Clinical Application of Pharmacogenetic Testing for the Guidance of Psychiatric Treatments

Results of a multicentric, retrospective, naturalistic study (GENEPSI)

Miquel Tuson PhD
AB-Biotics, Barcelona, Spain

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WHAT IS PHARMACOGENETICS?

Genome- Sequencing 10th Anniversary

"It is not the analysis of disease genetic risk factors that shows the most immediate promise for human health,

…but **the application of genetic information to permit safer and more efficacious use of drugs**"[1]

1) Caplan A. *What Will Drive Genomics Over the Next 10 Years*, Science 2011

SCIENTIFIC BASIS

- ✓ FDA has included pharmacogenetic labelling in several psychiatric medications
  - ➢ *eg.* Aripirazole, Citalopram, Clobazam, Atomoxetine, Fluvoxamine[1]
- ✓ Guidelines from the Clinical Pharmacogenetics Implementation Consortium
  - ➢ *eg.* Guideline on tricyclic dosing according to CYP2C19 and 2D6[2]
- ✓ Meta-analyses and findings replicated in >1 independent cohort
  - ➢ *eg.* 5-HTTLPR in caucasians, BDNF, GRIK4[3]

1) Drozda et al. 2014; 2) Hicks et al. 2013; 3) Kato et al. 2010, Niitsu et al. 2013, Kawaguchi et al. 2014

THINGS TO CONSIDER

- ✓ Performing a pharmacogenetic test can affect the attitude of the patient towards post-test treatment regimen:
  - Increased adherence
  - Increased placebo effect

- ✓ This has been shown in patients following statin therapy, should also apply to psychiatric patients[1]

1) Charland et al. 2014

THINGS TO CONSIDER

- ✓ Genetic results must be translated into clinical practice
- ✓ Knowledge transfer between laboratory and clinician shown to be poor (Danish study running 2003-2009)[1]
- ➢ Need to provide drug-specific recommendations together with test results whenever possible
  - *eg.* In 2C19 PMs max. citalopram dose is 20 mg/day, consider reducing amitriptyline starting dose by 50%

1) Jürgens et al. 2012

THINGS TO CONSIDER

- ✓ Effect of drugs likely to depend on multiple genes
- ✓ Most genes likely to make small contributions

Example: Citalopram

- Dosing and adverse effects depend partially on CYP2C19
- Adverse effects also depend on 5HTTLPR
- Likelihood of good response linked to BDNF, GRIK4, ABCB1

METHODS: TEST IMPLEMENTATION

An initial interpretation of the results obtained from the patients genetic profile is displayed in a table below. For each drug examined, the result is indicated according to the following code:

- Standard — No genetic variants relevant to the treatment have been found.
- Need for drug dose monitoring and/or less likelihood of positive response.
- Increased likelihood of positive response and/or lower risk of adverse drug reactions.
- Increased risk of adverse drug reactions.

Antidepressants					
Amitriptyline		Bupropion		Citalopram	
Clomipramine		Desipramine		Desvenlafaxine	Standard
Duloxetine		Escitalopram	Standard	Fluoxetine	
Fluvoxamine		Imipramine		Mirtazapine	Standard
Nortriptyline		Paroxetine		Sertraline	
Trimipramine		Venlafaxine			

Antipsychotics					
Aripiprazole		Clozapine		Haloperidol	
Olanzapine	Standard	Paliperidone		Perphenazine	
Pimozide		Quetiapine	Standard	Risperidone	
Ziprasidone	Standard				

Stabilizers and anticonvulsants					
Carbamazepine		Clobazam	Standard	Clona	
Lamotrigine	Standard	Levetiracetam	Standard	Lith	
Lorazepam	Standard	Phenobarbital	Standard	Phen	
Topiramate	Standard	Valproic Acid	Standard	Vigabatrin	Standard

Others					
Methadone	Standard	Methylphenidate		Naloxone	Standard
Pramipexol	Standard				

Summary table + drug-specific recommendations detailed to the level of the existing evidence

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Amitriptyline		Bupropio	
Clomipramine		Desiprami	
Duloxetine		Escitalopra	
Fluvoxamine		Imipramin	
Nortriptyline		Paroxetin	
Trimipramine		Venlafax	

Aripiprazole		Clozapine	
Olanzapine	Standard	Paliperido	
Pimozide		Quetiapin	
Ziprasidone	Standard		

Aripiprazole

Genes analysed for this drug
CYP2D6

Analysis result
Poor metabolizer of the drug (CYP2D6)

Recommendation
The analysis indicates that the patient is a CYP2D6 poor metabolizer of this drug. Consider reducing the starting dose to 50%, and proceed to titrate dose in response to efficacy (do not exceed the maximum dose of 10mg/day).

