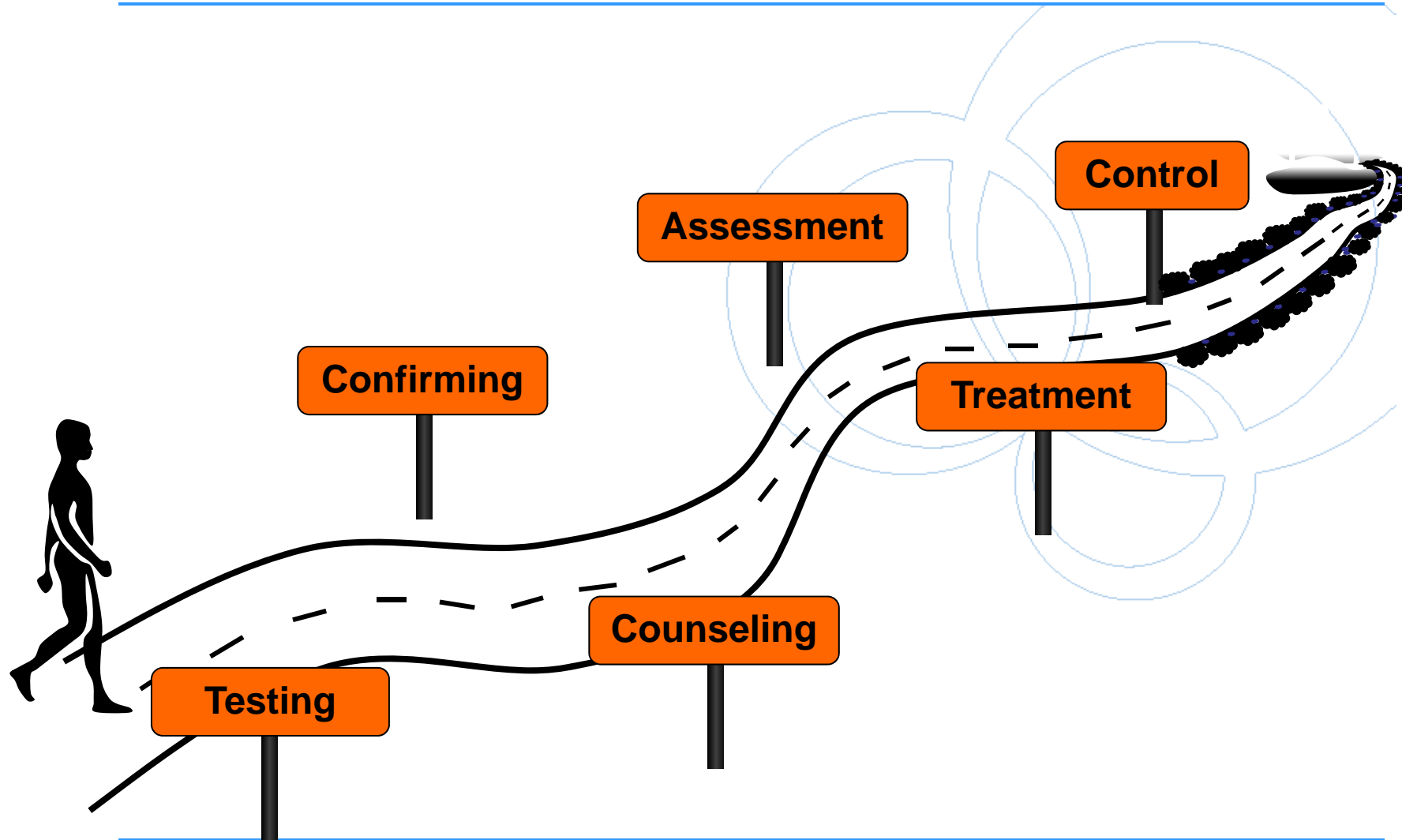


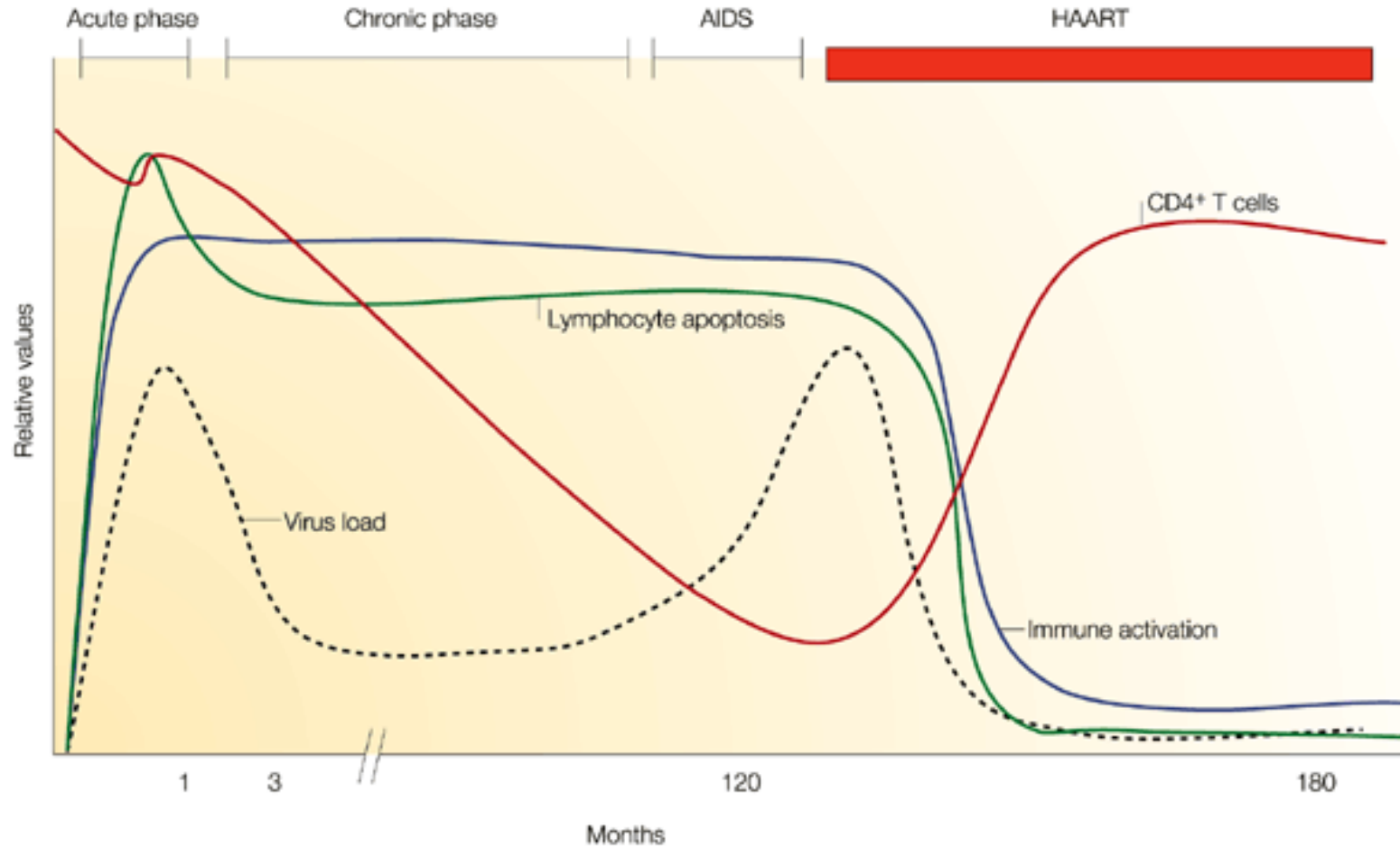
Aplicabilitat clínica de la farmacogenètica en el món del VIH

Francesc Vidal i Marsal
Hospital Universitari de Tarragona Joan XXIII,
IISPV, Universitat Rovira i Virgili

HIV Screening Is the First Step on the Road to a Control



Història natural de la infecció i efecte del tractament sobre la càrrega viral i els limfòcits T CD4+



Nature Reviews | Immunology

Causes de canvi / abandonament del primer TARV (n=312)

