Medicina de Precisión en enfermedades infecciosas. Farmacogenómica de la Tuberculosis.

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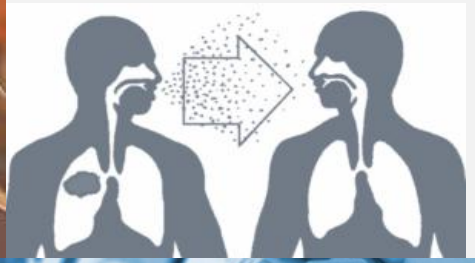
Unidad de Investigación Traslacional

ALAG 2019
6 TO 9 OCTOBER
MENDOZA, ARGENTINA
Genome architecture: its expression in phenotypes and populations
XVII Latin American Congress of Genetics,
XLVII Argentine Congress of Genetics,
LII Annual Meeting of the Society of Genetics of Chile,
VI Congress of the Uruguayan Society of Genetics,
V Latin American Congress of Human Genetics and
V Latin American Symposium of Cytogenetics and Evolution

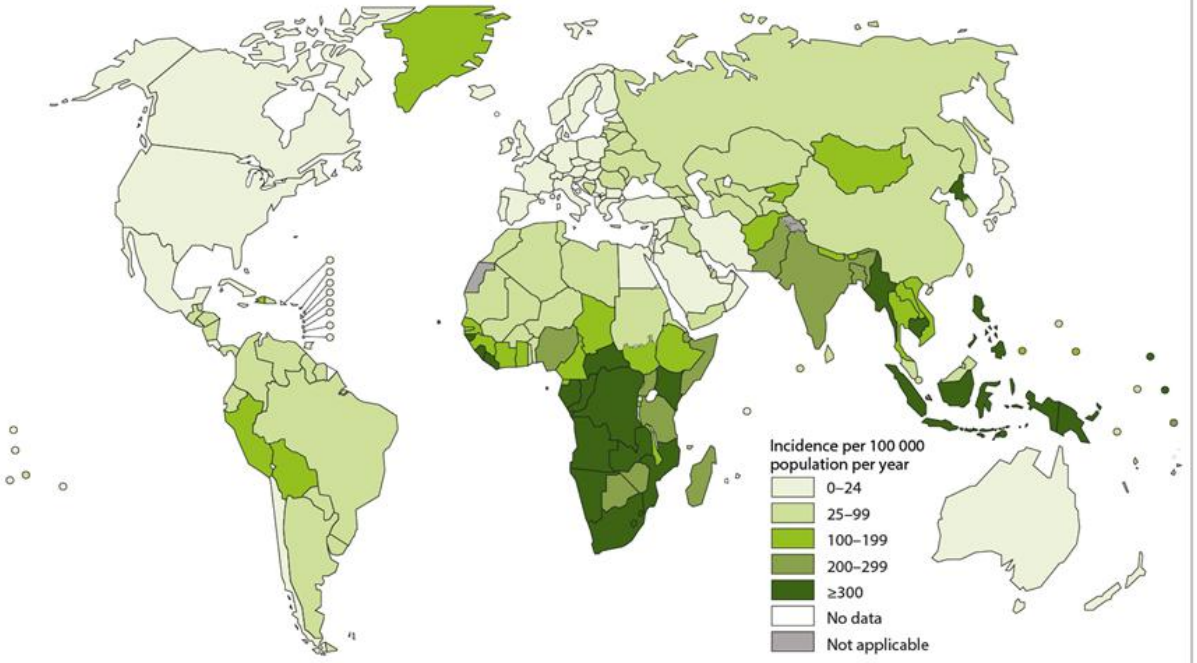
Hospital de Infecciosas
Francisco J. Muñiz




Fotografía de Vanguardia Liberal


Lowered Immunity

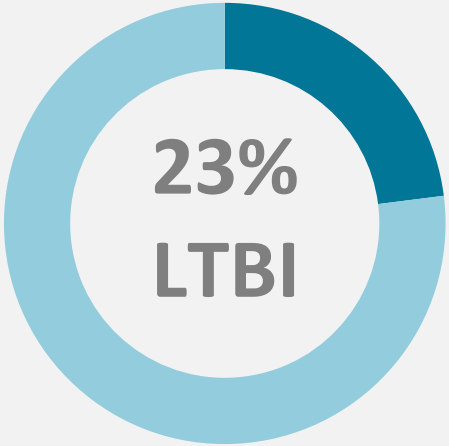
Estimated TB incidence rates, 2017



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: *Global Tuberculosis Report 2018*. WHO, 2018.

World Health Organization



10 M

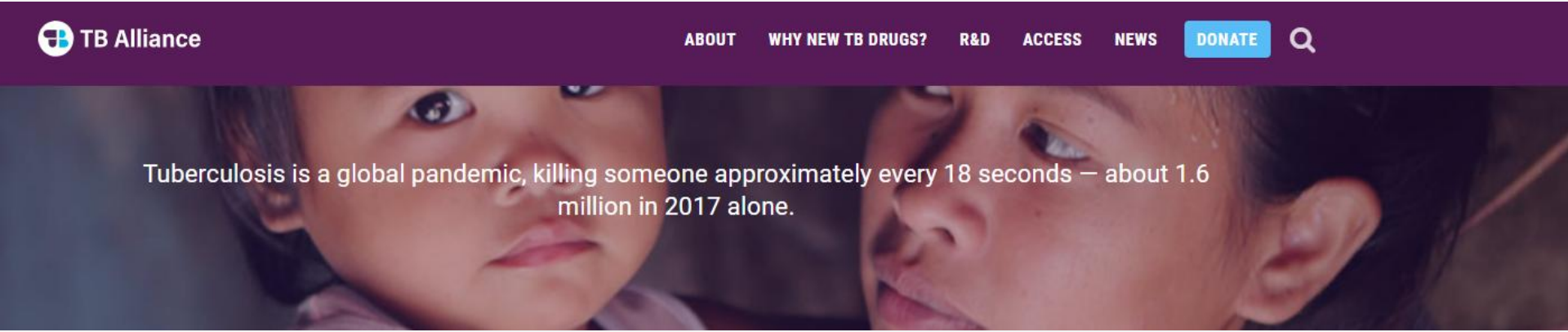
de casos nuevos de tuberculosis.

9°

causa mundial de muerte.

1°

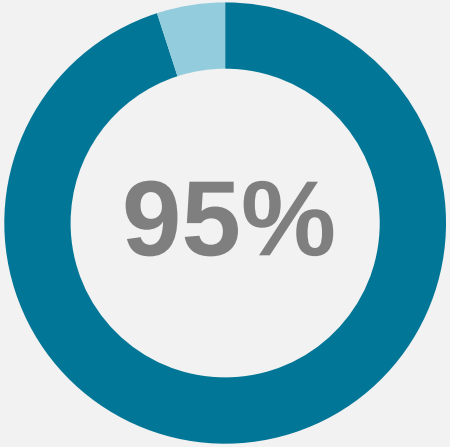
causa de muerte por enfermedades infecciosas.



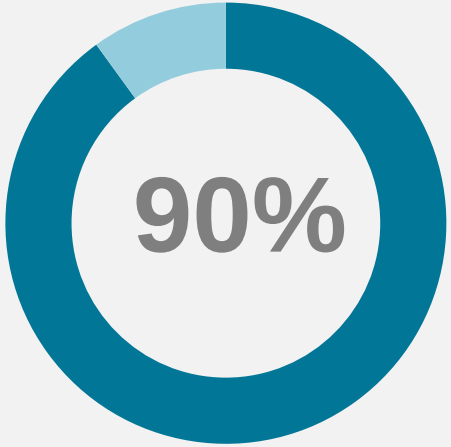
World Health Organization. Global tuberculosis report 2018. 20th ed. Geneva: World Health Organization; 2018.

