NUTRIRE IL BENESSERE:
risorse esogene ed endogene

Monza, 7 febbraio 2018

L'uso dei test farmacogenetici nella pratica clinica psichiatrica: verso la personalizzazione dei trattamenti farmacologici Focus sui disturbi dell'umore

UNIVERSITA' DEGLI STUDI DELL'INSUBRIA
Marta Ielmini

The utility of Pharmacogenetic testing to tailor psychiatric medication. Focus on mood disorders

- Mood disorders are characterized by significant changes in a person's mood, alterations in cognition, appetite, sleep and psychomotor function.
- High mortality, rates both from suicide and an increased risk for seroius medical illnesses including heart desease, diabetes and stroke.
- High morbidity due to lost workdays and income, and an increase risk for comorbid substance and alcohol abuse

By **2020 depression** will be the **second leading cause of Disability**
adjusted Life Years worlwide calculated for all ages

Prendes-Alvares et al, 2017; Reddy MS, 2010.

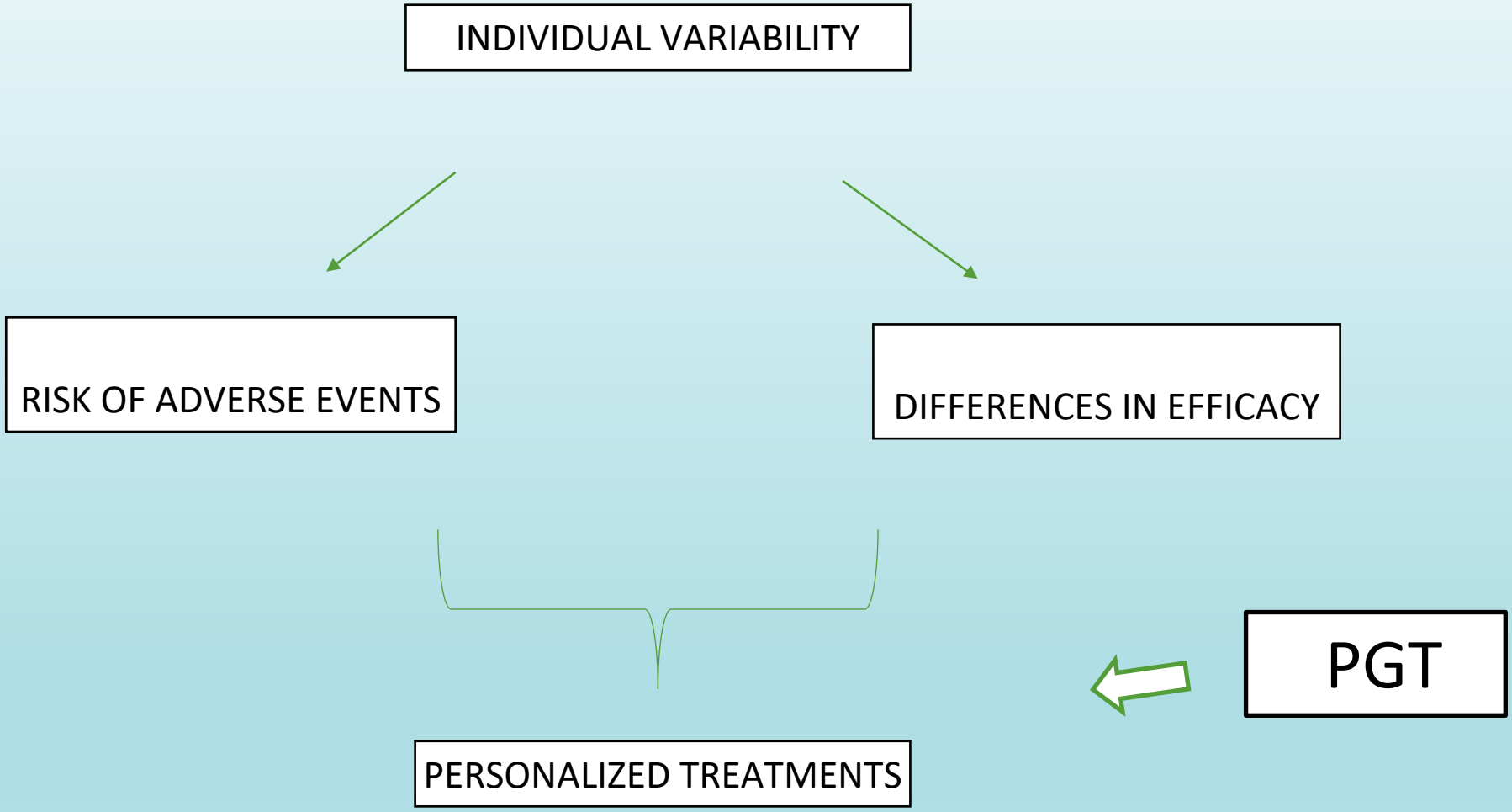
The utility of Pharmacogenetic testing to tailor psychiatric medication. Focus on mood disorders

- Wide number of treatments versus wide spectrum of health care providers → critical shortage of psychiatrists

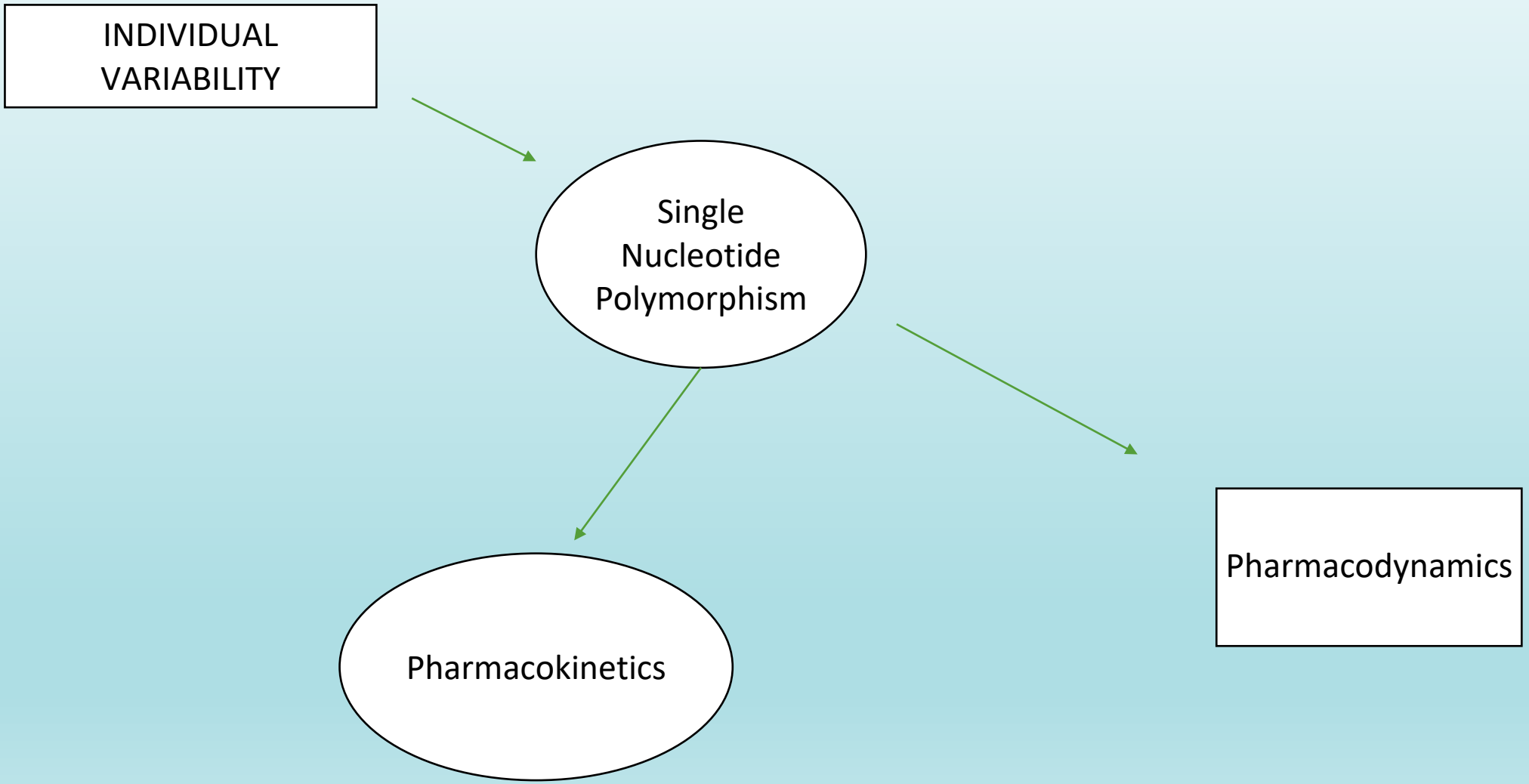
- 60%-70% of prescriptions of psychiatric medication are written by family medicine pratictioners, internal medicine practitioners, gynecologists

Maciel et al, 2017; Mark et al, 2009.