Toxicitat
58.3%

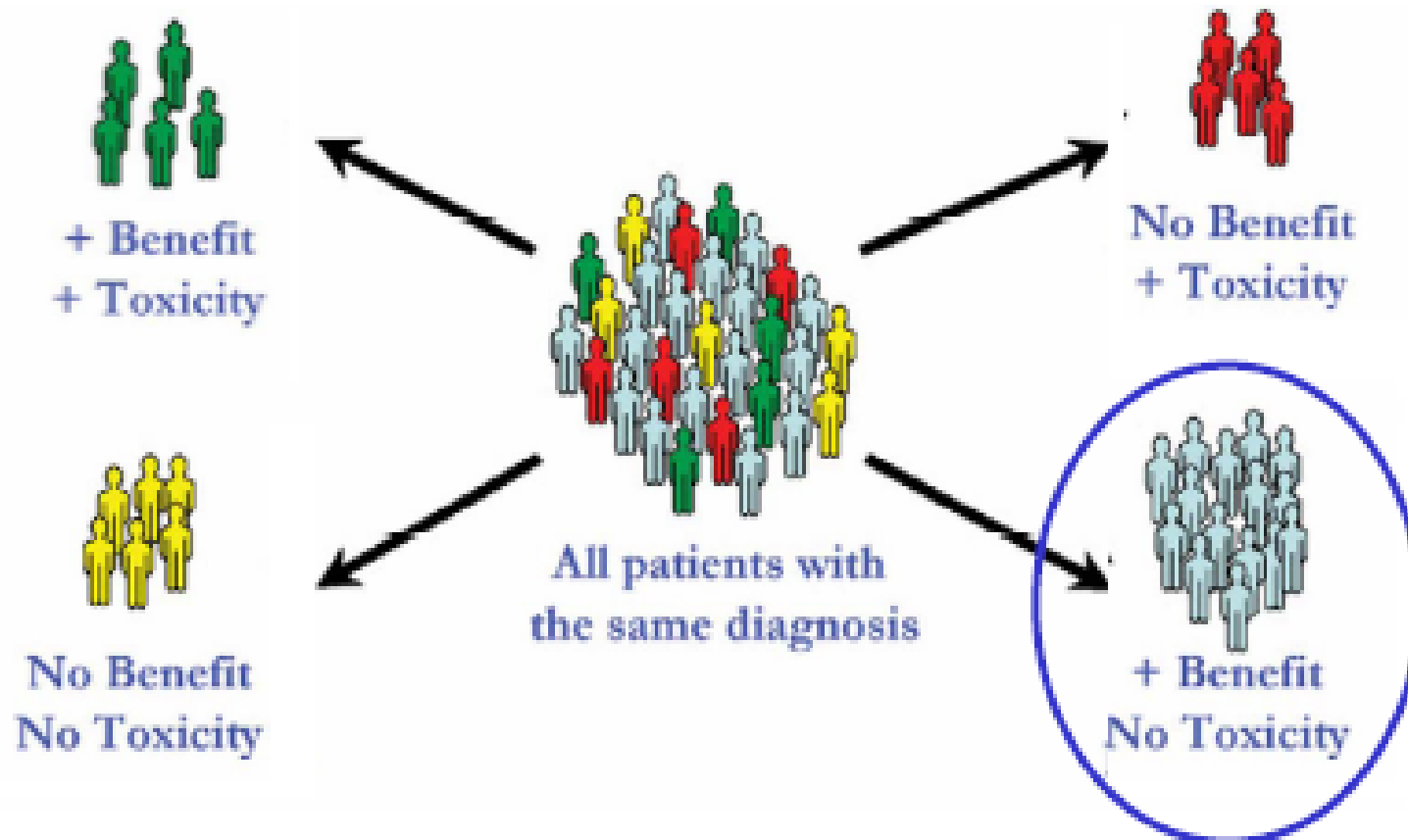
Fracàs virològic
14.1%

No adherència
19.6%

Altres
8.0%

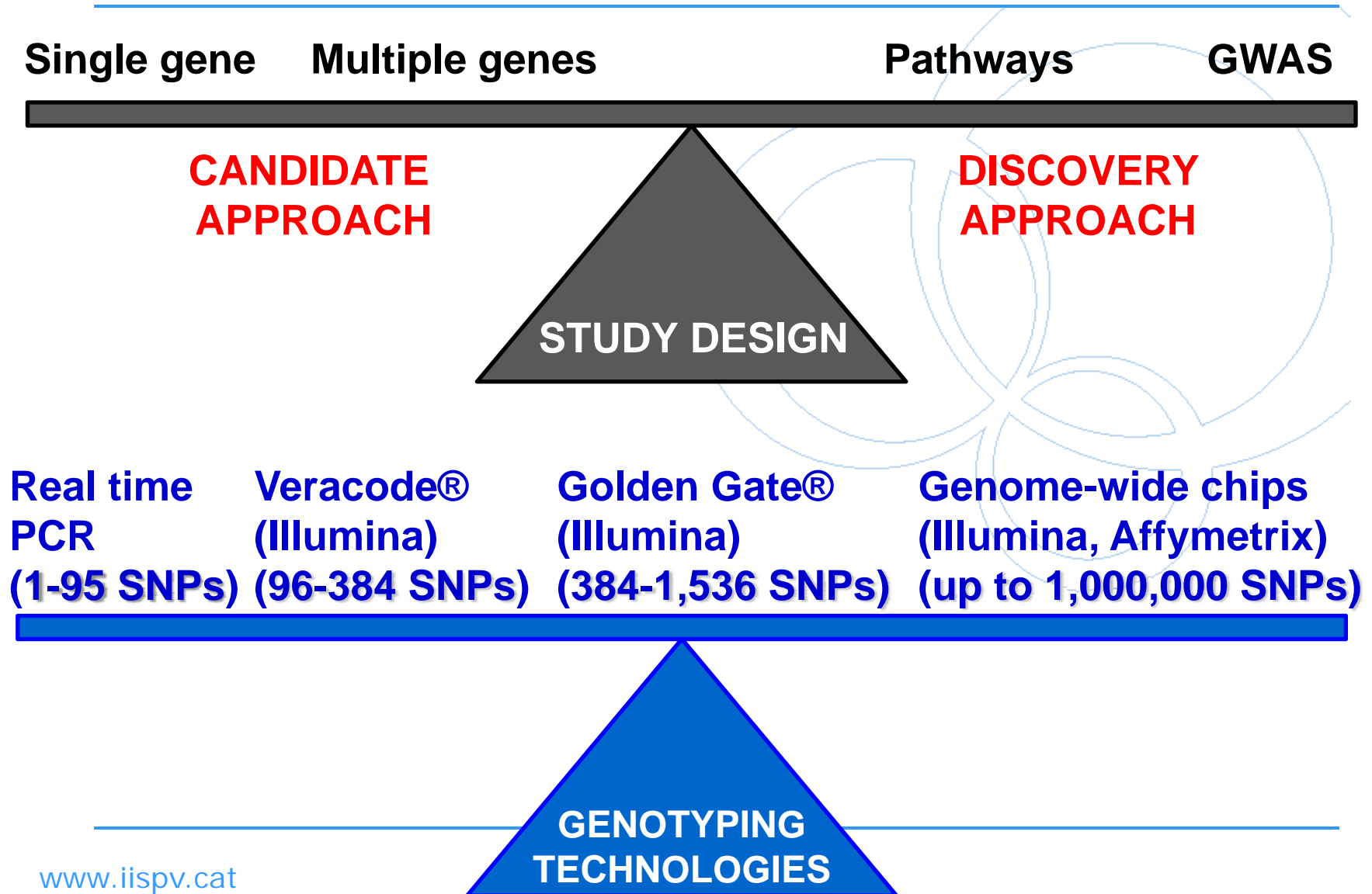
25%!

variaciones genéticas del individuo influyen en la respuesta a los fármacos en términos de eficacia y toxicidad



Candidate vs. Discovery approach

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Hipersensibilitat a abacavir i HLAB5701

Drug Rash with eosinophilia and systemic syndrome DRESS,
due to abacavir



www.aids-images.ch

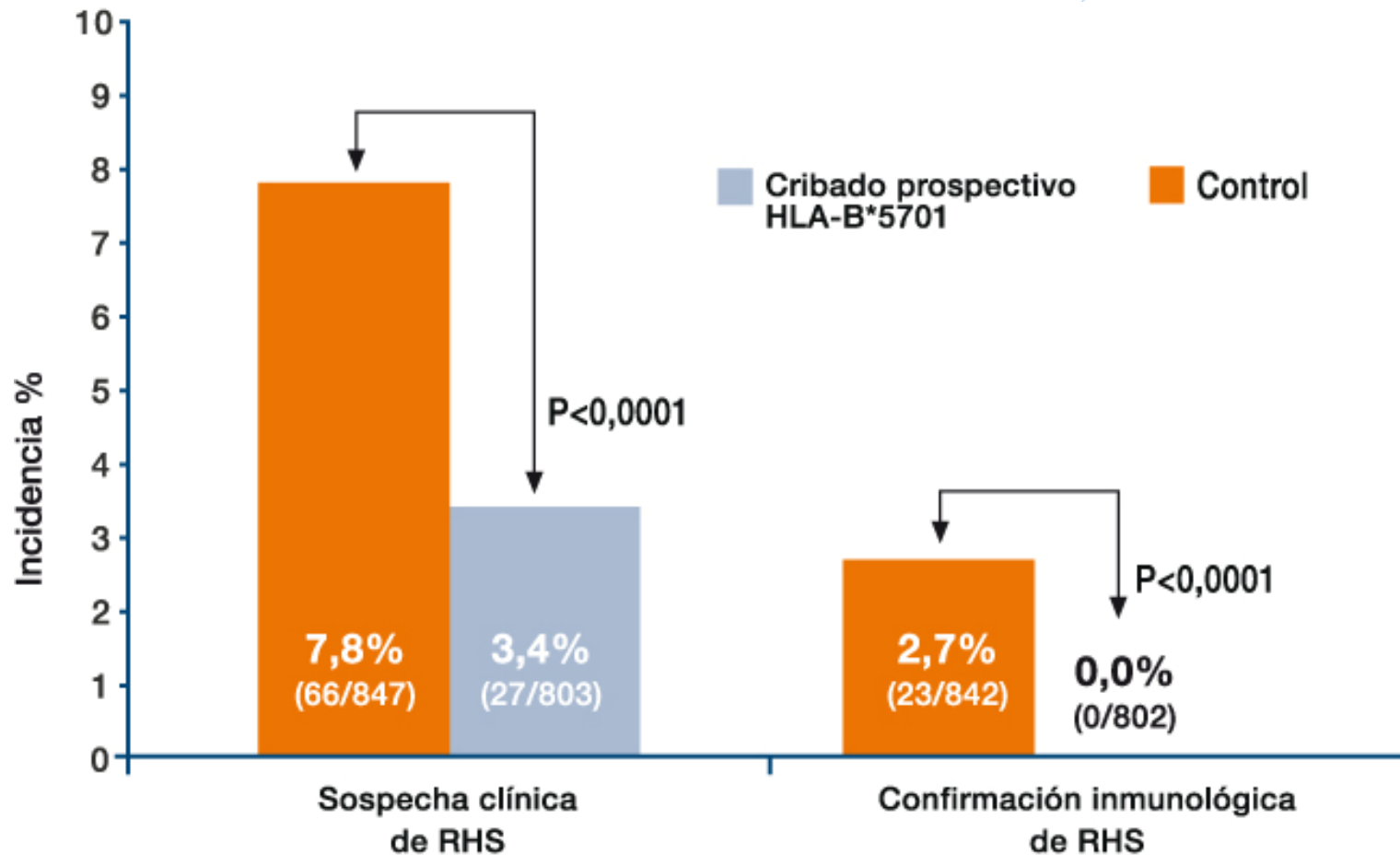
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