2015

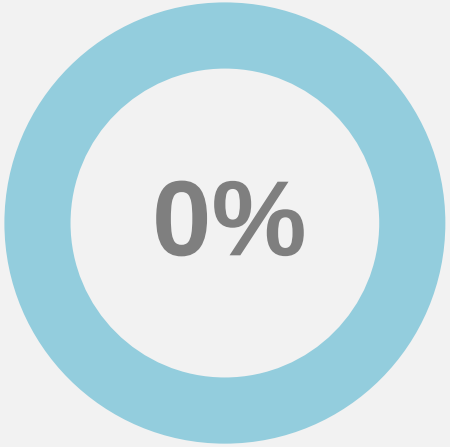
2035



Reducción de muertes por TB.



Reducción los casos nuevos

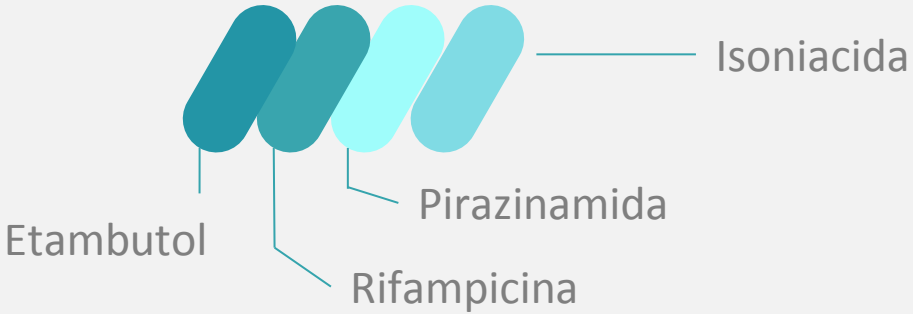


Gastos a las familias.

TRATAMIENTO DE LA TUBERCULOSIS

La totalidad de pacientes con tuberculosis recibe el mismo esquema de tratamiento.

- Fase intensiva (2 meses)



puede reducir en un 90% el riesgo a desarrollar una TB activa si se toma durante 9 meses.

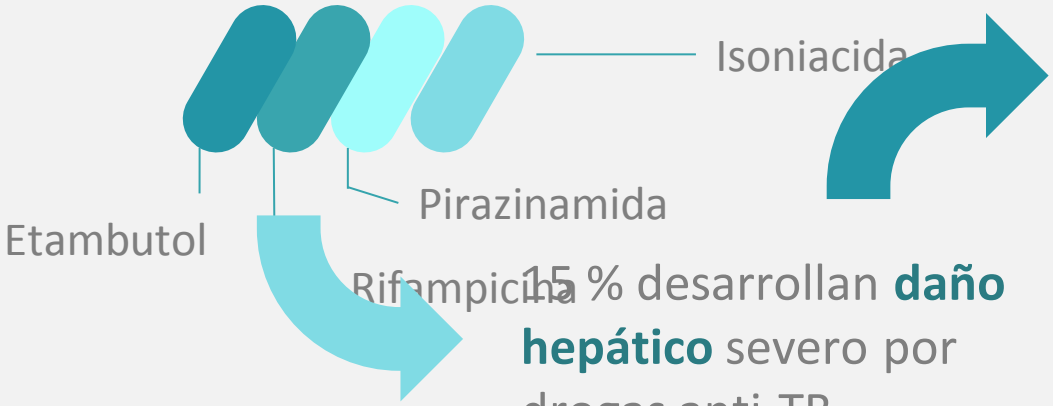
La terapia estándar actual para los casos de la **ITBL y profilaxis.**

- Fase consolidación (4-7 meses)

CDC. Latent Tuberculosis Infection: A Guide for the Primary Health Care. 2013

TRATAMIENTO DE LA TUBERCULOSIS

- Fase intensiva (2 meses)



15 % desarrollan **daño hepático** severo por drogas anti-TB.

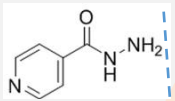
- Potencialmente fatal
- Falta de adherencia
- Más contagios
- Aumento de resistencia antibiótica
- Más estudios médicos
- Más días de internación

O'Connell TM, Watkins PB. The application of metabonomics to predict drug-induced liver injury. Clinical pharmacology and therapeutics. 2010;88(3):394-9.

Varios estudios han asociado a la isoniacida como la principal responsable de hepatotoxicidad.

- **Huang YS, *et al***. *Journal of the Chinese Medical Association : JCMA. 2014;77(4):169-73.*
- **Yamada S, *et al*.** Pharmacogenomics. 2009;10(9):1433-45.
- **Saukkonen JJ, *et al*.** *American journal of respiratory and critical care medicine. 2006;174(8):935-52.*
- **Nolan C.M., *et al*.** JAMA. 1999;281:1014–1018.
- **Boelsterli U.A., *et al*.** J Gastroenterol Hepatol. 2014;29:678–687
- **Centers for Disease Control and Prevention (CDC)** Severe isoniazid-associated liver injuries among persons being treated for latent tuberculosis infection—United States, 2004–2008. MMWR Morb Mortal Wkly Rep. 2010;59:224–229.
- **Black M., *et al*.** Gastroenterology. 1975;69:289–302. [PubMed] [Google Scholar]
- **Maddrey W.C., *et al*.** Ann Intern Med. 1973;79:1–12.

METABOLISMO DE ISONIACIDA



Isoniacida

Amidasa

Hidracina

NAT2

Acetil-hidracina

NAT2

Diacetil-hidracina

NAT2

Acetil-isoniacida

Amidasa

CYP2E1

Metabolitos Hepatotóxicos

GSTs

Detox

[Solución propuesta] —— Detectar a los pacientes sensibles ANTES de medicarlos.