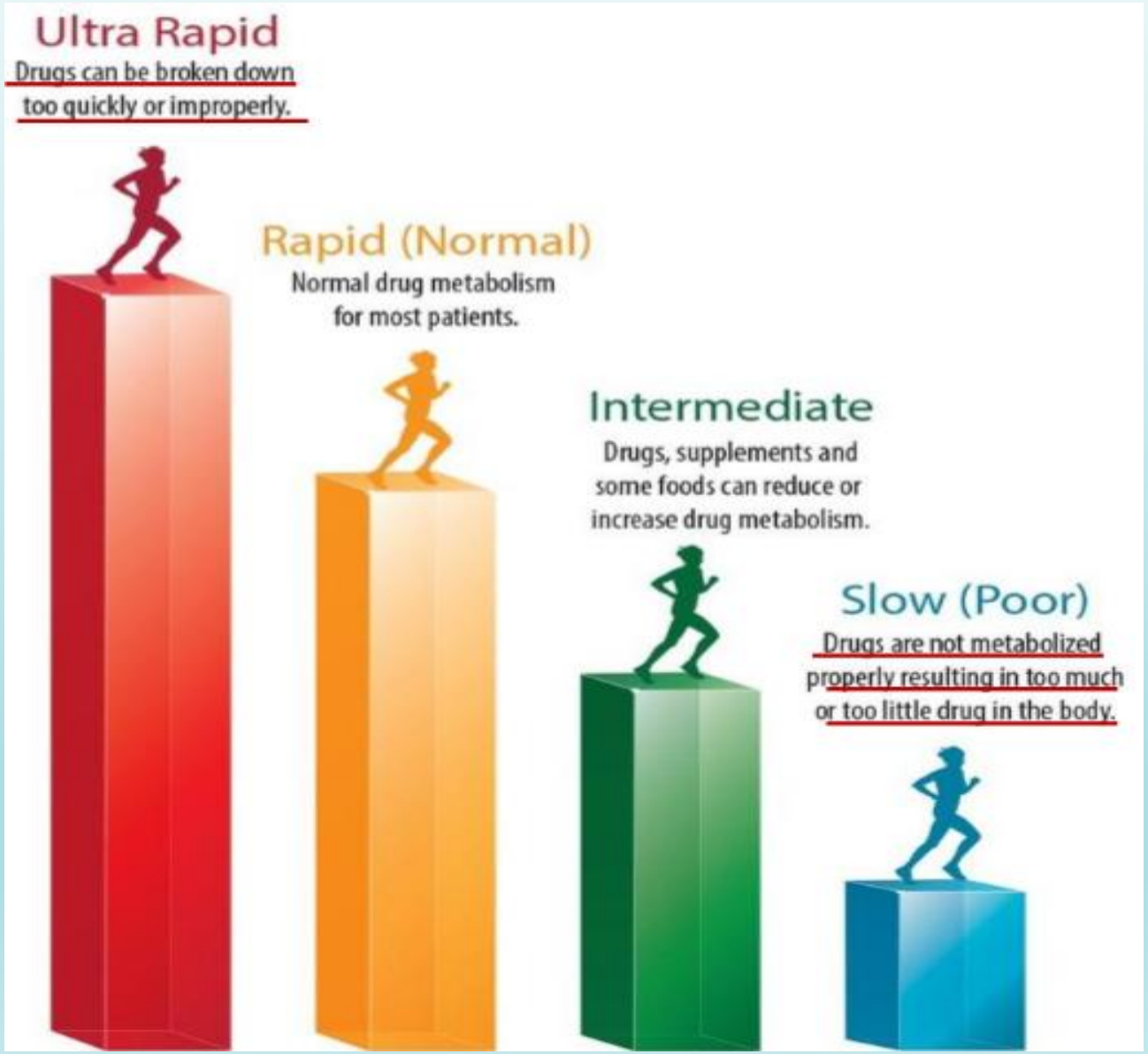
The utility of Pharmacogenetic testing to tailor psychiatric medication. Focus on mood disorders



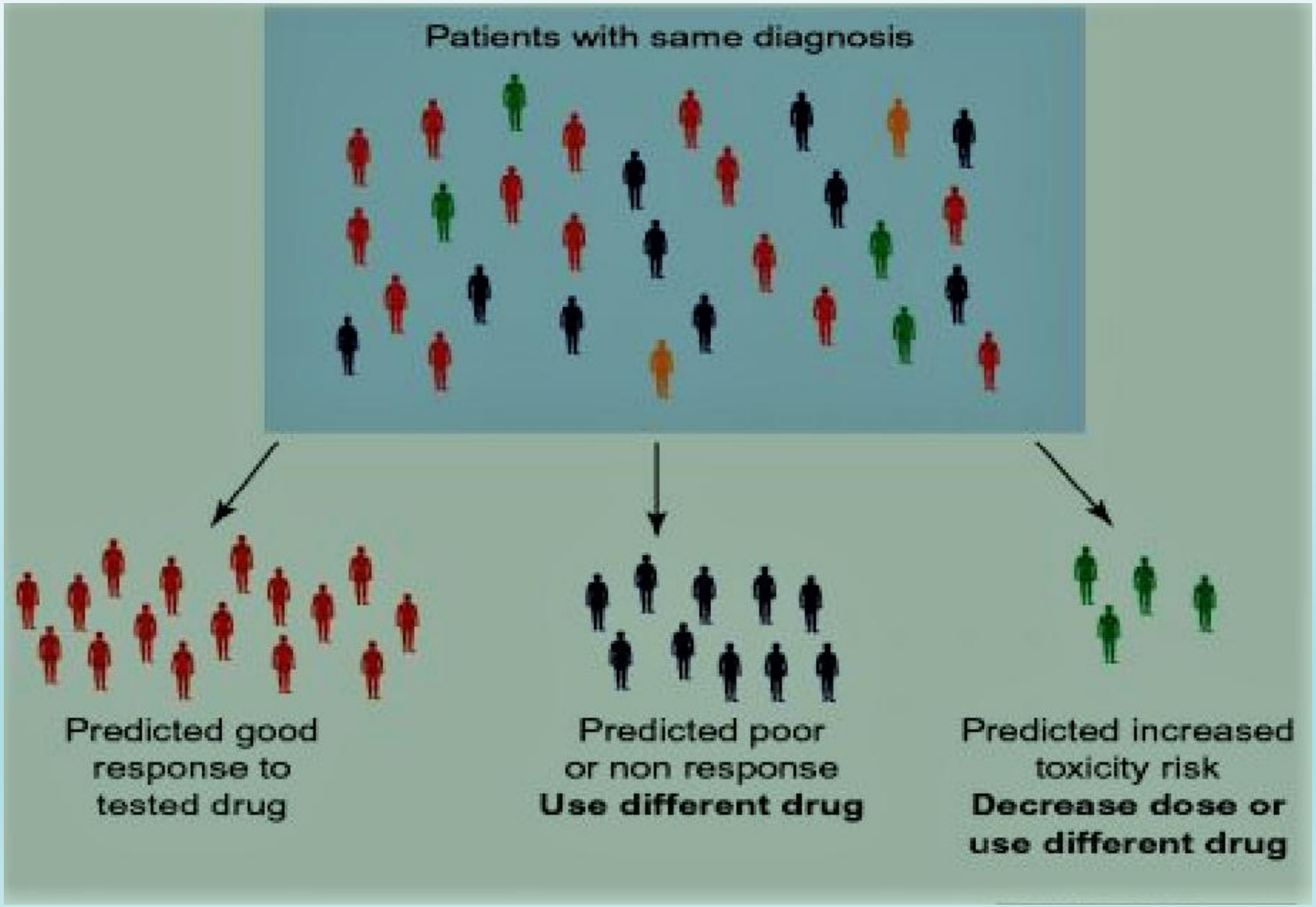
The utility of Pharmacogenetic testing to tailor psychiatric medication. Focus on mood disorders



The utility of Pharmacogenetic testing to tailor psychiatric medication. Focus on mood disorders



The utility of Pharmacogenetic testing to tailor psychiatric medication. Focus on mood disorders



The utility of Pharmacogenetic testing to tailor psychiatric medication. Focus on mood disorders

- The potential to tailor psychiatric medication choice and dose based on pharmacogenetic test results holds great promise for patients and providers **to shorten the time between diagnosis and effective illness management.**

  [Basset and Costain, 2012]

- Studies in 2013 showed that when pharmacogenetic testing of these genes was used to guide **the pharmacological treatment of depression the likelihood of treatment response and remission doubled**

  [Hall-Flavin et al, 2013]

- A pilot study showed a **positive attitude among psychiatrists** towards the integration of genetic testing and genetic counseling into psychiatric patient care

  [Thomson et al, 2014]

- Organizations such as **the US FDA (US Food and Drug Administration) and the EMA (European Medicines Agency) already recommend the use of pharmacogenetic testing in clinical practice**. Specifically, the FDA currently indicates several pharmacogenetic biomarkers labeling of several teraphies.

  [U.S Food and Drug Administration, 2013]

The utility of Pharmacogenetic testing to tailor psychiatric medication. Focus on mood disorders

✓ FDA has included pharmacogenetic labelling in several psychiatric medications

eg. Aripirazole, Citalopram, Clobazam, Atomoxetine, Fluvoxamine[1]

FDA Table of Pharmacogenomic Biomarkers in Drug Labeling

Guidelines from the Clinical Pharmacogenetics 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

The utility of Pharmacogenetic testing to tailor psychiatric medication. Focus on mood disorders

Obstacles:

- Literature data;
- Privacy;
- Medical reporting time;
- Use of genetic information;
- Costs

(Sanchez-Iglesias et al., 2016; O'Connor et al., 2012; Crews et al., 2012; Ventola, 2013)

The utility of Pharmacogenetic testing to tailor psychiatric medication. Focus on mood disorders

Dovepress

Published online 2016 Jan 19. doi: 10.2147/PGPM.S93480

Initial assessment of the benefits of implementing pharmacogenetics into the medical management of patients in a long-term care facility

Juan-Sebastian Saldivar, David Taylor, Elaine A Sugarman, Ali Cullors, Jorge A Garces, Kahuku Oades, and Joel Centeno

- The US FDA reports spending US$30 medications in 2014 and US$136 billi that is spent on prescription drugs, an additional US$0.50 is spent on ADRs

SpringerLink FULL-TEXT ARTICLE

- between 1.3% a Europe

Drugs Aging. 2012 Mar 1;29(3):225-32. doi: 10.2165/11599430-000000000-00000.

