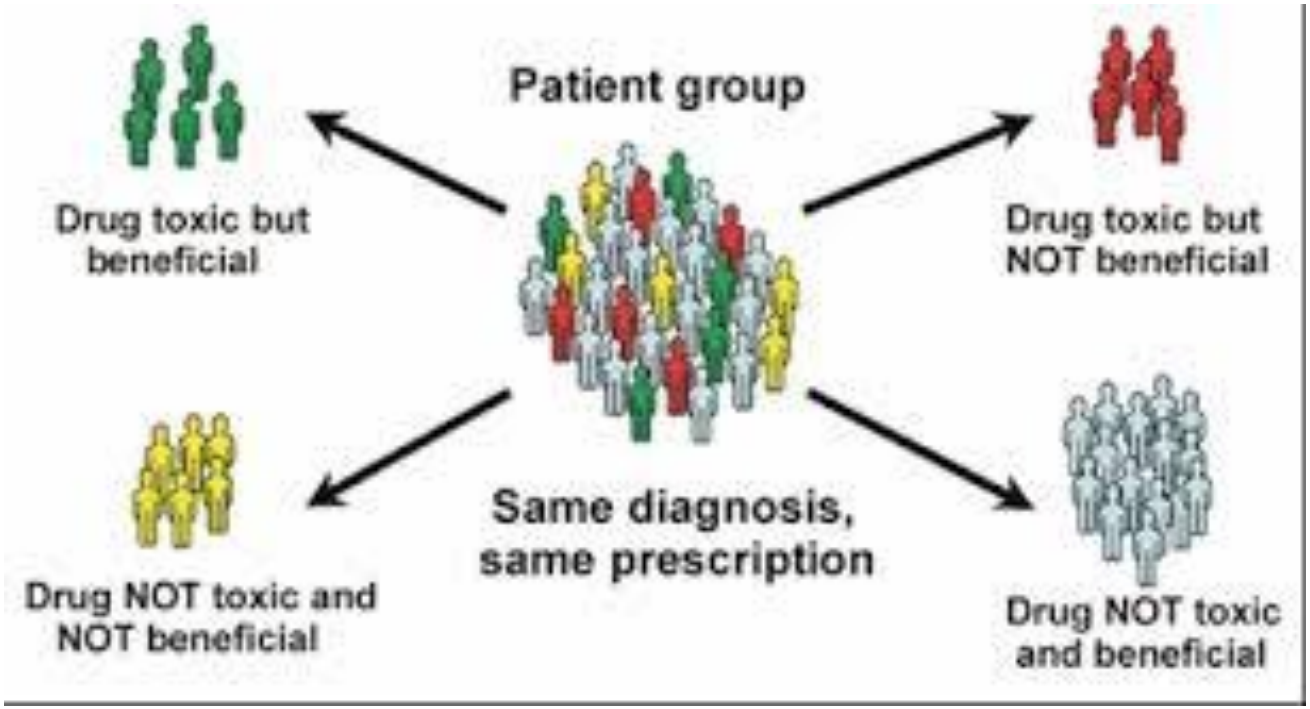
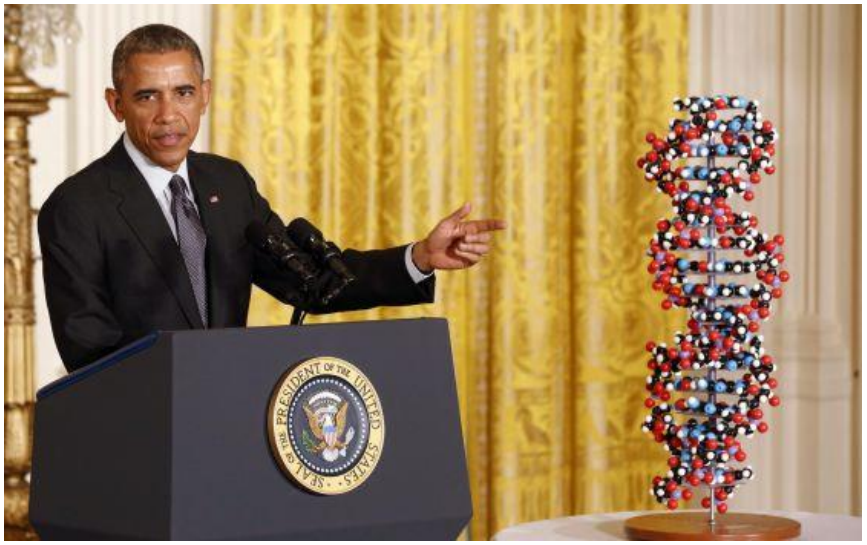
Because the “One Size Fits All” concept has never been TRUE …