Esquema de tratamiento GLOBAL

Esquema de tratamiento PERSONALIZADO

NAT 2

191G>A, *14
282C>T, *13
341T>C, *5
481C>T, *11
590G>A, *6
803A>G, *12
857G>A, *7

CYP2E1

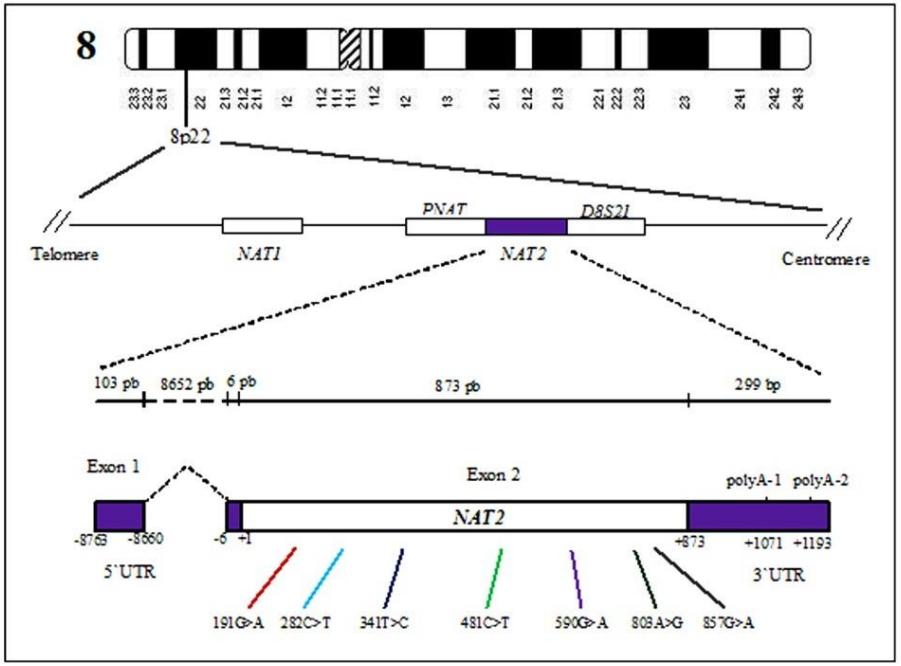
CYP2E1 Rsa/Pst1
CYP2E1 DraI
CYP2E1 VNTR

GSTs

GSTM1 null
GSTT1 null

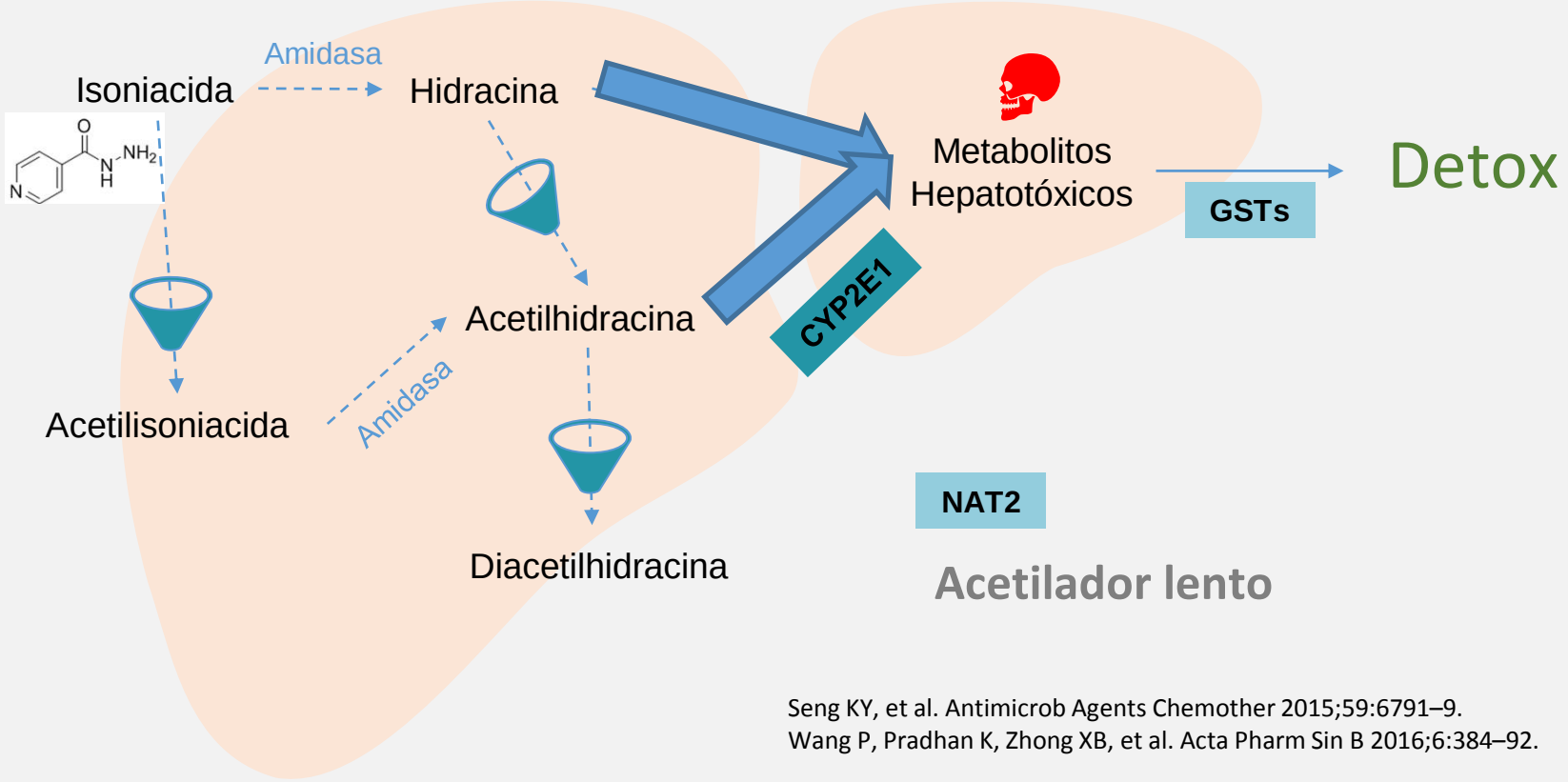
NAT 2

191G>A, *14
282C>T, *13
341T>C, *5
481C>T, *11
590G>A, *6
803A>G, *12
857G>A, *7



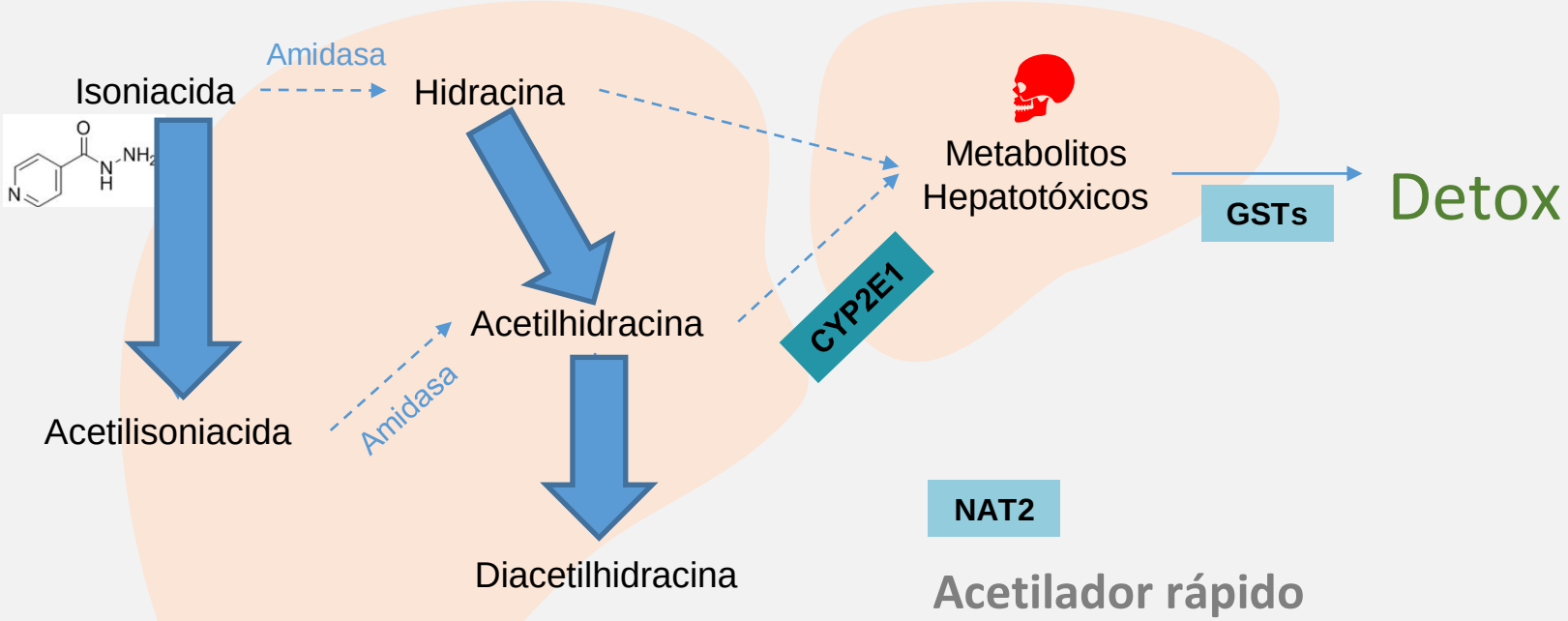
Acetilador rápido (AR)
Acetilador Intermedio (AI)
Acetilador lento (AL)

METABOLISMO DE ISONIACIDA



Seng KY, et al. Antimicrob Agents Chemother 2015;59:6791–9.
Wang P, Pradhan K, Zhong XB, et al. Acta Pharm Sin B 2016;6:384–92.