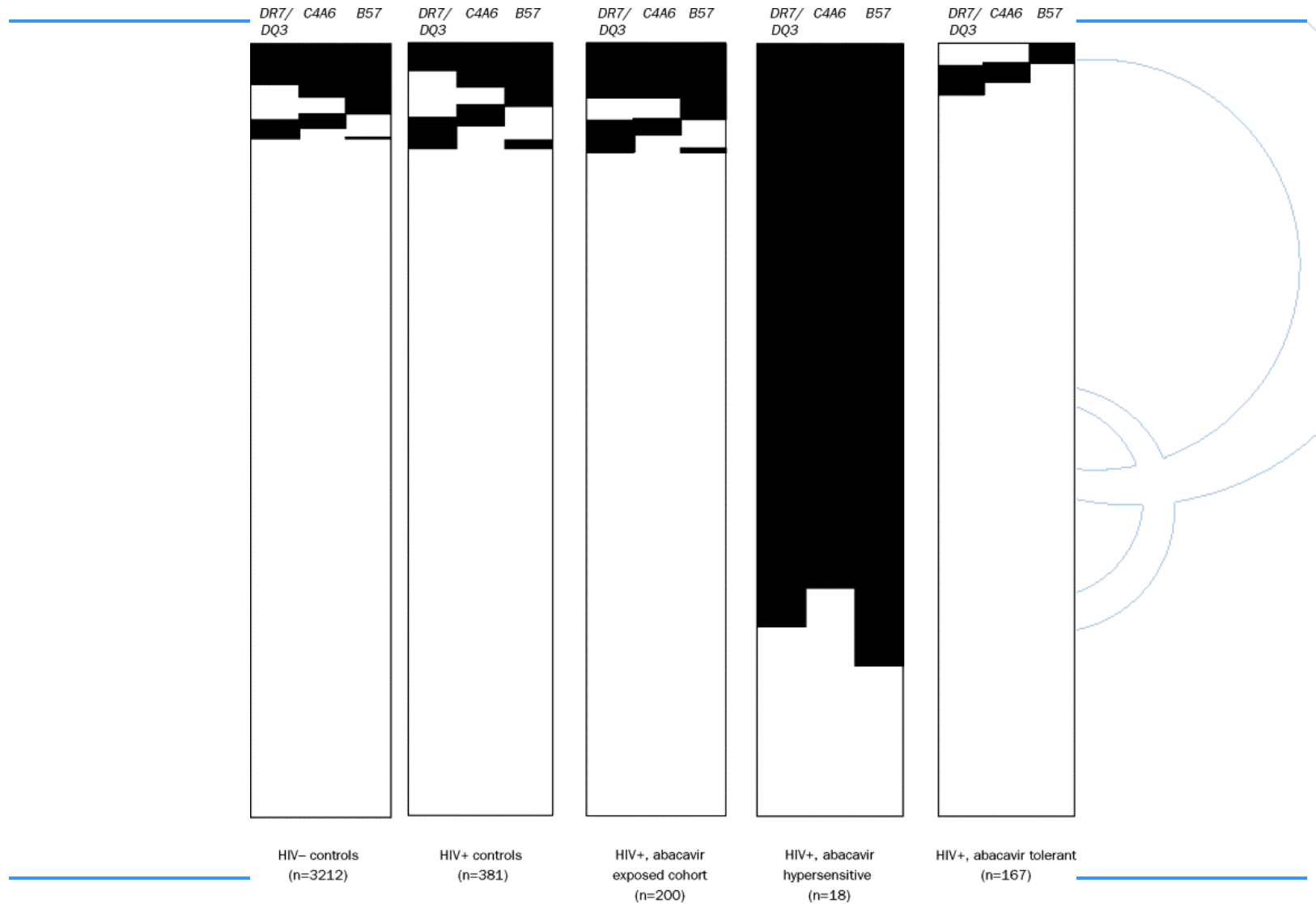
HLA-B*5701 Screening for Hypersensitivity to Abacavir

Simon Mallal, M.B., B.S., Elizabeth Phillips, M.D., Giampiero Carosi, M.D.,
Jean-Michel Molina, M.D., Cassy Workman, M.B., B.S., Janez Tomažič, M.D.,
Eva Jägel-Guedes, M.D., Sorin Rugina, M.D., Oleg Kozyrev, M.D.,
Juan Flores Cid, M.D., Phillip Hay, M.B., B.S., David Nolan, M.B., B.S.,
Sara Hughes, M.Sc., Arlene Hughes, Ph.D., Susanna Ryan, Ph.D.,
Nicholas Fitch, Ph.D., Daren Thorborn, Ph.D., and Alastair Benbow, M.B., B.S.,
for the PREDICT-1 Study Team*

Criterios de valoración principales



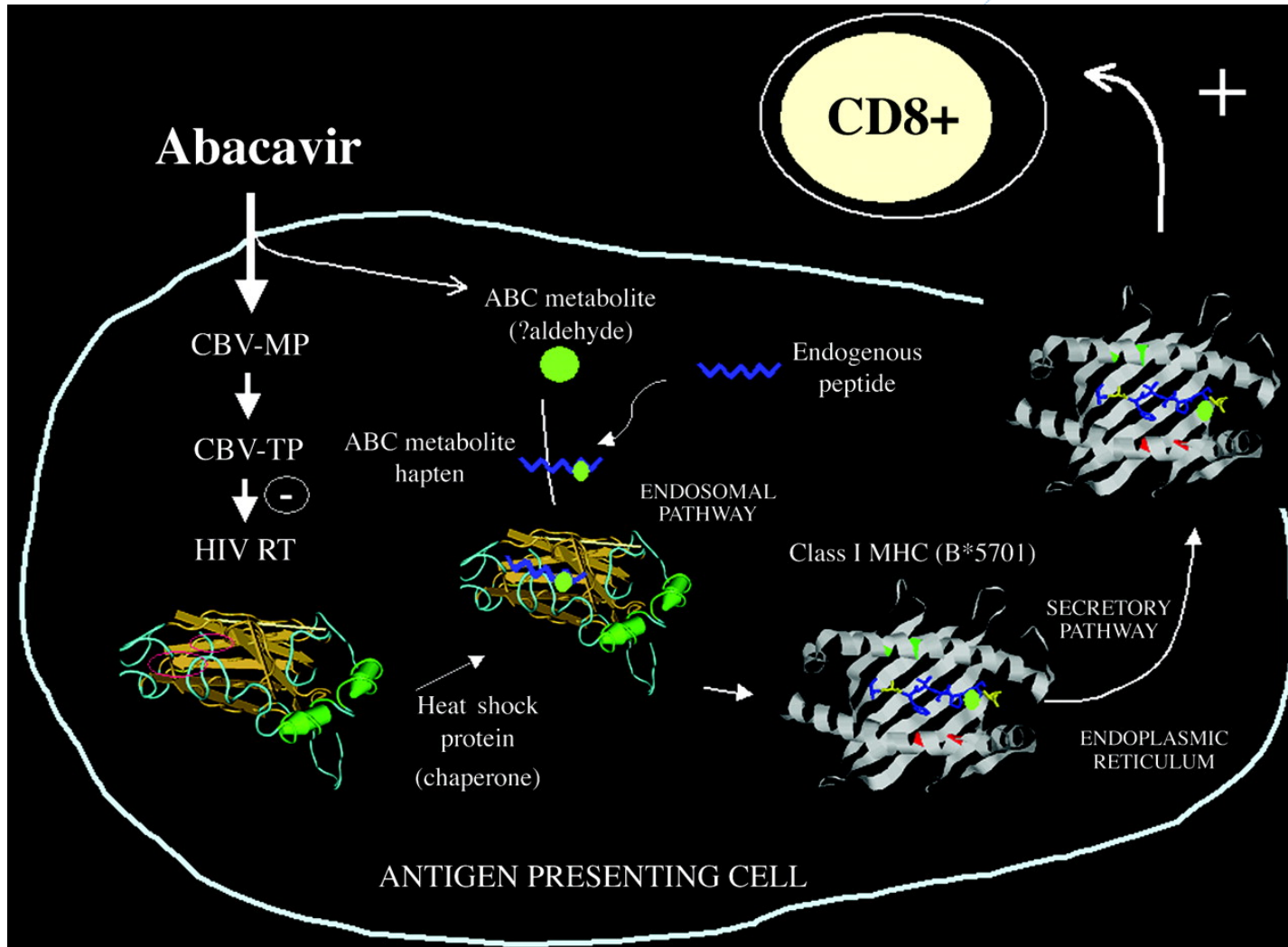
RHS i HLAB*5701: dades inicials



www.iispy.cat
 Dades semblants: Hetherington S, et al. Lancet 2002

Mallal S, et al. Lancet 2002

Pathogenic model for the generation of a hypersensitive response to abacavir.