Adverse drug reaction-related hospitalizations in persons aged 55 years and over study in the Netherlands.

Ruiter R[1], Visser LE, Rodenburg EM, Trifirò G, Ziere G, Stricker BH.

OXFORD ACADEMIC

- Medication-related problems are thought to cause between 10 and all hospital admissions in o

Pharmacist-led interventions to reduce unplanned admissions for older people: a systematic review and meta-analysis of randomised controlled trials

Rebecca Thomas; Alyson L. Huntley ✉; Mala Mann; Dyfed Huws; Glyn Elwyn; Shantini Paranjothy; Sarah Purdy

The utility of pharmacogenetic testing to support the treatment of bipolar disorder

The utility of Pharmacogenetic testing to tailor psychiatric medication in the clinical practic

Marta Ielmini, Nicola Poloni, Ivano Caselli, Jordi Espadaler, Miquel Tuson, Alessandro Grechi, Camilla Callegari

Background

- Bipolar Disorder is a severe psychiatric illness, characterised by mood swings, with a life time prevalence of 2.4%

[Merikangas et al., 2011]

- Although effective treatments already exist, variability in outcome leads to a large numbers of **treatment failures**, included misdiagnosis of the disorder followed by inadeguate or inappropriate treatment and problems due to **drug-resistent, rapid-cycling and cognitive decline despite drug therapy**

[Nasrallah HA, 2015; Peedicayil,2014]

- Interindividual variation in drug response depends on a number of factors, including diagnostic accuracy, drug-drug interactions, renal and hepatic function**, medical and psychiatric comorbidity**. In addition, **genetically determined pharmacokinetic and pharmacodynamic variability** can influence medication response

[Mrazek, 2010]

- The potential to tailor psychiatric medication choice and dose based on pharmacogenetic test results holds great promise for patients and providers to **shorten the time between diagnosis and effective illness management**.

[Basset and Costain, 2012]

- Studies in 2013 showed that when pharmacogenetic testing of these genes was used to guide the pharmacological treatment of **depression the likelihood of treatment response and remission doubled**

[Hall-Flavin et al, 2013]

Studio: *obiettivi*

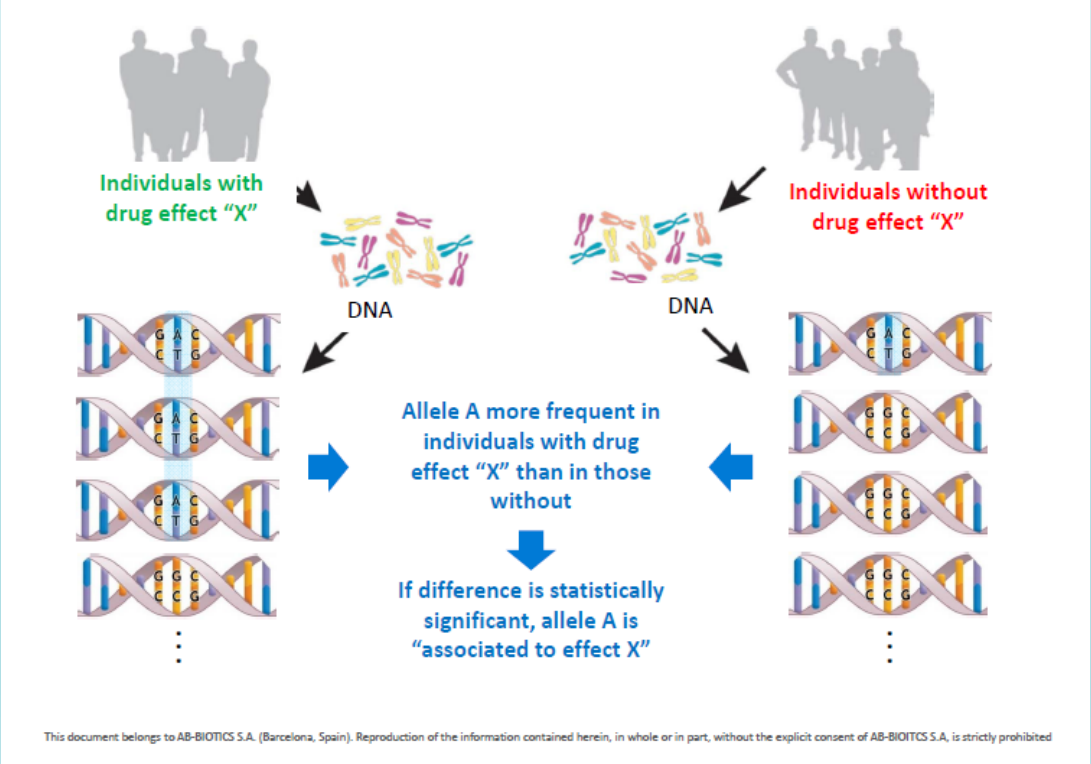
- Valutazione della % di pazienti sottoposta a una terapia farmacologica ottimale o subottimale secondo il test genetico *Neurofarmagen*
- Valutazione le mutazioni clinicamente rilevanti all'interno della popolazione
- Valutazione a T1 e T2 delle eventuali modifiche della terapia farmacologica apportate dai clinici di riferimento, dell'andamento psicopatologico e degli effetti avversi
- Analisi Mirror sull'accesso ai servizi d'urgenza e sulle giornate di ricovero

Studio: Materiali e Metodi

Popolazione

- 30 pazienti affetti da Disturbo Bipolare (DSM 5)
- Utenti delle ASST Sette Laghi di Varese e ASST Santi Paolo e Carlo di Milano
- Non stabilizzati dalla terapia in corso (CGIs ≥ 3)
- ≥ 18 anni
- Che accettino di sottoporsi al test genetico
- Che abbiano prestato consenso informato scritto

Test Genetico Neurofarmagen



Antipsicotici					
Aloperidolo		**Aripiprazolo**	Standard	**Clozapina**	Standard
Olanzapina		**Paliperidone**		**Perfenazina**	Standard
Pimozide	Standard	**Quetiapina**	Standard	**Risperidone**	
Tioridazina	Standard	**Ziprasidone**	Standard	**Zuclopentixolo**	

TABELLA RIASSUNTIVA

Di seguito viene fornita sotto forma di tabella una prima interpretazione dei risultati ottenuti a partire dal profilo genetico del paziente. Per ciascuno dei farmaci analizzati, il risultato viene indicato secondo la seguente legenda:

Standard ▶ Non è stata rilevata alcuna variazione genetica per il trattamento in questione. Si raccomanda di seguire le indicazioni riportate nell´SPC.

▶ Necessità di monitoraggio specifico della dose e/o minore probabilità di risposta positiva.

▶ Maggiore probabilità di risposta positiva e/o minor rischio di reazioni avverse.

▶ Maggior rischio di reazioni avverse di diverso tipo.

Risultati a: caratteristiche sociodemografiche

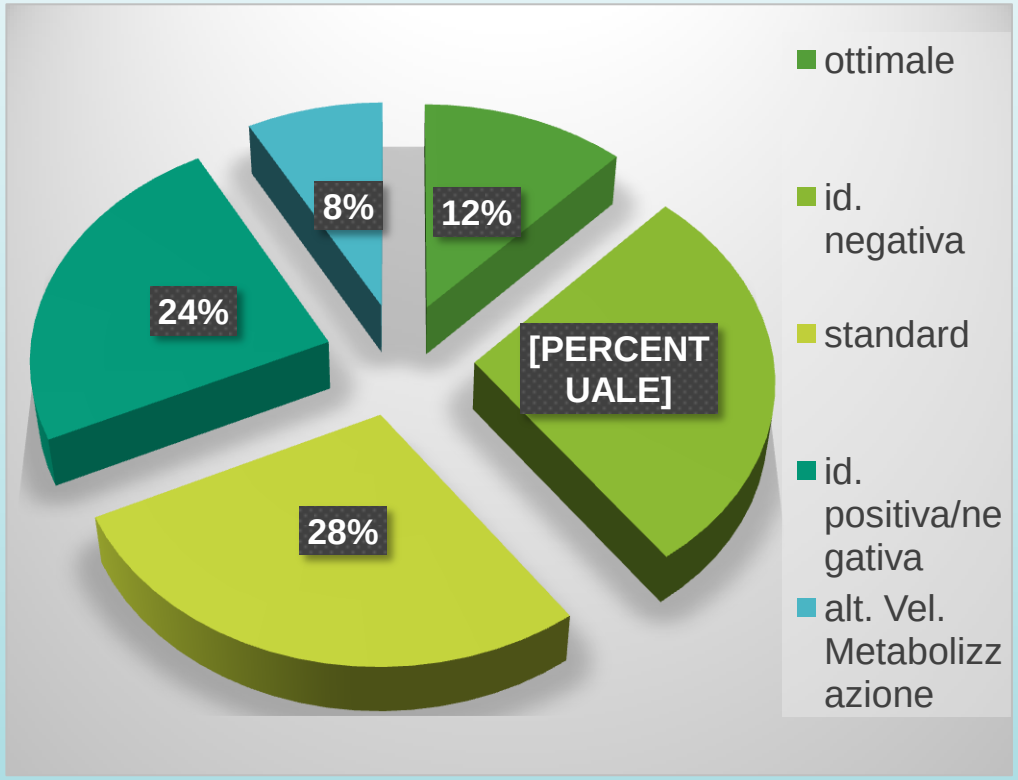
Genere,		
Maschi	**48%**	**N= 12**
Femmine	**52%**	**N= 13**
Età Media	**54.8**	**DS=15.22**
Nazionalità		
Italiana	**96%**	**N=24**
Altra	**4%**	**N=1**
Occupazione,		
occupati	**40%**	**N=10**
disoccupati	**16%**	**N=4**
pensionati	**36%**	**N=9**
I.C.	**8%**	**N=2**
Caregiver		
1	**40%**	**N=10**
2	**44%**	**N=11**
3 o più	**16%**	**N=4**