… we need Personalised Precision Medicine

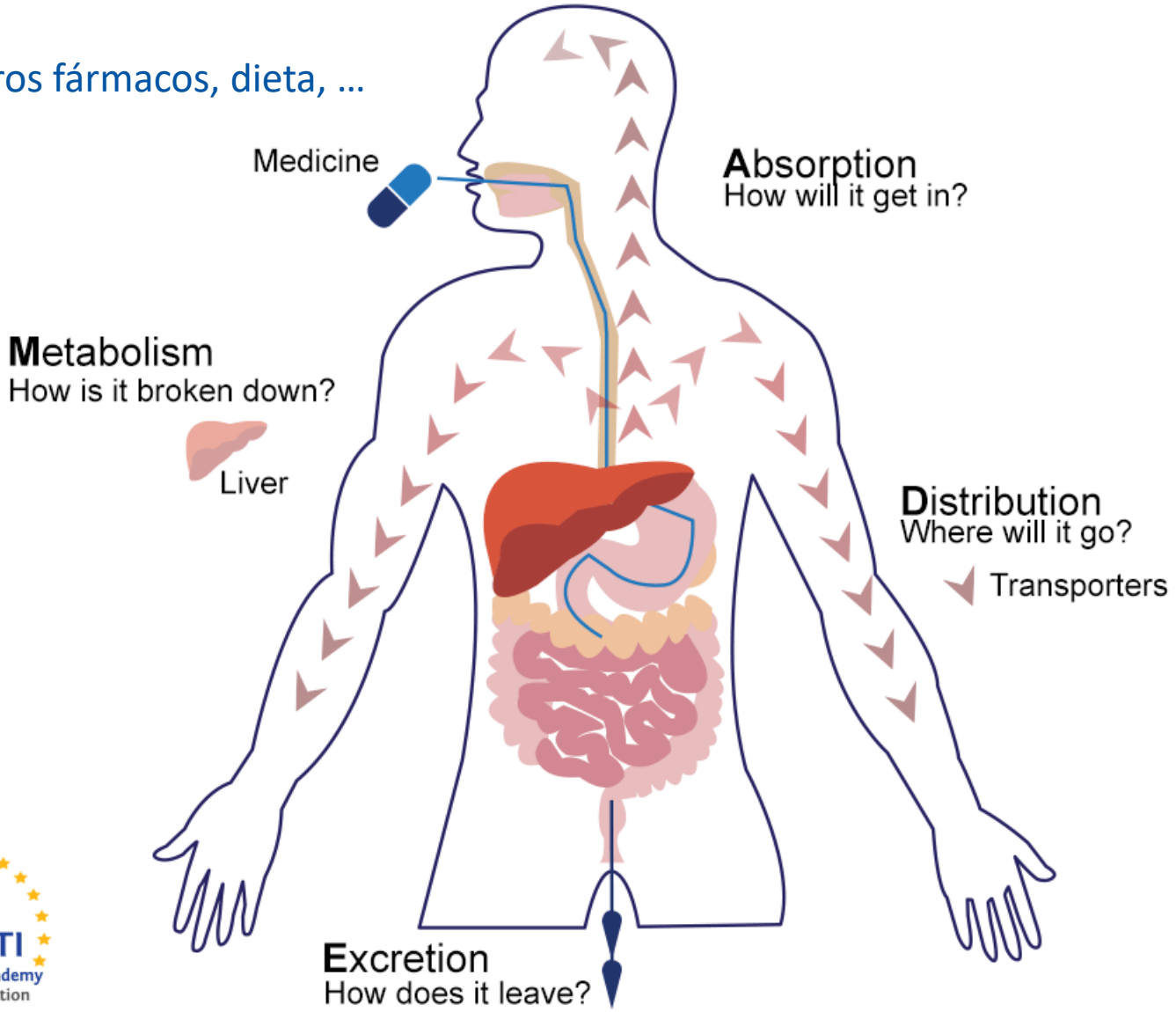




- **Farmacogenética:** es uno de los pilares de la *medicina personalizada*
  - Estudia los aspectos genéticos relacionados con la **variabilidad** de la respuesta a los medicamentos en individuos o poblaciones, basados en el **ADN**
  - Pretende predecir, en función de la dotación genética del