METABOLISMO DE ISONIACIDA



Seng KY, Hee KH, Soon GH, et al. Population pharmacokinetic analysis of isoniazid, acetylisoniazid, and isonicotinic acid in healthy volunteers. Antimicrob Agents Chemother 2015;59:6791–9.
Wang P, Pradhan K, Zhong XB, et al. Isoniazid metabolism and hepatotoxicity. Acta Pharm Sin B 2016;6:384–92.

Toxicol Rep. 2016; 3: 826–831.
Published online 2016 Oct 17. doi: 10.1016/j.toxrep.2016.10.004
PMCID: PMC5616082
PMID: 28959610

Prevention of isoniazid toxicity by NAT2 genotyping in Senegalese tuberculosis patients

A. Toure, Dr.,[a,c,*] M. Cabral,[a] A. Niang,[d] C. Diop,[a] A. Garat,[b,c] L. Humbert,[b] M. Fall,[a] A. Diouf,[a] F. Broly,[b,c] M. Lhermitte,[b,c] and D. Allorge[b,c]

Table 4

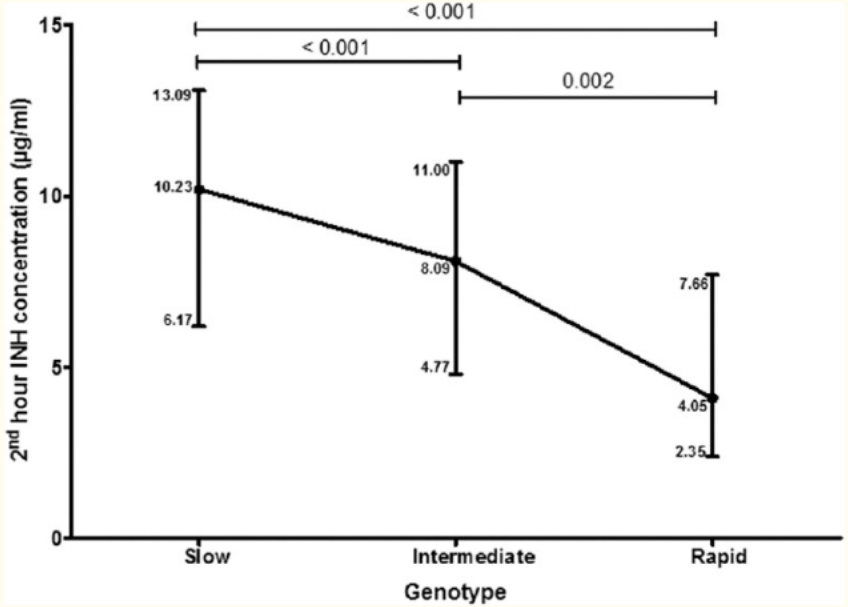
Plasma Isoniazid and Acetylisoniazid concentrations in slow and rapid acetylator TB patients (N = 79) after 3 and 6 h from the administration of a dose (5 mg/kg body weight) of INH.

	Slow Acetylators		Rapid Acetylators	
	3 h (mg/L)	**6 h (mg/L)**	**3 h (mg/L)**	**6 h (mg/L)**
Isoniazid	6.79 + 2.70 (2.8–13.10)	3.5 + 2.25 (0.1–9.5)	2.37 + 0.6 (1.3–3.5)	1.53 + 0.67 (0.5–3.1)
Acétylisoniazid	1.52 + 0.60 (0.2–3.7)	0.77 + 0.6 (0.1–2.2)	1.13 + 0.8 (0.2–3.1)	0.41 + 0.32 (0.1–1.2)

Indian J Med Res. 2017 Jan; 145(1): 118–123.
doi: 10.4103/ijmr.IJMR_2013_15
PMCID: PMC5460557
PMID: 28574024

N-acetyltransferase gene polymorphisms & plasma isoniazid concentrations in patients with tuberculosis

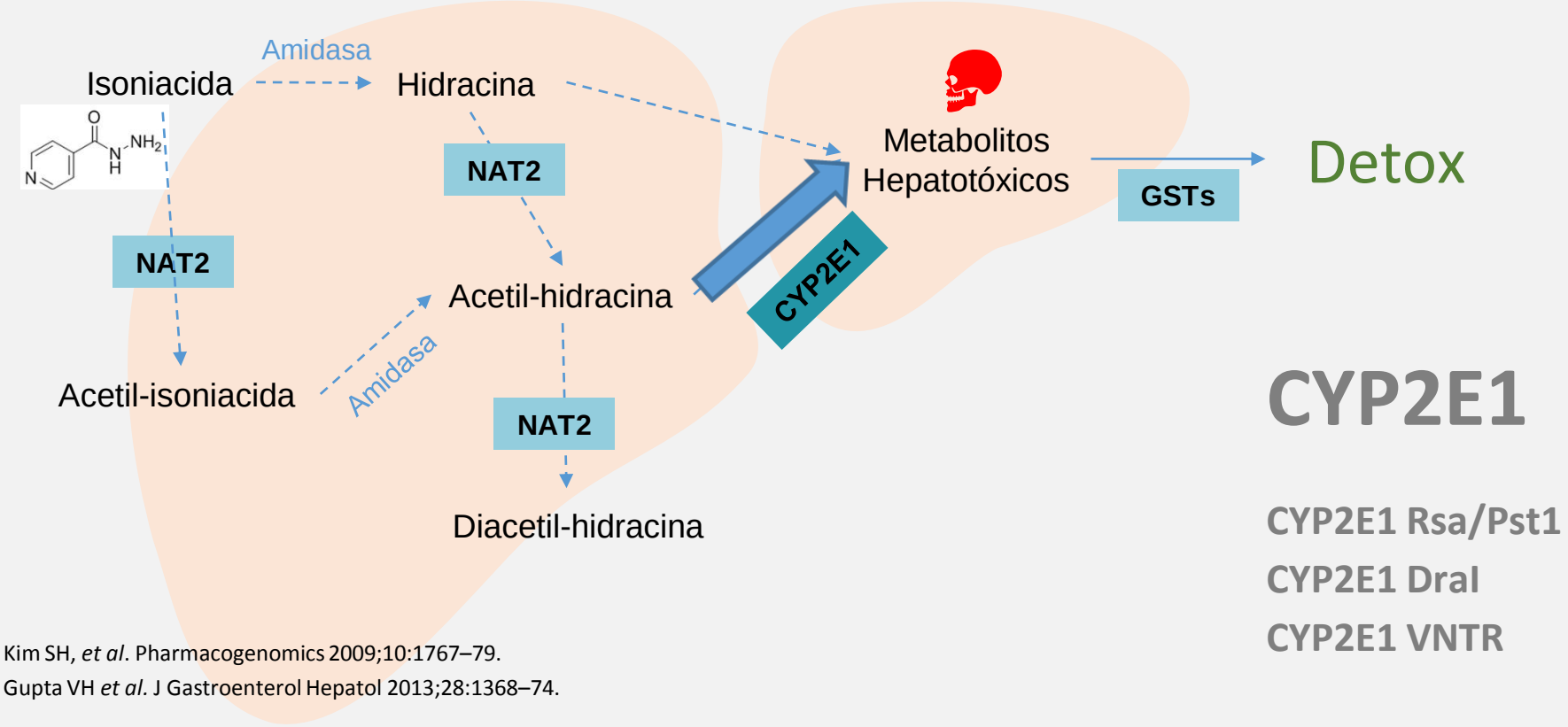
A. K. Hemanth Kumar,[1] K. Ramesh,[2] T. Kannan,[3] V. Sudha,[1] Hemalatha Haribabu,[2] J. Lava
Soumya Swaminathan,[5] and Geetha Ramachandran[1]



Figure

Median two-hour isoniazid concentrations in the different genotypes. The vertical bars denote inter-quartile range.