Risultati b: Caratteristiche cliniche

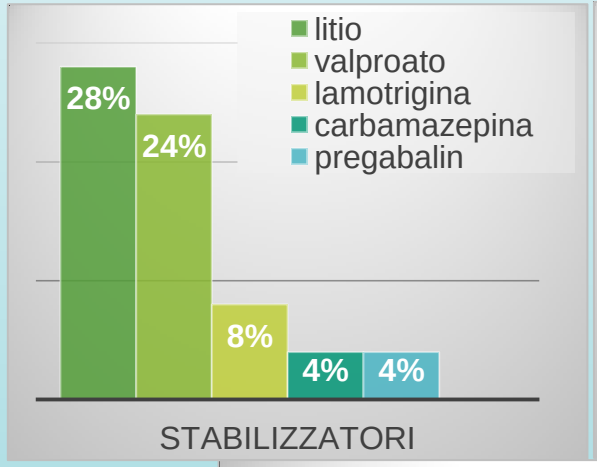
Diagnosi		
Disturbo Bipolare I	**52%**	**N=16**
Disturbo Bipolare II	**48%**	**N=14**
Comorbidità Psichiatrica		
Nessuna	**76%**	**N=23**
1	**16%**	**N=5**
2 o più	**8%**	**N=2**
Comorbidità Organica		
No	**76%**	**N=23**
1	**16%**	**N= 5**
2 o più	**8%**	**N=2**
Servizio		
CPS	**68%**	**N=20**
CRM	**12%**	**N=4**
SPDC	**16%**	**N=5**
Amb. Ansia e Depressione	**4%**	**N=1**
Sintomi al T0		
Sintomi depressivi	**56%**	**N=17**
Sintomi maniacali	**24%**	**N=7**
Stato misto	**20%**	**N=6**

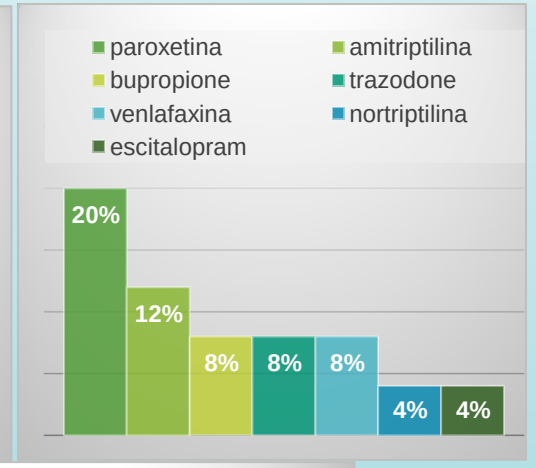
	N	Media	DS	Min	Max
Anni di trattamento	30	9,52	7,26	2	30
N precedenti terapie	30	3.52	1.3266	2	6

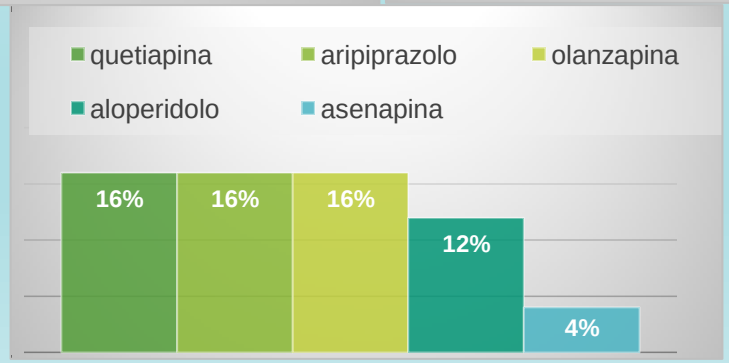
Risultati c: Terapia al T0 secondo il test farmacogenetico



CGI s: 4,83 (DS 3,7)
HDRS: 18,36 (DS 8.9)
YMRS: 14,72 (DS 5.6)



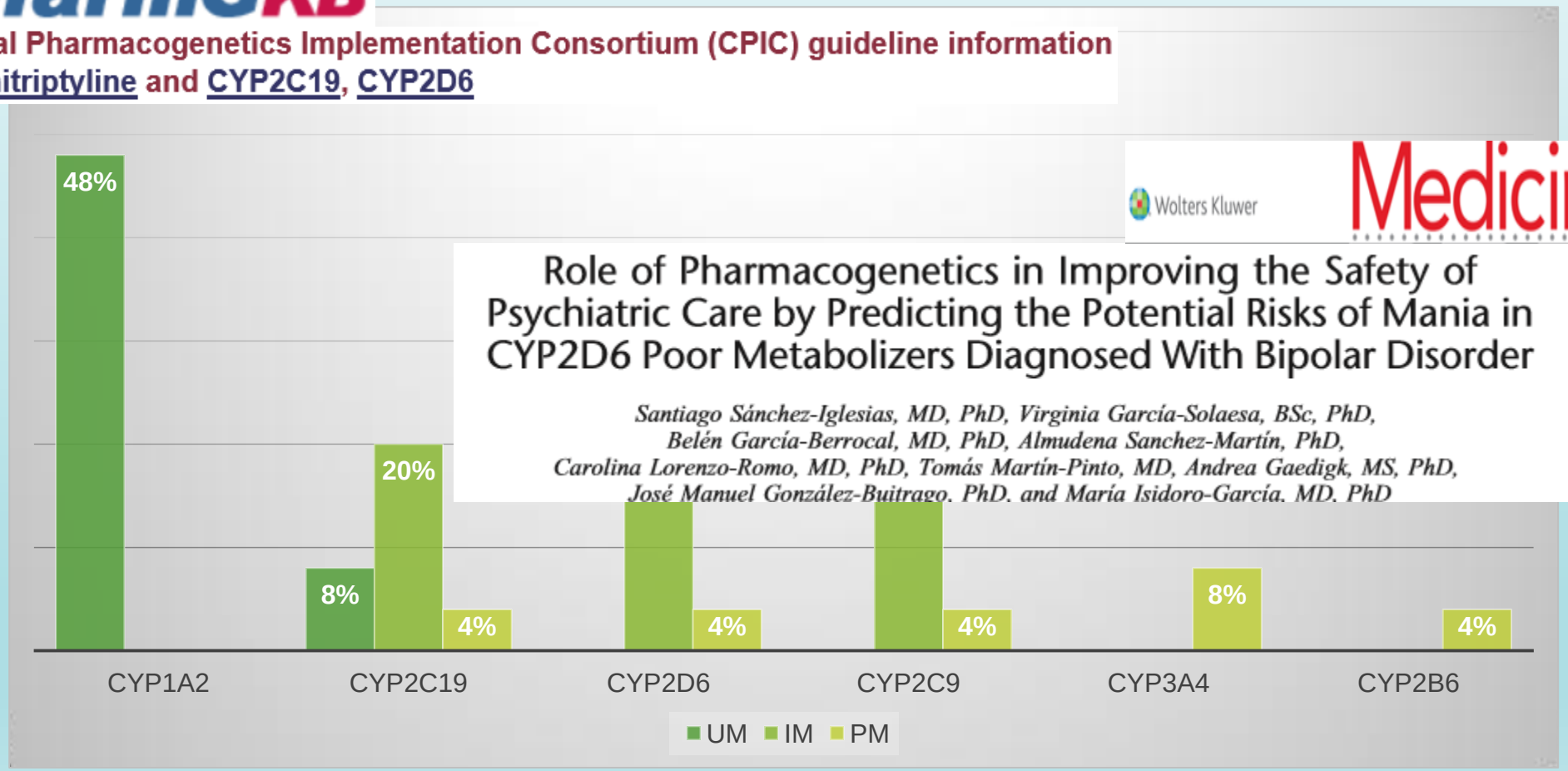




Risultati d: polimorfismi di rilievo dal punto di vista farmacocinetico

PharmGKB

Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline information for amitriptyline and CYP2C19, CYP2D6