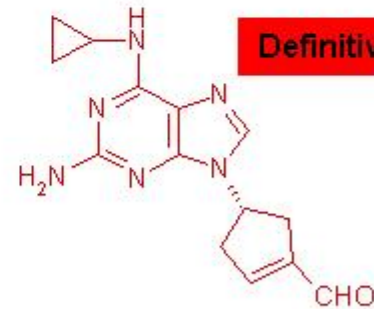
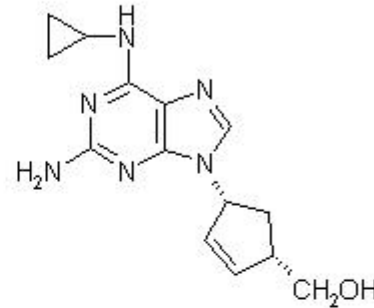
Martin A M et al. PNAS 2004;101:4180-4185

PNAS

ABC Hypersensitivity: From Bedside to Laboratory and Back to Clinic



Clinical phenotype

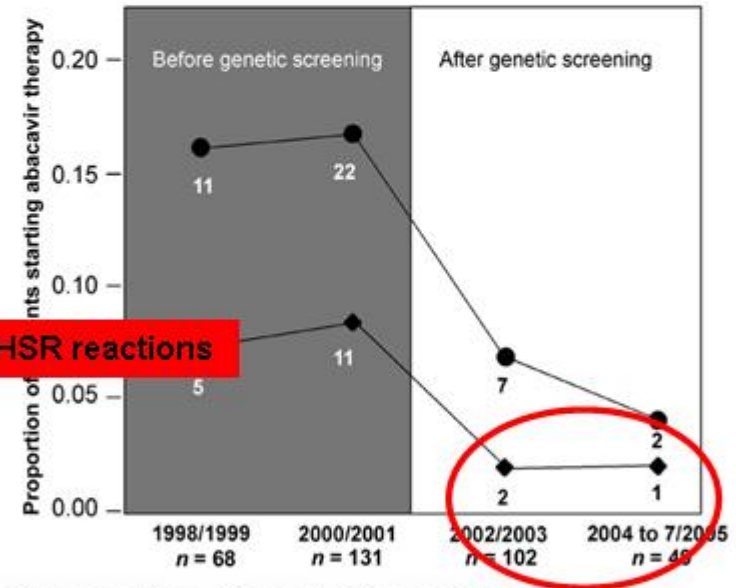


Definitive ABC HSR reactions

Causal chemical

Clinical genotype

Association with HLA-B*5701



Prospective Genetic Screening Decreases the Incidence of Abacavir Hypersensitivity Reactions in the Western Australian HIV Cohort Study

A. Rauch,^{1,2} D. Nolan,¹ A. Martin,¹ E. McKinnon,¹ C. Almeida,¹ and Simon Mallat¹

¹Centre for Clinical Immunology and Biomedical Statistics, Perth, Australia; and ²Division of Infectious Diseases, University Hospital Bern, Switzerland

(See the editorial commentary by Phillips on pages 103–5)

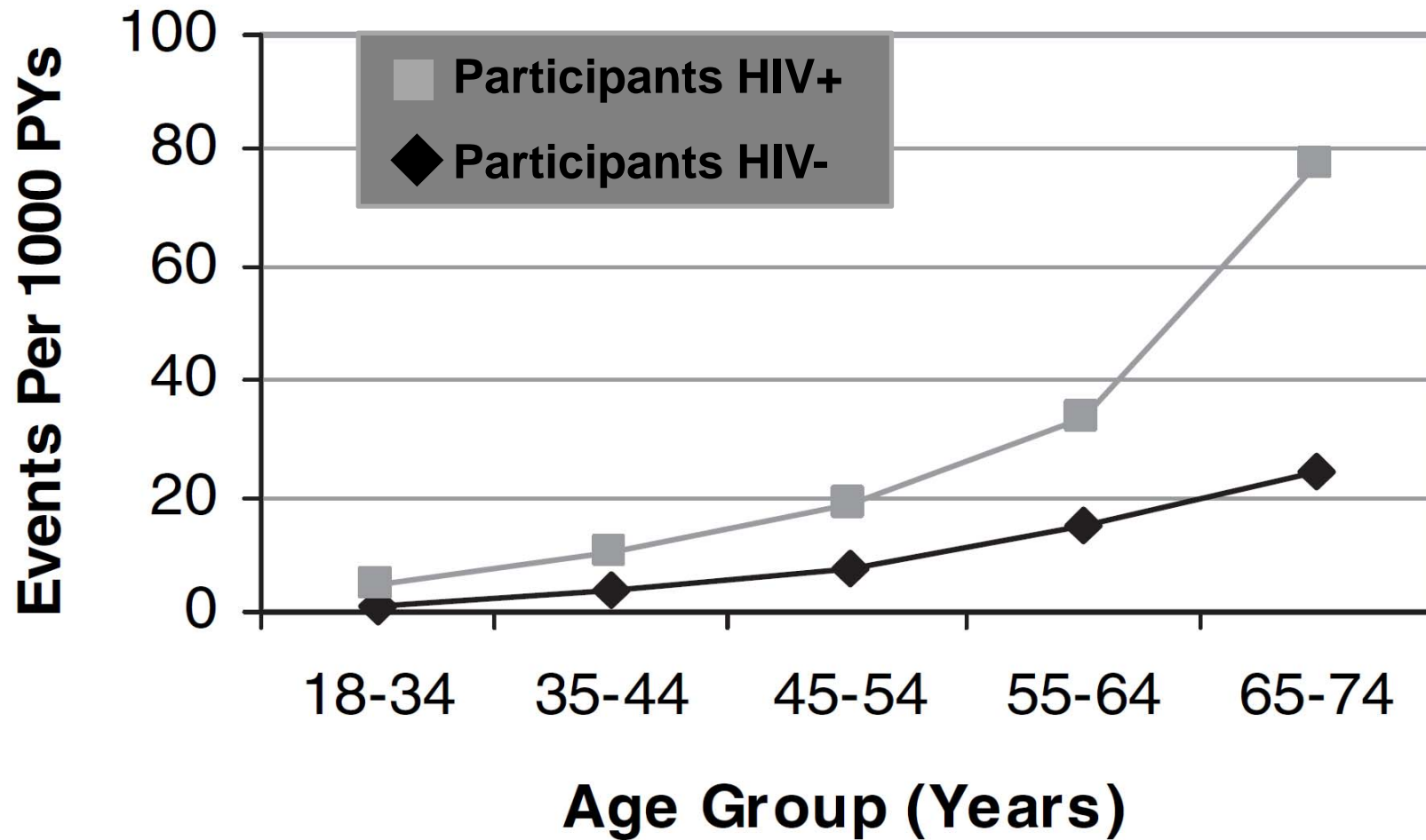
Exemples de efectes adversos atribuïts al TARV i fàrmac/s presuntament implicats

Efecte advers	Fàrmac/s
Lipodistrofia	NRTI/PI
Dislipèmia	PI
Resistència insulina	NRTI/PI
Arteriosclerosi	NRTI/PI
Hiperbilirrubinèmia	ATV
RHS, hepatopatia	NVP
Neuropatia perifèrica	NRTI
Neurotoxicitat	EFV
Dany renal	TFV
RHS	ABC

Alguns efectes adversos del TARV, fàrmacs presuntament implicats i gens candidats