METABOLISMO DE ISONIACIDA



CYP2E1

CYP2E1 Rsa/Pst1

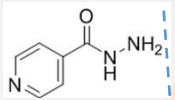
CYP2E1 DraI

CYP2E1 VNTR

Kim SH, *et al*. Pharmacogenomics 2009;10:1767–79.

Gupta VH *et al*. J Gastroenterol Hepatol 2013;28:1368–74.

METABOLISMO DE ISONIACIDA



Isoniacida

Amidasa

Hidracina

NAT2

Acetil-hidracina

NAT2

Diacetil-hidracina

NAT2

Acetil-isoniacida

Amidasa

CYP2E1

Metabolitos Hepatotóxicos

GSTs

Detox

GSTs

GSTM1 null

GSTT1 null

Gupta VH, et al. Ann Hepatol 2013;12:959–65.
Huang YS, et al. J Hepatol 2007;47:128–34.
Kim SH, et al. Tuberculosis 2010;90:39–43.

Open access Research

BMJ Open

Association of genetic polymorphisms of *CYP2E1, NAT2, GST* and *SLCO1B1* with the risk of anti-tuberculosis drug-induced liver injury: a systematic review and meta-analysis

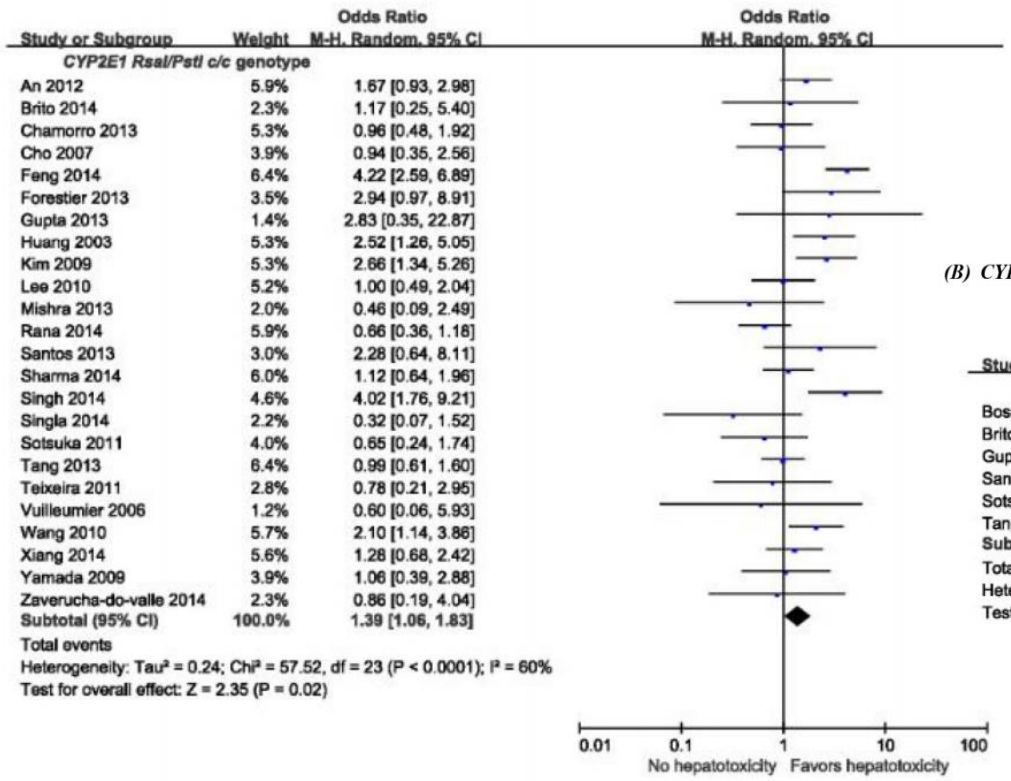
Seungwon Yang,[1] Se Jung Hwang,[2] Jung Yun Park,[3] Eun Kyoung Chung,[2,4] Jangik I Lee[3,5]

Received 19 November 2018
Accepted 11 June 2019

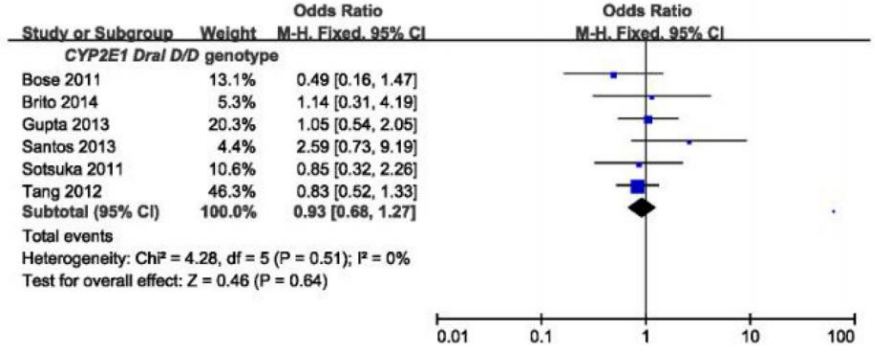
n=54 estudios

CYP2E1

(A) CYP2E1 RsaI/PstI c1/c1 genotype compared to c1/c2 + c2/c2 genotypes

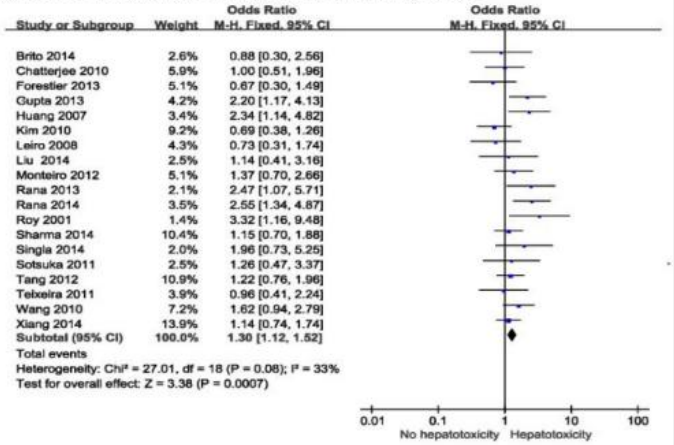


(B) CYP2E1 DraI D/D genotype compared to D/C + C/C genotypes.