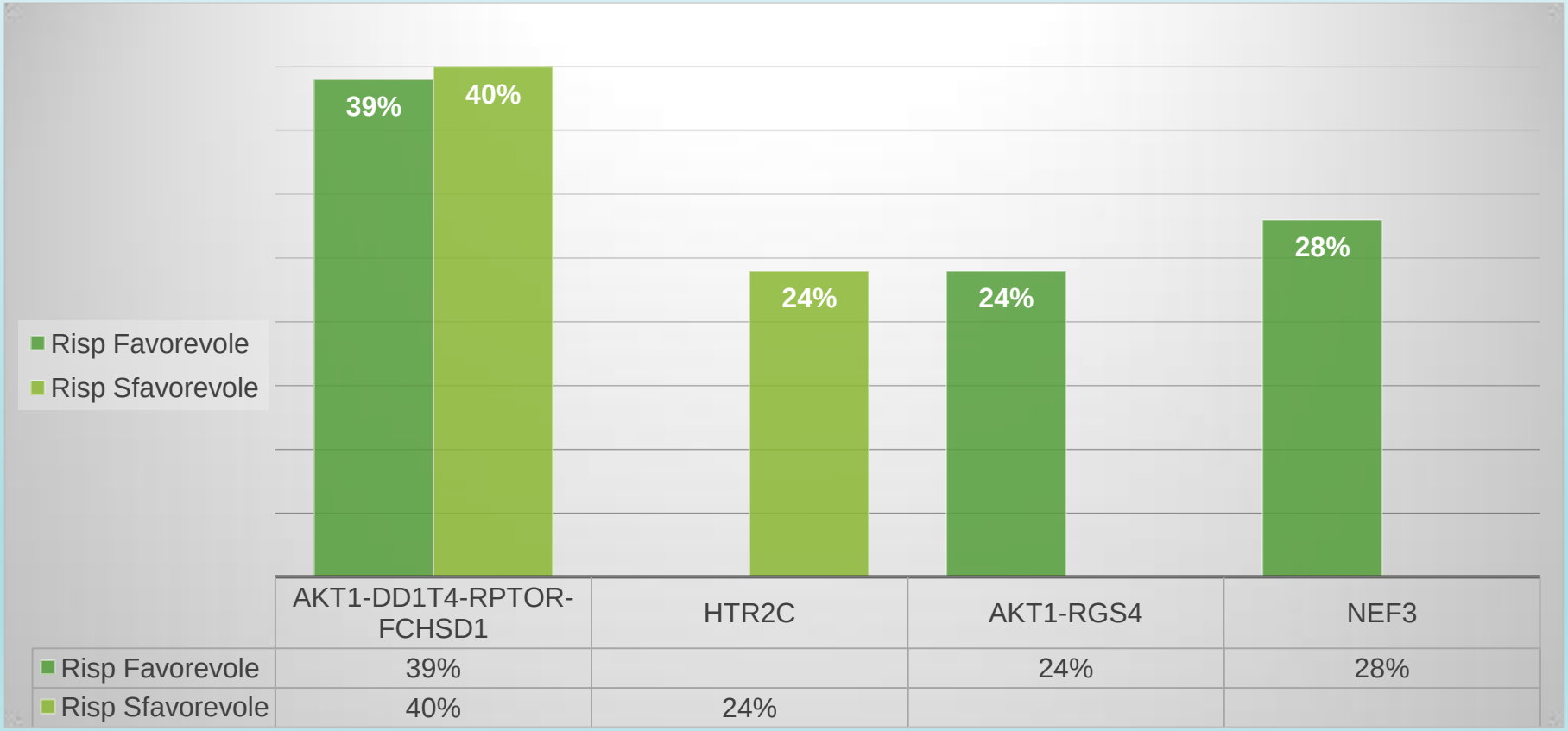


Wolters Kluwer Medicine

Role of Pharmacogenetics in Improving the Safety of Psychiatric Care by Predicting the Potential Risks of Mania in CYP2D6 Poor Metabolizers Diagnosed With Bipolar Disorder

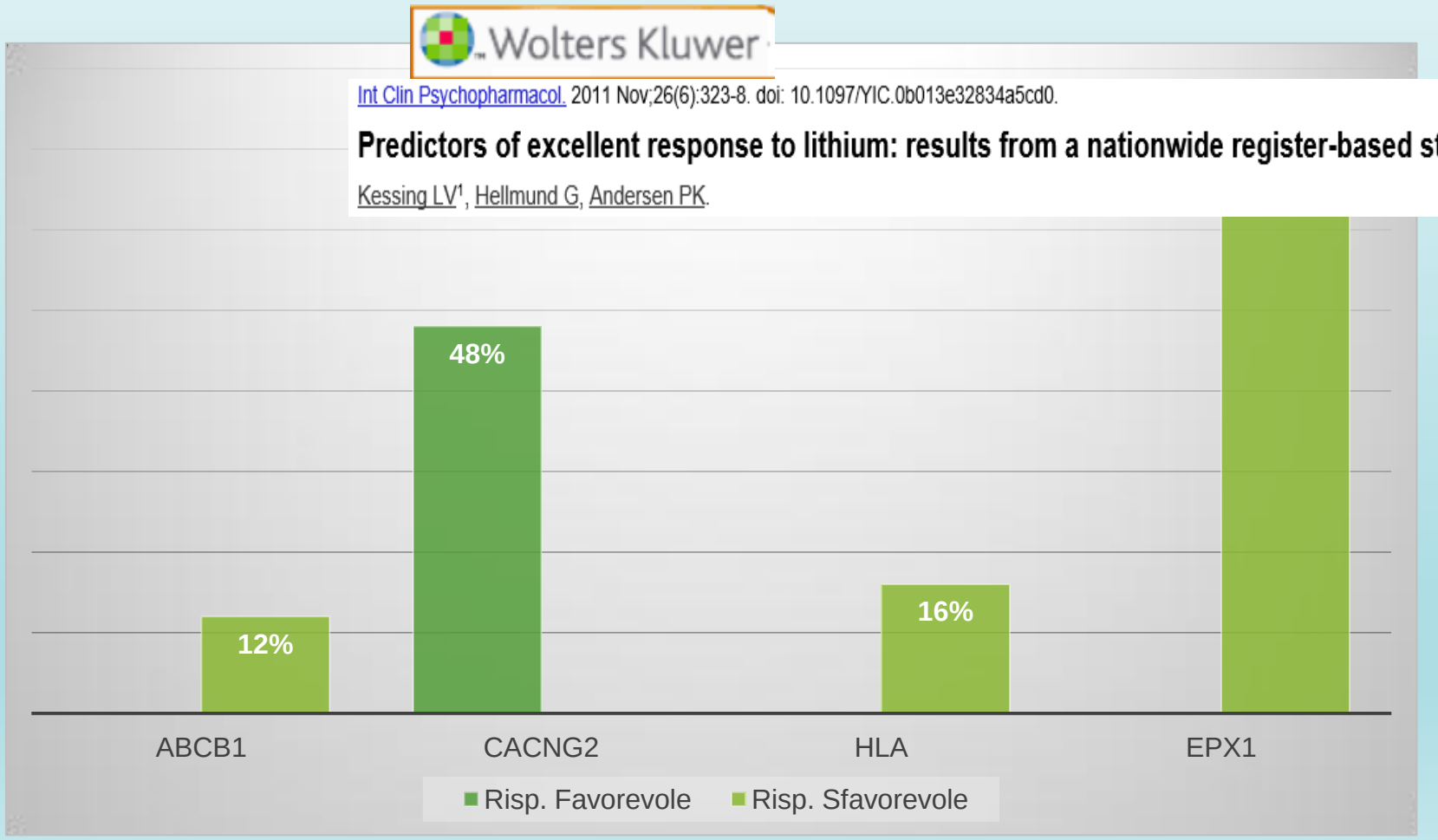
Santiago Sánchez-Iglesias, MD, PhD, Virginia García-Solaesa, BSc, PhD, Belén García-Berrocal, MD, PhD, Almudena Sanchez-Martín, PhD, Carolina Lorenzo-Romo, MD, PhD, Tomás Martín-Pinto, MD, Andrea Gaedigk, MS, PhD, José Manuel González-Buitrago, PhD, and María Isidoro-García, MD, PhD

Risultati e: polimorfismi di rilievo da un punto di vista farmacodinamico nel trattamento con antipsicotici



	AKT1-DD1T4-RPTOR-FCHSD1	HTR2C	AKT1-RGS4	NEF3
Risp Favorevole	39%		24%	28%
Risp Sfavorevole	40%	24%		

Risultati f: polimorfismi farmacodinamici e farmacocinetici rilevanti nel trattamento con stabilizzatori