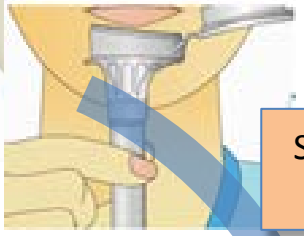
Stabilizers and anticonvulsants					
Carbamazepine		Clobazam	Standard	Clona	
Lamotrigine	Standard	Levetiracetam	Standard	Lith	
Lorazepam	Standard	Phenobarbital	Standard	Phen	
Topiramate	Standard	Valproic Acid	Standard	Vigabatrin	Standard

Others					
Methadone	Standard	Methylphenidate		Naloxone	Standard
Pramipexol	Standard				

Summary table + **drug-specific recommendations** detailed to the level of the existing evidence

METHODS: TEST WORKFLOW

Saliva Sample



Stable at room temperature

DNA Analysis & Interpretation

User-friendly Pharmacogenetic Report

STUDY DESIGN AND RESULTS

STUDY DESIGN

- ✓ Study conducted at 3 clinical settings in Madrid (Spain), coordinated by IRB from "Hospital Clínico San Carlos" (Madrid)
- ✓ Naturalistic, retrospective, multi-centric
- ✓ Entry criteria:
  - o ≥18 years old, with a psychiatric diagnosis for at least 12 months
  - o Already on treatment
  - o CGI-S ≥ 3 at baseline
  - o Genotyped (to avoid bias due to increased adherence & placebo)

1) Clinical Global Impression of Severity, a Likert-type scale ranging from 1 (healthy) to 7 (among the worst cases ever seen by the practitioner)

STUDY DESIGN

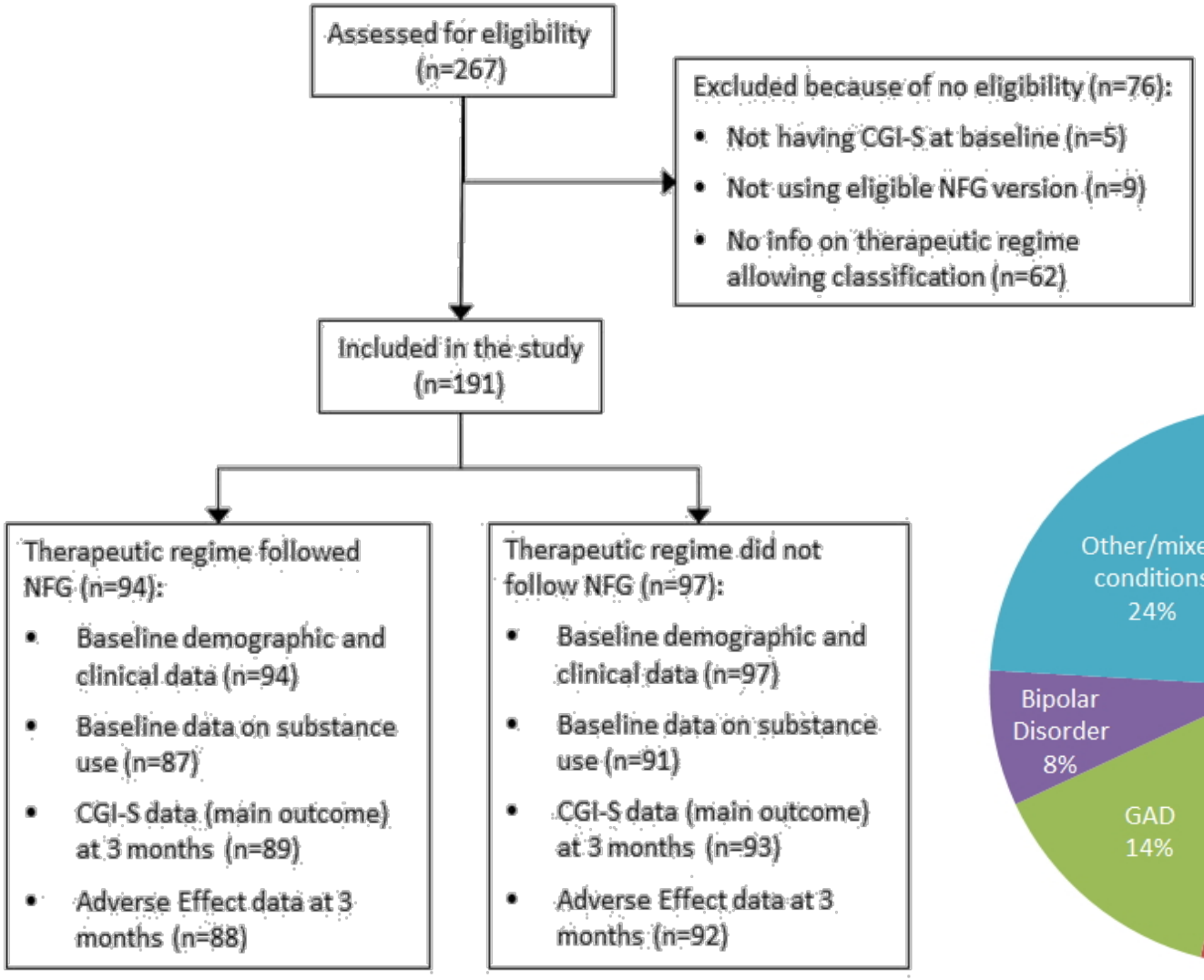
- ✓ Analysis based on the comparison among these two groups:

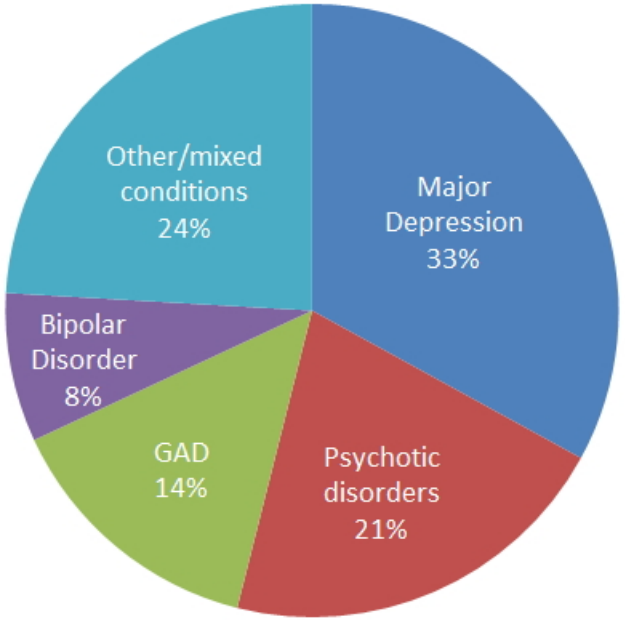
1. Patients whose **regime followed the pharmacogenetic test recommendations**

2. Those whose **regime did not**:

- o Psychiatrist decided a different medication was better suited than the one proposed by the test
- o In polymedicated patients, psychiatrist decided that changing other drugs than the ones recommended by the test was enough
- o Drugs recommended by the test contraindicated or not recommended due to patient's non psychiatric medication/condition

STUDY SAMPLE





STUDY SAMPLE

	Followed recommendations NFG (N=94)		Do not follow recommendations NFG (N=97)	
Sex (%)				
· Male	38	40,4%	39	40,2%
· Female	56	59,6%	58	59,8%
· Data Missing	0	0,0%	0	0,0%
Age (median, min & max)	48.0	(20 – 83)	44.0	(22 – 89)
Years evolution of current disorder (median, min & max)	13.0	(2 – 60)	13.0	(1 – 51)
CGI-S current disorder (average and SD)	4.32	(0.66)	4.48	(0.77)
Type of current disorder				
· Major depression	32	34,0%	31	32,0%
· Bipolar disorder	9	9,6%	6	6,2%
· Anxiety disorder	15	16,0%	12	12,4%
· Psychotic disorder	13	13,8%	27	27,8%
· Other disorders / mixed	25	26,6%	21	21,6%
· Data Missing	0	0,0%	0	0,0%
Tobacco (%)				
· No	50	53,2%	59	60,8%
· Yes	37	39,4%	32	33,0%
· Data Missing	0	0,0%	0	0,0%
Alcohol consumption (equiv. to ≥1 glass of wine per day)				
· No	79	84,0%	82	84,5%
· Yes	8	8,5%	9	9,3%
· Data Missing	0	0,0%	0	0,0%
Substance abuse (%)				
· No	80	85,1%	80	82,5%
· Yes	7	7,4%	11	11,3%
· Data Missing	7	7,4%	6	6,2%
Non-psychiatric medication (%)				
· No	71	75,5%	78	80,4%
· Yes	23	24,5%	19	19,6%
· Data Missing	0	0,0%	0	0,0%
Hospitalization (%)				
· No (outpatients)	61	64,9%	65	67,0%
· Yes (inpatients)	29	30,9%	28	28,9%
· Data Missing	4	4,3%	4	4,1%