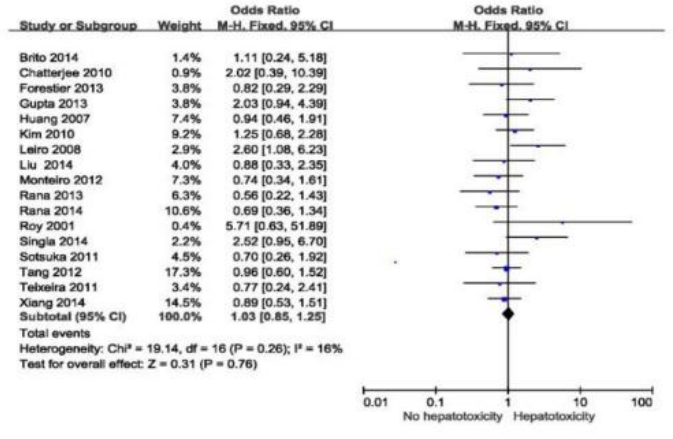


GSTs

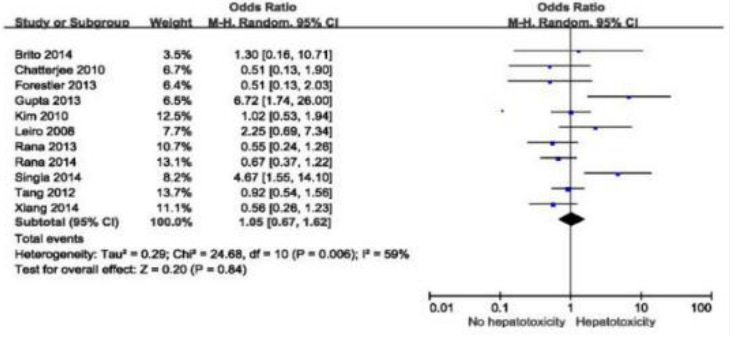
(A) GSTM1 null genotype compared to the non-null genotype



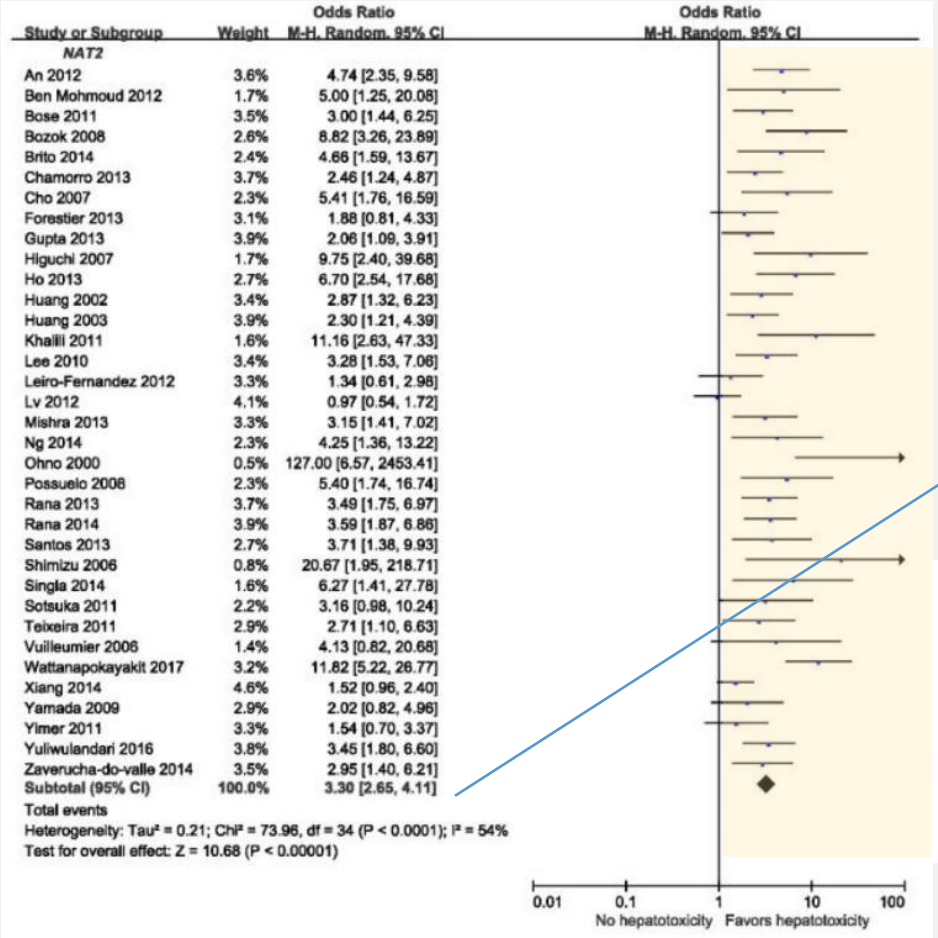
(B) GSTT1 null genotype compared to the non-null genotype



(C) GSTM1/GSTT1 dual-null genotype compared to the one- and non-null genotypes



NAT 2



Perfil AL

OR = 3,30 [2,65 – 4,11]

In conclusion, the risk of ATDILI during tuberculosis therapy was significantly increased in patients with tuberculosis carrying *NAT2* slow acetylator, *CYP2E1 Rsa*I/*Pst*I c1/c1, or *GSTM1* null genotypes. Screening for these genetic polymorphisms, particularly for the *NAT2* slow acetylator genotype, may be of great clinical benefit to identify patients at high risk for ATDILI and minimise the risk of ATDILI. Future studies are pertinent to develop

)18-027940 on 1 August 2

PHARMGKB

isoniazid × Add a term to make a combination...

isoniazid

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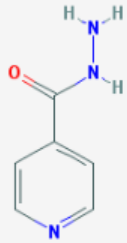
- Drug Labels
- Clinical Annotations
- Variant Annotations
- Literature
- Pathways
- Related To
- Links & Downloads