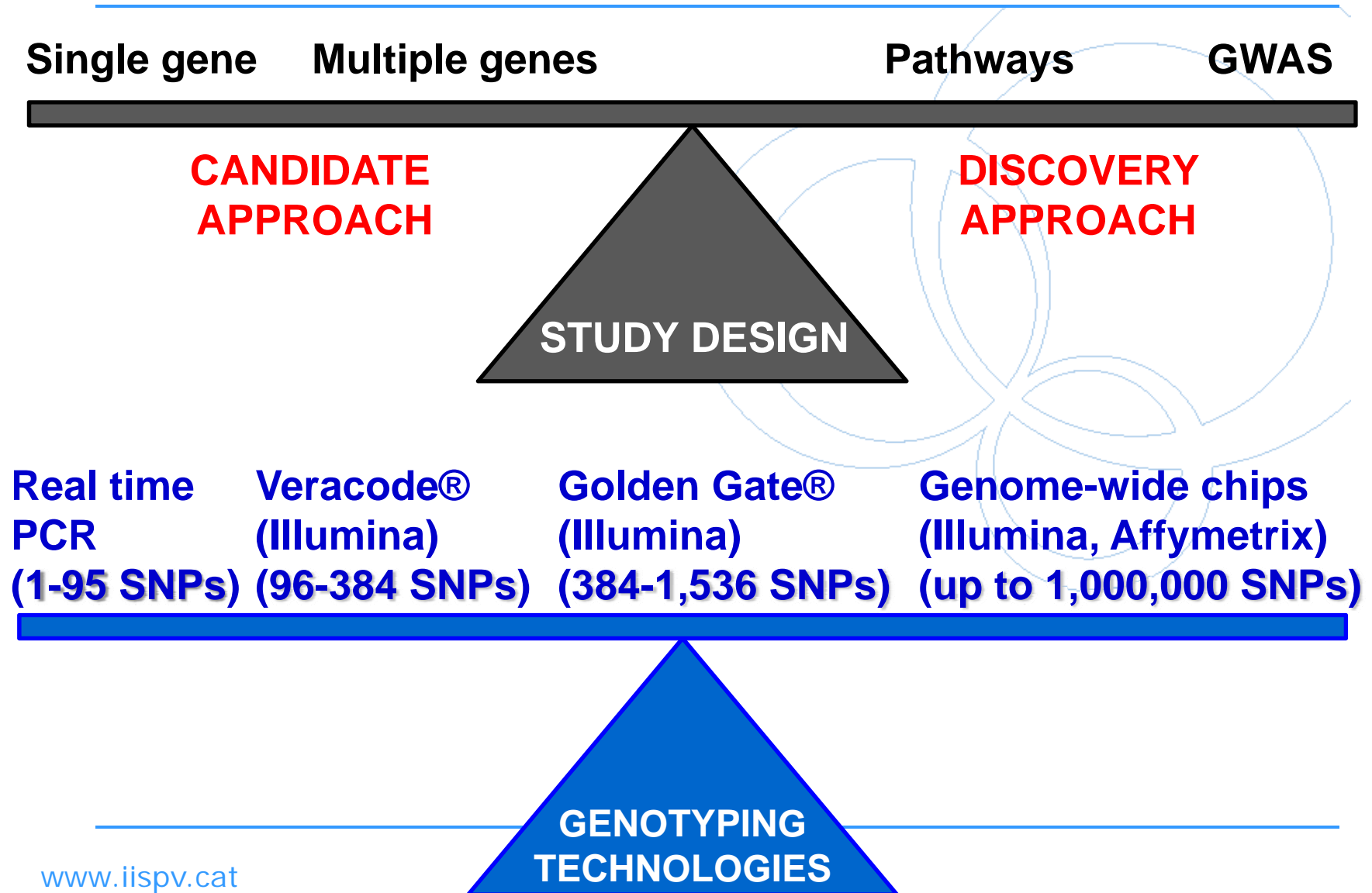
Efecte advers	Fàrmac/s	Gens candidats
Lipodistrofia	NRTI/PI	TNF- α , IL-6, APOC3 IL-1 β , PPAR- γ , lamina, ADN mitocondrial
Dislipèmia	PI	ApoC3, A5, E, TNF- α , IL-6, PPAR γ , SREBP1
Resistència insulina	NRTI/PI	TNF- α , IL-6, PPAR γ
Arteriosclerosi	NRTI/PI	MCP-1, SDF-1, CX3CR1
Hiperbilirrubinèmia	ATV	UGT1A1
RHS, hepatopatia	NVP	HLA, CYP2B6, MDR1
Neuropatia perifèrica	NRTI	ADN mitocondrial
Neurotoxicitat	EFV	CYP2B6, CYP3A4
Dany renal	TFV	MRP2, MRP4
<u>RHS</u>	<u>ABC</u>	<u>HLA-B*5701</u>