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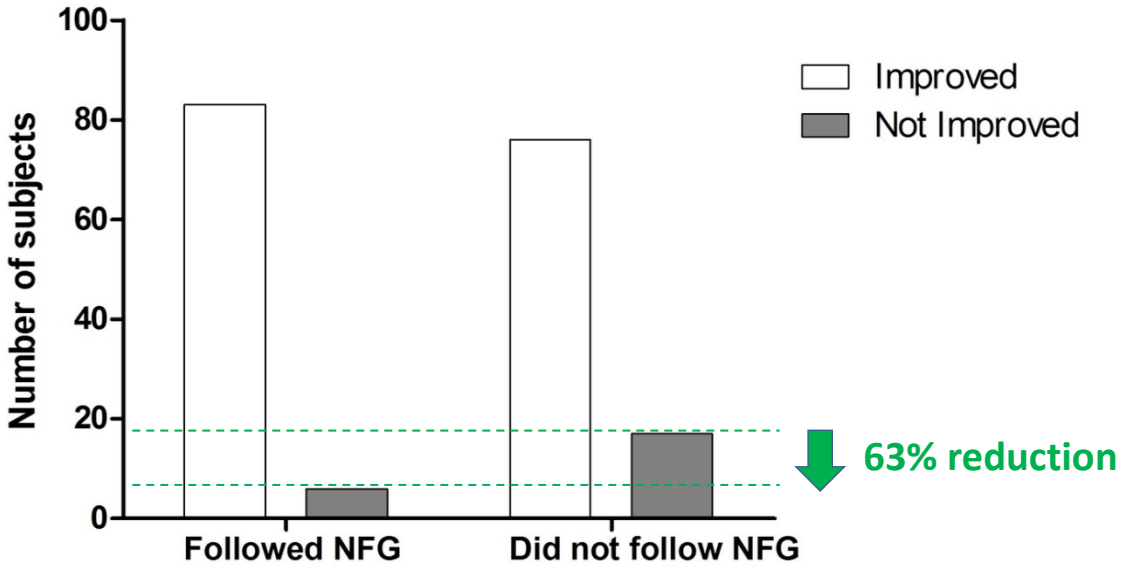
✓ No differences at baseline for any of the clinical or demographic characteristics