paciente, **con qué medicamento y/o a qué dosis** se ofrece mayor beneficio terapéutico y/o menor probabilidad de desarrollar una reacción adversa

DISEÑO DE PANELES EN BASE A:

Farmacocinética (ADME)
Farmacodinamia
Interacciones: otros fármacos, dieta, …



Modified from

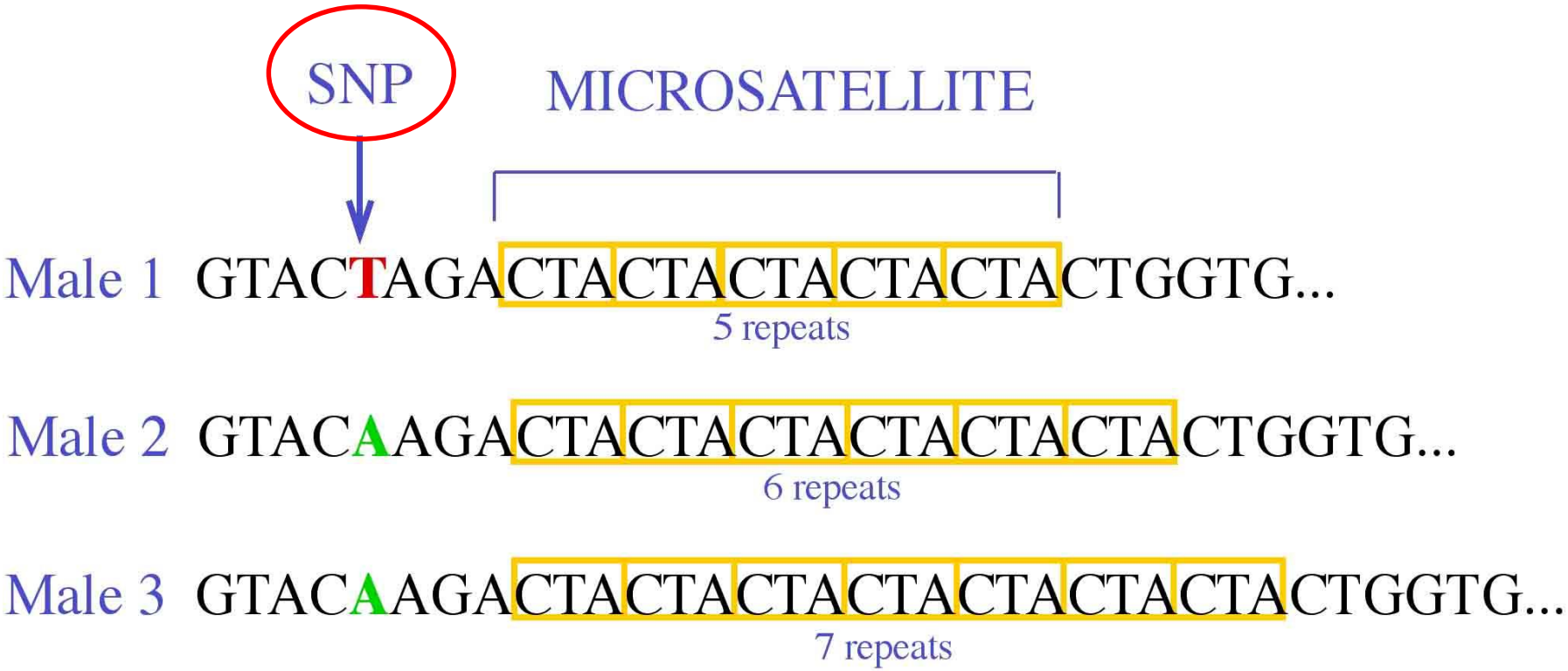
EUPATI
European Patients' Academy on Therapeutic Innovation
www.eupati.eu