PRESCRIBING INFO 2 | DRUG LABELS 2 | CLINICAL ANNOTATIONS 18 | PATHWAYS 1

Structure



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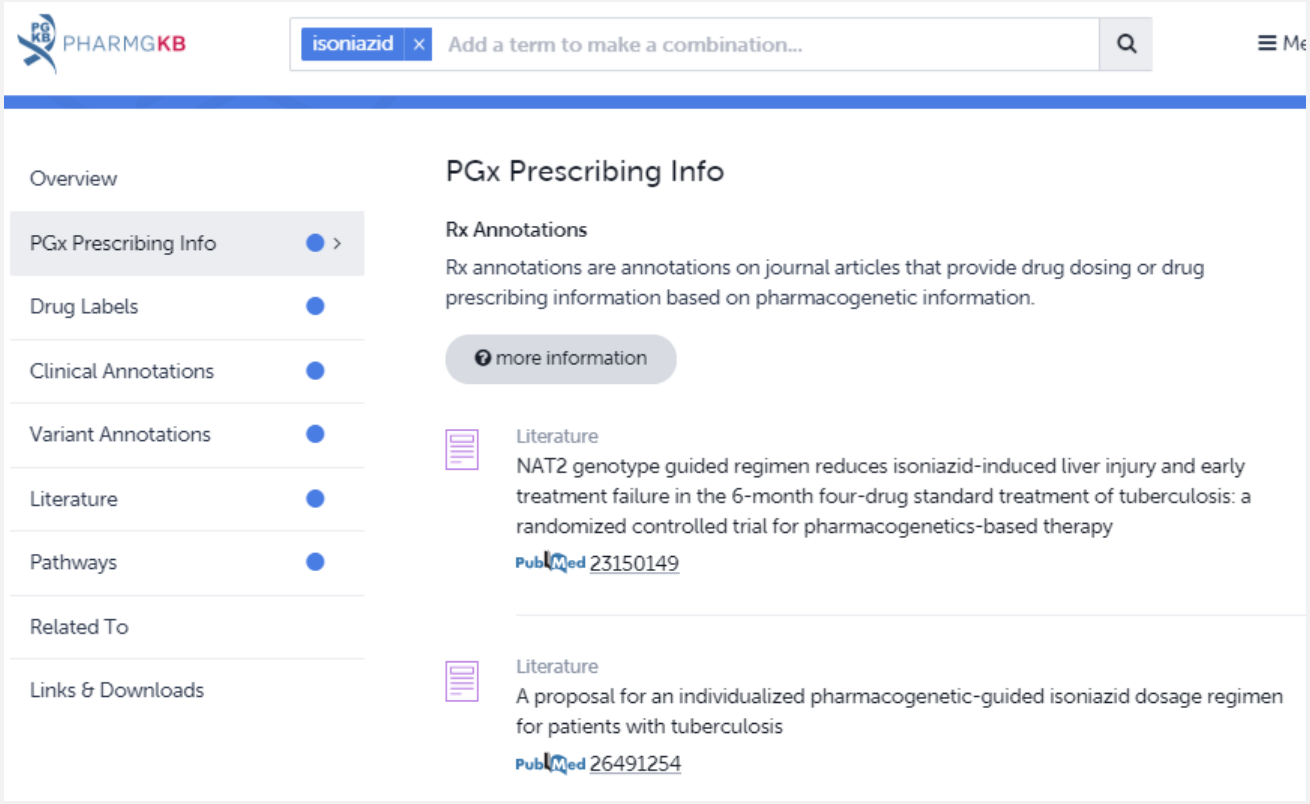
3D version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Variant Annotations
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Rx Annotations
Rx annotations are annotations on journal articles that provide drug dosing or drug prescribing information based on pharmacogenetic information.
more information
Literature
NAT2 genotype guided regimen reduces isoniazid-induced liver injury and early treatment failure in the 6-month four-drug standard treatment of tuberculosis: a randomized controlled trial for pharmacogenetics-based therapy
PubMed 23150149
Literature
A proposal for an individualized pharmacogenetic-guided isoniazid dosage regimen for patients with tuberculosis
PubMed 26491254

NAT2 genotype guided regimen reduces isoniazid-induced liver injury and early treatment failure in the 6-month four-drug standard treatment of tuberculosis: a randomized controlled trial for pharmacogenetics-based therapy

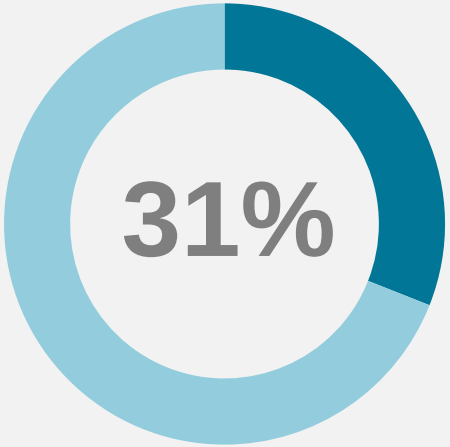
PubMed 23150149

Dosing protocol

NAT2 STATUS	BODY WEIGHT (KG)	DOSE IN NAT2 GENOTYPED-GUIDED TREATMENT ARM (MG/DAILY; N=78)	DOSE IN STANDARD TREATMENT ARM (MG/DAILY; N=77)
SA	<40	100	200
SA	>=40	150	300
IA	<40	200	200
IA	>=40	300	300
RA	<40	300	200
RA	>=40	450	300

SA = slow acetylator, without NAT2*4; IA = intermediate acetylator, heterozygous for NAT2*4; RA = rapid acetylator, homozygous for NAT2*4

La reducción del riesgo absoluto en la población combinada de acetiladores rápidos y lentos con respecto a eventos desfavorables.



Reducción de riesgo

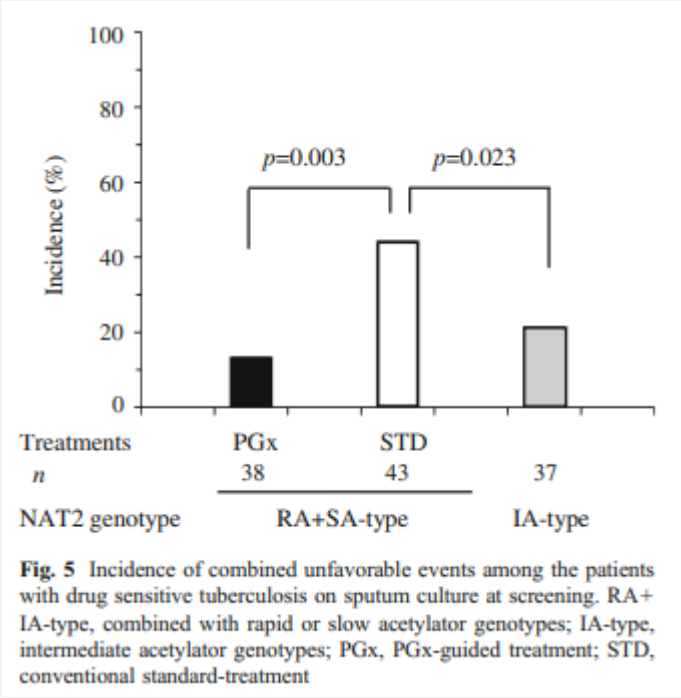


Fig. 5 Incidence of combined unfavorable events among the patients with drug sensitive tuberculosis on sputum culture at screening. RA+IA-type, combined with rapid or slow acetylator genotypes; IA-type, intermediate acetylator genotypes; PGx, PGx-guided treatment; STD, conventional standard-treatment

Literature

A proposal for an individualized pharmacogenetic-guided isoniazid dosage regimen for patients with tuberculosis

PubMed 26491254

Dosing protocol

Pharmacogenetic arm (n=28)

NAT2 STATUS	WEIGHT: 40KG	50KG	60KG	70KG	80KG
Slow-acetylators*	100mg	200mg	200mg	200mg	300mg
Intermediate-acetylators	200mg	200mg	300mg	300mg	300mg
Rapid-acetylators	300mg	300mg	300mg	400mg	400mg

PHARMGKB

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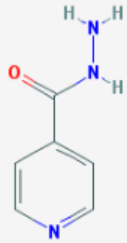
- Links & Downloads

PRESCRIBING INFO	DRUG LABELS	CLINICAL ANNOTATIONS	PATHWAYS
2	2	18	1

Structure



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Overview
PGx Prescribing Info
Drug Labels
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Drug Labels

View Drug Label Legend

PharmGKB annotates drug labels containing pharmacogenetic information approved by the US Food and Drug Administration (FDA), European Medicines Agency (EMA), the Pharmaceuticals and Medical Devices Agency, Japan (PMDA), and Health Canada (Santé Canada) (HCSC). PharmGKB annotations provide a brief summary of the PGx in the label, an excerpt from the label and a downloadable highlighted label PDF file. A list of genes and phenotypes found within the label is mapped to label section headers and listed at the end of each annotation. PharmGKB also attempts to interpret the level of action implied in each label with the "PGx Level" tag.

See the legend for more information about drug label sources and PGx Levels.

We welcome any information regarding drug labels containing PGx information approved by the FDA, EMA, PMDA, HCSC or other Medicine Agencies around the world - please contact us.