The risk of coronary artery disease is increased in HIV infected individuals

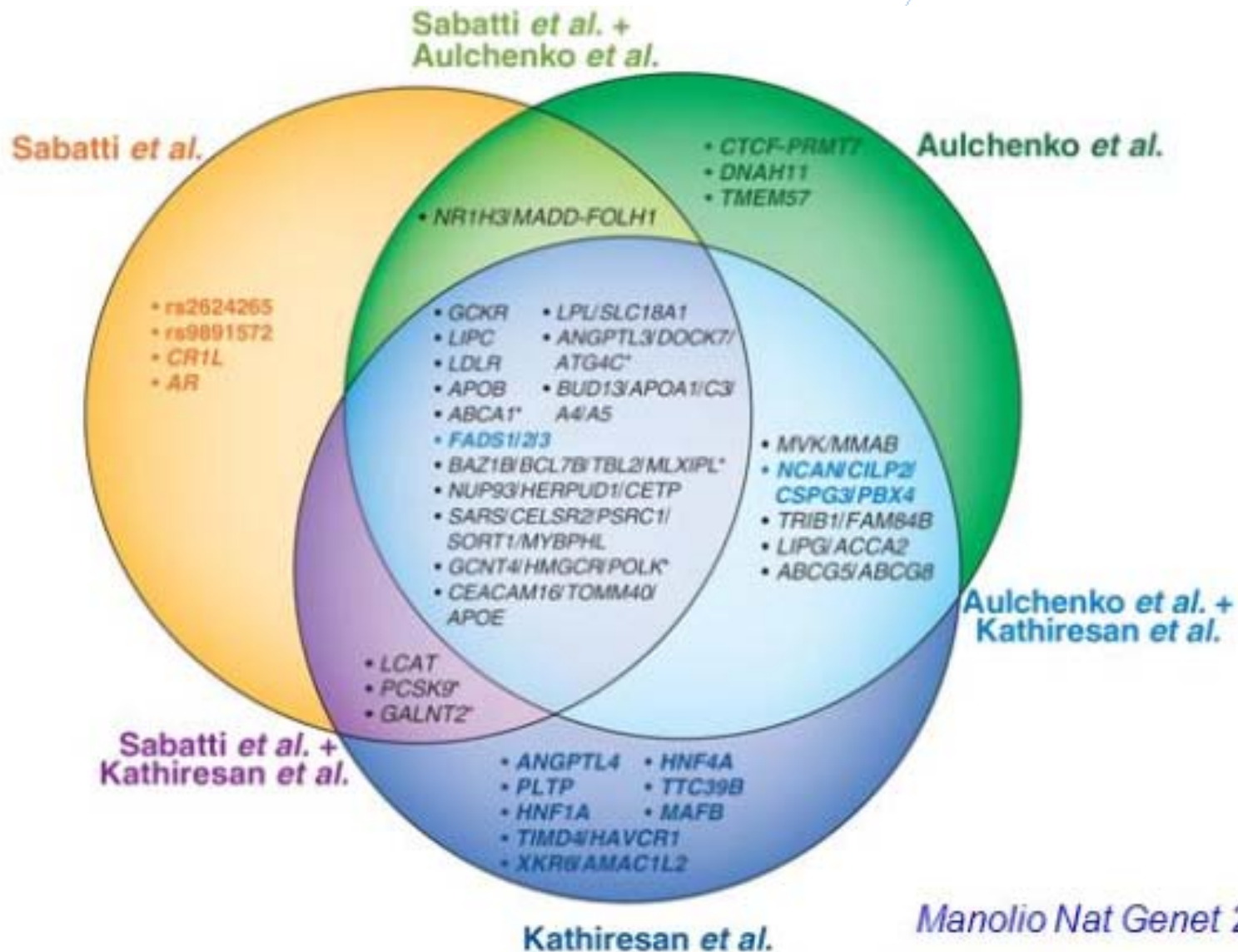


Candidate vs. Discovery approach

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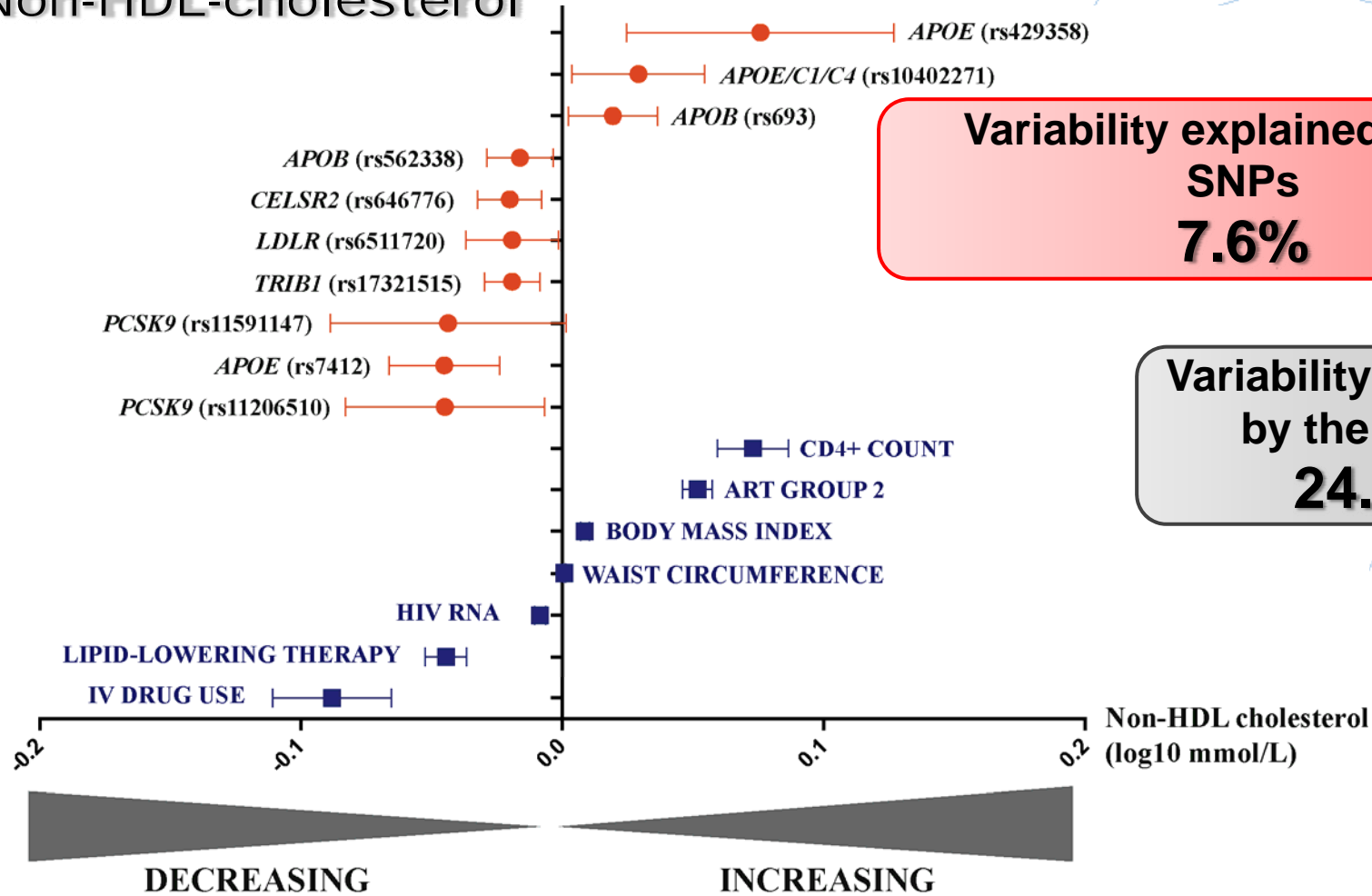


Locus asociados con niveles de lípidos



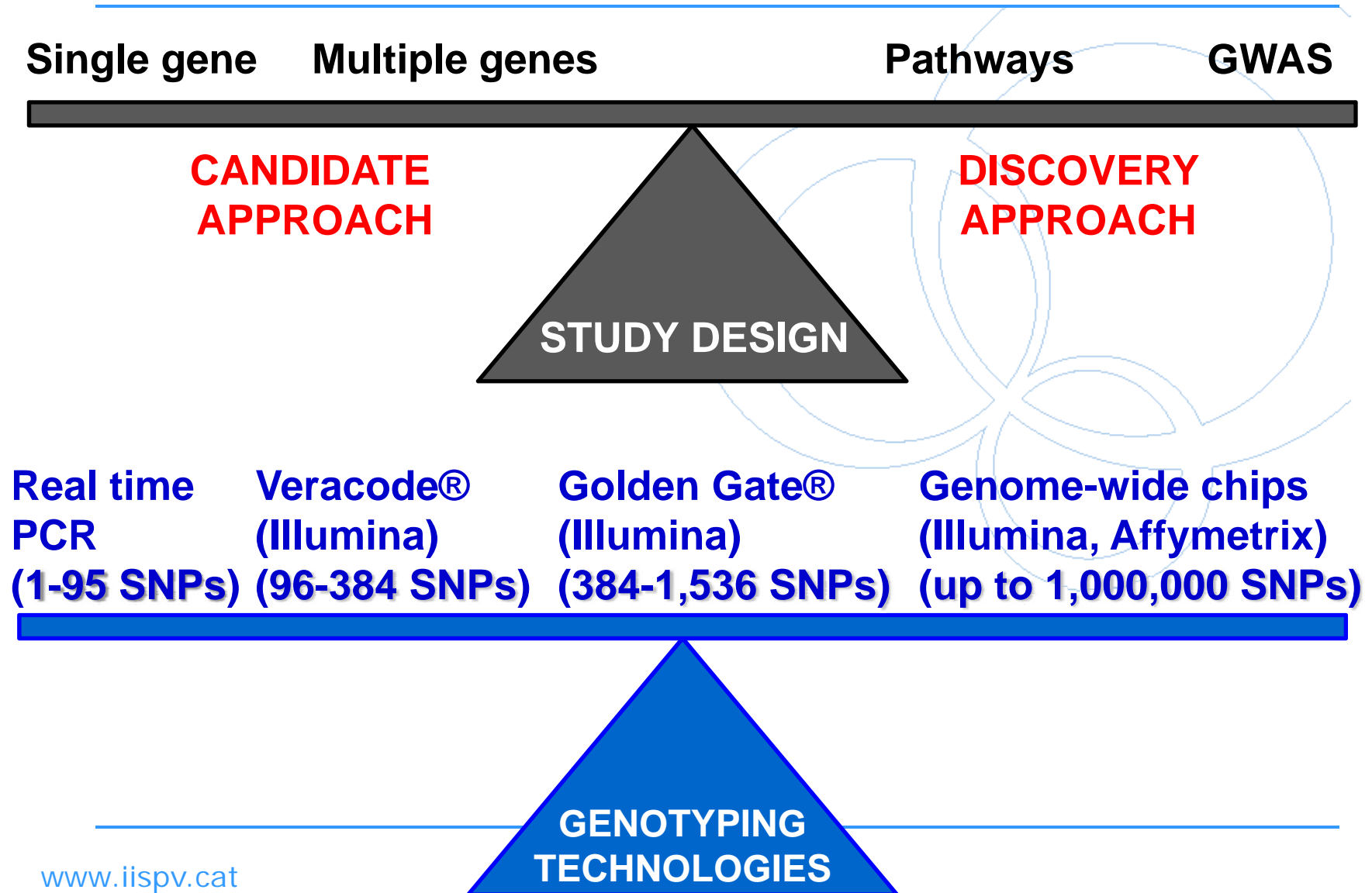
Contribution of multiple genetic variants to dyslipidemia associated with antiretroviral therapy