Instituto de Investigación Sanitaria La Fe

PHARMACOgenetics

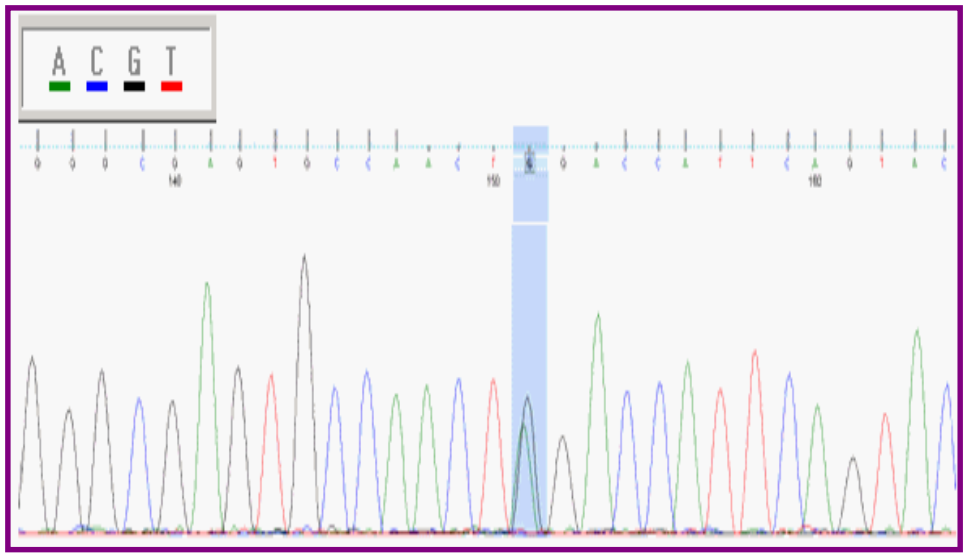
Tailored
Stratify
Personalised medicine
Treatment
Drug
International Consortium Personalised Medicine
Chronic Disease
Multiple
Aging Population
HIV, Tuberculosis, Hepatitis C

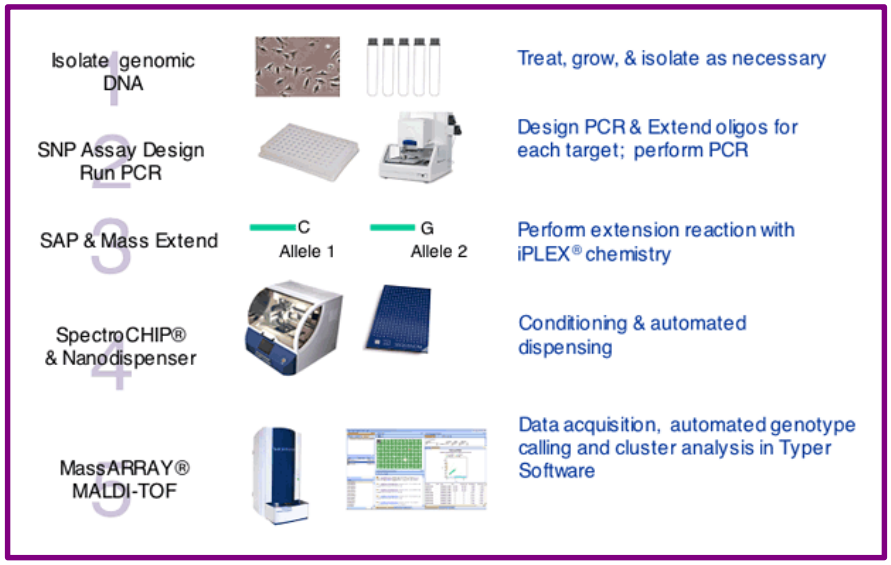
Polimorfismos Genéticos



Metodología:

Secuenciación vs Sequenom





-Secuenciación es más exhaustiva y mucho más cara:

~1gen/paciente

Aprox. 500€/paciente

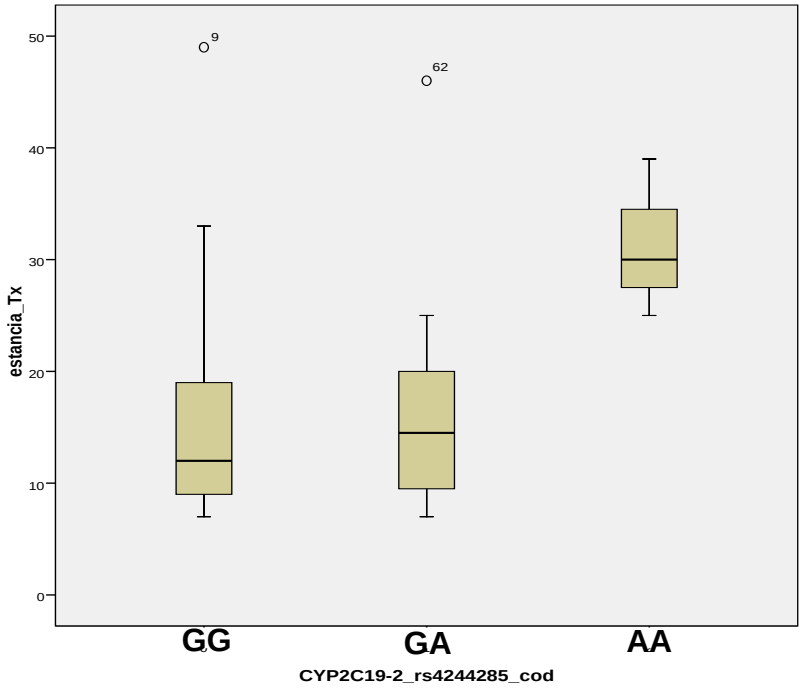
Número de datos??

-Mass Array-Sequenom (Genotipado por espectrocopía de masas MALDI-TOF) analiza fragmentos cortos específicos conocidos y es mucho más económica:

~40polimorfismos/40pacientes: 1.600datos

Aprox. 100€/paciente

Un ejemplo: Trasplante Renal
Farmacogenética + Interacciones FG

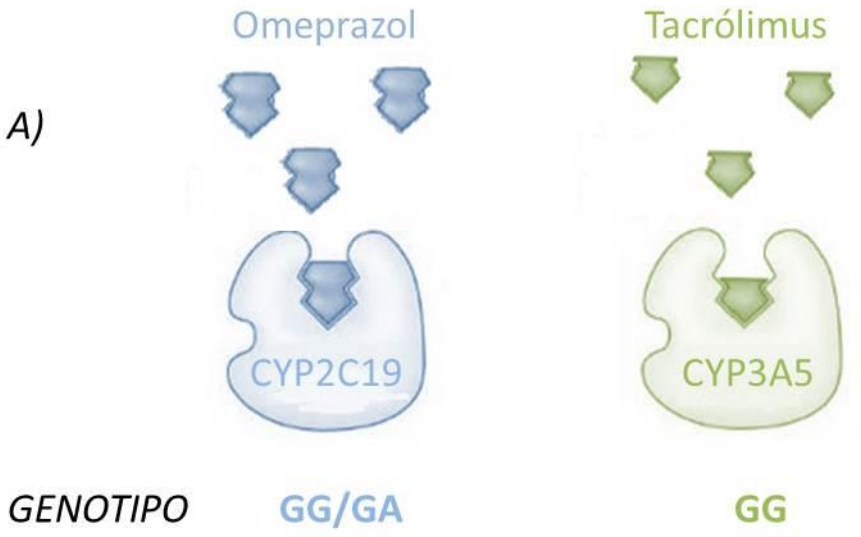


Estancia hospitalaria durante el trasplante, en función del genotipo en el SNP **rs4244285 de CYP2C19**