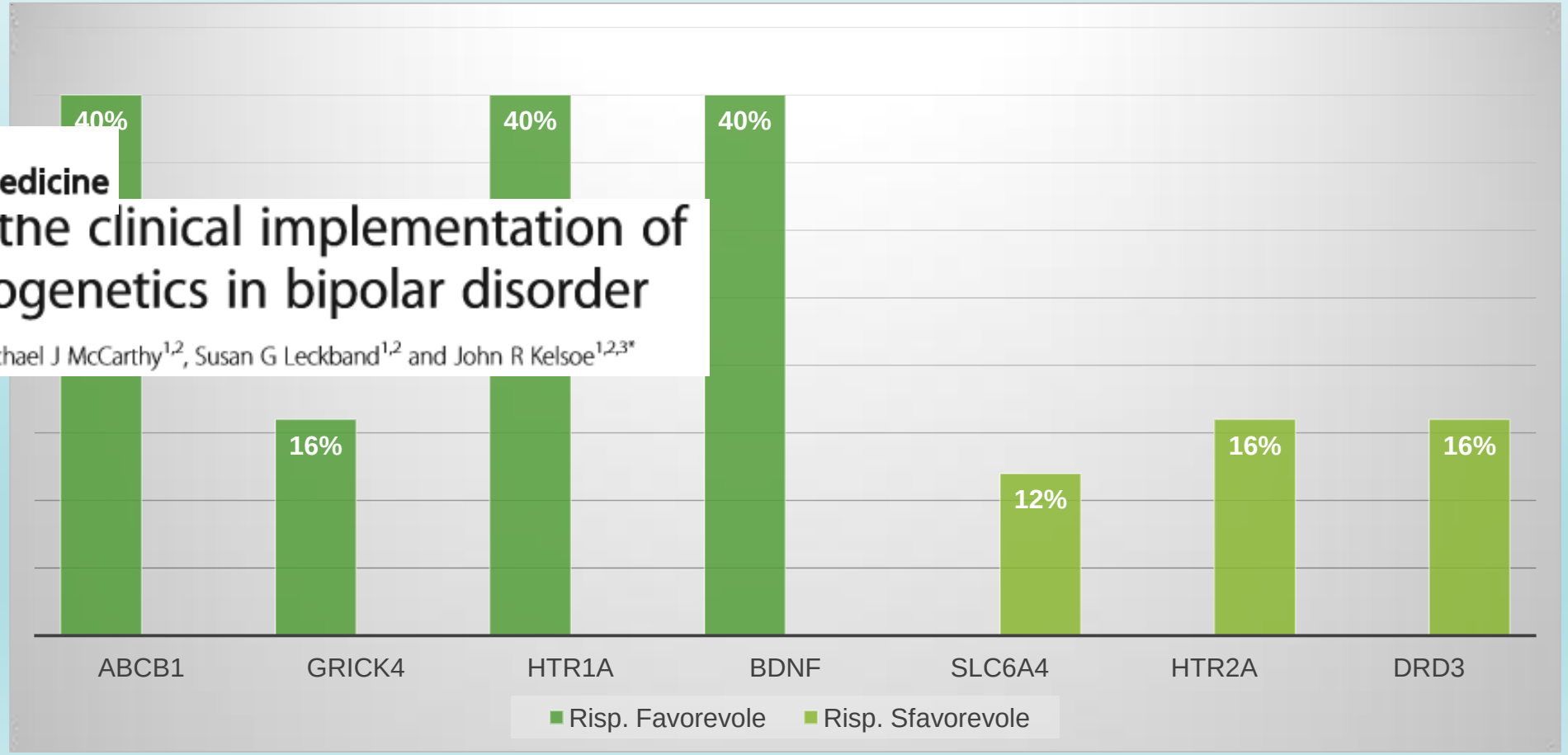


Risultati g: polimorfismi farmacocinetici e farmacodinamici rilevanti nel trattamento con Antidepressivi

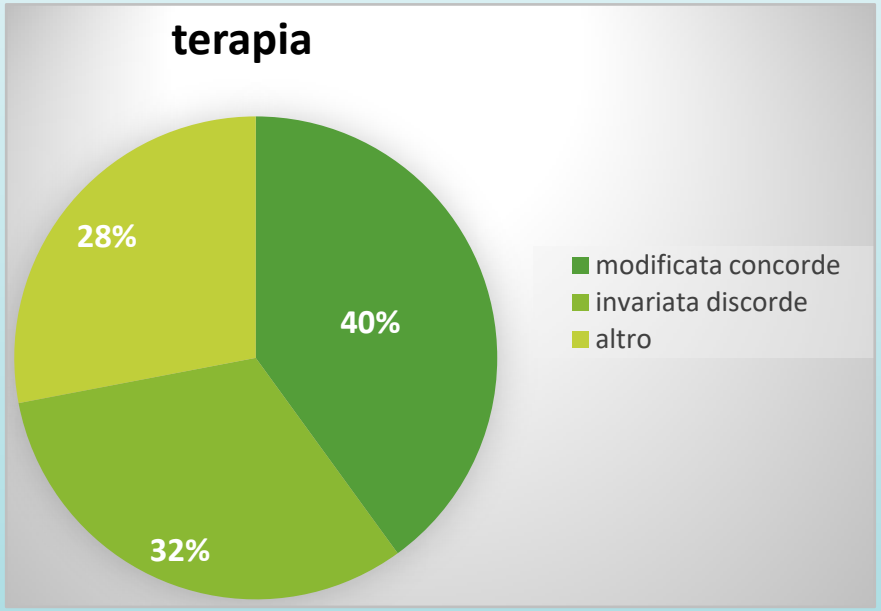
BMC Medicine

Towards the clinical implementation of pharmacogenetics in bipolar disorder

Naji C Salloum[1,2], Michael J McCarthy[1,2], Susan G Leckband[1,2] and John R Kelsoe[1,2,3*]



Risultati h: rivalutazione della terapia nel corso del tempo



30 SOGGETTI ARRUOLATI

- 4 SOGGETTI PER DATI MANCANTI AL T1 E T2

26 SOGGETTI

- 2 SOGGETTI, 1 PER CAMBIO T A T1 E T2, 1 PER CAMBIO AL SOLO T2

24 SOGGETTI CON TERAPIA INVARIATA DA T1 A T2

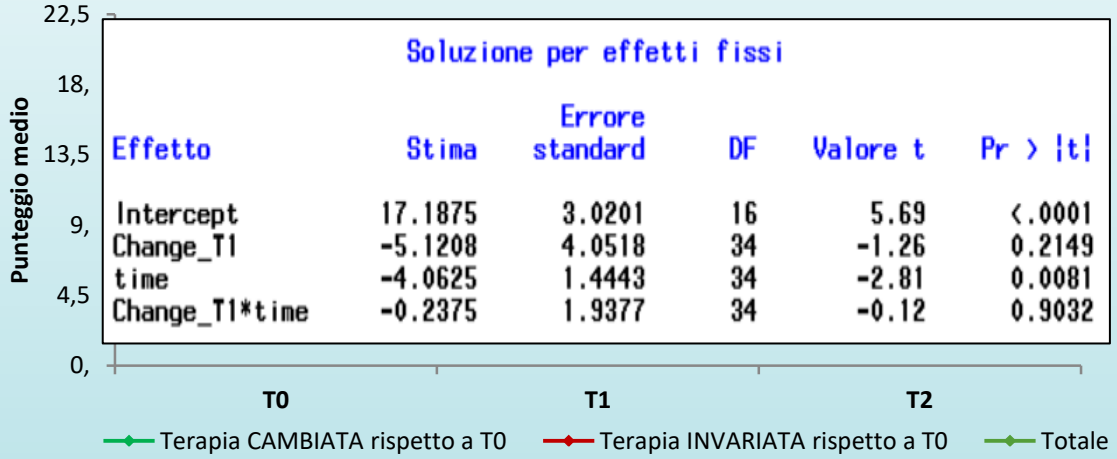
-1 NON CAMBIA IN MODO CONORDE AL T0

13 CAMBIO T CONCORDE AL TEST

10 T INVARIATA IN MODO NON CONCORDE AL TEST

Risultati i: confronto dell'andamento psicopatologico nei 2 sottogruppi

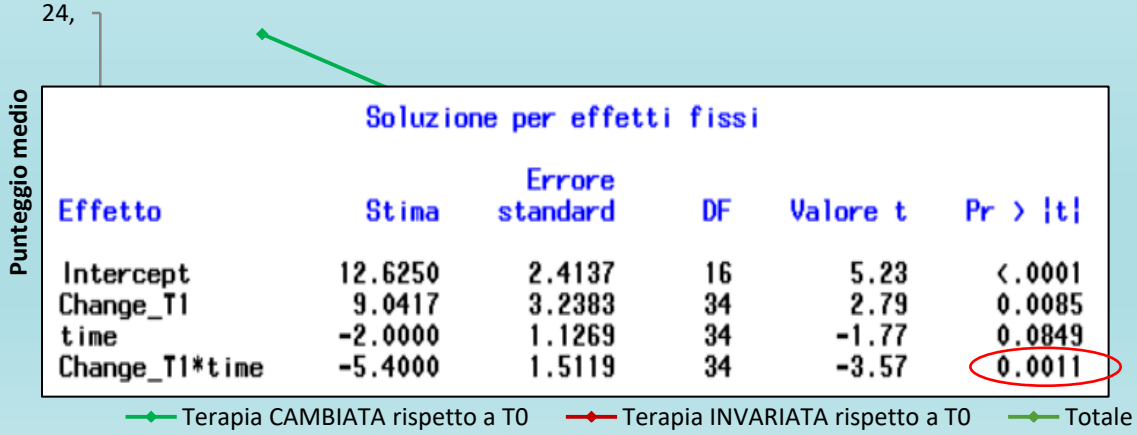
YMRS



Soluzione per effetti fissi

Effetto	Stima	Errore standard	DF	Valore t	Pr > |t|
Intercept	17.1875	3.0201	16	5.69	<.0001
Change_T1	-5.1208	4.0518	34	-1.26	0.2149
time	-4.0625	1.4443	34	-2.81	0.0081
Change_T1*time	-0.2375	1.9377	34	-0.12	0.9032

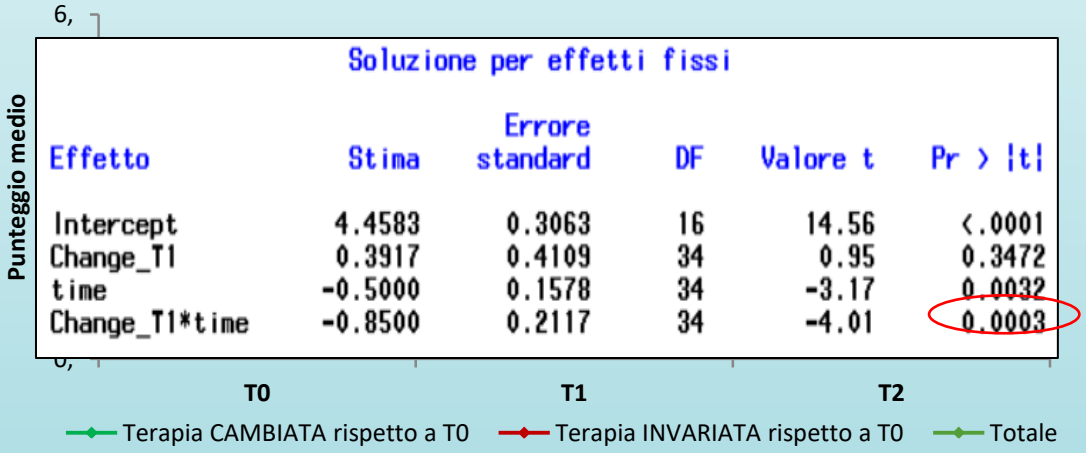
HDRS



Soluzione per effetti fissi

Effetto	Stima	Errore standard	DF	Valore t	Pr > |t|
Intercept	12.6250	2.4137	16	5.23	<.0001
Change_T1	9.0417	3.2383	34	2.79	0.0085
time	-2.0000	1.1269	34	-1.77	0.0849
Change_T1*time	-5.4000	1.5119	34	-3.57	0.0011