Non-HDL-cholesterol

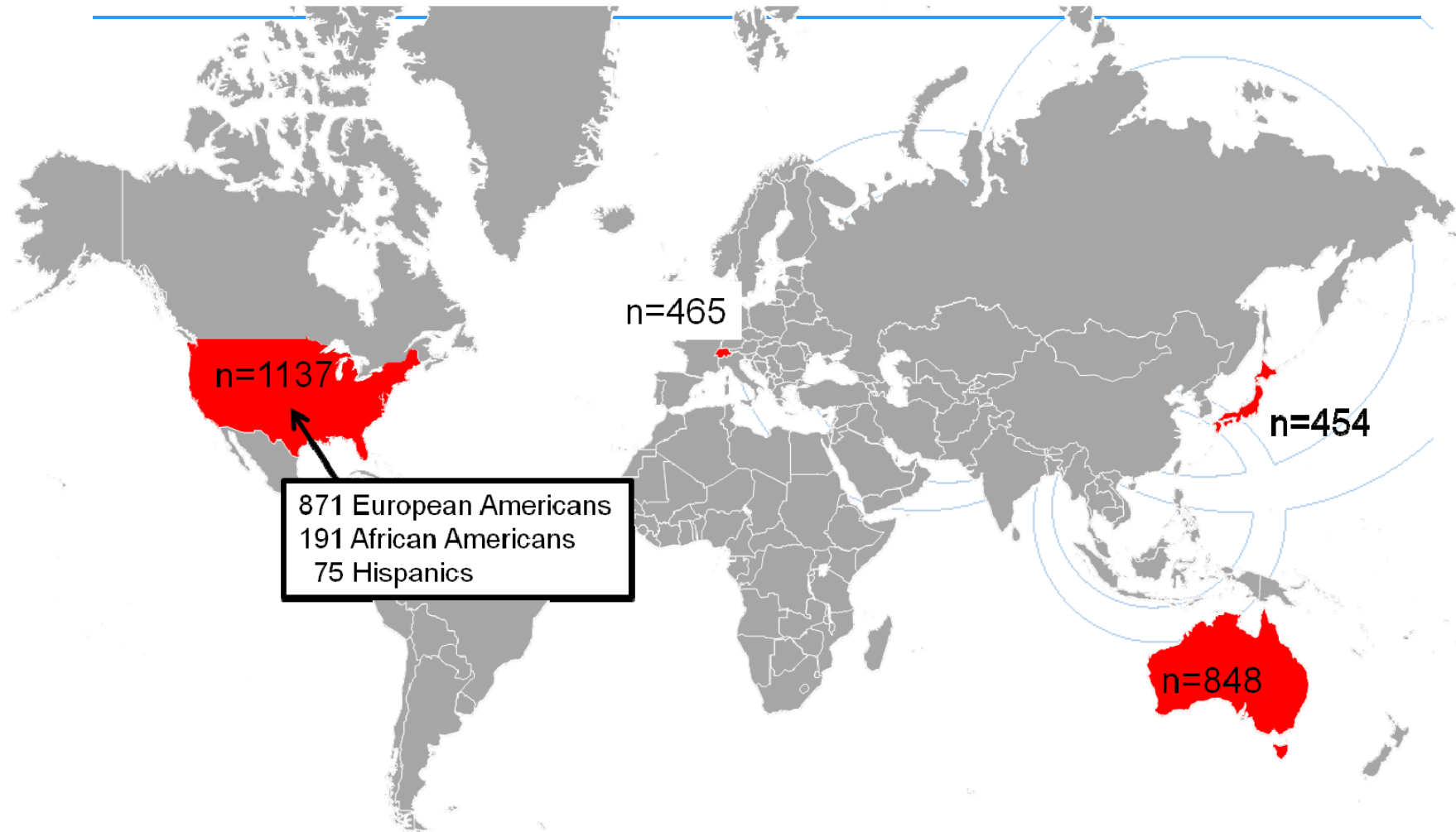


Candidate vs. Discovery approach

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Estudios GWAS y hepatitis C



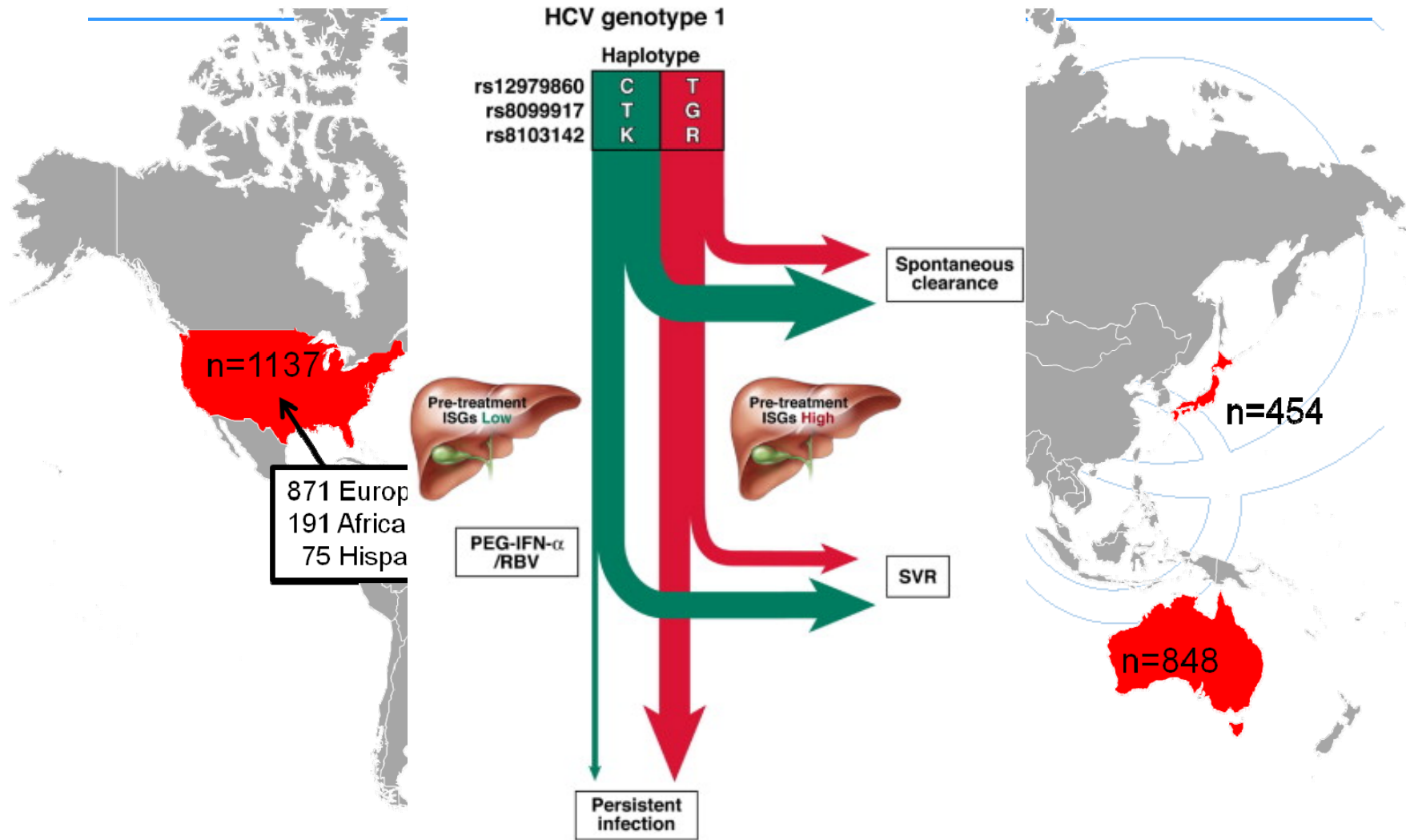
Ge D, et al. Nature 2009;461:399-401.

Tanaka Y, et al. Nat Genet 2009;41:1105-9.

Suppiah V, et al. Nat Genet 2009;41:1100-4.

Rauch A, et al. Gastroenterology 2010; Jan 7.

Estudios GWAS y hepatitis C



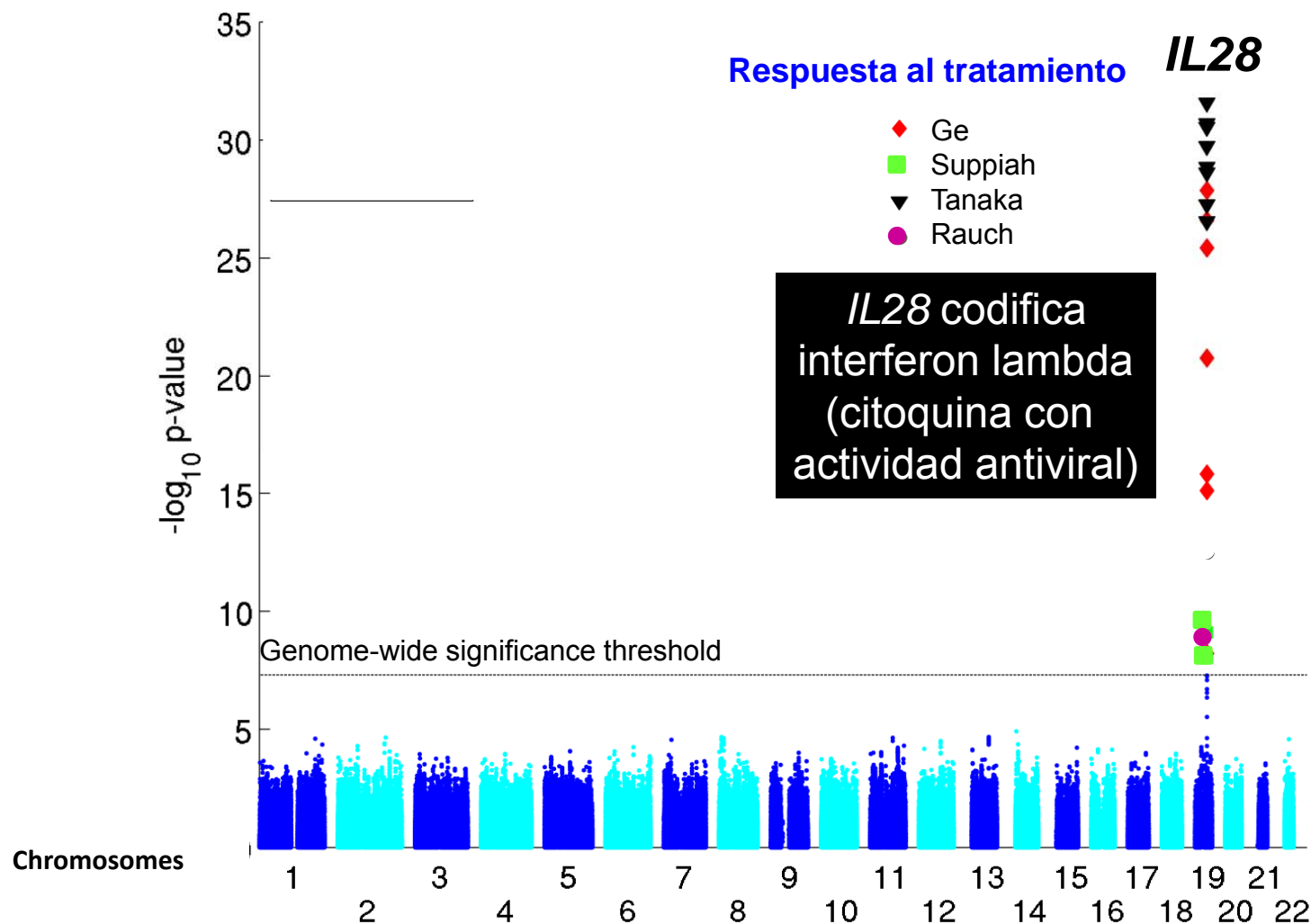
Ge D, et al. *Nature* 2009;461:399-401.