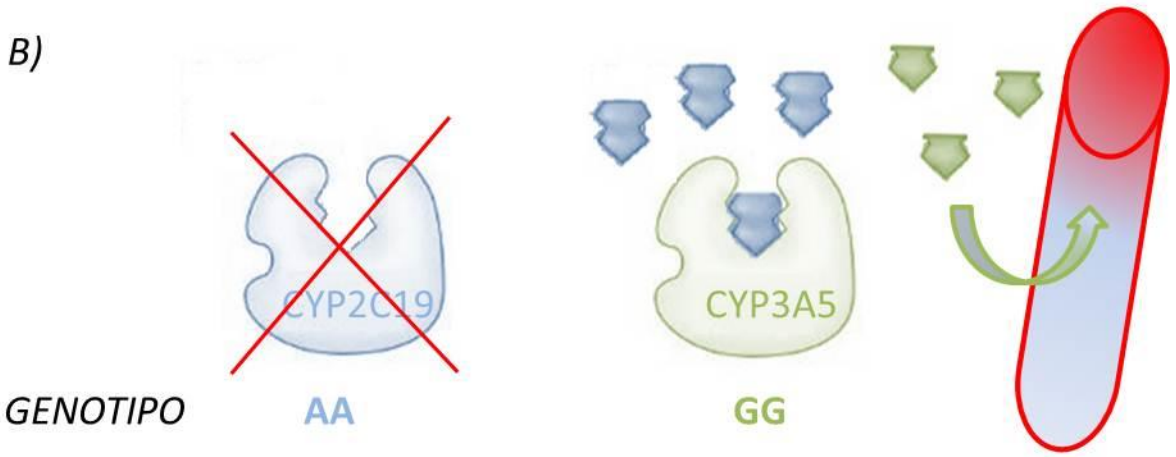
Estancia (días)	GG (n=51)	GA (n=20)	AA (n=4)
Media	**15,00**	**16,20**	**31,33**
IC 95	12,47-17,53	12,08-20,32	13,71-48,96
Mediana	**12,00**	**14,50**	**30,00**
Desv. típ.	8,799	8,806	7,095
Mínimo	7	7	25
Máximo	49	46	39

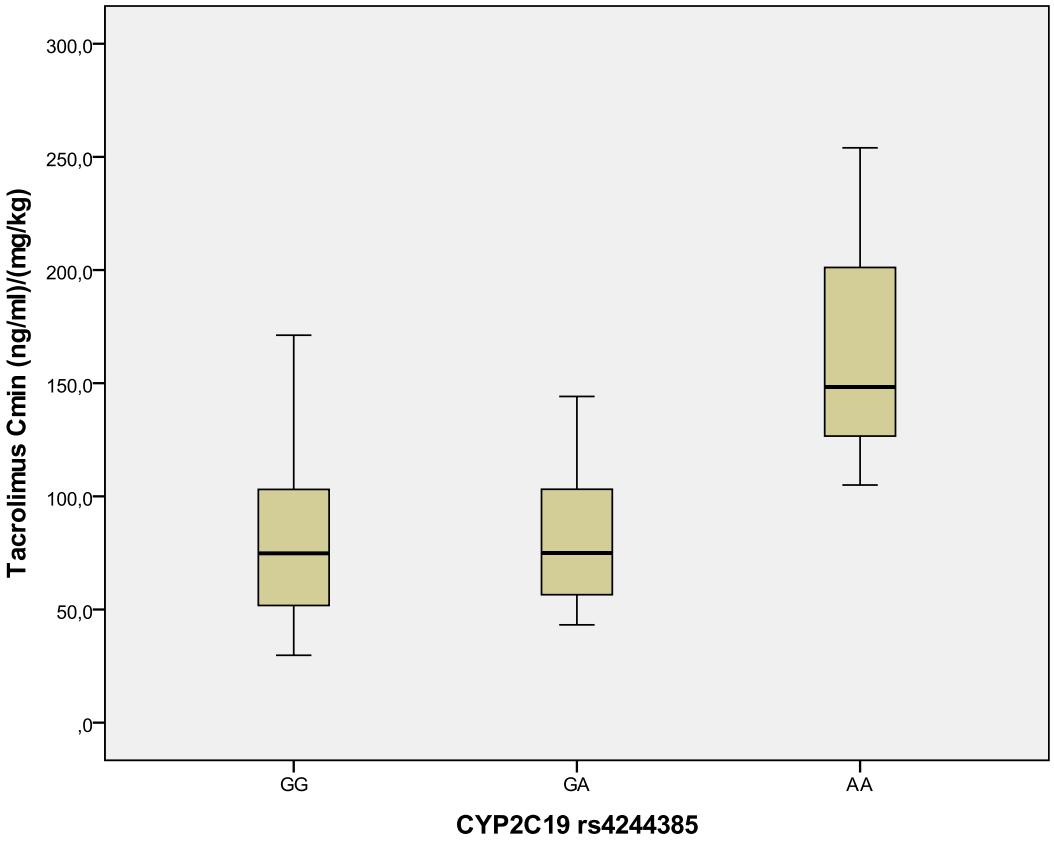
AA duplica la estancia hospitalaria en el trasplante renal