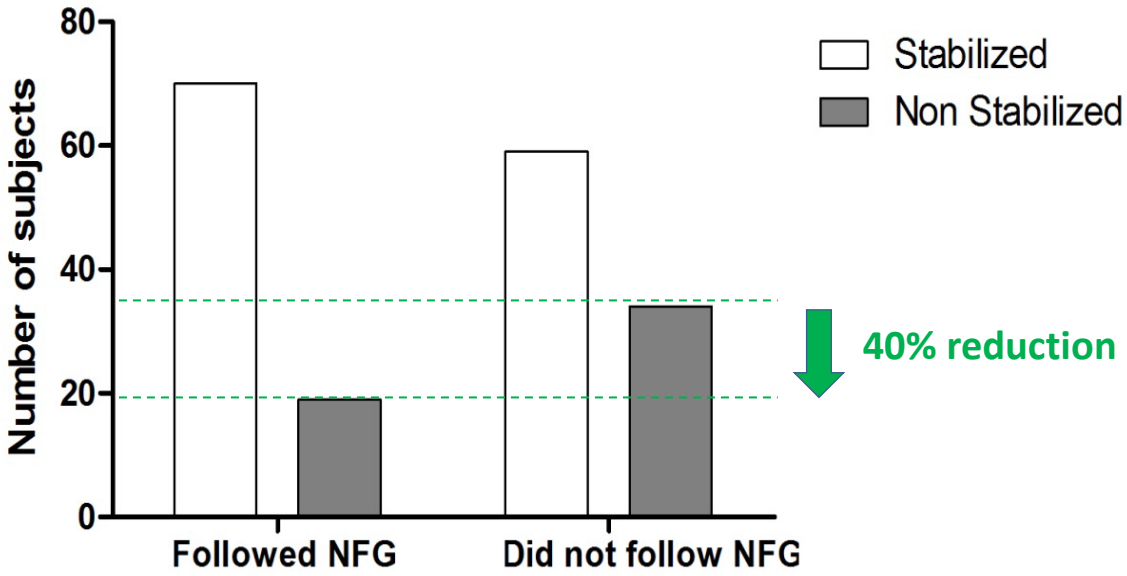
MAIN OUTCOME

- ✓ Number of patients whose condition did not improve decreased 3-fold in the group following NFG (6.7% vs. 18.3%, Chi-square P = 0.019)
- ✓ Effect remains significant after adjusting for all baseline variables in a logistic model, **adjusted OR = 3.05** (95%CI: 1.14-8,15)



ADDITIONAL RESULTS

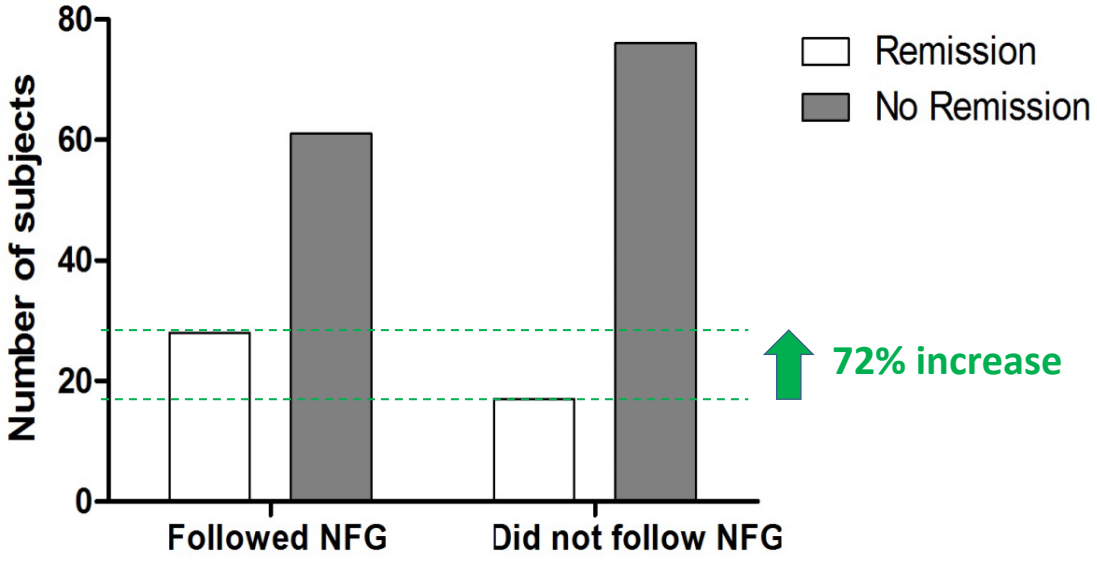
- ✓ Number of patients with CGI-$S_{t=3}$ >3 reduced almost 2 times in the group following NFG (23% vs. 38%, Chi-square P = 0.033)[1]
- ✓ Patients with CGI-S=3 at baseline excluded from this analysis (6 patients per group)



1) OR = 2.06 (95%CI: 1.05 – 4.03)