Tanaka Y, et al. *Nat Genet* 2009;41:1105-9.

Suppiah V, et al. *Nat Genet* 2009;41:1100-4.

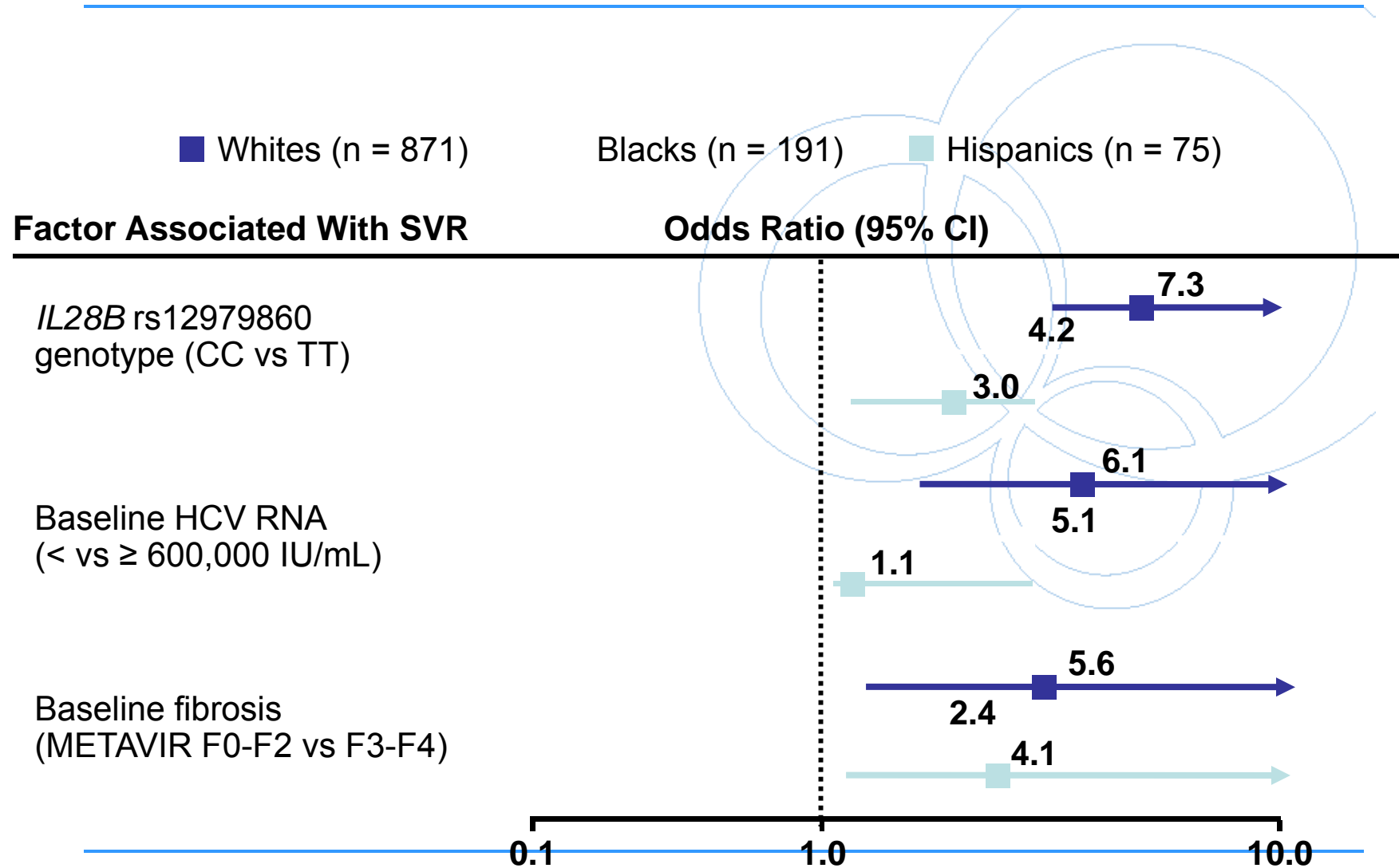
Rauch A, et al. *Gastroenterology* 2010; Jan 7.

Variantes genéticas en el gen *IL28B* y la respuesta al tratamiento de la hepatitis C

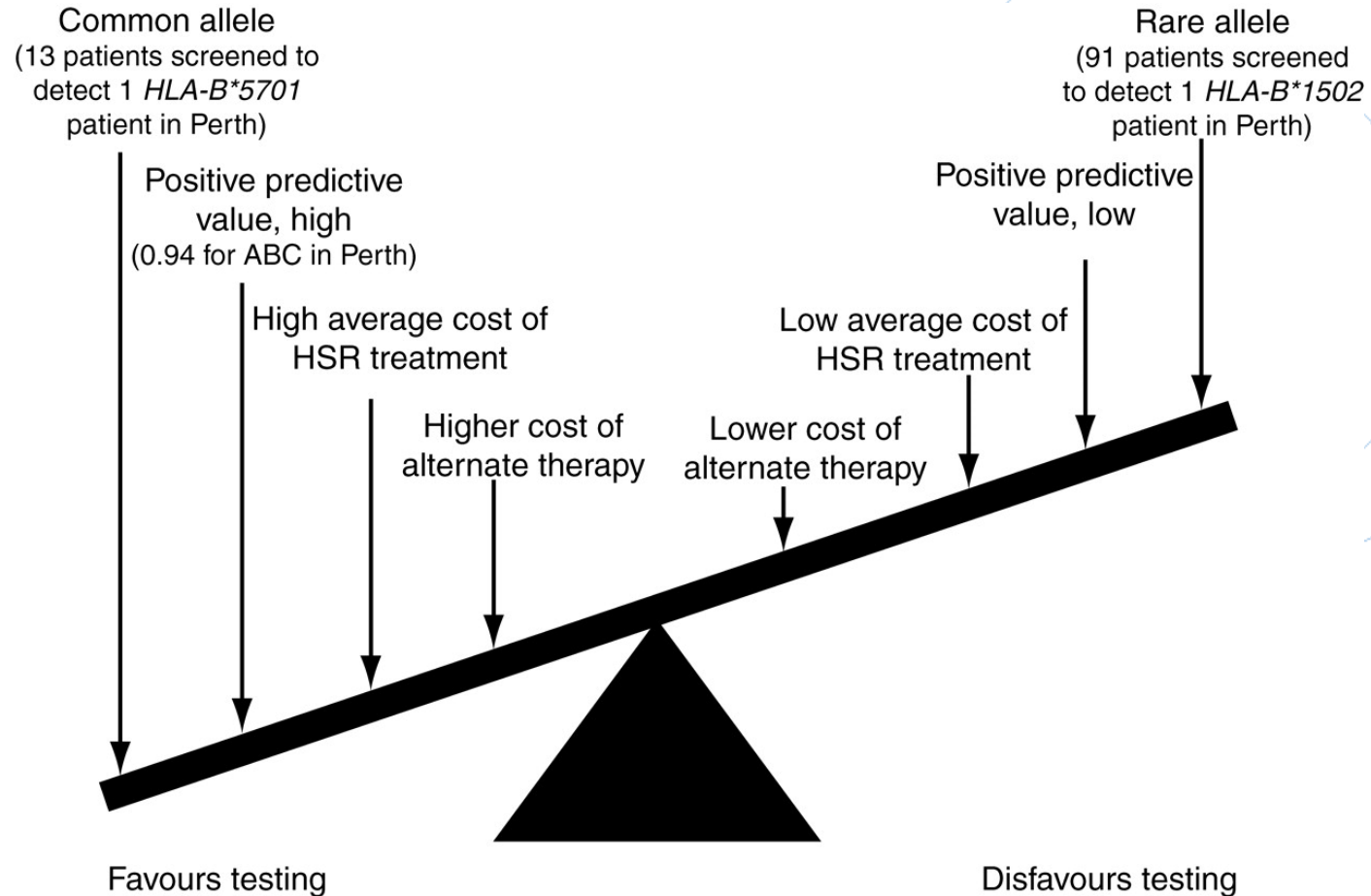


Ge D, et al. *Nature* 2009;461:399-401. Tanaka Y, et al. *Nat Genet* 2009;41:1105-9. Suppiah V, et al. *Nat Genet* 2009;41:1100-4. Rauch A, et al. *Gastroenterology* 2010; Jan 7.

New Predictors: *IL28B* Genotype a Strong Predictor of SVR With PegIFN/RBV



Where does the balance fall for pharmacogenetic screening?



Lucas, A. et al. J. Antimicrob. Chemother. 2007 59:591-593; doi:10.1093/jac/dkl557

Conclusions

- Aplicabilitat farmacogenètica
 - Eficàcia
 - Toxicitat
 - Exemples (potencialment) útils:
 - HLAB*5701 i RHS per abacavir
 - IL28B i RVS al tractament pel VHC
 - Estudis farmacogenètics:
 - Fenotip molt ben definit
 - Gens candidats vs multigen o GWAS
-

Aplicabilitat clínica de la farmacogenètica en el món del VIH

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Hospital Universitari de Tarragona Joan XXIII,
IISPV, Universitat Rovira i Virgili