En A) las variantes en el rs4244285 de CYP2C19 tienen actividad normal, omeprazol es metabolizado por su enzima preferente y tacrólimus por el suyo mientras que



en B), la variante AA implica una menor funcionalidad del enzima, lo que provoca un aumento de omeprazol no metabolizado que pasará a presentar **inhibición competitiva en la metabolización de tacrólimus por CYP3A5.** El efecto final es una menor metabolización de tacrólimus con un aumento de sus niveles en sangre





Niveles de tacrólimus durante la primera semana postrasplante, en función del genotipo en el SNP **rs4244285 de CYP2C19**

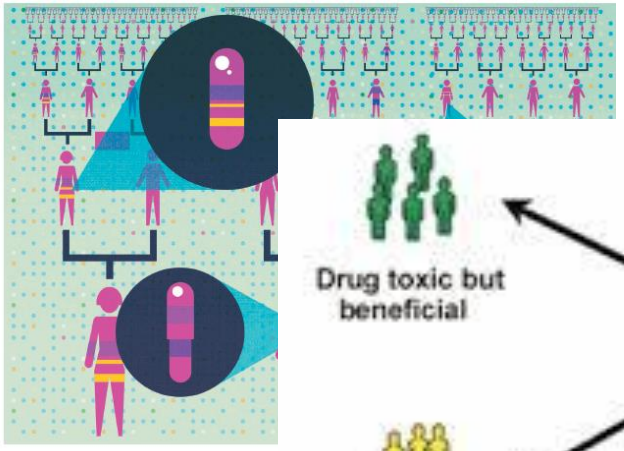
Se confirma el **aumento de niveles de tacrólimus** en sangre en los pacientes AA en rs4244385 de CYP2C19.

Además los 4 pacientes AA presentaron disfunción del injerto (necrosis tubular aguda).

Bosó et al. DrugMetabDispos 2013

¿Cuántos fármacos habrán sido descartados en sus respectivos ensayos clínicos, sólo por no haberse probado en la población adecuada?

OUTLOOK PRECISION MEDICINE



PHARMACOGENETICS

The right dru

Personalized prescribing is gaining momen become standard clinical practice?