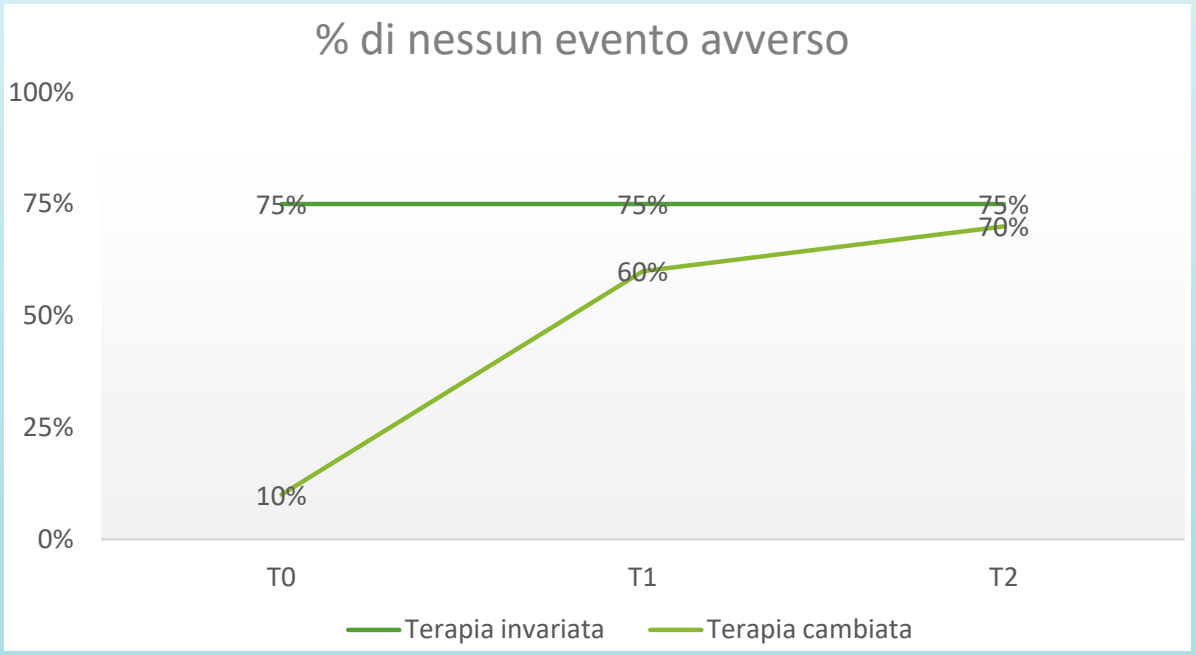
CGI severità



Soluzione per effetti fissi

Effetto	Stima	Errore standard	DF	Valore t	Pr > |t|
Intercept	4.4583	0.3063	16	14.56	<.0001
Change_T1	0.3917	0.4109	34	0.95	0.3472
time	-0.5000	0.1578	34	-3.17	0.0032
Change_T1*time	-0.8500	0.2117	34	-4.01	0.0003

Risultati I: confronto degli AES nei 2 sottogruppi

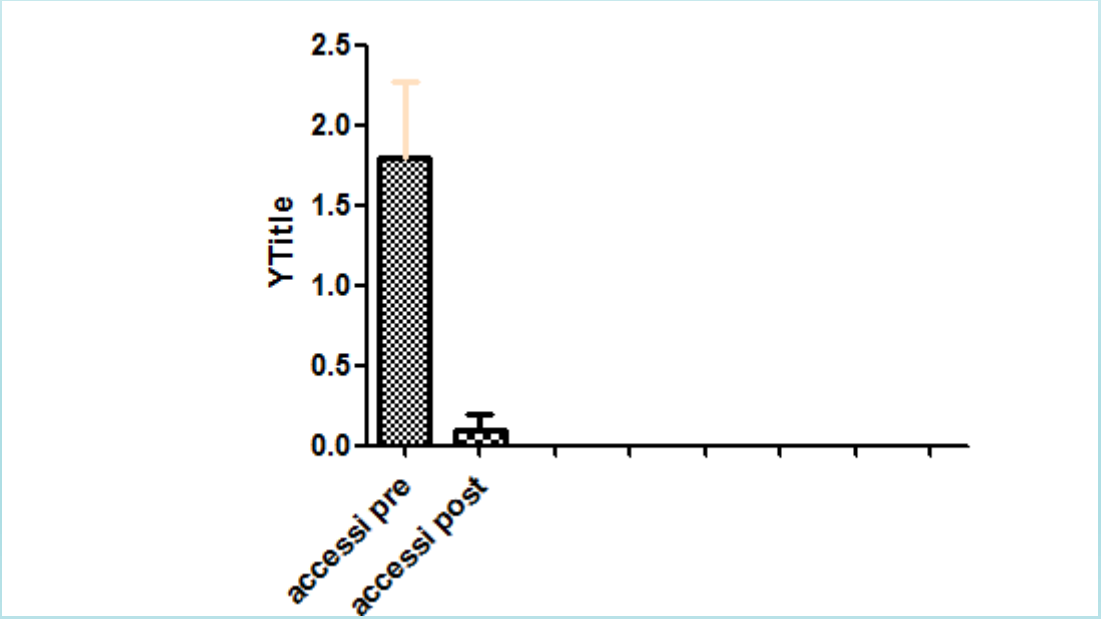


T0		T1		T2			
		N	%	N	%	N	%
Gr A	0	1	10	6	60	7	70
	1	4	40	2	20	2	20
	≥ 2	5	50	2	20	1	10
totale		10		10		10	
Gr B	0	6	75	6	75	6	75
	1	0	0	1	12.5	1	12.5
	≥ 2	2	25	1	12.5	1	12.5
totale		8		8		8	

Risultati: Mirror analysis accessi in PS

Colonna1	Colonna2
accessi pre	**accessi post**
3	**0**
2	**0**
1	**0**
1	**0**
5	**0**
2	**0**
2	**0**
0	**0**
0	**0**
2	**1**

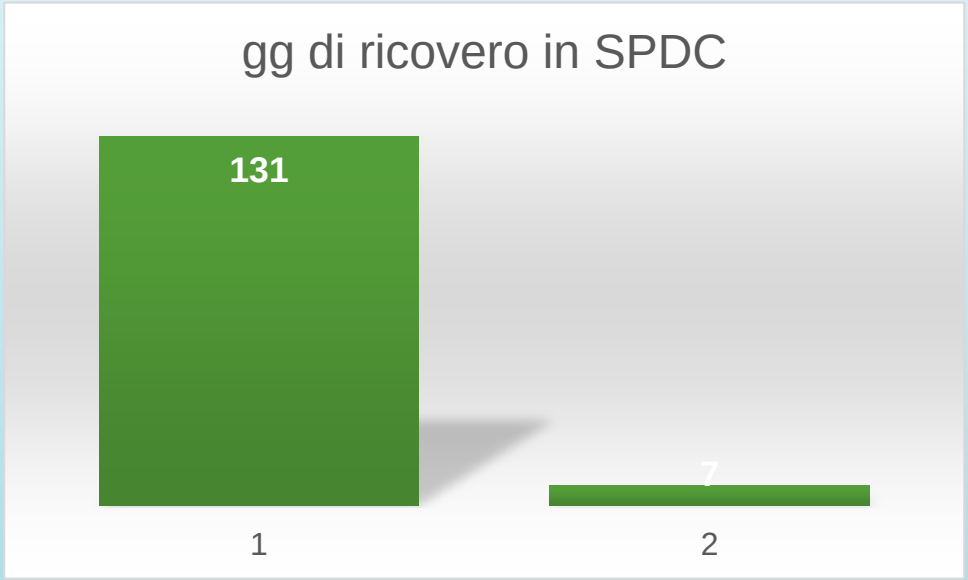
Paired T test: 0,005



Risultati m: Mirror analysis gg di ricovero

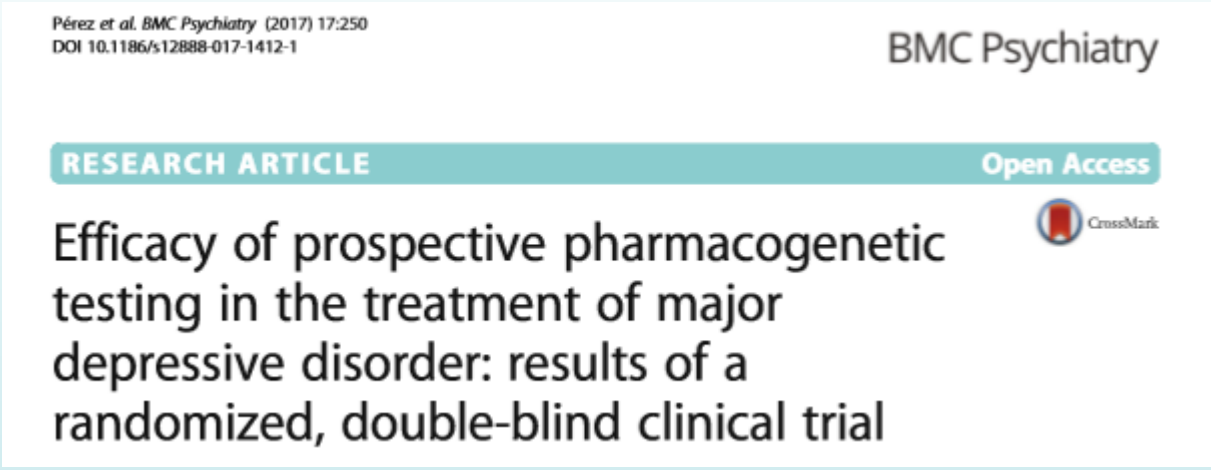
gg ricov pre t0	gg ricov post T0
6	0
18	0
55	0
21	0
9	0
0	0
0	0
17	7
5	0
0	0