	TESTING LEVEL	SOURCE	GENES	TITLE
Read Now	Informative PGx	FDA	NAT2	Annotation of FDA Label for isoniazid,pyrazinamide,rifampi...AT2
Read Now	Informative PGx	PMDA	NAT2	Annotation of PMDA Label for isoniazid and NAT2

[Solución propuesta] —— Detectar a los pacientes sensibles ANTES de medicarlos.

Perfil acetilador NAT2

Una herramienta costeable que analiza el **ADN** del paciente y permite saber cual es la dosis del fármaco anti-TB óptima para él.

pacientes mejoran su calidad de vida durante el tratamiento evitando el daño hepático.

médicos mejoran su éxito en el tratamiento de sus pacientes y en la prevención de efectos adversos.

Sistema de salud optimiza recursos al evitar tratamientos prolongados e internaciones.

Equipo

Julián Chamorro
Licenciado en Ciencias Biológicas
Doctor de la Universidad de Buenos Aires

Gabriela de Larrañaga
Bioquímica
Doctora de la Universidad de Buenos Aires
Investigadora Carrera de Investigador GCBA
Investigadora del CONICET

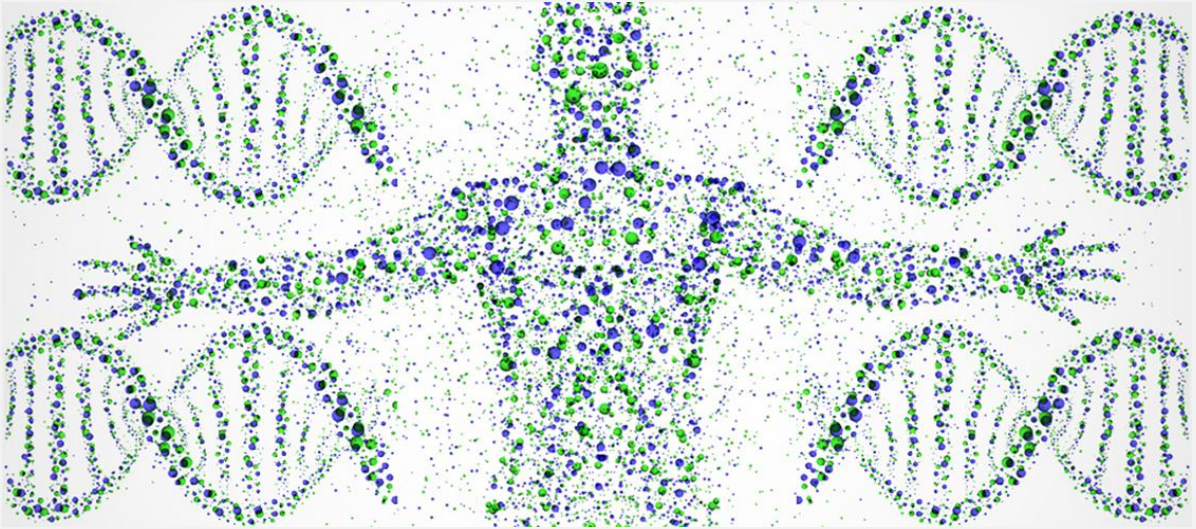
Hospital de Infecciosas F. J. Muñiz
Ciudad Autónoma de Buenos Aires

Hospital de Infecciosas Francisco J. Muñiz

Buenos Aires Ciudad

CONICET

Nuestro aporte a la medicina personalizada.



J Infect Dev Ctries. 2012 Sep 17;6(9):671-4. doi: 10.3855/jidc.2111.

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HEPATOLOGY

Sex, ethnicity, and slow acetylator profile are the major causes of hepatotoxicity induced by antituberculosis drugs

Julián G Chamorro,* Jorge P Castagnino,† Rosa M Musella,† Mabel Nogueras,‡ Federico M Aranda,* Ana Frías,† Mabel Visca,† Omar Aidar,† Silvia Perés* and Gabriela F de Larrañaga*

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Effect of gene-gene and gene-environment interactions associated with antituberculosis drug-induced hepatotoxicity.

Chamorro JG[1], Castagnino JP, Aidar O, Musella RM, Frías A, Visca M, Nogueras M, Costa L, Perez A, Caradonna F, de Larrañaga GF.

Líneas en curso:

FARMACOGENÉTICA DE LA TUBERCULOSIS. PIRAZINAMIDA

FARMACOGENÉTICA DE LA TUBERCULOSIS. Estudio Multicéntrico.

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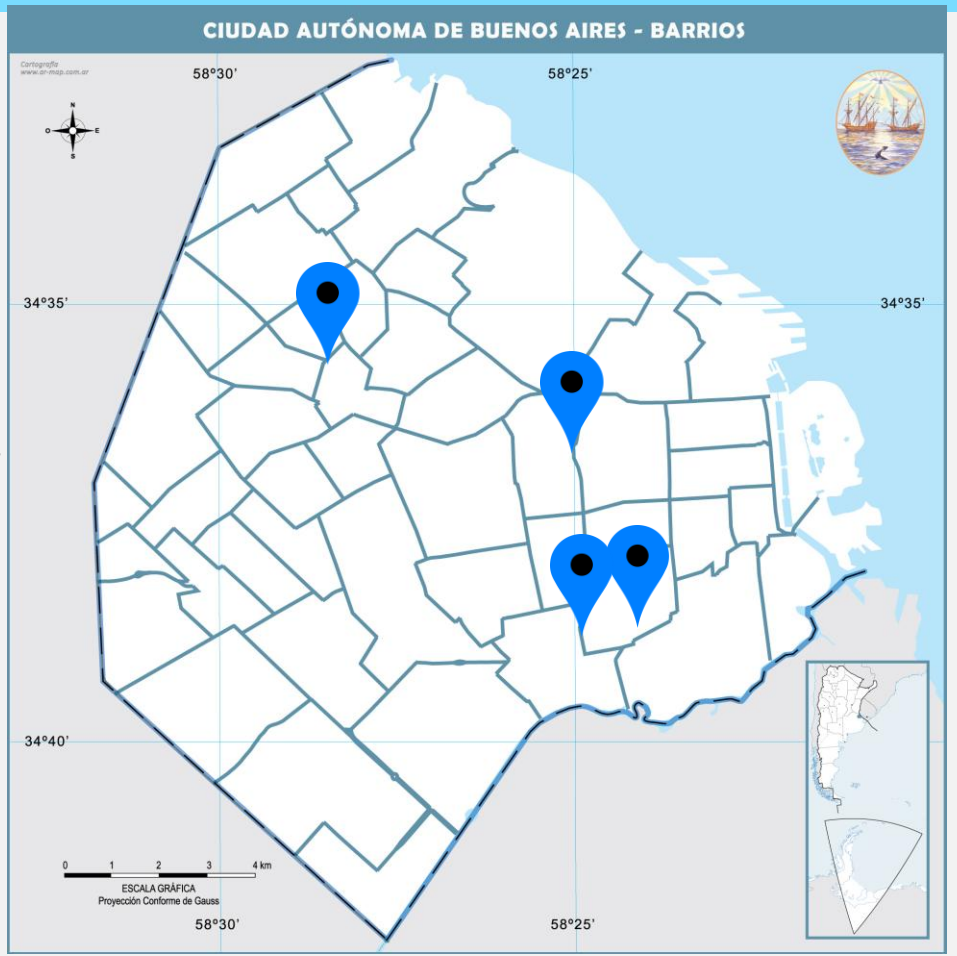

Líneas en camino:

FARMACOGENÉTICA DE LA TUBERCULOSIS.

Trial

Muchas Gracias