ADDITIONAL RESULTS

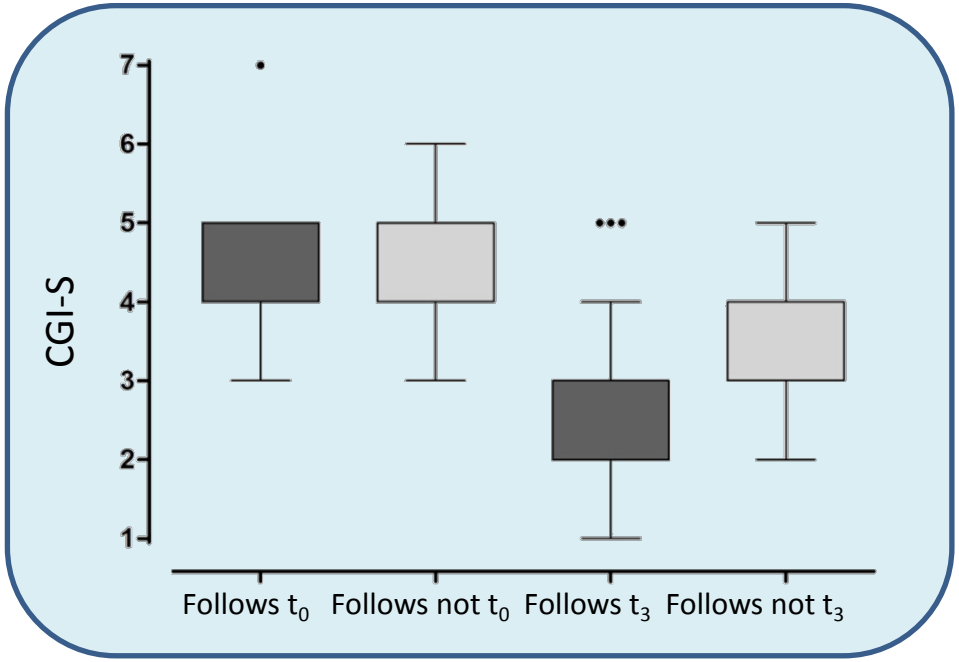
- ✓ Number of patients with CGI-$S_{t=3}$ ≤ 2 increased by 72% in the group following NFG (31.5% vs. 18.3%, Chi-square P = 0.039)[1]



1) OR = 2.05 (95%CI: 1.03 – 4.09)

ADDITIONAL RESULTS

- ✓ Amount of CGI-S score change evaluated against all baseline characteristics
- ✓ Only baseline severity and following recommendations had significant effect (final model r=0.37, P < 0.0001)



PROSPECTIVE STUDY IN PROGRESS

Title

✓ Randomized, parallel-group controlled clinical trial of the effectiveness of the pharmacogenetic information provided by NEUROPHARMAGEN® in the treatment of patients diagnosed of major depressive disorder (according to DSM-IV).

Protocol version approved by IRB/IEC and Spanish AEMPS V4.0 (includes amendment no. 1, 2 & 3)

Design

✓ Randomized, parallel-group controlled prospective study
✓ Single-blind study with blinded primary endpoint evaluation
✓ n ~ **518** patients included (for approx. 420 randomized)
✓Follow up period: **3 months**
✓ Multicentric nationwide study
✓Number of centers: **18 major hospitals** (approx. **30 patients / center**)

Pathology in study

✓ Major Depressive Disorder (according to DSM-IV)

Milestones of the study

✓ FPFV: July 2014 – LPLV: June 2015

PARTICIPATING HOSPITALS

Nombre hospital	Provincia	Investigador Principal
HOSP. UNIV. CENTRAL ASTURIAS	ASTURIAS	Dr. Julio Bobes García
HOSP. DEL MAR	BARCELONA	Dr. Víctor Pérez Solá
HOSP. DE LA SANTA CREU I SANT PAU	BARCELONA	Dr. Enric Álvarez Martínez
HOSP. CLINIC DE BARCELONA	BARCELONA	Dr. Eduard Vieta Pascual
HOSP. BELLVITGE	BARCELONA	Dr. José Manuel Menchón Magriñá
HOSP. MUTUA DE TERRASSA	BARCELONA	Dr. Josep Gascón Barrachina
CONSORCI SANITARI DEL MARESME	BARCELONA	Dr. Josep Cañete Crespillo
CORP. SANITARIA PARC TAULI	BARCELONA	Dr. Diego J. Palao Vidal
HOSP. GENERAL DE JEREZ	CADIZ	Dr. José María Villagrán
HOSP. CLINICO UNIV. SAN CECILIO GRANADA	GRANADA	Dr. Rafael Navarro Pichardo
HOSP. FUNDACION JIMENEZ DIAZ	MADRID	Dr. Enrique Baca García
HOSP. 12 DE OCTUBRE	MADRID	Dr. Roberto Rodríguez-Jiménez
HOSP. UNIV. RAMON Y CAJAL	MADRID	Dr. Jerónimo Saiz Ruiz
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… Thank You!!!