Paired T Test: p< 0,0429



Fisher's exact test: p< 0.0001

The utility of Pharmacogenetic testing to tailor psychiatric medication. Focus on mood disorders



- Prospective, multicenter, double blind, parallel controll trial
- Aim: evaluate efficacy and tollerability of PGT information in the selection of drug treatments for MDD
- Recruitment and randomization: CGI-S
- At 4-8-12 weeks PGI-I, HDRS-17, FIBSER, CGI-S , SDI, SATMED-Q

Perez et al, 2017

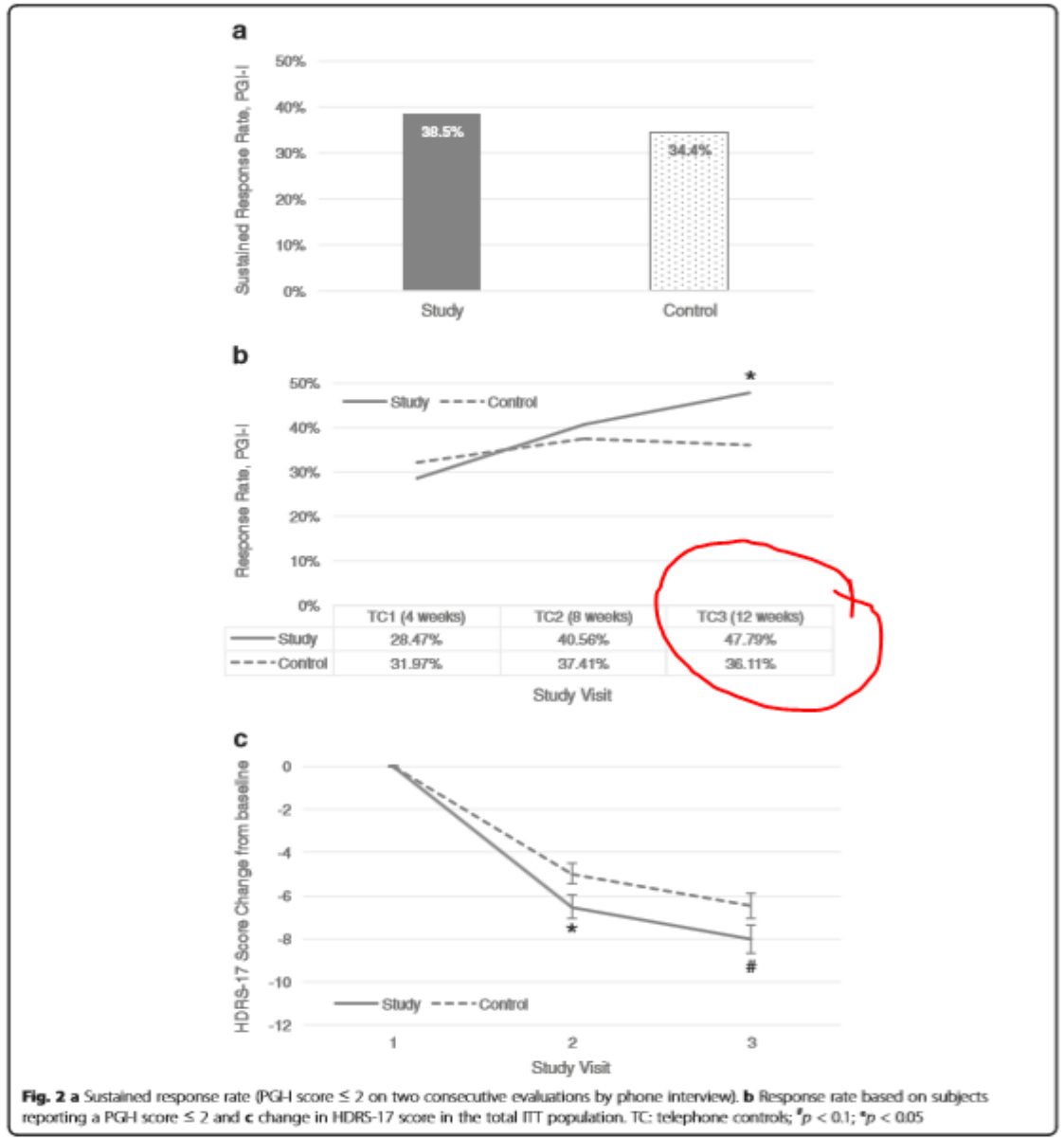


Fig. 2 **a** Sustained response rate (PGI-I score ≤ 2 on two consecutive evaluations by phone interview). **b** Response rate based on subjects reporting a PGI-I score ≤ 2 and **c** change in HDRS-17 score in the total ITT population. TC: telephone controls; $^{\#}p < 0.1$; $^{*}p < 0.05$

-PGI-I score: PGx guided group reached a higher n° of responders at week 12 (p= 0.047)

-HDRS-17 score: PGx guided group reached a higher reduction in HDRS at 6 and at 12 weeks (p 0.03 and p 0.07)

-significant results favoring the PGx-guided group were found also in clinician-rated CGI-S, FIBSER and SDI

Perez et al, 2017

Pérez et al. BMC Psychiatry (2017) 17:250
DOI 10.1186/s12888-017-1412-1

BMC Psychiatry

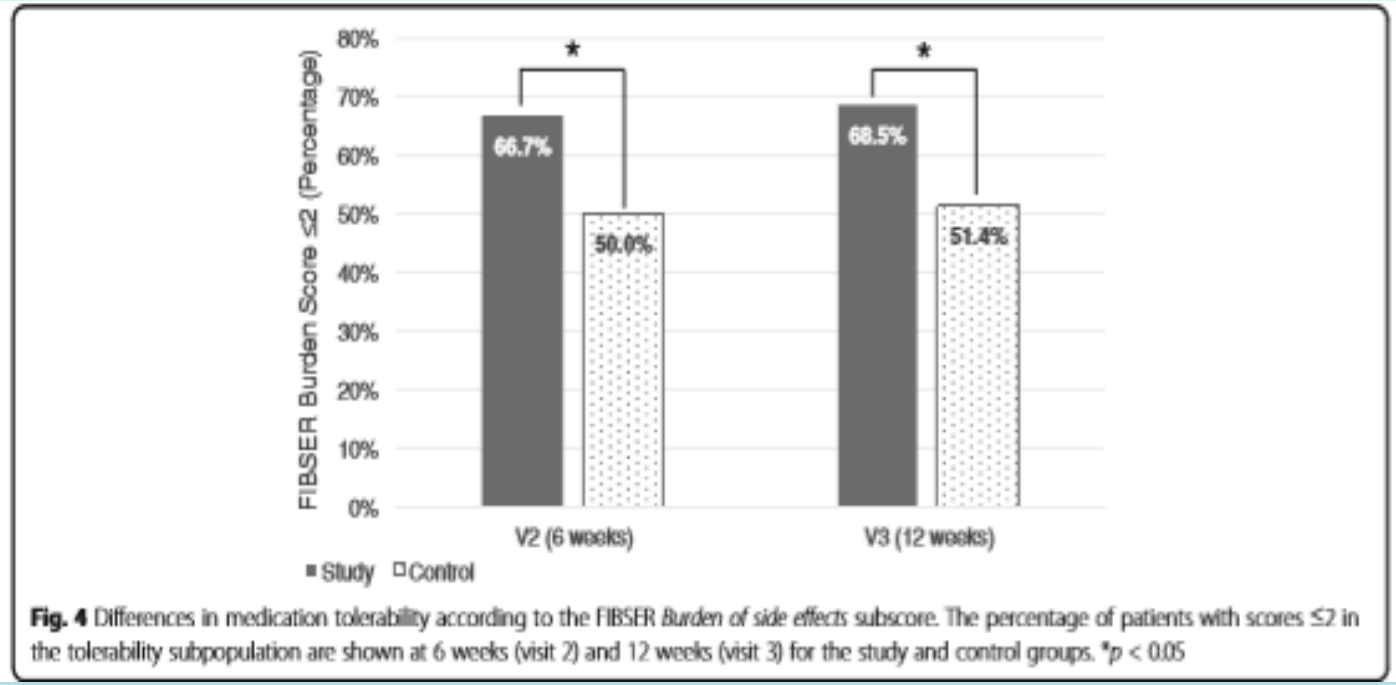


Fig. 4 Differences in medication tolerability according to the FIBSER *Burden of side effects* subscore. The percentage of patients with scores ≤2 in the tolerability subpopulation are shown at 6 weeks (visit 2) and 12 weeks (visit 3) for the study and control groups. *$p < 0.05$

Medication Tolerability

-177 patients presenting AES at baseline without differences between the 2 subgrouops at baseline.

-at 6 weeks the n° of patients presenting a FIBSER score ≤ 2 was higher in the PGx- guided group (66.7% vs 50%, **p= 0.029**)

-also at 12 weeks the n° of patients presenting a FIBSER score ≤ 2 was higher in the PGx- guided group (68.5% vs 51.4%, **p= 0.026)**

Perez et al, 2017

Conclusion

- Utility of PGT to taylor psychiatric medication vs persistent distrust by psychiatrists
- Usefulness of PGT in identifying more effective and more tolerated treatments
- Fewer access to emergency services and fewer hospitalizations

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Merikangas KR, Jin R, He JP, et al. (2011) Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Arch Gen Psychiatry. 68(3):241-51.

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