BY LIAM DREW

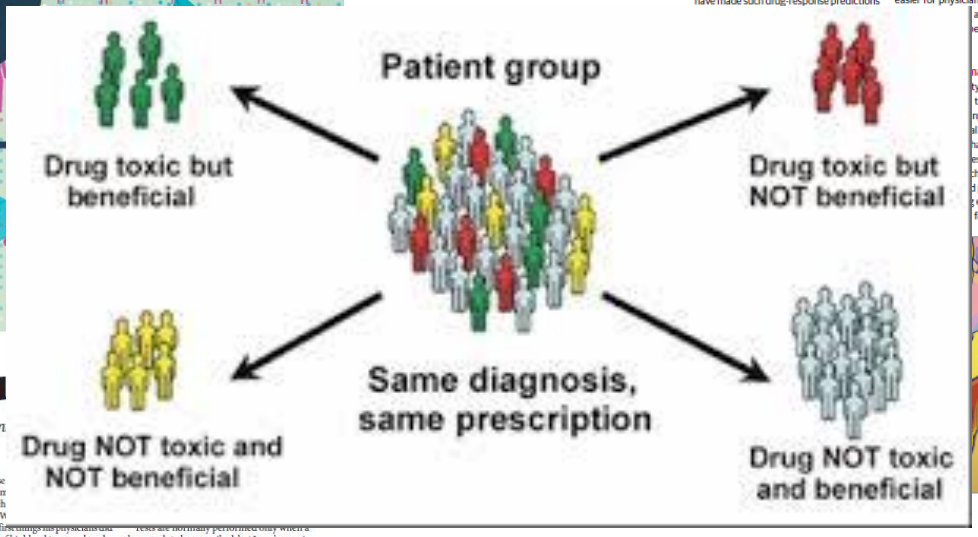
For ten-year-old leukaemia patient Jason Saunders, the usual chemotherapy was not going to work. Given the standard drug treatment, there was a strong chance that toxic metabolites would build up in his body and make him sick, requiring a break in his therapy that would allow the cancer to return.

This is because Jason is one of the 10% of Caucasians with a genetic variation that reduces his ability to metabolize thiopurines, the drugs most commonly used to treat acute lymphoblastic leukaemia. Rather than having two high-activity copies of the *TPMT* gene that produces the enzyme responsible for metabolizing these

Luckily for him Children's Research nessee, knew that. W cancer, one of the first things his physicians did was take a sample of his blood to assess how he might respond to the drugs. As a result, Jason was given a lower dose of thiopurines than normal, and he tolerated the therapy without needing a break. He is now in remission.

Testing leukaemia patients for their *TPMT* status is one of the most common examples of treatment being tailored to match patients' genetics, so robustly does it predict the likelihood of adverse effects from thiopurines. The test is now mandatory when starting this type

tests are normally performed only when a drug needs to be prescribed, but Jason's experience was different. Instead of testing only his *TPMT* status, he was screened for variability across a host of genes involved in various drug responses, as part of the hospital's PGEN4Kids scheme. The results were then incorporated into his health records. If he is ever prescribed another drug for which those genes can predict an adverse response, the information will be presented to his doctor immediately. The choice of which drug to use, and at what dose,



Medical News & Perspectives

Getting Pharmacogenomics Into the Clinic

Jennifer Abbasi

What if there were a way to know if a depressed patient would respond to an antidepressant—before it was prescribed? Or to predict a bleeding event from an antiplatelet therapy? In recent years, advances in genetic testing have made such drug-response predictions

for clinical implementation at the University of Chicago's Center for Personalized Therapeutics.

In the meantime, major efforts are under way to prove that pharmacogenomic tests have clinical utility and to make it easier for physicians to choose these tests

act on the results, trans- etter outcomes for their

nacogenomics Work?

y affects essentially ev- the human genome and ng to affect genes whose l for drug response," said harmD, chair of the phar- es department at St Jude ch Hospital. l pharmacogenes encode enzymes, and each indi- for a particular gene can

be categorized into 1 of 5 phenotypes that describe the enzyme's activity—ultrarapid metabolizer, rapid metabolizer, normal metabolizer, intermediate metabolizer, and poor metabolizer—Nutescu explained.

Other genes encode the enzymes that are the site of action where drugs exert their effects; patients with variations in these genes may be more sensitive or resistant to certain drugs than normal.

Knowing this information can help clinicians choose the right medication or dose for a patient.

A patient who has a genetic variant associated with slow metabolism of the drug thinner warfarin, for example, might experience major bleeding on a standard dose. In contrast, a patient with a variant associated with fast warfarin metabolism might not get any benefit from the standard dose, putting them at greater risk of a major stroke or thromboembolism.